According to still further features in the described preferred embodiments step (b) is effected at least twice.

According to still further features in the described preferred embodiments removing comprises subjecting the tissue to a detergent solution.

According to still further features in the described preferred embodiments the detergent solution comprises TRITON-X-100.

According to still further features in the described preferred embodiments the detergent solution further comprises ammonium hydroxide.

According to still further features in the described preferred embodiments the Triton-X-100 is provided at a concentration selected from the range of 0.1-2 % (v/v).

According to still further features in the described preferred embodiments the Triton-X-100 is provided at a concentration of 1 % (v/v).

According to still further features in the described preferred embodiments the ammonium hydroxide is provided at a concentration selected from the range of 0.05-1.0 % (v/v).

According to still further features in the described preferred embodiments the ammonium hydroxide is provided at a concentration of 0.1 % (v/v).

According to still further features in the described preferred embodiments subjecting the tissue to the detergent solution is effected for at least 24-48 hours.

According to still further features in the described preferred embodiments subjecting the tissue to the detergent solution is effected for 2-4 times.

According to still further features in the described preferred embodiments the tissue comprises a myocardium tissue.

According to still further features in the described preferred embodiments the tissue comprises a vascular tissue.

According to still further features in the described preferred embodiments the tissue comprises tissue segments.

According to still further features in the described preferred embodiments each of the tissue segments is 2-4 mm thick.

According to still further features in the described preferred embodiments the cellular components comprise cell nuclei, nucleic acids, residual nucleic acids, cell membranes and/or residual cell membranes.

According to still further features in the described preferred embodiments the myocardium-derived decellularized ECM maintains mechanical and structural properties of a myocardium tissue ECM

According to still further features in the described preferred embodiments the myocardium-derived decellularized ECM is capable of remodeling upon seeding with cells.

According to still further features in the described preferred embodiments the myocardium-derived decellularized ECM maintains at least 90 % of a collagen content and at least 80 % of an elastin content of a myocardium tissue.

According to still further features in the described preferred embodiments the myocardium-derived decellularized ECM is characterized by a stress value of at least 0.4 MPa when strained to 40 %.

According to still further features in the described preferred embodiments the myocardium tissue is a pig myocardium tissue.

According to still further features in the described preferred embodiments the at least one cell type is cardiomyocyte and the myocardium-derived decellularized ECM exhibits spontaneous beating.

According to still further features in the described preferred embodiments the spontaneous beating is in concert.

According to still further features in the described preferred embodiments the at least one type of cells comprises cardiomyocytes.

According to still further features in the described preferred embodiments the at least one type of cells comprises cardiac fibroblasts.

The present invention successfully addresses the shortcomings of the presently known configurations by providing a novel method of decellularizing natural tissues which results in matrices which are completely devoid of cellular components and thus non-immunogenic when implanted in a subject, maintain the structural and mechanical properties of the natural tissue ECMs and are remodeled when seeded with cells.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of the preferred embodiments of the present invention only, and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for a fundamental understanding of the invention, the description taken with the drawings making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

In the drawings:

FIGs. 1 a-f are photographs depicting myocardium tissue segments from pig (Figures 1a-e) or rat (Figure 1f) hearts subjected to the decellularization process of the present invention. Figure 1a – The heart of an adult pig. The left ventricle wall is marked by a circle and the right atrium is marked by an arrow; Figure 1b – myocardium segments of 2-4 mm thick sliced from left ventricle; Figure 1c – myocardium segments after partial decellularization. Myocardium segments were subjected to 12 hours of proteolytic digestion in 0.05 % trypsin and two cycles of incubation in a detergent solution (1 % Triton-X-100 / 0.1 % ammonium hydroxide), 48 hours each. Cellular remnants are visible in the center of the segment (marked by an arrow); Figure 1d – myocardium segments from the left ventricle after complete decellularization as described in Example 1 of the Examples section which follows. Preservation of vascular structures is demonstrated (marked by arrows); Figure 1e – myocardium segments from right atrium after complete decellularization. Note that the three-dimensional (3D) structure of the inner wall is preserved; Figure 1f – The heart of an adult rat after the complete decellularization process.

FIG. 2 is a photomicrograph depicting Hematoxylin and Eosin (H&E) staining of a matrix after decellularization. Matrices after decellularization were frozen with

OCT medium and 5 μm frozen sections were stained with H&E. Note that no cell nuclei are present in the matrix. Magnification is x 40.

FIGs. 3a-d are photomicrographs depicting the assessment of nuclear and nucleic acid removal using fluorescent DAPI staining. Matrices after a complete [2 cycles in 0.05 % trypsin (24 hours each) and 4 cycles in a detergent solution (1 % Triton-X-100 / 0.1 % ammonium hydroxide; 48 hours each); Figures 3a and b;] or a partial [12 hours digestion in 0.05 % trypsin and two cycles of 48 hours each in a detergent solution (1 % Triton-X-100 / 0.1 % ammonium hydroxide); Figure 3c and d)] decellularization process were washed in PBS and incubated for 20 minutes with 1 μg/ml DAPI. Samples were exposed to UV and examined by a fluorescent microscope. Note the absence of cell nuclei in the completely processed matrices (Figures 3a-b), whereas some could be found in the partially processed ones (Figures 3c-d). Also note that while in the partially processed matrices some residual non-nuclear staining is seen (Figures 3c-d) indicating incomplete removal of cellular DNA from broken nuclei, in the completely processed matrices no residual staining is seen (Figures 3a-b). All samples were similarly exposed to UV light for photography.

FIGs. 4a-d are photomicrographs depicting assessment of cell membrane removal using fluorescent DiO staining. Matrices following partial [12 hours digestion in 0.05 % trypsin and two cycles of 48 hours each in a detergent solution (1 % Triton-X-100 / 0.1 % ammonium hydroxide); Figures 4a and b] or complete [two cycles of 24 hours each in 0.05 % trypsin and four cycles of 48 hours each in a detergent solution (1 % Triton-X-100 / 0.1 % ammonium hydroxide); Figures 4c and d] decellularization process were washed in PBS and incubated in the dark at room temperature for two hours with 5 μg/ml DiO stain. Samples were inspected by a fluorescent microscope with a blue filter. Figures 4c and 4d represent the same field with (Figure 4c) or without (Figure 4d) the additional exposure to a white light. All size bars represent 100 μm. Note the presence of membrane residues in the partially processed matrices (Figures 4a-b) and the complete absence of membrane residues in the completely processed decellularized matrices (Figures 4c-d). All samples were similarly exposed to fluorescence for photography.

FIGs. 5a-b are bar graphs depicting preservation of collagen (Figure 5a) and elastin (Figure 5b) after complete decellularization of myocardial tissue segments.

Complete decellularization was performed according to the decellularization protocol described in Example 1 of the Examples section which follows and included two cycles of 24 hours each in 0.05 % trypsin and four cycles of 48 hours each in 1 % Triton-X-100/ 0.1 % ammonium hydroxide. Fresh myocardial tissue segments (fresh) and myocardium-derived decellularized ECM matrices (decellularized) were lyophilized and the total collagen and elastin contents were measured. Results are presented as the average (± SD) amount of collagen or elastin [in milligrams (mg)] per 100 mg of original fresh tissue (dry weight, n = 5 in each case). Note that about 90 % of the collagen and about 80 % of the elastin were preserved in the matrices following complete decellularization.

FIGs. 6a-c are photomicrographs depicting SEM analysis of myocardium-derived decellularized matrices. Matrices were fixed in 2.5 % glutaraldehyde, dehydrated in ascending concentrations of ethanol and subjected to SEM analysis. Note the highly fibrous and porous matrix with various thicknesses of collagen fibers and high crosslinking levels. Size bars represent 25 μm (Figure 6a), 8 μm (Figure 6b) and 2.5 μm (Figure 6c).

FIG. 7 is a bar graph depicting the glycosaminoglycan (GAG) content in the myocardium-derived decellularized matrix of the present invention. GAG content was quantified from lyophilized samples of the decellularized matrix of the present invention and a commercial bovine tendon type I collagen (Sigma) using the safranin O assay by extrapolation from a chondroitin sulfate standard curve. Bovine serum albumin (BSA) served as a negative control. Results are presented as average ± SD of microgram GAG per mg sample as determined in six samples in each case. Note the significantly high GAG content in the myocardium-derived decellularized matrix of the present invention as compared to the commercial collagen type I matrix.

FIGs. 8a-c are graphs depicting mechanical properties of the myocardium-derived decellularized matrices of the present invention. Matrices were decellularized according to the protocol described in Example 1 of the Examples section that included two cycles of 24 hours each in 0.05 % trypsin and four cycles of 48 hours each in 1 % Triton-X-100 / 0.1 % ammonium hydroxide. Figure 8a – Cyclic strain. Matrices were pulled from "rest point" (0 stress, 0 strain) at a constant strain rate of 0.05 mm per second to 15 % strain and released to the rest point at the same rate.

Results are presented as the stress [in mega Pasqual (MPa) units] as a function of the percentage of strain as measured for six decellularized matrix samples. Each colored curve represents an average (of six samples) of a separate strain-release cycle [(straining to 15 % strain (arrow pointing up) and releasing back to rest point (arrow pointing down)] and the bold black line represents an average of all samples in all 6 cycles. No significant decrease in elasticity is observed as indicated by retaining maximal stress during the 6 cycles of straining to 15 %. Figure 8b – Strain – relaxation. Matrices were quickly pulled (0.5 mm per second) to 20 % strain and kept there for 10 minutes. Results presented as the load (in Newton [N] units) as a function of time [in seconds (s)] as measured for 6 decellularized matrices (each represented by a colored curve, bold black line indicating average of the six samples). No significant decrease in elasticity is observed as indicated by minimal decrease in load over time. Figure 8c – Strain to break. Matrices were slowly pulled (strain rate of 0.05 mm per second) until torn. The experiment was performed on 6 decellularized matrices. Shown is a representative graph of the stress (in MPa units) as a function of percentage of strain for one decellularized matrix. Note the high strength and flexibility as indicated by withstanding a stress of up to 0.42 MPa when pulled to 40 % strain.

FIGs. 9a-g are SEM (Figures 9a-d) and QuantomiX^{TM} WET-SEM^{TM} (Figures 9e-g) analyses of cardiac fibroblasts seeded on the myocardium-derived decellularized matrices of the present invention. Adult sheep cardiac fibroblasts were seeded at a concentration of approximately 10^4 cells per 1 cm^2 matrix and following 28 days of static culturing the matrices were subjected to SEM or WET-SEM analyses. Size bars represent the following: Figure 9a – 8 μm; Figure 9b – 25 μm; Figure 9c – 80 μm; Figure 9d – 250 μm; Figure 9e – 10 μm; Figure 9f – 20 μm; Figure 9g – 500 μm. Note the significant cell density following 28 days in culture (Figures 9a-d) and the remodeling of the matrix by the fibroblasts into about 1 mm^3 spheroids (Figures 9d and f). Also note the new collagen fibers surrounding the cells populating the scaffold (indicated by arrows in Figure 9e).

FIGs. 10a-e are fluorescent photomicrographs depicting cardiac fibroblast cells cultured on the decellularized matrices of the present invention. Cardiac fibroblasts were stained with the DiO stain, following which the fibroblasts were seeded on the decellularized matrices. Shown are the stained cells on the decellularized matrices at various time points after seeding: Figure 10a – 10 hours (Magnification x 20); Figure 10b – 4 days (Magnification x 10); Figure 10c – 12 days (Magnification x 4); Figure 10d – 18 days (Magnification x 4; Figure 10e – 24 days (Magnification x 4). Note that three weeks after seeding the matrices began to shrink and formed dense cell populated spheres (Figures 10d and e).

FIGs. 11a-d are photomicrographs depicting histochemical H&E staining of seeded matrices. Decellularized myocardium-derived matrices were seeded with cardiac fibroblasts and 14 (Figures 11a-b) or 21 (Figures 11c-d) days post seeding the matrices were either fixed in paraformaldehyde and embedded in paraffin blocks (Figures 11a and c) or frozen in OCT block (Figures 11b and d) and sections of 5 μm were prepared and stained with H&E. Note that 14 days post seeding the cells were distributed throughout the scaffold (Figures 11a-b) and that 21 days post seeding the scaffolds shrunk and the cells were populated more densely (Figures 11c-d).

FIGs. 12a-b are bar graphs depicting the viability (in percentages) of fibroblasts (Figure 12a) or cardiomyocytes (Figure 12b) after seeding on the decellularized matrices of the present invention. Cells were statically seeded at a concentration of 10^4 cells per 1-cm^2 scaffolds (decellularized matrices). Every second change of medium (e.g. every 4-6 days) the cells were transferred to new wells and alamarBlue was added to the medium (1/15 v/v). After 3 hours of incubation with alamarBlue, samples of 100 μl from each well were taken for fluorescent reading at 535 nm / 590 nm. Values were normalized according to a standard curve of fluorescence per cell (not shown). Results are presented as the viability (in percentages, relative to the initial viability measured for each sample) as a function of days post-seeding.

FIGs. 13a-b are photographs of a native (Figure 13a) and a lyophilized, decellularized - porcine blood vessel (Figure 13b). Note the clean, vasculature-free vessel obtained following the decellularization process described in Example 4 of the Examples section which follows.

FIGs. 14a-b are photomicrographs of H&E staining depicting a natural (Figure 14a) and a decellularized (Figure 14b) artery. Arrows mark the elastin fibers. Note that the decellularized artery preserves the collagen and elastin structure of the natural artery tissue. Magnification is x 4.

FIG. 15 is a bar graph depicting the collagen and elastin contents in the distal, center and proximal areas of decellularized arteries as percentages of dry artery weight.

FIGs. 16a-d are SEM images of native (Figures 16a-c) and decellularized (Figure 16d) arteries. Figure 16a - Image of an artery at low magnification (size bar = 1 mm); Figure 16b - Higher magnification of the outer surface of the artery shown in Figure 16a demonstrating layers of cells (size bar = 20 μm); Figure 16c - Higher magnification of the inner surface of the artery shown in Figure 16a demonstrating a monolayer of cells (size bar = 50 μm); Figure 16d - Image of a decellularized artery, demonstrating the complete absence of cells following the decellularization process (size bar = 8 μm).

FIG. 17 is an image of an agarose gel electrophoresis of DNA samples extracted from native (lane b) or decellularized (lane c) arteries. Lane a - molecular weight size marker in kilo base pair (kb). Note that while the native artery exhibits an intense DNA band (lane b), no DNA is seen in the decellularized matrix [including absence of low molecular weight DNA in the decellularized matrix (not shown)].

FIGs. 18a-c are photomicrographs of H&E staining (Figures 18a-b) or α - actin immunohistochemistry (Figure 18c; actin in dark purple) of a collagen decellularized artery scaffold seeded with smooth muscle cells. Magnification is x 10 in Figures 18a and c and x 40 in Figure 18b.

FIGs. 19a-f are photomicrographs depicting recellularized porcine carotid artery (PCA) with cells expressing red fluorescent protein (RFP) or green fluorescent protein (GFP). Figure 19a - Expression of RFP by endothelial cells four weeks after seeding (Magnification x 40); Figure 19b - Smooth muscle cells (SMC) expressing GFP four weeks post seeding (Magnification x 40); Figure 19c - Wet SEM image of Figure 19a (Size bar = 20 μm); Figure 19d - Wet SEM image of Figure 19b (Size bar = 20 μm); Figure 19e-f - Masson stained SMC seeded scaffold following 3 months in culture (Size bar = 100 μm).

FIGs. 20a-f are photomicrographs of H&E staining (Figures 20a-c) or SMC actin immunostaining (Figures 20d-f) of decellularized artery scaffolds following 4 weeks of seeding and culturing with SMCs. Figures 20a and d - Static seeding and culture; Figures 20b and e - Centrifugal seeding and static culture; Figures 20c and f - Centrifugal seeding and dynamic culture. H&E stains the cell nuclei in purple and the extracellular space in pink. Actin immunostaining stains the actin protein in green and the cell nuclei in blue. Note that in the scaffold seeded by centrifugal seeding (Figures 20b and e) the cell penetration through the scaffold is more efficient than in the scaffold seeded by static seeding (Figures 20a and d). Also note that in scaffold seeded by the centrifugal seeding and cultured using dynamic culturing (Figures 20 c and f) cell penetration is significantly more efficient than in scaffolds seeded by centrifugal seeding and cultured by static culturing (Figures 20b and e). Size bars represent 100 μm in Figures 20a-c and 50 μm in Figures 20d-f.

FIGs. 21a-c are photomicrographs depicting procollagen I immunostaining of decellularized artery scaffolds following 4 weeks of seeding and culturing with SMCs. Figure 21a - Static seeding and culture; Figure 21b - Centrifugal seeding and static culture; Figure 21c - Centrifugal seeding and dynamic culture. Cell nuclei are stained in purple and pro-collagen I is stained in brown. Note that vast amount of collagen secreted by cells that were seeded using a centrifugal method and cultured using a dynamic method (Figure 21c, marked by an arrow). Size bars represent 100 μm.

FIGs. 22a-c are images depicting RT-PCR analysis of elastin (Figure 22a), collagen III (Figure 22b) and GAPDH (Figure 22c) performed on mRNA samples derived from SMCs seeded on the decellularized artery scaffolds. Lane 1 - static seeding and culture; lane 2 - centrifugal seeding and static culture; lane 3 - centrifugal seeding and dynamic culture. Note that the mRNA level of elastin is significantly higher in scaffolds seeded using the centrifugal seeding and cultured by the dynamic culture (Figure 22a, lane 3) as compared to scaffolds seeded using the centrifugal seeding and cultured by static culture (Figure 22b, lane 2) or scaffolds seeded and cultured using the static method (Figure 22a, lane 1). The level of the GAPDH mRNA indicates that equal amounts of RNA were used in all assays.

FIGs. 23a-d are photomicrographs depicting H&E staining (Figures 23a and c) and CD31 immunostaining (Figures 23b and d) of coated artery-derived decellularized scaffolds seeded with HUVEC following 9 days in culture. Figures

23a-b – scaffolds coated with PBS; Figures 23c-d – scaffolds coated with corneal matrix (CM). CD31 immunostaining stains CD1 in green and cell nuclei in blue. Note that in the CM – coated scaffolds (Figure 23d) the cells penetrate the scaffold more efficiently that in the PBS – coated scaffolds (Figure 23b) as indicated by the deeper layers of nuclei stained in blue. Also note that in the CM – coated scaffolds (Figure 23d) the endothelial cells form a more continuous layer than in the PBS – coated scaffolds (Figure 23b) as indicated by the green labeling. Size bars represent 50 μm.

FIG. 24 is a graph depicting the proliferation of SMCs on artery-derived decellularized scaffolds at different time points. Cells were seeded and cultured using the indicated methods: blue – static seeding, static culturing; pink – centrifugal seeding, static culturing; green – centrifugal seeding, dynamic culturing. Proliferation was measured using Alamar-Blue reagent and results are presented as the number of cells x 10^6 as a function of time (in days) post seeding. N = 4, * $p < 0.05$.

FIGs. 25a-d are photomicrographs depicting H&E staining (Figures 25a-c) or Masson's trichrome staining (Figure 25d) of sections of artery-derived decellularized scaffolds which were subject to centrifugal seeding and dynamic culturing with SMCs. Figure 25a - 1 day post-seeding; Figure 25b - 3 weeks post-seeding; Figures 25c and d - 7 weeks post-seeding. Masson's trichrome staining stains the cell nuclei in brown, the elastin and SMCs in red-purple and the collagen in blue. Size bars represent 50 μm.

FIGs. 26a-d are photomicrographs depicting the assessment of the immune response to implanted artery-derived decellularized scaffolds. Implanted scaffolds were harvested one (Figures 26a-b) or two (Figures 26c-d) weeks post implantation and tissue sections were stained with H&E. Figures 26a and c – low magnification of x 100; Figures 26b and d – high magnification of x 400. Note the depth of cell penetration and thickness of capsule at two weeks post implantation (Figures 26c and d). In Figure 26d, arrow head pointing at a neutrophil cell; thick arrow pointing at a fibroblast; and the thin arrow pointing at a lymphocyte cell.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is of a method of generating completely decellularized ECMs from natural tissues such as myocardium or vascular tissues which are non-immunogenic when implanted in a subject, preserve the structural and mechanical properties of the natural tissue ECM and are remodeled upon seeding with cells. Specifically, the present invention can be used for tissue regeneration and/or repair applications such as of myocardial or vascular tissues.

The principles and operation of the method of generating the decellularized ECM according to the present invention may be better understood with reference to the drawings and accompanying descriptions.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details set forth in the following description or exemplified by the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

Heart failure is a main contributor to morbidity and mortality in the Western world. The main reason for the morbidity and mortality associated with heart failure is the inability of cardiomyocytes to proliferate and regenerate following injuries such as caused by myocardial infarction (MI). Thus, the current treatment regimens for malfunctioning heart tissues rely on heart transplantation. However, due to the limited availability of donated hearts, there is a need to develop engineered cardiac tissues which can replace injured or diseased hearts.

One preferred approach of tissue engineering is the use of decellularized natural tissues. Prior art studies describe various methods of decellularization of natural tissues (See for example, U.S. Pat. Appl. Nos. 20040076657, 20030014126, 20020114845, 20050191281, 20050256588 and U.S. Pat. Nos. 6,933,103, 6,743,574, 6,734,018 and 5,855,620; which are fully incorporated herein by reference). However, none of the prior art methods resulted in complete decellularized matrices which are non-immunogenic when implanted in a subject, maintain the mechanical and structural properties of the tissue ECM and are remodeled upon seeding with cells. In addition, to date, there is no report of a decellularized matrix which is derived from a myocardium tissue.

While reducing the present invention to practice, the present inventors have uncovered a novel method of decellularizing a natural tissue so as to obtain a matrix which is completely devoid of cellular components and exhibits mechanical and structural properties that are suitable for tissue regeneration.

As described in the Examples section which follows, decellularization according to the teachings of the present invention of myocardium or artery tissues resulted in matrices which are completely devoid of all cellular components (Figure 2 and Example 1; Figures 16a-d and Example 4), are non-immunogenic when implanted in a subject (Figures 26a-d, Example 4), maintain the ECM composition of the natural tissue (e.g., at least 90 % of the collagen and 80 % of the elastin; Figures 5a-b, 7 and Example 2; Figure 15 and Example 4), exhibit mechanical [e.g., elasticity and rigidity (Figures 8a-c, Example 2 and Table 1, Example 4)] and structural (Figures 6a-c and Example 2; Figures 14a-b and Example 4) properties of the tissue ECM and are remodeled upon seeding with cells (Figures 9a-f, 10a-e, 11a-d; Example 3). In addition, when seeded with cardiomyocytes, the myocardium-derived decellularized matrices of the present invention exhibited spontaneous pulsatile beating in concert, similar to that of natural myocardium tissues (Example 3).

Thus, according to one aspect of the present invention there is provided a method of generating a decellularized extracellular matrix (ECM) of a tissue. The method is effected by (a) subjecting the tissue to a hypertonic buffer to thereby obtain increased intercellular space within the tissue; (b) subjecting the tissue resultant of step (a) to an enzymatic proteolytic digestion to thereby obtain digested cellular components within the tissue; and subsequently (c) removing the digested cellular components from the tissue; thereby generating the decellularized ECM of the tissue.

As used herein the phrase "decellularized ECM of a tissue" refers to the extracellular matrix which supports tissue organization (e.g., a natural tissue) and underwent a decellularization process (*i.e.*, a removal of all cells from the tissue) and is thus completely devoid of any cellular components.

The phrase "completely devoid of any cellular components" as used herein refers to being more than 99 % (e.g., 100 %) devoid of the cellular components present in the natural (e.g., native) tissue. As used herein, the phrase "cellular components" refers to cell membrane components or intracellular components which make up the cell. Examples of cell components include cell structures (e.g., organelles) or molecules comprised in same. Examples of such include, but are not limited to, cell nuclei, nucleic acids, residual nucleic acids (e.g., fragmented nucleic acid sequences), cell membranes and/or residual cell membranes (e.g., fragmented membranes) which are present in cells of the tissue. It will be appreciated that due to the removal of all cellular components from the tissue, such a decellularized matrix cannot induce an immunological response when implanted in a subject.

The phrase "extracellular matrix (ECM)" as used herein, refers to a complex network of materials produced and secreted by the cells of the tissue into the surrounding extracellular space and/or medium and which typically together with the cells of the tissue impart the tissue its mechanical and structural properties. Generally, the ECM includes fibrous elements (particularly collagen, elastin, or reticulin), cell adhesion polypeptides (e.g., fibronectin, laminin and adhesive glycoproteins), and space-filling molecules [usually glycosaminoglycans (GAG), proteoglycans].

A tissue-of-interest (e.g., myocardium) may be an autologous or preferably a non-autologous tissue (e.g., allogeneic or even xenogeneic tissue, due to non-immunogenicity of the resultant decellularized matrix). The tissue is removed from the subject [e.g., an animal, preferably a mammal, such as a pig, monkey or chimpanzee, or alternatively, a deceased human being (shortly after death)] and preferably washed in a sterile saline solution (0.9 % NaCl, pH = 7.4), which can be supplemented with antibiotics such as Penicillin/Streptomycin 250 units/ml. Although whole tissues can be used, for several applications segments of tissues may be cut. Such tissue segments can be of various dimensions, depending on the original tissue used and the desired application. For example, for myocardium tissue regeneration tissue segments of 1-6 cm width, 1-6 cm length and 2-4 mm thick can be prepared (see Example 1 of the Examples section which follows). Alternatively, for vascular tissue regeneration, blood vessels with a diameter ranging from 5-10 mm can be cut to segments of 5-6 cm in length (see Example 4 of the Examples section which follows).

To remove the vasculature surrounding and feeding the tissue, the tissue is preferably washed at room temperature by agitation in large amounts (e.g., 50 ml per each gram of tissue segment) of EDTA solution (0.5-10 mM, pH-7.4). For example, as is described in Example 1 of the Examples section, myocardium tissue segments of

0.5-12 grams were washed in 50 ml/gram tissue of saline/EDTA solution for at least 4-5 times, 30 minutes each wash, until there was no evident of blood.

As mentioned hereinabove, the tissue of this aspect of the present invention is subjected to a hypertonic buffer to thereby obtain increased intercellular space within the tissue.

The hypertonic buffer used by the present invention can be any buffer or solution with a concentration of solutes that is higher than that present in the cytoplasm and/or the intercellular liquid within the tissue [e.g., a concentration of NaCl which is higher than 0.9 % (w/v)]. Due to osmosis, incubation of the tissue with the hypertonic buffer results in increased intercellular space within the tissue.

Preferably, the hypertonic buffer used by the method according to this aspect of the present invention includes sodium chloride (NaCl) at a concentration which is higher than 0.9 % (w/v), preferably, higher than 1 % (w/v), preferably, in the range of 1-1.2 % (w/v), e.g., 1.1 % (w/v).

According to this aspect of the present invention, the tissue is subjected to the hypertonic buffer for a time period leading to the biological effect, *i.e.*, cell shrinkage which leads to increased intercellular space within the tissue. For example, as is shown in Example 1 of the Examples section which follows, myocardium heart tissue segments of 2-4 mm thick were treated for 2 hours with a hypertonic buffer containing 1.1 % NaCl – 0.02 % EDTA.

Following treatment with the hypertonic buffer, the tissue is further subjected to an enzymatic proteolytic digestion which digests all cellular components within the tissue yet preserves the ECM components (e.g., collagen and elastin) and thus results in a matrix which exhibits the mechanical and structural properties of the original tissue ECM. It will be appreciated that measures are taken to preserve the ECM components while digesting the cellular components of the tissue. These measures are further described hereinbelow and include, for example, adjusting the concentration of the active ingredient (e.g., trypsin) within the digestion solution as well as the incubation time.

Proteolytic digestion according to this aspect of the present invention can be effected using a variety of proteolytic enzymes. Non-limiting examples of suitable proteolytic enzymes include trypsin and pancreatin which are available from various sources such as from Sigma (St Louis, MO, USA). According to one preferred embodiment of this aspect of the present invention, proteolytic digestion is effected using trypsin.

Digestion with trypsin is preferably effected at a trypsin concentration ranging from 0.01-0.25 % (w/v), more preferably, 0.02-0.2 % (w/v), more preferably, 0.05-0.1 (w/v), even more preferably, a trypsin concentration of about 0.05 % (w/v). For example, as is described in Example 1 of the Examples section which follows, a trypsin solution containing 0.05 % trypsin (w/v; Sigma), 0.02 % EDTA (w/v) and antibiotics (Penicillin/Streptomycin 250 units/ml), pH = 7.2] was used to efficiently digest all cellular components of the myocardium tissue.

It will be appreciated that for efficient digestion of all cellular components of the tissue, each of the tissue segments is preferably placed in a separate vessel containing the digestion solution (e.g., a trypsin solution as described hereinabove) in a ratio of 40 ml digestion solution per each gram of tissue. Preferably, while in the digestion solution, the tissue segments are slowly agitated (e.g., at about 150 rpm) to enable complete penetration of the digestion solution to all cells of the tissue.

It should be noted that the concentration of the digestion solution and the incubation time therein depend on the type of tissue being treated and the size of tissue segments utilized and those of skilled in the art are capable of adjusting the conditions according to the desired size and type of tissue. For example, when a myocardium tissue is treated, the tissue is preferably cut to segments of 2-4 mm thick and digestion is effected by two cycles of incubation in the digestion solution, each effected for 24 hours (*i.e.*, a total of 48 hours). Shorter incubation periods of such tissue segments can result in incomplete decellularization as is shown in Figures 3c-d and 4a-b and described in Example 1 of the Examples section which follows. Alternatively, when an artery tissue is treated, tissue segments of 5-6 cm in length are subjected to 2 cycles of digestion, each effected for 24 hours in the digestion solution.

Preferably, the tissue segments are incubated for at least about 20 hours, more preferably, at least about 24 hours. Preferably, the digestion solution is replaced at least once such that the overall incubation time in the digestion solution is at least 40-48 hours.

Following incubation in the digestion solution, the digested cellular components are removed from the tissue. Removal of the digested components from the tissue can be effected using various wash solutions, such as detergent solutions (e.g., ionic and non ionic detergents such as SDS Triton X-100, Tween-20, Tween-80) which can be obtained from e.g., Sigma (St Louis, MO, USA) or Biolab (Atarot, Israel, Merck Germany).

Preferably, the detergent solution used by the method according to this aspect of the present invention includes TRITON-X-100 (available from Merck). For efficient removal of all digested cellular components, TRITON-X-100 is provided at a concentration range of 0.05-2.5 % (v/v), more preferably, at 0.05-2 % (v/v), more preferably at 0.1-2 % (v/v), even more preferably at a concentration of 1 % (v/v).

Preferably, for optimized results, the detergent solution includes also ammonium hydroxide, which together with the TRITON-X-100, assists in breaking and dissolving cell nuclei, skeletal proteins, and membranes.

Preferably, ammonium hydroxide is provided at a concentration of 0.05-1.5 % (v/v), more preferably, at a concentration of 0.05-1 % (v/v), even more preferably, at a concentration of 0.1-1 % (v/v) (e.g., 0.1 %).

The concentrations of TRITON-X-100 and ammonium hydroxide in the detergent solution may vary, depending on the type and size of tissue being treated and those of skills in the art are capable of adjusting such concentration according to the tissue used.

Incubation of the tissue (or tissue segments) with the detergent solution can last from a few minutes to hours to even several days, depending on the type and size of tissue and the concentration of the detergent solution used and those of skills in the art are capable of adjusting such incubation periods. Preferably, incubation with the detergent solution is effected for at least 24-72 hours, and even more preferably, 2-4 cycles of incubation with the detergent solution are effected (e.g., a total of 192 hours).

The above described detergent solution is preferably removed by subjecting the matrix to several washes in water or saline (e.g., at least 10 washes of 30 minutes each, and 2-3 washes of 24 hours each), until there is no evident of detergent solution in the matrix.

Although as described hereinabove, incubation with the detergent solution enables the removal of cell nuclei, proteins and membrane, the method according to this aspect of the present invention optionally and preferably includes an additional step of removing nucleic acids (as well as residual nucleic acids) from the tissue to thereby obtain a nucleic acid – free tissue. As used herein the phrase "nucleic acid – free tissue" refers to a tissue being more than 99 % free of any nucleic acid or fragments thereof as determined using conventional methods (e.g., spectrophotometry, electrophoresis essentially as described in Example 1 of the Examples section which follows). Such a step utilizes a DNase solution (and optionally also an RNase solution). Suitable nucleases include DNase and/or RNase [Sigma, Bet Haemek Israel, 20 μg/ml in Hank balance salt solution (HBSS)]. It will be appreciated that the nuclease treatment is effected following or concomitant with the proteolytic digestion described in step (b).

Thus, the teachings of the present invention can be used to generate a scaffold suitable for tissue regeneration. As used herein the terms "scaffold" or "matrix" which are interchangeably used herein, refer to a two-dimensional or a three-dimensional supporting framework. Preferably, the scaffold of the present invention can be used to support cell growth, attachment, spreading, and thus facilitate cell growth, tissue regeneration and/or tissue repair. The scaffold of the present invention can be formed from any natural tissue such as vascular tissue (e.g., artery, vein), muscle tissue (e.g., myocardium, skeletal muscle), bladder tissue, nerve tissue and testicular tissue. As is described hereinabove, the natural tissue can be derived from a subject such as an animal (e.g., pig) or a deceased human being.

Using the above teachings, the present inventors have generated, for the first time, a scaffold which comprises a myocardium-derived decellularized ECM which is devoid of cellular components and is suitable for tissue regeneration.

As used herein the phrase "suitable for tissue regeneration" refers to a scaffold, which upon seeding and culturing with cells (*ex-vivo*) and/or upon implantation in a subject (*in-vivo*) is capable of regenerating or repairing a tissue-of-interest (e.g., a myocardium tissue).

Due to the unique decellularization method of the present invention, which is based on treating the tissue with a hypertonic buffer followed by an enzymatic proteolytic digestion using for example, trypsin, and subsequently removing the digested cellular components with the detergent solution, the scaffolds the present invention are completely devoid of cellular components.

For example, as is shown in Examples 1 and 4 of the Examples section which follows, myocardium-derived or artery-derived decellularized matrices prepared according to the teachings of the present invention were devoid of cells (see Figure 2 for myocardium-derived ECM and Figures 16a-d for artery-derived ECM), cell nuclei (see Figures 3a-b for myocardium-derived ECM), nucleic acids (see Figure 17 for artery-derived ECM) and cell membranes (see Figures 4c-d for myocardium-derived ECM). Methods of assessing the acellularity (*i.e.*, the complete absence of cellular components) of the scaffolds of the present invention are described in Example 1 of the Examples section which follows and include detection of cells, cell nuclei, nucleic acids, residual nucleic acids, membranes and residual membranes.

Preferably, scaffolds generated according to the teachings of the present invention maintain the mechanical and structural properties of the natural tissue ECM and thus are suitable for tissue regeneration and/or repair. As used herein the phrase "mechanical properties" refers to the elasticity (*i.e.*, the tendency of the matrix to return to its original shape after it has been stretched or compressed) and strength (*i.e.*, the resistance to tearing or breaking upon subjecting the matrix to a load or stress) of the scaffold. The phrase "structural properties" refers to the structure and shape of the matrix in terms of fiber configuration, diameter and/or composition (e.g., percentages of collagen, elastin and/or GAG). The mechanical and structural properties of the scaffold of the present invention enable the scaffold to regenerate and/or repair a damaged or diseased tissue when seeded with cells and/or implanted in a subject (e.g., a human being in need of tissue regeneration). It will be appreciated that the mechanical properties of a native or an engineered tissue are determined by the combination of mechanical and structural properties of the ECM and the cells present in the tissue. For example, in a myocardium tissue, the contraction of the myocardium tissue (*i.e.*, beating) is a result of the combined action of the cells on the unique ECM composition and structure of the myocardium tissue.

For example, as is shown in Example 2 of the Examples section which follows, myocardium-derived decellularized matrices were elastic (e.g., flexible) yet retained their strength following repetitive slow straining (Figure 8a) or constant quick straining to 20 % (Figure 8b). In addition, when strained to 40 % along one of the axis, the myocardium-derived decellularized matrices retained a strength of 0.42 MPa before tearing (Figure 8c).

Preferably, the myocardium-derived decellularized ECM maintains at least 90 % of the collagen content and at least 80 % of the elastin content of a native myocardium tissue.

According to one preferred embodiment of the present invention, scaffolds generated according to the method of decellularization of the present invention are capable of remodeling upon seeding with cells.

As used herein the phrase "capable of remodeling upon seeding with cells" refers to the ability of the matrix (or the scaffold) to change its geometrical shape and/or chemical composition as a result of cells being seeded and proliferating therein. A change in the geometrical shape can be, for example, becoming round (e.g., spheric), thick, dense, narrow and the like. A change in the chemical composition can be increased concentrations of one of the scaffold components such as elastin, collagen, GAG and the like. Such remodeling can occur following a certain period in culture or following implantation in a body. For example, as is shown in Figures 9a-f, 10a-e and 11a-d and is described in Example 3 of the Examples section which follows, three weeks following seeding and culturing with cardiac fibroblasts, the myocardium-derived scaffolds were remodeled, *e.g.,* began to shrink and formed dense cell population spheres.

Thus, the scaffolds of the present invention can be seeded with cells and cultured under suitable culturing conditions to thereby form an engineered tissue. The scaffolds can be seeded with one type or several types of cells depending on the desired application.

For example, for the engineering of a vascular tissue, the scaffold can be seeded with smooth muscle cells (SMCs) and/or endothelial cells as is further described in Example 4 of the Examples section which follows.

For engineering of a myocardium tissue, the scaffold is preferably seeded with cardiomyocyte and/or cardiac fibroblast as is further described in Example 3 of the Examples section which follows

Various methods can be used to seed and culture the cells within the scaffold of the present invention. These include, but are not limited to, static seeding, centrifugal seeding, static culturing and dynamic culturing (for seeding and culturing methods see Example 4 of the Examples section which follows).

It will be appreciated that a scaffold formed from a certain tissue can be used for the regeneration and/or repair of the same type of tissue or even for the regeneration and/or repair of a different type of tissue as long as both tissues share ECMs with similar composition and structure. For example, myocardium tissue for bladder wall tissue regeneration, blood vessels for bladder wall tissue regeneration, blood vessels for heart tissue (e.g., myocardium) regeneration and cardiac or blood vessels for testicular sac tissue regeneration and/or repair.

Preferably, the engineered myocardium tissue of the present invention which is seeded and cultured with cardiomyocytes exhibits spontaneous beating. As used herein the phrase "spontaneous beating" refers to an independent contraction of the matrix which results from the endogenous electrophysiological activity of the cardiomyocytes seeded on the matrix. Preferably, such spontaneous beating is obtained following 1-2 days in culture, however, it will be appreciated that spontaneous beating can also occur earlier, depending on the concentration of cells being seeded, the cardiomyocyte isolation method (e.g., the method described in Example 4) and the culturing conditions (e.g., medium used, medium supplements such as growth factors, amino acids, minerals and the like).

Preferably, the spontaneous beating of the engineered tissue is in concert. As used herein the phrase "beating in concert" refers to a well-coordinated beating which includes all cells of the tissue and wherein each cell contracts at a specific moment such that all cells of the tissue form an efficient muscle-like contraction. Such spontaneous concert pulsatile beating can be observed following 3-4 days of seeding the cells on the scaffolds and can continue, while cultured *ex vivo*, for at least 3 weeks (see Example 3 of the Examples section which follows).

Thus, the teachings of the present invention can be used to form a tissue *ex vivo* or *in vivo*.

As used herein, the phrase "*ex vivo*" refers to forming a tissue from living cells (derived from an organism) by culturing them on the scaffold of the present invention outside of the living organism (*e.g.*, in a culture medium).

For *ex vivo* tissue formation the scaffold is seeded with cells and is further subjected to growth conditions (e.g., culture medium with growth factors, amino acids, serum, antibiotic and the like, incubation temperature, % of CO_2) which enable the cells seeded thereon to populate and thus form the tissue-of-interest (e.g., a cardiac tissue, nerve tissue, bladder wall, testicular sac, kidney and the like).

The term "seeded" refers to a scaffold which is being encapsulated, entrapped, plated, placed and/or dropped with cells. It will be appreciated that the concentration of cells which are seeded on or within the scaffold of the present invention depends on the type of cells and decellularized scaffold used.

For example, to induce the formation of an artery (e.g., for bypass a damaged artery), an artery-derived decellularized scaffold is seeded with SMCs at a concentration of 100,000 - 200,000 per 1 cm^2 using the centrifugal method (e.g., by overnight incubation in a spinner flask) followed by culturing in the spinner flask for 7 weeks, essentially as described in Example 4 of the Examples section which follows.

Tissues which are formed *ex vivo* can be further implanted in a subject in need thereof (e.g., a subject in need of vascular or myocardium tissue regeneration and/or repair) using techniques known in the art (e.g., using a surgical tool such as a scalpel, spoon, spatula, or other surgical device) to thereby regenerate and/or repair the tissue-of-interest.

The phrase "*in vivo*" refers to forming a tissue within a living organism such as a plant or an animal, preferably in mammals, preferably, in human subjects.

For *in vivo* tissue formation, the scaffold is implanted in a subject in need thereof and the cells of the subject populate and proliferate therein to thereby form or repair the tissue-of-interest.

As used herein the term "about" refers to ± 10 %.

Additional objects, advantages, and novel features of the present invention will become apparent to one ordinarily skilled in the art upon examination of the following examples, which are not intended to be limiting. Additionally, each of the various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below finds experimental support in the following examples.

EXAMPLES

Reference is now made to the following examples, which together with the above descriptions, illustrate the invention in a non limiting fashion.

Generally, the nomenclature used herein and the laboratory procedures utilized in the present invention include molecular, biochemical, microbiological and recombinant DNA techniques. Such techniques are thoroughly explained in the literature. See, for example, "Molecular Cloning: A laboratory Manual" Sambrook et al., (1989); "Current Protocols in Molecular Biology" Volumes I-III Ausubel, R. M., Ed. (1994); Ausubel et al., "Current Protocols in Molecular Biology", John Wiley and Sons, Baltimore, Maryland (1989); Perbal, "A Practical Guide to Molecular Cloning", John Wiley & Sons, New York (1988); Watson et al., "Recombinant DNA", Scientific American Books, New York; Birren et al. (Eds.) "Genome Analysis: A Laboratory Manual Series", Vols. 1-4, Cold Spring Harbor Laboratory Press, New York (1998); methodologies as set forth in U.S. Pat. Nos. 4,666,828; 4,683,202; 4,801,531; 5,192,659 and 5,272,057; "Cell Biology: A Laboratory Handbook", Volumes I-III Cellis, J. E., Ed. (1994); "Culture of Animal Cells - A Manual of Basic Technique" by Freshney, Wiley-Liss, N. Y. (1994), Third Edition; "Current Protocols in Immunology" Volumes I-III Coligan J. E., Ed. (1994); Stites et al. (Eds.), "Basic and Clinical Immunology" (8th Edition), Appleton & Lange, Norwalk, CT (1994); Mishell and Shiigi (Eds.), "Selected Methods in Cellular Immunology", W. H. Freeman and Co., New York (1980); available immunoassays are extensively described in the patent and scientific literature, see, for example, U.S. Pat. Nos. 3,791,932; 3,839,153; 3,850,752; 3,850,578; 3,853,987; 3,867,517; 3,879,262; 3,901,654; 3,935,074; 3,984,533; 3,996,345; 4,034,074; 4,098,876; 4,879,219; 5,011,771 and 5,281,521; "Oligonucleotide Synthesis" Gait, M. J., Ed. (1984); "Nucleic Acid Hybridization" Hames, B. D., and Higgins S. J., Eds. (1985); "Transcription and Translation" Hames, B. D., and Higgins S. J., Eds. (1984); "Animal Cell Culture" Freshney, R. I., Ed. (1986); "Immobilized Cells and Enzymes" IRL Press, (1986); "A Practical Guide to Molecular Cloning" Perbal, B., (1984) and "Methods in Enzymology" Vol. 1-317, Academic Press; "PCR Protocols: A Guide To Methods And Applications", Academic Press, San Diego, CA (1990); Marshak et al., "Strategies for Protein Purification and Characterization - A Laboratory Course

Manual" CSHL Press (1996); all of which are incorporated by reference as if fully set forth herein. Other general references are provided throughout this document. The procedures therein are believed to be well known in the art and are provided for the convenience of the reader. All the information contained therein is incorporated herein by reference.

EXAMPLE 1
DECELLULARIZATION OF MYOCARDIUM-DERIVED ECM AND ASSESSMENT OF THE DECELLULARIZED MATRIX

Cellular components are the main cause for immune responses against xenografts, therefore, for tissue regeneration and/or repair, tissue-derived decellularized matrices must be devoid of all cellular components. Prior art studies have suggested that removal of cellular components can be effected by digesting the tissues with proteases such as trypsin. However, excess enzymatic digestion might ultimately result in undesired damage to the ECM structure, strength and elasticity. Thus, to obtain a tissue-derived decellularized matrix devoid of all cellular components yet capable of exhibiting the mechanical properties desired for such tissue constructs, the present inventors have devised, after laborious experimentations, the following efficient and well-calibrated decellularization protocol.

Materials and Experimental Methods

Dissection of myocardium tissues - Hearts of adult male and female pigs were harvested in a local slaughterhouse (Iblin Village, Israel). Immediately after harvest, hearts were soaked and kept in cold sterile saline (pH = 7.4) supplemented with antibiotics (Penicillin/Streptomycin 250 units/ml), until isolation process was performed in the laboratory (maximum time periods in cold sterile saline was two hours). Myocardium muscle tissue was manually dissected into slices parallel to the epicardium, with or without the epicardial membrane. Visual fatty accumulations, if any, were removed.

Preliminary washes - To remove residual blood, the myocardium tissue segments were washed at room temperature by agitation in large amounts (e.g., 50 ml per gram tissue segment) of EDTA (0.5-10 mM, pH-7.4) in saline. Solution was changed every 30 minutes, at least four or five times, until there was no evident blood. Myocardium tissue segments were then agitated for two hours in a hypertonic buffer consisting of 1.1 % NaCl – 0.02 % EDTA. Incubation of the myocardium tissue segments in the hypertonic buffer induces an osmotic pressure which results in diffusion of water out of the cells and/or the intercellular space, resulting in increased intercellular space, thus enhancing accessibility of tissue substrates for the subsequent enzymatic digestion.

Enzymatic cell digestion - Myocardium tissue segments were subjected to one or two cycles of 24 hours each of enzymatic cell digestion in trypsin-EDTA [0.05-0.25 % trypsin (w/v), 0.02-0.1 % EDTA (w/v), antibiotics (Penicillin/Streptomycin 100-250 units/ml), pH = 7.2]. The tissue segment were agitated at 150 revolutions per minutes (rpm) in separate sterile vessels at 37 °C. Ratio of digestion solution volume to tissue weight was at least 40 ml of digestion solution per each gram of tissue.

Enzymatic nucleic acid removal - To assure nucleic acid removal, Trypsin digested matrices were subjected to digestion with 5-25 μg/ml DNase I (Roche, France) in Hank's Buffered Salt Solution (HBSS), pH = 7.2, with antibiotics (Penicillin/Streptomycin 100-250 units/ml). Matrices were agitated at 150 rpm overnight at 37 °C.

Detergent decellularization - Cells and cellular components were further removed from matrices with Triton® X-100 (0.1-2 %; Merck) and ammonium hydroxide (0.05-1.0 %, Frutarom) in an isotonic solution of 0.9 % NaCl. Segments were agitated at 150 rpm for 48 hours at 4 °C in the detergent solution, following which the detergent solution was replaced with a fresh detergent solution. This step was repeated two-four more times. Decellular matrices were then subjected to several washes in sterile saline (at least 10 washes of 30 minutes each, and 2-3 washes of 24 hours each), until the complete removal of the detergent residue (as evident by no foaming of the wash solution after vigorous shaking).

Lyophilization and sterilization - Matrices were washed several times in large volumes of double-distilled sterile water to remove remaining salts. The matrices were then spread in 6-cm tissue culture plastic dishes, and excess water was removed. For lyophilization, the matrices were snap-frozen in liquid nitrogen and lyophilized for 12 hours. Dry matrices were then cut into the desired shape and size (e.g. ~11-13 mm squares or disks, suitable for placing in 24-well culture plates). Lyophilized matrices were sterilized in cold ethylene-oxide gas and ventilated for at least one week before further use. Alternatively, matrices were exposed to ultra-violet light radiation for a few hours under sterile condition, desiccated with silica gel beads to prevent re-hydration by air moisture. Alternatively, non-lyophilized matrices were soaked overnight in 70 % ethanol, washed with sterile water and kept in PBS at 4 °C. Under these sterilization methods shelf life of decellularized matrices was practically eternal.

This process of decellularization was optimized for complete removal of cellular components on one hand, and minimum loss of matrix collagen and desired mechanical properties on the other.

Decellularization assessment - For initial evaluation of acellularity (*i.e.*, absence of cellular components), the decellularized matrices were fixed in 10 % formalin in PBS, blocked in paraffin and 5 μm sections were subjected to standard Hematoxylin and Eosin (H&E) staining.

Presence of cell nuclei - The presence of nuclei was detected using a fluorescent staining with DAPI (4',6-diamidino-2-phenylindole, Molecular Probes, Inc., Eugene, OR, USA). This fluorophore incorporates into nuclear double-stranded compact DNA, regardless if cells are viable or not. Decellularized matrices were immersed for 20 minutes at room temperature in 0.5 μg/ml DAPI in PBS (pH = 7), washed in PBS and inspected by a fluorescent microscope (excitation - 358 nm, emission - 461 nm).

Presence of cell membranes - The presence of cell membranes was detected by fluorescent staining with lipophilic DiO (3,3'-dioctadecyloxacarbocyanine perchlorate, Molecular Probes, Inc., Eugene, OR, USA). In aqueous solutions DiO hardly fluoresces, but becomes photo-stably and highly fluorescent when incorporates into bilayered phospholipid membranes. Decellularized matrices were immersed for 2 hours at room temperature with 5 μg/ml DiO stain in PBS (pH = 7), washed in PBS and inspected by a fluorescent microscope (excitation - 484 nm, emission - 501 nm).

Presence of residual nucleic acids - The presence of residual nucleic acids was detected by phenol-chloroform extraction from NaOH - digested matrices. Matrices were digested over-night at 90 °C in 10 mM NaOH. DNA was extracted from the aqueous digest by the well-known phenol-chloroform method. Extracted

DNA was visualized by electrophoresis on 0.8 % agarose gel and quantified by photometric absorbance at 280/260 nm.

In all the above described decellularization assessment methods cells seeded on coverslips served as positive control, rat-tail type I collagen hydrogel (3.0 mg/ml) served as negative control.

Experimental Results

ECM decellularization process - The decellularization process presented here has been optimized for complete removal of cells and cellular components, while minimally compromising the ECM composition and mechanical properties. Figures 1a-f depict myocardium tissues undergoing the decellularization process of the present invention.

Segments of myocardium tissue (2-4 mm thick) were removed from the left ventricular wall and the right atrium (Figures 1a-b) of a pig heart. Following washes, incubation in a hypertonic buffer and the subsequent enzymatic digestion with trypsin, the rigid muscle tissue segments softened, however the tissue segments did not loose their solid brown color, indicating that cells were still present in the tissue. Omitting or shortening this step resulted in inefficient decellularization of muscle segments thicker than 1 mm (Figure 1c). Notably, segments less than 1.5 mm thick were harder to slice, exhibited inferior mechanical properties and were less convenient to work with. During the incubation with the detergent solution (0.1-2 % Triton® X-100 and 0.05-1.0 % ammonium hydroxide in an isotonic solution of 0.9 % NaCl), tissue segments became slimy-spongy, lost their solid color and became translucent white (Figure 1d). When soaked in liquid, the decellular segment generally retained the original visual shape and size of the tissue segment prior to the process (Figures 1d-f). Remarkably, after the decellularization process the vascular structures under the pericardia membrane remained visually intact (Figure 1d). In addition, after the decellularization process the three-dimensional structure of the myocardium tissue is preserved (see for example, the inner wall of the right atrium shown in Figure 1e). After lyophilization (and before or after cold-gas sterilization), the dry foam-like material was very easy to work with, and readily cut to the desired scaffold size and shape. A custom-made puncher can be used to cut scaffolds to desired size and shape, as well as increase the manufacturing throughput. The dry scaffolds were easily re-hydrated at room temperature in buffered saline or culture medium.

Decellularized matrices are devoid of cells and cell nuclei – Initial verification of decellularization was performed by Hematoxylin and Eosin (H&E) staining of paraffin or frozen sections prepared from the decellularized matrices. Matrices derived from up to 4 mm thick fresh myocardium tissue, with or without epicardial membrane, were frozen and 5 μm thick sections were subjected to H&E staining. As shown in Figure 2, no cell nucleus could be visible in the matrix, reflecting the acelullarization of the myocardium tissue.

To further confirm that the matrices were indeed devoid of cell nuclei, processed matrices were stained with DAPI. In all matrices prepared from up to 4 mm thick fresh muscle tissue, no nuclei could be found (Figures 3a-b). Partially processed matrices exhibited incomplete removal of cell nuclei (Figure 3c-d). Phenol extraction verified the absence of nucleic acids in the completely treated decellular matrices which were derived from up to 4 mm thick tissues (data not shown).

Decellularized matrices are devoid of cell membranes - Matrices were stained with the DiO stain for detection of residual cell membranes. Matrices, which were partially processed, *e.g.*, that were treated with 0.05 % trypsin for only 12 hours and were subjected to only two cycles of 48 hours each in the detergent solution, exhibited some membrane structures as shown in Figures 4a-b. However, no cell membranes were detected in any of the decellular matrices which were subjected to the complete decellularization treatment protocol described under Materials and Experimental Methods hereinabove (Figures 4c-d).

Optimization of trypsin concentration and incubation time - The concentration of trypsin and the number of washes in trypsin (one or two cycles of 24 hours each) were optimized for complete decellularization on one hand and preservation of the ECM mechanical properties on the other hand. The present inventors have uncovered, through laborious experimentations that one cycle 24 hours in a solution of 0.25 % trypsin resulted in a decellularized matrix with poorer mechanical properties as compared to two cycles of 24 hours each in a solution of 0.05 % trypsin. In addition, one cycle of 24 hours in a solution of 0.1 % trypsin resulted in a decellularized matrix with similar mechanical properties as two cycles of 24 hours each in a solution of 0.05 %, but incomplete decellularization.

Optimization of removal of cellular components with the detergent solution – The present inventors have found that the number of wash cycles (for 48 hours each) in the detergent solution [Triton® X-100 (0.1-2 %) and ammonium hydroxide (0.05-1.0 %) in an isotonic solution of 0.9 % NaCl] resulted in no effect on the mechanical properties of the matrix but affected the decellularization process, depending on tissue thickness. For tissue segments of 2-4 mm thick it was found that 2-4 cycles of 48 hours each in the detergent solution are optimal. For tissue segments less than 2 mm thick, 2 cycles of 48 hours each in the detergent solution are sufficient.

Altogether, these findings demonstrate that the decellularization protocol devised by the present inventors resulted in the complete removal of cells, cell nuclei and cell membranes from fresh tissues (e.g., myocardium tissue as exemplified herein), even when using tissue segments as thick as 4 mm.

EXAMPLE 2

ASSESSMENT OF ACELLULARIZED MATRIX COMPONENTS AND MECHANICAL PROPERTIES

To assess the suitability of the myocardium-derived decellularized matrix of the present invention as a scaffold for tissue regeneration, the present inventors have quantified the amount of collagen, elastin and glycosaminoglycans (GAGs) in the matrices and evaluated the structural and mechanical properties of the decellular matrices, as follows.

Materials and Experimental Methods

Collagen quantification – The content of collagen in the decellularized matrix was quantified using the hydroxyprolin assay with slight modifications (Neuman, R. & Logan, M., 1950). Briefly, matrix was hydrolyzed (7N HCl, 105 °C, 16-20 hours), diluted and brought to pH = 6. Free hydroxyprolin (Fluka, Switzerland) is oxidized to a pyrrole by chloramine T (in Acetate-Citrate buffer pH = 6) and the reaction is followed by the pink color resultant of the pyrrole intermediate when reacted with 4-dimethylaminobenzaldehyde (in perchloric acid and iso-propanol) (15 minutes, 58 °C). After cooling, samples' absorbance was spectrometrically measured at 558 nm, and compared to standard hydroxyprolin (Fluka) and collagen type I (Sigma) curves, prepared along with the sample.

Elastin quantification - Elastin was quantified by digestion of the ECM in 0.1 N NaOH and the direct weighing of non-solubilized elastin deposit. Elastin is not a native component of the myocardium itself, however it is present in the blood vessels that vascularize the heart. Loss of elastin serves in this case as an additional parameter for the effect of the decellularization process on the composition of ECM of the resulting matrix.

Glycosaminoglycans quantification - Glycosaminoglycans (GAGs) were quantified using a modification of the colorimetric safranin O assay (Carrino DA et al, 1991). Briefly, samples were digested for 20 hours at 60 °C by papain (60 units per sample; Sigma) and proteinase K (Roche Diagnostics, 250 μg per sample). After centrifugation (3000 g for 10 minutes), supernatants were concentrated by sedimentation in ethanol (80 %, 2-4 hours at -20 °C) and centrifugation (3500 g, 1 hour at 4 °C). Pellets were suspended in PBS and added to 10 volumes of safranin O solution (0.02 % safranin O [Sigma], 50 mM sodium acetate, pH = 4.8), left for one hour and centrifuged. The GAG-safranin O complex in the pellet was solubilized in 1 ml of de-complexation buffer (4 M guanidine-HCL, 10 % iso-propanol, 50 mM sodium acetate, pH = 6). Absorbance was measured spectrometrically at 536 nm. A standard curve was prepared from ascending concentrations of chondroitin-6-sulfate which were treated the same as the samples.

Assessments of decellular matrix structure - The fibrilar alignment and structure of decellular matrices were examined histochemically, using Masson's trichrome staining, and compared to that of native cardiac tissue. Fresh cardiac tissue and myocardium-derived decellularized matrix were fixed in 4 % paraformaldehyde, paraffin blocked, sectioned (5 μm thick) and stained. Hematoxylin stains nuclei in dark blue-black; Biebrich scarlet reagent stains muscle cytoplasm in red; and Aniline blue reagent stains collagen in blue. In addition, structure of the collageneous network was assessed by scanning electron microscopy (SEM), with a JSM-5400 (JEOL, Japan). Decellularized matrix was fixed in 2.5 % glutaraldehyde (in PBS), gradually dehydrated in ascending ethanol concentrations (30-99 %), air dried and spattered with gold.

SEM and QuantomiX™ WET-SEM - were performed according to standard methods: samples for SEM analysis were fixed for 1 hour in 2.5 % glutaraldehyde in PBS, washed three times, 10 minutes each in PBS and once in water, dehydrated in ascending ethanol concentrations, air dried and spattered with gold. Images were captured with a JSM-5400 (JEOL, Japan). For WET-SEM analysis non-fixed samples were stained with Uranyl Acetate and images were captured by QuantomiX™ LTD (QuantomiX Ltd, IL).

Mechanical properties of the decellularized matrix - Tensile strength of the decellularized matrices was measured uni-axially using a rheological measurement instrument (TA500, Lloyd Instruments) equipped with a 10 Newton (N) load cell and a custom-made clamping apparatus. Matrices were first positioned by the clamps at "rest point" (0 stress, 0 strain) and pre-conditioned by ten cycles of strain – release (cyclic strain), where maximum strain was 15 % and strain/un-strain (displacement, relative to initial length) rate was 0.05 mm per second and a cyclic stress - strain curve was plotted. After 2 minutes resting at rest point the matrices were stretched rapidly (0.5 mm per second) to 20 % strain and held at that displacement for ten minutes, allowing strain relaxation, and a stress – relaxation time curve was plotted. After 10 minutes resting at rest point the matrices were stretched at constant strain rate of 0.05 mm per second until complete tearing (assigned as 40 % stress decrease), and a stress - strain curve was plotted (strain to break). Peak of stress - strain curve indicates relative tensile strength of the matrix, while curve slope indicates matrix resistance (inverse of elasticity).

Experimental Results

Decellularized matrices preserve the majority of the collagen and elastin contents of the original tissue – Quantification of collagen (by the hydroxyproline assay) or of elastin (by direct weighing of the solid elastin deposit) were performed in lyophilized fresh or decellularized myocardium tissues and revealed that about 90 % of the collagen and 80 % of the elastin present in the fresh myocardium tissue were preserved following the complete decellularization process (Figures 5a-b). These results demonstrate that the decellularization protocol devised by the present inventors enables the preservation of most of the collagen and elastin constituents of the ECM present in the original fresh tissues.

Decellularized matrices exhibit high GAG quantities - Quantification of Glycosaminoglycan (GAG) was performed according to the modified safranin O assay and revealed that the myocardium-derived decellularized matrices of the present invention exhibit higher GAG content as compared to the commercially available bovine type I collagen matrix (Figure 7).

Decellularized matrices exhibit high porous and fibrous structures - SEM imaging of the matrices was used to analyze the porous and fibrous structure of the decellularized matrices of the present invention. As shown in Figures 6a-c, the myocardium-derived decellularized matrices of the present invention were highly fibrous, with collagen fibers in various thickness and crosslinking levels, and exhibited high porosivity.

Decellularized matrices are flexible, yet retain the strength of the original tissue ECM - Mechanical assays revealed that the decellular matrices of the present invention are very elastic yet retain their strength, as demonstrated by returning to similar stress values at repetitive 15 % straining (Figure 8a), minimal decrease of stress at constant 20 % strain (Figure 8b), and withstanding up to 0.42 MPa when strained to 40 % (Figure 8c).

Altogether, these finding demonstrate that the decellularized matrices of the present invention preserve the majority of collagen and elastin contents present in the original fresh myocardium tissue, contain higher GAG quantities as compared to other commercial ECM components (e.g., the commercial collagen type I), are highly fibrous and porous, maintain the mechanical properties of the tissue ECM such as withstanding up to 0.42 MPa when strained to 40 %.

EXAMPLE 3

THE MYOCARDIUM-DERIVED DECELLULARIZED MATRICES ARE SUITABLE SCAFFOLDS FOR TISSUE REGENERATION

To evaluate the suitability of the myocardium-derived decellular matrices as scaffolds for cardiac tissue engineering, the decellular matrices were tested for their ability to support the attachment, morphology and long-term viability of different types of cells including cardiac muscle, fibroblast and endothelial cells, as follows.

Materials and Experimental methods

Isolation of cardiac fibroblasts - Cardiac fibroblasts were isolated from an adult sheep heart. Briefly, heart tissue was diced to ~1 mm^3 segments that were washed in sterile PBS and placed in culture plates without medium. After 10-12 minutes the medium was slowly added to the plates (DMEM with 10 % FCS, Gibco) and the tissue segments were incubated untouched for one week (37 °C, 5 % CO_2, humidified atmosphere) before first passage. These primary cardiac fibroblasts were split 1/8 with 0.05 % Trypsin – 0.02% EDTA, and were not used for more then five passages.

Isolation of cardiac myocytes - Cardiac myocytes were isolated from neonatal 1-2 days old Sprague-Dawley rats. Hearts were washed in PBS-G (0.1 % glucose and Penicillin/Streptomycin in PBS) and diced. Following gentle agitation for 12 hours in 0.05 % trypsin - 0.02 % EDTA in HBSS, cardiac cells were dissociated by gentle agitation for 10 minutes at 37 °C in 200 units/mL collagenase type 2 (Worthington) in PBS-G. Cell suspension was collected and added to two volumes of medium. This step was repeated until complete dissociation of the diced hearts. Cell suspension was centrifuged for 5 minutes at 1000 rpm, suspended in DMEM with 10 % FCS, run through a 100 μm-pore sieve to remove clusters and pre-plated for one hour in culture dishes in an incubator, to allow adherence of fibroblasts. Non-attached myocyte-enriched cell suspension was collected, centrifuged as before and re-suspended in F-10 nutrient mixture (Life Industries, IL) supplemented with 5 % fetal calf serum (FCS), 5 % donor horse serum (DHS), 1 mM $CaCl_2$ and Penicillin/Streptomycin. Proliferation of any remaining fibroblasts was inhibited by addition of 25 μg/ml bromo-deoxy uridine (BrdU, Sigma) to the culture medium during the first three days of culture.

Seeding of cells on the decellularized matrices of the present invention - Cells were seeded onto the decellularized matrices of the present invention by slowly pipetting cell suspension onto static scaffolds, at a cell concentration of 10^4 cell per cm^2 matrix. Myocytes were seeded and cultured in F-10 nutrient mixture (Life Industries, IL) supplemented with 5 % FCS, 5 % DHS, 1 mM $CaCl_2$ and Penicillin/Streptomycin, and fibroblasts were seeded and cultured in DMEM (Life Industries, IL) supplemented with 10 % FCS and Penicillin/Streptomycin.

Evaluation of cell adherence and distribution on the decellularized matrices – The extent of cardiac myocyte or fibroblast cell adherence was studied by washing the seeded decellularized matrices with gentle agitation in the culture medium (as described above) and moving the matrices to new culture dishes with fresh medium. Fibroblast-seeded matrices were washed three hours after seeding and myocytes-seeded matrices were washed 24 hours after. At ascending time points after seeding (e.g., 2, 7, 13, 21 and 27 days post seeding), samples of seeded matrices were fixed and stained and the attached cells were counted. Distribution of cells within seeded scaffolds was examined by H&E histochemical staining of frozen sections or paraffin block sections.

DiO staining (Molecular Probes) – was performed according to manufacturer's instructions. Cells were stained for 2 hours prior to seeding and the fluorescence generated by the DiO stain was followed using a fluorescent microscope (488/514 nm). Being non-toxic and photo-stable, DiO staining enables a simple semi-3D tracking of cell distribution and morphology on and within each scaffold for as long as 4 weeks without having to "sacrifice" samples for analyses.

The alamarBlue® assay (Serotec) - was performed according to manufacturer's instructions. Being non-toxic, this assay enables to follow cell viability over a period of time for each sample, decreasing measurement variability due to sampling different scaffolds, thus increasing reliability of the assay.

Immunostaining - To evaluate the formation of tissue-like structures, cardiomyocytes were immunostained as follows: anti-Connexin43 was used for gap junctions staining, anti-cardiac Troponin I was used as specific cardiomyocyte marker, and anti-alpha actinin was used for cytoskeletal staining (all primary antibodies from Chemicon, 1:250, overnight at 4 °C). Cy3-conjugated secondary antigen (Jackson, 1:500, 1 hour at RT) was used for fluorescent staining. In addition, cytoskeletal actin was stained for two hours with phalloidin-FITC (Sigma, 0.5 μg/ml in PBS), followed by three washes of 10 minutes each in PBS.

SEM and ET-SEM - were performed as described in Example 1, hereinabove.

Experimental Results

Cardiac fibroblasts adhere to the decellularized matrices of the present invention - The adhesion of cells to the scaffolds was tested by slowly pipetting cell suspension of 10^4 cardiac fibroblast and myocytes cells per 1 cm^2 scaffold surface in 24-well culture plate. The matrices were agitated gently to release dead and non-adhered cells, moved to new wells with fresh medium and further incubated. This procedure was performed three hours after seeding fibroblasts and 24 hours after seeding myocytes. Cells which remained in the original wells, where the matrices were seeded, were collected and counted microscopically by trypan blue exclusion on a haemacytometer. The number of these cells was subtracted from the number of seeded cell to calculate the number of adhered cells. 94.2 % of the seeded cardiac fibroblasts remained adhered to the matrices after three hours (ranging 91-97 %, SD = 1.82, n = 12) and 89 % of the seeded cardiac myocytes remained adhered to the matrices 24 hours after seeding (ranging 78-93 %, SD = 5.08, n = 10) (data not shown).

The decellularized matrices of the present invention can be remodeled by the seeded cells - As is shown by the DiO staining, the seeded scaffolds began to shrink after approximately two weeks in culture, demonstrating the remodeling ability of the decellularized matrix by the seeded cells (Figures 10a-e). By three to four weeks some of the scaffolds were contracted by the fibroblasts and became 1-2 mm spheres, as demonstrated by SEM analysis (Figures 9a-d). Evidently, the seeded fibroblasts deposited new collagen fibers to their proximity, as demonstrated by QuantomiX™ WET-SEM™ analysis (Figure 9e-g).

The decellularized matrices of the present invention are well populated with cells - H&E staining of paraffin or frozen sections showed that at two and three weeks post seeding the scaffolds were well-populated with cells, and that cells were evenly distributed within the scaffolds (Figure 11a-d).

The cells populated on the decellularized matrices of the present invention are viable - Viability of cells seeded on the scaffolds was quantitated using the alamarBlue® assay. After seeding medium was changed every 2-3 days. Every second medium change scaffolds were gently moved to new wells to prevent artifact results caused by the outgrowth of fibroblasts from the matrix onto the culture dish. The density and distribution of the cardiac fibroblasts in the scaffolds was shown by the DiO staining (Figures 10a-e) and the histochemical H&E staining (Figures 11a-d). The viability of cells on each scaffold, which was measured two days after seeding, was denoted 100 %. Further measurements for each scaffold were related to it's own initial viability value. As is shown in Figures 12a-b, both cardiac fibroblasts and cardiomyocytes were highly viable (80 % or more) for the first three weeks post seeding. In addition, at four weeks post seeding, ~77 % and ~68 % of the cardiac fibroblasts or the cardiomyocytes, respectively, remained viable.

The decellularized matrices of the present invention support the spontaneous concert pulsatile beating of cardiomyocytes which are seeded thereon - Neonatal rat cardiomyocytes were seeded at 10^4 cells per 1 cm^2 on various sizes of scaffolds, including 1 cm^2 (in 24-well plates), ~2 cm^2 (in 12-well plates), 5-6 cm^2 (in 6-well plates), and even as large as ~12 cm^2 (~5 x 2.5 cm in 6-cm plates). During culturing period the culture medium (F-10 with 10 % FCS, 1 mM $CaCl_2$, antibiotics) was replaced every 2-3 days. BrdU was added during the first 3 days to prevent proliferation of fibroblasts. Scaffolds of all sized began to show spontaneous beating as shortly as 1-2 days post seeding. By 3-4 days post seeding most matrices exhibited spontaneous concert pulsatile beating, clearly visible by the naked eye, some rather vigorous. Some of the matrices continued to beat as long as three weeks. Such long-term concert pulsatile beating indicates the formation of mature functioning electro-physiological cardiac tissue phenotype.

Altogether, these findings demonstrate that the decellularized matrices of the present invention are capable of supporting the adherence, growth and viability of cells (e.g., fibroblasts or cardiomyocytes), are capable of being remodeled by the cells seeded thereon and are capable of spontaneous concert pulsatile beating when seeded with cardiomyocytes.

EXAMPLE 4

ARTERY-DERIVED DECELLULARIZED MATRICES

Decellularized matrices prepared from an artery tissue according to the teachings of the present invention were evaluated for their complete decellularization, structural and mechanical characteristics and non-immunogenic properties using histological analysis, DNA analysis, scanning electron microscopy (SEM), collagen measurements and RT-PCR analysis and stress-strain analyses, as follows.

Materials and Experimental Methods

Preparation of artery-derived decellularized matrices - Porcine blood vessels were obtained aseptically from terminated animals. The blood vessels from the descending aorta to the bifurcation (branching) of the femoral arteries were harvested. Upon harvesting, blood vessels with a diameter ranging from 5 mm to 10 mm were cut into segments of 5-6 cm in length and were subjected to the decellularization method essentially as described in Example 1, hereinabove. Specifically, arteries were incubated in 0.05 % trypsin solution (containing 0.02 % EDTA) for two consecutive incubation periods of 24 hours each at 37 °C (using fresh trypsin solution for each incubation period). The detergent used for the decellularization processes was 1 % Triton X-100 with 1 % ammonium hydroxide. The arteries were incubated in the detergent solution for three consecutive incubation periods of 72 hours each, at 4 °C (using fresh detergent solution for each incubation period). Scaffolds were then washed three times, 24 hours each, with saline to remove traces of cell debris and agents. Scaffolds were washed for 48 hours with double distilled water (DDW), lyophilized and sterilized using cold gas (ethylene oxide).

Assessment of decellularized matrices – was performed as described under "Materials and Experimental Methods" of Examples 1 and 2 of the Examples section which follows.

Culture media for cells seeded on artery-derived matrices - Smooth muscle cells (SMCs) were cultured on DMEM low glucose medium (Gibco USA) supplemented with 10 % fetal calf serum (FCS) and Penicillin/Streptomycin (at a concentration of 250 units/ml). Human umbilical cord vascular endothelial cells (HUVEC) or bovine corneal endothelial cells (BCEC) were cultured on M199 medium (Gibco USA) supplemented with 20 % FCS, Penicillin/Streptomycin (at a concentration of 250 units/ml) and 5 ng/ml bFGF.

Seeding techniques - SMC were seeded on the outer side of the decellularized arteries and HUVEC or BCEC on the inner side of the decellularized arteries. Seeding techniques included the static or the centrifugal (*i.e.*, dynamic) seeding methods, as follows.

Static seeding - For the static seeding, cells were trypsinized, centrifuged and resuspended in 50 μL of fresh medium. Sterilized scaffolds were ventilated for a few days and soaked overnight in sterile fresh medium (according to cell type) before seeding. The scaffolds were cut into pieces of 1 cm x 1 cm. Cell suspension was carefully pipetted onto the scaffold: SMC on the outer side of the scaffold and HUVEC or BCEC on the inner side. The cells were allowed to attach to the scaffolds for 20 minutes, following which the scaffolds were immersed in medium and placed in an incubator of 37 °C with 5 % CO_2.

Centrifugal (or dynamic) seeding - For the dynamic seeding, SMC were trypsinized, centrifuged and resuspended in 5 ml of fresh DMEM low glucose medium. Patches of scaffolds were placed, lumen side down, in a tube filled with agarose. The agarose served as a substrate for nailing the scaffolds, using sterile syringe needles. The cell suspension was pipetted onto the scaffold and the scaffolds were subjected to 10 rounds of centrifugation, 1 minute each, at 2500 rpm. Scaffolds were then placed in tissue culture dishes, immersed in medium and placed in an incubator of 37 °C with 5 % CO_2.

Culturing techniques - Seeded matrices were cultured over time using the static or the dynamic approaches, as follows.

Static culturing - For the static culture, scaffolds were immersed in the relevant medium and placed in an incubator. Medium was changed every other day.

Dynamic culturing - For the dynamic culture, scaffolds were placed in a 100 ml spinner flask (Bellco Glass). Culture medium (50 ml) was added to the seeded scaffold and culturing was effected by subjecting the spinner flasks to stirring of 40 rpm for 7 weeks in an incubator. Medium was changed every 3 days.

In all cases, SMC were allowed to grow for 4 weeks. Seeded scaffolds were then fixed, processed and subjected to histological analysis.

Immunostaining analysis - was performed using the α-smooth muscle actin antibody (Sigma, A2547, dilution 1:500), procollagen I (Chemicon, MAB1913, dilution 1:100).

Coating scaffolds – For HUVEC adhesion and viability studies, plates/scaffolds were coated with four different coatings: PBS (control), 0.2 % gelatin (Sigma), 5 μg/ml fibronectin (Biological industries, IL) or corneal matrix (CM). For CM coating, BCEC were allowed to grow until confluency, following which the scaffolds were treated with 0.5 % Triton X-100 and 50 mM ammonium hydroxide in

PBS. After a few minutes of treatment, the cells were detached from the surface, leaving an intact ECM. This ECM was washed with PBS and then stored at 4 °C in PBS supplemented with 1 % Penicillin /Streptomycin and 0.4 % fungizone (Gibco, USA). All other solutions were used to coat the plates/scaffolds on the day of the experiment and were left on the plate for 2 hours in an incubator prior to use.

Immunogenisity and host response - To study host immunogenic response to the decellularized matrix, 0.5 cm x 0.8 cm pieces of decellularized matrices were implanted subcutaneously in 4-5 weeks old C57 Black male mice. Sham mice in which an incision was made but no polymer (*i.e.*, the decellularized matrix) was implanted were also included in the study. Mice were divided randomly into 2 groups according to the evaluated time points: 1 week and 2 weeks post-surgery. Each group consisted of 5 experimental mice and 3 sham mice. At the end of each time point, the mice were sacrificed and their lymph nodes, implanted scaffolds and surrounding skin were harvested. In the control sham group the site of incision was taken . Due to technical reasons the scaffolds and the surrounding skin harvested after 1 week were paraffin-embedded, while the scaffold and surrounding skin harvested after 2 weeks were frozen. All samples were sliced and subjected to histological (H&E) and immunohistological [macrophage staining using anti-F4/80 antigen (# MCA497R), dilution 1:100; Serotec (Raleigh, NC)] evaluations by a well-experienced pathologist.

RT-PCR analysis of TNF-α and IL-1β from lymph nodes of implanted mice – To further evaluate the immunogenicity of the decellularized matrices of the present invention, samples of both lymph nodes (i.e., from the treated side and the untreated side of the animal) were dissected and RNA was extracted using the Tri-reagent (Sigma) with a pellet pestle. The extracted RNA was reverse-transcribed and amplified with the following PCR primers: for TNF-α transcripts - TNF-α Fw: 5'- GAT TTG CTA TCT CAT ACC AGG AGA A (SEQ ID NO:7) and TNF-α Rev: 5'- GAC AAT AAA GGG GTC AGA GTA AAG G (SEQ ID NO:8); for IL-1β transcripts - IL-1β Fw: 5'- CAT GGA ATC TGT GTC TTC CTA AAG T (SEQ ID NO:9) and IL-1β Rev: 5'- GTT CTA GAG AGT GCT GCC TAA TGT C (SEQ ID NO:10); for mouse GAPDH transcripts - GAPDH Fw: 5'- ACC CAG AAG ACT GTG GAT GG (SEQ ID NO:11) and GAPDH Rev: 5'- CTT GCT CAG TGT CCT

TGC TG (SEQ ID NO:12). Products were electrphoressed on 2 % agarose gels and quantified using the ImageJ software (NIH, USA).

Evaluation of the formation of new ECM components (e.g., elastin and procollagen III) following seeding with SMCs - RNA samples of SMCs that were seeded on scaffolds were subjected to DNAse treatment and then reverse-transcribed using Reverse-iT™ 1st strand synthesis kit (Abgene, Surrey, UK). cDNA was amplified in a thermal cycler (PTC-200, MJ Research) after adding ReddyMix™ PCR master mix. PCR primers for elastin were: Elastin Fw: 5'- CCT TGG AGG TGT GTC TCC AG (SEQ ID NO:1), Elastin Rev: 5'- ACT TTC TCT TCC GGC CAC AG (SEQ ID NO:2); PCR primers for procollagen III were: procollagen III Fw: 5'- GCA GGG AAC AAC TTG ATG GT (SEQ ID NO:3), procollagen III Rev: 5'- CGG ATC CTG AGT CAC AGA CA (SEQ ID NO:4); Standardization was conducted with sheep GAPDH using the following PCR primers: GAPDH Fw: 5'- AGG TCG GAG TCA ACG GAT TT (SEQ ID NO:5), GAPDH Rev: 5'- CCT TCT CCA TGG TAG TGA AGA CC (SEQ ID NO:6). Products were electrphoressed on 2 % agarose gels. Quantification of bands' intensity was accomplished by using ImageJ software (NIH, USA).

Assessment of mechanical properties of the decellularized scaffolds – was performed as described in Example 2, hereinabove.

Experimental Results

Artery-derived decellularized matrices are devoid of cellular components and maintain the collagen and elastin content and structure of the native artery – Artery-derived decellularized matrices were prepared as described under "Materials and Experimental Methods" hereinabove. Figures 13a-b demonstrate a porcine artery before (Figure 13a) and after (Figure 13b) the decellularization process. Histological evaluation of the decellularized artery-derived matrix revealed the absence of cell nuclei and the preservation of the collagen and elastin structure following decellularization (Figures 14a-b). In addition, quantification of the elastin and collagen contents in decellularized matrices demonstrated that decellularized matrices from various sections of the arteries (e.g., the proximal, center of distal sections) maintain similar quantities of collagen (about 30-35 % of the dry artery weight) or elastin (about 15-20 % of the dry artery weight). Moreover, SEM analysis revealed the absence of cell nuclei from both the outer and the luminal sides of the processed decellularized artery-derived matrices (Figures 16a-d).

Artery-derived decellularized matrices are devoid of nucleic acids - Traces of porcine DNA in the arteries following the decellularization process may evoke an immune response when implanted to other species. To determine whether the decellularized artery-derived matrices of the present invention are devoid of DNA, genomic DNA was extracted from the native or the decellularized arteries and DNA samples were subjected to agarose gel electrophoresis. As is shown in Figure 17, no traces of genomic DNA were detected following decellularization.

Artery-derived decellularized matrices are suitable scaffolds for cell proliferation in vitro - Decellularized matrices were pre-coated with fibronectin (5 μg/ml, 2 hours in a 37 °C incubator), following which smooth muscle cells (SMCs) were seeded on one side of the matrix at a seeding density of 5-20 x 10^6 cells (Figures 18a-c). It will be appreciated that in order to obtain an engineered tissue such as a vessel, endothelial cells are seeded on the counterlateral side of the decellularized matrices after obtaining a confluent layer of smooth muscle cells. Further histological and immunocytochemical evaluations performed using markers for smooth muscle cells such as anti–alpha smooth muscle actin (Figures 19e and f), which labels smooth muscle actin, demonstrates a successful seeding of SMCs on the collagen artery-derived decellularized matrices. One week after seeding, the scaffolds were confluent with endothelial cells, but the cells were disoriented (data not shown). Four weeks after seeding the decellularized scaffolds with endothelial and SMCs, a layer of endothelial cells had developed as seen in Figures 19a and c. The SMC seeded on the outer perimeter of the vessel remained attached to the scaffold for a period of three months in culture (Figures 19e and f). The Masson staining revealed a limited SMC cell migration into the vessel wall but the pale red color indicates the development of neo muscular tissue derived from the SMC seeded scaffolds.

Centrifugal seeding and dynamic culturing results in efficient penetration of SMCs to the scaffolds - To determine the optimal conditions for SMC and endothelial seeding and growth on the decellularized scaffolds, several seeding and culture techniques were utilized. These include static seeding followed by static culturing, centrifugal seeding followed by static culturing and centrifugal seeding followed by dynamic culturing. The efficiency of the various seeding and culturing techniques was evaluated using histological (e.g., H&E staining) and immunohistochemical (e.g., using α-smooth muscle actin immunostaining) analyses. As is shown in Figures 20a-f, centrifugal seeding resulted with better penetration of SMCs into the scaffolds than a static seeding, whereas a dynamic environment resulted in even greater penetration and alignment of the cells along the elastin fibers.

Centrifugal seeding and dynamic culturing results in efficient remodeling of the decellularized scaffolds with new collagen deposits - Secretion of collagen and elastin by the seeded cells is an important process, which leads to the biochemical and mechanical remodeling of the scaffold into an artery. Therefore, Masson's staining was used to detect the collagen and elastin secreted by the SMC after seeding and culturing on the scaffolds. The secretion of collagen was detected by immunostaining of the newly produced collagen type I, as expressed by its precursor, procollagen I. As is shown in Figures 21a-c the vast amount of new collagen secreted by the SMC cells was deposited in scaffolds seeded using a centrifugal method and cultured using a dynamic method. To further examine whether other ECM components are produced following seeding with SMCs, the level of elastin, collagen type III and GAPDH mRNA was detected by RT-PCR analysis. As is shown in Figures 22a-c, the level of elastin mRNA was 2.3 times higher in scaffolds seeded with cells using the centrifugal method and static culturing as compared with scaffolds seeded and cultured using the static methods. In addition, the level of elastin mRNA in scaffolds subjected to dynamic culturing was 4 times higher than that of scaffolds subjected to static culturing method. On the other hand, the levels of collagen III mRNA were similar in scaffolds seeded or cultured using the different approaches.

Centrifugal seeding and dynamic culturing results in efficient proliferation of cells seeded on the decellularized matrices - The proliferation of cells on the decellularized scaffolds was examined using Alamar-Blue reagent. This assay was performed on SMC every week, for 4 weeks, and values were normalized to the number of cells. As is shown in Figure 24, a significant difference in the number of cells was observed 6 days following seeding the scaffolds using the different seeding methods. However, at day 27-post seeding, the culture conditions became dominant, showing that cells cultured in a dynamic environment proliferate better when compared to cells cultured in a static environment.

In an attempt to further improve the seeding conditions, another dynamic seeding approach was used. SMC were seeded overnight in a spinner flask to allow adhesion of cells to the decellularized scaffolds, followed by culturing in the spinner flask for 7 weeks. As is shown in Figures 25a-d, one day after seeding, a uniform coverage of the scaffold by the cells was accomplished (Figure 25a). At three weeks post-seeding, the cells have proliferated but their penetration capacity was still limited (Figure 25b). At 7 weeks post-seeding, cells have already aligned circumferentially along the artery wall, covering most of its area (Figures 25c and d).

Coating of scaffolds with corneal matrix (CM) results in uniform coverage of HUVEC – The effect of coating scaffolds was determined in scaffolds coated with CM or PBS (*i.e.*, uncoated, bare scaffolds) using histological (H&E) and immunohistochemical staining. Figures 23a-d show representative staining of Human Umbilical Cord Vascular Endothelial Cord (HUVEC) following 9 days in culture on PBS or CM coated scaffolds. While seeding of HUVEC on the bare scaffold resulted in their incomplete coverage of the scaffold surface (Figures 23a and b), coating of the scaffold with CM resulted in a more uniform coverage of HUVEC (Figures 23c and d).

The decellularized matrices of the present invention are non-immunogenic when implanted in a subject - To eliminate any possible complications when using scaffolds as vascular grafts *in vivo*, the immune reaction against the decellularized scaffolds was tested in C57 black mice following implantation of patches of 0.5 cm x 0.8 cm. The implanted patches were harvested at different time points (one and two weeks post-implantation) and the immune response was examined by histological analysis of inflammatory or immune cells and by RT-PCR analysis of pro-inflammatory factors (TNF-α and IL-1β) of RNA extracted from the lymph nodes of the implanted animals. One and two weeks post surgery the surrounding tissues of the sham mice (not shown) presented similar results to those observed in animals implanted with the polymers (*i.e.*, the decellularized matrices of the present invention) (Figures 26a-d). These included several granulocytes and elongated fibroblasts (typical for a wound healing response). Furthermore, RT-PCR analysis of the proinflammatory factors TNF-α and IL-1β revealed no increase in the proinflammatory factors between one to two weeks and was similar in the sham-operated mice (data not shown).

The artery-derived decellularized matrices maintain the mechanical properties of the artery ECM – The mechanical properties of the artery-derived decellularized scaffolds of the present invention were tested using the strain-stress and/or load-elongation methods described in Example 2 hereinabove and in Fung, Y.C. Biomechanics: Mechanical properties of living tissues, 2nd Edn. Springer-Verlag, NY (1993), and were compared to those of native artery tissues or decellularized scaffolds following seeding with cells. Briefly, decellularized artery-derived matrices were seeded with SMCs using the centrifugal seeding method followed by dynamic culturing in spinner flasks for 2 weeks. Scaffolds (seeded or un-seeded decellularized matrices or native artery tissues) were subjected to stress-strain (elongation) analyses which included straining the scaffolds uniaxially until break while recording the scaffold's circumferential stress. As is shown in Table 1 hereinbelow, following decellularization, the scaffolds exhibited a slight decrease in elasticity, as evident in a change of the ultimate stress from 2.3 ± 0.08 MPa in native arteries to 2.24 ± 0.15 MPa in decellularized scaffolds, and an increase in the stiffness, as evident in a change of the ultimate strain from 145.9 ± 8.8 % in native arteries to 108.5 ± 14.5 % in decellularized scaffolds and by the change in Young's modulus value from 2.7 ± 0.7 MPa in native arteries to 4.8 ± 1.8 MPa in decellularized scaffolds. However, following seeding the decellularized scaffolds with SMC (e.g., using the centrifugal seeding and dynamic culturing for two weeks) the matrices regained the mechanical properties of the native artery tissues as evident by elasticity of 3.02 ± 0.37 MPa, ultimate strain of 145.3 ± 17.8 % and Young's modulus value of 4 ± 1 MPa.

Table 1
Mechanical properties of native, unseeded or seeded decellularized matrices

	Native arteries	*Decellularized artery-derived matrices*	*SMCs-seeded decellularized artery-derived matrices*
Ultimate Stress (MPa)	2.3 ± 0.08	2.24 ± 0.15	3.02 ± 0.37
Ultimate Strain (%)	145.9 ± 8.8	108.5 ± 14.5	145.3 ± 17.8
Young's Modulus (MPa)	2.7 ± 0.7	4.8 ± 1.8	4 ± 1

Table 1: Presented are the ultimate stress (measured in MPa), ultimate strain (measured in percentages with respect to the strain at the rest point) and Young's modulus values (presented in MPa) according to the strain-stress curves. Results represent average ± SD as measured for at least 8 samples in each case.

Altogether, these results demonstrate that artery-derived decellularized matrices prepared according to the teachings of the present invention are completely devoid of cellular component, are suitable scaffolds for cells in terms of cell adherence, population, proliferation, viability and mechanical properties, are remodeled upon seeding with cells and are non-immunogenic when implanted in a subject. In addition, these results demonstrate the superiority of the centrifugal seeding and dynamic culturing methods over the static seeding and culturing methods of cells on the scaffolds of the present invention.

Analysis and Discussion

The results presented in Examples 1-4 hereinabove demonstrate, for the first time, a method of generating a completely decellularized matrix from a natural tissue (e.g., a myocardium or an artery) which is non-immunogenic and which exhibits structural and mechanical properties of the tissue ECM and thus is suitable for tissue regeneration.

It is well accepted that ECM-based scaffolds are superior to synthetic ones, in terms of their biologic properties, such as cell adherence, proliferation and differentiation. However most scaffolds presented so far were lacking the mechanical strength and/or elasticity required for tissue reconstruction or tissue engineering, and methods for cross-linking were needed. The decellular myocardium matrix of the present invention possesses the advantageous combination of a biological scaffold with mechanical properties required for tissue engineering and tissue reconstruction, and particularly that of the heart.

The decellularization method was optimized for complete removal of cellular components, such as nuclei, remaining DNA of broken nuclei, cellular membranes and proteins. All materials used in the decellularization process are generally recognized as safe ("GRAS") according to the FDA. The process is simple, inexpensive and reproducible. Loss of ECM components during the process was relatively minimal, as evaluated by quantification of collagen and elastin. The glycosaminoglycan content in the decellularized matrix of the present invention is higher compared to the commercially available type I collagen (Sigma) often used in cardiac tissue engineering studies. This fact may prove advantageous, as glycosaminoglycans are important for the normal differentiation and maturation of tissues. The resulting decellularized matrix of the present invention was shown to be non-immunogenic when implanted in a subject.

After lyophilization and sterilization, the dry scaffolds exhibited remarkably long shelf life. The scaffolds of the present invention could be easily cut into the desired shape and size, and are easy to work with after re-hydration. The scaffolds are not sensitive to degradation by hydrolysis, and can be kept in sterile PBS for more than 8 months, without change of collagen content.

Seeding of cells on the scaffolds showed that the scaffolds support long term adherence and viability of the seeded cells, and that the seeded cells readily remodeled the scaffolds *in vitro*. Cardiomyocytes formed concert spontaneous beating shortly post seeding, indicating that upon seeding with cells the scaffolds support the formation of normal myocardium phenotype (*i.e.*, engineered tissue).

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims. All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention.

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WHAT IS CLAIMED IS:

1. A method of generating a decellularized extracellular matrix (ECM) of a tissue, comprising:

(a) subjecting the tissue to a hypertonic buffer to thereby obtain increased intercellular space within the tissue;

(b) subjecting the tissue resultant of step (a) to an enzymatic proteolytic digestion to thereby obtain digested cellular components within the tissue; and subsequently

(c) removing said digested cellular components from the tissue;

thereby generating the decellularized ECM of the tissue.

2. The method of claim 1, further comprising:

(d) subjecting the tissue resultant of step (a) to a nuclease treatment to thereby obtain nucleic acid – free tissue.

3. The method of claim 2, wherein step (d) is effected following or concomitant with step (b).

4. The method of claim 1, wherein said hypertonic buffer comprises 1 – 1.2 % NaCl.

5. The method of claim 1, wherein said hypertonic buffer comprises 1.1 % (w/v) NaCl.

6. The method of claim 1, wherein said enzymatic proteolytic digestion comprises trypsin digestion.

7. The method of claim 6, wherein said trypsin is provided at a concentration selected from the range of 0.05-0.25 % (w/v).

8. The method of claim 6, wherein said trypsin is provided at a concentration of 0.05 % (w/v).

9. The method of claim 6, wherein said enzymatic proteolytic digestion is effected for about 24 hours.

10. The method of claim 1, wherein step (b) is effected at least twice.

11. The method of claim 1, wherein said removing comprises subjecting the tissue to a detergent solution.

12. The method of claim 11, wherein said detergent solution comprises TRITON-X-100.

13. The method of claim 12, wherein said detergent solution further comprises ammonium hydroxide.

14. The method of claim 12, wherein said Triton-X-100 is provided at a concentration selected from the range of 0.1-2 % (v/v).

15. The method of claim 12, wherein said Triton-X-100 is provided at a concentration of 1 % (v/v).

16. The method of claim 13, wherein said ammonium hydroxide is provided at a concentration selected from the range of 0.05-1.0 % (v/v).

17. The method of claim 13, wherein said ammonium hydroxide is provided at a concentration of 0.1 % (v/v).

18. The method of claim 11, wherein said subjecting the tissue to said detergent solution is effected for at least 24-48 hours.

19. The method of claim 11, wherein said subjecting the tissue to said detergent solution is effected for 2-4 times.

20. The method of claim 1, wherein the tissue comprises a myocardium tissue.

21. The method of claim 1, wherein the tissue comprises a vascular tissue.

22. The method of claim 1, wherein the tissue comprises tissue segments.

23. The method of claim 22, wherein each of said tissue segments is 2-4 mm thick.

24. A scaffold formed by the method of claim 1.

25. A scaffold comprising a myocardium-derived decellularized ECM which is completely devoid of cellular components.

26. The scaffold of claim 25, wherein said cellular components comprise cell nuclei, nucleic acids, residual nucleic acids, cell membranes and/or residual cell membranes.

27. The scaffold of claim 25, wherein said myocardium-derived decellularized ECM maintains mechanical and structural properties of a myocardium tissue ECM.

28. The scaffold of claim 25, wherein said myocardium-derived decellularized ECM is capable of remodeling upon seeding with cells.

29. The scaffold of claim 27, wherein said myocardium-derived decellularized ECM maintains at least 90 % of a collagen content and at least 80 % of an elastin content of a myocardium tissue.

30. The scaffold of claim 27, wherein said myocardium-derived decellularized ECM is characterized by a stress value of at least 0.4 MPa when strained to 40 %.

31. The scaffold of claim 27, wherein said myocardium tissue is a pig myocardium tissue.

32. An engineered tissue comprising the scaffold of claim 24 and a population of at least one cell type seeded and proliferated therein.

33. An engineered tissue comprising the scaffold of claim 25 and a population of at least one cell type seeded and proliferated therein.

34. The engineered tissue of claim 33, wherein said at least one cell type is cardiomyocyte and whereas said myocardium-derived decellularized ECM exhibits spontaneous beating.

35. The engineered tissue of claim 34, wherein said spontaneous beating is in concert.

36. A method of *ex vivo* forming a tissue, the method comprising:

(a) seeding the scaffold of claim 24 with at least one type of cells; and

(b) providing said cells with growth conditions so as to allow said cells to populate in said scaffold;

thereby *ex vivo* forming the tissue.

37. A method of *ex vivo* forming a myocardial tissue, the method comprising:

(a) seeding the scaffold of claim 25 with at least one type of cells; and

(b) providing said cells with growth conditions so as to allow said cells to populate in said scaffold;

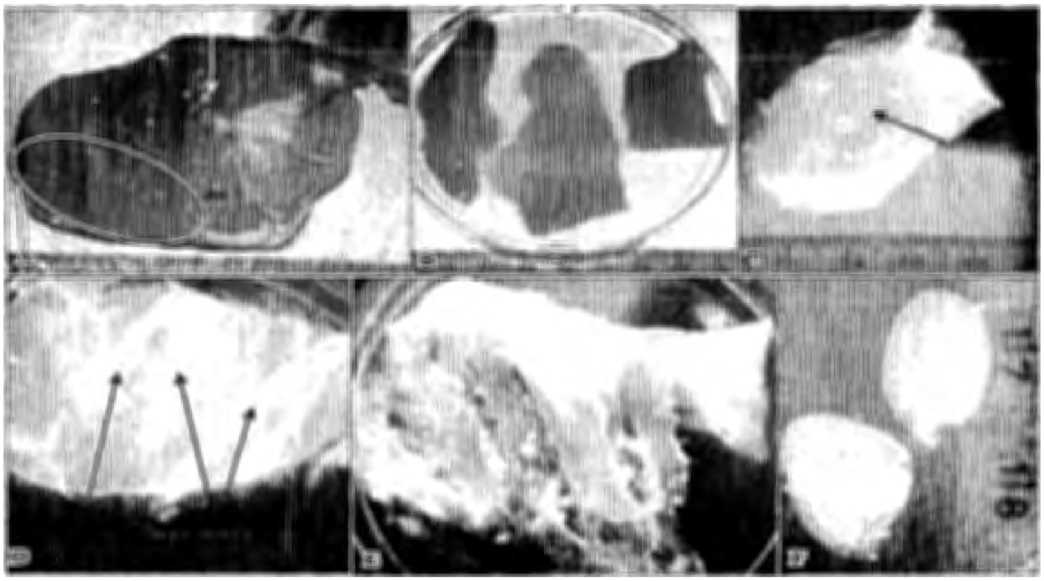
thereby *ex vivo* the forming the myocardial tissue.

38. The method of claim 37, wherein said at least one type of cells comprises cardiomyocytes.

39. The method of claim 37, wherein said at least one type of cells comprises cardiac fibroblasts.

40. A method of *in vivo* forming of a tissue, the method comprising implanting the scaffold of claim 24 in a subject thereby *in vivo* forming the tissue.

41. A method of *in vivo* forming a myocardial tissue, the method comprising implanting the scaffold of claim 25 in a subject thereby *in vivo* forming the myocardial tissue.



Figs. 1a-f

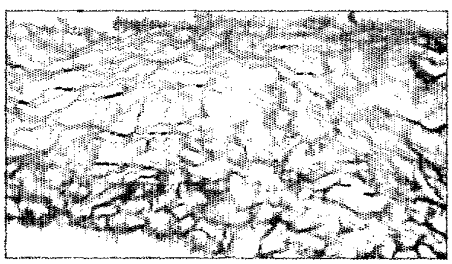
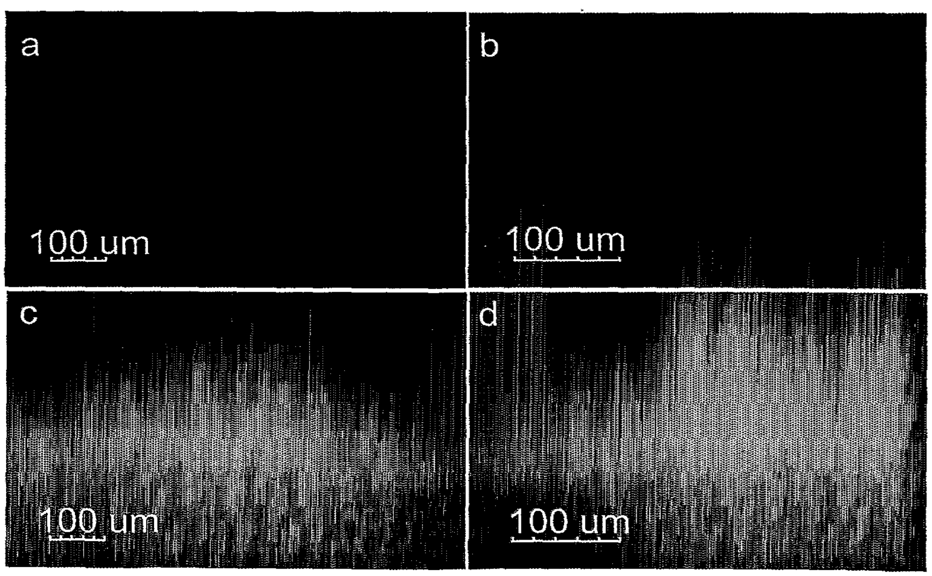
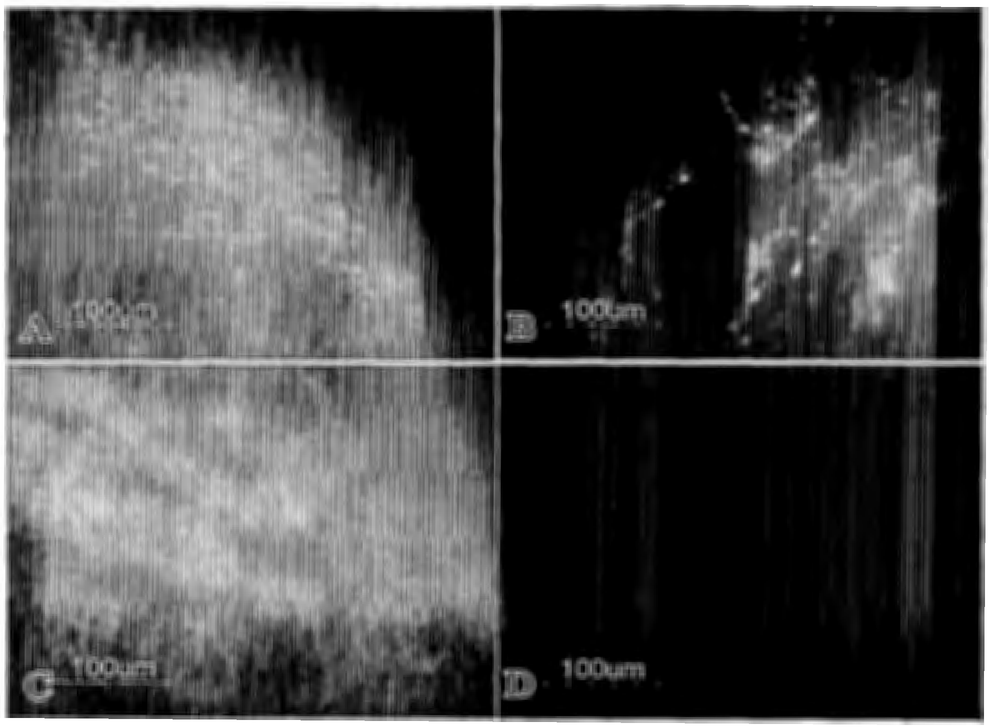


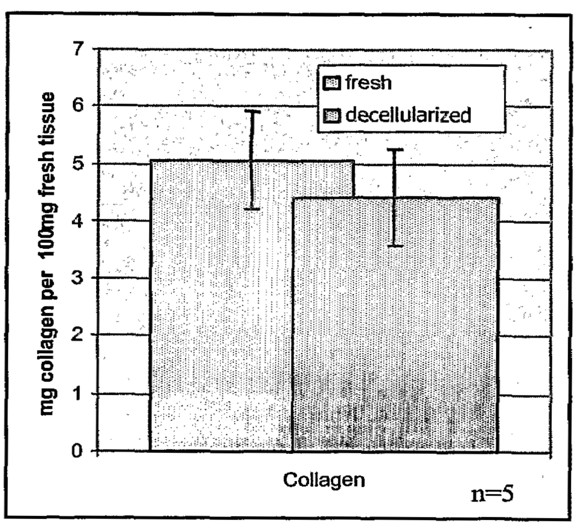
Fig. 2



Figs. 3a-d



Figs. 4a-d



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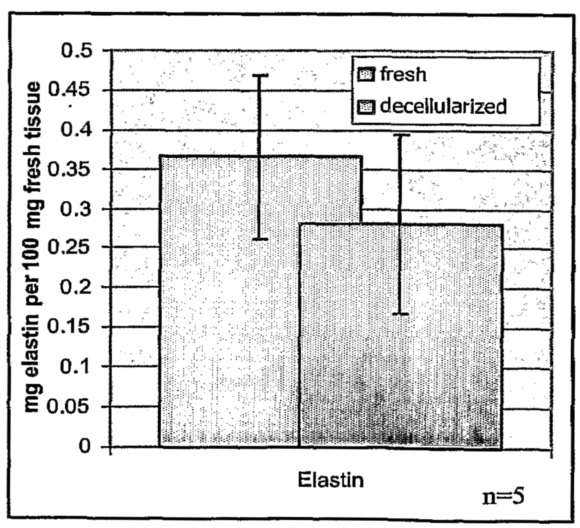


Fig. 5b

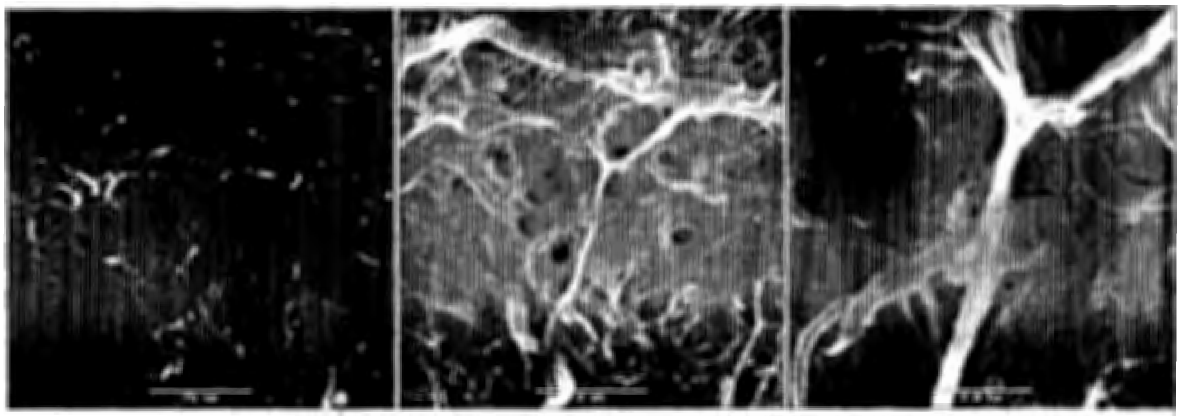


Fig. 6a Fig. 6b Fig. 6c

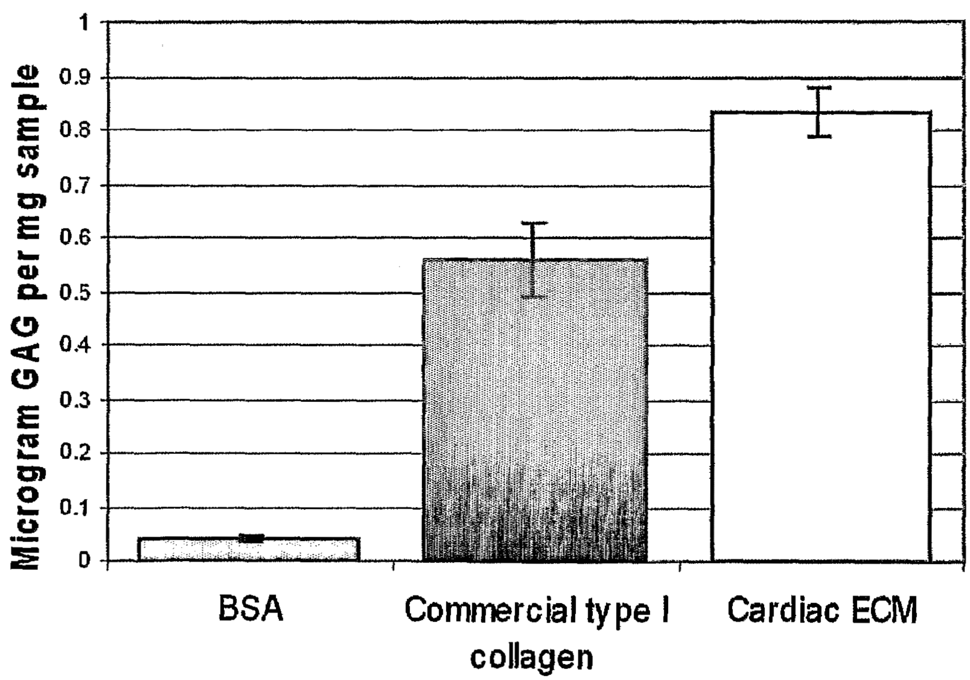


Fig. 7

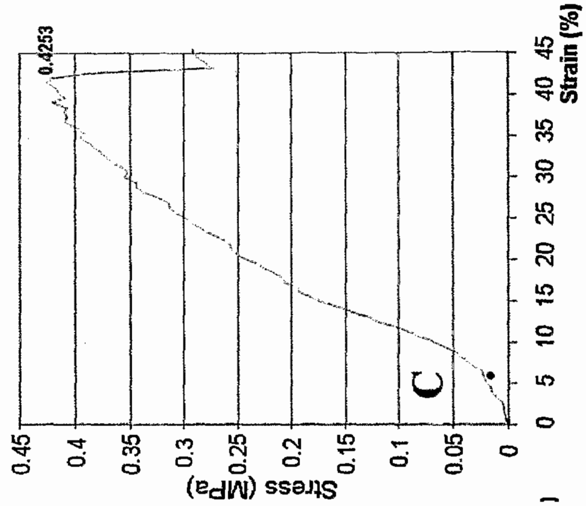


Fig. 8c

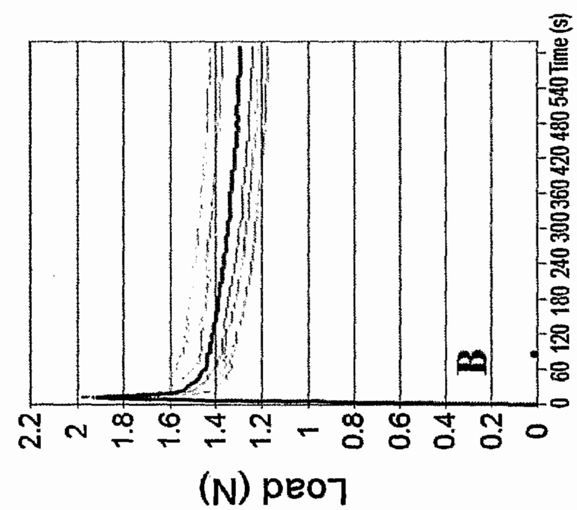


Fig. 8b

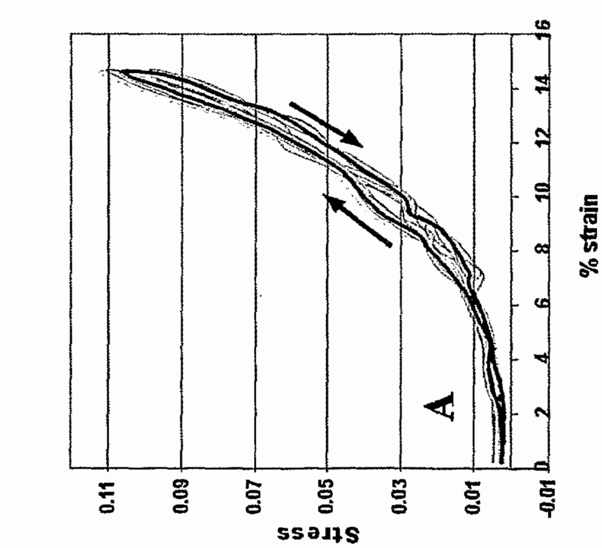


Fig. 8a

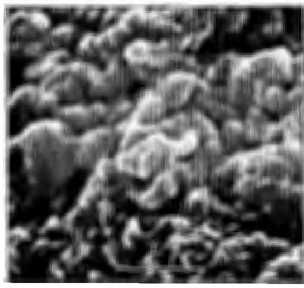


Fig. 9a

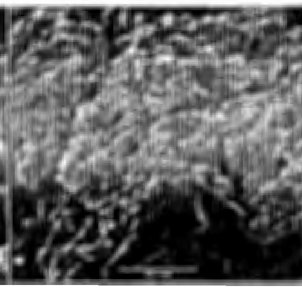


Fig. 9b

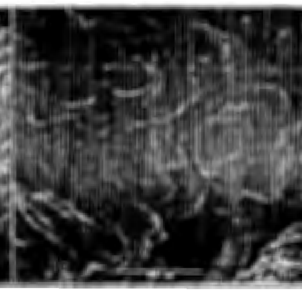


Fig. 9c

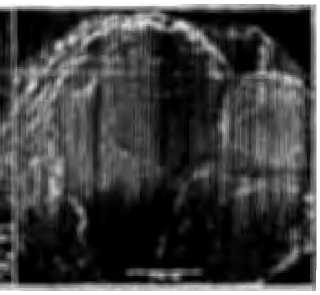


Fig. 9d


Fig. 9e

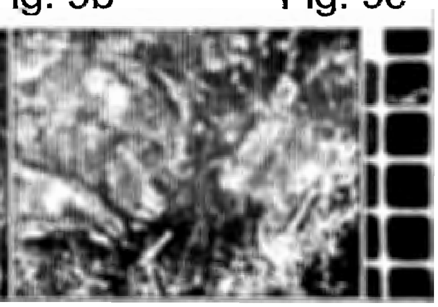


Fig. 9f

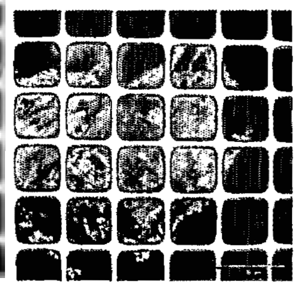
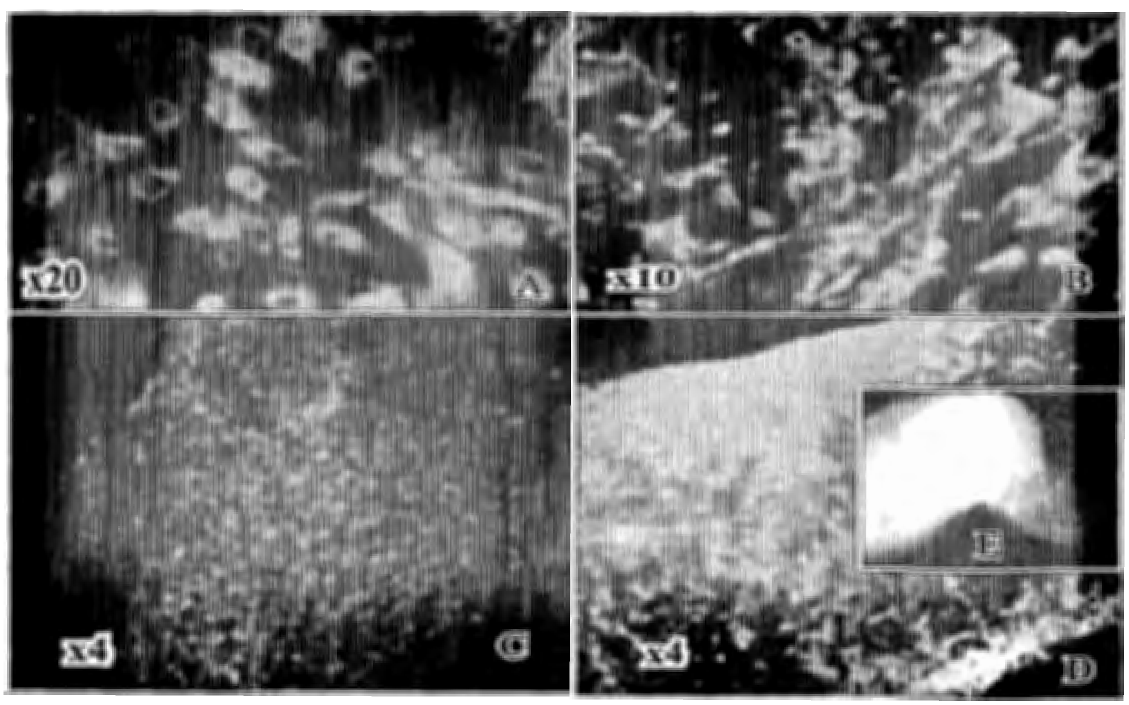
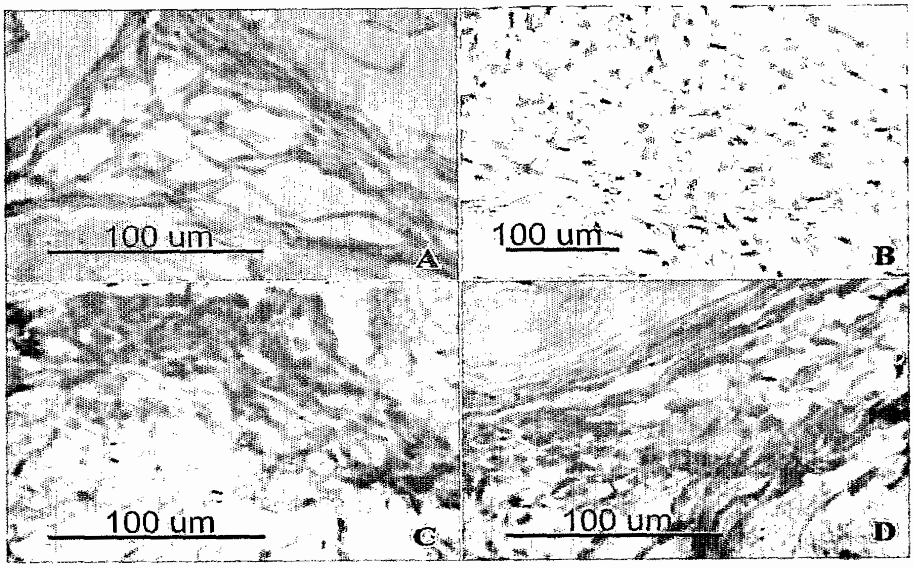


Fig. 9g



Figs. 10a-e



Figs. 11a-d

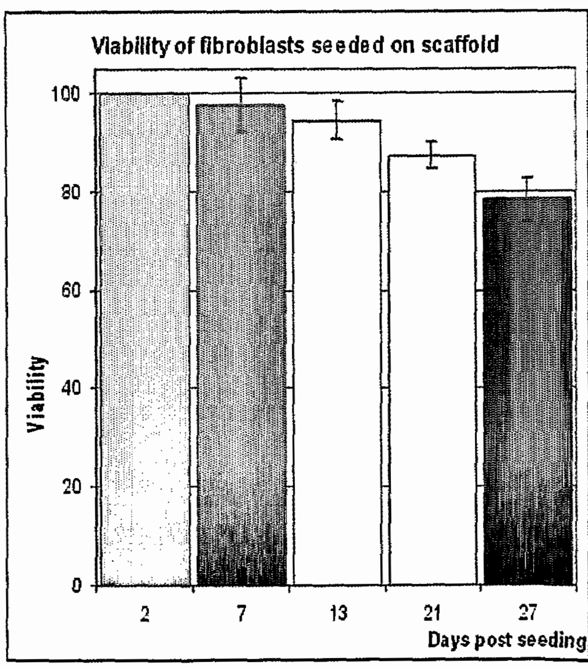


Fig. 12a

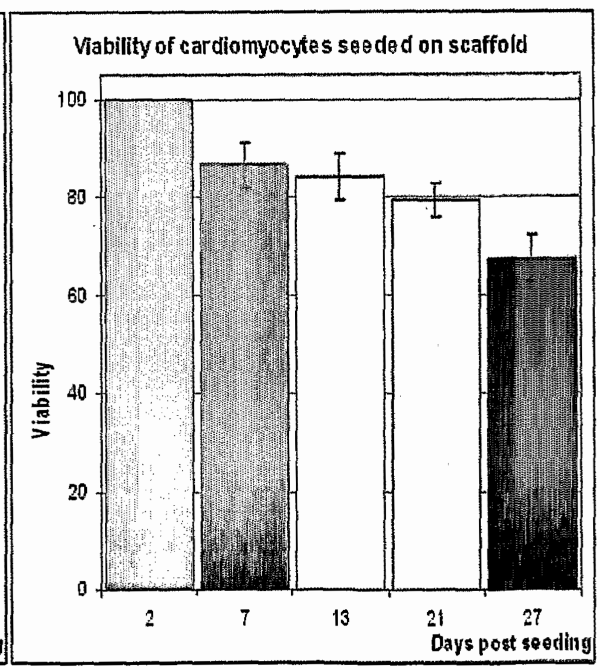


Fig. 12b

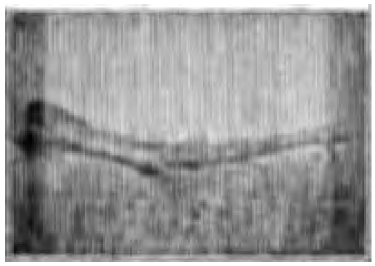


Fig. 13a

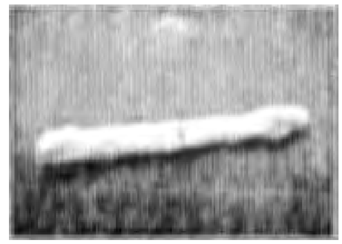


Fig. 13b

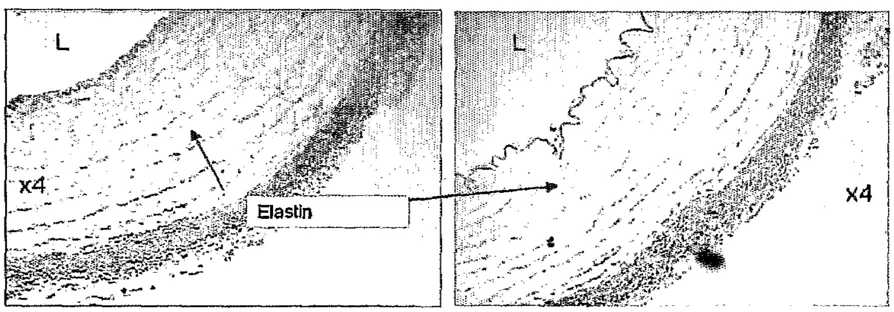


Fig. 14a

Fig. 14b

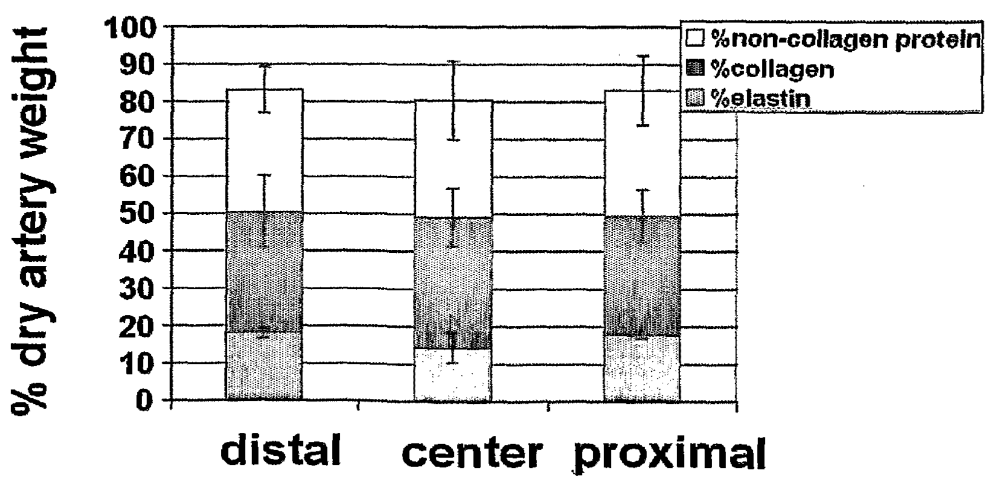
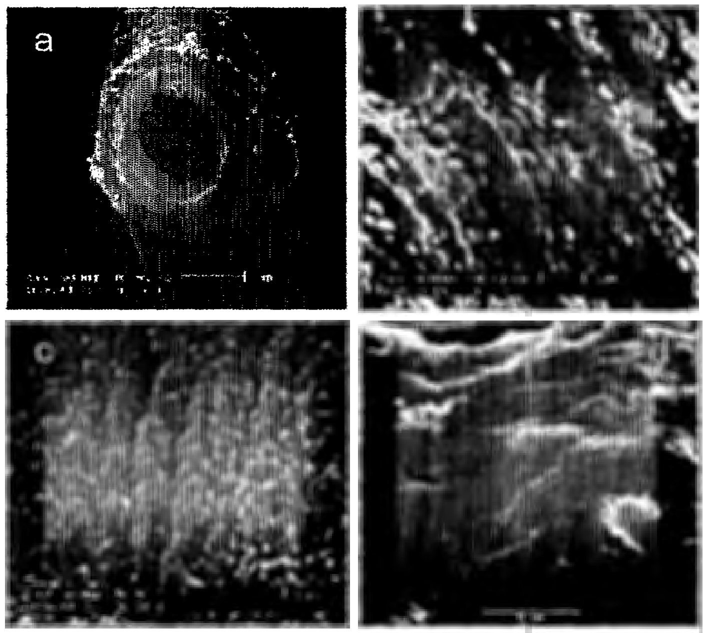


Fig. 15



Figs. 16a-d

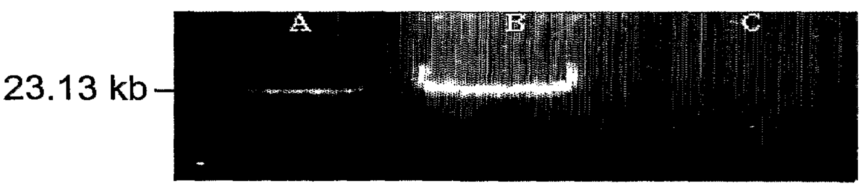


Fig. 17

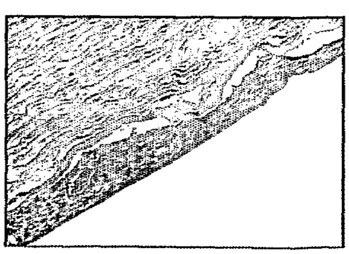


Fig. 18a

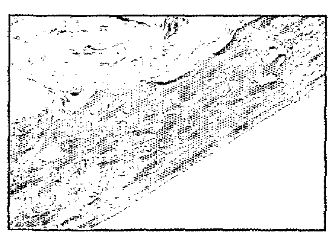


Fig. 18b

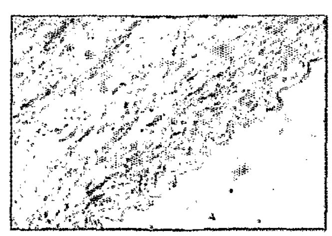
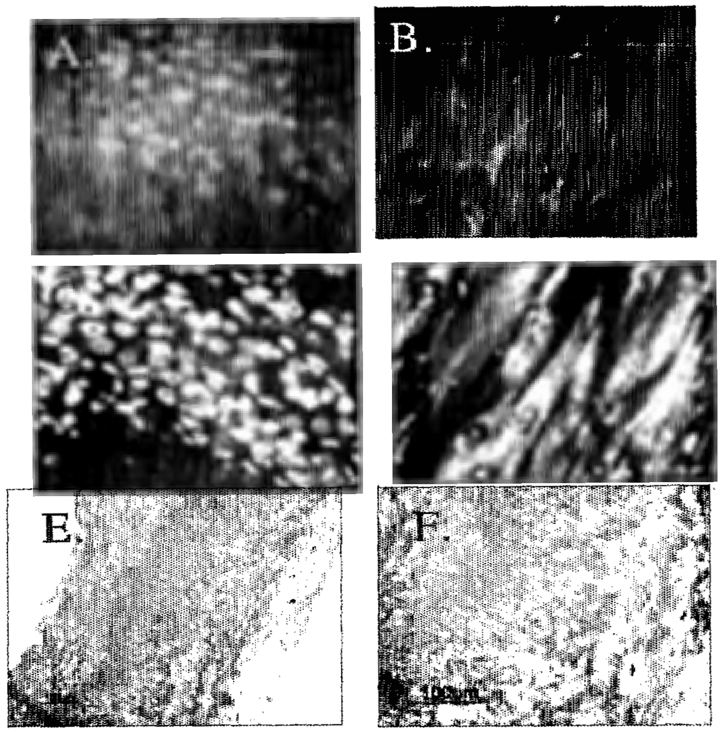
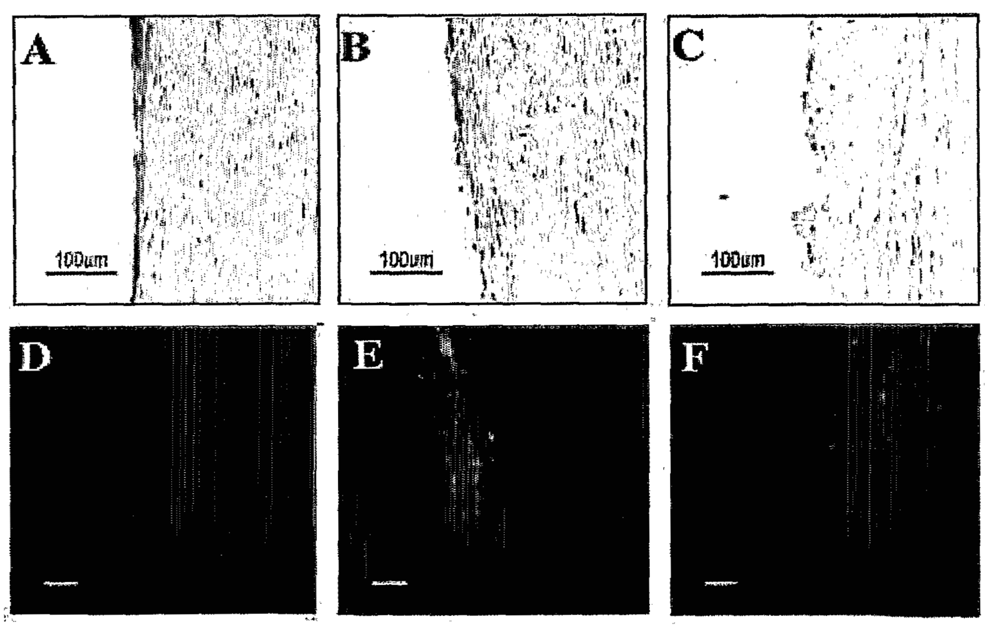


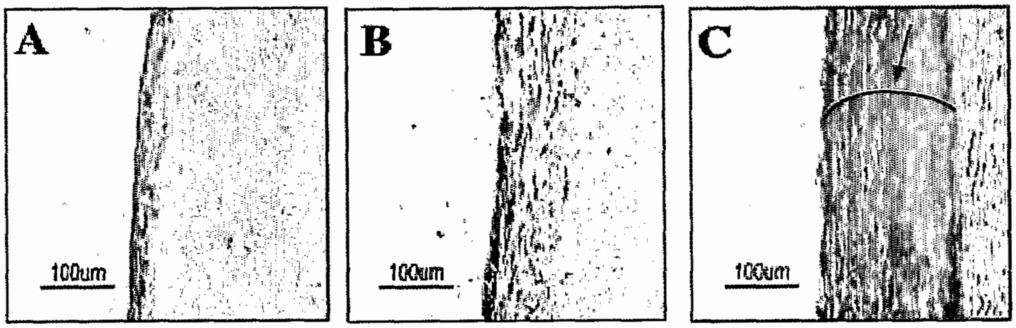
Fig. 18c



Figs. 19a-f



Figs. 20a-f



Figs. 21a-c

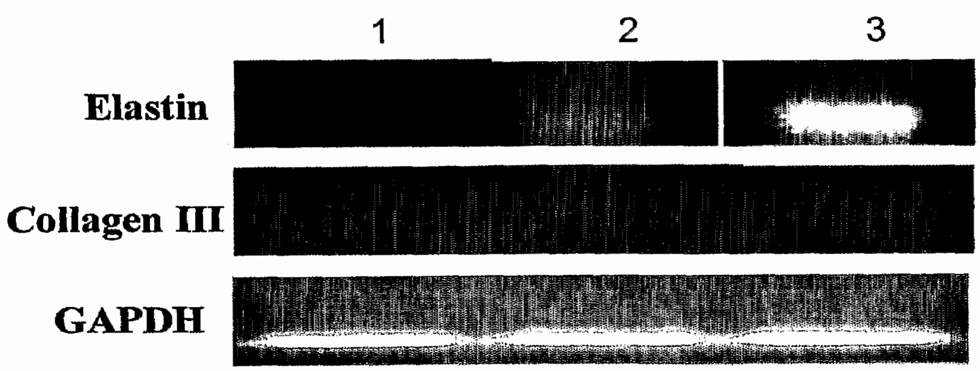
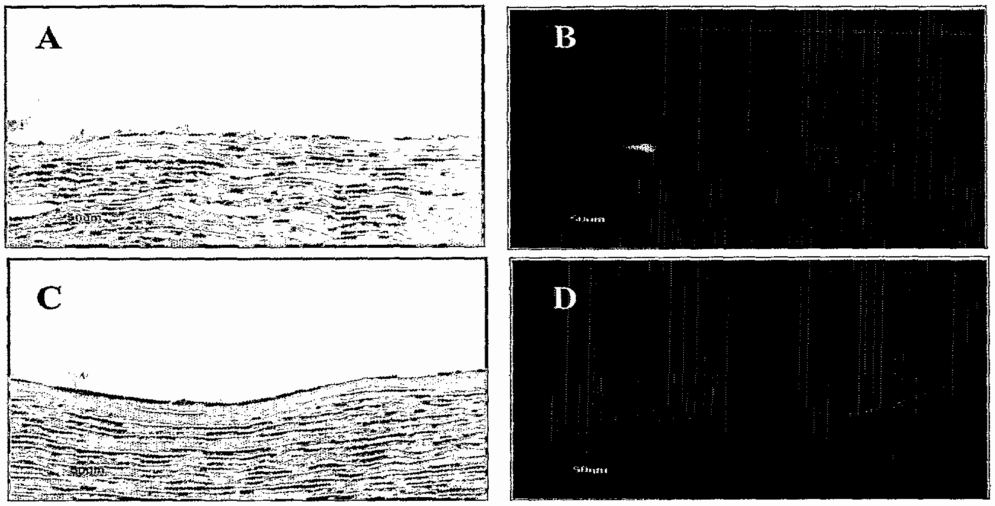


Fig. 22a

Fig. 22b

Fig. 22c



Figs. 23a-d

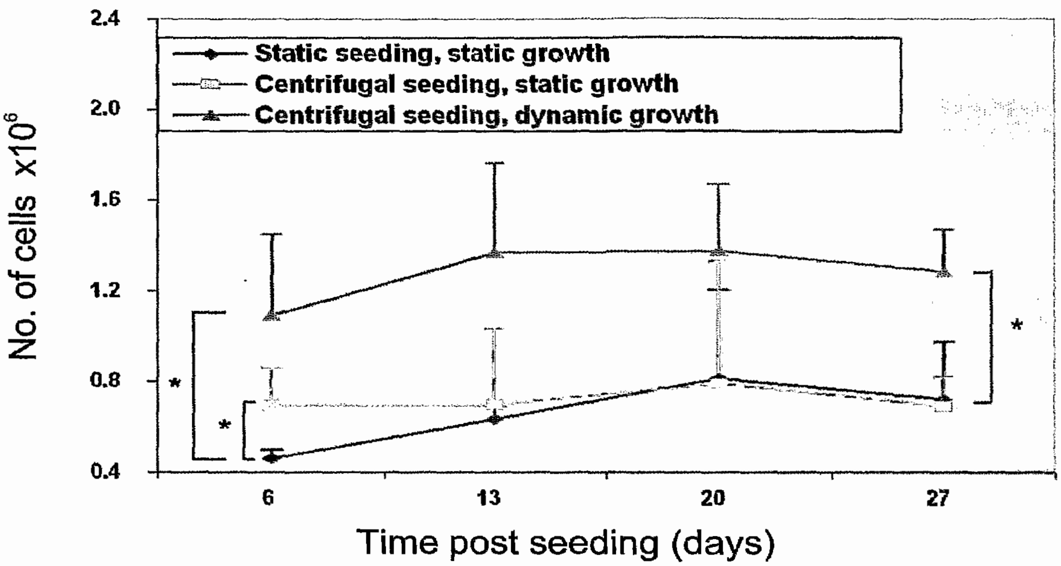
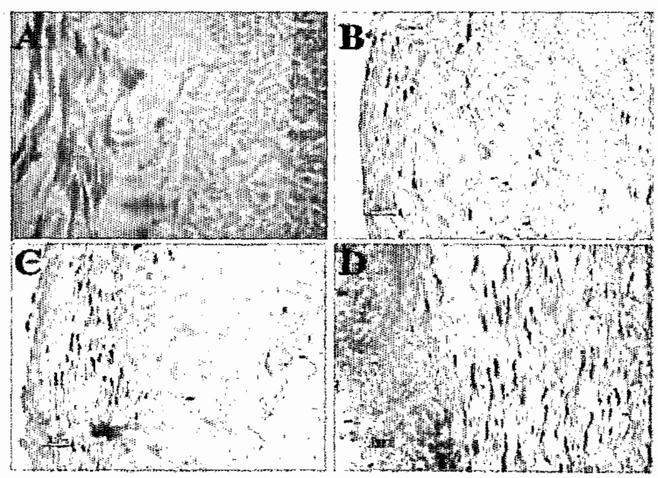
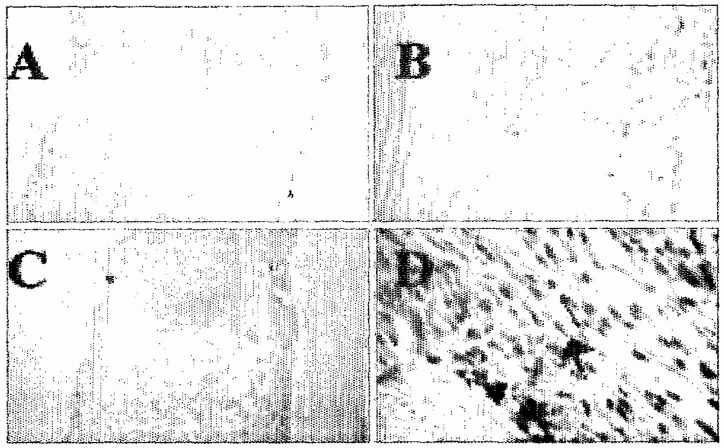


Fig. 24



Figs. 25a-d



Figs. 26a-d

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Marcelle, Machluf
Yuval, Eitan

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WO 2007/138572 A2

(54) Title: METHODS AND DEVICES FOR TREATMENT OF CARDIAC VALVES

(57) Abstract: Disclosed are methods for treatment of cardiac valve including augmenting a cardiac leaflet with the help of a ring associated with a membrane. Also disclosed are methods for treatment of cardiac valves including augmenting the tissue surrounding a cardiac valve, for example with the help of a tubular or annular implant, allowing relocation of the valve. In embodiments, the methods of the present invention improve leaflet coaptation, which in embodiments is useful for treating conditions such as ischemic mitral regurgitation. Also disclosed are devices useful for implementing the methods of the present invention.

METHODS AND DEVICES FOR TREATMENT OF CARDIAC VALVES

RELATED APPLICATIONS

The present application gains benefit of the filing dates of US patent application Nos. 60/809,848 filed 1 June 2006; 60/814,572 filed 19 June 2006; 60/832,142 filed 21 July 2006; 60/832,162 filed 21 July 2006 and 60/860,805 filed 24 November 2006 all which are incorporated by reference as if fully set forth herein.

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to the field of surgery and especially to methods and devices useful for augmenting cardiac valve leaflets or in augmenting tissue surrounding a cardiac valve, for example to allow relocation of the intact cardiac valve. Embodiments of the teachings of the present invention allow, for example, improving leaflet coaptation, for example in order to treat ischemic mitral regurgitation.

The human heart **10**, depicted in cross sectional long axis view in Figure 1, is a muscular organ that pumps deoxygenated blood through the lungs to oxygenate the blood and pumps oxygenated blood to the rest of the body by rhythmic contractions of four chambers.

After having circulated in the body, deoxygenated blood from the body enters the right atrium **12** through the vena cava **14**. Right atrium **12** contracts, pumping the blood through a tricuspid valve **16** into the right ventricle **18**. Right ventricle **18** contracts, pumping the blood through the pulmonary semi-lunar valve **20** into the pulmonary artery **22** which splits to two branches, one for each lung. The blood is oxygenated while passing through the lungs and reenters the heart to the left atrium **24**.

Left atrium **24** contracts, pumping the oxygenated blood through the mitral valve **26** into the left ventricle **28**. Left ventricle **28** contracts, pumping the oxygenated blood through the aortic semi-lunar valve **30** into the aorta **32**. From aorta **32**, the oxygenated blood is distributed to the rest of the body.

Physically separating left ventricle **28** and right ventricle **18** is interventricular septum **33**. Physically separating left atrium **24** and right atrium **12** is an interatrial septum.

Mitral valve **26**, depicted in Figure 2A (top view) and in Figure 2B (cross sectional long axis view) is defined by an approximately circular mitral annulus **34** that defines a mitral lumen **36**. Attached to the periphery of mitral annulus **34** is an anterior leaflet **38** and a smaller posterior leaflet **40**, leaflets **38** and **40** joined at commissures **41**. Each leaflet is between about 0.8 and 2.4 mm thick and composed of three layers of soft tissue.

The typical area of mitral lumen **36** in a healthy adult is between 4 and 6 cm^2 while the typical total surface area of leaflets **38** and **40** is approximately 12 cm^2. Consequently and as depicted in Figure 2B, leaflets **38** and **40** curve downwards into left ventricle **28** and coapt to accommodate the excess leaflet surface area, producing a coaptation surface **42** that constitutes a seal. The typical length of coaptation surface **42** in a healthy heart **10** of an adult is approximately 7-8 mm.

The bottom surface of anterior leaflet **38** and posterior leaflet **40** are connected to papillary muscles **44** at the bottom of left ventricle **28** by posterior chordae **46** and anterior chordae **48**.

During diastole, left atrium **24** contracts to pump blood downwards into left ventricle **28** through mitral valve **26**. The blood flows through mitral lumen **36** pushing leaflets **38** and **40** downwards into left ventricle **28** with little resistance.

During systole left ventricle **28** contracts to pump blood upwards into aorta **32** through aortic semi-lunar valve **30**. Mitral annulus **34** contracts pushing leaflets **38** and **40** inwards and downwards, reducing the area of mitral lumen **36** by about 20% to 30% and increasing the length of coaptation surface **42**. The pressure of blood in left ventricle **28** pushes against the bottom surfaces of leaflets **38** and **40**, tightly pressing leaflets **38** and **40** together at coaptation surface **42** so that a tight leak-proof seal is formed. To prevent prolapse of leaflets **38** and **40** upwards into left atrium **24**, papillary muscles **44** contract pulling the edges of leaflets **38** and **40** downwards through posterior chordae **46** and anterior chordae **48**, respectively.

As is clear from the description above, an effective seal of mitral valve **26** is dependent on a sufficient degree of coaptation, in terms of length, area and continuity of coaptation surface **42**. If coaptation surface **42** is insufficient or non-existent, there is mitral valve insufficiency, that is, regurgitation of blood from left ventricle **28** up into left atrium **24**. A lack of sufficient coaptation may be caused by any number of physical anomalies that allow leaflet prolapse (e.g., elongated or ruptured chordae **46** and **48**, weak papillary muscles **44**) or prevent coaptation (e.g., short chordae **46** and **48**, small leaflets **38** and **40**).

Mitral valve insufficiency leads to many complications including arrhythmia, atrial fibrillation, cardiac palpitations, chest pain, congestive heart failure, fainting, fatigue, low cardiac output, orthopnea, paroxysmal nocturnal dyspnea, pulmonary edema, shortness of breath, and sudden death.

There are a number of pathologies that lead to a mitral valve insufficiency including collagen vascular disease, ischemic mitral regurgitation, myxomatous degeneration of leaflets **38** and **40** and rheumatic heart disease.

In ischemic mitral regurgitation (resulting, e.g., from myocardial infarction, chronic heart failure, or surgical or catheter revascularization), leaflets **38** and **40** and chordae **46** and **48** have normal structure and the mitral valve insufficiency results from altered geometry of left ventricle **28**. As a result of ischemia, portions of the heart walls necrose. During healing, the necrotic tissue is replaced with unorganized tissue leading to remodeling of the heart which reduces coaptation through distortion of mitral annulus **34** and sagging of the outer wall of left ventricle **28** which displaces papillary muscles **44**.

In Figures 3A (top view) and 3B (cross sectional long axis view), The reduction of coaptation resulting from ischemia is depicted for a mitral valve **26** of an ischemic heart **50** that has undergone mild remodeling and suffers from ischemic mitral regurgitation. In Figure 3B is seen how an outer wall of left ventricle **28** sags outwards, displacing papillary muscles **44** downwards which, through chordae **46** and **48**, pulls leaflets **38** and **40** downwards and apart, reducing coaptation. The incomplete closure of mitral valve **26** is seen in Figures 3A and 3B.

Initially, ischemic mitral regurgitation is a minor problem, typically leading only to shortness of breath during physical exercise due to the fact that a small fraction of blood pumped by left ventricle **28** is pumped into left atrium **24** and not through aortic semi-lunar valve **30**, reducing heart capacity. To compensate for the reduced capacity, left ventricle **28** beats harder and consequently remodeling continues. Ultimately leaflet coaptation is entirely eliminated as leaflets **38** and **40** are pulled further and further apart, leading to more blood regurgitation, further increasing the load on left ventricle **28**, and further remodeling. Ultimately, the left side of the heart fails and the person dies.

Apart from humans, mammals that suffer from mitral valve insufficiency include horses, cats, dogs, cows and pigs.

Currently, it is accepted to use open-heart surgical methods to improve mitral valve functioning by many different methods that force parts of the heart to adopt a shape that reduces some symptoms of improper valve function, including: modifying the subvalvular apparatus (e.g. lengthening the chordae) to improve leaflet coaptation; implanting an annuloplasty ring, e.g., as described in United States Patents 3,656,185, 6,183,512 and 6,250,308 to force mitral valve annulus **34** into a normal shape; or implanting devices in the mitral valve to act as prosthetic leaflets, e.g., United States Patent applications published as US 2002/065554, US 2003/0033009, US 2004/0138745 or US 2005/0038509. It has been found that such methods often fail to provide sufficient long range improvement of valve function.

Surgical augmentation of a mitral valve anterior leaflet **38** for improving mitral valve leaflet coaptation for treating ischemic mitral valve regurgitation is taught by Kincaid et al (Kincaid EH, Riley RD, Hines MH, Hammon JW and Kon ND in Ann. Thorac. Surg. 2004, 78, 564-568). An incision is made in the anterior leaflet almost from commissure to commissure. The edges of a roughly elliptical patch of material (e.g., bovine pericardium, 1 cm wide, 3 cm long) are sutured to either side of the incision augmenting the anterior leaflet by an amount roughly equal to the surface area of the patch. Additionally, a flexible annuloplasty ring is implanted to reshape the mitral annulus. Although effective, such augmentation is considered a complex surgical procedure performed only by cardiac surgeons having above average skill.

It would be highly advantageous to have a way to restore cardiac valve function such as of a mitral valve by improving leaflet coaptation, to reduce mitral insufficiency, for example for treating subjects suffering from ischemic mitral valve regurgitation.

SUMMARY OF THE INVENTION

Embodiments of the present invention successfully address at least some of the shortcomings of the prior art by providing methods and devices for the treatment of cardiac valves, which in embodiments improves cardiac valve leaflet coaptation, which may be useful in treating conditions, for example mitral insufficiency such as ischemic mitral regurgitation. In embodiments, the present invention also provides devices reminiscent of annuloplasty rings that allow procedures such as leaflet augmentation or cardiac valve relocation to be performed quickly with less dependence on the skill level or degree of exhaustion of the performing surgeon.

In a first aspect, the present invention provides for innovative methods and devices for leaflet augmentation. Embodiments of the present invention successfully address at least some of the shortcomings of the prior art by providing methods and apparatuses for reconstructing and realigning cardiac valve leaflets, for example mitral valve leaflets, some embodiments of which may be useful in treating conditions, for example mitral insufficiency such as ischemic mitral regurgitation. Generally, such apparatuses of the present invention can be considered as annuloplasty rings that are configured to support a leaflet-augmenting membrane. Generally, in embodiments such a device is deployed substantially as an annuloplasty ring, where a native leaflet is detached from the mitral valve annulus and secured to the leaflet augmenting membrane of the device, effectively lengthening the leaflet, which in embodiments restores or increases leaflet coaptation.

Thus, according to the teachings of the present invention, there is provided an annuloplasty apparatus comprising a substantially complete ring defining a ring lumen including an inner portion configured to be operatively associated with a lumen of an in vivo cardiac valve and an outer portion configured to be operatively associated with a periphery of the lumen of the cardiac valve, the annuloplasty apparatus further including a membrane functionally associated with the ring, the membrane at least partially covering the ring lumen around the entire periphery of the ring lumen in a plane substantially parallel to a plane passing radially through the ring.

In some embodiments, the membrane is continuous and substantially entirely covers the ring lumen.

In some embodiments, the membrane is provided with a membrane opening through the ring lumen. In some embodiments, the membrane opening is located substantially in the center of the ring lumen. In some embodiments, the membrane opening is located off-center of the ring lumen. In some embodiments, the membrane opening has an area of at least about 10% of the area of the ring lumen. In some embodiments, the membrane opening has an area of at least about 20% of the area of the ring lumen. In some embodiments, the membrane opening has an area of no more than about 80% of the area of the ring lumen.

In some embodiments, at least a portion of the ring includes a portion being substantially covered by the membrane. In some embodiments, the portion covered by the membrane includes the ring outer portion.

In some embodiments, the membrane covering ring outer portion is configured for securing proximate to a cardiac annulus and/or the periphery of a cardiac annulus.

In some embodiments, the membrane covering the ring outer portion is configured to be sutured to the valve periphery.

In some embodiments, the membrane encircles the ring so as to be functionally associated therewith.

In some embodiments, the membrane is secured to the ring so as to be functionally associated therewith.

In some embodiments, the membrane is secured to the ring by a member of the group consisting of sewing, adhesion, gluing, suturing, riveting and welding.

In some embodiments, the ring is configured to be sutured.

In some embodiments, the membrane is configured to be intra-operatively modified by at least one member of the group of processes consisting of cutting, bending, folding and suturing.

In some embodiments, the membrane comprises a tissue from an animal source such as a material from the group of materials consisting of serous tissue, pericardium, pleura, peritoneum and aortic leaflet.

In some embodiments, the animal source is a source from the group consisting of bovine, porcine, equine and human.

In some embodiments, the membrane is at least about 0.2 millimeters thick. In some embodiments, the membrane is no more than about 2 millimeters thick.

In embodiments, the ring is substantially similar to prior art annuloplasty rings and is fashioned from materials and in a manner as is known in the art of annuloplasty rings. In some embodiments, the ring comprises a material selected from a group consisting of nitinol, stainless steel shape memory materials, metals, synthetic biostable polymer, a natural polymer, an inorganic material, titanium, pyrolytic carbon, a plastic, a titanium mesh and polydimethylsiloxane.

In embodiments, a biostable polymer from which a ring is fashioned comprises a material from the group including a polyolefin, polyethylene, polytetrafluoroethylene (Teflon®), and polycarbonate synthetic, a polyurethane, a fluorinated polyolefin, a chlorinated polyolefin, a polyamide, an acrylate polymer, an acrylamide polymer, a vinyl polymer, a polyacetal, a polycarbonate, a polyether, an aromatic polyester, a polyether (ether ketone), a polysulfone, a silicone rubber (*e.g.,* Silastic by Dow-Corning Corporation, Midland, MI, U.S.A.), a thermoset material, or a polyester (ester imide, for example Dacron® by Invista, Wichita, KS, U.S.A.) and/or combinations thereof.

In some embodiments, the ring comprises a material having a property selected from the group consisting of: flexible, plastic, elastic and rigid.

In some embodiments, the ring has height of no more than about 5.0 millimeters.

In some embodiments, the ring has height of at least about 1.0 millimeter.

According to the teachings of the present invention, there is also provided a method for performing an annuloplasty procedure in a heart (human or non-human, such as dog, cat, pig, horse or cow), comprising: (a) providing a substantially continuous ring defining a ring lumen and functionally associating a membrane to the ring so that the membrane covers a portion of the ring lumen; (b) detaching at least a portion of a first a cardiac valve leaflet from a periphery of the cardiac valve in a cardiac valve including at least two cardiac valve leaflets extending from the valve periphery of the cardiac valve; (c) securing, e.g., by suturing, the substantially continuous ring to the periphery of the cardiac valve; and (d) attaching a detached edge of the cardiac valve leaflet to the membrane, thereby restoring valve function by increasing the dimensions (e.g., length and/or surface area) of the leaflet.

In some embodiments, the method further comprises, subsequent to securing (c), (e) modifying the membrane to decrease the covered portion of the ring lumen, e.g., by trimming.

In some embodiments, the membrane at least partially covers the ring lumen around the entire periphery of the ring lumen, as described above for an annuloplasty apparatus of the present invention.

In some embodiments, the cardiac valve is a bicuspid valve. In some embodiments, the cardiac bicuspid valve is a mitral valve. In some embodiments, the cardiac valve is a tricuspid valve.

In some embodiments, the leaflet is detached from the periphery substantially entirely.

In some embodiments, the attaching of the detached edge of the leaflet is proximate to a luminal edge of the membrane.

In some embodiments, prior to the attaching of the detached edge of the first leaflet, the membrane is cut so as to expose a second of the cardiac leaflets.

In some embodiments, following the attaching of the detached edge of the first leaflet, the first leaflet and the second leaflet have a length of coaptation that is greater than 8 millimeters.

In some embodiments, the attaching the detached edge of the first cardiac leaflet to the membrane includes attaching the detached edge to the membrane using a method selected from the group consisting of suturing, adhering, gluing and welding.

In some embodiments, the ring is secured by suture to the heart.

In some embodiments, the suturing is through the membrane.

In some embodiments, the membrane is shaped to cover the second cardiac leaflet.

In some embodiments, the second cardiac leaflet is retracted substantially toward the valve periphery.

In some embodiments, the cardiac valve includes at least three cardiac valve leaflets.

According to a further aspect, the present invention provides for innovative methods and implants for augmentation of the tissue surrounding a cardiac valve (e.g., the surface area of tissue between the valve annulus and the valve itself is increased). Generally, an implant including a wall, the wall delimited by two edges each in the shape of a closed curve and defining a lumen. (e.g., a tube or annulus) is provided as a cardiac valve augmenting implant. The native valve is detached from the valve annulus and secured to one edge of the implant while the other edge is secured to the valve annulus, thereby augmenting the tissue surrounding the valve. In embodiments, the implant allows distal relocation of a cardiac valve from a native position attached to a native valve annulus located between a ventricle and an atrium downwards into the ventricle.

Thus according to the teachings of the present invention there is also provided a method of augmenting the tissue surrounding a cardiac valve, comprising: a) excising leaflets of a cardiac valve (*e.g.*, mitral valve, tricuspid valve) of a subject (human or non-human mammal) with an incision having a shape of a closed curve (e.g., circles, ovals, ellipses, oblate ovals, oblate ellipses and oblate circles), so as to define a valve seat edge of the incision and a valve periphery edge of the incision; b) providing an implant including a wall, the wall delimited by two edges each in the shape of a closed curve and defining a lumen. (e.g., a substantially tubular implant or a substantially annular implant) as a cardiac valve augmenting implant; c) securing (e.g., by suturing, adhesing, stapling) the first portion of the implant to the valve seat edge at a plurality (e.g., at least 3, generally at least 6, usually more) of locations; and d) securing (e.g., by suturing, adhesing, stapling) the second portion of the implant to the valve periphery edge at a plurality (e.g., at least 3, generally at least 6, usually more) of locations, thereby augmenting a surface area of tissue surrounding the cardiac valve with the implant, and in embodiments allowing relocation of the cardiac valve. In embodiments, spare portions of the implant are trimmed. It is important to note that the steps of the method may be performed in any rational order and not necessarily in the order listed above. For example, in embodiments, **a** precedes **c** and/or **d**; **a** succeeds **c** and/or **d**; **c** precedes **d**; **d** precedes **c**.

In embodiments, a valve (such as a mitral valve) is excised intact (that is, where the leaflets (in the case of a mitral valve, the posterior and the anterior leaflets) remain associated through the commissures from the valve annulus. In embodiments, the thus excised valve is secured to the second portion of the implant, preferably still intact.

In embodiments, the cardiac valve is a mitral valve.

In embodiments, the augmentation of the tissue surrounding the valve improves coaptation of leaflets of the cardiac valve.

As noted above, an implant used in augmenting the tissue surrounding a cardiac valve in accordance with the teachings of the present invention includes a wall, the wall delimited by two edges each in the shape of a closed curve and defining a lumen. Suitable closed curve shapes of the edges of an implant include, but are not limited to circles, ovals, ellipses, oblate ovals, oblate ellipses and oblate circles. Any suitable material or combination of materials may be used for fashioning a wall of an implant, both synthetic and biological as is detailed hereinbelow.

In embodiments, a valve augmenting implant is substantially a flat sheet of material with a hole therethrough, where the first edge is the outer edge of the flat sheet and the second edge is the edge of the hole. In such embodiments, the first region, that which is secured to the valve seat edge of the incision is a portion of the sheet closer to the first edge (edge of the sheet) than the second region which is closer to the second edge (the edge of the hole) and to which the valve periphery edge of the incision is secured. In embodiments, the flat sheet of material is in the shape of an annulus or ring. In embodiments the two edges are of the same shape. In embodiments, the two edges describe shapes that are substantially concentric.

In embodiments, augmentation of tissue surrounding the cardiac valve and subsequent relocation of a cardiac valve in accordance with the teachings of the present invention is performed with the use of a valve augmenting implant that is substantially an apparatus as described above comprising a ring including a membrane. However, instead of attaching a leaflet to the membrane, the valve is detached from a respective annulus (preferably substantially intact, that is where the leaflets are associated through substantially intact commissures) and then secured to the edge of the lumen defined by the hole in the membrane. In such embodiments, the first portion of the implant that is secured to the valve seat edge is the ring or in proximity to the ring while the second portion of the implant that is secured to the valve periphery edge is near the periphery of the hole in the membrane.

In embodiments, augmentation of tissue surrounding the cardiac valve and subsequent relocation of a cardiac valve in accordance with the teachings of the present invention is performed with the use of a substantially tubular cardiac valve augmenting implant that is substantially a tube of material having a proximal end and a distal end with a lumen passing therebetween, where the first edge is the rim of the proximal end and the second edge is the rim of the distal end. In such embodiments, the first region, that which is secured to the valve seat edge of the incision is a portion of the tube closer to the first edge (proximal rim) than the second region which is closer to the second edge (distal rim) and to which the mitral valve edge of the incision is secured. In embodiments, the tube is substantially parallel walled. In embodiments, the distal rim and the proximal rim are of substantially the same size. In embodiments, the distal end and the proximal end are coaxial. In embodiments, the distal end and the proximal end are not-coaxial. In embodiments, the proximal rim is substantially larger than the distal rim. In embodiments, the tubular wall is substantially a truncated cone. In embodiments, the distal end and the proximal end are coaxial. In embodiments, the distal end and the proximal end are not-coaxial. In embodiments, the tubular wall is substantially frustoconical. In embodiments, the ends of the truncated cone are substantially not parallel.

In embodiments, especially embodiments where the tubular cardiac valve augmenting implant is axially extensible and axially bendable, relocation of a heart valve in accordance with the teachings of the present invention allows long-term maintenance of leaflet coaptation, even in the event of continued cardiac remodeling, and reduces deformation of the valve during heart movement.

In embodiments, relocation of a cardiac valve in accordance with the teachings of the present invention is useful for restoring adequate sealing of leaky cardiac valves.

In embodiments, relocation of a cardiac valve in accordance with the teachings of the present invention is useful for restoring proper tension to improperly tensioned tendineae chordae.

Thus, according to the teachings of the present invention there is also provided a method for relocating a cardiac valve distally to a cardiac valve annulus, the method comprising: a) providing a substantially tubular cardiac valve augmenting implant comprising a substantially tubular wall defining a lumen, the implant having a proximal portion and a distal portion; b) detaching a cardiac valve from a cardiac valve annulus located between an atrium and a ventricle (*e.g.*, mitral valve, tricuspid valve) of a subject (human or non-human mammal); c) securing (*e.g.*, by suturing, adhesing and stapling) the cardiac valve to the distal portion of the tubular implant; and d) securing (*e.g.*, by suturing, adhesing and stapling) the proximal portion of the tubular implant in the proximity of the cardiac valve annulus so that the valve is distal to the valve annulus, thereby providing fluid communication between the atrium and the ventricle through the lumen and through the cardiac valve.

In embodiments, securing the cardiac valve to the distal portion of the substantially tubular implant precedes the detaching of the cardiac valve from the cardiac valve annulus.

In embodiments, securing the cardiac valve to the distal portion of the substantially tubular implant is subsequent to the detaching of the cardiac valve from the cardiac valve annulus.

In embodiments, the cardiac valve is detached from the cardiac valve annulus substantially intact, for example as a complete functioning unit. For example, in embodiments, the cardiac valve is detached so that leaflets of the valve are mutually associated through substantially intact commissures of the valve.

In embodiments, the cardiac valve is secured so that at least part of the cardiac valve is located over a distal end of the substantially tubular implant

In embodiments, the cardiac valve is secured inside the lumen.

In embodiments, the cardiac valve is secured abutting against a distal end of the substantially tubular implant.

In embodiments, the cardiac valve is secured to the tubular wall.

In embodiments, the cardiac valve is secured to a ring-shaped component distinct from the tubular wall secured to the tubular wall at the distal portion of the apparatus. In embodiments, the cardiac valve is secured over a ring-shaped component distinct from the tubular wall secured to the tubular wall at the distal portion of the apparatus. Such a ring-shaped component can be considered as a prosthetic cardiac valve annulus. In embodiments, the ring-shaped component is substantially rigid. In embodiments, a first sector of the ring-shaped component is substantially rigid and a second sector of the ring-shaped component is substantially less rigid than the first sector.

In embodiments, the proximal portion of the substantially tubular implant is attached to the inner rim of the cardiac valve annulus. In embodiments, the proximal portion of the substantially tubular implant is attached above the inner rim of the cardiac valve annulus so that at least a portion of the apparatus is located over the inner rim of the cardiac annulus, for example to a portion of an inner wall of the atrium above the cardiac annulus or to a ring-shaped component (such as a prior art annuloplasty ring) located above the inner rim of the cardiac valve annulus. In embodiments, the proximal portion of the substantially tubular implant is attached below the inner rim of the cardiac valve annulus.

According to the teachings of the present invention, there is also provided a substantially tubular cardiac valve augmenting implant configured for implantation in a mammalian heart comprising: a) a substantially tubular wall defining a lumen, comprising a proximal portion with a proximal end, a distal portion with a distal end, an outer surface and a luminal surface; and b) associated with the distal end, a ring-shaped component thicker in the radial direction than the wall wherein the tubular wall is fashioned of substantially impermeable materials. Although, the method of the present invention is potentially implementable with many substantially tubular implant (for example, with a tube of tissue from an animal source), it is advantageous to implement the method of the present invention using a substantially tubular cardiac valve augmenting implant of the present invention.

Generally, the proximal portion of the tubular wall of a substantially tubular implant of the present invention is configured for attachment to a cardiac valve annulus (i.e., near the valve seat edge of the incision used to detach the cardiac valve) and functions as an extender that relocates the valve distally (*i.e.*, lowers the valve into the ventricle).

In embodiments, a ring-shaped component associated with the distal end of the substantially tubular wall of a substantially tubular implant of the present invention functions as a prosthetic valve annulus, and in embodiments can be considered as an annuloplasty ring. In embodiments, the ring-shaped component is a prior-art annuloplasty ring associated with a substantially tubular wall.

In embodiments, at least a portion of the ring-shaped component is secured to the distal end of the substantially tubular wall by methods, including but not limited to, sewing, adhesion, gluing, suturing, riveting, stapling or welding.

The cross section of the ring (substantially perpendicular to the lumen of the ring) is of any suitable shape, including but not limited to round, oval, ovoid, square, rectangular, L-shaped and T-shaped.

In embodiments, the thickness of the ring-shaped component in the radial direction is at least about 1 millimeter, at least about 2 millimeter and even at least about 3 millimeter. In embodiments, the thickness of the ring-shaped component in the radial direction is no more than about 6 millimeter.

In embodiments, the ring-shaped component has a height of at least about 0.4 millimeter. In embodiments, the ring-shaped component has a height of no more than about 2.5 millimeter.

In embodiments, the ring-shaped component associated with the distal end of the substantially tubular wall is configured for attachment of the periphery of a cardiac valve, that is to say, the periphery of a substantially intact cardiac valve or components thereof are attachable to the ring-shaped component. In embodiments, the ring-shaped component is piercable, that is can be pierced without substantially degrading structural properties of the ring-shaped component, *e.g.* by sutures or staples used to secure a valve to the ring-shaped component.

In embodiments, the ring-shaped component protrudes into the lumen of the substantially tubular wall, in embodiments by at least about 1 millimeter, at least about 2 millimeter and even at least about 3 millimeter. In embodiments, the ring-shaped component protrudes into the lumen of the substantially tubular wall by no more than about 5 millimeter. In such a way, in embodiments the ring-shaped component defines a ledge to which the periphery of a cardiac valve is attachable. In embodiments, the ring-shaped component is substantially flush with the outer surface of the substantially tubular wall.

In embodiments, the ring-shaped component protrudes outwards from the outer surface of the substantially tubular wall, in embodiments by at least about 1 millimeter, at least about 2 millimeter and even at least about 3 millimeter. In embodiments, the ring-shaped component protrudes outwards from the outer surface of the substantially tubular wall, by no more than about 5 millimeter. In such a way, in embodiments the ring-shaped component defines a ledge to which the periphery of a cardiac valve is attachable. In embodiments, the ring-shaped component is substantially flush with the luminal surface of the wall.

In embodiments, the ring-shaped component is substantially flat. In embodiments, the ring-shaped component is not flat, *e.g.* curved.

In embodiments, the ring-shaped component describes a circle or an oblate circle. In embodiments, the ring-shaped component describes an ellipse or an oblate ellipse. In embodiments, the ring-shaped component describes an ovoid or an oblate ovoid.

In embodiments, the ring-shaped component is substantially rigid, that is substantially non-deformable both axially and radially.

In embodiments, the ring-shaped component is substantially radially non-expandable, that is, is not configured for increasing a circumference in the manner of a stent or the like. In embodiments, the ring-shaped component is substantially radially non-collapsible, that is, is not configured for decreasing a circumference in the manner of a stent or the like.

In embodiments, the ring-shaped component is substantially axially rigid.

In embodiments, the ring-shaped component is substantially flexible, that is, is deformable without changing circumference.

In embodiments, the ring-shaped component is substantially uniform, having substantially uniform properties around the circumference.

In embodiments, the ring-shaped component comprises at least two sectors, a first sector and a second sector more flexible than the first sector. In embodiments, the first sector is substantially rigid. In embodiments, the first sector is substantially flexible and the second sector even more flexible.

The ring-shaped component is fashioned of any suitable material or materials, including monolithic, woven, braided, molded, stamped and laminated materials. In embodiments, the ring shaped component comprises, essentially consists of or even consists of materials such as nitinol, stainless steel shape memory materials, metals, synthetic biostable polymer, a natural polymer, an inorganic material, titanium, pyrolytic carbon, a plastic, a titanium mesh and polydimethylsiloxane. Suitable biostable polymers include polymers such as polyolefins, polyethylenes, polytetrafluoroethylenes, polycarbonates, polyurethanes, fluorinated polyolefins, chlorinated polyolefins, polyamides, acrylate polymers, acrylamide polymers, vinyl polymers, polyacetals, polyethers, aromatic polyesters, polyetherether ketones, polysulfones, silicone rubbers, thermoset materials, polyesters and/or combinations thereof.

In embodiments, the thickness of the tubular wall is at least 0.05 millimeter at least about 0.1 millimeter and even at least about 0.2 millimeter. In embodiments, the thickness of the tubular wall is no more than about 2 millimeter, no more than about 1 millimeter and even no more than about 0.5 millimeter.

In embodiments the cross-sectional area of the lumen at the proximal end of the substantially tubular wall is less than about 28.3 cm^2 (equivalent to a circular lumen having a diameter of about 6 cm), less than about 19.6 cm^2 (equivalent to a circular lumen having a diameter of about 5 cm) and even less than about 15.9 cm^2 (equivalent to a circular lumen having a diameter of about 4.5 cm).

In embodiments the cross-sectional area of the lumen at the proximal end of the substantially tubular wall is greater than about 1.8 cm^2 (equivalent to a circular lumen having a diameter of about 1.5 cm), greater than about 3.1 cm^2 (equivalent to a circular lumen having a diameter of about 2 cm), greater than about 4.9 cm^2 (equivalent to a circular lumen having a diameter of about 2.5 cm) and even greater than about 7.1 cm^2 (equivalent to a circular lumen having a diameter of about 3 cm).

In embodiments, the cross-sectional area of the lumen at the proximal end of the substantially tubular wall is substantially equal to the cross-sectional area of the lumen at the distal end of the substantially tubular implant.

In embodiments, the cross-sectional area of the lumen at the proximal end of the substantially tubular implant is greater than the cross-sectional area of the lumen at the distal end of the substantially tubular implant. In embodiments, the cross-sectional area of the lumen at the distal end of the substantially tubular implant is less than about 90%, less than about 80%, less than about 70% and even less than about 60% of the cross-sectional area of the lumen at the proximal end of the substantially tubular implant.

In embodiments exceptionally suitable, for example, for implantation in a human heart, the cross-sectional area of the lumen at the proximal end of the substantially tubular implant is between about 15.9 cm^2 (equivalent to a circular lumen having a diameter of about 4.5 cm) and about 7.1 cm^2 (equivalent to a circular lumen having a diameter of about 3 cm) and the cross-sectional area of the lumen at the distal end of the substantially tubular implant is between about 5.3 cm^2 (equivalent to a circular lumen having a diameter of about 2.6 cm) and about 8.6 cm^2 (equivalent to a circular lumen having a diameter of about 3.3 cm)

In embodiments, the luminal surface is substantially smooth, allowing a smooth flow of blood through the lumen.

In embodiments, the proximal portion of the substantially tubular wall is radially expandable. In embodiments, the proximal portion of the tubular wall is radially elastic. In such a way, the proximal portion can be stretched to smoothly conform to the size of a native cardiac valve annulus

In embodiments, the substantially tubular wall is axially bendable.

In embodiments, the length (rest length, that is length in an unstressed state) of the substantially tubular wall and the ring-shaped component together is greater than about 2 millimeter and even greater than about 3 millimeter. In embodiments, the length of the substantially tubular wall and the ring-shaped component is less than about 30 millimeter, less than about 25 millimeter and even less than about 10 millimeter.

In embodiments, the substantially tubular wall is axially extensible. In embodiments, the substantially tubular wall is reversibly axially extensible and compressible. In embodiments, the substantially tubular wall is elastically axially extensible and compressible. In embodiments, the axial extensibility is from about 2 mm to about 12 mm. In embodiments, the axial extensibility is at least about 1.3 times, at least about 1.5 times and even at least about 2 times the length the of the tubular wall.

In embodiments, the substantially tubular wall is substantially radially non-expandable, that is, is not configured for increasing a circumference. In embodiments, the substantially tubular wall is substantially radially non-collapsible, that is, is not configured for decreasing a circumference.

In embodiments, the substantially tubular wall is substantially radially rigid, that is, substantially radially non-deformable.

In embodiments, the substantially tubular wall is substantially radially flexible, that is, is deformable without changing circumference.

In embodiments, the substantially tubular wall consists essentially of one material.

In embodiments, the distal portion of the substantially tubular wall consists essentially of a first material and the proximal portion of the substantially tubular wall consists essentially of a second material.

In embodiments, at least one impermeable material from which the substantially tubular wall is fashioned essentially consists of polyester (*e.g.*, Dacron). In embodiments, at least one impermeable material from which the substantially tubular wall is fashioned essentially consists of woven polyester (*e.g.*, Dacron).

In embodiments, at least one impermeable material comprises a tissue from an animal source. In embodiments, the tissue is selected from the group consisting of serous tissue, pericardium, pleura and peritoneum. In embodiments, the animal source is a source from the group consisting of bovine, porcine, equine and human.

In embodiments, the substantially tubular wall is radially pleated, in embodiments the radial pleating being such that the substantially tubular wall is axially bendable and substantially radially rigid, analogously to a concertina.

In embodiments, the apparatus further comprises at least one reinforcement component functionally associated with the substantially tubular wall. In embodiments, the at least one reinforcement component provides the substantially tubular wall, at least in part, with axial bendability. In embodiments, the at least one reinforcement component provides the substantially tubular wall, at least in part, with axial extensibility. In embodiments, the at least one reinforcement component provides the substantially tubular wall, at least in part, with radial rigidity.

In embodiments, at least one reinforcement component is encased within the substantially tubular wall. In embodiments, at least one reinforcement component is secured to the outside surface of the substantially tubular wall. In embodiments, at least one the reinforcement component is secured to the luminal surface of the substantially tubular wall.

In embodiments, at least one the reinforcement component comprises a helical coil coaxial with the substantially tubular wall, such as a parallel-walled or conical helical spring.

In embodiments, at least one reinforcement component comprises a reinforcement ring coaxial and associated with the substantially tubular wall. In embodiments, at least one reinforcement component comprises a series of reinforcement rings coaxial and associated with the substantially tubular wall.

The present invention also provides for the manufacture of implants such as annuloplasty apparatus and cardiac valve augmenting implants such as described herein. Thus according to the teachings of the present invention there is also provided for the use of a sheet of an implantable material for the manufacture of a cardiac valve augmenting implant, the implant including a wall comprising the material, the wall delimited by two edges each having a shape of a closed curve and defining a lumen.

In embodiments, the wall is substantially annular. In embodiments, a first edge is a periphery of the wall and a second edge is a periphery of the hole of the wall.

In embodiments, the wall is substantially tubular. In embodiments, a first edge is a periphery of a proximal end of the wall and a second edge is a periphery of a distal end of the wall.

In embodiments, the second edge is configured to be secured to an excised cardiac valve and a first edge is configured to be secured to a mitral valve seat, e.g., in proximity of a mitral valve annulus.

According to the teachings of the present invention there is also provided a method of producing a cardiac implant, comprising: a) providing a sheet of implantable material; and b) fashioning the material in the shape of a wall of the cardiac implant, the wall delimited by two edges each having a shape of a closed curve and defining a lumen.

In embodiments, the wall is substantially annular. In embodiments, a first edge is a periphery of the wall and a second edge is a periphery of the hole of the wall.

In embodiments, the wall is substantially tubular. In embodiments, a first edge is a periphery of a proximal end of the wall and a second edge is a periphery of a distal end of the wall.

In embodiments, the second edge is configured to be secured to an excised cardiac valve and a first edge is configured to be secured to a mitral valve seat.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

As used herein, the terms “comprising” and “including” or grammatical variants thereof are to be taken as specifying the stated features, integers, steps or components but do not preclude the addition of one or more additional features, integers, steps, components or groups thereof. This term encompasses the terms "consisting of" and "consisting essentially of".

The phrase "consisting essentially of" or grammatical variants thereof when used herein are to be taken as specifying the stated features, integers, steps or components but do not preclude the addition of one or more additional features, integers, steps, components or groups thereof but only if the additional features, integers, steps, components or groups thereof do not materially alter the basic and novel characteristics of the claimed composition, device or method.

As used herein, the indefinite articles "a" and "an" mean "at least one" or "one or more".

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of the preferred embodiments of the present invention only, and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for a fundamental understanding of the invention, the description taken with the drawings making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

In the drawings:

FIG. 1 (prior art) is a schematic depiction of a healthy heart in cross section;

FIGS. 2A and 2B (prior art) depict a mitral valve of a healthy heart;

FIGS. 3A and 3B (prior art) depict a mitral valve of a heart suffering from ischemic mitral regurgitation related to incomplete coaptation of the leaflets of the mitral valve;

FIG. 4 shows an aerial view of an improperly functioning mitral valve with a detached anterior leaflet, according to an embodiment of the invention;

FIGS. 5-6 show an annuloplasty apparatus being deployed in the mitral valve shown in Figure 4, according to an embodiment of the invention;

FIGS. 7, 8A and 8B show augmentation of the anterior mitral valve leaflet using the annuloplasty apparatus shown in Figures 5-6, according to an embodiment of the invention; and

FIGS 9, 10A and 10B show reconstruction of both the anterior and posterior mitral valve leaflets using the annuloplasty apparatus shown in Figures 5-6, according to an embodiment of the invention.

FIG. 11 depicts an aerial view of an improperly functioning mitral valve, severed from a valve annulus about the periphery of the valve so as to leave the valve leaflets associated through the commissures so that the valve is substantially intact, according to embodiments of the invention;

FIGS. 12A-12F depict various stages of an embodiment of the method of the present invention where the tissue surrounding a mitral valve such as depicted in Figure 11 is augmented with an implant that is substantially a ring such as depicted in Figure 5, the method leading to valve relocation downwards into the left atrium and increased leaflet coaptation;

FIG. 13 depicts a substantially tubular cardiac valve augmenting implant, according to embodiments of the invention;

FIGS. 14A and 14B depict mitral valve leaflets being attached to the valve augmenting implant of Figure 12, according to embodiments of the invention.

FIG. 15 depicts the valve augmenting implant of Figure 4 implanted in a heart, in cross section;

FIG. 16 depicts the valve augmenting implant of Figure 4 implanted in a heart, in cross section subsequent to continued remodeling;

FIGS. 17A-17E, 18A-18D, 19A-19D and 20A-20C depict embodiments of the substantially tubular valve augmenting implant of the present invention;

FIG. 21 depicts an embodiment of a valve attached to a substantially tubular valve augmenting implant of the present invention;

FIGS. 22A, 22B and 22C depict embodiments of attachment of the proximal portion of a substantially valve augmenting implant of the present invention relative to a cardiac valve annulus; and

FIGS. 23A, 23B and 23C depict embodiments of ring-shaped components of substantially tubular valve augmenting implants of the present invention, in top view, cross section and perspective.

DESCRIPTION OF EMBODIMENTS

The present invention relates to methods and devices for treatments of cardiac valves by tissue augmentation that in embodiments are useful for improving cardiac leaflet coaptation, especially of the mitral valve. Generally, according to the teachings of the present invention the subvalvular apparatus is preserved.

The principles and uses of the teachings of the present invention may be better understood with reference to the accompanying description, Figures and examples. In the Figures, like reference numerals refer to like parts throughout.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details set forth herein. The invention can be implemented with other embodiments and can be practiced or carried out in various ways.

Embodiments of the present invention successfully address at least some of the shortcomings of the prior art by providing a simple method of augmenting cardiac valve leaflets. Thus, the teachings of the present invention allow a cardiac leaflet to be augmented and therefore embodiments are useful for treating a condition where cardiac valve augmentation is beneficial, such as mitral valve insufficiency, for example ischemic mitral regurgitation.

Embodiments of the present invention successfully address at least some of the shortcomings of the prior art by providing a simple method of augmenting the tissue around a cardiac valve. In embodiments, this leads to cardiac valve relocation that improves leaflet coaptation. Thus, the teachings of the present invention allow a cardiac valve to be augmented and therefore embodiments are useful for treating a condition where cardiac valve relocation is beneficial, such as mitral valve insufficiency, for example ischemic mitral regurgitation.

As noted above and depicted in Figures 3A and 3B, in a heart **50** suffering from ischemic mitral regurgitation mitral valve **26** and associated chordae **46** and **48** are patent. The insufficient coaptation of leaflets **38** and **40** that leads to the regurgitation of blood is a result of deformation of mitral valve annulus **34** and misdirected pulling forces applied through chordae **46** and **48** to leaflets **38** and **40**, both resulting from necrosis and consequent deformation of the wall of left ventricle **28**. In such cases, the regurgitation may be treated by improving leaflet coaptation. Embodiments of the present invention are useful in augmenting cardiac valve leaflets, especially for treating a condition where such augmentation is beneficial. Embodiments of the present invention are useful in augmenting the tissue surrounding a cardiac valve, especially for treating a condition where such augmentation is beneficial. In order to simplify understanding the teachings of the present invention embodiments of the present invention will be discussed in the context of treating a mitral valve suffering from ischemic mitral regurgitation where the teachings of the present invention are directed to increasing leaflet coaptation and thus treat the ischemic mitral regurgitation, such as mitral valve **50** depicted in Figures 3A and 3B.

By treating a condition is meant curing the condition, treating the condition, preventing the condition, treating symptoms of the condition, curing symptoms of the condition, ameliorating symptoms of the condition, treating effects of the condition, ameliorating effects of the condition, and preventing results of the condition.

Leaflet Augmentation

A first aspect of the present invention relates to augmentation of a cardiac leaflet, for example a posterior mitral valve leaflet. A mitral valve leaflet is detached, an annuloplasty ring with an attached membrane implanted in the substantially usual way, and the leaflet reattached to the membrane, effectively augmenting the leaflet, that in embodiments improves leaflet coaptation. An embodiment of leaflet augmentation in accordance with a method of the present invention is discussed with reference to Figures 4, 5, 6, 7, 8A, 8B, 9, 10A and 10B.

Referring to Figure 4, an aerial view of a malfunctioning mitral valve **26** is shown along with mitral valve annulus **34** and adjacent left atrium floor tissue **52**. Posterior leaflet **40** has been left intact while anterior leaflet **38** has been surgically incised, separated from annulus **34** and is shown floating in lumen **36**.

Figure 5 shows an annuloplasty apparatus **54** of the present invention including a ring **56** and a membrane **58** substantially coplanar with ring **56**. It is seen that membrane **58** partially covers the lumen of ring **56** around the entire periphery of the lumen of the ring **56**.

Ring **56** may be rigid, fashioned from any one or more of various materials, for example, titanium, stainless steel, pyrolytic carbon and various plastics, as noted above. Alternatively, ring **56** may be flexible, fashioned from any one or more of various materials, including a titanium mesh, Dacron, silicon rubber, polyethylene, and polytetrafluorethylene, as noted above

Membrane **58** covers ring **56** and is configured so as to allow sutures or the like to pass through membrane **58** without substantial tearing of membrane **58**, allowing annuloplasty apparatus **54** to be secured in heart tissue such as annulus **34** or in proximity thereof with sutures **60**. In embodiments, annuloplasty apparatus **54** is secured to heart tissue by passing sutures **60** through membrane **58** preferably proximate to ring **56**, for example through membrane **58** and looping around ring **56**.

In Figure 5, membrane **58** covers ring **56** and sutures **60** have been passed through ring **56** and through mitral valve annulus **34**.

Figure 6 shows annuloplasty apparatus **54** fully sutured to the vicinity of mitral valve annulus **34** with inverted mattress knots in sutures **60**. Membrane **58** extends inwards to partially obstruct lumen **36**.

Figures 7 shows anterior leaflet **38** exposed along with a portion of membrane **58a** that has been trimmed to be suitable for attachment of anterior leaflet **38** thereto.

Figure 8A shows an annular edge **62** of an anterior leaflet **38** attached to a trimmed portion **58a** of membrane **58** with sutures **64**.

Figure 8B shows a cross sectional long axis view of heart **50**, with annuloplasty apparatus **54** after anterior leaflet **38** has been augmented in accordance with the teachings of the present invention. Ring **56** of annuloplasty apparatus **54** is secured to the vicinity of mitral annulus **34** with sutures **60** to function substantially as a prior art annuloplasty ring. Membrane **58** of annuloplasty apparatus **54** is trimmed to two portions. Portion **58b** above posterior leaflet **40** is trimmed to close with ring **56** so as not to interfere with blood flow through mitral valve **26** and proper functioning of posterior leaflet **40**. Anterior leaflet **38** is secured to portion **58a** of membrane **58** with sutures **64** through annular edge **62** where anterior leaflet **38** was removed from annulus **34**. Portion **58a** effectively augments anterior leaflet **38**, increasing the surface area and the length of anterior leaflet **38**. Augmentation of anterior leaflet **38** restores and increases coaptation surface **42** between leaflets **38** and **40** (compare with Figure 3B). As depicted in Figure 8B, coaptation surface **42** has a length of approximately 10 to 12 millimeters

It is expected that in embodiments, due to the extent of augmentation of coaptation **42** between augmented anterior leaflet **38** and posterior leaflet **40**, continued remodeling of heart **50** will not result in clinically significant loss or reduction of coaptation

In certain pathologies, a posterior leaflet **40** is severely misaligned or, as seen in rheumatic hearts or hearts suffering from mitral annular calcification, severely misshapen. In other instances, a posterior leaflet **40** includes tissue defects, e.g., congenital defects, following debridement of endocarditis and following excision of cardiac tumors. In such cases, an annuloplasty apparatus of the present invention such as **54** is implanted in heart **50** substantially as described above but membrane **58** is trimmed substantially differently so that the portion of membrane **58** close to posterior leaflet **40** acts as a prosthetic posterior leaflet as depicted in Figures 9, 10A and 10B.

In Figure 9 is seen how annuloplasty apparatus **54** is secured to mitral annulus **34** with inverted mattress sutures **60** and membrane **58** trimmed to two portions **58a** proximate to anterior leaflet **38** and **58b** proximate to posterior leaflet **40**.

In Figure 10A, is seen that anterior leaflet **38** is secured to portion **58a** of membrane **58** with sutures **64**, substantially as described above.

In Figure 10B is seen how anterior leaflet **38** augmented with portion **58a** of membrane **58** coapts with portion **58b** of membrane **58** at coaptation surface **42** rather than with posterior leaflet **40**.

As noted above, it is expected that in embodiments, due to the extent of augmentation of coaptation **42** between augmented anterior leaflet **38** and membrane portion **58b**, continued remodeling of heart **50** will not result in clinically significant loss or reduction of coaptation

Augmentation of tissue surrounding a cardiac valve

As noted above, an additional aspect of the present invention relates to augmentation of the tissue surrounding a cardiac valve. Generally, an implant including a wall, the wall delimited by two edges each in the shape of a closed curve and defining a lumen. (e.g., a tube or annulus) is provided as a cardiac valve augmenting implant. The cardiac valve is detached from the valve annulus and secured to one edge of the implant while the other edge of the implant is secured to the valve annulus, thereby augmenting the tissue surrounding the valve. In embodiments, the implant allows distal relocation of a cardiac valve from a native position attached to a native valve annulus located between a ventricle and an atrium downwards into the ventricle. In embodiments, such relocation alleviates the deforming effect of forces applied to the valve, for example through the valve annulus and tendineae chordae, resulting from deformation of the heart, for example due to cardiac remodeling. In embodiments, relocation of a heart valve in accordance with the teachings of the present invention increases the magnitude of leaflet coaptation by allowing for realignment of the cardiac valve leaflets (for example mitral valve leaflets), improving valve function. Some embodiments of the aspect of the invention may be useful in treating conditions, for example mitral insufficiency such as ischemic mitral regurgitation.

Augmentation of tissue surrounding a cardiac valve in accordance with the teachings of the present invention is described hereinbelow with reference to a mitral valve such as mitral valve **26** of heart **50** depicted in Figures 3 where the purpose of the augmentation is to restore coaptation of leaflets **38** and **40**.

Using standard methods with which one skilled in the art is familiar, the subject is attached to a cardio-pulmonary bypass. Heart **50** is accessed using any open surgical approach, *e.g.*, median sternotomy, right or left thoracotomy. Alternatively, the heart is accessed using minimally invasive techniques, for example using a port access approach. The interior of heart **50** is exposed by any of several approaches, *e.g.*, right or left sided atriotomy, transseptal incision, with or without left atrial roof opening. During repair heart **50** may be fibrillating or arrested.

With the interior of heart **50** exposed, mitral valve **26** is detached from mitral valve annulus **34** substantially intact so as to leave leaflets **38** and **40** associated through commissures **41** so that valve **26** is floating freely within left ventricle **28** as depicted in Figure 11. The incision that detaches mitral valve **26** from mitral valve annulus **34** defines a valve seat edge **68** and a valve periphery edge **70**. For reference, annulus **34** is shown adjoining a subaortic curtain **66**.

Subsequently, a cardiac valve augmenting implant is implanted, the implant including a wall, the wall delimited by two edges each in the shape of a closed curve and defining a lumen. Such implants include substantially annular implants and substantially tubular implants.

Substantially annular cardiac valve augmenting implant

In embodiments, augmentation of tissue surrounding a cardiac valve is performed with the use of a substantially annular cardiac valve augmenting implant. In such embodiments, a first region at or near the periphery of the wall (first edge) of the implant is secured at or near a valve seat edge **68**. In such embodiments, a mitral valve **26** is secured (at or near a valve periphery edge **70** of mitral valve **26**) to a second region of the implant at or near the edge of the lumen (second edge) of the implant defined by the hole in the implant.

An embodiment of augmenting tissue surrounding a cardiac valve in accordance with the teachings of the present invention is discussed with reference to Figures 12A-12F.

As depicted in Figure 12A, after preparing a mitral valve **26** as discussed above with reference to Figure 11, an annuloplasty apparatus **54** is placed in heart **50** in proximity to mitral valve **26**. Annuloplasty apparatus **54** is as discussed above and includes a ring **56** and a membrane **58** with a hole therethrough. Ring **56** and membrane **58** together constitute a wall of apparatus **54**. The periphery of ring **56** defines the periphery of the wall of apparatus **54** which is also the first edge of apparatus **54**. The rim of the hole through membrane **58** defines the second edge of apparatus **54** and thus defines the lumen of apparatus **54**. Not depicted is that the hole through membrane **58** has been trimmed to a desired size to accommodate mitral valve **26**. Sutures **64** are passed through mitral valve **26** near valve periphery edge **70** and through membrane **58** in a first region of membrane **58** near the periphery of the hole through membrane **58**.

As depicted in Figure 12B, sutures **64** are tightened and knotted so as to secure mitral valve **26** to membrane **58**, making a strong and leak-proof seal between valve periphery edge **70** and the second edge of apparatus **54**.

As depicted in Figure 12C, sutures **60** are passed through a region of heart tissue near valve seat edge **68** and through ring **56** of apparatus **54**.

As depicted in Figure 12D, sutures **60** are tightened and knotted using inverted mattress sutures so as to secure apparatus **54** through ring **56** in proximity to valve seat edge **68**, making a strong and leak-proof seal between valve seat edge **68** and the first edge of apparatus **54**.

As depicted in Figure 12E, subsequent to augmentation of tissue surrounding a cardiac valve with a substantially annular cardiac valve augmenting implant such as apparatus **54** in accordance with the teachings of the present invention, coaptation **42** of leaflets **38** and **40** is restored and or improved to a significant extent. It is expected that in embodiments, due to the extent of augmentation of coaptation **42**, continued remodeling of heart **50** will not result in clinically significant loss or reduction of coaptation, as depicted in Figure 12F.

In embodiments, a substantially annular cardiac valve augmenting implant is devoid of a ring as described above and instead is simply an annular membrane. Use and implantation of such an implant is substantially similar to the described above. In such embodiments, the valve augmenting implant is substantially a sheet of implantable material (e.g., a membrane) with a hole therethrough, where the first edge of the implant is the outer edge of the sheet and the second edge of the implant is the edge of the hole. In such embodiments, the first region, that which is secured to the valve seat edge of the incision which is a portion of the sheet closer to the first edge (edge of the sheet) than the second region which is closer to the second edge (the edge of the hole) and to which the valve periphery edge of the incision is secured. In embodiments, the flat sheet is in the shape of an annulus or ring. In embodiments the two edges are of the same shape. In embodiments, the two edges describe shapes that are substantially concentric.

Substantially tubular cardiac valve augmenting implant

In embodiments, augmentation of tissue surrounding the cardiac valve is performed with the use of a substantially tubular cardiac valve augmenting implant that is substantially a tube of material having a proximal end and a distal end with a lumen passing therebetween, where the first edge is the rim of the proximal end of the tube and the second edge is the rim of the distal end of the tube. In such embodiments, the first region, that which is secured to the valve seat edge of the incision is a portion of the tube closer to the first edge (proximal rim) than the second region which is closer to the second edge (distal rim) and to which the valve periphery edge of the incision is secured.

Embodiments of augmentation of tissue surrounding a cardiac valve in accordance with a method of the present invention with a substantially tubular implant is discussed with reference to Figures 13, 14A, 14B, 15, 16, 17A-17E, 18A-18D, 19A-19D, 20A-20C, 21, 22A-22C and 23A-23C.

Figure 13 shows a tubular cardiac valve augmenting implant **72** of the present invention having a substantially tubular wall **74** (of impermeable pleated woven Polyester (Dacron®)) defining a lumen **75**. Tubular implant **72** additionally comprises a proximal portion having a proximal end **76**, and a ring-shaped component **78**, a ring of titanium mesh associated with the distal end **80** of tubular wall **74** by sutures. As used herein, the terms "proximal" and "proximally" indicate an object or action located closer to mitral valve annulus **34**, while "distal" and "distally" indicate an object or action located farther from annulus **34**.

Tubular implant **72** of proper shape and size has been chosen, ring-shaped component **78** is sutured to a region near valve periphery edge **70** of mitral valve **26** as seen in Figure 14A, using, for example, non-interrupted sutures **64** so that valve **26** abuts ring shaped component **78** at distal end **80** of tubular implant **72**. .

Sutures **64** are tightened so that ring-shaped component **78** and valve periphery edge **70** are in sealing contact. Figure 14B shows valve periphery edge **70** abutting and secured to distal end **80** with sutures **64**.

Referring to Figure 15, prior to attaching proximal end **76** of tubular implant **72** to valve seat edge **68** in proximity of mitral valve annulus **34**, the surgeon optionally measures and trims proximal end **76** of tubular wall **74** so that valve augmenting implant **72** fits properly in and does not extend above mitral valve annulus **34**. The surgeon also optionally aligns valve augmenting implant **72** in mitral valve annulus **34** and observes the proper positioning of chordae tendineae **46** and **48** so that there is no impingement on leaflets **38** and **40** and verifies that coaptation surface **42** is sufficiently large.

The surgeon then secures proximal end **76** of tubular implant **72** near to valve seat edge **68** near mitral valve annulus **34** with the help of sutures. Tubular implant **72** relocates the position of leaflets **38** and **40** distally into left ventricle **28**. As a result chordae **46** and **48** do not pull leaflets **38** and **40** too far downwards. In such a way, sufficient leaflet coaptation **42** is restored.

Relocation of mitral valve **26** and leaflets **38** and **40** allows the surgeon to forgo radical undermining and/or relocation of papillary muscles **44**, a complex procedure that has not been effective in reducing progressive remodeling and malfunction of papillary muscles **44**.

Figure 15 shows a portion of heart **50** in a cross sectional long axis view, with leaflets **38** and **40** fully attached to tubular implant **72**. Leaflets **38** and **40** are shown in the closed position during ventricular systole.

As noted above, tubular wall **74** is substantially a tube of pleated woven polyester as is known in the surgical arts for use as an arterial graft. The pleating of such a woven polyester tube provides tubular wall **74** with radial rigidity preventing collapse, deformation and obstruction of the lumen of tubular wall **74** yet provides tubular wall with axial bendability and elastic extensibility (up to about 50% of the length of tubular wall **74**). This bendability and elastic extensibility of tubular wall **74** allows tubular wall **74** to adapt by bending and stretch in response to the pulling of chordae **46** and **48**.

Although in embodiments, a tubular wall of a tubular valve augmenting implant of the present invention is parallel-walled so that the area of the lumen at the distal end and at the proximal end are substantially the same, in embodiments, such as tubular wall **74** of tubular implant **72**, the lumen at the distal end has a smaller area than the lumen at the proximal end. Such an arrangement helps prevent entry of the tubular wall into the aorta during ventricular contraction.

Figure 16 shows mitral valve **26** attached to ring-shaped component **78** following relocation of mitral valve **26** using tubular implant **72** as described above after a period of time where remodeling of papillary muscle ventricular wall **82** has occurred. Remodeling of wall **82** has caused papillary muscles **44** to move outwards, for example, in directions **84** and **86**. Wall **74** of implant **72** stretches so that mitral valve **26** moves more distally into left ventricle **28**, conforming to this motion and compensating for valvular distortion caused by remodeling thereby maintaining coaptation of leaflets **38** and **40**.

As shown, cardiac wall **82** remodeling is uneven. The resultant inequality in force, however, does not cause leaflet **38** to exhibit signs of tenting, tethering, reduction of coaptation **42** and/or regurgitation. Instead, longitudinally flexible tubular wall **74** has stretched downwards and towards the left side of the heart. In embodiments, tubular wall **74** is elastically axially extensible and compressible. In embodiments, the axial extensibility is from about 2 mm to about 12 mm.

Extension of tubular wall **74** has allowed ring-shaped component **78** to tilt in a manner that equalizes the unequal pull of chordae **46** and **48** so that coaptation surface **42** is maintained.

In embodiments, (seen Figure 18C) wall **74** is substantially non-stretchable and ring-shaped component **78** extends into lumen **88** by anywhere from 5 to 15 millimeters.

In embodiments (as discussed with reference to Figure 15), the proximal end of the tubular wall is trimmable, that is, can be shortened by a desired extent without adversely affecting the functioning of the tubular implant. In embodiments, prior to attachment of the proximal end of the tubular wall to the vicinity of the cardiac annulus, the proximal portion of the tubular wall is trimmed so that the height of leaflet coaptation surface **42** is set to between 10 and 15 millimeters, ensuring that leaflets **38** and **40** will properly coapt and that regurgitation through leaflets **38** and **40** will not recur, even in the face of post-operative remodeling of ventricular wall **82** (Figure 16) and the pull of papillary muscles **44**.

In embodiments, the tubular wall of an implant is secured to the vicinity of the cardiac valve annulus at a location along the wall to provide a desired degree of leaflet coaptation, and subsequently excess tubular wall that extends into the atrium is trimmed.

In exemplary embodiments, tubular implant **72** is provided in various sizes and shapes that depend, *inter alia*, on the diameter and/or shape of mitral valve annulus **34** (Figure 16) and/or the valve periphery edge **70** and whether there is a necessity to alter the shape of mitral valve **26** and/or leaflets **38** and **40**.

As a non-limiting example, the surgeon may choose a tubular implant having a diameter of proximal end **76** of 28 millimeters. In a tubular implant **72** having a tubular wall **74** that is substantially parallel to a longitudinal axis passing through lumen **88**, ring **78** will have an effective orifice area of 480 millimeters^2.

In some instances, the surgeon opts to reduce the native diameter of valve periphery edge **70** in order to increase coaptation of leaflets **38** and **40**. In some embodiments, tubular wall **74** is sloped along its entire outer surface, thereby reducing the cross section of lumen **88** of the tubular implant at ring-shaped component **78**.

As a non-limiting example, the surgeon may choose a tubular implant having a tubular wall diameter of 28 millimeters at proximal end **76** while lumen **88** of the tubular implant, as measured at ring-shaped component **78**, has a smaller diameter, thereby reducing effective orifice area to 466 millimeters^2, as seen in Figure 18A. Upon attachment of mitral valve **26**, the diameter of valve periphery edge **70** will be reduced, thereby increasing coaptation of leaflets **38** and **40**.

In other embodiments, as seen in Figure 18B, a side of tubular wall **90** is sloped with respect to a proximal portion **76** while opposite wall side **92** is substantially parallel to a luminal axis **94**, thereby reducing and offsetting ring-shaped component **78** and leaflets **38** and **40**.

In other embodiments (e.g., 18C), a ring-shaped component **78** projects radially inward into lumen **88**, thereby providing a lip or ledge for attachment components such as sutures **64**, so the attachment of a mitral valve **26** to ring-shaped component **78** is within lumen **88**.

Alternatively, ring-shaped component **78** comprises a flexible distal lip **96**, as seen in Figure 18D, that deflects into lumen **88** during securing, and retracts out of lumen **88** following attachment to the tubular implant.

In other embodiments, a ring-shaped component **78** includes a projection **98** that projects radially outward from tubular wall **74**, as seen in Figure 19A, to enhance the ease of placing securing components such as sutures.

In still other embodiments, a ring-shaped component **78** includes a bend **100**, as seen in Figure 19B, for example: to compensate for tenting of either leaflet **38** or leaflet **40**.

Many different configurations of a ring-shaped component **78** may be conceived by one skilled in the art upon perusal of the description herein.

There are many configurations of materials, material properties and attachment methods between a tubular wall **74** and a ring-shaped component **78** which may be conceived by one skilled in the art upon perusal of the description herein.

Described above have been ring-shaped components that are substantially uniform, that is the extent of rigidity or flexibility, was well as other properties is substantially at all locations about the ring-shaped component.

In embodiments, the ring-shaped component comprises at least two sectors, a first sector and a second sector more flexible than the first sector. In embodiments, the first sector is substantially rigid. In embodiments, the first sector is substantially flexible and the second sector is even more flexible. Such a configuration is known, for example, in the field of annuloplasty, where it is known that a sector of a ring close to an anterior leaflet **38** is preferably more flexible than a sector of a ring close to a posterior leaflet **40**. For example, in Figure 19C, ring **78** comprises two sectors: a rigid sector **102**, for example comprising a solid metal; and a more flexible sector **104**, for example comprising a metal mesh. Many combinations of material properties and configurations that are optionally used in a ring such as **78** may be conceived by one skilled in the art upon perusal of the description herein. In some embodiments, such as in Figure 19D, ring **78** is of a uniformly flexible material.

In embodiments, following full excision of mitral valve **26** from valve annulus **34**, a properly configured stapler is used to attach the valve to a ring-shaped component **78**. For example, a Proximate Prolapse and Hemorrhoids (PPH) Stapler by Johnson and Johnson (not shown) may be used to staple a valve periphery edge **70** to a ring-shaped component **78**.

When ring **78** is substantially oval (Figure 20B), the stapler gently bends oval ring-shaped component **78** into a circle (Figure 20C) during stapling. Upon removal of the stapler, oval ring **78** returns to oval shape (Figure 20B). To allow oval-to-circular-to-oval transposition, such a ring-shaped component **78** optionally comprises a semi-rigid material, for example a metal mesh.

In embodiments, a cardiac valve is secured inside the lumen of a tubular wall as depicted in Figure 17B and 17D. In embodiments, the cardiac valve is secured over a distal end of the tubular implant as depicted in Figure 19A. In embodiments, the cardiac valve is secured abutting against a distal end of the tubular implant as depicted in Figures 17A, 17C, 18A, 18B, 18C, 18D, 19B, 19C, 19D, 20A and 20C

In embodiments, a cardiac valve **26** is secured to the tubular wall **74**, as depicted in Figure 21, for example with sutures **64**.

In embodiments, the proximal portion **76** of a tubular wall **74** is attached to the inner rim of the cardiac valve annulus **34**, as depicted in Figure 15 or Figure 20A. As depicted in Figures 22A and 22C, in embodiments the proximal portion of the tubular wall **74** is attached above the inner rim of the cardiac valve annulus **34** so that at least a portion of the implant is located over the inner rim of the cardiac annulus **34**, for example to a portion of an inner wall of the atrium **24** above the cardiac annulus **34** (Figure 22A) or to a ring-shaped component **106** (such as a prior art annuloplasty ring) located above the inner rim of the cardiac valve annulus **34** (Figure 22C). In embodiments, the proximal portion **76** of the tubular wall **74** of the tubular implant is attached below the inner rim of the cardiac valve annulus **34**, Figure 22B.

As discussed hereinabove, many different shapes of ring-shaped components **78** are suitable for implementing the teachings of the present invention. In addition to the above, in Figure 23A is depicted a ring-shaped component having a rectangular cross-section that describes an ellipse. In Figure 23B is depicted a ring-shaped component having a circular cross-section that describes a circle that is bent and is not flat. In Figure 23C is depicted a flat ring-shaped component having an L-shaped cross-section that describes a circle.

In embodiments, the cross-sectional area of the lumen at the proximal end is substantially equal to the cross-sectional area of the lumen at the distal end, for example, as depicted in Figures 17A-17D. In embodiments, the cross-sectional area of the lumen at the proximal end is greater than the cross-sectional area of the lumen at the distal end, as depicted in Figures 18A and 18B.

In embodiments, such as depicted in Figure 17D, secured to the luminal surface (in non-depicted embodiments, secured to the outer surface) of the tubular wall (fashioned of woven polyester) is a series of rings or hoops **110** (*e.g.*, of rigid titanium or nitinol wire) as reinforcement components, arranged coaxially with the axis tubular wall. The series of loops provide the tubular wall with radial rigidity and also allow axial bendability without kinking or folding that would otherwise obstruct the lumen of the tubular wall. In embodiments, the rings flexibly elastic so as to provide a radial flexibility, that is allow elastic radial deformation without changing circumference or allowing collapse of the lumen. In Figure 17C, reinforcement component **108** is a conical section helical spring.

Embodiments, such as depicted in Figure 17E, are provided with a conical section helical spring **108** (*e.g.*, of titanium or nitinol wire) as a reinforcement component encased within tubular wall **74**. Tubular wall **74** comprises two layers **74a** and **74b** of serous tissue (peritoneum) with the respective basement layers facing each other and sandwiching helical spring **108** therebetween, mutually secured with biological glue or other suitable adhesive. In such a way, the smooth serous layer of the serous tissue face outward in contact with blood while the tough basement layers hold helical spring **108**. Helical spring **108** is sandwiched and glued between the serous layers when slightly lengthened and released only when dry so as to bias the entire construct to a shortened configuration, substantially pleating the serous tissue. In such a way, helical spring **108** provides, in part, not only radial flexibility as described above, but also both axial extensibility and axial bendability to the tubular wall. Secured to the distal end of tubular wall **74** (by sutures) and engaging of the end of helical spring **108** is a slightly flexible and piercable ring-shaped component **78** of titanium mesh.

In most of the embodiments discussed above, the teachings of the present invention have been discussed where a mitral valve is relocated by implantation of a cylindrical tubular implant where the distal end and the proximal end of the tubular wall are substantially of similar size and shape. In embodiments, implants having tubular walls with other shapes are implanted including tubular implants that are frustoconical (distal and proximal ends are not parallel).

In embodiments where the teachings of the present invention are applied to augmenting the tissue surrounding a mitral valve it is important that subsequent to deployment of the implant, the mitral valve has a mitral lumen large enough to allow passage of sufficient blood. It is important to note that a person weighing between 60 and 100 kg has a usual cardiac output of about 4 to 6 l blood / minute and about 15 l blood / minute during maximum effort. It is known that a mitral valve lumen having a diameter of at least about 28 mm diameter is needed to transfer 15 l blood minute without undue stress. Thus, generally it is desirable that the implant be configured so that the diameter of the mitral valve lumen subsequent to implantation be at least about 28 mm in diameter. For example, in embodiments the edge of the implant to which the valve edge is secured is at least about 28 mm in diameter.

In the embodiments described above, the cardiac (e.g., mitral) valve is first detached from the respective annulus, and then secured to an edge of an implant of the present invention. In embodiments, a cardiac valve is first secured to an edge of an implant and then detached from the respective annulus.

In the embodiments described above, the cardiac (e.g., mitral) valve is detached from the respective annulus substantially intact as a complete functioning unit where the leaflets of the valve are mutually associated through commissures of the valve as depicted in Figure 11. Such embodiments are exceptionally simple to implement. In embodiments, the cardiac valve is detached not intact, for example, each leaflet separately. In such embodiments, for example, each leaflet is secured to the edge of the implant separately. Such embodiments allow repair or replacement of a damaged leaflet.

When implementing the teachings of the present inventions, the membranes of an annuloplasty apparatus or the walls of a cardiac valve augmenting implants, whether as sheets with holes, annuli, tubes or other, may comprise any suitable material or combination of materials, whether synthetic or biological. Preferably at least one material from which an implant is fashioned is impermeable to prevent the flow of blood through the implant once implanted. Typically, the thickness of the tubular wall is at least 0.05 millimeter at least about 0.1 millimeter and even at least about 0.2 millimeter. Typically, the thickness of the tubular wall is no more than about 2 millimeter, no more than about 1 millimeter and even no more than about 0.5 millimeter.

Typical synthetic materials suitable for fashioning a membrane of an annuloplasty apparatus or a wall of a cardiac valve augmenting implant of the present invention include but are not limited to fluorinated hydrocarbons such as polytetrafluoroethylene, urethane, elastomer, polyamide, polyethylene, polyester (e.g., Dacron®), silicon rubber and titanium mesh.

Sources of typical biological materials suitable for fashioning a membrane of an annuloplasty apparatus of a wall of a cardiac valve augmenting implant of the present invention include but are not limited to materials from a human source, an equine source, a porcine source or a bovine source. In embodiments, biological materials used for fashioning an implant of the present invention include but are not limited to autologous tissue, homologous tissue and heterologous tissue. Specific examples include venous tissue, arterial tissue, serous tissue, dura mater, pleura, peritoneum, pericardium and aortic leaflet. In embodiments, the tissue is toughened, for example by crosslinking in the usual way.

The present invention also provides for the manufacture of implants such as annuloplasty apparatus and cardiac valve augmenting implants such as described herein. Thus according to the teachings of the present invention there is also provided for the use of a sheet of an implantable material (as described hereinabove) for the manufacture of a cardiac valve augmenting implant, the implant including a wall comprising the material, the wall delimited by two edges each having a shape of a closed curve and defining a lumen.

In embodiments, the wall is substantially annular. In embodiments, a first edge is a periphery of the wall and a second edge is a periphery of the hole of the wall.

In embodiments, the wall is substantially tubular. In embodiments, a first edge is a periphery of a proximal end of the wall and a second edge is a periphery of a distal end of the wall.

In embodiments, the second edge is configured to be secured to an excised cardiac valve and a first edge is configured to be secured to a mitral valve seat, e.g., in proximity of a mitral valve annulus.

According to the teachings of the present invention there is also provided a method of producing a cardiac implant, comprising: a) providing a sheet of implantable material (as described hereinabove); and b) fashioning the material in the shape of a wall of the cardiac implant, the wall delimited by two edges each having a shape of a closed curve and defining a lumen.

In embodiments, the wall is substantially annular. In embodiments, a first edge is a periphery of the wall and a second edge is a periphery of the hole of the wall.

In embodiments, the wall is substantially tubular. In embodiments, a first edge is a periphery of a proximal end of the wall and a second edge is a periphery of a distal end of the wall.

In embodiments, the second edge is configured to be secured to an excised cardiac valve and a first edge is configured to be secured to a mitral valve seat.

While the description of methods and apparatus of the invention have been directed to restoring proper function to mitral valves, it will be clear to those familiar with the art, that the methods and apparatus are also applicable to restoring proper function to a tricuspid valve (not shown), in some cases with minor modification which one skilled in the art is able to formulate upon perusal of the specification.

Further, while the description of methods and apparatus were directed to improperly functioning mitral valves with dysfunction of papillary muscle wall, it will be clear to those familiar with the art, that the methods and apparatus are also applicable to any disorder causing improper closure of mitral valve including, *inter alia*: mitral valve prolapse; rheumatic heart disease; mitral annular calcification; cardiac tumors; congenital defects; endocarditis; atherosclerosis; hypertension; left ventricular enlargement; connective tissue disorders such as Marfan's syndrome; and untreated syphilis.

The various embodiments of the present invention, especially the methods of augmenting tissue, have been described herein primarily with reference to treatment of living human subjects. It is understood, however, that embodiments of the present invention are performed for the veterinary treatment of a non-human mammal, especially horses, cats, dogs, cows and pigs.

The various embodiments of the present invention, especially the methods of augmenting tissue, have been described herein primarily with reference to treatment of living subjects. It is understood that application of the present invention for training and educational purposes (as opposed to treating a condition) falls within the scope of the claims, whether on a living non-human subject or on a dead subject, whether on a human cadaver or on a non-human body, whether on an isolated cardiac valve, or on a valve in a heart isolated (at least partially) from a body, or on a body.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims. All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention.

WHAT IS CLAIMED IS:

1. An annuloplasty apparatus comprising:

a) a substantially complete ring defining a ring lumen having:

an inner portion configured to be operatively associated with a lumen of an in vivo cardiac valve;

an outer portion configured to be operatively associated with a periphery of said lumen of said cardiac valve; and

b) a membrane functionally associated with said ring, said membrane at least partially covering said ring lumen around the entire periphery of said ring lumen in a plane substantially parallel to a plane passing radially through said ring.

2. The apparatus according to claim 1, wherein said membrane is provided with a membrane opening through said ring lumen.

3. The apparatus according to claim 2, wherein said membrane opening is located substantially in the center of said ring lumen.

4. The apparatus according to claim 2, wherein said membrane opening is located off-center of said ring lumen.

5. The apparatus according to claim 2, wherein said membrane opening has an area of at least about 10% of the area of said ring lumen.

6. The apparatus according to claim 1, wherein at least a portion of said ring includes a portion being substantially covered by said membrane.

7. The apparatus according to claim 1, wherein said membrane is at least about 0.2 millimeters thick.

8. The apparatus according to claim 1, wherein said membrane is no more than about 0.5 millimeters thick.

9. The apparatus according to claim 1, wherein said ring has height of no more than about 5.0 millimeters.

10. The apparatus according to claim 1, wherein said ring has height of at least about 1.0 millimeter.

11. A method for performing an annuloplasty procedure in a heart, comprising:

a) providing a substantially continuous ring defining a ring lumen and functionally associating a membrane to said ring so that said membrane covers a portion of said ring lumen;

b) detaching at least a portion of a first cardiac valve leaflet from a periphery of a lumen of an in vivo cardiac valve, said valve including at least two cardiac valve leaflets extending from said periphery of said cardiac valve;

c) securing said continuous ring to said periphery of said cardiac valve lumen; and

d) attaching a detached edge of said cardiac valve leaflet to said membrane thereby restoring valve function by increasing the dimensions of said leaflet.

12. The method according to claim 11, further comprising:

e) modifying said membrane to decrease said covered portion of said ring lumen; and

13. The method according to claim 11, said membrane at least partially covering said ring lumen around the entire periphery of said ring lumen in a plane substantially parallel to a plane passing radially through said ring.

14. The method according to claim 11, wherein said leaflet is detached from said periphery substantially entirely.

15. The method according to claim 11, wherein said attaching of said detached edge of said leaflet is proximate to a luminal edge of said membrane.

16. The method according to claim 11, wherein prior to said attaching of said detached edge of said first leaflet, said membrane is cut so as to expose a second of said cardiac leaflets.

17. The method according to claim 11, wherein said membrane is shaped to cover said second cardiac leaflet.

18. A method of augmenting the tissue surrounding a cardiac valve, comprising:

a) excising leaflets of a cardiac valve with an incision having a shape of a closed curve so as to define a valve seat edge of said incision and a valve periphery edge of said incision;

b) providing an implant including a wall, the wall delimited by two edges each in the shape of a closed curve and defining a lumen as a cardiac valve augmenting implant;

c) securing a first portion of said implant to said valve seat edge at a plurality of locations; and

d) securing a second portion of said implant to said valve periphery edge at a plurality of locations,

thereby augmenting a surface area of tissue surrounding said cardiac valve with said implant.

19. The method of claim 18, wherein said implant is substantially annular having an outer periphery and a hole defining said lumen, wherein said first portion is nearer to said outer periphery than to a periphery of said hole and wherein said second portion is nearer to said periphery of said hole than to said outer periphery.

20. The method of claim 18, wherein said implant is substantially tubular having a distal end and a proximal end, wherein said first portion is nearer to said proximal end than to said distal end and wherein said second portion is nearer to said distal end than to said proximal end.

21. The method of claim 18, wherein said securing said first portion of said implant to said valve seat edge around a plurality of locations of said proximal overlap region is performed substantially simultaneously for said plurality of locations.

22. The method of claim 18, wherein:
said excising;
said placing said implant to define said proximal overlap zone; and
said securing said first portion of said implant to said valve seat edge
are substantially simultaneous.

23. The method of claim 18, wherein said relocation of said cardiac valve improves coaptation of leaflets of said cardiac valve.

24. A cardiac valve augmenting implant comprising:
a) a substantially tubular wall defining a lumen, comprising a proximal portion with a proximal end, a distal portion with a distal end, an outer surface and a luminal surface; and
b) associated with said distal end, a ring-shaped component thicker in the radial direction than said wall
configured for implantation in a mammalian heart.

25. The implant of claim 24, wherein said proximal portion of said tubular wall is configured for attachment to a cardiac valve annulus.

26. The implant of claim 24, wherein said ring-shaped component is configured for attachment of the periphery of a cardiac valve.

27. The implant according to claim 24, wherein said proximal portion of said tubular wall is radially expandable.

28. The implant according to claim 24, wherein said tubular wall is axially bendable.

29. The implant according to claim 24, wherein said tubular wall is axially extensible.

30. The implant according to claim 24, wherein said tubular wall is substantially radially non-expandable.

31. The implant according to claim 24, wherein said tubular wall is substantially radially non-collapsible.

32. The implant of claim 24, further comprising at least one reinforcement component functionally associated with said tubular wall.

33. A method for relocating a cardiac valve distally to a cardiac valve annulus, the method comprising:

a) providing a substantially tubular implant comprising a substantially tubular wall defining a lumen, said apparatus having a proximal portion and a distal portion;

b) detaching a cardiac valve from a cardiac valve annulus located between an atrium and a ventricle of a subject;

c) securing said cardiac valve to said distal portion of said tubular implant; and

d) securing said proximal portion of said tubular implant in the proximity of said cardiac valve annulus so that said valve is distal to said valve annulus,

thereby providing fluid communication between said atrium and said ventricle through said lumen and through said cardiac valve.

34. The method according to claim 33, wherein said cardiac valve is detached substantially intact.

35. The use of a sheet of implantable material for the manufacture of a cardiac valve augmenting implant, said implant including a wall comprising said material, said wall delimited by two edges each having a shape of a closed curve and defining a lumen.

36. The use of claim 35, wherein said wall is substantially annular.

37. The use of claim 36, wherein a first said edge is a periphery of said wall and a second said edge is a periphery of a hole of said wall.

38. The use of claim 35, wherein said wall is substantially tubular.

39. The use of claim 38, wherein a first said edge is a periphery of a proximal end of said wall and a second said edge is a periphery of a distal end of said wall.

40. The use of claim 35, wherein a second said edge is configured to be secured to an excised cardiac valve and a first said edge is configured to be secured to a mitral valve seat.

41. A method of producing a cardiac implant, comprising:

a) providing an sheet of implantable material; and

b) fashioning said material in the shape of a wall of the cardiac implant, said wall delimited by two edges each having a shape of a closed curve and defining a lumen.

42. The method of claim 41, wherein said wall is substantially annular.

43. The method of claim 42, wherein a first said edge is a periphery of said wall and a second said edge is a periphery of a hole of said wall.

44. The method of claim 41, wherein said wall is substantially tubular.

45. The method of claim 44, wherein a first said edge is a periphery of a proximal end of said wall and a second said edge is a periphery of a distal end of said wall.

46. The method of claim 41, wherein a second said edge is configured to be secured to an excised cardiac valve and a first said edge is configured to be secured to a mitral valve seat.

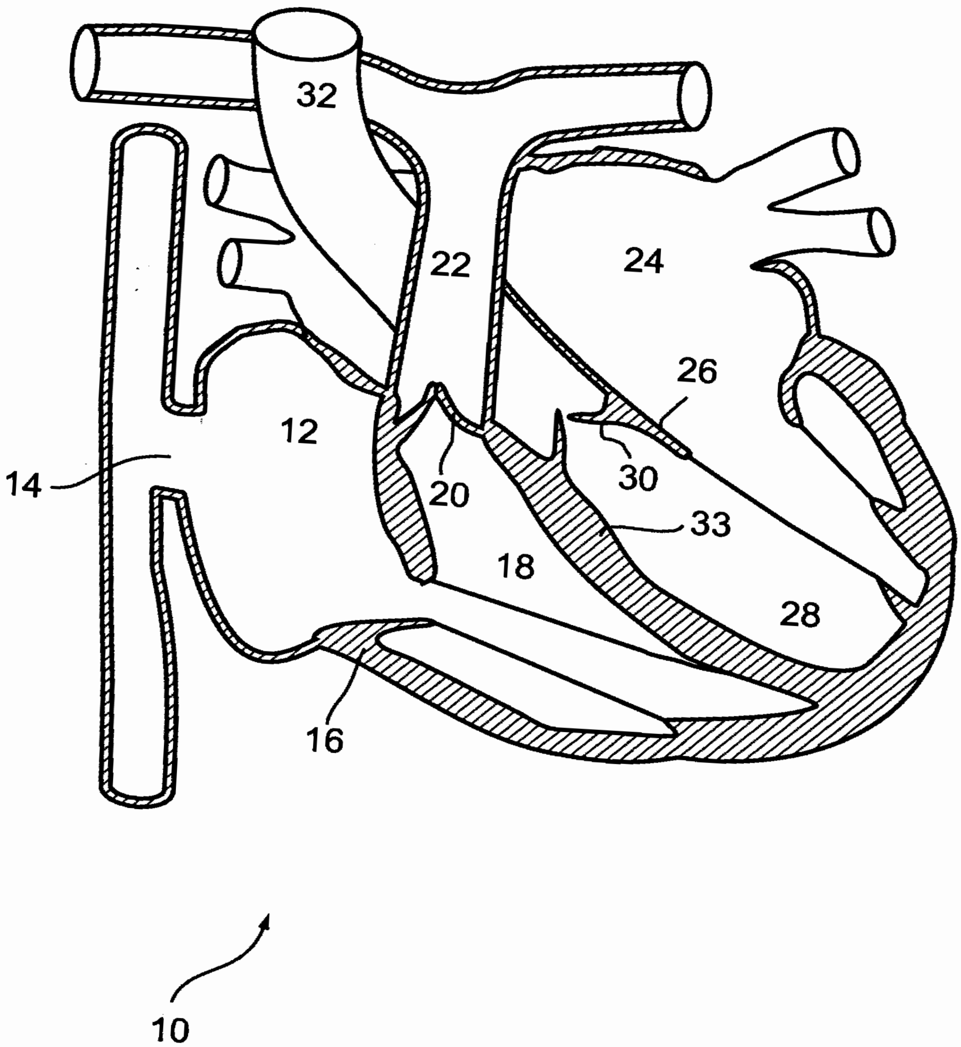

Fig. 1(Prior Art)

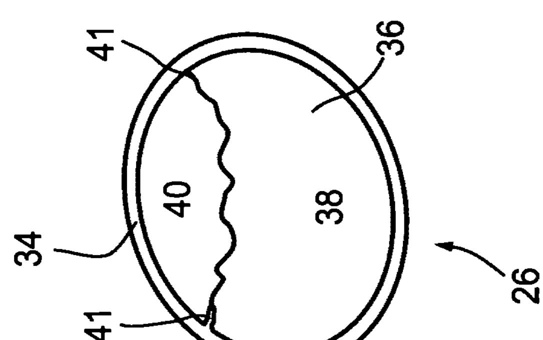

Fig. 2a (Prior Art)

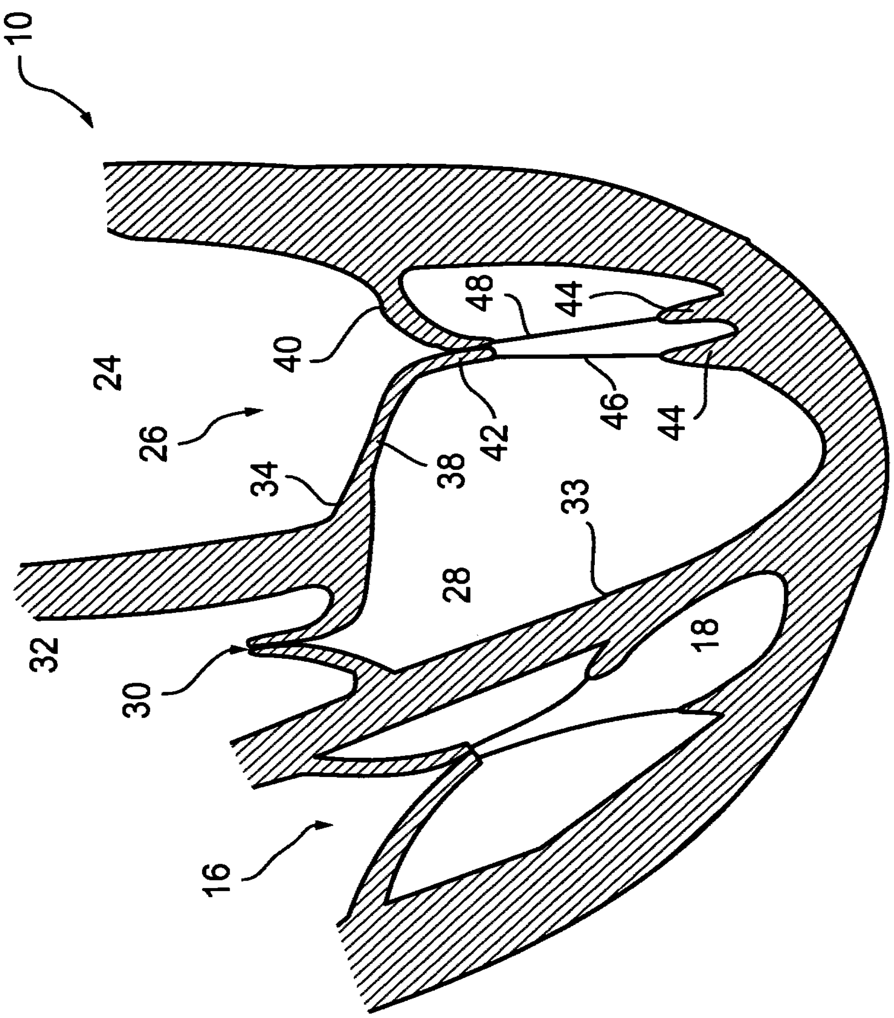

Fig. 2b (Prior Art)

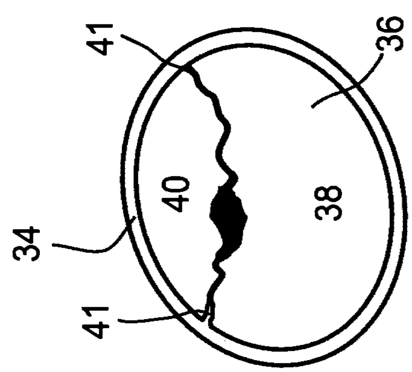

Fig. 3a (Prior Art)

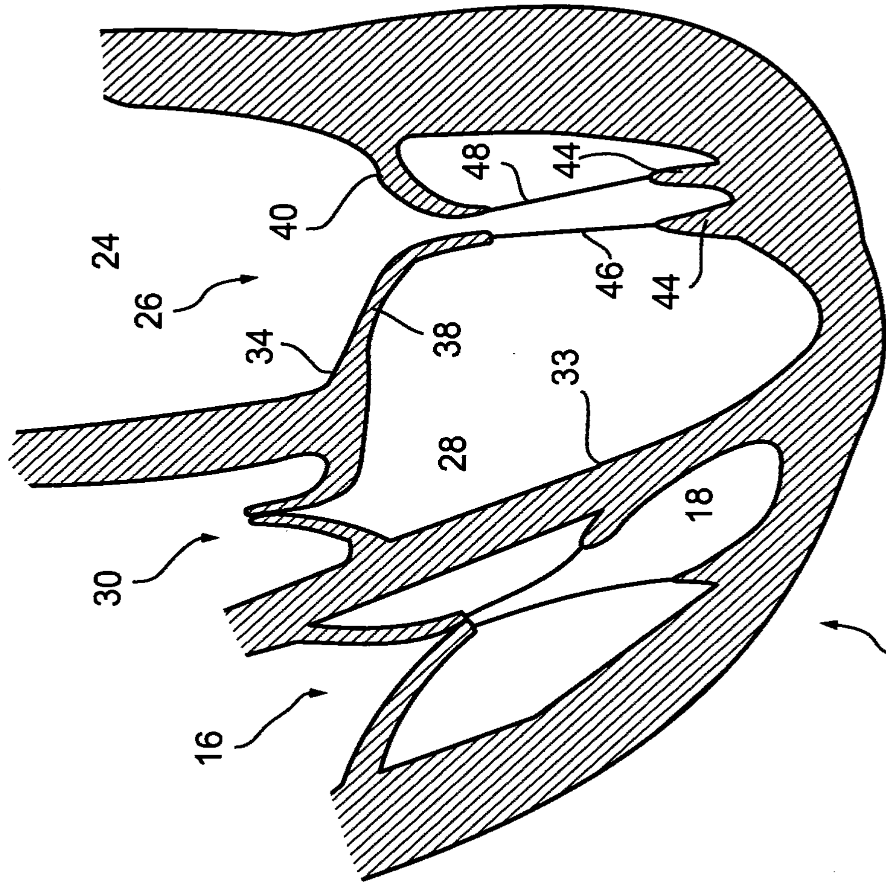

Fig. 3b (Prior Art)

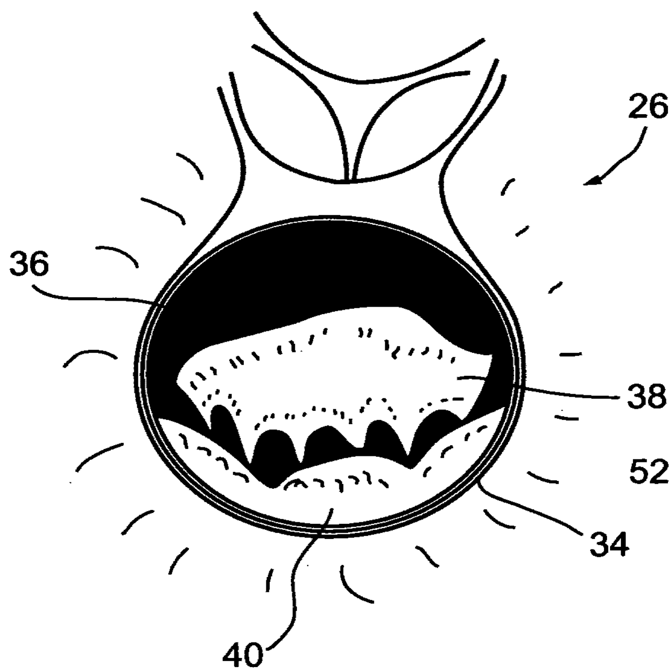

Fig. 4

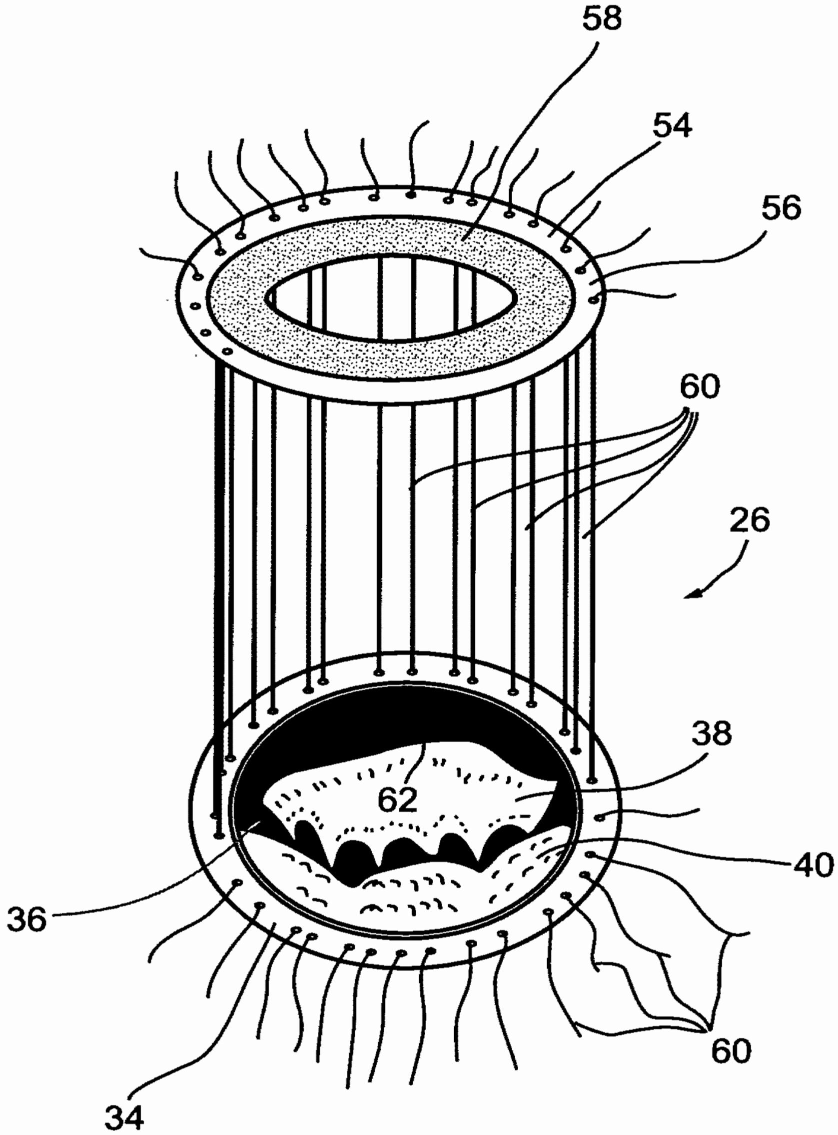

Fig. 5

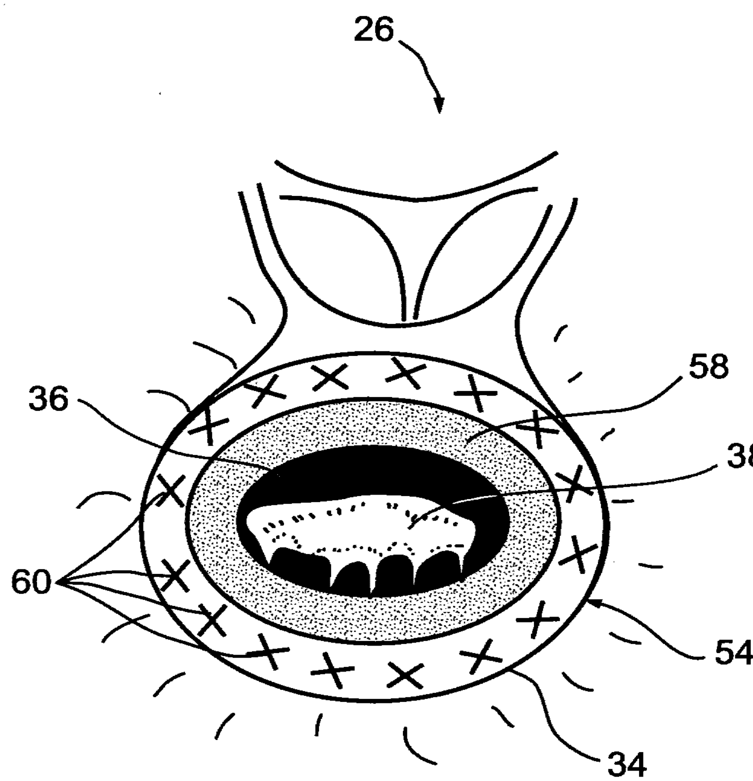

Fig. 6

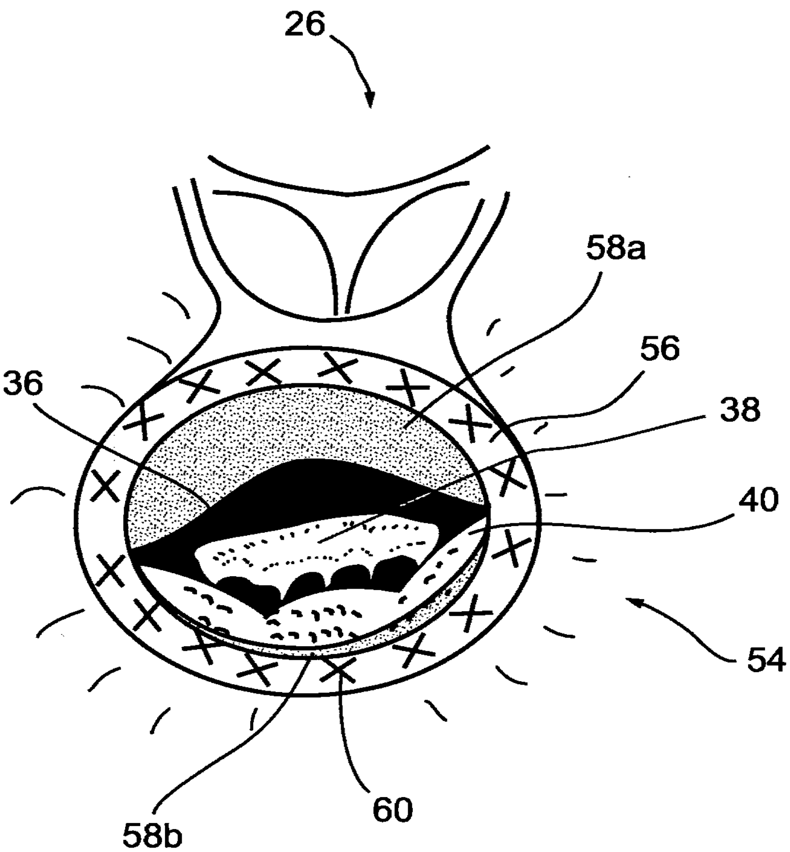

Fig. 7

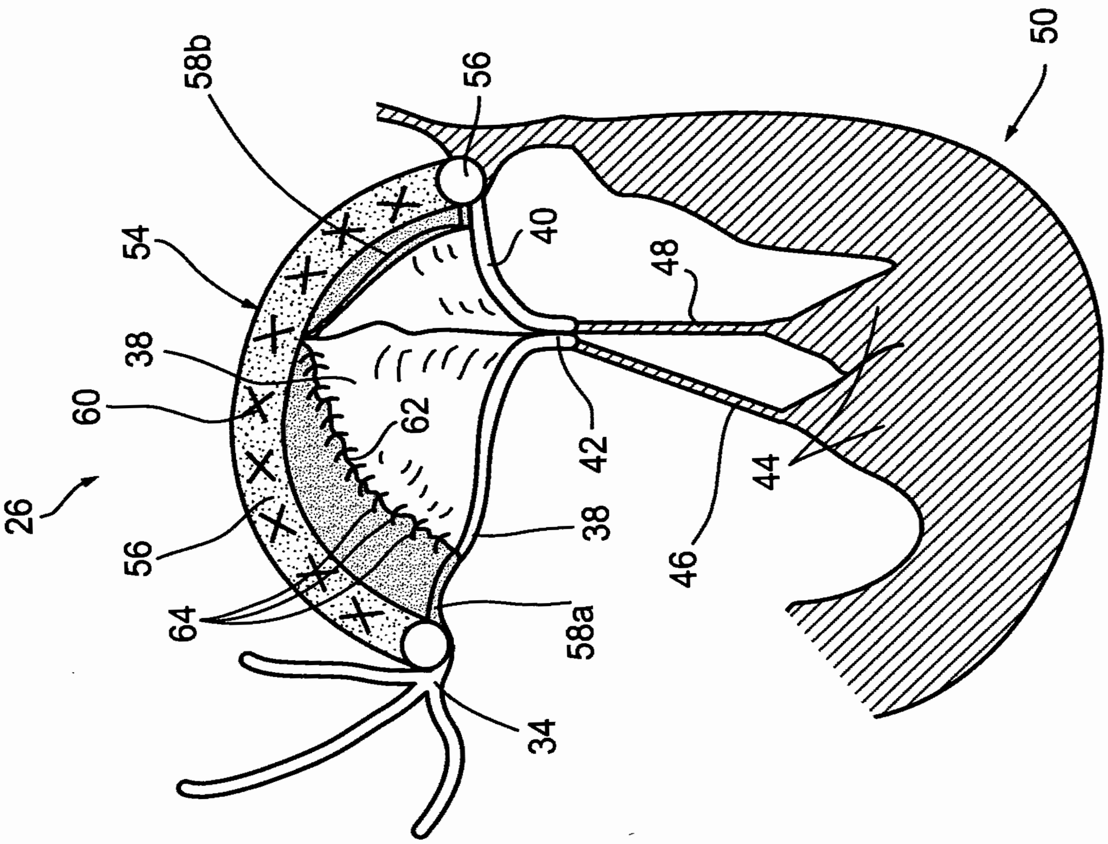

Fig. 8b

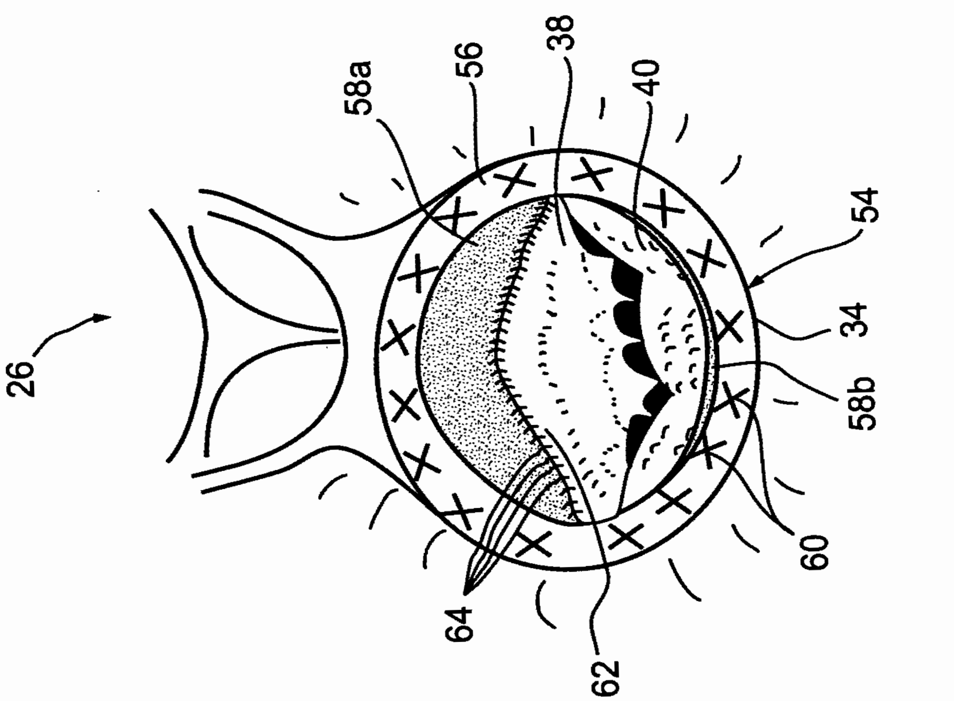

Fig. 8a

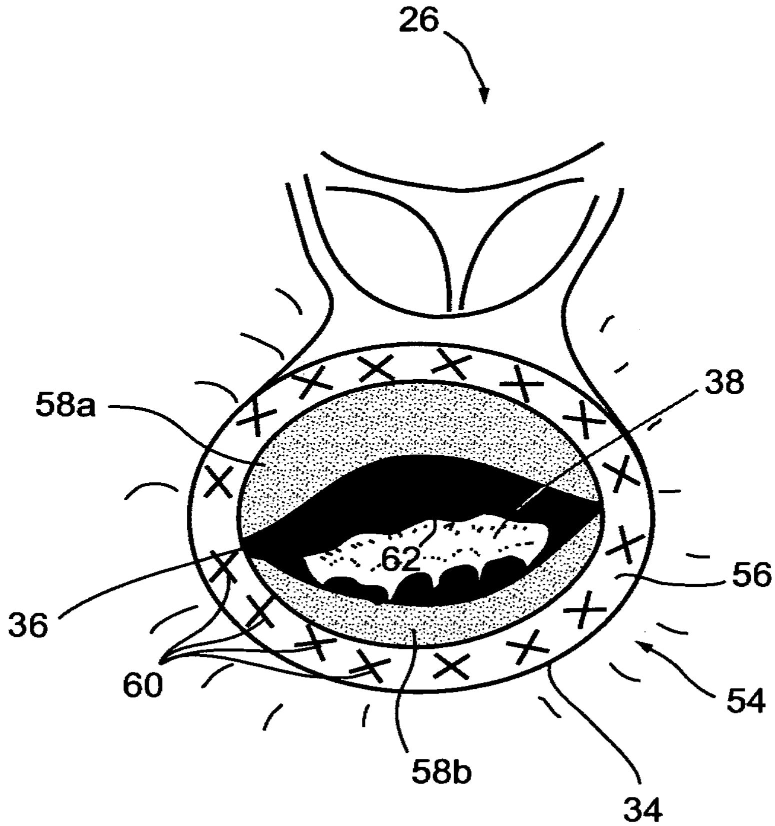

Fig. 9

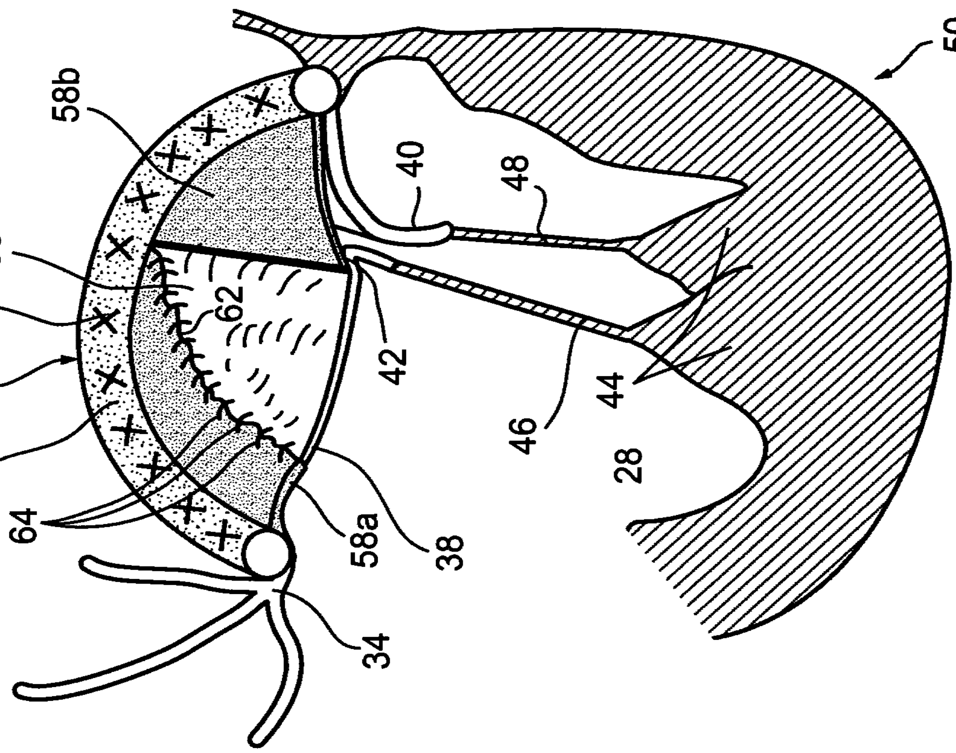

Fig. 10b

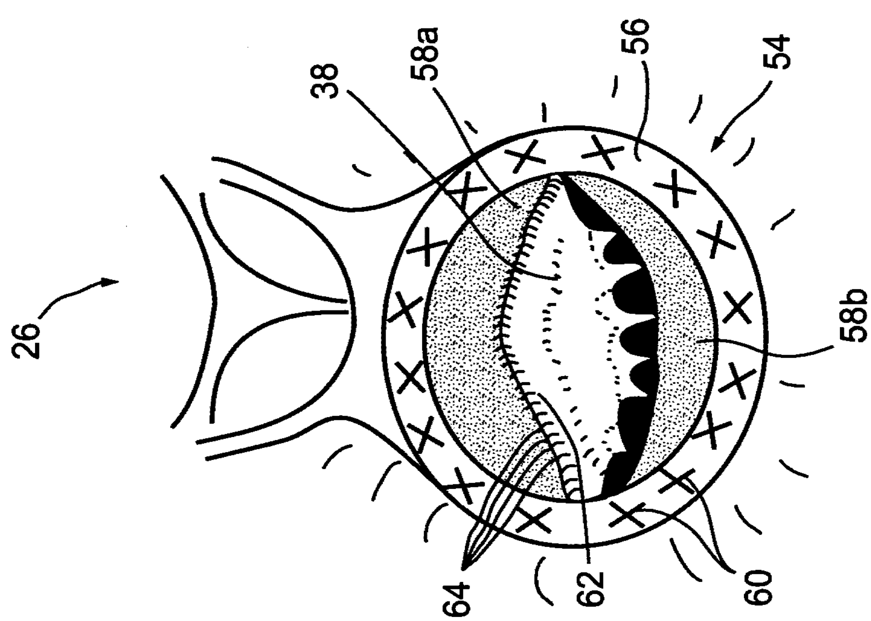

Fig. 10a

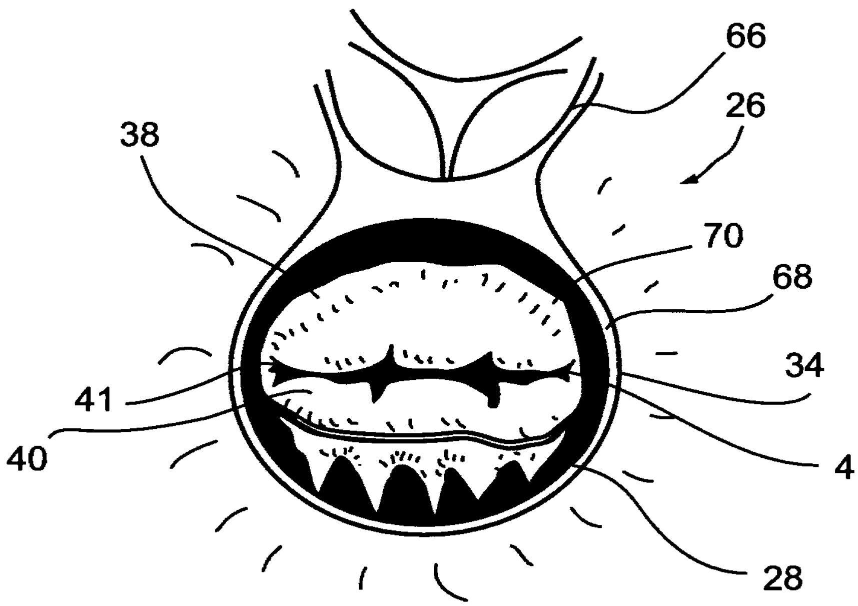

Fig. 11

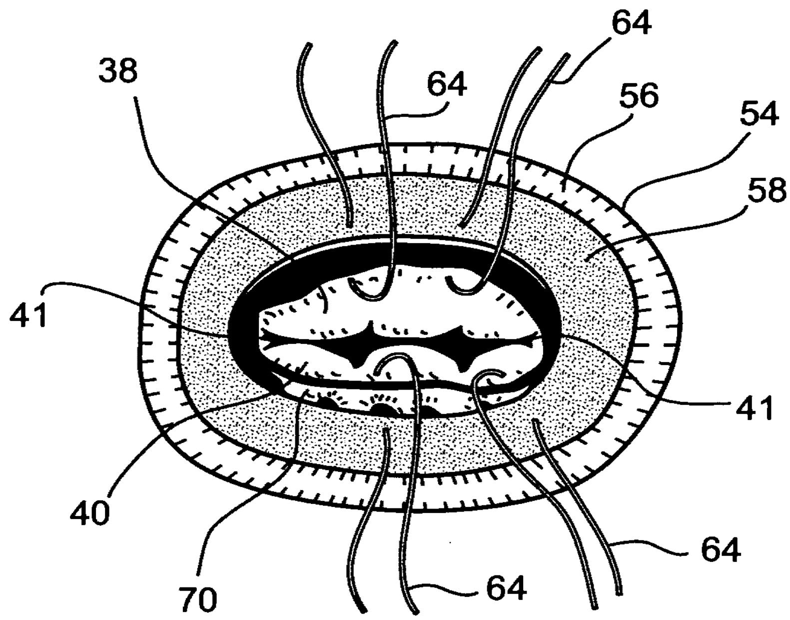

Fig. 12a

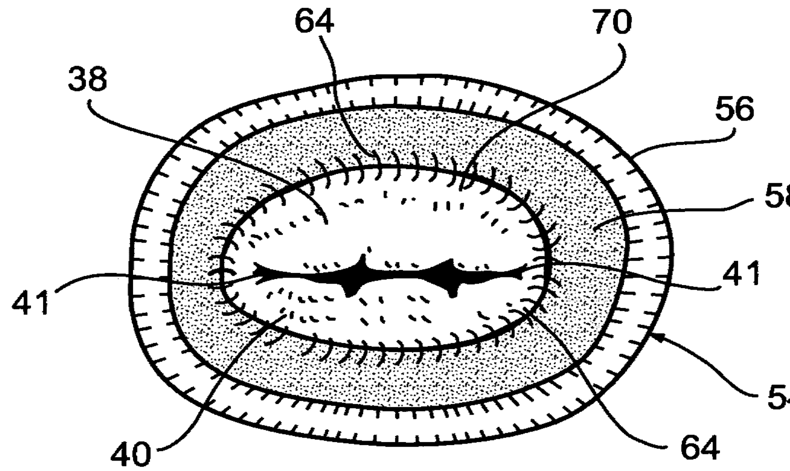

Fig. 12b

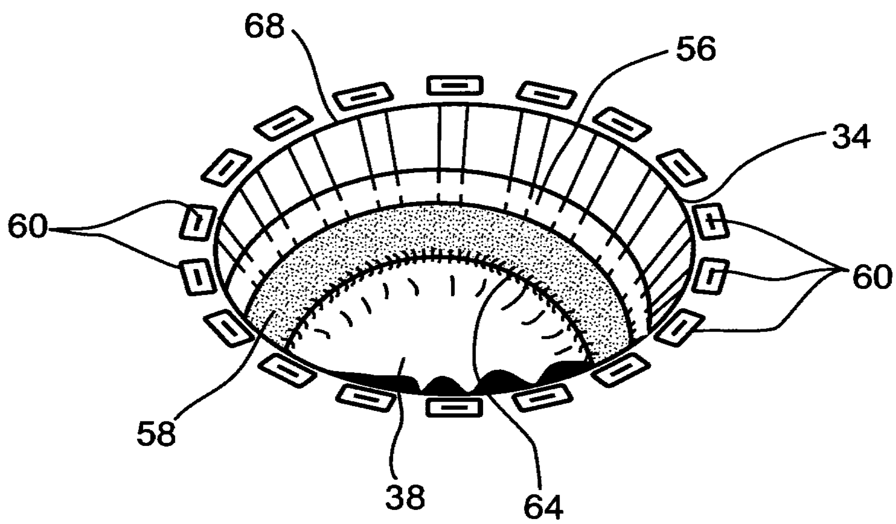

Fig. 12c

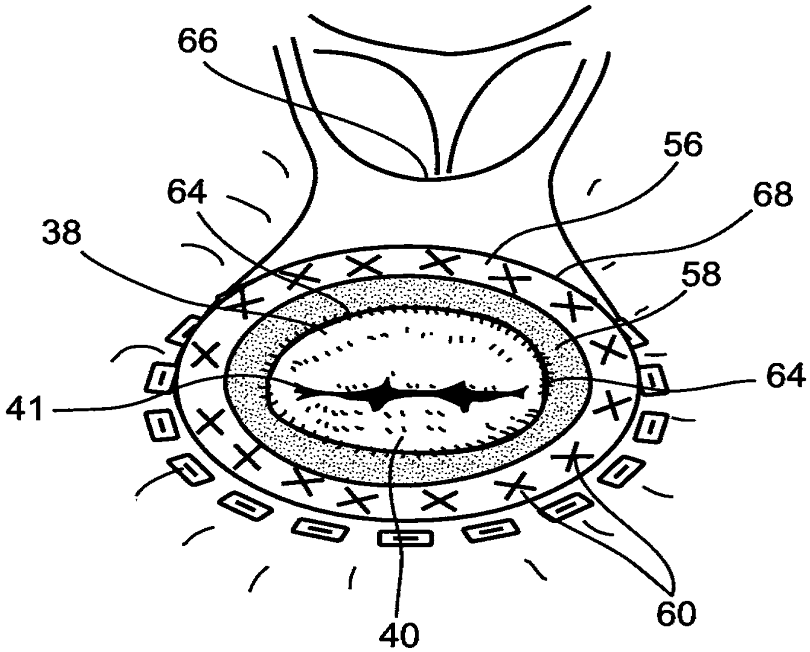

Fig. 12d

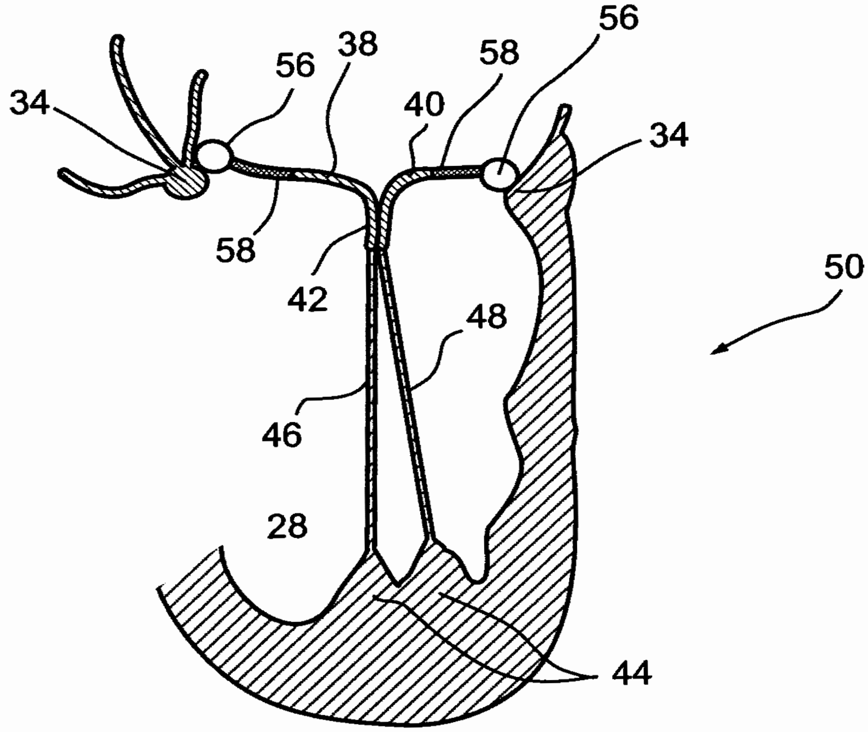

Fig. 12e

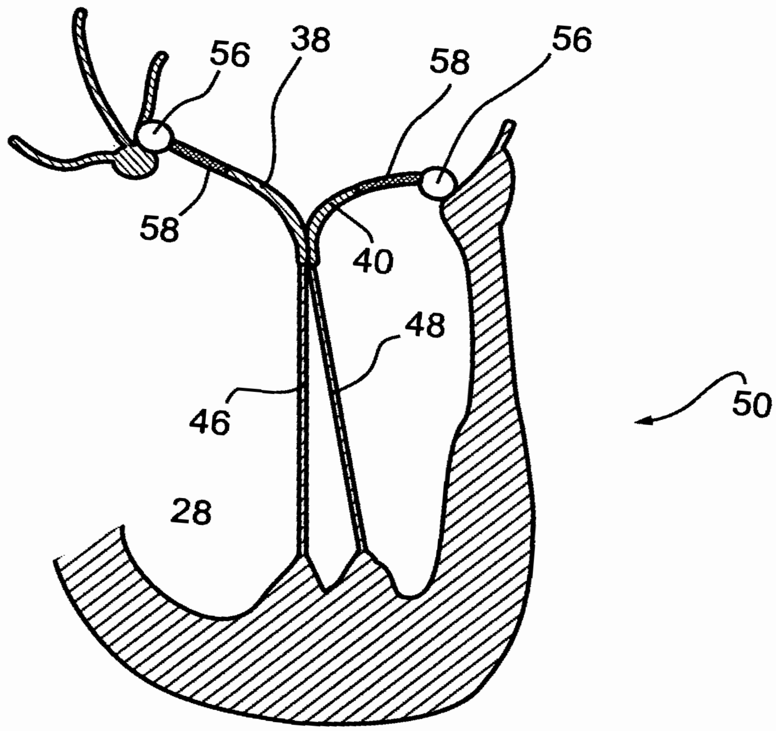

Fig. 12f

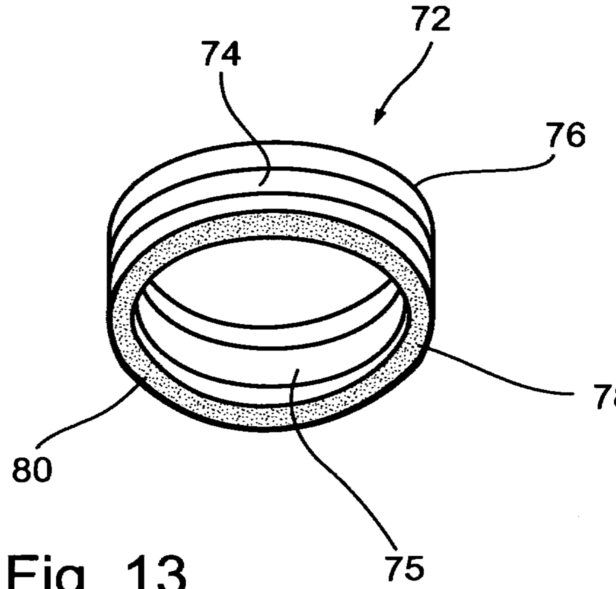

Fig. 13

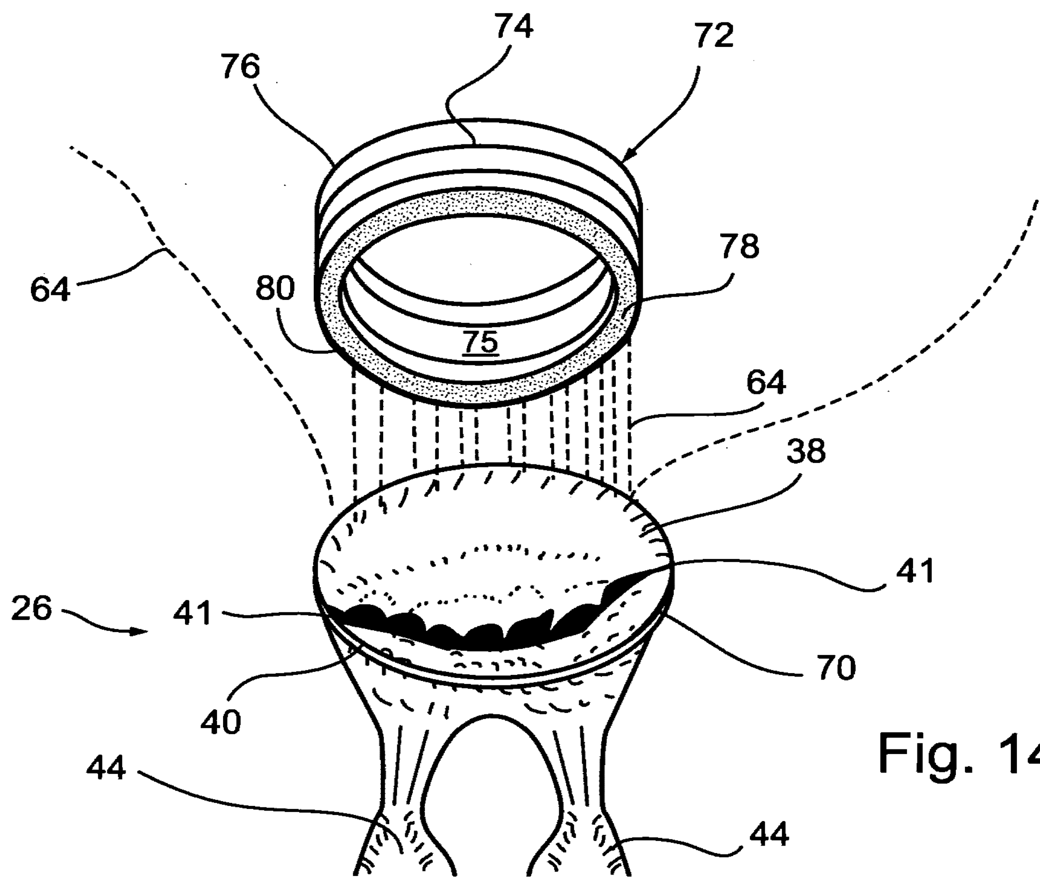

Fig. 14a

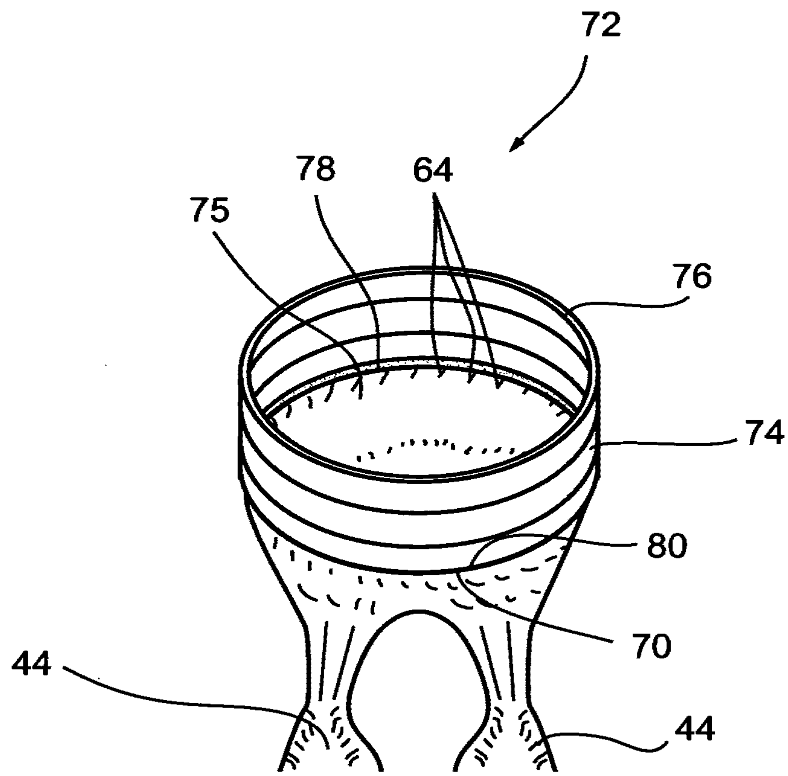

Fig. 14b

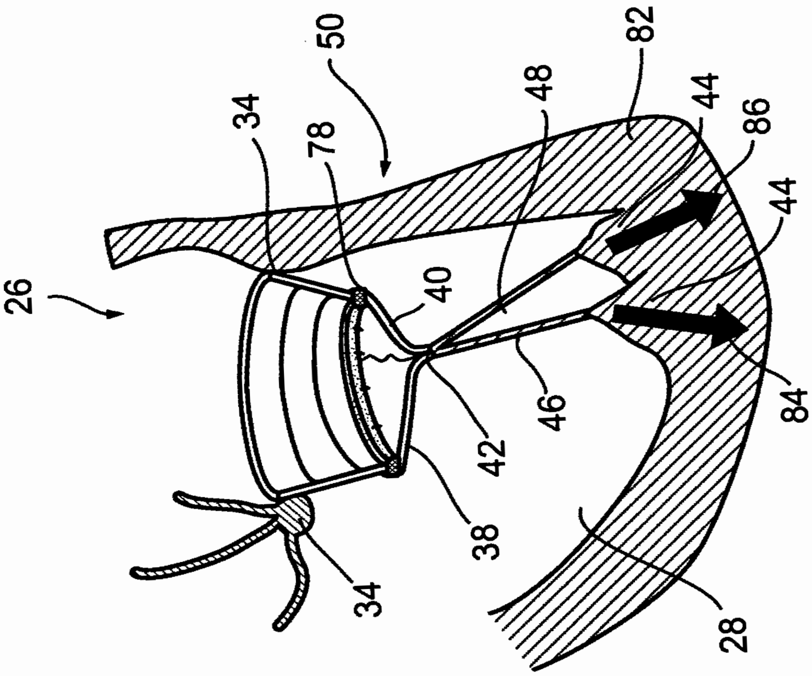

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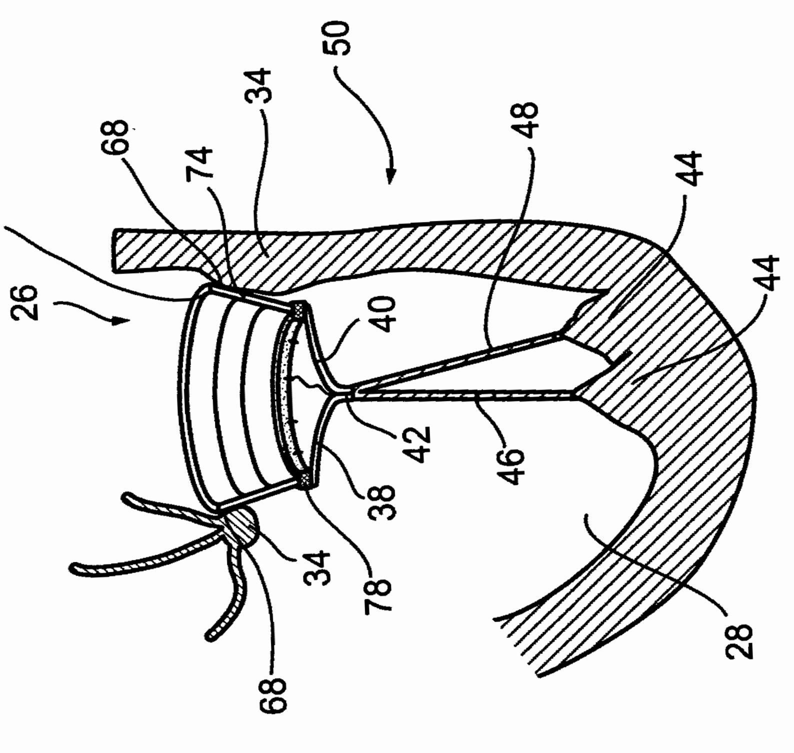
Fig. 16



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48
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34
78
68
28

Fig. 15

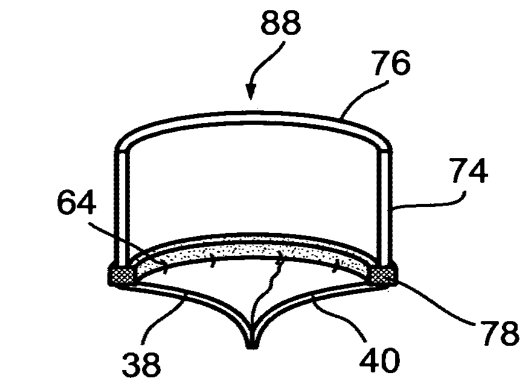

Fig. 17a

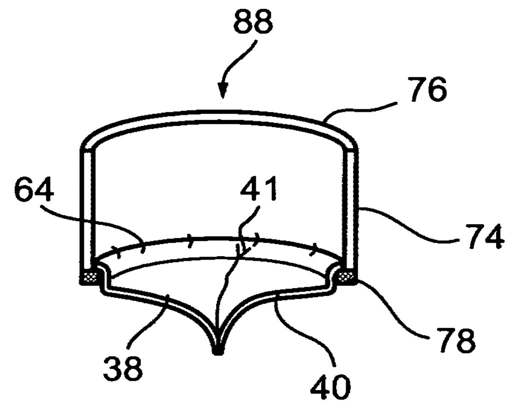

Fig. 17b

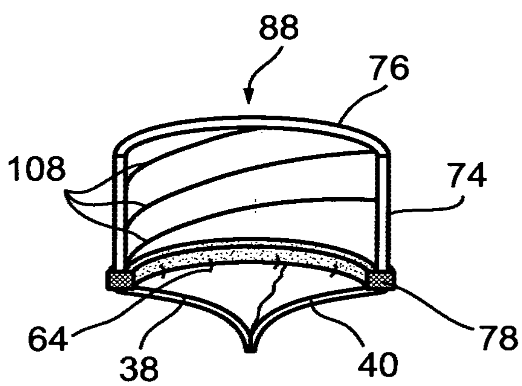

Fig. 17c

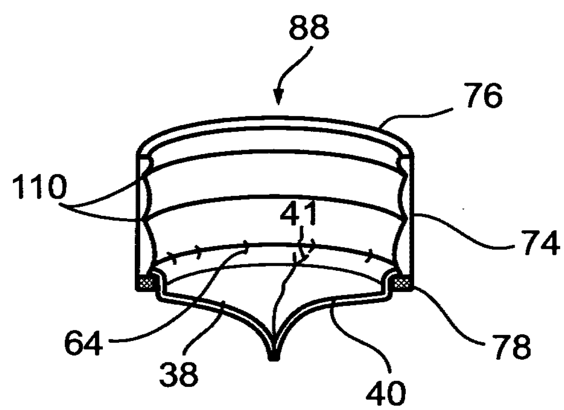

Fig. 17d

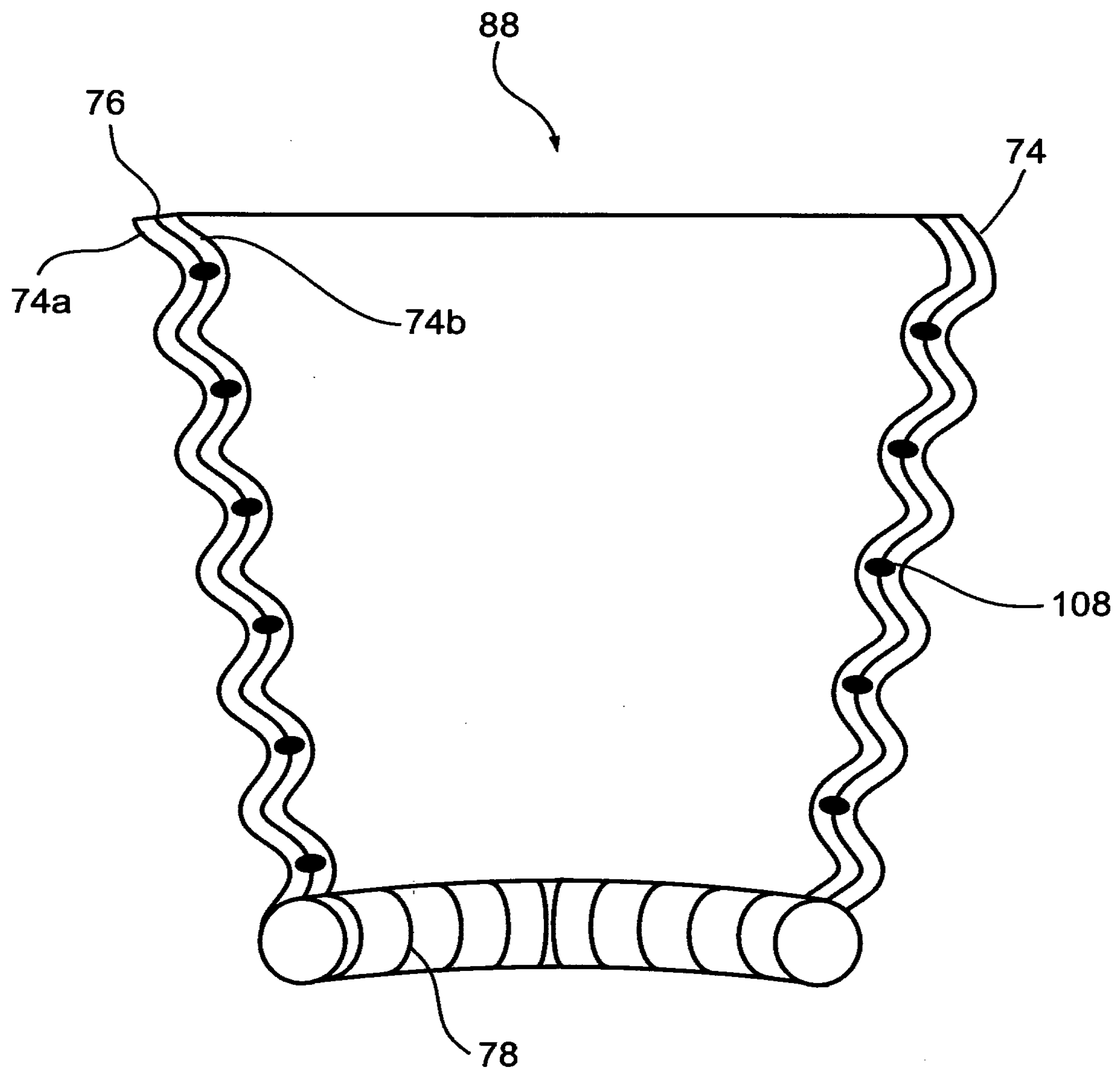

Fig. 17e

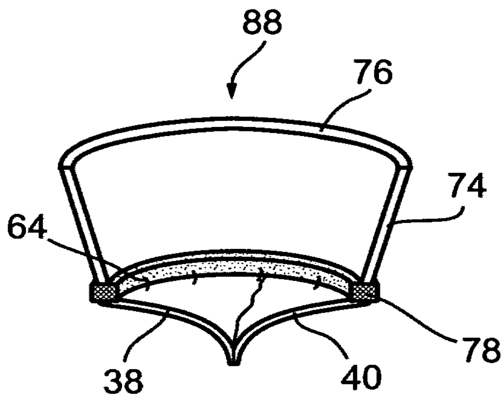

Fig. 18a

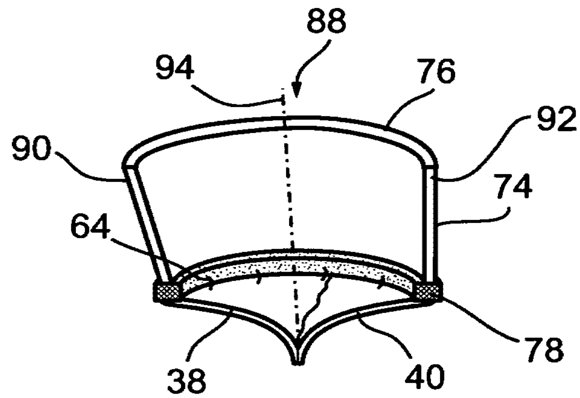

Fig. 18b

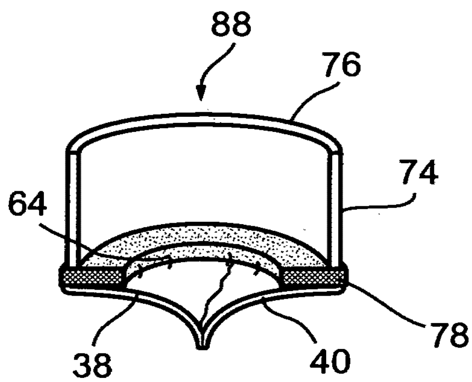

Fig. 18c

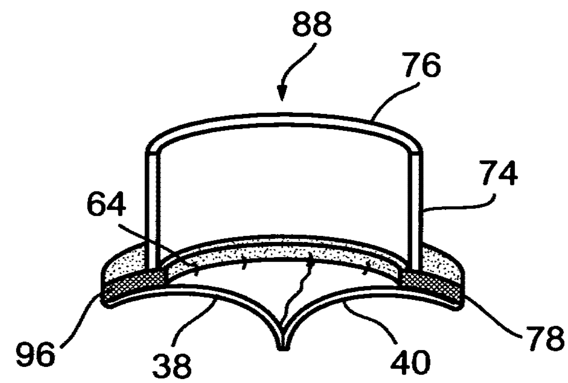

Fig. 18d

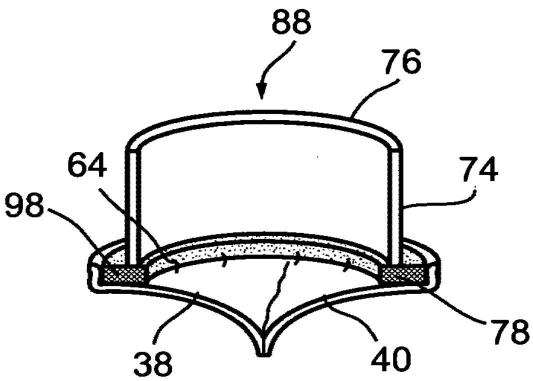

Fig. 19a

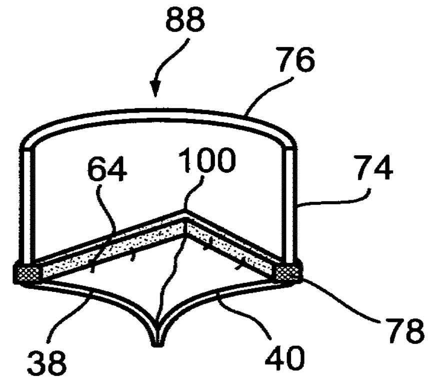

Fig. 19b

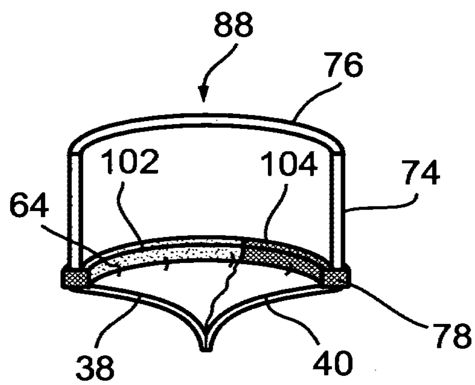

Fig. 19c

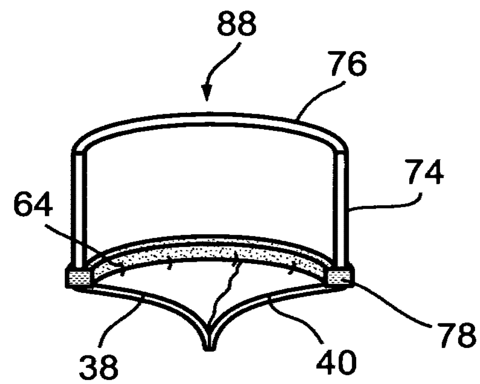

Fig. 19d

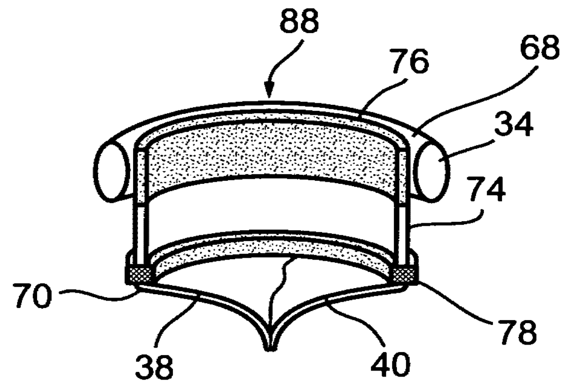

Fig. 20a

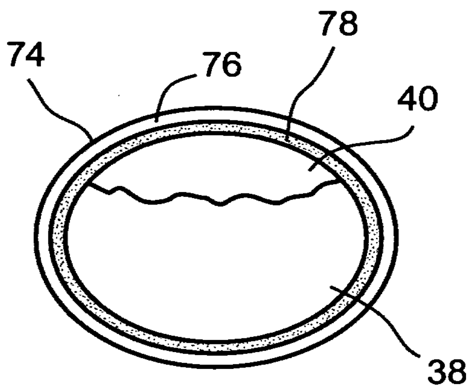

Fig. 20b

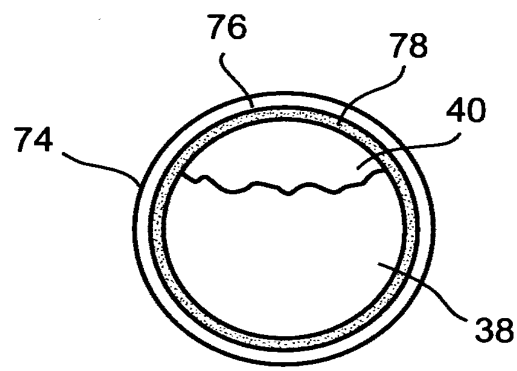

Fig. 20c

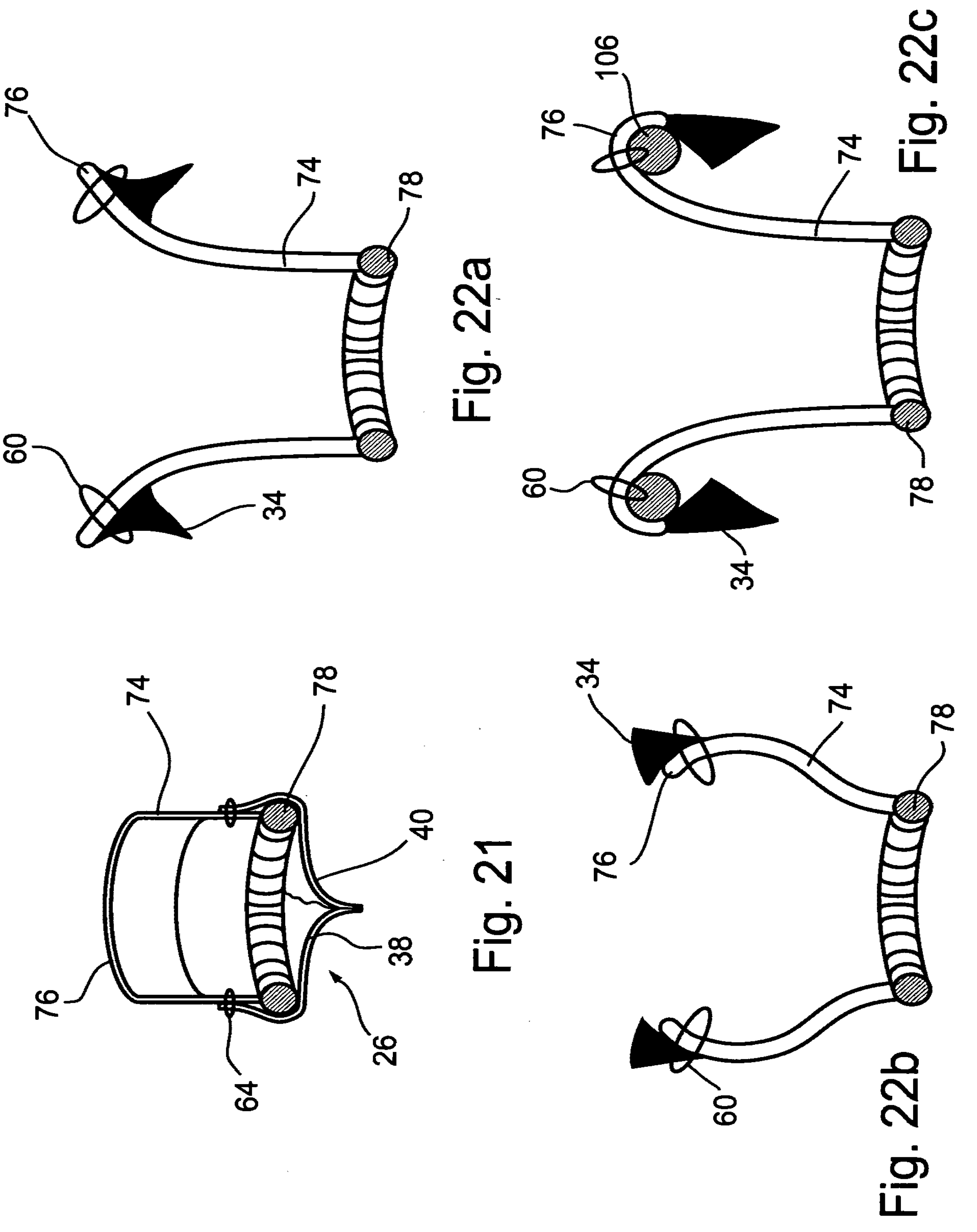

Fig. 22a

Fig. 22c

Fig. 21

Fig. 22b

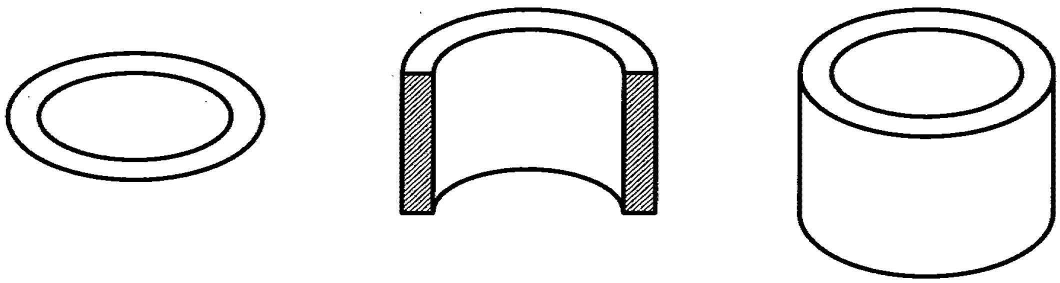

Fig. 23a

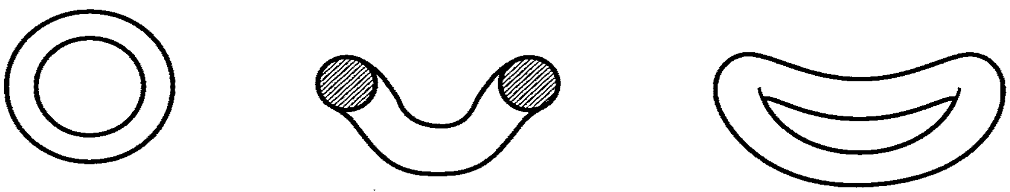

Fig. 23b

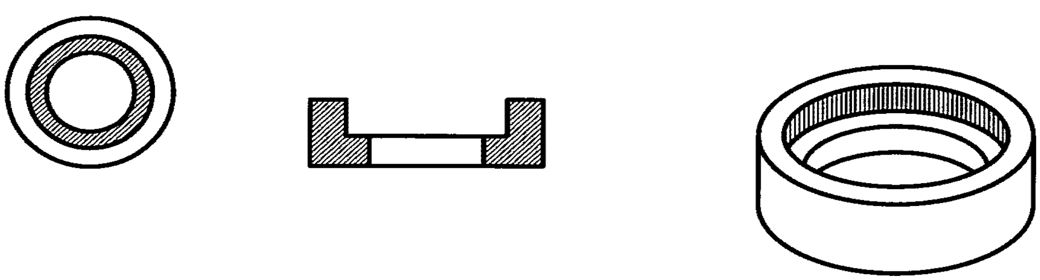

Fig. 23c

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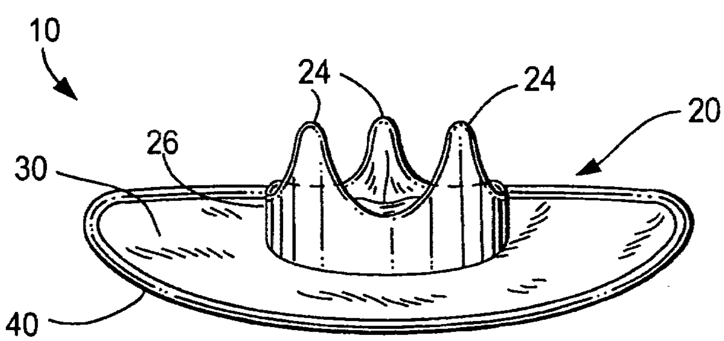

(57) Abstract: A prosthetic heart valve includes a valve core and a mounting retainer that extends radially out from the core to an outer perimeter portion. The outer perimeter portion has a different shape than a perimeter of the valve core when both perimeters are viewed along an axis that will be the axis of blood flow through the valve core when the prosthetic heart valve is in use in a patient. The outer perimeter portion is used to mount the valve to another structure such as a native valve annulus in a valve replacement procedure. The mounting retainer bridges the gap(s) between the valve core and the outer perimeter portion, and may also provide attachment sites for other native tissue structures (like chordae tendonae), which attachment sites can be at or at least closer to original (native) attachment sites for those tissue structures.

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PROSTHETIC HEART VALVE STRUCTURES AND RELATED METHODS

Background of the Invention

[0001] This invention relates to prosthetic or replacement heart valves, and to methods of using such valves. While the invention will be initially described in its use in replacing a patient's mitral heart valve, the invention also has other uses, some of which will be specifically mentioned later in this specification.

[0002] The mitral valve is located between the left atrium and the left ventricle of the heart. Various conditions can cause a person's mitral valve to become either incompetent (i.e., no longer closing properly) or stenotic (i.e., no longer opening properly). For example, inability of the mitral valve to close properly allows blood to regurgitate from the left ventricle back into the right atrium during contractions of the left ventricle. Such mitral regurgitation ("MR") increases the load on the heart and/or decreases blood flow throughout most of the body, which can have serious adverse consequences for the individual.

[0003] Among the possible treatments for mitral valve diseases are replacement of the mitral valve with an artificial, prosthetic valve. An alternative treatment is so-called "repair," which often involves implanting an "annuloplasty ring" inside the left atrium around the base of the native mitral valve. Such a ring can be beneficial by ensuring that the valve annulus cannot enlarge and/or change shape in such a way that the leaflets of the valve no longer meet one another (or coapt) in the interior of the valve when the valve is supposed to be closed.

[0004] As currently practiced, each of these treatments (i.e., replacement or repair) may have certain advantages and disadvantages (or at least suboptimal aspects). For example, valve replacement typically involves implanting a relatively large prosthetic valve having a rigid or relatively rigid circular perimeter in the native mitral valve annulus, the native shape of which tends to be D-shaped rather than circular. The result can be some reshaping of the annulus from the native D shape to a more nearly circular shape. This may not be optimal for the left ventricle or other adjacent structures of the heart. The chordae tendonae and papillary muscles that are naturally connected between the mitral valve leaflets and lower portions of the left ventricle may be preserved in some way, but at the very least they are displaced by the replacement valve. This displacement changes their alignment, which can be suboptimal for ventricular function. On the other hand, repair using an annuloplasty ring means that the valve must continue to rely on its native leaflets, and those leaflets may have deficiencies of various kinds (or may develop such deficiencies over time), which may still (or again) leave the patient with suboptimal mitral valve performance.

Summary of the Invention

[0005] In accordance with the present invention a prosthetic heart valve includes a heart valve per se ("heart valve core") and a mounting retainer structure that extends out from the heart valve core to an outer perimeter of the entire assembly. As viewed along the axis along which blood will flow through the heart valve core when the apparatus is in use in a patient, the outer perimeter of the heart valve core is smaller and has a different shape than the outer perimeter of the entire assembly. (The outer perimeter of the entire assembly may be alternatively referred to as the outer perimeter of the mounting retainer structure.) For example, the outer perimeter of the heart valve core may be circular or substantially circular, while the outer perimeter of the mounting retainer structure may be non-circular (e.g., shaped somewhat like the letter D ("D-shaped")).

[0006] The outer perimeter of the mounting retainer structure may be or may include a cuff or cuff structure for use in securing the entire assembly in the patient (e.g., by attachment to the patient's native valve apparatus). For example, the cuff structure may be or may include a sewing cuff structure that is designed for sutures to pass through and thereafter be retained by the structure. The cuff structure may also be or may include structure that can affect the shape of the native valve annulus (e.g., by helping it retain its native shape, by helping to restore it to its native shape, or by providing some deliberate therapeutic modification relative to the native shape).

[0007] Structure of the mounting retainer structure between the heart valve core and the outer perimeter of the mounting retainer structure may provide one or more sites for attachment of chordae tendonae (or tissue associated with chordae tendonae). These sites can be at or at least closer to native attachment sites, which can be an additional advantage of the invention.

[0008] Further features of the invention, its nature and various advantages, will be more apparent from the accompanying drawings and the following detailed description.

Brief Description of the Drawings

[0009] FIG. 1 is a simplified "top" or "plan" view of an illustrative embodiment of a prosthetic heart valve structure in accordance with the invention.

[0010] FIG. 2 is a simplified perspective view of an illustrative embodiment of a prosthetic heart valve structure in accordance with the invention.

[0011] FIG. 3 is similar to FIG. 2, but shows another illustrative embodiment of a prosthetic heart valve structure in accordance with the invention.

[0012] FIG. 4 is a simplified top view of a native heart valve that may be in need of replacement in accordance with the invention.

[0013] FIG. 5 is a simplified top view of a native heart valve structure at an intermediate stage in a valve replacement procedure in accordance with the invention.

[0014] FIG. 6 is a view similar to FIG. 5 showing additional possible features in accordance with the invention.

[0015] FIG. 7 is a view similar to FIG. 1 showing additional possible features in accordance with the invention.

Detailed Description

[0016] An illustrative embodiment 10 of a heart valve structure in accordance with the invention is shown in FIG. 1. Heart valve structure 10 includes a portion 20, which is a heart valve per se. To simplify the terminology used herein, the entirety of structure 10 is generally referred herein to as the heart valve or the heart valve structure, while the actual valve portion 20 of the structure is generally referred to as the heart valve core.

[0017] Heart valve core 20 can be constructed in any of many different ways, using any of many different materials and having any of many different sizes, shapes, operating characteristics, etc. In general, almost any known heart valve construction can be used for heart valve core 20. The illustrative core 20 shown in FIG. 1 is a tri-leaflet core. Such valves typically have relatively flexible leaflets 22, e.g., of tissue or polymer material. Illustrative core 20 is shown having three commissure regions 24 (see also FIGS. 2 and 3). Leaflets 22 and commissures 24 are shown surrounded by an annular core perimeter structure 26 (see again FIGS. 2 and 3). As is the case in most known prosthetic heart valves, core perimeter structure 26 is basically circular in plan view (i.e., a view like FIG. 1 that is taken along what will be the axis of blood flow through the valve when the valve is in use in a patient). Perimeter structure 26 has the structural integrity required to keep commissures 24 and the bases of leaflets 22 in proper spatial relationship to one another.

[0018] Again, the foregoing depiction and description of core 20 is only illustrative, and core 20 can instead have any of many other constructions. For example, core 20 could instead be a single-leaflet mechanical valve, a bi-leaflet mechanical valve, a ball-type mechanical valve, or any other type of mechanical valve. Similarly, the shape (e.g., the plan view perimeter shape) of core 20 can be different from the shape shown in FIGS. 1-3. Core 20 (e.g., the perimeter 26 of core 20) can be rigid or relatively rigid or can have any desired degree of flexibility. In short, a vast range of options is available for use in constructing core 20.

[0019] Valve structure 10 typically takes advantage of the fact that many modern prosthetic heart valves have extremely good flow characteristics when open. Thus valve core 20 can be considerably smaller than the native heart valve that it will be used to replace and still provide adequate blood flow when in use in a patient. This is especially true for a mitral valve, which has a relatively long period of time during which it is open and which has relatively low blood flow velocity through it; but it can also be true for other heart valves. Accordingly, valve core 20 is typically sized to be smaller than the native valve that valve 10 will be used to replace. In particular, perimeter 26 is typically sized to be smaller than the native valve annulus (or other surrounding native structure).

[0020] FIG. 1 shows valve core 20 surrounded by a mounting retainer structure 30 (see also FIGS. 2 and 3). Retainer structure 30 is secured to perimeter 26 and extends radially out from that perimeter annularly all the way around core 20 (or at least part of the way around core 20). The attachment of retainer structure 30 to perimeter 26 is preferably sufficiently fluid-tight, and structure 30 itself is also preferably impervious to blood flow, at least after healing (although it may at least initially have one or more openings or through-apertures as will be described later). Retainer structure 30 can be flat or relatively flat, or it can have any desired three-dimensional shape. It can be relatively thin, or it can have any desired thickness, which can be different in different areas of the retainer structure. Retainer structure 30 can be rigid, relatively rigid, or flexible to any desired degree, and elements of different relative rigidity or flexibility or of different constructions can be combined to produce structure 30. At a minimum, mounting structure 30 preferably has sufficient structural integrity to support core 20 at least at an approximate desired location relative to an outer perimeter portion 40 of structure 30.

[0021] The above-mentioned outer perimeter portion 40 of mounting structure 30 warrants further discussion as follows. Outer perimeter portion 40 is typically used to secure valve 10 in a patient. For example, outer perimeter portion 40 may be sutured to the native valve annulus. (At least most of the native valve leaflets will have been removed or at least displaced prior to thus implanting valve 10.) This suturing is typically done annularly all the way around portion 40 and the native valve annulus. In plan view (i.e., looking along the axis of blood flow through core 20 when the valve is in use in a patient), outer perimeter portion 40 is both larger and different in shape than the outer perimeter 26 of core 20. For example, core perimeter 26 may be circular or substantially circular, while the outer perimeter 40 of the entire valve may be D-shaped. Other material of mounting retainer structure 30 spans and at least substantially fills the space(s) or radial distance between core perimeter 26 and ultimate outer perimeter 40.

[0022] If desired, at least the outer perimeter portion 40 of valve 10 can have any of a range of special properties. For example, these properties can be or can include any of the many properties that are known for prosthetic heart valve cuffs (e.g., sewing cuffs). Alternatively or in addition outer perimeter portion can be made with any desired degree of rigidity or flexibility. Similarly, outer perimeter portion 40 can be flat or substantially flat and in a plane that is substantially perpendicular to the axis of blood flow through valve core 20 in use, or it can have any desired three-dimensional shape (e.g., the undulating or saddle shape shown in FIG. 3). If outer perimeter portion 40 is or includes a structural member (e.g., to give it at least some degree of rigidity), that structural member may extend only part way around perimeter 40. For example, the structural member may be C-shaped, rather than a complete D shape.

[0023] Some of the possibilities mentioned in the preceding paragraph are illustrated by FIGS. 2 and 3.

Thus FIG. 2, for example, illustrates a valve 10 having a flat or relatively flat mounting retainer structure 30 and associated outer perimeter portion 40. FIG. 3, on the other hand, illustrates an alternative embodiment in which outer perimeter portion 40 is rigid or substantially rigid and three-dimensional (i.e., an undulating or saddle shape as one proceeds annularly around the ring). Again, rigidity or flexibility of portion 40 can be different between different embodiments, and so can many other shape and/or constructional aspects of portion 40.

[0024] Continuing on with some of the possible features of outer perimeter portion 40, that portion may be especially adapted for suturing into a patient. Thus, as has been said, portion 40 may be constructed to include what may be called a sewing cuff that is well suited for sutures to pass through but to also retain sutures that have been passed through. Alternatively or additionally, portion 40 may include a solid core (e.g., of metal), which can be helpful to give portion 40 a particular shape (in either two dimensions or three dimensions as described earlier) and to enable portion 40 to hold that shape.

[0025] Mounting retainer structure 30 and/or outer perimeter portion 40 can be made of or can include any of many different materials. Examples include typical valve sewing cuff materials such as polyester fabric, other synthetic materials such as reinforced silicone, polyurethane, acetal resin (Delrin®), or PEEK, metals or metal alloys such as nitinol or titanium, biological materials such as animal pericardium, and combinations thereof.

[0026] It is important to note that mounting retainer structure 30 and its outer perimeter portion are not merely a structure like a sewing cuff around valve core 20. The typical sewing cuff around a valve has the same plan view perimeter shape as the perimeter of the valve itself. For example, both of these perimeters may be circles (typically concentric). In accordance with the present invention, these two perimeters have different plan view shapes (e.g., circular for the perimeter of valve core 20 and D-shaped for outer perimeter 40). This enables outer perimeter portion 40 to be made with any plan view shape that is best for attachment to a native tissue structure such as a native mitral valve annulus, while valve core 20 can have the different plan view perimeter shape that is best for the valve portion per se. Thus again, outer perimeter portion 40 preferably has approximately the same size and shape as the anticipated healthy native tissue structure (e.g., native valve annulus 120 (FIG. 4)) to which portion 40 is or will be attached. As has been said, valve core 20 can be significantly smaller and has a different perimeter shape than portion 40. Mounting retainer structure 30 bridges what would otherwise be the gap(s) or space(s) between elements 20 and 40.

[0027] If desired, valve 10 can be used to provide attachment points or locations for native tissue structures that are associated with the native valve and that are not excised as part of the valve replacement procedure. An example of this are chordae tendonae of the mitral valve. FIG. 4 shows a native mitral valve 100 that is going to be replaced by a valve 10. Valve 100 includes annulus 120, anterior leaflet 130a, and posterior leaflet 130p. Reference number 140 indicates the general location where one of the load-bearing chordae is attached to anterior leaflet 130a. (Other such chordae are attached to the leaflets at other locations, but only representative location 140 is indicated in FIG. 4 to avoid unnecessarily complicating the drawing.) In preparation for implanting valve 10, leaflet 130a is cut as indicated by dotted line 150. Some or all of the leaflet tissue (which is still attached to the upper end of the representative one 140 of the chordae) may be folded over on itself as shown at 160 in FIG. 5. Sutures may be used to stabilize this folding of tissue. These sutures or additional sutures may be used to secure folded tissue 160 to mounting retainer 30 at the approximate original (native) location of the upper end of the representative one 140 of the chordae as shown in FIG. 4. This is done as valve 10 is being placed in the site of the native valve. Again, feature 160 is only one representative feature, which may be replicated at other locations for other chordae of the valve (see FIG. 6 in which in addition to feature 160 from FIG. 5, similar features 160b, 160c, and 160d are provided for other chordae at other locations and used in the same way that feature 160 is described as being used in connection with FIG. 5).

[0028] Continuing with FIGS. 5 and 6, even if it is not possible to attach some or all of features 160, 160b, 160c, and 160d to mounting retainer structure 30 at exactly their original locations (e.g., because of the presence of valve core 20), the construction of valve 10 typically allows such features to be anchored closer to their original locations (i.e., at least somewhat radially inward from valve annulus 120) than would be possible if the native valve were replaced by a conventional prosthetic valve (which would be larger than core 20 and which would therefore substantially fill the entire orifice defined by annulus 120). The best that can be done for the chordae in the conventional case is to leave them attached at or very close to the native valve annulus. This is not close to their native attachment locations and may therefore be suboptimal for such purposes as having the chordae help to maintain the native shape of the left ventricle. Attachment of the chordae to mounting retainer 30 closer to their native attachment locations is closer to optimal. For example, it comes closer to having the chordae maintain their original (native) angular alignment relative to the papillary muscle tissue.

[0029] FIG. 7 shows an alternative to FIG. 1 in which mounting retainer structure 30 is provided with features 230, 230b, 230c, and 230d that can used to facilitate attachment of features like 160, 160b, 160c, and 160d, respectively, in FIGS. 5 and 6 to retainer 30. In the particular example shown in FIG. 7, each of features 230, 230b, etc., is a slit though retainer 30. As valve 10 is being implanted, each of features 160, 160b, etc., can be passed through the corresponding one of slits 230, 230b, etc. Each of features 160, 160b, etc. can then be attached (e.g., sutured) to retainer 30. Slits 230, 230b, etc. become closed and leak-proof as a result of these operations. In addition to facilitating attachment of features 160, etc. to valve 10, pre-located and preformed slits 230, etc.

help to get chordae like 140 attached to valve 10 at the best locations.

[0030] It will be understood that slits or other features having different shapes and locations can be incorporated into retainer 30 to accommodate various surgical techniques and facilitate preservation of native tissue structures associated with the valve that is being replaced.

[0031] An example of another possible use of a valve (like 10) of this invention is as a prosthetic replacement for a patient's native tricuspid valve.

[0032] In addition to the advantages already described (e.g., the ability to re-attach subvalvular apparatus like chordae at or near the original (native) location(s)), valves in accordance with this invention can have other important advantages. For example, in a double valve replacement procedure (e.g., replacement of the mitral and aortic valves), the smaller core 20 of the present valves can help reduce the possibility of interference between the two valves. Another possible advantage is that by spacing valve core 20 radially inward from perimeter portion 40, the valve design of this invention allows greater freedom of choice with respect to various aspects of each of these two components. For example, the shape of perimeter portion 40 can be selected relatively independently of the shape of the perimeter 26 of valve core 20. Perimeter 26 can be circular as shown in FIG. 1, which may be best for optimal performance of valve core 20, while perimeter portion 40 is D-shaped (as is also shown in FIG. 1), which may be best for helping to preserve the native shape of native valve annulus 120 (FIG. 4) (or perimeter portion 40 may have a shape and rigidity to influence the geometry and/or functionality of anatomical structures affected by the use of a valve). Mounting retainer 30 spans the space(s) between perimeters 26 and 40 and can therefore fill a gap or gaps having any shape(s) (in either two or three dimensions) between perimeters 26 and 40 that are differently sized and/or shaped in any way. Stated another way, this invention allows virtually any valve technology (for core 20) to be combined with virtually any mounting technology (for perimeter portion 40). The mounting technology choices that are thus available for selection include, for example, virtually any cuff (e.g., sewing cuff) technology.

[0033] It will be understood that the foregoing is only illustrative of the principles of this invention, and that various modifications can be made by those skilled in the art without departing from the scope and spirit of the invention. For example, although non-mechanical valve cores 20 are shown in the FIGS., it has been made clear above that mechanical valve cores can be used instead if desired.

What Is Claimed Is:

1. A prosthetic heart valve comprising:

a valve core; and

a mounting retainer structure that extends radially out from the valve core to an outer perimeter portion that is adapted for attaching the heart valve to another structure, the outer perimeter portion having a different shape than a perimeter of the valve core when both perimeters are viewed along an axis that will be the axis of blood flow through the valve core when the prosthetic heart valve is in use in a patient.

2. The prosthetic heart valve defined in claim 1 wherein the shape of the valve core perimeter is substantially circular, and wherein the shape of the outer perimeter portion is non-circular.

3. The prosthetic heart valve defined in claim 2 wherein the shape of the outer perimeter portion is approximately D-shaped.

4. The prosthetic heart valve defined in claim 1 wherein the outer perimeter portion lies in a plane that is substantially perpendicular to the axis of blood flood.

5. The prosthetic heart valve defined in claim 1 wherein the outer perimeter portion undulates transverse to a plane that is substantially perpendicular to the axis of blood flow, the undulation being along the outer perimeter portion as one proceeds around the valve core.

6. The prosthetic heart valve defined in claim 1 wherein the mounting retainer structure between the valve core and the outer perimeter portion is adapted for use in attaching another native tissue structure to the mounting retainer structure.

7. The prosthetic heart valve defined in claim 6 wherein the mounting retainer structure includes a through-aperture located between the valve core and the outer perimeter portion for passage of the another native tissue structure through the through-aperture.

8. A prosthetic heart valve comprising:
a valve core; and
a mounting retainer structure that extends radially out from the valve core to an outer perimeter portion that is adapted for attaching the heart valve to another structure, the outer perimeter portion being substantially rigid.

9. The prosthetic heart valve defined in claim 8 wherein the outer perimeter portion and a perimeter of the valve core have different shapes when viewed along the axis of blood flow through the valve core when the prosthetic valve is in use in a patient.

10. The prosthetic heart valve defined in claim 9 wherein the shape of the valve core perimeter is substantially circular, and wherein the shape of the outer perimeter portion is non-circular.

11. The prosthetic heart valve defined in claim 10 wherein the shape of the outer perimeter portion is approximately D-shaped.

12. The prosthetic heart valve defined in claim 8 wherein the outer perimeter portion lies in a plane that is substantially perpendicular to the axis of blood flood.

13. The prosthetic heart valve defined in claim 8 wherein the outer perimeter portion undulates transverse to a plane that is substantially perpendicular to the axis of blood flow, the undulation being along the outer perimeter portion as one proceeds around the valve core.

14. The prosthetic heart valve defined in claim 8 wherein the mounting retainer structure between the valve core and the outer perimeter portion is adapted for use in attaching another native tissue structure to the mounting retainer structure.

15. The prosthetic heart valve defined in claim 14 wherein the mounting retainer structure includes a through-aperture located between the valve core and the outer perimeter portion for passage of the another native tissue structure through the through-aperture.

16. A method of replacing a patient's native heart valve with a prosthetic heart valve comprising:

providing a prosthetic heart valve that includes a valve core and a mounting retainer structure that extends radially out from the valve core to an outer perimeter portion, the outer perimeter portion having a different shape than a perimeter of the valve core when both perimeters are viewed along an axis that will be the axis of blood flow through the valve core when the prosthetic heart valve is in use in a patient; and

using the outer perimeter portion to secure the prosthetic heart valve to tissue of the patient.

17. The method defined in claim 16 further comprising:

attaching other tissue of the patient that was attached to a leaflet of the patient's native heart valve to the mounting retainer structure intermediate the valve core and the outer perimeter portion.

18. The method defined in claim 17 wherein the other tissue includes chordae tendonae.

19. A method of replacing a patient's native heart valve with a prosthetic heart valve comprising:

providing a prosthetic heart valve that includes a valve core and a mounting retainer structure that extends radially out from the valve core to an outer perimeter portion, the outer perimeter portion being substantially rigid; and

using the outer perimeter portion to secure the prosthetic heart valve to tissue of the patient.

20. The method defined in claim 19 further comprising:

attaching other tissue of the patient that was attached to a leaflet of the patient's native heart valve to the mounting retainer structure intermediate the valve core and the outer perimeter portion.

21. The method defined in claim 20 wherein the other tissue includes chordae tendonae.

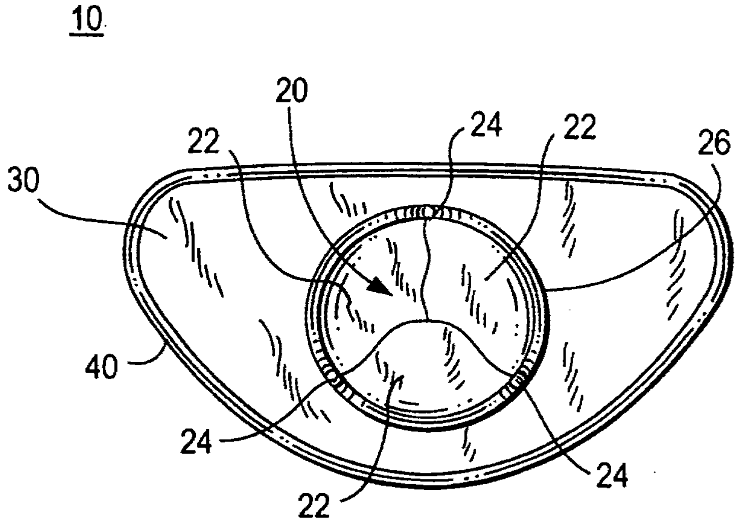

FIG. 1

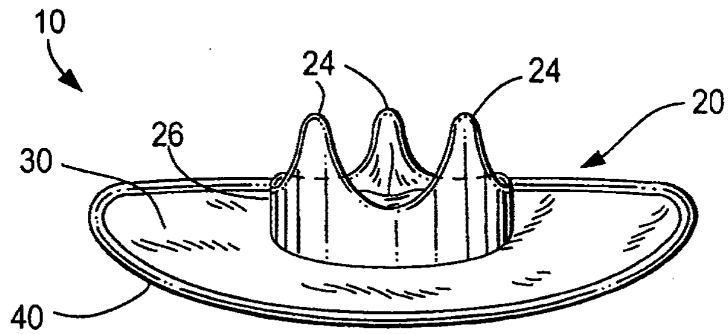

FIG. 2

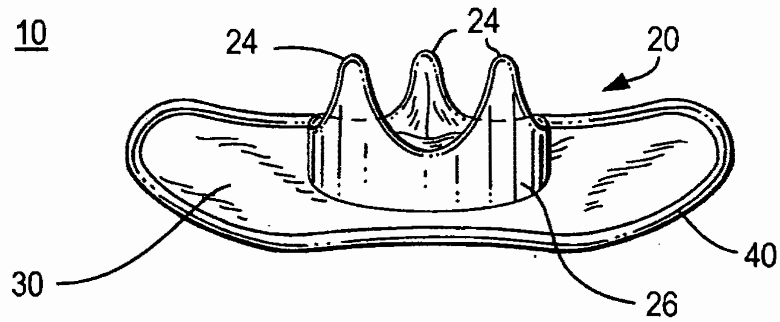

FIG. 3

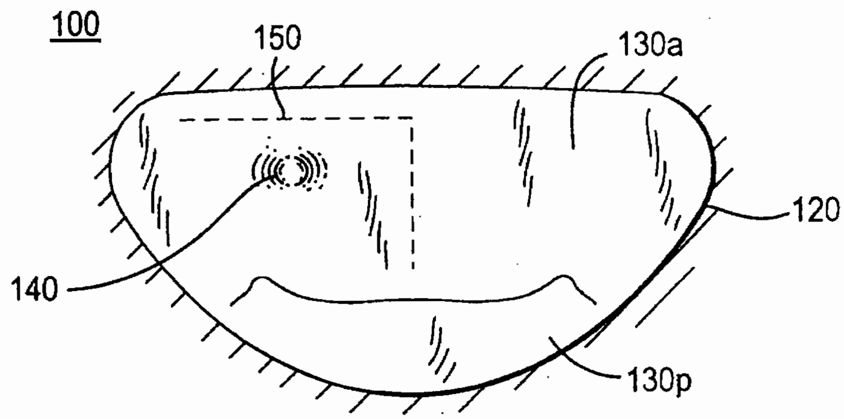

FIG. 4

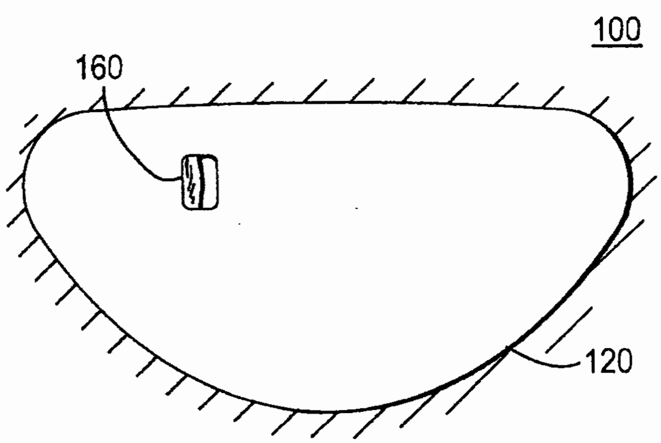

FIG. 5

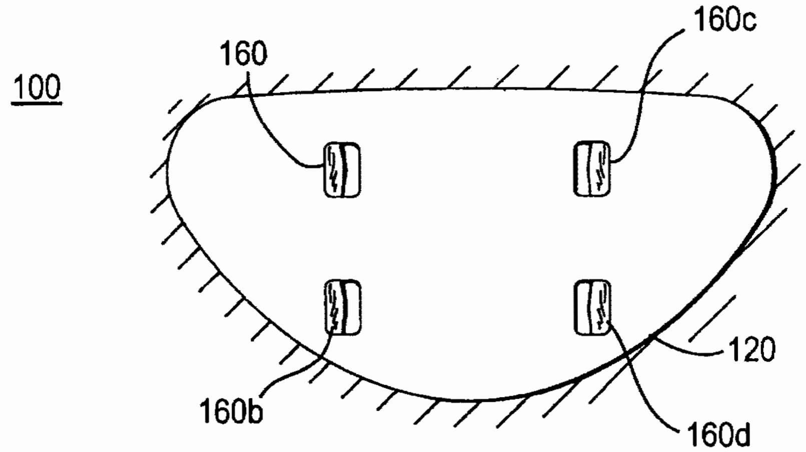

FIG. 6

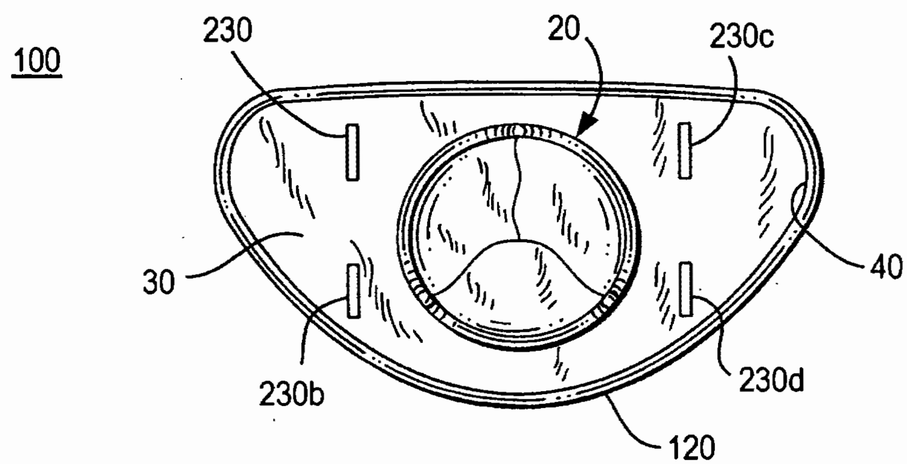

FIG. 7

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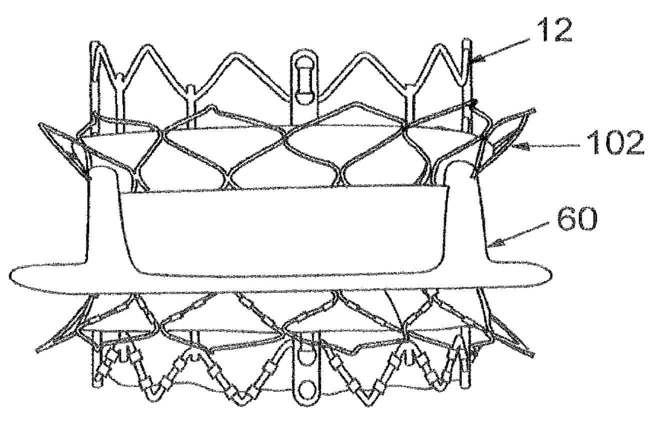

FIG. 8

(57) Abstract: In one aspect, the present disclosure concerns a percutancously delivered adapter stent that is deployed within a previously implanted prosthetic valve and serves as an anchor or platform for implanting a percutaneously delivered replacement valve within the previously implanted valve. The adapter stent can be delivered to the implantation site via the patient's vasculature and positioned within the previously implanted valve. The stent can then be deployed to cause the stent to expand and become anchored to the inner surface of the previously implanted valve. Subsequently, the replacement valve can be positioned within the adapter stent and deployed to cause the replacement valve to expand and become anchored to the adapter stent. The adapter stent and the replacement valve can be mounted on the same catheter for delivery to the implantation site.

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METHOD AND APPARATUS FOR REPLACING A PROSTHETIC VALVE

FIELD

[001] The present invention relates to embodiments of a method and apparatus for replacing a previously implanted prosthetic valve, such as a surgically implanted prosthetic heart valve, without removing the previously implanted valve from the body.

BACKGROUND

[002] Prosthetic valves, such as prosthetic heart valves, are implanted in the body to replace a failing or diseased natural valve. Should the prosthetic valve begin to fail, it also may need to be replaced with another prosthetic valve. Surgically implanted, prosthetic heart valves, such as a prosthetic aortic valve, typically are replaced about every 15 years. The current method for replacing a surgically implanted, prosthetic heart valve involves open heart surgery wherein the patient's chest is opened and the existing prosthetic valve is removed and replaced with a new prosthetic valve. As can be appreciated, this is a traumatic and high risk procedure accompanied by substantial morbidity and mortality, and in some cases, cannot even be attempted due to the advanced age and/or medical condition of the patient.

[003] Therefore, it would be preferable to replace a prosthetic heart valve with a percutaneously implanted valve that is delivered to the implantation site via the patient's vasculature and deployed within the previously implanted valve. However, because existing prosthetic heart valves can vary widely in size and shape, there are substantial difficulties associated with the development and validation of a percutaneously delivered replacement valve that is compatible with different types of existing prosthetic heart valves. More particularly, difficulties arise because a replacement valve that does not conform to the geometry of the previously implanted valve may not be able to adequately

anchor to the previously implanted valve and/or form an effective seal with the previously implanted valve.

SUMMARY

[004] In one aspect, the present disclosure concerns a percutaneously delivered adapter stent that is deployed within a previously implanted prosthetic valve and serves as an anchor or platform for implanting a percutaneously delivered replacement valve within the previously implanted valve. The replacement valve can be any known percutaneous valve. The adapter stent can be adapted to provide a suitable mounting platform for implanting a percutaneous replacement valve in a wide range of existing surgical valves, which typically vary widely in size and shape from patient to patient. In one advantageous feature, the adapter stent increases the frictional forces between the percutaneous replacement valve and the failing surgical valve, thereby providing a more predictable orientation and securement of the percutaneous replacement valve. Hence, this technique is particularly suited for replacing a surgically implanted prosthetic heart valve, but also could be used for replacing a percutaneously implanted prosthetic valve.

[005] The adapter stent can be delivered to the implantation site via the patient's vasculature and positioned within the previously implanted valve. The stent can then be deployed to cause the stent to expand and become anchored to the inner surface of the previously implanted valve. Subsequently, the replacement valve can be positioned within the adapter stent and deployed to cause the replacement valve to expand and become anchored to the adapter stent.

[006] In particular embodiments, the adapter stent and the replacement valve can be mounted on the same delivery catheter for delivery to the implantation site. In one implementation, for example, the adapter stent and the replacement valve can be crimped around respective first and second balloons of a double-balloon catheter. In this approach, the adapter stent is positioned in the previously implanted valve and expanded into contact with the previously

implanted valve by inflating the first balloon. The catheter is then re-positioned to place the replacement valve in the deployed adapter stent, after which the valve is expanded into contact with the adapter stent by inflating the second balloon. In another implementation, the adapter stent and the replacement valve are self-expandable. The self-expandable adapter stent and valve can be mounted on a common delivery catheter adapted to retain the stent and the valve in compressed positions while they are advanced through the patient's vasculature. Using the catheter, the adapter stent and the valve can be successively positioned and deployed within the previously implanted valve.

[007] The adapter stent in exemplary embodiments can comprise an expandable frame that mounts a flexible annular sealing member. The sealing member provides a seal between the previously implanted valve and the replacement valve to prevent or at least minimize blood flow between the original and replacement valves.

[008] The adapter stent may be configured to have a length that is greater than the length of the previously implanted valve that needs to be replaced. This allows the stent to extend over the entire inner surface of the previously implanted valve to provide sufficient surface area for anchoring the replacement valve and to ensure that the previously implanted valve does not interfere with the positioning and deployment of the replacement valve. In certain embodiments, the adapter stent, when expanded, has enlarged end portions that flare or extend radially outwardly past the adjacent ends of the previously implanted valve to assist in securing the adapter stent in place.

[009] In one representative embodiment, a method is provided for percutaneously implanting a replacement prosthetic valve at a site occupied by a previously implanted prosthetic valve. The method includes positioning an adapter stent within the previously implanted valve, deploying the adapter stent to cause the adapter stent to become anchored to the previously implanted valve, positioning the replacement valve within the deployed adapter stent, and deploying the replacement valve to cause the replacement valve to become anchored to the adapter stent.

[010] In another representative embodiment, a method of percutaneously implanting a replacement prosthetic valve in a patient at a site occupied by a previously implanted prosthetic valve includes advancing a catheter carrying an adapter stent through the patient's vasculature to position the adapter stent within the previously implanted valve. The catheter also carries the replacement valve. The method further includes deploying the adapter stent to cause the adapter stent to become anchored to the previously implanted valve, re-positioning the catheter to position the replacement valve within the deployed adapter stent, and deploying the replacement valve to cause the replacement valve to become anchored to the adapter stent.

[011] In another representative embodiment, an assembly is provided for percutaneous replacement of a previously implanted prosthetic valve without removal of the previously implanted valve. The assembly comprises an adapter stent comprising a frame and an annular sealing member. The adapter stent is adapted to be deployed within the previously implanted valve. The assembly also includes a percutaneous, replacement prosthetic valve comprising a frame and a flexible valve member. The valve is adapted to be deployed within the deployed adapter stent such that the sealing member provides a seal between the previously implanted valve and the replacement valve.

[012] In yet another representative embodiment, an assembly for percutaneous replacement of a previously implanted prosthetic valve comprises a percutaneous, replacement prosthetic valve comprising a frame and a flexible valve member. The assembly also includes means for anchoring and sealing the replacement valve to the previously implanted valve, said means being separately deployable within the previously implanted valve prior to deploying the replacement valve within said means.

[013] The foregoing and other features and advantages of the invention will become more apparent from the following detailed description, which proceeds with reference to the accompanying figures.

BRIEF DESCRIPTION OF THE DRAWINGS

[014] FIG. 1 is a side elevation view of one embodiment of an assembly comprising a percutaneous prosthetic valve and an adapter stent for anchoring the prosthetic valve within a previously implanted prosthetic valve.

[015] FIG. 2 is a perspective view of the prosthetic valve shown in FIG. 1.

[016] FIG. 3 is a schematic side view of an embodiment of a double-balloon catheter showing the prosthetic valve and the adapter stent of FIG. 1 crimped around respective balloons on the catheter for percutaneous delivery to an implantation site.

[017] FIGS. 4A-4G illustrate the successive steps of one specific embodiment of an implantation procedure employing the double-balloon catheter shown in FIG. 2 for implanting the adapter stent and the prosthetic valve inside a failing surgically implanted, prosthetic valve previously implanted in the aortic orifice of a patient.

[018] FIG. 5 is a schematic side view of one embodiment of delivery catheter that can be used to implant a self-expanding adapter stent and replacement valve inside a previously implanted valve.

[019] FIG. 6 is a side elevation view of another embodiment of an adapter stent that can be used to anchor a replacement valve within a previously implanted prosthetic valve.

[020] FIG. 7 illustrates another embodiment of an implantable assembly for replacing a previously implanted prosthetic valve.

[021] FIG. 8 illustrates the assembly of FIG. 7 deployed within a previously implanted surgical valve.

DETAILED DESCRIPTION

[022] As used herein, the singular forms “a,” “an,” and “the” refer to one or more than one, unless the context clearly dictates otherwise.

[023] As used herein, the term “includes” means “comprises.” For example, a device that includes or comprises A and B contains A and B but may optionally

contain C or other components other than A and B. A device that includes or comprises A or B may contain A or B or A and B, and optionally one or more other components such as C.

[024] In one aspect, the present disclosure concerns a percutaneously delivered adapter stent that is deployed within a previously implanted prosthetic valve and serves as an anchor or platform for implanting a percutaneously delivered replacement valve within the previously implanted valve. As used herein, the term “stent” refers generally to any luminal structure. The replacement valve can be any known percutaneous valve. The adapter stent can be advanced through the patient’s vasculature and positioned within the previously implanted valve. The adapter stent can then be deployed to cause the adapter stent to expand and become anchored to the inner surface of the previously implanted valve. The replacement valve can then be positioned within the adapter stent and deployed to cause the replacement valve to expand and become anchored to the adapter stent. In one respect, the adapter stent is configured to increase the frictional forces between the replacement valve and the failing previously implanted valve, thereby providing a more predictable orientation and securement of the replacement valve. In the following description, the adapter stent and the replacement valve are shown and described in connection with replacing a previously implanted aortic valve. However, the embodiments described herein can also be used to replace prosthetic valves implanted at other locations in the heart or in other body channels having native valves, such as veins or other organs.

[025] FIG. 1 shows an assembly 10 comprising a percutaneous prosthetic heart valve 12 and an adapter stent 30, according to one embodiment. The adapter stent 30 can be deployed within a failing, previously implanted valve, such as the prosthetic aortic valve 60 shown in FIG. 4A. Once the adapter stent 30 is deployed within the previously implanted valve, the new valve 12 can be deployed within the adapter stent 30 to replace the previously implanted valve 60. The previously implanted valve 60 shown in the figures is a surgical valve (i.e., a valve implanted via open heart surgery), although the adapter stent 30

and the replacement valve 12 can also be deployed within a previously implanted percutaneous valve.

[026] The valve 12 and the adapter stent 30 are each crimpable or compressible to a reduced diameter for percutaneous delivery to the implantation site, such as using a delivery catheter. When expanded to their functional size (FIG. 1), the outer diameter of the valve 12 desirably is approximately equal to the inner diameter of the adapter stent and the outer surface of the valve 12 generally conforms to an inner surface portion of the adapter stent 30 to promote attachment of the valve 12 to the adapter stent 30. Methods for implanting the adapter stent 30 and the valve 12 are described in greater detail below.

[027] As shown in FIGS. 1 and 2, the valve 12 in the illustrated embodiment includes an annular frame 14 that mounts a flexible valve member 16. The frame 14 in the illustrated embodiment comprises a plurality of angularly-spaced axial struts, or support members, 18 that extend axially (longitudinally) along the frame and a plurality of support posts, or beams, 20 (one of which is shown in FIGS. 1 and 2) spaced in the illustrated example at 120-degree intervals from each other around the frame 14. The support posts 20 can be formed with apertures 22 to facilitate attachment of the valve member 16 to the posts 20, such as, for example, by suturing the valve member 16 to the posts. The frame 14 can also include a plurality of axially-spaced, circumferential bands, or struts, 24 attached to the axial struts 18 and the support posts 20. The struts 24 are formed with multiple bends that allow the frame 14 to be crimped to a smaller diameter for delivery to an implantation site and expanded to its functional size for anchoring the valve assembly to the adapter stent 30 at the implantation site. For example, each of the struts 24 in the illustrated configuration includes a plurality of linear strut members 26a, 26b arranged in a zig-zag or saw-tooth configuration defining bends between adjacent strut members.

[028] In alternative embodiments, the frame can have other configurations. For example, one or more of the circumferential bands 24 can have a curved or

serpentine shape rather than a zig-zag shape. Further, the frame 14 can include various attachment elements (not shown), such as barbs, staples, flanges, and the like for enhancing the ability of the frame to anchor to the adapter stent 30.

[029] The frame 14 can be made from any of various suitable ductile and/or elastic materials and is typically made of a metal, such as stainless steel, titanium, or other biocompatible metals. The frame 14 or components thereof can also be made from a shape memory alloy such as nickel titanium (NiTi) shape memory alloys, as marketed, for example, under the trade name Nitinol. The shape-memory components allow the valve 12 to be self-expandable; that is, the valve 12, when restrained in a radially compressed state by an outer restraint (e.g., a sheath covering the valve), automatically expands to its functional size when the outer restraint is removed.

[030] The valve member 16 can have a leafed-valve configuration, such as the tricuspid valve configuration shown in the illustrated embodiment. The valve member 16 can be formed from three pieces of pliant material connected to each other at seams aligned with posts 20 to form collapsible leaflets 28 (FIG. 2). The valve member 16 can be made from biological matter, such as natural tissue, pericardial tissue (such as bovine, porcine or equine pericardium), a harvested natural valve or other biological tissue. Alternatively, the valve member 16 can be made from biocompatible polymers or similar materials.

[031] Various other prosthetic valve configurations also can be used. Examples of other valves that can be utilized are disclosed in U.S. Patent No. 6,730, 118, U.S. Patent No. 6,767,362, and U.S. Patent No. 6,908,481, which are incorporated herein by reference.

[032] The adapter stent 30 in exemplary embodiments includes an expandable frame 32 that mounts a flexible annular sealing member 34. The frame 32 is shown in FIG. 1 in its expanded, functional size, and is configured to be crimpable to a reduced diameter for percutaneous delivery, such as on a delivery catheter. The frame 32 can be made from any of various suitable ductile and/or elastic materials and is typically made of a metal, such as stainless steel, titanium, or other biocompatible metals. The frame 14 or

components thereof can also be made from a shape memory material, which allows the stent 30 to be self-expandable.

[033] The frame 32 is the illustrated embodiment comprises a plurality of longitudinally extending, zig-zag struts 36 joined to each other at junctures 38. The frame 32 has a length L measured between the opposite ends thereof that desirably is greater than the length of the previously implanted valve that needs to be replaced. In this manner, the frame 32, when deployed within the previously implanted valve, can extend over the entire inner surface area of the previously implanted valve to provide sufficient surface area for anchoring the replacement valve 12 and to ensure that the previously implanted valve does not interfere with the positioning and deployment of the replacement valve 12. In particular embodiments, for example, the length L of the frame is about 10 mm to about 40 mm, with about 30 mm being a specific example.

[034] As shown, the frame 32 in exemplary embodiments has a generally cylindrical intermediate portion 44 extending between the opposite end portions 40, 42, which are enlarged or flared relative to the intermediate portion 44 when the frame is expanded. Each end portion 40, 42 desirably expands to a diameter that is greater than the diameter of the previously implanted valve. Hence, when the adapter stent 30 is deployed within the previously implanted valve, the end portions 40, 42 can extend radially outwardly past the adjacent ends of the previously implanted valve to assist in securing the adapter stent in place.

[035] In alternative embodiments, the frame 32 can have various other shapes or configurations. For example, the frame 32 can be generally cylindrical or tubular along its entire length without enlarged end portions. The frame 32 optionally can be provided with various attachment elements (not shown), such as barbs, staples, flanges, and the like for enhancing the ability of the frame to anchor to the previously implanted valve 60 (FIG. 4A). If desired, the frame 32 may be provided with attachment elements along the inner surface for enhancing the ability of the frame 32 to securely engage the frame 14 of the percutaneously delivered replacement valve 12.

[036] The sealing member 34 provides a seal between the previously implanted valve 60 and the replacement valve 12 to prevent or at least minimize blood flow between the valves. As shown in FIG. 1, the sealing member 34 desirably extends nearly the entire length of the frame 32 to maximize the surface area that can contact the previously implanted valve 60 and the replacement valve 12. In other embodiments, however, the sealing member can extend along only a portion of the frame 32, such as the intermediate portion 44. With reference to the embodiment shown in FIG. 1, the sealing member 34 is secured to the inner surface of the frame 32. Alternatively, the sealing member can be secured to the outer surface of the frame 32 as shown in FIG. 6 to prevent the leakage of blood. In another implementation, a sealing member 34 can be secured to both the inner and outer surfaces of the frame 32.

[037] In particular embodiments, the sealing member 34 is made of a natural or synthetic biocompatible elastomeric material, such as foam rubber, thermoplastic elastomers (e.g., polyurethanes) or other polymeric elastomers, such as a polymeric sponge. The sealing member 34 can be secured to or formed on the frame using any suitable techniques or mechanisms, such as by suturing the sealing member to the frame or co-molding the sealing member to the frame. The sealing member 34 also can be formed on the frame using conventional coating techniques, such as spray coating, dip coating, or roll coating.

[038] The valve 12 and the adapter stent 30 can be implanted using a double-balloon catheter. FIG. 3, for example, shows the distal end portion of an exemplary embodiment of a double-balloon catheter, indicated at 70. The catheter 70 includes a shaft 72, on which there are mounted first and second, spaced-apart balloons 74, 76, respectively, between a respective pair of rings 80, 82. The adapter stent 30 and the replacement valve 12 are crimped around the first balloon 74 and the second balloon 76, respectively. The shaft 72 contains two lumens (not shown), each of which is fluidly connected to a respective balloon 74, 76 for successive and separate inflation of each balloon. The shaft 72 also contains another lumen to accept a guide wire 78 so that the

catheter can be advanced over the guide wire 78 for guiding the catheter through the patient's vasculature.

[039] The catheter 70 can be introduced percutaneously into the patient's vasculature (e.g., into a peripheral artery such as the femoral artery) and advanced to the implantation site. For example, for replacing a prosthetic aortic valve, the catheter in certain embodiments has a length of at least about 80 cm, usually about 90-100 cm, to allow transluminal positioning of the shaft from the femoral and iliac arteries to the ascending aorta. Alternatively, the shaft may have a shorter length, e.g. about 20-60 cm, for introduction through the iliac artery, through the brachial artery, through the carotid or subclavian arteries, or through a penetration in the aorta itself. In the femoral approach, the catheter desirably is long enough and flexible enough to traverse the path through the femoral artery, iliac artery, descending aorta and aortic arch. At the same time, the catheter desirably has sufficient pushability to be advanced to the ascending aorta by pushing on the proximal end, and has sufficient axial, bending, and torsional stiffness to allow the physician to control the position of the distal end, even when the catheter is in a tortuous vascular structure. Alternatively, the catheter may be passed through a port between ribs in the patient's thorax above the heart and through an incision in the heart wall (e.g., through the apex of the left ventricle) or through an incision in the aortic arch, in a so-called minimally-invasive procedure.

[040] A procedure for implanting the valve 12 and the adapter stent 30 using the catheter 70, according one embodiment, is illustrated in FIGS. 4A-4G. FIG. 4A illustrates the previously implanted valve 60 implanted in the aortic annulus between the left ventricle chamber 86 and the ascending aorta 88. As noted above, the illustrated valve 60 is a surgical valve, although the adapter stent 30 and the replacement valve 12 can also be implanted within an existing percutaneous valve. The catheter 70 can be introduced percutaneously into the patient's vasculature and advanced to the implantation site using known techniques. For example, a blood vessel (e.g., the femoral artery) typically is dilated using a conventional dilator to allow an introducer sheath to be inserted

into the blood vessel. The guide wire 78 can then be inserted into the blood vessel via the introducer sheath and advanced to the implantation site. Subsequently, the catheter 70 can be advanced over the guide wire 78 to position the adapter stent 30 in the previously implanted valve 60. More precisely, the adapter stent 30 desirably is positioned such that the end portions 40, 42 are located outside the adjacent ends of the previously implanted valve 60, as shown in FIG. 4B.

[041] As depicted in FIG. 4C, the balloon 74 is then inflated to deploy the adapter stent 30, which expands to its functional size and engages the inner surface of the previously implanted valve 60. As shown, in its expanded stated, the end portion 40, 42 flare radially outwardly past the adjacent ends of the previously implanted valve to assist in retaining the adapter stent 30 in place against the valve 60. In addition, the adapter stent 30, in the illustrated example, also extends over the entire inner surface area of the existing valve 60 and causes the flexible leaflets 62 of the valve to expand radially outwardly, thereby providing a surface area suitable for mounting the replacement valve 12.

[042] Thereafter, the balloon 74 is deflated (FIG. 4D) and the catheter 70 is retracted slightly to position the replacement valve 12 within the deployed adapter stent 30 (FIG. 4E). The second balloon 76 is then inflated to deploy the replacement valve 12, which expands to its functional size and engages the inner surface of the adapter stent 30 (FIG. 4F). Once the replacement valve 12 is deployed, the balloon 76 can be deflated and the catheter 70 can be removed from the body (FIG. 4G).

[043] The adapter stent 30, as well as the valve 12, can be positioned at the implantation site with the assistance of fluoroscopy and radiopaque markers, ultrasonic imaging, and the like. For example, rings 80, 82 on the catheter shaft 72 can be made of any of various suitable metals that are visible during fluoroscopy for use in positioning the adapter stent and/or the valve. Alternatively, radiopaque markers can be provided on portions of the adapter stent 30 and/or the valve 12.

[044] In an alternative approach, the replacement valve 12 can be mounted on the first balloon 74 and the adapter stent 30 can be mounted on the second balloon 76. In this approach, the adapter stent 30 is first deployed within the previously implanted valve 60 while the first balloon 74 and the replacement valve 12 are positioned in the aorta 88. After the adapter stent 30 is deployed, the catheter 70 is advanced further into the left ventricle 86 to position the first balloon 74 and the replacement valve 12 within the deployed adapter stent 30. The replacement valve 12 can then be deployed by inflating the first balloon 74.

[045] As noted above, the frame 32 of the adapter stent 30 and the frame 14 of the replacement valve 12, or portions thereof, can be made of a shape-memory material, which allows the adapter stent 30 and the valve 12 to be self-expandable. FIG. 5 is a schematic view of the distal end portion of a delivery catheter, indicated at 90, which can be used to implant a self-expanding replacement valve and adapter stent in the previously implanted valve 60. The catheter 90 includes a shaft 92 and an outer sheath 94, which is moveable longitudinally relative to the shaft 92. The shaft 92 can include a lumen for receiving a guide wire 78. The valve 12 and the adapter stent 30 are mounted to the shaft 92 in their compressed states. The outer sheath 94 extends over the valve 12 and the adapter stent 30 to retain the valve and adapter stent in their compressed states until each is positioned for deployment at the implantation site.

[046] The catheter 90 can be introduced into the body and advanced through the patient's vasculature in the same manner as the balloon catheter 70. The adapter stent 30 is first positioned in the previously implanted valve 60 and the outer sheath is retracted to expose the adapter stent 30, which permits the adapter stent to expand into contact with the previously implanted valve. The catheter 90 is then advanced slightly to position the valve 12 in the deployed adapter stent 30. The outer sheath 94 can then be retracted to expose the valve 12, which permits the valve to expand into contact with the adapter stent.

[047] Although less desirable, the adapter stent 30 and the replacement valve 12 can be delivered and implanted at the site of the previously implanted valve

using separate catheters. For example, the adapter stent 30 and the valve 12 can be mounted on separate balloon catheters. In this approach, the adapter stent 30 is implanted using a first balloon catheter, which is then removed from the body to allow a second balloon catheter carrying the replacement valve to be inserted into the body.

[048] As noted above, surgical valves, such as valve 60, typically vary widely in size and shape from patient to patient. Advantageously, the adapter stent 30 can be adapted to provide a suitable mounting platform for implanting a percutaneous replacement valve in a wide range of surgical valves varying in size and shape.

[049] FIG. 7 illustrates another exemplary embodiment of an assembly 100 comprising a percutaneous prosthetic valve 12 and an adapter stent 102. The adapter stent 102, like adapter stent 30, includes a radially compressible and expandable frame 102 that mounts a flexible annular sealing member 106. FIG. 8 illustrates the adapter stent 102 and the prosthetic valve 12 deployed within a previously implanted surgical valve 60. The adapter stent 102 has a length L that is preferably greater than the length of the previously implanted valve 60 but need not be longer than the new valve 12. In certain embodiments, the adapter stent 102 has a length L of about 10 mm and the new valve 12 has a length of about 20 mm.

[050] In view of the many possible embodiments to which the principles of the disclosed invention may be applied, it should be recognized that the illustrated embodiments are only preferred examples of the invention and should not be taken as limiting the scope of the invention. Rather, the scope of the invention is defined by the following claims. I therefore claim as my invention all that comes within the scope and spirit of these claims.

I claim:

1. An assembly for percutaneous replacement of a previously implanted prosthetic valve without removal of the previously implanted valve, the assembly comprising:

an adapter stent comprising a frame and an annular sealing member, the adapter stent being adapted to be deployed within the previously implanted valve; and

a percutaneous, replacement prosthetic valve comprising a frame and a flexible valve member, the valve being adapted to be deployed within the deployed stent such that the sealing member provides a seal between the previously implanted valve and the replacement valve.

2. The assembly of claim 1, wherein the sealing member comprises an elastomer.

3. The assembly of claim 1, wherein the sealing member extends substantially the entire length of the frame of the adapter stent.

4. The assembly of claim 1, wherein the sealing member is mounted on the outside of the frame of the adapter stent.

5. The assembly of claim 1, wherein the sealing member is mounted on the inside of the frame of the adapter stent.

6. The assembly of claim 1, wherein the frame of the adapter stent has an inlet end portion, an outlet end portion, and an intermediate portion extending between the end portions, the end portions being greater in diameter than the intermediate portion.

7. The assembly of claim 1, wherein the frame of the adapter stent has a length of at least about 10 mm.

8. The assembly of claim 1, wherein the frames of the replacement valve and the adapter stent are self-expandable.

9. The assembly of claim 1, wherein the replacement valve is a prosthetic heart valve.

10. An assembly for percutaneous replacement of a previously implanted prosthetic valve without removal of the previously implanted valve, comprising;

a replacement prosthetic valve having a frame and a flexible valve member, the replacement prosthetic valve being radially expandable and collapsible; and

means for anchoring and sealing the replacement valve to the previously implanted valve, said means being separately deployable within the previously implanted valve prior to deploying the replacement valve within said means.

11. The assembly of claim 10, wherein said means comprises an expandable frame and an annular sealing member secured to the frame.

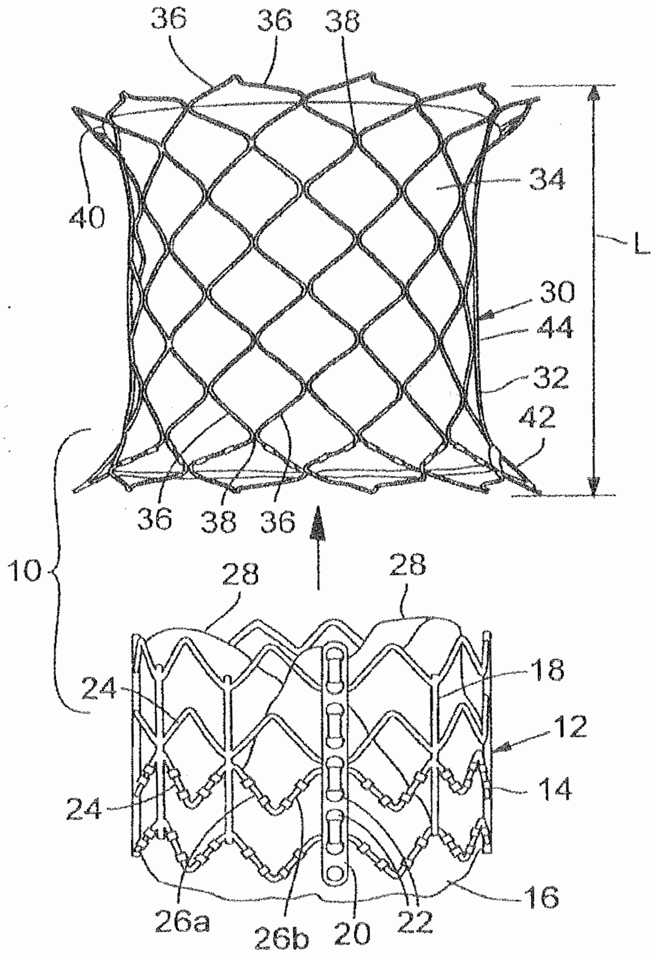
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FIG. 1

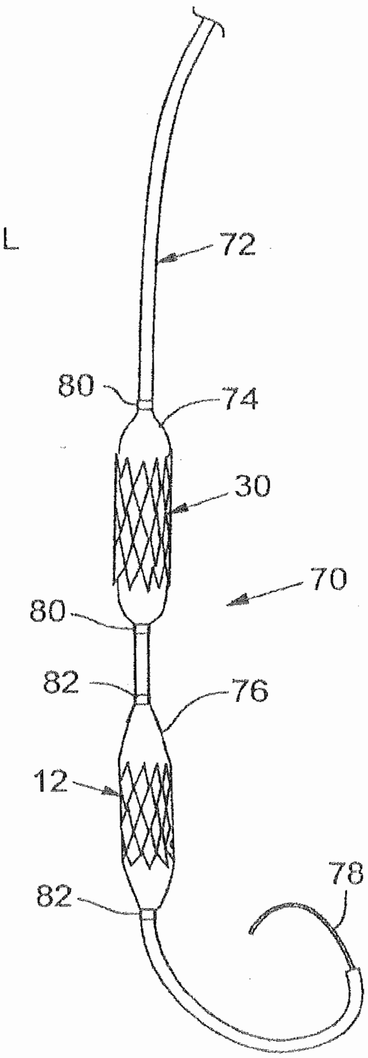
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FIG. 3

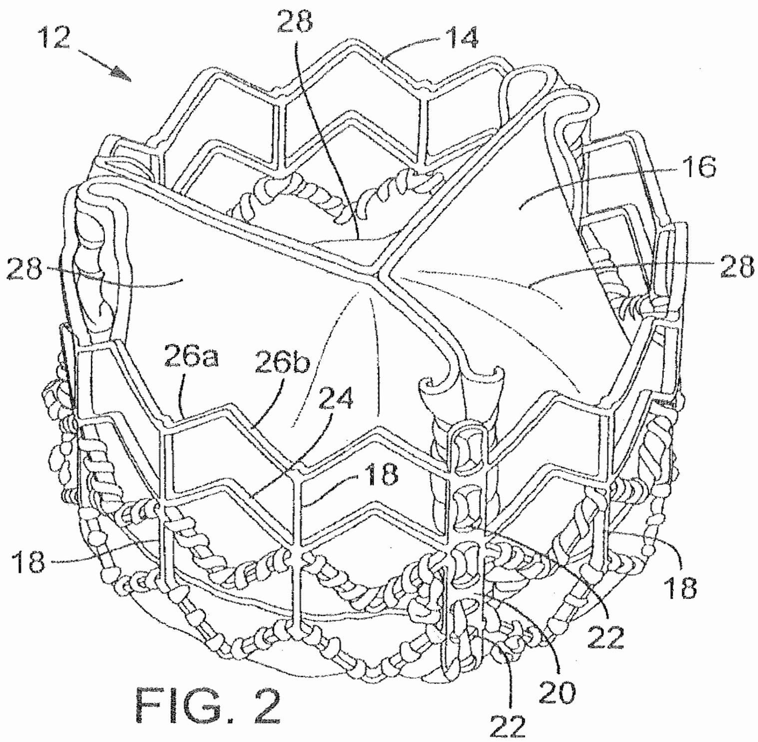

FIG. 2

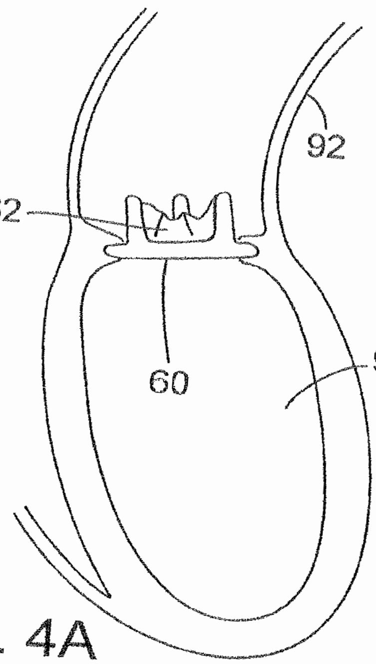

FIG. 4A

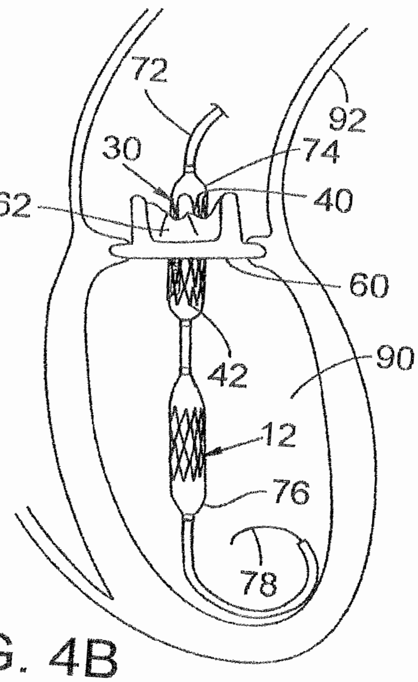

FIG. 4B

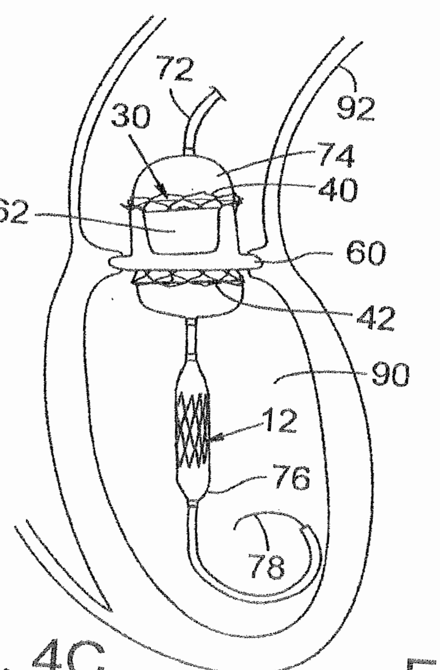

FIG. 4C

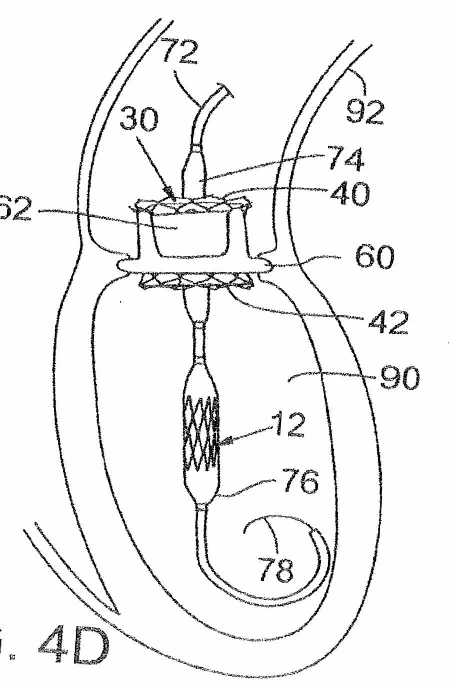

FIG. 4D

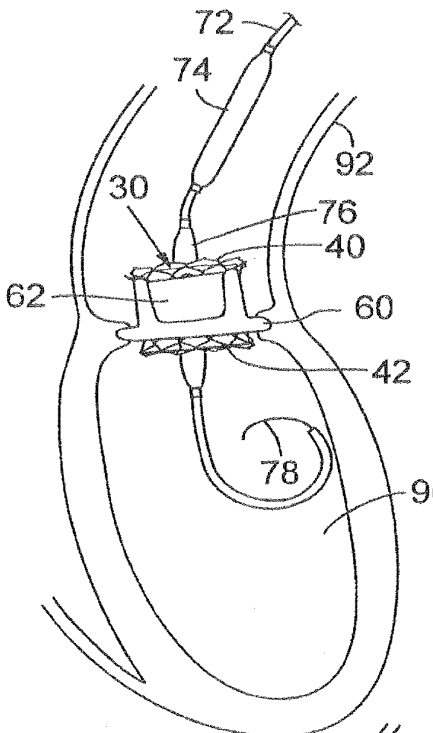
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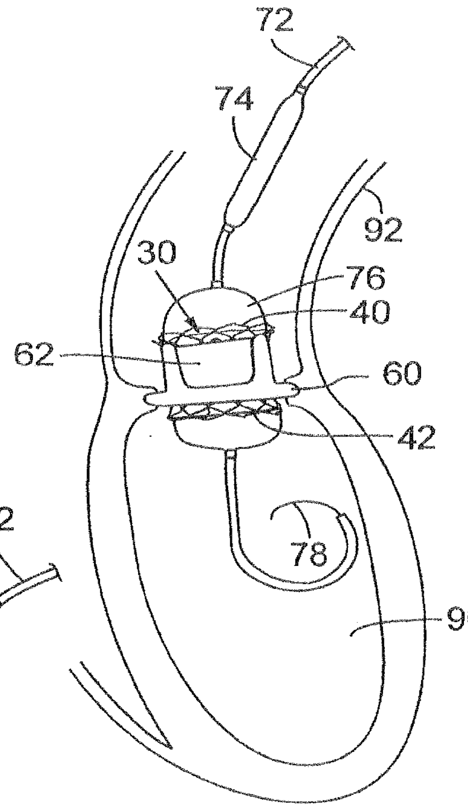
FIG. 4E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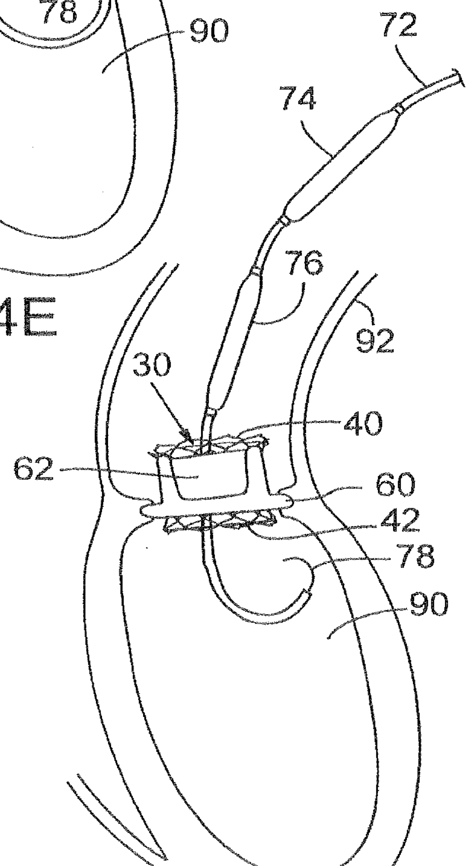
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FIG. 4G

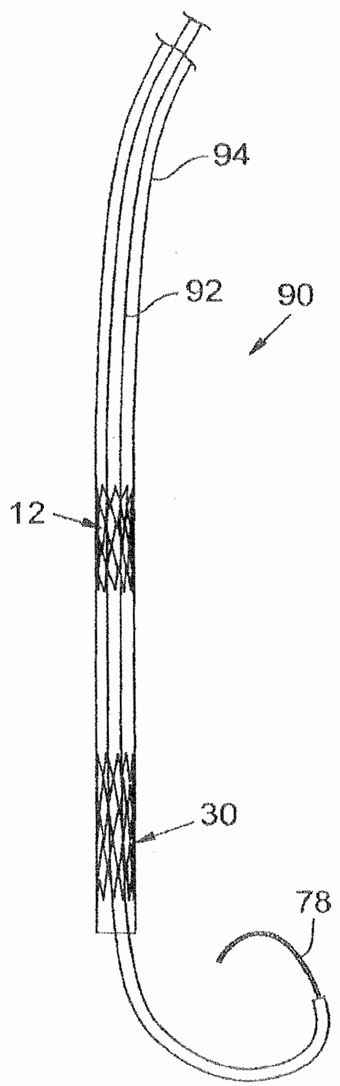

FIG. 5

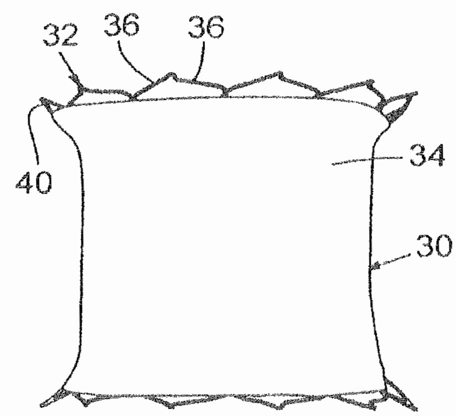

FIG. 6

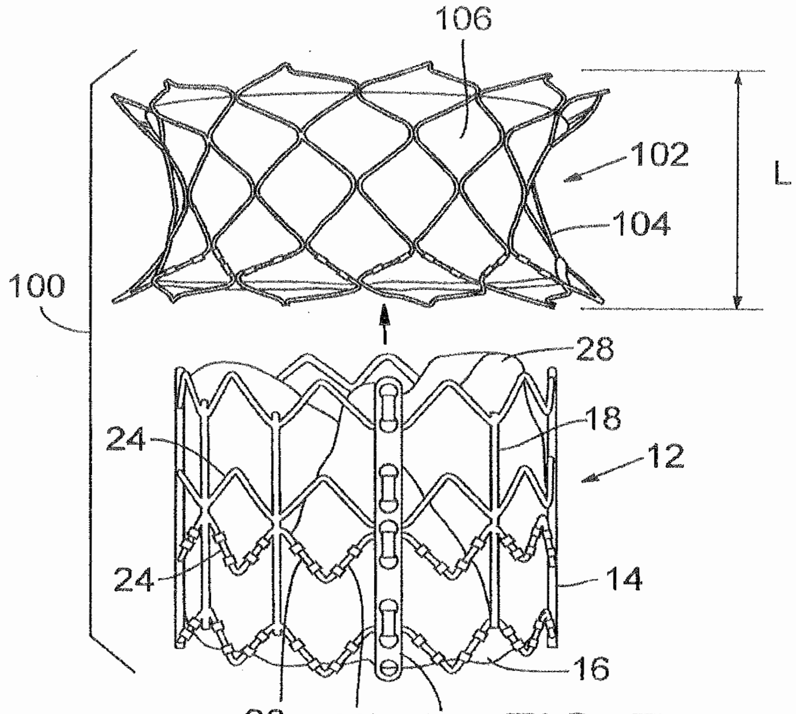

FIG. 7

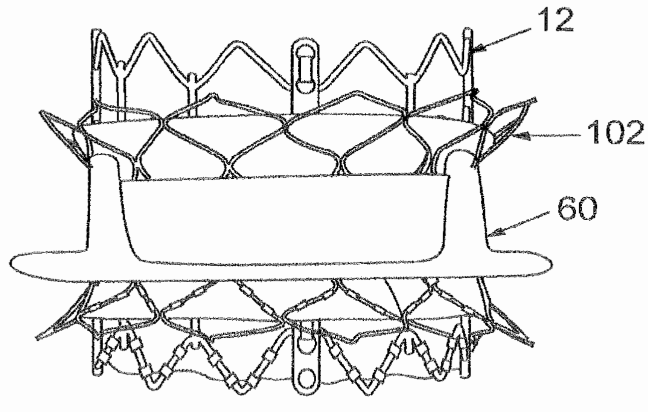

FIG. 8

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/055160

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61F2/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/014104 A1 (CRIBIER ALAIN [FR]) 16 January 2003 (2003-01-16) cited in the application column 5, line 36 - line 39 column 5, line 64 - column 6, line 14 column 8, line 32 - line 45 column 8, line 62 - line 67 column 9, line 14 - line 15 column 9, line 40 - line 41 column 10, line 41 - line 58 column 12, line 1 - line 26 column 12, line 55 - column 13, line 8 column 14, line 61 - line 63 column 16, line 57 - line 61 column 19, line 41 - line 55 column 20, line 33 - line 38 figures 2A-8B,14-15F ----- -/--	1-7,9-11

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 June 2008	16/07/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Geuer, Melanie

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/055160

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	US 2006/195184 A1 (LANE ERNEST [US] ET AL) 31 August 2006 (2006-08-31) paragraphs [0006] - [0016], [0075] - [0079], [83167], [0171]; figures 1-4,17A-19	1-6,8-11
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/055160

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Form PCT/ISA/210 (patent family annex) (April 2005)

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25 June 2009 (25.06.2009)

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(72) Inventors; and

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(74) Agent: **BARLOCCI, Anna**; ZBM Patents, S. L., Balmes, 114, 4°, E-08008 Barcelona (ES).

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(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

(54) Title: PROSTHETIC HEART VALVE AND METHOD FOR MAKING SUCH A VALVE

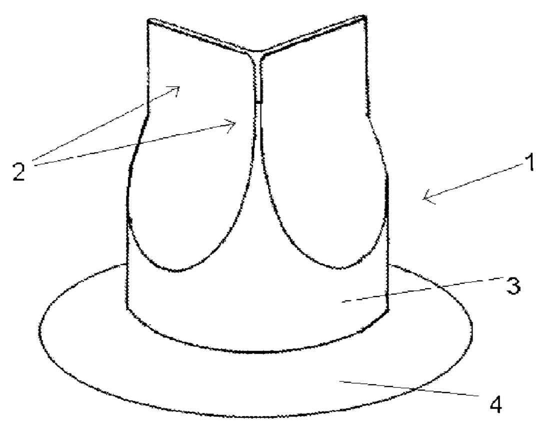

Figure 3(a)

(57) Abstract: The present invention relates to a method of making a prosthetic heart valve comprising the steps of placing a piece of biological tissue (12) in or over a mould (10), and simultaneously tanning said tissue and shaping it to an appropriate shape. Furthermore, it relates to a prosthetic heart valve of a single piece of biological tissue, said valve comprising a cylindrical base and leaflets, characterised in that said cylindrical base and leaflets have a continuous peripheral wall.

WO 2009/156471 A1

Prosthetic heart valve and method for making such a valve

The present invention relates to a prosthetic heart valve from biological tissue and to a method of making such a valve.

The human heart has a right side and a left side. The function of the right side of the heart is to collect de-oxygenated blood from the body, in the right atrium, and pump it, via the right ventricle, into the lungs so that carbon dioxide can be dropped off and oxygen picked up. The left side collects oxygenated blood from the lungs into the left atrium. From the left atrium the blood moves to the left ventricle which pumps it out to the body.

Starting in the right atrium, the blood flows through the tricuspid valve to the right ventricle. Here it is pumped out through the pulmonary valve and travels through the pulmonary artery to the lungs. From there, blood flows back through the pulmonary vein to the left atrium. It then travels through the mitral valve to the left ventricle, from where it is pumped through the aortic valve to the aorta. From the aorta, the blood is divided between major arteries which supply the upper and lower body.

The tricuspid valve, pulmonary valve and aortic valve each comprise three leaflets (or cusps). The mitral valve has two leaflets. All heart valves are non-return valves, i.e. they ensure blood flow in only one direction and open under the influence of pressure differences. The mitral valve and tricuspid valve ensure that blood can flow from the atria to the ventricles and not the other way. The pulmonary valve and aortic valve ensure blood flow from the ventricles to the pulmonary vein and aorta respectively.

A malfunctioning heart valve may result in either backward flow (regurgitation) or impeded forward flow (stenosis). Certain heart valve pathologies may necessitate the complete surgical replacement of the natural heart valves with heart valve prostheses.

US 4,441,216 discloses a method for making a replacement heart valve. In this document, the replacement heart valve is made by taking a piece of pericardial tissue, tanning the tissue and cutting three leaflets. The leaflets are then connected to each other and to a stent via stitching.

US 2003/0130729 describes a percutaneously implantable replacement heart valve device. The replacement heart valve device comprises a stent member and a biological tissue artificial valve means disposed within the inner space of the stent member. The method of making the replacement heart valve device involves taking a rectangular fragment of animal pericardium, treating, drying, folding and rehydrating it in such a way that it forms a two- or three-leaflet valve. At its cylindrical base, two borders are stitched together.

It is an object of the present invention to provide an improved prosthetic heart valve and an improved method of making a prosthetic heart valve. This object is achieved by a method of making a prosthetic valve according to claim 1 and a prosthetic heart valve according to claim 8.

According to one aspect of the invention, the method of making a prosthetic heart valve comprises the steps of placing a piece of biological tissue in or over a mould, and simultaneously tanning said tissue and forming it to an appropriate shape.

Traditionally, biological tissue is tanned in a first step. After tanning, the tissue is cut into several pieces of appropriate shape. These pieces are then sutured back together to form the prosthetic heart valve. Inventors however have found that the biological tissue can be tanned and given the appropriate shape simultaneously by placing it in or over a mould and applying appropriate tension. There is thus no need for cutting tissue into several pieces and then suturing them back together. The result is a heart valve that resembles a human heart valve much better. Since the heart valve is from a single biological tissue (thus also from a single animal), the tissue of the heart valve is more homogeneous. Additionally, no sutures are required. Sutures in a prosthetic heart valve device are problematic for a number of reasons. They cause local stress concentrations and limit the life time of a prosthetic heart valve and are the main cause for leakage occurring in prosthetic heart valves. Also, a prosthetic heart valve aims at being anatomically correct in comparison to a normal heart valve, and sutures are not anatomically correct.

Preferably, in some methods according to the invention, the step of placing the biological tissue in or over a mould comprises using two moulds, a positive mould with substantially the desired shape of the valve and a negative mould with a negative shape of said positive mould. Using two moulds with a positive and a negative shape is advantageous in the process of shaping the heart valve.

Optionally, said step of placing the biological tissue in or over a mould comprises the steps of placing the tissue over said positive mould and then placing said negative mould over the biological tissue. Another option is that said step of placing the biological tissue in or over a mould comprises the steps of placing the biological tissue in said negative mould and then placing the positive mould within the negative mould.

Optionally, the mould that the tissue is placed over has a bottom ring and said step of placing said biological tissue over a mould includes folding the tissue around said bottom ring. The result of folding the tissue around such a bottom ring is to have a heart valve with a ring which can be fixed to a support structure. When the prosthetic heart valve device (prosthetic heart valve and support structure) is positioned appropriately in a patient's body (e.g. for an aortic heart valve, at the connection of the heart to the aorta), leaks around the outside of the valve may, in certain cases, be avoided. Optionally, said bottom ring may be a conical bottom ring. This shape may be given to further reduce leaks around the valve. Yet another option is that the bottom ring is ridged or undulated, which may also be beneficial in reducing leaks around the valve.

However, the appropriate mould and also whether a plurality of moulds should be used, depends to a large extent on the desired shape of the valve. In this sense, two kinds of valves should be distinguished: "open" valves and "closed" valves. "Open" valves have a substantially open cylindrical shape in a relaxed state. Their leaflets are merely defined by parts of the cylinder that can move inwardly when appropriate pressure conditions are created. "Closed" valves have a partly cylindrical shape which however is closed by three (or two) leaflets at one side. In use, under suitable pressure, these leaflets may move outward to open and let blood pass. Open and closed valves work in the same way, but their default state is different (respectively open and closed). Clearly, the mould to be used for shaping the valve depends on the desired end shape of the valve.

Preferably, the tanning step occurs by subjecting the biological tissue to a glutaraldehyde solution. The tanning step occurs simultaneously with the shaping of the heart valve, with the biological tissue placed in or over a mould. The goal of the tanning step is to make the tissue biocompatible. Other aldehydes are known in the art and may be used. The best results have been obtained with glutaraldehyde solutions with concentrations between 0.1 and 1%, preferably around 0.65%.

Optionally, in the method according to the invention, said step of forming the tissue to an appropriate shape includes applying tension to the tissue. By applying tension (e.g. by pulling, by using two moulds or by creating a vacuum) in appropriate points at appropriate moments, the tissue takes the desired form of the heart valve.

In some embodiments, the method of making a prosthetic heart valve includes an additional step of cutting the biological tissue to form the leaflets of the valve. The whole process was started with a single piece of biological tissue. After the tissue has been given the appropriate shape to function as a heart valve and has been tanned, in some embodiments, the leaflets are formed by making cuts in the single piece of biological tissue and as such “opening” the tissue. This way no form of suturing is required to form the leaflets. As mentioned before, sutures are a source of inconvenience in prosthetic heart valves. These cuts may be made when the tissue is placed over the mould, using the shape of the mould as a guide in the cutting process. The cuts may also be made after it has been released from the mould and fixed on a support structure, together forming a heart valve device, hereinafter further described. This may be a bit more complicated, but it has the advantage of having the valve in its mounted position when cutting. This avoids possible cutting errors due to the valve being mounted in a support structure slightly differently. It is however also possible to use an additional mould or guide for the cutting process or to cut without any additional guide or tool.

According to a second aspect of the invention, a method of making a prosthetic heart valve device is provided, said method comprising the steps of making a prosthetic heart valve according to the invention and the additional step of attaching the prosthetic heart valve to a support structure. The support structure, in use, has the function of supporting the heart valve, and mostly supporting the leaflets of the heart valve to keep them in their desired shape.

According to another aspect of the invention, a prosthetic heart valve of a single piece of biological tissue is provided, said valve comprising a substantially cylindrical base and leaflets, characterised in that said cylindrical base and leaflets have a continuous peripheral wall. The single piece of biological tissue ensures a homogeneous heart valve, and the continuous peripheral wall avoids the need of any sutures (which are known to cause problems during the life-time of the heart valve).

Preferably, the heart valve is formed using a method according to the invention. The method of making a prosthetic heart valve described here within is the most advantageous way of providing a heart valve of homogeneous tissue without any sutures.

In an aspect of the invention, the invention provides a prosthetic heart valve of a single piece of biological tissue, said valve being an open valve and having a continuous peripheral wall.

In another aspect according to the invention, a prosthetic heart valve device is provided comprising a prosthetic heart valve of a single piece of biological tissue and a support structure for supporting said valve, said valve comprising a cylindrical base and leaflets, said cylindrical base and leaflets having a continuous peripheral wall. The support structure is provided such that the leaflets in use can maintain their original shape and function properly. Any suitable support structure may be used.

In some embodiments, the support structure of the heart valve device comprises three legs for fixing three leaflets of the valve. The present invention is especially aimed at prosthetic aortic heart valves. Aortic heart valves comprise three leaflets. However, within the scope of the present invention, any suitable support structure may be used such as e.g. balloon expandable or self-expandable stents.

A preferred way of connecting the leaflets to the support structure is through suturing. It is to be noted that these sutures are not sutures for closing or forming the heart valve (the peripheral wall of the heart valve is continuous); the heart valve itself is completely free from sutures and thus has a continuous peripheral wall. The sutures serve merely to attach the valve to the support structure. Another preferred way of fixing the leaflets of the valve to the support structure is by using bendable piercing members (like staples) along the support structure. It is possible to provide the support structure with these piercing members already during its manufacturing. It is also possible to provide them separately. These piercing members can be bent around the support perforating the tissue of the heart valve, and as such securing the valve in place. Other mechanical means, such as clamps or clips could also be used for fixing the leaflets along the support structure.

In some embodiments, the support structure comprises two annular discs for positioning the prosthetic heart valve in place, said two annular discs interconnected by a cylinder. By using two annular discs interconnected by a cylinder, the support structure can be positioned at the junction of e.g. the left heart ventricle and the aorta, in the place of the original malfunctioning heart valve (if the prosthetic heart valve is an aortic heart valve). Additionally, in combination with the heart valve comprising a bottom ring (if a mould with a bottom ring has been used) it avoids leaks around the prosthetic heart valve device.

Preferably, the support structure of the heart valve device is collapsible. Optionally, the support structure is made from nitinol. Heart valve replacement can occur in open heart surgery, but preferably it occurs percutaneously by using a catheter or in minimally invasive surgery, such as thoracotomy or sternotomy (or similar). To enable this, the support structure needs to be collapsible. One way of giving the support this collapsibility is to manufacture it (or its parts) with nitinol. Nitinol is a shape memory alloy and additionally has the necessary characteristic of biocompatibility. Alternatively, it is possible to use other shape memory alloys. A valve device with a nitinol support structure as such is self-expandable. It can expand to its proper size and shape once delivered in the appropriate position. Alternatively, the valve device may be made with a different support structure which may expand to its desired form using other known conventional means, such as by mechanical means or by a balloon. One known alternative way is e.g. the use of a balloon expandable stent as the support structure. Materials which may be used for the support structure in this case are e.g. stainless steel and cobalt chromium alloys.

The present invention is especially aimed at providing prosthetic heart valves and heart valve devices for replacing aortic and pulmonary heart valves. However, the invention may explicitly also be used to provide a prosthetic tricuspid or mitral valve.

These and further possible embodiments of the invention and their advantages will be explained, only by way of non-limiting example, with reference to the appended figures, in which:

Figure 1(a) is a perspective view of a preferred mould used in the method according to the present invention;

Figure 1(b) is a perspective view of another preferred mould used in the method according to the present invention;

Figure 1(c) is a top view of the mould shown in figure 1(a);

Figure 1(d) is a perspective view of yet another preferred mould used in the method according to the present invention;

Figures 2(a)-2(d) show perspective views of different steps in a preferred method of making a “closed” valve according to the present invention;

Figures 2(e)-2(h) show perspective views of different steps in a preferred method of making an “open” valve according to the present invention;

Figures 3(a)-3(c) show perspective, schematic views of three possible heart valves according to the invention.

Figures 4(a)-4(c) show perspective views of support structures that may be used in heart valve devices according to the present invention;

Figures 5(a) and 5(b) shows in perspective view two steps in a preferred method of making a “closed” heart valve device according to the present invention;

Figure 5(c) shows the top view of the heart valve device shown in 5(a);

Figure 5(d) shows a perspective view of an “open” heart valve device according to an embodiment of the present invention.

Before the heart valve is actually made, suitable tissue needs to be harvested. Preferably, biological tissue is tissue from bovine, equine or porcine pericardium. In principle, other biological tissue may be used as well. Preferably, the whole pericardial sac is harvested and is inspected for defects, such as blood in the tissue, or anatomical defects. Then the fat tissue is removed. Once a clean pericardium has been selected, it is normally put in a clean container in sterile distilled water or similar for cleansing and transportation. During the cleansing, the distilled water may be refreshed a number of times. The tissue is then transported to the laboratory where the heart valve is going to be made.

From the selected pericardium, the most suitable tissue must now be selected. Positive criteria used for this selection may include: homogeneous colour and texture of tissue, well hydrated, absence of blood, absence of grooves and homogeneous thickness (depending on the application, the desired thickness may be different, e.g. of at least a 100 microns. The invention is not limited in this sense.). A piece of tissue is then cut from the pericardium. This piece of tissue should of course be big enough to be placed over the mould used in the manufacturing process, and the exact dimensions of the selected piece may vary with the desired size of the heart valve and the mould chosen.

With reference to figures 1(a) and (b), two possible moulds (10) which may be used in the method according to the invention are shown. In figure 1(a), the mould includes a bottom ring (11), a cylindrical base (19) for forming a continuous cylindrical base in the resulting heart valve, and a three winged structure at the top for forming three leaflets. In figure 1(b), the mould does not have such a bottom ring, but has the same cylindrical base and the same three winged structure. In another mould that may be used, the bottom ring may be conical in shape (not disclosed in any figure). Yet another option is that the bottom ring (11) of the mould may be ridged or undulated (not disclosed in any figure) such that the resulting heart valve also comprises an undulated or ridged bottom ring. Both figures 1(a) and 1(b) refer to moulds that are suitable for making a "closed" heart valve. "Closed" valves have a partly cylindrical shape which is closed by three (or two) leaflets at one side. In use, under suitable pressure, these leaflets may move outward to open and let blood pass. The moulds shown in figures 1(a) and 1(b) have an appropriate shape with (in this case) three wings (17) for forming the leaflets of the heart valve.

Figure 1(c) shows a top view of the mould shown in figure 1(a). It more clearly shows the three wings (17) of the structure at the top of the mould. The cylindrical base (19) indicated in figure 1(a) may also be more pronounced, i.e. the point where the base transforms into the leaflets may be higher.

Figure 1(d) shows a cylindrical mould, which is suitable for making an “open” valve. “Open” valves have a substantially open cylindrical shape in a relaxed state. Their leaflets are merely defined by parts of the cylinder that can move inwardly when appropriate pressure conditions are created.

Figures 2(a) and 2(b) show the first steps according to the invention. The mould (10) shown in these figures has a substantially flat bottom ring. As has been mentioned before, this ring may also be conical or the mould may not have a ring. The biological tissue (12) has been made available and it is placed over the mould. The tissue placed over the mould is shown as hatched in this figure. The top side of the mould should be covered as completely as possible, in order for the tissue to take the shape of the mould. The goal of the bottom ring of the mould is that by covering the ring with tissue, a ring is formed which may reduce, in certain cases, the leaks around the valve when in use. Tension is applied to the tissue to shape it more accurately.

A negative mould (15), which has the negative shape of the positive mould (such as shown in figure 2(c)) may be placed over the tissue to help shape the tissue. At this point, the tanning process begins. The tissue including the mould (and optionally a second mould) is placed in a tanning solution. Preferably, a glutaraldehyde solution with a concentration between 0.1% and 1%, most preferably around 0.65%, is used. It is important to note that the shaping of the tissue and the tanning of the tissue occur simultaneously. This allows the valve to be formed from a single piece of biological tissue without any sutures.

The order of using the two moulds may also be reversed. The tissue may first be placed in negative mould (15) and then positive mould (10) may be used to help the tissue take the proper shape. In the following, the tanning and shaping process is described in a method using two moulds. It should however be noted that the tanning and shaping may also occur using a single mould.

Steps of an alternative method according to the present invention are illustrated in figures 2(e) - 2(g). Figure 2(e) shows a single piece of biological tissue (12) and a mould (10’). The mould (10’) is suitable for making an “open” valve. The biological tissue is placed over the mould (10’), similarly to the steps described before with respect to figures 2(a) and 2(b). Also, when forming an “open” valve, a negative mould (15’) may be used. This is illustrated in figure 2(g). Negative mould (15') has the negative shape of positive mould (10').

The tanning (and shaping) process may pass through various phases. One possibility is that after some 15 minutes, the negative mould is taken away and it is ensured that the tissue takes the desired shape of the mould by forcing it in the appropriate shape. The tissue may extend beyond the borders of the mould, since some form of tension may have been applied to the tissue to give it the appropriate shape. In a next step, the tissue, still on the positive mould, is placed in a fresh glutaraldehyde solution for a few hours, e.g. approximately two hours.

An alternative possibility is that the positive mould is taken away after some 15 minutes and the tissue stays positioned in the negative mould. It is important to also ensure in this case that the tissue assumes the desired shape, i.e. the tissue is manipulated in such a way that it has no folds. Then, the tissue, still in the negative mould, is placed in a glutaraldehyde solution for a few hours, e.g. approximately two hours.

Optionally, the next step may be to cut the tissue along the three wings of the mould to form three leaflets. This is illustrated in figure 2(d). Suitable scissors (13) or other cutting means may be used. The cut may be performed on the top of the union of the leaflets, e.g. by cutting parallel to the vertical plane of the valve. Alternatively, the cut may be performed slightly below the union of the leaflets by cutting in a plane perpendicular to the vertical plane of the valve. Additionally, it is possible to use both cutting methods. In the case of the open valve of figure 2(h), cuts are also made to provide a valve with a cylindrical shape, which is open on both sides. Notice that in this case, no cuts are made to form leaflets of the valve.

After these hours in the glutaraldehyde solution, the remaining mould is removed when it is ensured that the tissue has taken the appropriate shape. Yet another possibility is leaving the valve in or over the mould for a longer time. The benefit of removing the mould after a while is to put the tissue in contact with the glutaraldehyde along its entire surface, which accelerates the tanning process. By keeping the valve in the mould longer, the tanning process may be slower, but the valve will keep its shape better. A way to balance both these advantages and disadvantages can be to provide the mould with a plurality of perforations along its surface or to make the mould out of a meshed material, such that it is permeable to a certain extent.

The tanning may continue until the desired tanning level has been obtained. At this point, tissue that sticks out beyond the desired shape of the valve may be cut. But this should be done carefully; the final cut is only made after the heart valve has been fixed on a support structure.

At this point, the heart valve is ready to be positioned on a support structure. For reasons of clarity, the tissue is no longer hatched. Figures 3(a) and 3(b) show two possible embodiments of the heart valve (1) according to the invention. Figure 3(a) shows a heart valve (1) comprising three leaflets (2), a cylindrical base (3) and a bottom ring (4). If another mould is used, the resulting heart valve may look differently, as illustrated in figure 3(b). The cylindrical base (3) is much less pronounced and it does not have a bottom ring. Additionally in figure 3(b), the leaflets have already been separated through cuts (5). Both figures 3(a) and 3(b) refer to closed heart valves. Figure 3(c) illustrates an open valve (1'), which may result from the previously described process. In figure 3(c), the cylindrical base (3') cannot be readily be distinguished from the leaflets (2'). The composition of open valve (1') comprising a cylindrical base (3') and leaflets (2') can more clearly be recognized in figure 5(d). Also the open valve according to the present invention has a continuous peripheral wall.

A support structure (20) is shown in figure 4. It comprises a bottom annular disc (21), a top annular disc (23) connected with each other through a cylindrical structure (22). In the case of a prosthetic heart valve device used as a replacement aortic valve, the bottom disc (21) may be regarded as the ventricular disc and the top disc (23) may be regarded as the aortic disc. The top disc (23) preferably comprises three legs (24) for supporting three leaflets of the heart valve. In order to be able to replace a heart valve percutaneously or by minimally invasive surgery (i.e. not through open heart surgery), the support structure has to be made collapsible. A preferred way of making the support structure collapsible is by making it from nitinol. The heart valve device in this case is self-expandable. Alternative collapsible support structures may also be used. Suitable means for expanding the valve device once it has been delivered in the appropriate position may then need to be provided.

Another possible support structure is shown in figure 4(b), which shows a schematic view of a balloon expandable stent. A self-expandable stent may also be used, such as shown in figure 4(c). Such alternative structures are well known in the art. The invention is not limited to any particular support structure. Instead the heart valve according to the present invention may be used with any suitable support structure.

In a next step, to form a heart valve device ready for implant in the body, the support structure is placed over the heart valve. The legs (24) of the support structure are connected to the three leaflets (2), preferably though suturing or using mechanical means such as bendable piercing members, clips, or clamps. This has been shown, very schematically, in figure 5(a). The valve is also connected to the support along its bottom periphery. Non absorbable polyester may be used for suturing. In a next step, the leaflets (2) may be formed by cutting the tissue along the three dotted lines, indicated in figure 5(b). This way, the three leaflets (2) are formed. It is important to note that even though the legs may be sutured or otherwise attached to the support structure, the valve still has a continuous peripheral wall. As is also schematically indicated in figure 5(b), the remaining extra tissue is cut of along the bottom of the support. As was mentioned before, it is also possible that the three leaflets have already been formed by cutting in an earlier step.

For reasons of clarity, the tissue (12) is not shown as hatched in these figures. In figures 5(a) and 5(b), the tissue (12) that sticks out beyond its desired form has been left out, also for reasons of clarity. In figure 5(c), the top view of a heart valve device is shown and this extra tissue is shown. Part of this tissue may already have been removed in a previous step.

It is also foreseen that with an alternative design of the support structure the valve may be placed over the support structure (instead of the other way around). In this case, the support structure would still have three legs but would not have a top disc. The way of fixing the valve to the support structure is further similar to what was described before.

An open valve mounted on a similar support structure as shown in figures 5(a)-5(c) is shown in figure 5(d). The three leaflets 2’ of the heart valve device are formed by the parts of the cylindrical valve which are not attached to the three legs (24) of the support structure. The material in between the legs will move inward and outward in use due to the prevailing pressure conditions. The cylindrical base (3’) of the open valve is not visible, since it is covered by the support structure.

Once the prosthetic heart valve device has been made available, it should be inspected to ensure it has the appropriate dimensions and it is well connected to the support structure. If the inspection results are positive, the device should be made sterile before it can be implanted in a patient's body. The sterilization may take place through a chemical process or through radiation. These techniques are well known in the art.

Claims

1. A method of making a prosthetic heart valve (1,1') comprising the steps of placing a piece of biological tissue (12) in or over a mould (10, 10'), and simultaneously tanning said tissue and forming it to an appropriate shape.

2. A method of making a prosthetic heart valve according to claim 1, characterised in that the step of placing the biological tissue in or over a mould comprises using two moulds, a positive mould (10; 10') with substantially the desired shape of the valve and a negative mould (15; 15') with a negative shape of said positive mould (10; 10').

3. A method of making a prosthetic heart valve according to claim 2 and the step of placing the biological tissue in or over a mould comprises the steps of placing the tissue over said positive mould (10; 10') and then placing said negative mould (15; 15') over the biological tissue or comprises the steps of placing the biological tissue in said negative mould and then placing the positive mould within the negative mould.

4. A method of making a prosthetic heart valve according to any previous claim, characterised in that the mould has a bottom ring (11) and said step of placing said biological tissue in or over a mould includes folding the tissue around said bottom ring (11).

5. A method of making a prosthetic heart valve according to any previous claim, characterised in that said step of forming the tissue to an appropriate shape includes applying tension to the tissue.

6. A method of making a prosthetic heart valve according to any previous claim, including the additional step of cutting the biological tissue to form the leaflets (2; 2') of the valve.

7. A method of making a prosthetic heart valve according to any previous claim, characterised in that the prosthetic heart valve is a closed valve.

8. A method of making a prosthetic heart valve according to any of claims 1-5, characterised in that the prosthetic heart valve is an open valve.

9. A method of making a prosthetic heart valve device comprising the steps of claim 1 and the additional step of attaching the prosthetic heart valve to a support structure (20).

10. A prosthetic heart valve (1) of a single piece of biological tissue (12), said valve comprising a cylindrical base (3; 3') and leaflets (2; 2'), characterised in that said cylindrical base and leaflets have a continuous peripheral wall.

11. A prosthetic heart valve according to claim 10, characterised in that is a closed valve.

12. A prosthetic heart valve according to claim 10, characterised in that it is an open valve.

13. A prosthetic heart valve according to any of claims 10-12, characterised in that the heart valve is made by a method according to any of the claims 1-6.

14. A prosthetic heart valve device comprising a prosthetic heart valve according to any of claims 10-13 and a support structure (20; 20'; 20'') for supporting said valve.

15. A prosthetic heart valve device according to claim 14, characterised in that the support structure (20) comprises three legs (24) and the leaflets (2) of the valve are each connected to one of said legs.

16. A prosthetic heart valve device according to claim 14 or 15, characterised in that the support structure comprises two annular discs (21,23) for positioning the prosthetic heart valve in place, said two rings interconnected

by a cylindrical structure (22).

17. A prosthetic heart valve device according to claim 14, characterised in that the support structure is a balloon expandable or a self-expandable stent.

18. A prosthetic heart valve device according to any of claims 14-16, characterised in that the support structure is collapsible.

19. A prosthetic heart valve device according to claim 18, characterised in that, said support structure is made from nitinol.

20. A prosthetic heart valve device according to claim 18, characterised in that, said support structure is made from stainless steel or a cobalt chromium alloy.

21. A prosthetic heart valve device according to any of claims 14-20, characterised in that it is a prosthetic aortic or pulmonary heart valve device.

22. A prosthetic heart valve device according to any of claims 14-21, characterised in that is a percutaneous heart valve device.

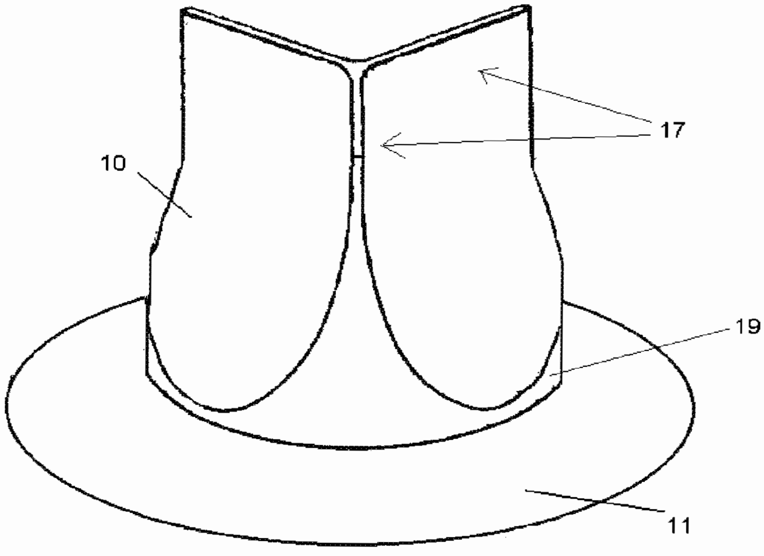

Figure 1(a)

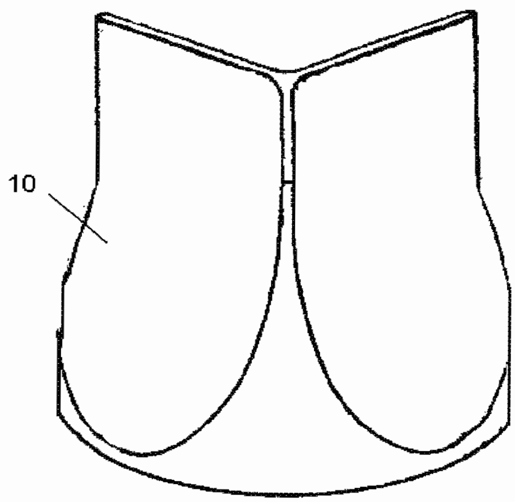

Figure 1(b)

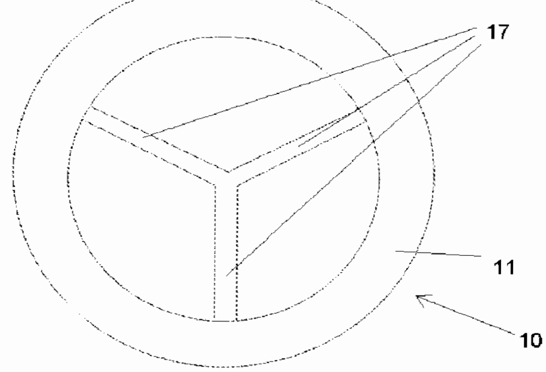

Figure 1(c)

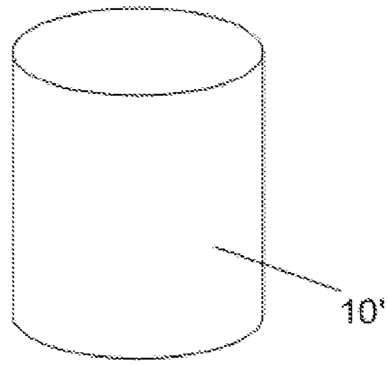

Figure 1 (d)

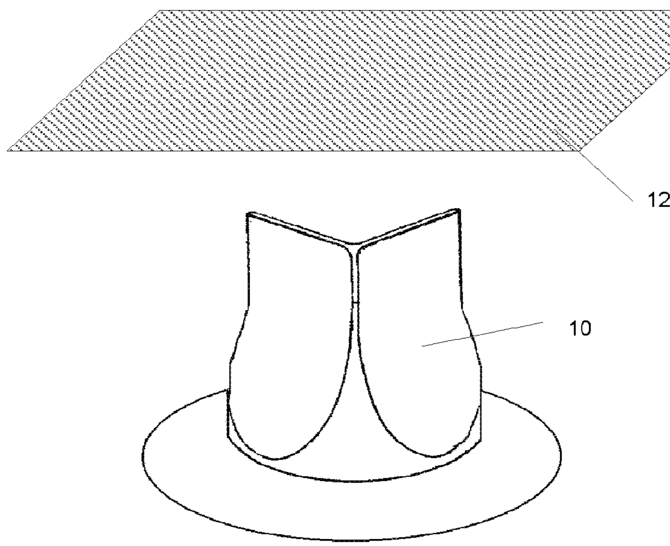

Figure 2(a)

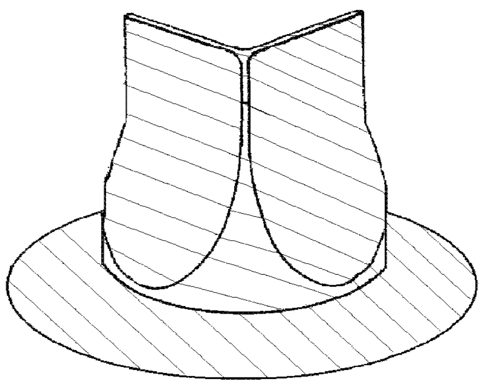

Figure 2(b)

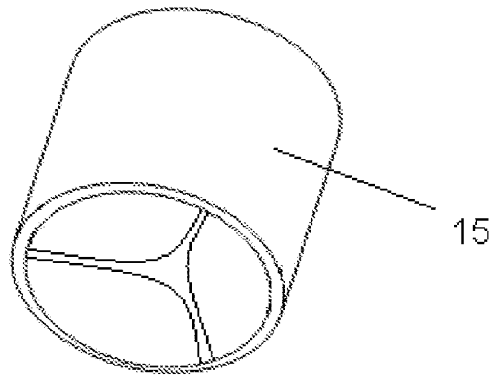

Figure 2(c)

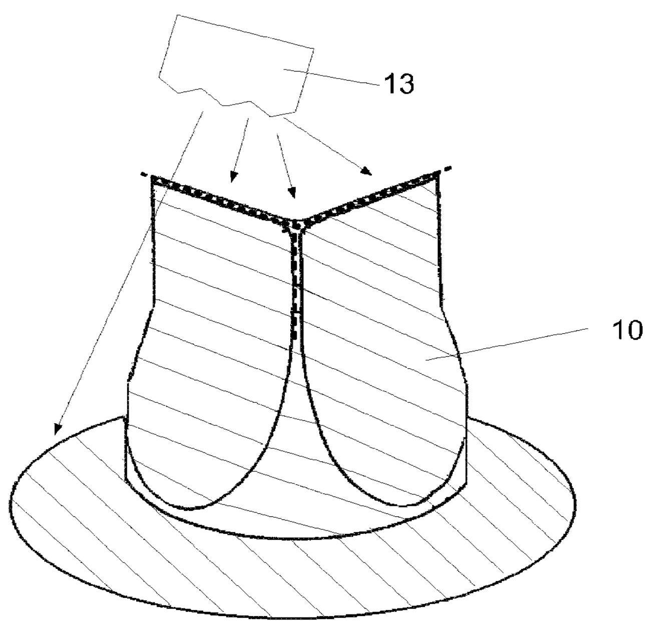

Figure 2(d)

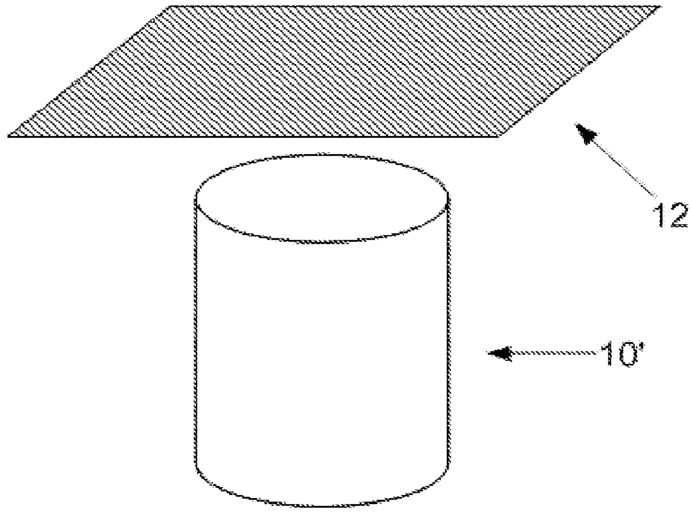

Figure 2(e)

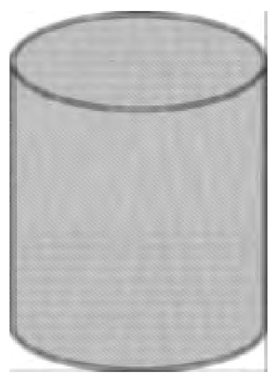

Figure 2(f)

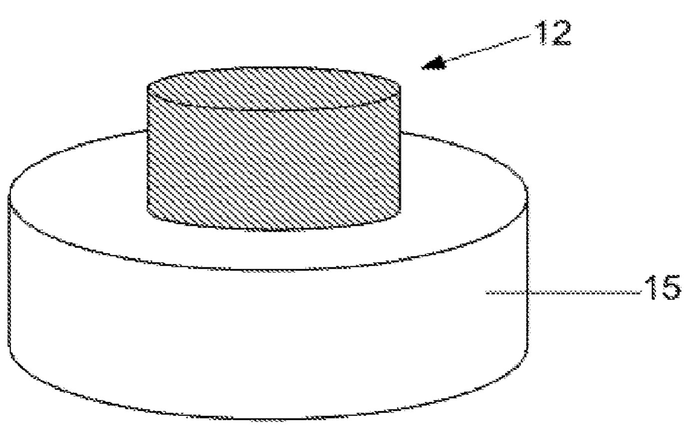

Figure 2(g)

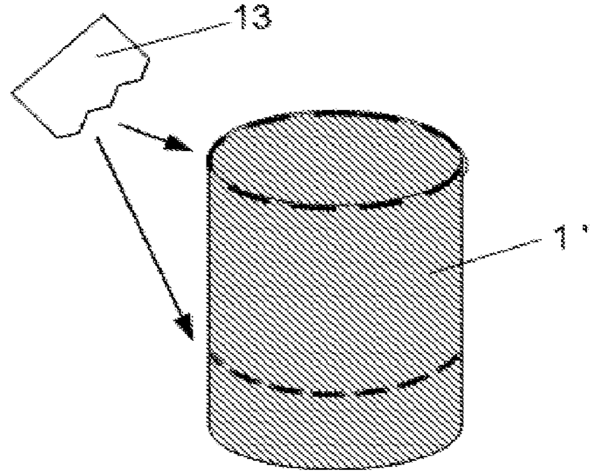

Figure 2(h)

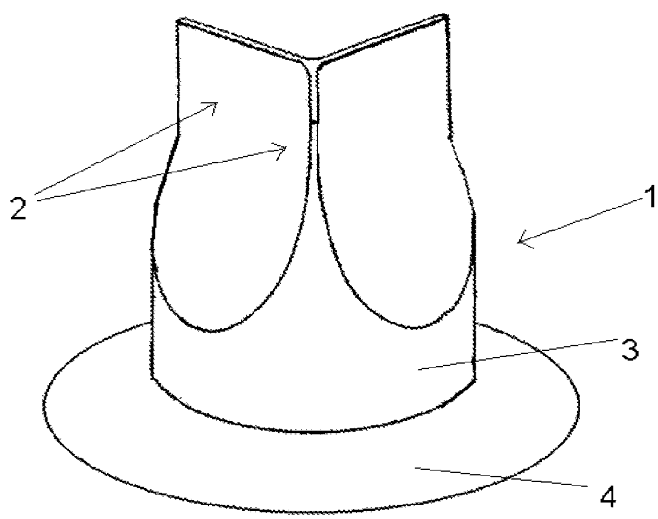

Figure 3(a)

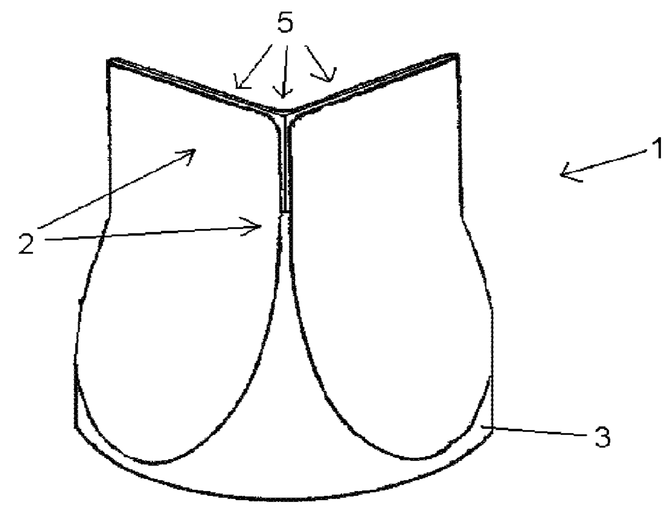

Figure 3(b)

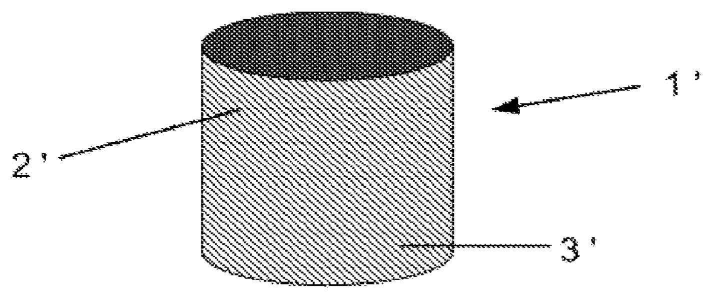

Figure 3(c)

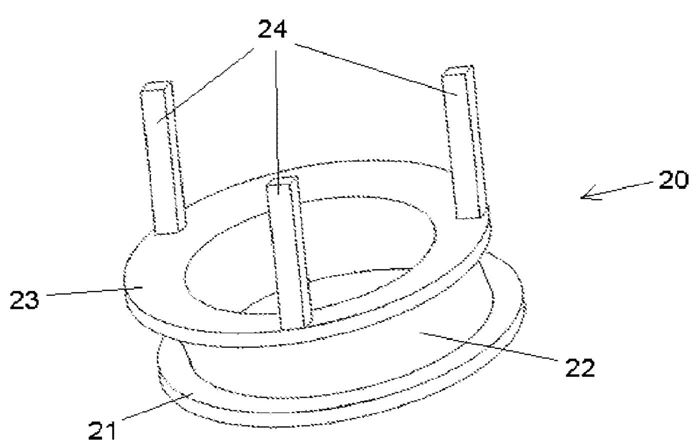

Figure 4 (a)

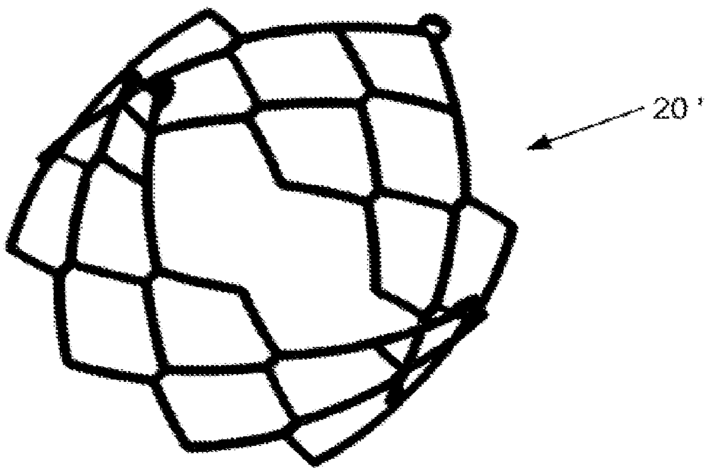

Figure 4 (b)

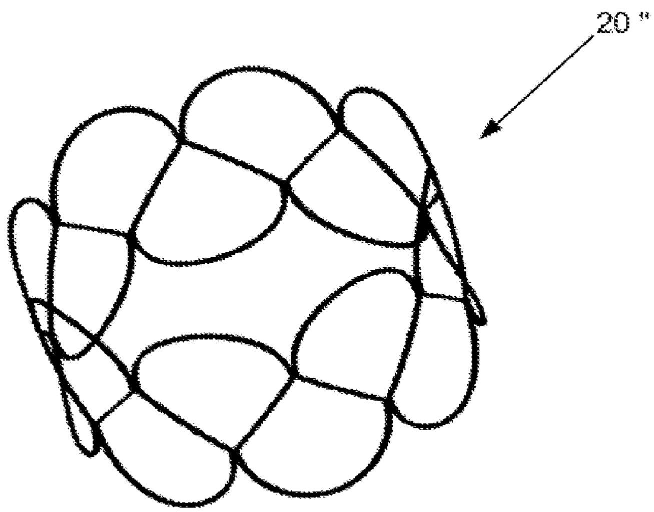

Figure 4(c)

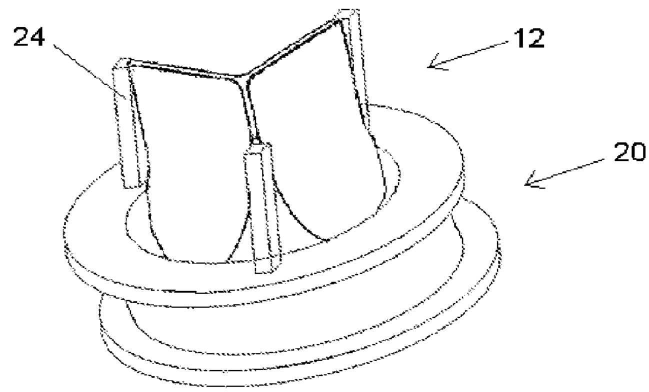

Figure 5(a)

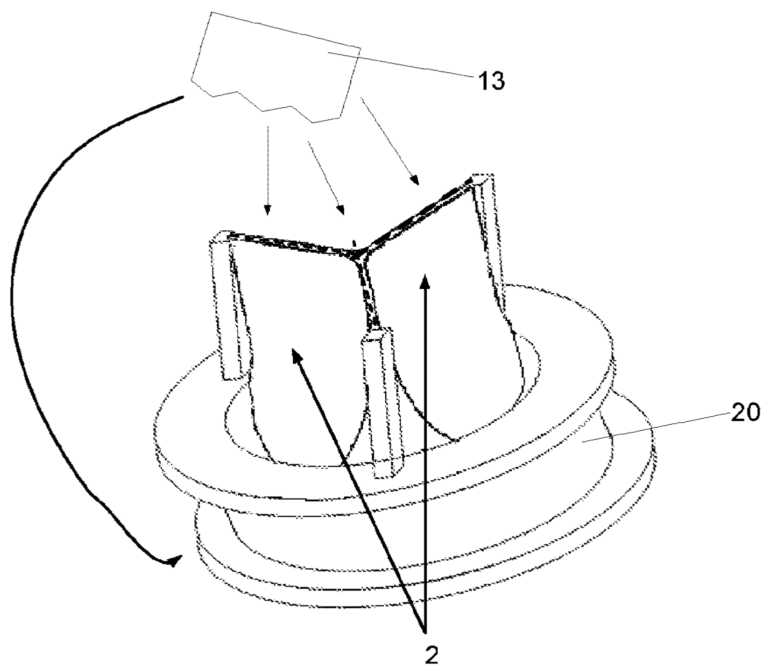

Figure 5(b)

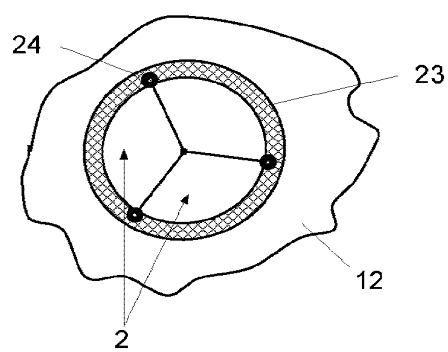

Figure 5(c)

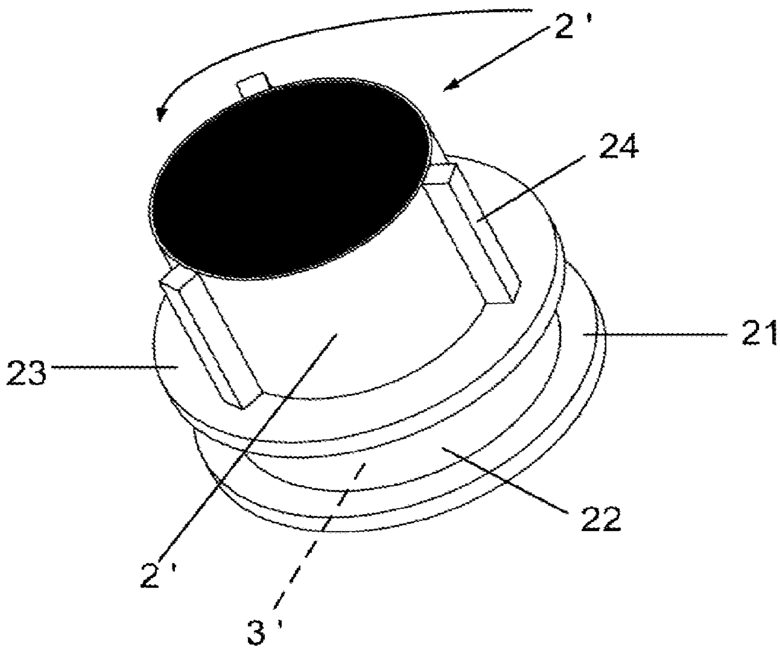

Figure 5(d)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/057970

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61F2/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 046 165 A (ROSS D N; BODNAR E) 12 November 1980 (1980-11-12) page 2, line 99 - page 3, line 31 figures 1-3 -----	1-3, 5-15, 17-22
X	US 6 129 758 A (LOVE JACK W [US]) 10 October 2000 (2000-10-10) column 12, lines 55-64 figure 5b -----	1-3,5-9
X	WO 2007/046000 A (UNIV NANYANG [SG]; YEO JOON HOCK [SG]; LIM KHEE HIANG [SG]; GOETZ WOLF) 26 April 2007 (2007-04-26) paragraph [0040] figures 2,4a,4b ----- -/--	1-3, 5-14, 17-22

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Espuch, Antonio

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/057970

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/26587 A (INTERNAT HEART INST OF MONTANA [US]) 19 April 2001 (2001-04-19) page 12, lines 26-28 page 14, lines 18-28 figures 17,18 -----	1-3, 5-14,21, 22
X	EP 1 671 604 A (PURDUE RESEARCH FOUNDATION [US]) 21 June 2006 (2006-06-21) paragraph [0038] figures 6a,6b	10-12, 14-22
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1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/057970

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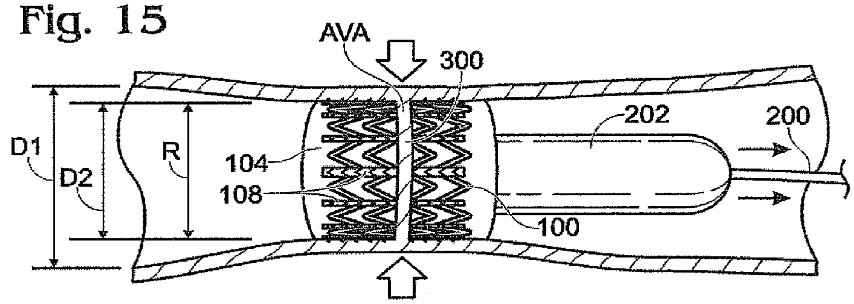
(54) **Title:** TRANSCATHETER HEART VALVE WITH MICRO-ANCHORS

Fig. 15



(57) **Abstract:** Various embodiments of methods and apparatus for treating defective heart valve are disclosed herein. In one exemplary embodiment, a transcatheter heart valve is disclosed that includes an expandable shape memory stent and a valve member supported by the stent. A plurality of micro-anchors can be disposed along an outer surface of the stent for engaging native tissue. The transcatheter heart valve can be configured to be advanced into a dilated valve annulus via a balloon catheter. The balloon can be inflated to expand the transcatheter heart valve from a collapsed diameter to an over-expanded diameter such that the micro-anchors engage tissue along the surrounding valve annulus. After engaging the tissue, the balloon can be deflated and the shape memory stent can retract or recoil toward its predetermined recoil diameter. As the stent recoils, the surrounding tissue is pulled inward by the stent such that the diameter of the valve annulus is reduced.

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TRANSCATHETER HEART VALVE WITH MICRO-ANCHORS

FIELD

[0001] The disclosed technology relates generally to methods and devices for improving valve function of a heart. For instance, embodiments of the disclosed technology can be used to treat aortic insufficiency in a human heart.

BACKGROUND

[0002] The aortic valve in the human heart is a one-way valve that separates the left ventricle from the aorta. The aorta is a large artery that carries oxygen-rich blood out of the left ventricle to the rest of the body. Aortic insufficiency is a condition in which the aortic valve does not fully close during ventricular diastole, thereby allowing blood to flow backward from the aorta into the left ventricle. This leakage of blood through the aortic valve back into the left ventricle is often referred to as aortic valve regurgitation.

[0003] Aortic insufficiency is typically caused by aortic root dilatation (annuloaortic ectasia), which is idiopathic in over 80% of the cases. Aortic insufficiency may also result from other factors, such as aging and hypertension. In any case, the regurgitation of blood resulting from aortic insufficiency substantially reduces the pumping efficiency of the left ventricle. Therefore, even during periods of rest, the heart must work hard simply to maintain adequate circulation through the body. Over time, this continuous strain on the heart can damage the left ventricle. For example, the additional strain on the heart may result in a thickening of the heart muscle (hypertrophy). When heart-wall thickening occurs due to aortic insufficiency, the geometry of the heart can be adversely affected and the heart can be permanently damaged.

[0004] Although aortic insufficiency is relatively common, the treatment of this condition still represents a substantial clinical challenge for surgeons and cardiologists. For example, because aortic insufficiency has a long latency period, afflicted patients may already be at significant risk for heart failure by the time the symptoms arise. In many cases, when patients are not monitored well for aortic insufficiency and are left untreated, the patient's left ventricle may become irreversibly damaged before therapy can be delivered. Therefore, even if a defective aortic valve is replaced with a prosthetic valve, the patient may never fully recover and their survival rate may be substantially impaired.

[0005] Existing methods of treating aortic insufficiency suffer from a number of significant disadvantages. For example, open heart surgical valve replacement is often too traumatic for older and/or frail individuals. Replacement of the aortic valve using existing catheterization techniques is also challenging because it is difficult to anchor a prosthetic valve within a soft and dilated annulus. More particularly, when a prosthetic valve is delivered to the site of the aortic valve and expanded, it engages and continuously exerts an outward force against the aortic valve wall. This continuous outward pressure is necessary for anchoring the prosthetic valve within the native valve but may also cause the already-dilated native aortic annulus to become further expanded. The tissue along the annulus of a valve suffering from aortic insufficiency is typically soft and flexible (as opposed to being hard and calcified as with aortic stenosis) and therefore the further expansion of the aortic annulus may lead to dislodgement of the prosthetic valve. Such dislodgement could require delivery of a still larger valve or result in death of the patient. A prosthetic valve with a very large diameter may be delivered via a catheterization technique to reduce the possibility of dislodgement. However, it follows that such a valve would also have a large diameter in its crimped condition. The delivery of such a large-diameter prosthetic valve is much more challenging and dangerous than the delivery of a relatively small prosthetic valve of the type currently used to treat aortic stenosis.

[0006] Therefore, a need exists for new and improved methods and devices for treating aortic insufficiency.

SUMMARY

[0007] Embodiments of the disclosed technology are directed to percutaneous (e.g., catheter-based) and/or minimally invasive surgical (MIS) procedures for treating aortic insufficiency. These less invasive therapies, which do not require open-heart surgery, provide patients with a more attractive option for early treatment of aortic insufficiency, thus mitigating or even avoiding the risk of damage to the left ventricle. These less invasive therapies also provide an urgently needed treatment option for patients who cannot be treated by open-heart surgery because they are too sick or frail to withstand the treatment. Unfortunately, at the present time, these "high-risk" patients are typically left untreated.

[0008] According to one exemplary embodiment disclosed herein, a system is provided for replacing the native aortic valve using a catheter-based approach. The system includes a transcatheter heart valve (THV), sometimes referred to herein as a "bioprosthesis." The transcatheter heart valve of this embodiment comprises a support structure, such as a stent, formed of, for example, a shape-memory material. The support structure can be configured to be radially compressible into a compressed state, expandable into an over-expanded state having a first diameter, and self-adjustable into a functional state having a second diameter less than the first diameter. The transcatheter heart valve can also include a flexible valve member or membrane, such as a prosthetic one-way valve member, within an interior of the support structure. In particular implementations, one or more grabbing mechanisms such as micro-anchors, are disposed on an outer surface of the support structure, where the grabbing mechanisms can be configured to penetrate or otherwise securably engage the support structure to surrounding native tissue, such as along a valve orifice when the support structure is expanded within the valve orifice.

[0009] In particular implementations, at least one of the one or more grabbing mechanisms comprises a projection having a hook, a sharpened barb, tree-shaped barbs, or an anchor-shaped barb. In some embodiments, at least one of the one or more grabbing mechanisms comprises a strip of projections disposed circumferentially around the support structure. In other implementations, at least one of the one or more grabbing mechanisms comprises a strip of projections disposed along a vertical axis of the support structure. At least one of the one or more grabbing mechanisms can include a projection that changes shape after a period of time. For example, the projection can be initially held in an undeployed state by a resorbable material.

[0010] The support structure, the one or more grabbing mechanisms, or both the support structure and the one or more grabbing mechanisms can be formed of a shape memory alloy, such as of Nickel-Titanium (Nitinol), in some embodiments. The support structure can be constructed with sufficient radial strength to maintain the native aortic valve in a dilated condition such that the prosthetic valve member can effectively replace the function of the native aortic valve, but is configured such that its diameter is not substantially greater than the native valve's diameter.

[0011] The flexible membrane can be a valve assembly having an inlet side and an outlet side, the valve assembly being configured to allow flow from the inlet side to the outlet side but prevent flow from the outlet side to the inlet side. In some embodiments, the flexible membrane is configured to replace an aortic valve.

[0012] Embodiments of a prosthetic heart valve can comprise an inner and outer support structure that can be delivered separately from one another. For example, one embodiment comprises an outer support structure configured to be radially compressible, expandable into an over-expanded state having a first diameter, and self-adjustable into a functional state having a second diameter less than the first diameter. The prosthetic heart valve can also comprise one or more grabbing mechanisms disposed on an outer surface of the outer support structure, the one or more grabbing mechanisms being configured to penetrate or otherwise securably engage the outer support structure to surrounding native tissue, and an inner support structure configured to be radially compressible and expandable into an expanded state within the interior of the outer support structure, where a flexible valve member can be secured within an interior of the inner support structure.

[0013] As with other embodiments, embodiments comprising an inner and outer support structure can also include at least one grabbing mechanism that comprises a projection having a hook, a sharpened barb, tree-shaped barbs, or an anchor-shaped barb. One or more of the outer support structure, the inner support structure, or the one or more grabbing mechanisms can be formed of a shape memory alloy. The flexible membrane can be configured to replace an aortic valve. The inner support structure can be configured to securably engage the interior of the outer support structure upon being expanded within the outer support structure.

[0014] In one exemplary method disclosed herein, the transcatheter heart valve can be "over-expanded" within a native aortic valve using a balloon catheter. More particularly, an expandable prosthetic heart valve can be positioned within a patient's aortic valve and expanded, such as by inflating a balloon of a balloon catheter around which the prosthetic heart valve is disposed, to an over-expanded diameter thereby causing one or more projections on an outer surface of the prosthetic heart valve to engage native tissue of the patient's aortic valve. The prosthetic heart valve can be allowed to retract toward a recoil diameter less than the over-expanded diameter (e.g., a "memorized" (if the support structure comprises a shape-memory alloy) or "recoil" diameter), such as by deflating the balloon. As the prosthetic heart valve recoils (reduces in diameter), the one or more projections are engaged with the native tissue of the patient's aortic valve, thereby reducing a diameter of the patient's native aortic valve. This can occur because the projections (*e.g.* micro-anchors) on the support structure are securely engaged with the tissue of the valve annulus. Conventional valves cannot undergo such over-expansion due to materials used and methods of manufacture.

[0015] In some embodiments, the expandable prosthetic heart valve comprises a support structure made of a shape memory alloy that causes the support structure to have the recoil diameter when the support structure is not acted on by any external force. In certain embodiments, the one or more projections include hooks, barbs, or anchors. At least one of the one or more projections changes its shape after penetrating the native tissue of the patient's aortic valve in some embodiments.

[0016] This exemplary method of implanting an over-expanded transcatheter heart valve has a number of advantageous features over known transcatheter heart valves. For example, unlike existing transcatheter heart valves, the over-expanded transcatheter heart valve does not apply an outward radial force on the native valve annulus after implantation. This is advantageous because, as discussed above, a regurgitating valve typically results from a diseased or aging valve annulus that is already substantially dilated. The application of a continuous outward radial force on a weakened and dilated annulus will usually dilate the annulus further. This could result in serious damage to the anatomical structure of the heart and, as the weakened aortic root dilates further, could eventually lead to dislodgement of the transcatheter heart valve.

[0017] By reducing the diameter of the surrounding annulus, it is also possible to replace the native aortic valve using a smaller transcatheter heart valve than would be typically required to treat aortic insufficiency. Due to the recoil of the support structure, the final diameter of the over-expanded transcatheter heart valve is substantially smaller than a conventional THV. A conventional THV must be expanded to a diameter that is capable of being securely maintained in a dilated valve annulus, whereas the over-expanded transcatheter heart valve constricts the annulus and therefore can have a smaller outer diameter. As a result of the smaller final diameter, the over-expanded transcatheter heart valve can also employ a smaller valve member. The smaller valve member allows the over-expanded transcatheter heart valve to be crimped to a much smaller diameter and have a smaller profile during advancement through the patient's vasculature. It will be recognized by those skilled in the art that a smaller diameter facilitates advancement of the transcatheter heart valve through a patient's vasculature.

[0018] Some methods for treating aortic insufficiency can comprise a two-stage delivery. For example, one method comprises positioning an outer stent within a patient's aortic valve, expanding the outer stent to an over-expanded diameter, thereby causing projections on the outer surface of the outer stent to engage tissue of the patient's aortic valve, allowing the outer stent to retract toward a recoil diameter that is less than the over-expanded diameter while the projections are engaged with the tissue of the patient's aortic valve, thereby causing the diameter of the patient's native aortic valve to be reduced, positioning a prosthetic heart valve within the outer stent, and expanding the prosthetic heart valve while the prosthetic heart valve is positioned within the outer stent.

[0019] In some embodiments, the act of expanding the prosthetic heart valve comprises frictionally securing the prosthetic heart valve within the outer stent, engaging grooves provided within the outer stent with complementary members of the prosthetic heart valve, or engaging a snap mechanism that causes the prosthetic heart valve to be secured within the outer stent, and/or inflating a balloon of a balloon catheter around which the outer stent is disposed. In certain embodiments, the act of allowing the outer stent to retract comprises deflating the balloon of the balloon catheter. In some methods, the outer stent comprises a shape memory alloy. In some methods, the prosthetic heart valve comprises a compressible and expandable inner support structure and a valve membrane secured in an interior of the inner support structure

[0020] The foregoing and other features and advantages of the invention will become more apparent from the following detailed description, which proceeds with reference to the accompanying figures.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] FIG. 1 is an anatomic anterior view of a human heart, with portions broken away and in section to view the interior heart chambers and adjacent structures.

[0022] FIG. 2 is a perspective view of a transcatheter heart valve formed with a shape-memory stent in accordance with an embodiment of the disclosed technology.

[0023] FIG. 3 is a perspective view of another embodiment of a transcatheter heart valve formed with a shape memory support structure according to the disclosed technology.

[0024] FIG. 4 shows an elevation view of one embodiment of a projection (or micro-anchor) that can be used with embodiments of a transcatheter heart valve.

[0025] FIG. 5 illustrates an elevation view of another embodiment of a projection (or micro-anchor) that can be used with a transcatheter heart valve.

[0026] FIG. 6 illustrates an elevation view of another embodiment of a projection (or micro-anchor) that can be used with a transcatheter heart valve.

[0027] FIG. 7 illustrates an elevation view of another embodiment of a projection (or micro-anchor) that can be used with a transcatheter heart valve.

[0028] FIG. 8 illustrates an elevation view of another embodiment of a projection (or micro-anchor) that can be used with a transcatheter heart valve.

[0029] FIG. 9 illustrates an elevation view of another embodiment of a projection (or micro-anchor) that can be used with a transcatheter heart valve.

[0030] FIG. 10 is a perspective view of a transcatheter heart valve formed with a shape memory support structure in accordance with another embodiment of the disclosed technology.

[0031] FIG. 11 is a simplified side view of a balloon catheter delivery system that is configured to over-expand the shape memory support structure at a target area inside a patient's body in accordance with an embodiment of the disclosed technology.

[0032] FIGS. 12-15 are simplified sectional views of a transcatheter heart valve being deployed in accordance with an embodiment of the disclosed technology.

[0033] FIGS. 16-20 show simplified sectional views of one embodiment of a transcatheter heart valve being deployed in a two-stage process according to an exemplary method of the disclosed technology.

[0034] FIGS. 21-25 show perspective views of additional embodiments of projections (or micro-anchors) that can be used with a transcatheter heart valve.

[0035] FIG. 26 is an elevation view of another embodiment of a transcatheter heart valve according to the disclosed technology. In particular, the embodiment illustrated in FIG. 26 has two attachable sections.

DETAILED DESCRIPTION

[0036] As used in this application and in the claims, the singular forms "a," "an," and "the" include the plural forms unless the context clearly dictates otherwise. Additionally, the term "includes" means "comprises." Although the operations of exemplary embodiments of the disclosed method may be described in a particular, sequential order for convenient presentation, it should be understood that the disclosed embodiments can encompass an order of operations other than the particular, sequential order disclosed. For example, operations described sequentially may in some cases be rearranged or performed concurrently. Further, descriptions and disclosures provided in association with one particular embodiment are not limited to that embodiment, and may be applied to any embodiment disclosed herein. Moreover, for the sake of simplicity, the attached figures may not show the various ways in which the disclosed system, method, and apparatus can be used in combination with other systems, methods, and apparatuses.

[0037] In vertebrate animals, the heart is a hollow muscular organ having four pumping chambers as seen in FIG. 1. The left and right atria 2, 4 and the left and right ventricles 6, 8, are each provided with their own one-way valve. The natural heart valves are identified as the aortic 10, mitral (or bicuspid) 12, tricuspid 14, and pulmonary 16, and are each mounted in an annulus comprising dense fibrous rings attached either directly or indirectly to the atrial and ventricular muscle fibers. Each annulus defines a flow orifice.

[0038] The atria 2, 4 are the blood-receiving chambers, which pump blood into the ventricles 6, 8. The ventricles 6, 8 are the blood-discharging chambers. The synchronous pumping actions of the left and right sides of the heart constitute the cardiac cycle. The cycle begins with a period of ventricular relaxation, called ventricular diastole. The cycle ends with a period of ventricular contraction, called ventricular systole. The four valves 10, 12, 14, 16 ensure that blood does not flow in the wrong direction during the cardiac cycle; that is, to ensure that the blood does not back flow from the ventricles 6, 8 into the corresponding atria 2, 4, or back flow from the arteries into the corresponding ventricles 6, 8. The mitral valve 12 is between the left atrium 2 and the left ventricle 6, the tricuspid valve 14 between the right atrium 4 and the right ventricle 8, the pulmonary valve 16 is at the opening of the pulmonary artery, and the aortic valve 10 is at the opening of the aorta. As discussed, in aortic insufficiency, the aortic valve 10 can become dilated, thus preventing the valve from fully closing. Embodiments of the present disclosure can be deployed to the aortic valve, specifically to the area of the aortic valve annulus, to treat aortic insufficiency.

[0039] FIG. 2 is a perspective view of an exemplary transcatheter heart valve 100 (also referred to as bioprosthesis 100). Bioprosthesis 100 includes a tubular support structure 102, a flexible membrane 104 (e.g., a valve member), a membrane support 106, and one or more grabbing mechanisms 108 affixed about a circumference of the support structure 102.

[0040] The support structure 102 in FIG. 2 can be formed of a shape memory material, such as Nitinol. In one exemplary embodiment, the support structure 102 can be radially compressed into a compressed state for delivery through the patient's vasculature, but can self expand to a natural, uncompressed or functional state having a preset diameter. In other words, the support structure 102 moves or tends toward a preset diameter when free of external forces. Furthermore, the support structure 102 can be expanded beyond its natural diameter to an over-expanded diameter. After the support structure 102 is in this over-expanded state, the support structure returns toward its preset diameter (or naturally recoils to the preset or recoil diameter).

[0041] The support structure 102 can be generally tubular in shape and has a longitudinal flow path along its structural axis. The support structure 102 can include a grated framework, such as a stent, configured to secure bioprosthesis 100 within or adjacent to the defective valve annulus of the heart. The support structure 102 further provides stability and prevents the bioprosthesis 100 from migrating after it has been implanted.

[0042] In alternative embodiments, the support structure 102 can comprise other shape memory alloys, or other materials capable of providing sufficient support for the bioprosthesis 100. Such materials can include other metals, metal alloys such as stainless steel or cobalt chromium, and/or polymers. The support structure 102 can have configurations other than that shown in FIG. 2. For example, the support structure 102 can have a different shape, more or fewer vertical support bars, and/or additional structures for added stability. The support structure 102 can comprise a strut mesh and/or sleeve structure.

[0043] The flexible membrane 104 is a valve member that is positionable in the flow path of the support structure 102 and that is configured to permit flow in a first direction but substantially resist flow in a second direction. In certain implementations, the flexible membrane 104 comprises a biological tissue formed into a valve member. The biological tissue which forms the valve member can comprise pericardial tissue harvested from an animal heart, such as porcine, bovine, or equine pericardium. The flexible membrane 104 can also comprise, alternatively or additionally, biocompatible materials including synthetic polymers such as polyglycolic acid, polylactic acid, and polycaprolactone, and/or other materials such as collagen, gelatin, chitin, chitosan, and combinations thereof.

[0044] The membrane support 106 can be positionable in the flow path and affixed to the support structure 102. Membrane support 106 can comprise polyethylene terephthalate (PET) (e.g., Dacron), or any other suitable material. The membrane support 106 can be positioned such that it folds under and around the bottom of the flexible membrane 104. The membrane support 106 can be sutured or otherwise affixed to the flexible membrane 104. In some embodiments, the membrane support 106 can comprise a skirt on the exterior surface of the flexible membrane 104, and a thinner ribbon on the interior surface of the flexible membrane 104, within the flow path. In this embodiment, the ribbon and skirt structures of the membrane support 106 can be sutured together, with a portion of the flexible membrane between them. In some embodiments, the membrane support 106 can be a thin layer of material, such as a layer of PET that can be from about 0.01 mm thick to about 0.2 mm thick. In some embodiments, the thickness of the membrane support 106 can vary from the center to the edge. For example, in one embodiment, the membrane support 106 can be about 0.07 mm thick at an edge, and about 0.05 mm thick at the center. In another specific embodiment, the membrane support 106 can be about 0.13 mm thick at the edge, and about 0.10 mm thick at the center. Additional details of the support structure 102, the flexible membrane 104, and the membrane support 106 are described in U.S. Patent Nos. 6,730,188 and 6,893,460, both of which are hereby incorporated herein by reference. Furthermore, U.S. Patent Nos. 6,730,188 and 6,893,460 describe additional prosthetic valve that can be modified according to the disclosed technology and used as part of any of the disclosed apparatus or systems or used with any of the disclosed methods or procedures.

[0045] In certain embodiments, grabbing mechanisms 108 are configured as strips of projections or micro-anchors 110. The grabbing mechanisms 108 can vary from implementation to implementation, but in certain implementations comprise any structure capable of at least partially penetrating and engaging the target tissue. For example, the projections 110 can be designed to at least partially penetrate and/or otherwise engage (*e.g.* by clamping or grabbing) the surrounding tissue upon over-expansion and to contract the aortic annulus and surrounding native tissue along with the support structure 102 upon recoil of the support structure 102. In other embodiments, the projections 110 may include barbed projections, umbrella projections, and/or hooks also designed to at least partially penetrate the tissue upon over-expansion and contract the aortic annulus and surrounding tissue upon recoil of the support structure 102.

[0046] As shown in FIG. 2, the grabbing mechanisms 108 can be positioned and coupled to the support structure 102 as vertical, or axial, strips of projections 110. In an alternative embodiment shown in FIG. 3, the grabbing mechanisms 109 can be positioned and coupled to the support structure 102 as one or more horizontal, or circumferential, strips of projections 111. For example, one or more strips of projections 111 can be disposed around the circumference of the support structure 102. Such grabbing mechanisms 109 can extend substantially around the circumference of the support structure 102, and/or strips of projections 111 can extend only partially around the circumference of the support structure 102, such as horizontal arcs of projections. In some embodiments, projections can be provided in one or more localized areas of the support structure 102, in addition to or instead of being provided in linear strips. In certain embodiments, one or more strips of projections can be provided along one or more struts or wires of the support structure 102, substantially paralleling the angles of the support structure 102. In another embodiment, the strips can be disposed circumferentially around the support structure 102 and located along the commissural supports (e.g. portions of the support structure wherein adjacent prosthetic leaflets meet and attach to the support structure) of support structure 102.

[0047] Some implementations of the bioprosthesis 100 shown in FIGS. 2 and 3 can comprise only one grabbing mechanism 108, 109. Alternative embodiments can comprise two or more grabbing mechanisms 108, 109. Further, the grabbing mechanisms 108, 109 can be manufactured separately from the support structure 102 and attached to the support structure through a suitable means (e.g., sutures, adhesive, weld, snap-fit mechanism, friction, and the like). Alternatively, the grabbing mechanisms 108, 109 can be formed as an integral feature of the support structure. Each grabbing mechanism 108, 109 generally comprises one or more projections or micro-anchors 110, 111. The projections or micro-anchors 110 can have any suitable dimension. For instance, the projections 110 can have a length from approximately 1 mm to approximately 2 mm. Projections 110 can be smaller in some embodiments, such as having a length from about .001 mm to about 1 mm. Alternatively, projections 110 can be larger in some embodiments, such as having a length from about 2 mm to about 6.5 mm or larger. In some embodiments, a grabbing mechanism 108, 109 can include a plurality of projections 110, where at least a first projection can be a different size from a second projection. A single grabbing mechanism can include a plurality of sizes of projections.

[0048] In some embodiments, the projections can be formed of a shape memory material that is configured to change shape. For instance, in one implementation, the projections can change shape after penetrating the tissue. For example, barbs at the tip of the projections can change in angle or configuration in relation to the projection after penetrating the tissue in order to more securely engage with the tissue. In another embodiment, the projections can change shape after expansion of the support structure 102. For example, the projections 110 can lay flat against the support structure 102 while the bioprosthesis is in its contracted configuration, and the projections can expand and the barbs can change shape to extend laterally outward from the projection to prevent the projection from slipping out of the tissue once the bioprosthesis 100 has been expanded.

[0049] In one variation, one or more projections can be configured with a delayed release mechanism, such that at least a portion of each projection changes shape after a period of time. This may be achieved by incorporating a resorbable material into the projection for temporarily holding the projection in a constrained condition. As the resorbable material is resorbed by the body, the projection becomes free to assume its relaxed condition. As the projection moves to its relaxed condition, its shape can change to more securely engage and hold the surrounding tissue. For example, barbs or hooks associated with the projection can initially be held against the main body portion of the projection until the resorbable material is resorbed. At that time, the barb or hook can extend outwardly from the main body portion, thereby creating a more secure attachment to the tissue in which the projection is inserted.

[0050] FIGS. 4-9 show elevation views of various embodiments of projections 400, 402, 404, 406, 408, 410 that can be used with embodiments of a transcatheter heart valve according to the present disclosure. In general, the projections 400, 402, 404, 406, 408 include a main body portion and one or more barbs. For instance, the illustrated projections include projection 400 with a single sharpened barb 401, projection 402 with a hook-shaped barb 403, projection 404 with an anchor-shaped (arrow head) barb 405, projection 406 with multiple branch-like barbs 407, projection 408 with multiple tree-shaped sharpened barbs 409, and hook-shaped projection 410. Suitable projections further include spikes, staples, fasteners, tissue connectors, or any other suitable projection capable of engaging with a patient's native tissue. Embodiments of suitable projections 400, 402, 404, 406, 408, 410 can be designed to penetrate the aortic valve annulus and engage or lodge within the thickness of the aortic valve annulus such that when the bioprosthesis retracts toward its natural state, the projections pull the patient's native tissue inward towards the center of the flow path, substantially without dislodging from their engaged positions. The barbs can be formed on the projections 400, 402, 404, 406 408 by laser cutting or other appropriate manufacturing method. Suitable materials for projections include Nitinol, other shape memory alloys, stainless steel, cobalt chromium, titanium, Elgiloy, HDPE, nylon, PTFE, other biocompatible polymers, resorbable materials, and combinations thereof. Other suitable materials are known in the art, and the projections of the present disclosure are not limited to those discussed.

[0051] FIGS. 21-25 illustrate additional possible embodiments of projections 416, 418, 420, 422, 424. FIG. 21 shows a projection 416 that has a square cross-sectional base and a pyramidal pointed tip, wherein a cutout between the base and the tip can facilitate engagement within a patent's native tissue. FIG. 22 shows a pointed projection 418 that can extend at an angle from the surface of a support structure or bioprosthesis. FIG. 23 shows an asparagus tip-like projection 420. FIG. 24 shows a conical projection 422. FIG. 25 shows another embodiment of a tree-like projection 424.

[0052] FIG. 10 is a perspective view of another embodiment of a transcatheter heart valve 100a (also referred to as bioprosthesis 100a) according to the disclosed technology. Bioprosthesis 100a includes a support structure 102a having a tubular or cylindrical base, a flexible membrane 104a (e.g., valve member), a membrane support 106a and at least one grabbing mechanism 108a affixed about a circumference of the support structure 102a. The support structure 102a is expandable from a first reduced diameter to a second enlarged diameter, and has a flow path along a structural axis. The support structure 102a generally can include a tubular framework, such as a stent, which primarily secures bioprosthesis 100a within or adjacent to the defective valve annulus of the heart. In this embodiment, the support structure 102a is configured to approximate the shape of the flexible membrane 104a such that the upper end of support structure 102a comprises peaks at the commissure supports and valleys (e.g. U-shaped cusps) between the commissure supports.

[0053] FIG. 26 is a perspective view of another embodiment of a transcatheter heart valve having two attachable sections 700, 702 that can be delivered separately. This embodiment can reduce the cross-sectional profile during delivery because each section 700, 702 can have a smaller delivery profile than the entire assembled bioprosthesis. In the illustrated embodiment, outer section 700 comprises an outer stent structure 710, and inner section 702 comprises an inner stent structure 720 and a valve member 722. In this embodiment, the inner stent structure 720 and the valve member 722 together form the expandable prosthetic heart valve. The outer section 700 can optionally include a temporary valve member 712, which can be thinner or less durable than the more permanent valve member 722. The temporary valve member 712 can be mounted on or otherwise secured to the outer stent structure 710 using any suitable mechanism (e.g., sutures, snaps, screws, friction, hooks, barbs, adhesives, and/or a slide structure). Furthermore, the temporary valve member 712 can be configured to have a diameter and flexibility suitable to receive the inner section 702 during valve delivery. The valve member 722 can be any valve as described herein and can be mounted to or otherwise secured to the inner stent structure 720 using any suitable means (e.g., sutures, snaps, screws, a slide structure, friction, hooks, barbs, and/or an adhesive).

[0054] In some embodiments, the outer section 700 can comprise a thin compressible member 712 that can facilitate securing the inner section 702 within the outer section 700. Such a compressible member 712 can create a tight seal between the outer section 700 and the inner section 702 as the inner section presses into the compressible material. Further details regarding a compressible member 712 are disclosed in U.S. Patent Application Publication No. 2008/0208327, which is hereby incorporated herein by reference.

[0055] According to one exemplary delivery procedure, and as more fully explained below in connection with FIGS. 16-20, the outer section 700 is delivered to the aortic valve first. The outer stent structure 710, like embodiments discussed above, can comprise a shape memory alloy such as Nitinol, and can have a predetermined recoil (or natural) diameter. The outer section 700 can be over-expanded to a diameter greater than its recoil diameter. For example, the outer section 700 can be disposed around a balloon catheter and delivered to the interior of the native heart valve. The balloon of the balloon catheter can then be inflated, causing the outer section 700 to expand to a diameter beyond its recoil diameter. In particular implementations, the outer section 700 comprises one or more grabbing mechanisms 708 configured to engage with the native tissue when the outer stent structure 710 is over-expanded. For example, the grabbing mechanisms 708 can be any of the grabbing mechanisms described above. Once the balloon of the balloon catheter is deflated and removed, the outer section 700 will contract to its memorized or recoil diameter. On account of the engagement of the grabbing mechanisms 708 to the surrounding tissue, the contraction of the outer section 700 will cause the size of the aortic annulus to be reduced as well. Inner section 702 can then be delivered and engaged with the outer section 700.

[0056] In an alternative method of delivering the two part bioprosthesis, the outer section 700 can be delivered to the interior of a native heart valve in a crimped state, and allowed to expand to its predetermined natural diameter, once positioned. A balloon can then be inserted within the outer section 700. When the balloon is expanded, the outer section can be over-expanded to a diameter greater than its natural diameter to allow the grabbing mechanisms of the outer section 700 to engage with the native valve tissue. When the balloon is deflated, contraction of the outer section 700 can cause the size of the aortic annulus to be reduced. When compared to the previous method, this can allow for delivering the outer section 700 in a smaller crimped state, because the outer section 700 is not crimped over the balloon for delivery; the balloon is not inserted until after the outer section 700 is first allowed to expand to its natural diameter. Inner section 702 can then be delivered and engaged with the outer section 700.

[0057] FIG. 11 is a simplified illustration of a balloon catheter 200, which can be used to deliver and deploy a bioprosthesis (such as bioprosthesis 100 shown in FIG. 2 above) into a native heart valve. In one embodiment, the balloon catheter 200 advances the bioprosthesis 100 through an outer sheath of the delivery system over a guide wire 204. The balloon catheter 200 can also be configured to aid in the delivery and positioning of the bioprosthesis 100 within the native valve. For example, as shown in FIG. 11, the balloon catheter 200 can include a tapered nose cone tip 206 at its distal end that allows a balloon portion 202 and bioprosthesis 100 to cross easily into the native valve. The balloon portion 202 can be inflated (*e.g.*, using a controlled volume of saline), causing the bioprosthesis 100 to expand within and engage the native hart valve.

[0058] In one exemplary method, the guide wire 204 is inserted into the femoral artery of a patient, advanced through the aortic arch of a patient, and into the aortic valve. The balloon catheter 202 is advanced through the outer sheath of the delivery system, over the guide wire 204, and into the aortic valve. The bioprosthesis 100 is then positioned and secured within the native valve by inflating the balloon portion 202. FIGS. 12-15, described below, illustrate one exemplary procedure for deploying the bioprosthesis 100 into the native valve. The balloon portion 202 can then be deflated, and the balloon catheter 202 retracted from the patient's aorta and femoral artery. An exemplary delivery system designed to deliver the bioprosthesis 100 is the RETROFLEX II catheter assembly available from Edwards Lifesciences in Irvine, CA. Furthermore, although the operation described above is a percutaneous transfemoral procedure, it should be understood that embodiments of the disclosed technology include the use of a shorter catheter assembly or semi-rigid cannula for deploying a bioprosthesis in a minimally invasive surgical (MIS) procedure, such as a trans-apical procedure. In a transapical procedure, the catheter or cannula is inserted through a gap between the ribs and is advanced through a small incision formed along the apex of the heart. This technique advantageously provides the surgeon with a direct line of access to the aortic valve. U.S. Patent Application Publication Nos. 2008/0065011, 2007/0005131, and 2007/008843 disclose further details regarding suitable delivery methods, and are hereby incorporated herein by reference.

[0059] FIGS. 12-15 are schematic cross-sectional views of a patient's aorta illustrating delivery of the support structure and valve of FIG. 2. As shown in FIG. 12, in one embodiment, the bioprosthesis 100 may be introduced into the patient's body using a percutaneous delivery technique with the balloon portion 202 of the balloon catheter 200 deflated, and the bioprosthesis 100 operably disposed thereon. The bioprosthesis can be contained in a radially crimped or compressed state. In embodiments using a self-expandable bioprosthesis 100, the bioprosthesis 100 can be held in a compressed state for delivery, by, for example, containing the bioprosthesis within an outer covering or sheath 201. The outer covering 201 can be removed or retracted, or the bioprosthesis 100 pushed through the outer covering 201, to allow the self-expandable bioprosthesis 100 to self-expand. In embodiments having a bioprosthesis that does not self-expand, such an outer covering may not be needed to retain the bioprosthesis in a crimped state, but can nonetheless be used if desired (*e.g.* to reduce friction during delivery).

[0060] In the embodiment illustrated in FIG. 12, the projections 110 of the grabbing mechanisms 108 are disposed around the outside circumference of support structure 102.

[0061] In the illustrated embodiment, the bioprosthesis 100 is introduced and positioned across the native aortic valve annulus (AVA) 300 by being inserted at least partially through native valve leaflets 302 and expanded. Because the AVA of an aortic valve suffering from aortic insufficiency is dilated, diameter D1 of the AVA 300 is expected to be larger than the diameter of a healthy AVA.

[0062] As shown in FIG. 13, outer sheath or covering 201 can be retracted or removed from over the bioprosthesis 100. In embodiments having a bioprosthesis 100 comprising a shape memory alloy, the bioprosthesis can expand from its crimped or compressed diameter d to a predetermined or memorized diameter R once the sheath 201 is removed.

[0063] As shown in FIG. 14, the balloon portion 202 of the balloon catheter 200 is expanded to increase the diameter of the support structure 102 from its relaxed diameter R (FIG. 13) to an over-expanded diameter OE such that the outer diameter of the bioprosthesis 100 equals or exceeds the original diameter D1 of the AVA 300. In this manner, the AVA 300 may expand beyond the diameter D1 as well. During the expansion, the projections 110 of the grabbing mechanisms 108 are forced to contact and can penetrate or otherwise engage (*e.g.* clamp or grab) the target tissue, which may include the AVA 300 and some of the tissue surrounding the AVA. This causes the bioprosthesis 100 to adhere to the surrounding tissue.

[0064] Next, as shown in FIG. 15, the balloon portion 202 of the balloon catheter 200 can be deflated, and the balloon catheter 200 removed from the AVA 300. In embodiments where the support structure 102 is formed of a shape memory material, removing the expansion force of balloon 202 from support structure 102 allows the support structure 102 to return from an over-expanded diameter OE (FIG. 14) to a recoil or relaxed diameter R. The manufacture of the support structure (*i.e.*, stent) determines what the recoil diameter will be. For example, the recoil diameter of a support structure comprising a shape memory alloy can be the memorized or functional diameter of the support structure. The recoil diameter of a support structure comprising, for example, stainless steel and/or cobalt chromium can be that of the natural or resting diameter of the support structure, once it inherently recoils from being over-expanded by the balloon 202. As the diameter of bioprosthesis 100 decreases to the recoil diameter R, the diameter of the AVA 300 also decreases to a final diameter D2. The AVA 300 can decrease in diameter due to the projections 110 of the support structure 102 pulling the target tissue inward.

[0065] An existing bioprosthesis is generally configured to be radially expanded to a diameter capable of providing secure fixation in a dilated AVA. However, as discussed above, existing bioprostheses are not well suited for treating aortic insufficiency due to the lack of firm tissue in the aortic annulus. Using existing technology, a larger bioprosthesis could be used to create a more secure fixation; however, a larger bioprosthesis cannot be easily crimped down for delivery via a catheterization technique. In contrast, embodiments of the present bioprosthesis 100 allow for the collapsed diameter of bioprosthesis 100 to be a smaller diameter because bioprosthesis 100 may be assembled with a smaller stent and a smaller valve member. This smaller size is possible because, rather than stretch the AVA, the present bioprosthesis advantageously reduces the diameter of the AVA during implantation. As a result, a smaller overall structure can be achieved which allows the support structure 102 of bioprosthesis 100 to be crimped to the smaller collapsed diameter and thus have a smaller profile for delivery through a patient's vasculature. For example, in some embodiments, bioprosthesis 100 can be crimped to a size of from about 4 French to about 7 French.

[0066] In alternative embodiments, the bioprosthesis 100 need not be operably disposed on the balloon 202 during delivery. For example, the bioprosthesis 100 can be crimped onto the catheter 200 at a different location than the balloon 202. The bioprosthesis can be allowed to self-expand once positioned within a patient's native aortic valve, and the balloon 202 can be positioned inside the self-expanded bioprosthesis 100 and inflated to then over-expand the bioprosthesis 100.

[0067] FIGS. 16-20 show simplified elevation views of one embodiment of a transcatheter heart valve being deployed in a two-stage process according to one method of the present disclosure. The illustrated method can be used, for example, to deliver the transcatheter heart valve assembly shown in FIG. 11. In the method illustrated in FIGS. 16-20, the outer section 700 can be deployed to the aortic valve separately from valve member 702. FIG. 16 shows the outer section 700 on a balloon 202, positioned inside the leaflets 302 of the aortic valve annulus 300. The outer section 700 can be a self-expanding stent, such as a stent comprising a shape memory alloy, or the outer section 700 can be simply balloon expandable, such as a stent comprising stainless steel, cobalt chromium and/or other suitable biocompatible materials. FIG. 17 shows the balloon 202 in an inflated configuration, which can expand the outer section 700 such that grabbing mechanisms 708 engage with the native tissue of the leaflets 302 and/or the aortic valve annulus 300.

[0068] As shown in FIG. 18, the balloon 202 can be deflated and removed. The outer section 700 can reduce the diameter of the aortic valve annulus 300 as it retracts after the balloon 202 is removed. The outer section 700 can retract to a functional or memorized diameter if it comprises a shape memory alloy, or the outer section 700 can simply naturally recoil or retract due to the ductility of the material. The inner section 702 can be positioned within the outer section 700 using a catheter 200 and a balloon 202, as shown in FIG. 19. As shown in FIG. 20, the balloon 202 can be expanded, thus expanding the crimped inner section 702, allowing it to engage with the outer section 700.

[0069] The outer section 700 and the inner section 702 can be delivered on a single catheter 200 or on separate catheters. For example, a catheter 200 can include two expandable balloons, one distal to the other. A first balloon can be used to expand the outer section 700 then deflated and either guided through the lumen of the expanded outer section 700 or removed back through the lumen. The second balloon and inner section 702 can then be positioned within the outer section 700, and the second balloon can be expanded, allowing for the inner section 702 to engage with the outer section 700. The second balloon can then be deflated, and the catheter 200 removed, thus removing the first and second balloons. In alternative embodiments, separate catheters can be used, such that a first catheter is used to deliver a first balloon and the outer section 700 to the native valve, and a second catheter is used to deliver a second balloon and the inner section 702 to the native valve once the outer section has been deployed and the first catheter has been removed.

[0070] While FIG. 16 illustrates the outer section 700 being delivered while already crimped on the balloon 202, in alternative embodiments, the outer section 700 can be located at a different position on the catheter 200 than the balloon 202. For example, in some embodiments, a crimped outer section 700 can be delivered to a native aortic valve and allowed to self-expand, such as by removing an outer covering. The balloon 202 can then be positioned within the expanded outer section 700 and inflated, thereby over-expanding the outer section 700, allowing the grabbing mechanisms 708 to engage with the native tissue. The balloon can then be deflated and removed, and the inner section 702 can be delivered and engaged with the outer section 700.

[0071] It should be understood that embodiments of bioprosthesis 100 can be deployed using a non-inflatable, mechanical embodiment of delivery catheter 200. Furthermore, bioprosthesis 100 can be delivered using any suitable delivery method, including both transapical and femoral artery delivery methods. Additionally, although the disclosed embodiments concern aortic valve replacement, embodiments of the disclosed technology can be used to replace any dilated heart valve (e.g., a dilated mitral valve). Moreover, although bioprosthesis 100 is used as an exemplary embodiment of the disclosed technology, it should be understood that bioprosthesis 100 and bioprosthesis 100a may be considered interchangeable with one other, or with any other bioprosthesis made or adapted in accordance with the teachings of the disclosed technology.

[0072] Having illustrated and described the principles of the disclosed technology, it will be apparent to those skilled in the art that the disclosed embodiments can be modified in arrangement and detail without departing from such principles. In view of the many possible embodiments to which the principles of the disclosed technologies can be applied, it should be recognized that the illustrated embodiments are only preferred examples of the technologies and should not be taken as limiting the scope of the invention. Rather, the scope of the invention is defined by the following claims and their equivalents. I therefore claim all that comes within the scope and spirit of these claims.

I claim:

1. A prosthetic heart valve comprising:

a support structure configured to be radially compressible into a compressed state, expandable into an over-expanded state having a first diameter, and self-adjustable into a functional state having a second diameter less than the first diameter;

a flexible valve member secured within an interior of the support structure; and

one or more grabbing mechanisms disposed on an outer surface of the support structure, the one or more grabbing mechanisms being configured to penetrate or otherwise securably engage the support structure to surrounding native tissue.

2. The prosthetic heart valve of claim 1, wherein at least one of the one or more grabbing mechanisms comprises a projection having a hook, a sharpened barb, tree-shaped barbs, or an anchor-shaped barb.

3. The prosthetic heart valve of claim 1, wherein the support structure, the one or more grabbing mechanisms, or both the support structure and the one or more grabbing mechanisms are formed of a shape memory alloy.

4. The prosthetic heart valve of claim 1, wherein the flexible membrane is a valve assembly having an inlet side and an outlet side, the valve assembly being configured to allow flow from the inlet side to the outlet side but prevent flow from the outlet side to the inlet side.

5. The prosthetic heart valve of claim 1, wherein the flexible membrane is configured to replace an aortic valve.

6. The prosthetic heart valve of claim 1, wherein at least one of the one or more grabbing mechanisms comprises a strip of projections disposed circumferentially around the support structure.

7. The prosthetic heart valve of claim 1, wherein at least one of the one or more grabbing mechanisms comprises a strip of projections disposed along a vertical axis of the support structure.

8. The prosthetic heart valve of claim 1, wherein at least one of the one or more grabbing mechanisms includes a projection that changes shape after a period of time.

9. The prosthetic heart valve of claim 8, wherein the projection is initially held in an undeployed state by a resorbable material.

10. A prosthetic heart valve comprising:

an outer support structure configured to be radially compressible, expandable into an over-expanded state having a first diameter, and self-adjustable into a functional state having a second diameter less than the first diameter;

one or more grabbing mechanisms disposed on an outer surface of the outer support structure, the one or more grabbing mechanisms being configured to penetrate or otherwise securably engage the outer support structure to surrounding native tissue;

an inner support structure configured to be radially compressible and expandable into an expanded state within the interior of the outer support structure; and

a flexible valve member secured within an interior of the inner support structure.

11. The prosthetic heart valve of claim 10, wherein at least one of the one or more grabbing mechanisms comprises a projection having a hook, a sharpened barb, tree-shaped barbs, or an anchor-shaped barb.

12. The prosthetic heart valve of claim 10, wherein any one or more of the outer support structure, the inner support structure, or the one or more grabbing mechanisms are formed of a shape memory alloy.

13. The prosthetic heart valve of claim 10, wherein the flexible membrane is configured to replace an aortic valve.

14. The prosthetic heart valve of claim 10, wherein the inner support structure is configured to securably engage the interior of the outer support structure upon being expanded within the outer support structure.

Fig. 2

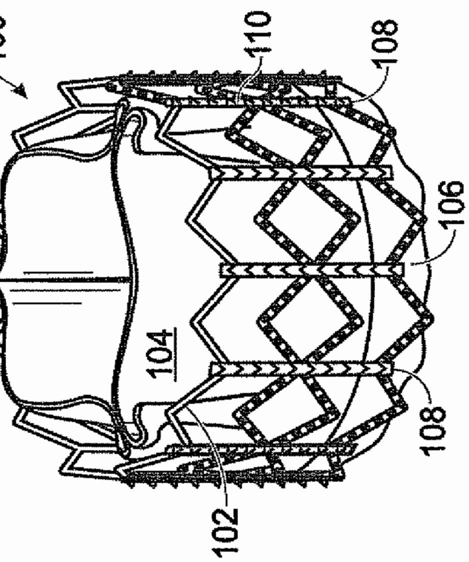


Fig. 3

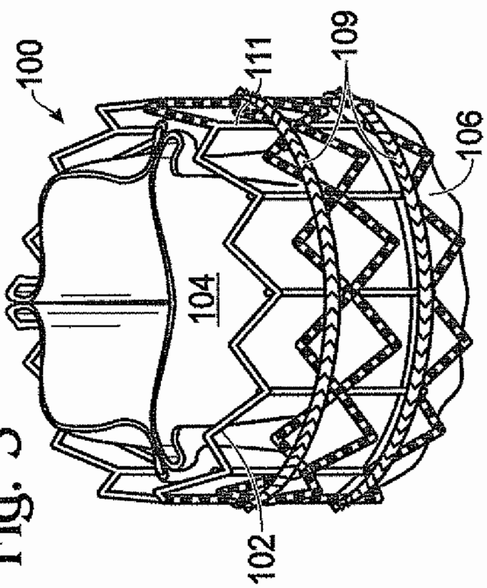


Fig. 1

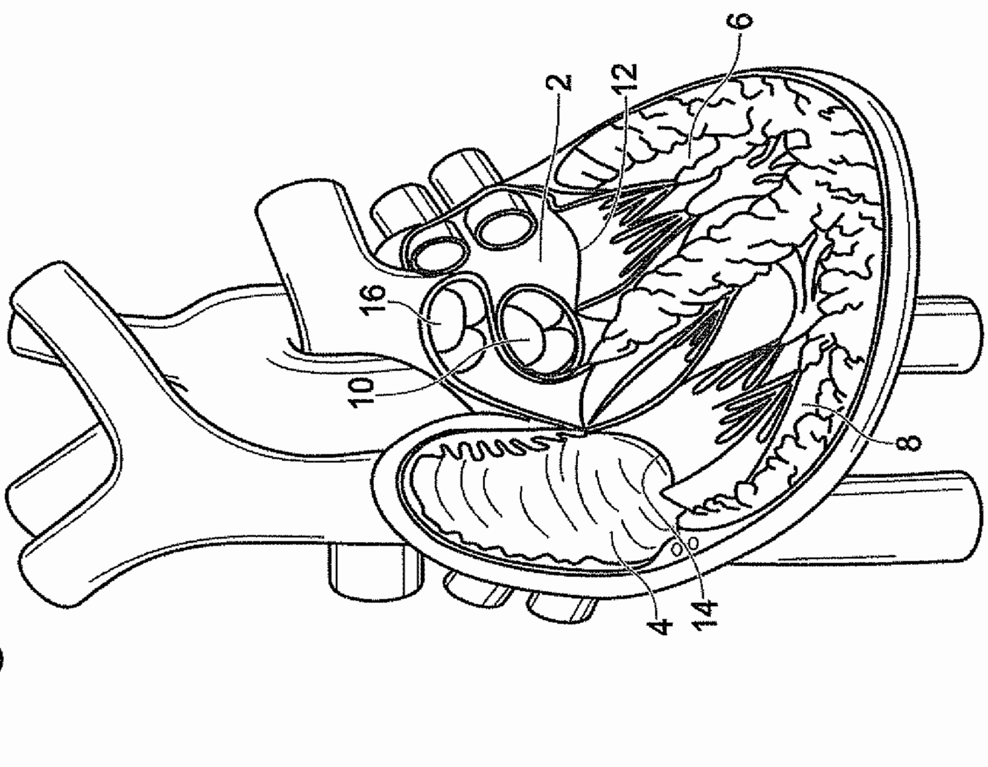


Fig. 4

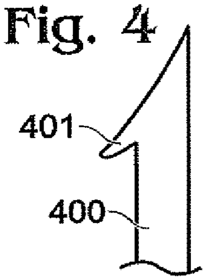


Fig. 5

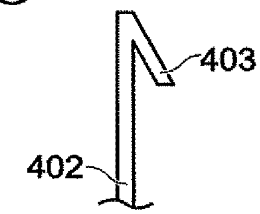


Fig. 6

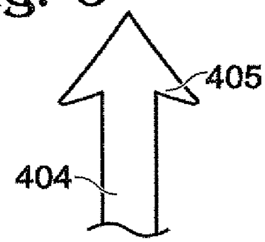


Fig. 7

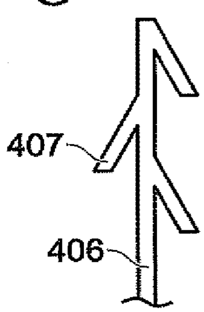


Fig. 8

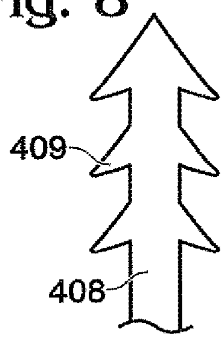


Fig. 9

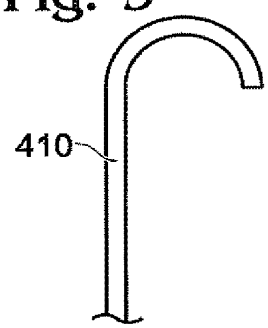


Fig. 10

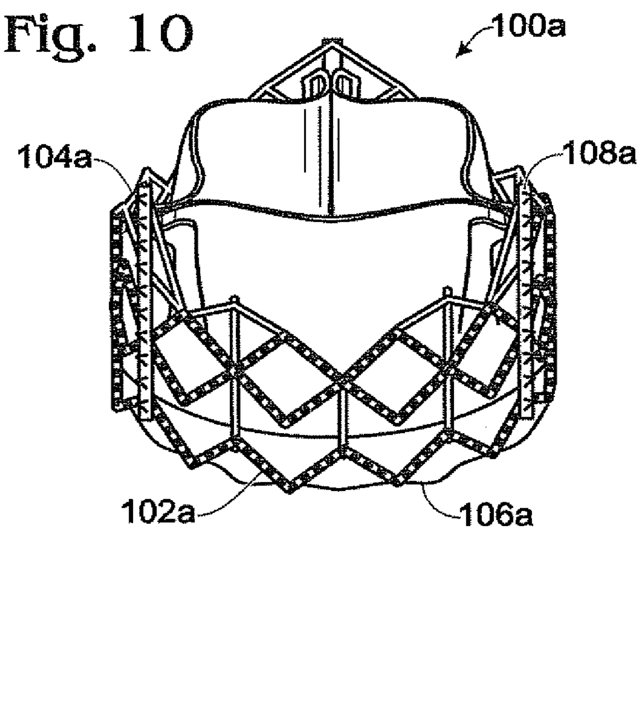


Fig. 11

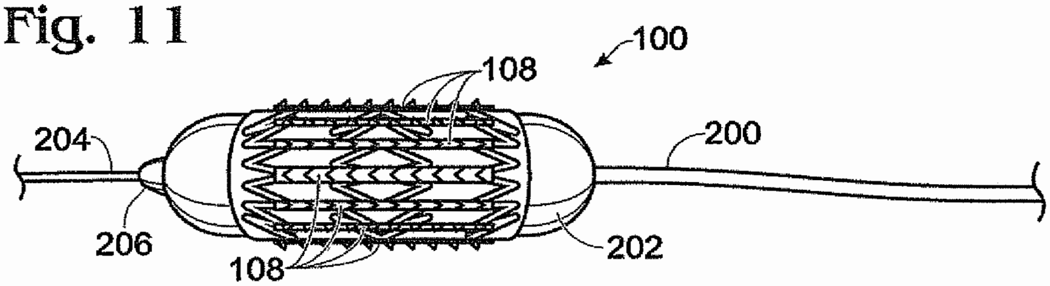


Fig. 12

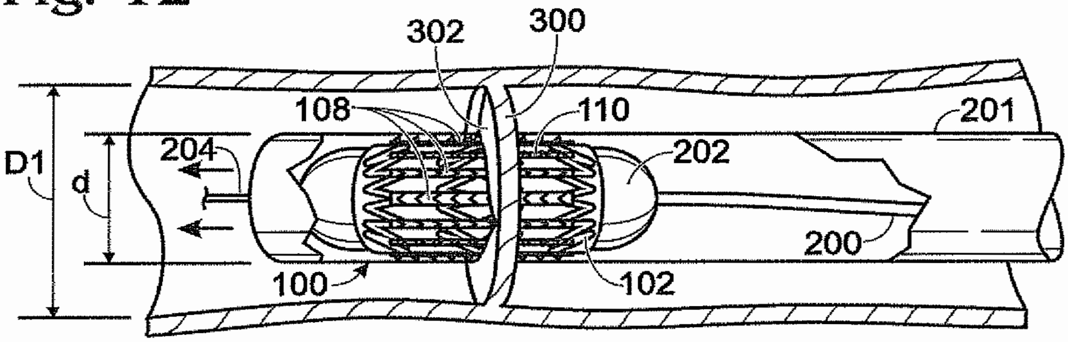


Fig. 13

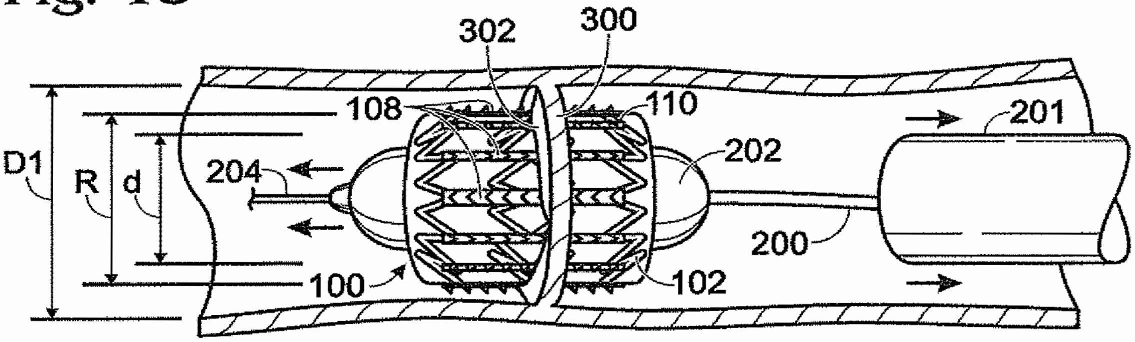


Fig. 14

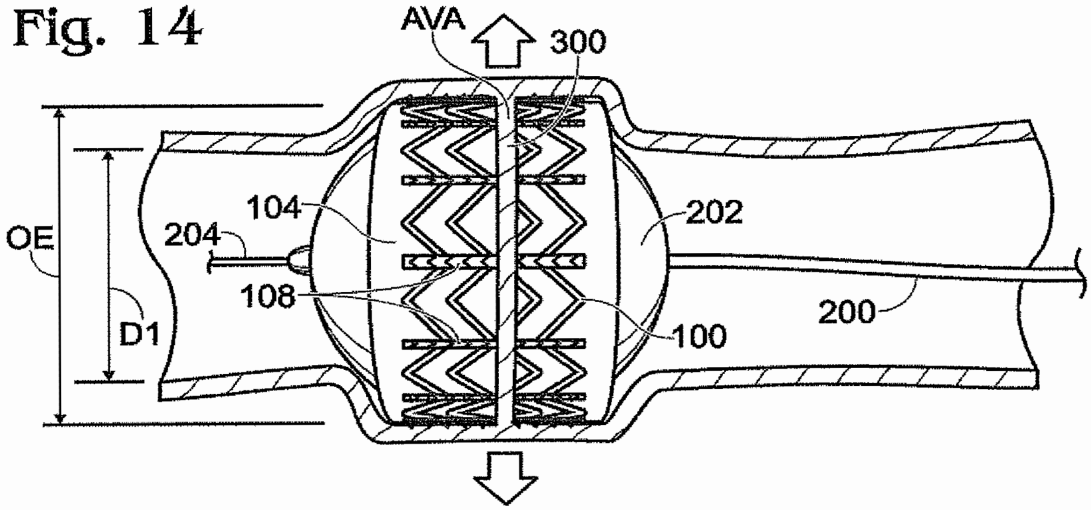


Fig. 15

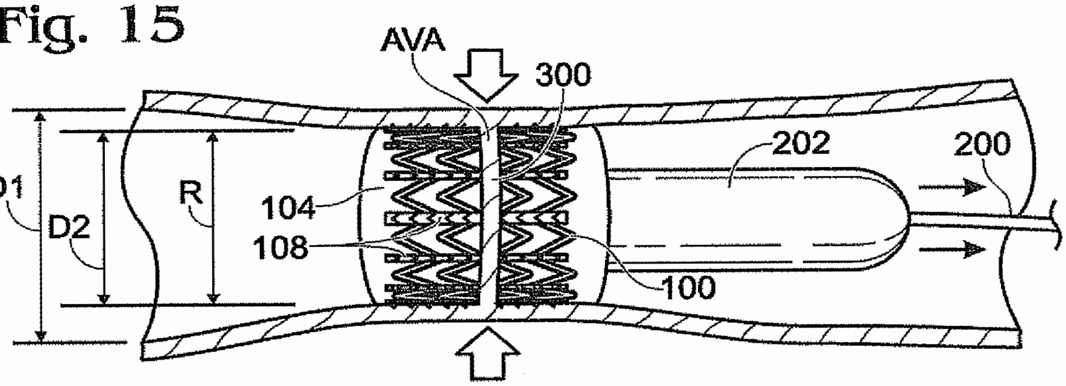


Fig. 16

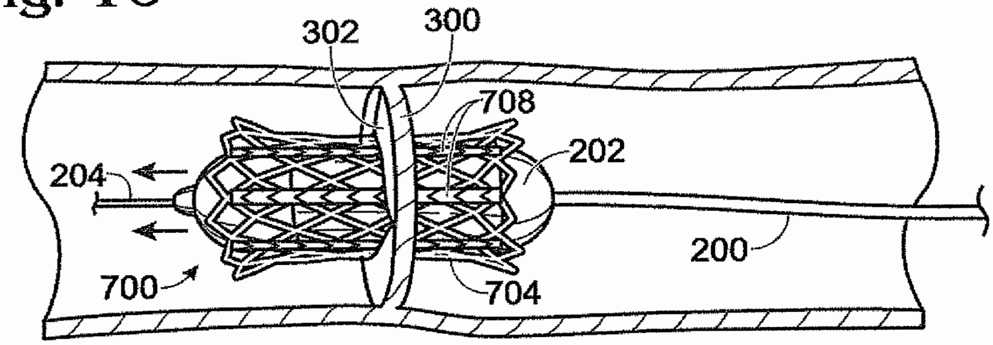


Fig. 17

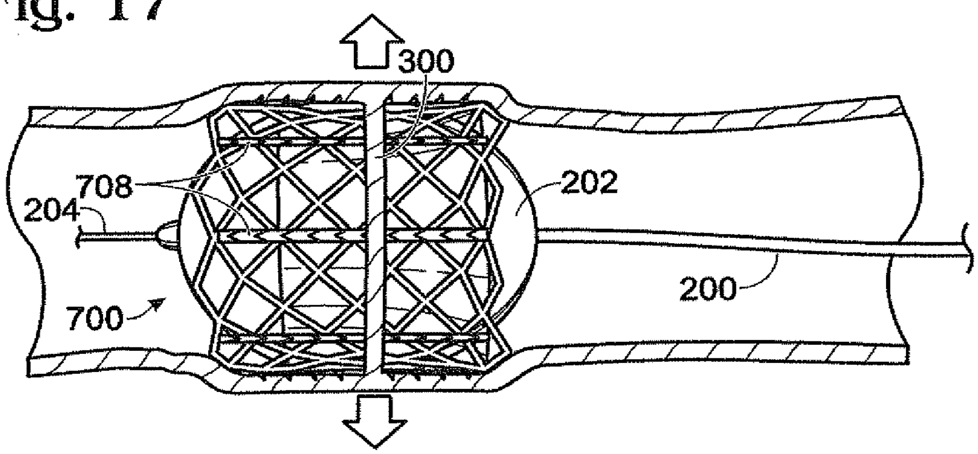


Fig. 18

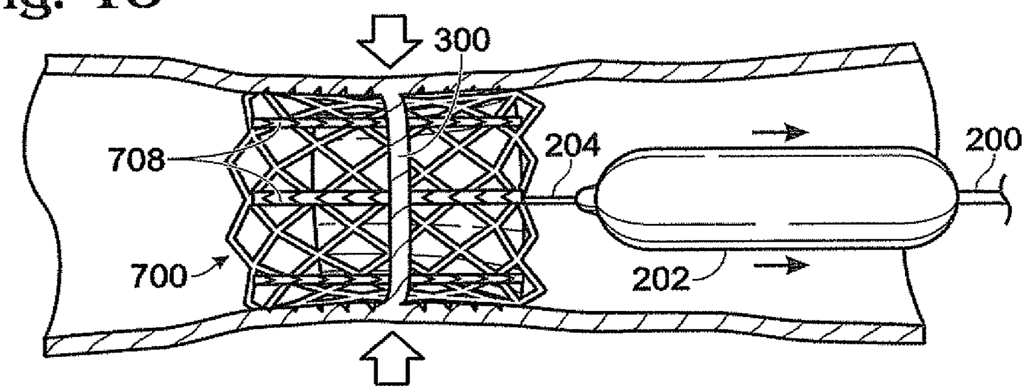


Fig. 19

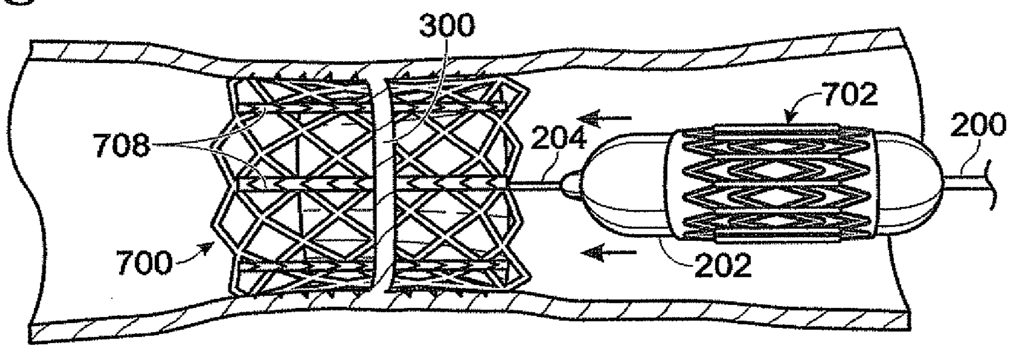


Fig. 20

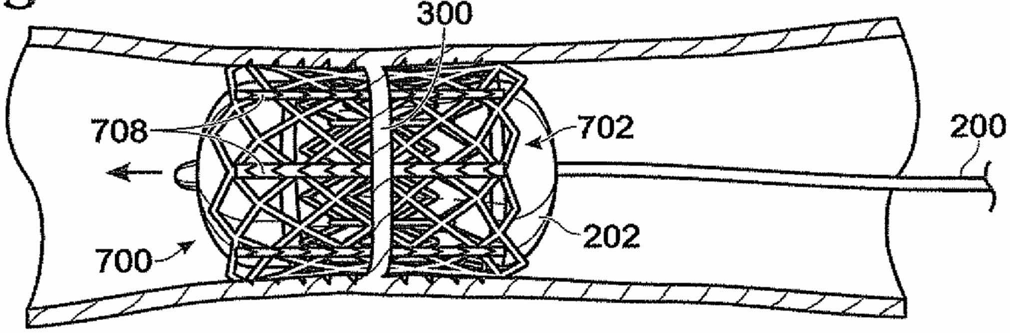


Fig. 21

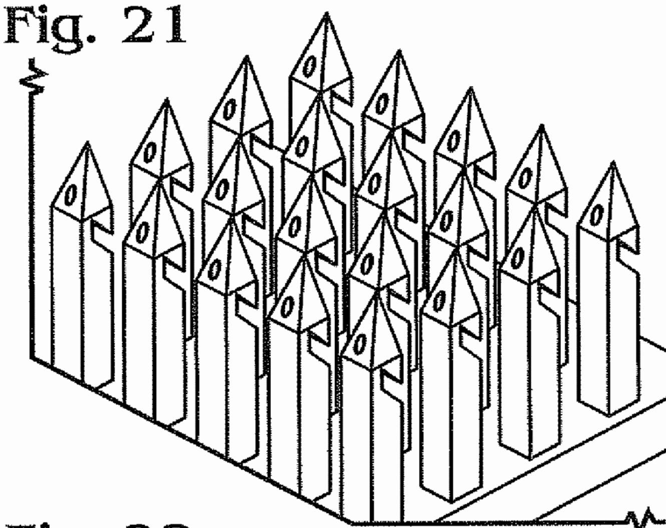


Fig. 23

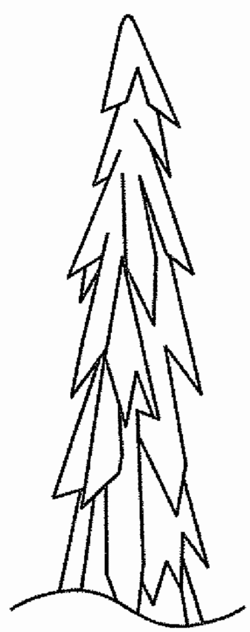


Fig. 22

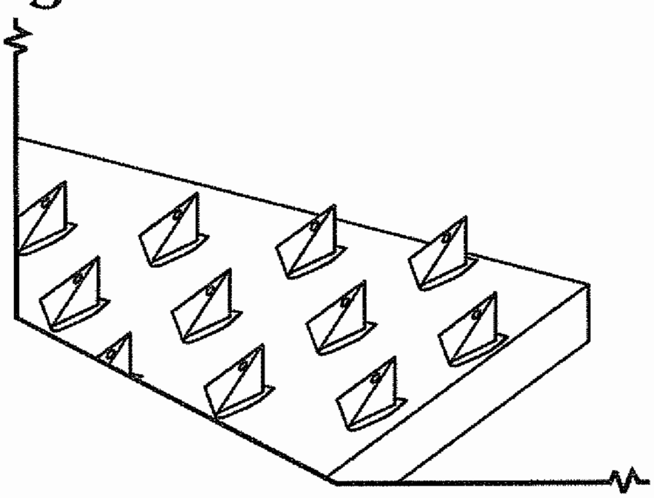
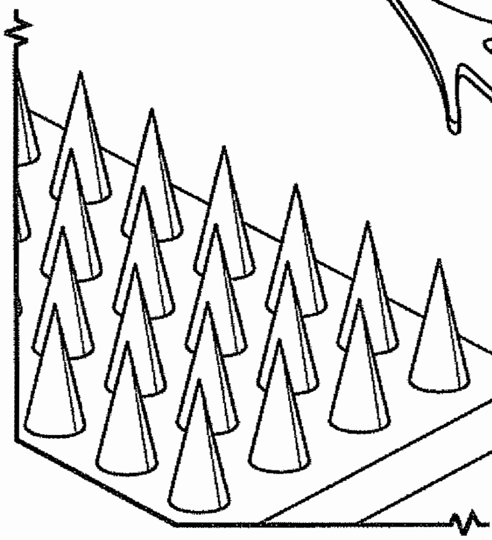


Fig. 25

Fig. 24



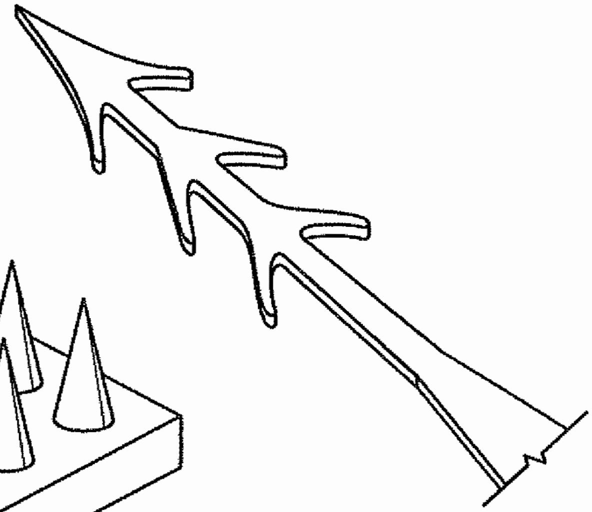
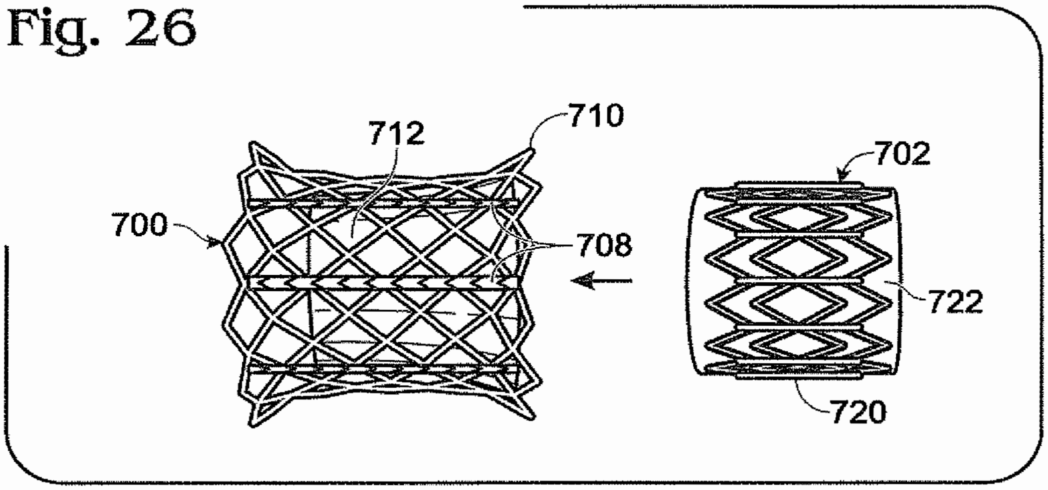


Fig. 26



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/080004

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61F2/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y A	WO 2007/053243 A (SADRA MEDICAL INC [US]; SALAHIEH AMR [US]; HILDEBRAND DANIEL [US]; SAU) 10 May 2007 (2007-05-10) paragraphs [0056], [0121]; figures -----	1-6 7-14 10-13
Y	WO 2006/127756 A (EDWARDS LIFESCIENCES CORP [US]; ROWE STANTON J [US]; WOOD LARRY [US];) 30 November 2006 (2006-11-30) paragraphs [0012], [0061], [0062], [0067], [0088] - [0092]; figures -----	7-9
Y	US 2006/129235 A1 (SEGUIN JACQUES [GB] ET AL SEGUIN JACQUES [GB] ET AL) 15 June 2006 (2006-06-15) paragraph [0081] - paragraph [0082]; figures -----	10-14

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 January 2009	23/01/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Neumann, Elisabeth

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/080004

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 2007/293942 A1 (MIRZAEE DARYUSH [US]) 20 December 2007 (2007-12-20) paragraphs [0034] - [0036], [0039]; figures	1,3-5
P,A		10,12,13
A	WO 2004/103223 A (CLEVELAND CLINIC FOUNDATION [US]) 2 December 2004 (2004-12-02) page 7, line 3 - line 9 page 16, line 6 - line 19 page 20, line 7 - page 21, line 14	1,10

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/080004

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 2007053243	A	10-05-2007	AU	2006309251	A1	10-05-2007
			CA	2623814	A1	10-05-2007
			EP	1926455	A2	04-06-2008
WO 2006127756	A	30-11-2006	CA	2607744	A1	30-11-2006
			CN	101180010	A	14-05-2008
			EP	1883375	A2	06-02-2008
			JP	2008541863	T	27-11-2008
			US	2006287719	A1	21-12-2006
US 2006129235	A1	15-06-2006	NONE			
US 2007293942	A1	20-12-2007	NONE			
WO 2004103223	A	02-12-2004	CA	2526347	A1	02-12-2004
			EP	1626682	A1	22-02-2006

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25 August 2008 (25.08.2008)

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(74) **Agents**: **SHOOP, Richard, D.** et al.; Shay Glenn LLP, 2755 Campus Drive, Suite 210, San Mateo, CA 94403 (US).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE,

[Continued on next page]

(54) Title: RETRIEVABLE CARDIAC DEVICES

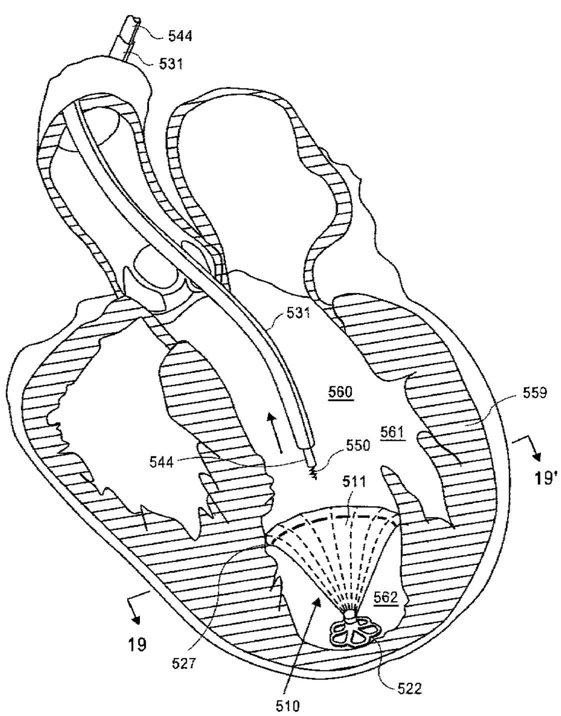

FIG. 18E

(57) Abstract: Removable cardiac implants, applicators for inserting, repositioning and/or removing them, and methods of using them are described. In particular, removable or repositionable ventricular partitioning devices are described. Systems including removable implants and applicators for inserting and/or removing them are also described.

WO 2010/024801 A1

ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

RETRIEVABLE CARDIAC DEVICES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application does not claim priority to any other patent application.

[0002] This application may be related to U.S. patent application Serial No. 10/463,959, filed on May 12, 2003 (titled "SYSTEM FOR IMPROVING CARDIAC FUNCTION") which is a continuation-in-part of prior U.S. patent application Ser. No. 09/635,511, filed on Aug. 9, 2000, which claims priority from U.S. provisional patent application No. 60/147,894 filed on Aug. 9,1999. This application is also a continuation-in-part of U.S. patent application Serial No. 11/151,164, filed on June 10, 2005, titled "PERIPHERAL SEAL FOR A VENTRICULAR PARTITIONING DEVICE." Each of these patent applications is herein incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0003] Described herein are systems, methods and devices for improving cardiac function, and may relate generally to the treating heart disease, particularly congestive heart failure, and more specifically, to a systems, methods, and devices for partitioning a patient's heart chamber.

[0004] Congestive heart failure annually leads to millions of hospital visits internationally. Congestive heart failure is the description given to a myriad of symptoms that can be the result of the heart's inability to meet the body's demand for blood flow. In certain pathological conditions, the ventricles of the heart become ineffective in pumping the blood, causing a back-up of pressure in the vascular system behind the ventricle.

[0005] The reduced effectiveness of the heart is usually due an enlargement of the heart. A myocardial ischemia may, for example, cause a portion of a myocardium of the heart to lose its ability to contract. Prolonged ischaemia can lead to infarction of a portion of the myocardium (heart muscle) wherein the heart muscle dies and becomes scar tissue. Once this tissue dies, it no longer functions as a muscle and cannot contribute to the pumping action of the heart. When the heart tissue is no longer pumping effectively, that portion of the myocardium is said to be hypokinetic, meaning that it is less contractile than the uncompromised myocardial tissue. As this situation worsens, the local area of compromised myocardium may in fact bulge out as the heart contracts, further decreasing the heart's ability to move blood forward. When local wall motion moves in this way, it is said to be dyskinetic, or akinetic. The dyskinetic portion of the myocardium may stretch and eventually form an aneurysmic bulge. Certain diseases may cause a global dilated myopathy, i.e., a general enlargement of the heart when this situation continues for an extended period of time.

[0006] As the heart begins to fail, distilling pressures increase, which stretches the ventricular chamber prior to contraction and greatly increases the pressure in the heart. In response, the heart tissue reforms to accommodate the chronically increased filling pressures, further increasing the work that the now comprised myocardium must perform.

[0007] Patients suffering from congestive heart failure are commonly grouped into four classes, Classes I, II, III and IV. In the early stages, Classes I and II, drug therapy is presently the most common treatment. Drug therapy typically treats the symptoms of the disease and may slow the progression of the disease, but it cannot cure the disease. Presently, the only permanent treatment for congestive heart disease is heart transplantation, but heart transplant procedures are very risky, extremely invasive and expensive and are performed on a small percentage of patients. Many patient's do not qualify for heart transplant for failure to meet any one of a number of qualifying criteria, and, furthermore, there are not enough hearts available for transplant to meet the needs of CHF patients who do qualify.

[0008] Substantial effort has been made to find alternative treatments for congestive heart disease. For example, surgical procedures have been developed to dissect and remove weakened portions of the ventricular wall in order to reduce heart volume. This procedure is highly invasive, risky and expensive and is commonly only done in conjunction with other procedures (such as heart valve replacement or coronary artery by-pass graft). Additionally, the surgical treatment is usually only offered to Class III and IV patients and, accordingly, is not an option for most patients facing ineffective drug treatment. Finally, if the procedure fails, emergency heart transplant is the only presently available option.

[0009] Mechanical assist devices have been developed as intermediate procedures for treating congestive heart disease. Such devices include left ventricular assist devices and total artificial hearts. A left ventricular assist device includes a mechanical pump for increasing blood flow from the left ventricle into the aorta. Total artificial heart devices, such as the Jarvik heart, are usually used only as temporary measures while a patient awaits a donor heart for transplant.

[0010] Other efforts to treat CHF include the use of an elastic support, such as an artificial elastic sock, placed around the heart to prevent further deleterious remodeling. Treatment of the heat by mechanical means typically requires accurate and effective placement of treatment devices. Once a treatment device is implanted, it is often difficult (if not impossible) to correct or adjust placement of a treatment device. Furthermore, removal of a treatment device may require further invasive procedures. Thus, it would be beneficial to provide device, systems and methods for removal of cardiac treatment devices that may address these problems.

[0011] Described herein are treatment devices that are configured to be removable (or re-positionable), systems for removing and/or repositioning such devices, and methods of removing and/or repositioning treatment devices.

SUMMARY OF THE INVENTION

[0012] Described herein are devices and systems including removable implants, applicators for inserting, repositioning and/or removing them, and methods of removing them. The implants described herein are cardiac implants that may be inserted into a chamber of a patient's heart, particularly the left ventricle. The implant may support the heart wall. In some variations the implant is a ventricular partitioning device for partitioning the ventricle into productive and non-productive regions.

[0013] An implant typically includes a frame comprising a plurality of struts formed of a relatively elastic and biocompatible material. For example, the frame may be formed of a metal or metal alloy. The frame may be formed of a shape memory alloy such as Nitinol. The implant may also include a membrane connected to the frame. The struts of the frame may include a first end that is connected to a hub, and a second end that includes a passive anchor. A passive anchor may be configured to secure the strut to the wall of the heart. For example, the passive anchor may be a sharp tip that is configured to partially penetrate the heart wall. The implant may also include a foot or anchor (including an active anchor) at the distal end.

[0014] In general, an implant may be inserted into a heart chamber using an applicator. An applicator typically includes a proximal end which may include a handle and may also include one or more controls for operating the applicator. The applicator may also include an elongate body extending distally. The distal end of the applicator may be adapted for releasably connecting to an implant. For example, the applicator may include an implant stabilization shaft that can connect and release the implant. The applicator may include one or more collapsing elements for collapsing the implant. For example, the applicator may include a lariat or collapse wire for collapsing the struts of the implant. In some variations the applicator includes a collapse sleeve or umbrella/cone for collapsing an implant. In some variations the applicator includes one or more engagement elements for engaging a collapsing element on the implant. For example, the applicator may include a capture wire, hook or the like that may engage a strand or other collapse element (e.g., collapse sleeve) on the implant that can assist in collapsing the struts of the implant.

[0015] The implant may also be adapted for disengaging from the wall of the heart. For example, the implant may be shortenable or movable so that any anchors on the implant, such as passive anchors on the struts or an active anchor on distal end, can be disengaged prior to removing the implant. In some variations the implant includes a shortenable region on the stem and/or foot that can be shortened to separate the struts from the heart wall by shortening the length of the stem and/or foot region. Since the implant is typically concave relative to the heart wall, foreshortening the implant in this way may cause passive anchors at the ends of the struts to withdraw from the wall of the heart. In some variations the struts themselves are shortenable. For example, the passive anchors may be retracted, allowing the implant to be removed.

[0016] In general, an implant may be removed and/or repositioned after it has been implanted, as described herein. For example, an implant may be positioned at a first location in a heart chamber such as within a cardiac ventricle, the struts forming the implant may be expanded to secure the implant in position. In some variations the implant may partition the chamber (e.g., when a membrane spans the strut regions). In some variations, the implant is disengaged from the applicator prior to repositioning or removal; in other variations, the implant is not disengaged from the applicator prior to repositioning or removal. To remove the implant from the first location in the heart, the implant (e.g., the struts of the implant) is at least partially collapsed. In some variations the implant may first be disengaged from the heart wall. The implant may be collapsed by activating a collapse element on the implant, on the applicator, or both. For example, a strand connected to the struts may be tensioned (e.g., by pulling) to collapse the struts. Thereafter, the implant may be drawn to the applicator. In some variations the implant may be repositioned. In some variations, the implant is withdrawn into a protecting element in the applicator, such as a cannula or sleeve. After repositioning, the implant may be again deployed. Alternatively, the implant may be removed from the patient by withdrawing the implant and actuator from the patient.

[0017] For example, described herein is a method of deploying a ventricular partitioning device comprising advancing a ventricular partitioning device having a membrane into a patient's left ventricle chamber in a contracted configuration, expanding the partitioning device into a deployed configuration at a first left ventricle location, at least partially collapsing the partitioning device into the contracted configuration, and withdrawing the partitioning device from the first left ventricle location. The method may also include the step of repositioning the partitioning device within the left ventricle and expanding the portioning device into the deployed configuration at a second left ventricle location so that the partitioning device partitions the left ventricle chamber into a main productive portion of the left ventricular chamber and a secondary, non-productive portion of the left ventricular chamber. In some variations, the method also includes the step of removing the partitioning device from the patient.

[0018] The step of expanding the partitioning device may include expanding a frame connected to the membrane. The membrane may be a reinforced membrane.

[0019] The step of expanding the partitioning device may include allowing a frame connected to the reinforced membrane to self-expand. Also, as mentioned above, the step of withdrawing the partitioning device may comprise pulling the device into a retrieval catheter.

[0020] In any of the variations described herein, the implant (e.g., the ventricular partitioning device) may be secured or anchored to the first left ventricle location, and after repositioning, may be anchored to the second location.

[0021] The method may also include a step of disengaging the ventricular partitioning device from the left ventricle in the first location. For example, any anchors on the implant may be collapsed, withdrawn, or otherwise removed. Thereafter, or simultaneously, the step of at least partially collapsing the partitioning device into the contracted position may comprise pulling on at least one strand connected to the partitioning device. In some variations, the step of at least partially collapsing the partitioning device into the contracted position comprises drawing a collapse sheath at least partially over the partitioning device.

[0022] Also described herein are methods of deploying a ventricular partitioning device including the steps of: advancing a ventricular partitioning device having a membrane into a patient's left ventricle chamber in a contracted configuration, expanding the partitioning device into a deployed configuration at a first left ventricle location, pulling on a strand in communication with the partitioning device to at least partially collapse the partitioning device into the contracted configuration after it has been expanded, retrieving the partitioning device into a retrieval catheter; and withdrawing the partitioning device from the first left ventricle location.

[0023] The step of pulling on a strand in communication with the partitioning device may include pulling on an expansive strand extending from the periphery of the reinforced membrane. The step of pulling on the stand in communication with the partitioning device may include pulling on a retrieval wire at least partially surrounding the expanded reinforced membrane.

[0024] Also described herein are devices for partitioning a chamber of a patient's heart into a main functional portion and a secondary non-functional portion. These devices (implants) may include: a membrane having a collapsed configuration for delivery through a delivery catheter and an expanded configuration for deployment within the heart chamber so as to partition the heart chamber into a main functional portion and a secondary non-functional portion, an expandable frame formed of a plurality of struts having a distal end secured to a hub, wherein the membrane is secured to the expandable frame, a distally extending stem, and a collapse element configured to convert the partitioning component from the expanded configuration to the folded configuration.

[0025] The collapse element may be a collapse sheath, a strand extending around the periphery of the partitioning component and extending therefrom, or the like.

[0026] Also described herein are devices for partitioning a chamber of a patient's heart into a main functional portion and a secondary non-functional portion that include: a membrane having an expanded configuration and a collapsed configuration, wherein the membrane forms a recess when in the expanded configuration, an expandable frame formed of a plurality of struts having a distal end secured to a hub, wherein the reinforced membrane is secured to the expandable frame, a non-traumatic distal tip, configured to engage a region of the ventricular wall; and a strand extending at least partially around the periphery of the membrane at or near the proximal end of the expandable frame, wherein the strand is configured to be tensioned to collapse the device from the expanded configuration to the collapsed configuration.

[0027] Also described herein is a system for partitioning a chamber of a patient's heart into a main functional portion and a secondary non-functional portion, the system comprising an implant configured for deployment into a heart chamber and an elongate applicator configured to insert and retrieve the implant. For example, the implant may include a plurality of struts, wherein the struts are configured to have a collapsed delivery configuration and an expanded deployed configuration, and a strand extending between the struts, wherein the strand may be tensioned to collapse the struts. The elongate applicator configured to insert and retrieve the implant may include a control at the proximal end of the applicator for controlling release of the implant from the applicator, and an elongate body extending from the proximal end to a distal end, wherein the distal end of the elongate body is configured to relaseably secure the implant. The strand extends proximally from the implant along the elongate body of the applicator so that the strand may be manipulated from the proximal end of the applicator.

[0028] The applicator may further comprise a port at the proximal end through which the strand may pass. In some variations, the applicator includes an implant capture element at the distal end of the applicator. The implant capture element may be selected from the group consisting of: an implant capture sleeve and an implant capture umbrella.

[0029] Also described herein are methods of deploying, repositioning and/or removing an implant comprising: advancing an implant into a patient's left ventricle chamber in a contracted configuration, wherein the implant comprises a plurality of struts formed of a shape memory material, expanding the implant into a deployed configuration at a first left ventricle location, changing the temperature of the implant to at least partially collapse the implant into the contracted configuration, retrieving the implant into a retrieval catheter, and withdrawing the implant from the first left ventricle location. In some variations, the step of changing the temperature of the implant comprises exposing the implant to cooled saline.

[0030] Also described herein are systems for partitioning a patient's ventricle, comprising: an implant configured for deployment into the patient's ventricle, the implant including a plurality of struts, wherein the implant is configured to have a collapsed delivery configuration and an expanded deployed configuration, and an applicator configured to insert and retrieve the implant, comprising a control at the proximal end of the applicator for controlling release of the implant from the applicator, an elongate body extending from the proximal end to a distal end, wherein the distal end of the elongate body is configured to releasably secure the implant, and a capture wire extendable from the applicator's distal end and configured to draw the implant toward the applicator's distal end. The applicator may also include a control at the proximal end for manipulating the capture wire.

[0031] In some variations, the capture wire is configured as a lariat. In some variations, the implant includes a strand that may be tensioned to collapse the implant from the expanded configuration, and the capture wire of the implant is configured as a hook that may engage the strand. The capture wire may be connected to the implant.

[0032] In some variations, the applicator further comprises an inflatable sleeve configured to extend from the distal end of the applicator and collapse the implant. As mentioned above, the applicator may include a capture umbrella configured to extend from the distal end of the applicator and collapse the implant.

[0033] The implant may also include collapse sleeve configured to collapse the struts. Thus, an applicator may include a collapse sleeve pullwire configured to engage the collapse sleeve on the implant.

[0034] Also described herein are systems for partitioning a patient's ventricle, the system comprising: an implant configured for deployment into the patient's ventricle and an elongate applicator configured to insert and retrieve the implant. The implant may include a plurality of struts, wherein the implant is configured to have a collapsed delivery configuration and an expanded deployed configuration, and a strand extending between the struts, wherein the strand may be tensioned to collapse the struts. The elongate applicator configured to insert and retrieve the implant may include a control at the proximal end of the applicator for controlling release of the implant from the applicator, an implant stabilization shaft extending distally from the proximal end, wherein the implant stabilization shaft is configured to releasably secure to the implant, and a strand capture element extending distally from the proximal end, wherein the strand capture element is configured to engage the strand on the implant and collapse the struts of the implant.

[0035] Also described herein are devices for partitioning a patient's ventricle into a main functional portion and a secondary non-functional portion that include: a membrane having an expanded configuration and a collapsed configuration, an expandable frame formed of a plurality of struts having a distal end secured to a hub, wherein the membrane is secured to the expandable frame, a stem extending distally from the hub, and a collapse sleeve configured to axially slide from the stem and to collapse the expandable frame and membrane into a collapsed configuration. These devices may also include a passive anchor at the ends of each of the struts of the expandable frame.

[0036] In some variations the devices include a non-traumatic foot at the distal end of the device. The devices may also include an attachment mechanism for a collapse sleeve pullwire.

[0037] Also described herein are removable or repositionable implants for partitioning a chamber of a patient's heart into a main functional portion and a secondary non-functional portion, comprising: a membrane, a plurality of struts secured to a hub at a first end, wherein the membrane is secured to the plurality of struts, and the plurality of struts and membrane have a collapsed delivery configuration and an expanded deployed configuration for deployment within a heart chamber, wherein the membrane forms a recess when in the expanded configuration, wherein end of each of the plurality of struts includes a passive anchor configured to secure to the wall of the patient's heart, and a stem extending distally from the hub, wherein the stem comprises a shortenable region configured to be decreased in length and permit the passive anchors to disengage from the wall of the patient's heart.

[0038] In some variations, the implant further includes a trigger configured to shorten the shortenable region of the stem. The trigger comprises a wire or line extending distally through the stem portion.

[0039] The shortenable region may be a collapsible region, or a telescoping region. In some variations, the device includes a lock for locking the shortenable region.

[0040] Also described herein are methods of removing an implant that has been deployed at a first ventricle location, wherein the implant includes a plurality of struts each having a passive anchor at a first end and connected to a hub at a second end and a stem extending from the hub. The method may include the steps of: shortening a shortenable region of the stem to disengage the passive anchors from the heart wall, at least partially collapsing the plurality of struts, and withdrawing the implant from the first left ventricle location.

[0041] In some variations, the step of shortening the shortenable region comprises applying pulling on a wire or string to shorten the shortenable region. The method may also include the step of unlocking the implant so that the shortenable region may be shortened. The step of at least partially collapsing the implant may include pulling on a strand or collapse line to draw the struts together.

[0042] The method may also include the step of repositioning the implant within the left ventricle and expanding the struts into a deployed configuration at a second left ventricle location. In addition, the method may also include the step of removing the implant from the patient.

INCORPORATION BY REFERENCE

[0043] All publications and patent applications mentioned in this specification are herein incorporated by reference in their entirety as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0044] FIG. 1 is a perspective view of one variation of a cardiac treatment device including a hub, a frame, and a stem thereof.

[0045] FIG. 2A is a cross-section of a system including a cardiac device with the cardiac device partially retracted into an applicator (e.g., delivery catheter).

[0046] FIG. 2B is a cross-sectional side view of a portion of FIG. 2A.

[0047] FIG. 3A is a side view of the system of FIG. 2A with the cardiac device further retracted.

[0048] FIG. 3B is a cross-sectional side view of a portion of FIG. 3A.

[0049] FIG. 4A is a side view of the system of FIG. 2A with the cardiac device fully retracted.

[0050] FIG. 4B is a cross-sectional side view of a portion of FIG. 4A.

[0051] FIG. 5A is a cross-sectional side view of a human heart with a portion of an applicator inserted therein.

[0052] FIGS. 5B-5K are cross-sectional side views of the human heart illustrating installation (FIGS. 5B-5E), removal (FIGS. 5E-5H), and subsequent final installation (FIGS. 5I-5K) of a cardiac device.

[0053] FIG. 6A is a perspective view of another variation of a cardiac device.

[0054] FIG. 6B is a cross-sectional side view of the human heart with the cardiac device of FIG. 6A installed.

[0055] FIG. 7A is a perspective view of another variation of a cardiac device.

[0056] FIG. 7B is a cross-sectional top plan view of the cardiac device on 7B-7B' in FIG. 7A.

[0057] FIG. 7C is a cross-sectional side view of the human heart with the cardiac device of FIG. 7A installed.

[0058] FIG. 8 is an elevational view of another variation of a partitioning device in an expanded configuration.

[0059] FIG. 9 is a plan view of the partitioning device shown in FIG. 8 illustrating the upper surface of the device.

[0060] FIG. 10 is bottom view of the partitioning device shown in FIG. 8.

[0061] FIG. 11 is a perspective view of the non-traumatic tip of the distally extending stem of the device shown in FIG. 8.

[0062] FIG. 12 is a partial cross-sectional view of the hub of the partitioning device shown in FIG. 9 taken along the lines 12-12'.

[0063] FIG. 13 is a transverse cross sectional view of the hub shown in FIG. 12 taken along the lines 13-13'.

[0064] FIG. 14 is a longitudinal view, partially in section of a reinforcing strut and membrane at the periphery of the partitioning device shown in FIG. 8.

[0065] FIG. 15 is a schematic elevational view, partially in section, of a delivery system with the partitioning device shown in FIGS. 8 and 9 mounted thereon.

[0066] FIG. 16 is a transverse cross-sectional view of the delivery system shown in FIG. 15 taken along the lines 16-16'.

[0067] FIG. 17 is an elevational view, partially in section, of the hub shown in FIG. 12 being secured to the helical coil of the delivery system shown in FIG. 15.

[0068] FIGS. 18A-18E are schematic views of a patient's left ventricular chamber illustrating the deployment of the partitioning device shown in FIGS. 8 and 9 with the applicator shown in FIG. 15 to partition a patient's heart chamber (left ventricle) into a primary productive portion and a secondary, non-productive portion.

[0069] FIG. 19 is a schematic plan view of the deployed device shown in FIG. 18E within a patient's heart chamber.

[0070] FIG. 20A is a partial schematic view of the partitioning device shown in FIGS. 8 and 9 in a contracted configuration resulting from pulling the free ends of the expansive strand at the periphery of the reinforced membrane.

[0071] FIG. 20B is a schematic view of the contracted device shown in FIG. 20A being pulled into an expanded distal end of an applicator to facilitate withdrawal of the partitioning device.

[0072] FIG. 20C is a schematic view of the contracted device shown in FIG. 20A pulled further into the inner lumen of the receiving applicator.

[0073] FIG. 21 is a schematic view of another variation of an inserter configured to apply and remove and/or reposition an implant.

[0074] FIG. 22A-22F illustrate retrieval of a cardiac implant as (partitioning device) using the applicator of FIG. 21.

[0075] FIG. 23A illustrates another variation of an applicator.

[0076] FIG. 23B shows a cross-section through a region of the applicator of FIG. 23A.

[0077] FIGS. 24A-24F illustrate a method of using the applicator similar to that shown in FIG. 23A to retrieve an implant.

[0078] FIGS. 25A and 25B show another variation of a system including an applicator and an implant in which the implant is secured to the applicator and released from the applicator, respectively.

[0079] FIG. 26A shows another variation of an applicator configured to deliver and reposition and/or remove an implant, and FIGS. 26B-26C illustrate operation of the applicator of FIG. 26A.

[0080] FIGS. 27A-27E illustrate the operation of a system including an implant having a collapse sleeve.

[0081] FIGS. 28A and 28B show front and side views, respectively, of an implant having a collapse sleeve, similar to the implant shown in FIGS. 27A-27E.

[0082] FIG. 29A shows an applicator including a retrieval element configured as a lariat. FIGS. 29B-29E illustrate operation of the applicator of FIG. 29A and an implant.

[0083] FIGS. 30A and 30B show front and side views, respectively, of an implant that may be used with the applicator shown in FIG. 29A and illustrated in FIGS. 29B-29E.

[0084] FIG. 31A shows another variation of a system including an applicator and an implant.

[0085] FIGS. 31B-31D illustrate retrieval of an implant using the system shown in FIG. 31A.

[0086] FIGS. 32A and 32B show another variation of an applicator configured for retrieval of an implant.

[0087] FIG. 33A and FIG. 33C-33H illustrate operation of an applicator similar to that shown in FIGS. 32A and 32B, and FIG. 33B shows a cross-section through a region of the applicator shown in FIGS. 33A and 33C-33H.

[0088] FIG. 34A, 34C and 34E show an implant having a shortenable stem region. FIG. 34C shows the implant of FIG. 34A in which the stem region has been shortened by tensioning an activating element. FIG. 34E shows the implant of FIGS. 34A and 34C during removal of the activating element. FIGS. 34B, 34D and 34F show a slightly enlarged view of the stem regions of the implants of FIGS. 34A, 34C and 34E, respectively.

[0089] FIGS. 35A-35E illustrate the operation of another system for deploying and removing an implant. The system includes an applicator (partially illustrated in FIGS. 35A-35E) and an implant.

[0090] FIG. 36A shows a cross-section of another variation of an implant, and FIGS. 36B-36C illustrate a method of removing an implant such as the one shown in FIG. 36A, in which temperature is changed to induce collapse of an implant so that it can be withdrawn.

DETAILED DESCRIPTION OF THE INVENTION

[0091] Described herein are deployable and retrievable cardiac treatment devices or implants, systems including retrievable devices, and methods of using them. For example, any of the implants described herein may be positioned in a patient's heart (and particularly the patient's ventricle, such as the left ventricle), deployed into the heat by expanding the device, and then, either immediately or after some time period, disengaged from the heart, at least partially collapsed, and repositioned and/or removed. The implants, which may also be referred to as cardiac treatment devices, may be configured to partition the heart (e.g., into a productive and non-productive region), or to support the wall of the heart. Examples of such implants are described herein. Applicators for deploying and/or retrieving any of the implants described herein are also taught, as are systems including the applicators and the implants. Methods of using these implants are also described.

[0092] FIGS. 1, 6A, 7A and 8 show variations of implants (e.g., device 34 in FIG. 1). Any of the implants described herein may also be referred to as cardiac treatment devices or treatment devices. Alternatively, these devices may be referred to as ventricular partitioning devices or partitioning devices. Such partitioning devices may be configured to partition a ventricle into function (or productive) and non-function (or non-productive) regions. FIGS. 2A-

2B, and 3 illustrate this implant (cardiac device 34) in more detail. The cardiac device 34 includes a frame 184 and a stem 186, or flexible body, and has a vertical axis 188. Partitioning devices, including ventricular partitioning devices, are only one class of implants which are described herein and may be used with the device removal or repositioning systems and methods described herein. Other such devices may be support devices that do not include a membrane, or do not partition a heart chamber, but predominantly support the cardiac tissue.

[0093] Referring now to FIG. 1, the frame 184 includes a frame hub 190, a plurality of main segments 192, and a membrane 194. The hub 190 in this example is a ring-shaped body with an outer surface with a diameter of about 5 mm, an inner surface with a diameter of about 4 mm, a thickness of about 3 mm, and a pin extending off-center across the inner surface creating a smaller and a larger gap. The pin has a length of about 3.5 mm and a diameter of about 1 mm and is located in a plane. The frame 184 has a diameter 209 of approximately 75 mm, however, other embodiments may have diameters of between 10 mm and 120 mm. The entire hub 190 in this example is made of nickel titanium.

[0094] In this example, the main segments 192 include first portions, or central segments, 210, second portions, or outer segments, 212, and passive anchors 214. The first portions 210 are connected to the hub 190 at a central portion of the outer surface and extend radially from the hub 190 at an angle away from the plane of the pin to a length of about 8 mm. The second portions 212 of the segments 192 are connected to ends of the first portions 210 and further extend radially from the hub 190 but at an angle towards the plane. The second portions 212 each have a length of 5-50 mm. The passive anchors 214 are formed at an end of each of the second portions 212. The passive anchors 214 have sharp ends that point slightly radially from the hub 190. The segments 192 are made from nickel titanium, which after a prescribed thermal process, allows for the segments 192 to hold their shape as illustrated in FIG. 1. The entire frame 184, or just portions of the frame 184, may also be made of stainless steel, polymers, or biodegradable materal(s).

[0095] In FIG. 1, the membrane 194 is stretched over the first 210 and second 212 portions of the segments 192 to give the frame 184 a disk like shape. The membrane 194 is made of expanded Polytetrafuoroethylene (ePTFE) and has a thickness of about 0.08 mm. Other embodiments may use a mesh membrane, or other appropriate permeable, semi-permiable, or impermeable membranes. While porous ePTFE material may be preferred, the membrane may be formed of suitable biocompatible polymeric material which includes Nylon, PET (polyethylene terephthalate) and polyesters such as Hytrel. The membrane may be foraminous in nature to facilitate tissue ingrowth after deployment within the patient's heart. The applicator (including delivery catheter and/or a guiding catheter) may be formed of suitable high strength polymeric material such as PEEK (polyetheretherketone), polycarbonate, PET, Nylon, and the like. Braided composite shafts may also be employed.

[0096] The stem 186 may be made of Polytetrafuoroethylene (PTFE) and is thus expandable and flexible. Referring again to FIG. 1, the stem 186 can be compressed or stretched by 30% of its length and can be bent from the vertical axis 188 of the device 34 by 90 degrees in any direction. The first hub 232, second hub 234, and active anchor 236 may be made of nickel titanium. In other embodiments, the hubs may be made of stainless steel.

[0097] FIG. 2A illustrates one variation of a systems including an applicator 30 and an implant 34. The implant shown is the variation described above from FIG. 1. The applicator shown in FIG. 2 includes a handle 44, a deployment member 46, which is partially within a catheter region (catheter tube 38). The proximal end of the deployment member 46 is secured to the handle 44. The handle may include one or more controls for deploying and/or retrieving an implant. For example, the handle may be formed of molded plastic and may include knobs, buttons, or other controls for operating the applicator to deploy or retrieve a device. The distal end of a portion of the applicator (e.g., the deployment member 46) may be adapted to releasably grasp the implant.

[0098] In use, the deployment member 46 may be inserted through the catheter tube 38 so that the distal end 54 of the deployment member 46 may exit the distal end of the tube 38. The deployment member 46 may connect to a cardiac implant device 34 such that a key (not visible) engages the hub 190 of the frame 184 of the implant by passing through the larger gap in the hub 190. The implant may then be secured to the deployment member, and may be deployed by manipulation of a control on the handle, e.g., by rotating the key to disengage the implant from the deployment member.

[0099] As illustrated in FIGS. 2A and 2B, the distal end 54 of the deployment member 46 may be pulled into the distal end of the catheter tube 38. As a proximal section of the frame 184 of the implant enters the catheter tube 38, it may be collapsed by the smaller diameter of the catheter opening of the applicator. For example, in the variation shown in FIG. 2, the first portions 210 of the segments 192 begin to collapse towards the stem 186 when the implant is drawn into the catheter tube. The segments 192 collapse, or fold, against a spring force that is created by the resilient nature of the nickel titanium material from which they are made. At the same time, the second portions 212 fan out radially away from the hub 190.

[00100] FIGS. 3A and 3B show a distal section of the frame 184 and the second portions 212 of the segments 192 beginning to enter the tube 38, so that the second portions have been bent back to collapse towards the stem 186 similarly to the first portions 210. FIGS. 4A and 4B illustrate this system 30 with the cardiac implant device 34 completely contained within the catheter tube 38.

[00101] FIGS. 5A-5J illustrate a human heart 242 while the implant 34 is being deployed. The heart 242 contains a right ventricle 244 and a left ventricle 246 with papillary muscles 248 and an akinetic (e.g., damaged) portion 250 with an apex 252. The distal end of the catheter 38 has been inserted through the aorta and aortic valve into the left ventricle 246 to a selected position where the ventricular partitioning device 34 can be deployed. The catheter tube 38 is then partially pulled off of the cardiac device 34 exposing the stem 186.

[00102] The active anchor 236 is then deployed. In the implant shown in FIGS. 1-5J, the implant includes an active anchor at the distal end. This anchor may be inserted into the tissue as illustrated in FIG. 5C. In other variations (e.g., described below), the distal end of the implant may be configured with one or more atraumatic feet that does not penetrate the tissue. In FIG. 5C, the active anchor at the distal end may be deployed into the tissue by operating (e.g., rotating) a control (e.g. an anchor knob) on the handle of the device. The active anchor 236 penetrates the myocardium of the heart 242 to secure the cardiac device 34 in the selected position at the apex 252 of the akinetic portion 250 of the left ventricle 246.

[00103] The catheter 38 is then completely removed from the distal end 54 of the deployment member 46, exposing the cardiac device 34. As the cardiac device 34 expands, due to the resilient nature of the segments 192, and the pre-set shape of the frame 184, the passive anchors 214 on the segments 192 penetrate the myocardium in a first direction. The membrane 194 seals a portion of the ventricle 246 and separates the ventricle 246 into two volumes.

[00104] If the cardiac device 34 has not been properly positioned, or if it is of the wrong size or shape for the particular heart, the device 34 may be repositioned or completely removed from the heart 242, as illustrated in FIGS. 5E-5H.

[00105] For example, in variations in which an active anchor at the distal end has been used, the implant may be removed by first releasing the active anchor. If the implant has been completely deployed, e.g., so that the applicator has been separated from the implant (which has been inserted into the tissue), then the implant may re-coupled to the applicator. For example, the distal end of a portion of the applicator, such as the deployment member 46, 54, may be connected to the implant. Thus, in FIG. 5E, the applicator has been re-coupled to the deployment member 46 of the applicator. A control (e.g., knob, etc.) on the handle may be manipulated to engage the applicator to the implant. In this variation a central portion of the implant, such as the hub, is configured to releaseably engage and re-engage the applicator. In some variations an additional tether or other element may be used to grab and position the deployed implant so that it can be engaged with the applicator. Examples and illustrations of these additional elements are provided in greater detail below.

[00106] Furthermore, the device may be repositioned before disengaging from the applicator.

[00107] After the applicator has been engaged with the implant (or before disengaging the implant), activation of a control on the applicator (e.g., rotation of an anchor knob on the handle of the applicator) may disengage the active anchor 236 from the left ventricle 246. The distal end 54 of the deployment member 46 may be retracted into the catheter 38 to once again fold the cardiac device 34 into the position shown in FIG. 4B, from where it can again be deployed. The passive anchors 214 may be removed from the myocardium in a second direction which is approximately 180 degrees from the first direction so that minimal damage is done to the myocardium. This is illustrated in FIGS. 5F-5H.

[00108] The implant 34 may then be properly re-positioned, as shown in FIG. 5I, and deployed in the new location using the applicator. Once positioned, the applicator may be activated to release the deployment member 46 as previously described. After deploying it as desired, the distal end of the applicator may be separated from the cardiac device 34 to allow removal of the deployment member 46 and removal of the applicator from the heart 242, as shown in FIG. 5J. FIG. 5K illustrates the heart 242 with the cardiac device 34 installed and the deployment mechanism 36 removed from the heart 242.

[00109] In this variation, the shape of the frame 184 allows the device 34 to be retrieved as long as the deployment member 46 is connected to the device 34. When the device 34 is retrieved, the passive anchors 214 withdraw from the myocardium in a direction that is approximately 180 degrees from, or opposite, the first direction to minimize the amount of damage done to the myocardium. The device 34 also provides support for the akinetic region 250, minimizes the bulging of the akinetic region 250, and reduces stress on the working parts of the myocardium. In general, the ePTFE membranes which may be used with the implants is biocompatible, has a non-thrombogenic surface, promotes healing, and accelerates endothelization. These membranes may be used to partition the heart, as previously described.

[00110] FIG. 6A illustrates another variation of a cardiac device 254. The cardiac device includes a hub 256, a frame 258, and a membrane 260. The hub 256 lies at a central portion of the frame 258 and an active anchor 262 is connected to the hub 256 and extends downwards therefrom. The frame 258 includes a plurality of segments 264 which extend radially and upwardly from the hub 256. A sharp passive anchor 266 lies at the end of each of the segments 264. The membrane 260 is stretched between the segments 264 to form a cone-shaped body.

[00111] FIG. 6B illustrates a sectional view of a human heart with the cardiac device 254 of FIG. 6A having been secured to an akinetic portion thereof.

[00112] FIG. 7A and FIG. 7B illustrate another variation of a cardiac device 268. The cardiac device includes a hub 270, a frame 272, and membrane 274. The hub 270 lies at a central portion of the frame 272 and an active anchor 276 extends downwardly from the hub 270. The frame 272 includes a plurality of segments 278 which extend radially and upwardly from the hub 270. The segments 278 are of different lengths such that an outer edge 280 of the cardiac device 268 is not planar. The device 268 has a vertical axis 282 which intersects a diameter 284 across the outer edge 280 of the device 268 at an angle other than 90 degrees. A sharp passive anchor 286 lies at the end of each of the segments 278. The membrane 274 is stretched between the segments 278 to form a cone-shaped body. Referring specifically to FIG. 7B, a cross-section perpendicular to the vertical axis 282 of the device 268 is circular.

[00113] FIG. 7C illustrates a sectional view of a human heart with the cardiac device 268 of FIG. 7A having been secured to an akinetic portion thereof. The outer edge 280 of the cardiac device 268 defines a non-planar cross-section of an inner surface of the left ventricle. The implant 268 can be sized and shaped for use on a wider variety of heart regions, including a variety of sizes and shapes of akinetic portions in left ventricles.

[00114] In some variations, the implants may include one or more collapsing elements that are configured to help collapse the implant from the expanded (deployed) configuration into the collapsed (or partially collapsed) position. For example, a sleeve or cover may be used to collapse the frame of the implant. In other variations, the implant may include a strand, wire, thread, cable, chain, etc. (which may generally be referred to as a "strand") for collapsing the device. For example, a strand may be included around the perimeter of the ribs or struts (e.g., spaced from the central hub region by any desired spacing). The strand may be a loop (e.g., joined at the ends) or it may have one or both ends free. Pulling on the strand may contract the struts, drawing them together towards the collapsed configuration.

[00115] FIGS. 8-11 illustrate one variation of a cardiac implant device including a strand which may be used to collapse the device. In this variation, the implant (partitioning device)10 includes a partitioning membrane 511, a hub 512, preferably centrally located on the partitioning device, and a radially expandable reinforcing frame 513 that is secured to the proximal or pressure side of the frame 513 as shown in FIG. 8. The struts 514 have distal ends 515 which are secured to the hub 512 and free proximal ends 516 which are configured to curve or flare away from a center line axis. Radial expansion of the free proximal ends 516 unfurls the membrane 511 secured to the frame 513 so that the membrane presents a pressure receiving surface 517 which defines in part the productive portion of the patient's partitioned heart chamber. The peripheral edge 518 of the membrane 511 may be serrated as shown.

[00116] The variation shown in FIGS. 8-11 also includes a continuous expansive strand 519 that extends around the periphery of the membrane 511 on the pressure side thereof. In operation, this strand may also help apply pressure to the pressure side of the flexible material of the membrane to effectively seal the periphery of the membrane against the wall of the ventricular chamber. The ends 520 and 521 of the expansive strand 519 are shown extending away from the partitioning device in FIGS. 8 and 9. As mentioned, the ends 520 and 521 may be left unattached or may be secured together, e.g. by a suitable adhesive, knot, or the like, or secured to the membrane 511 itself. While not shown in detail, the membrane 511 in this example has a proximal layer secured to the proximal faces of the struts 514 and a distal layer secured to the distal faces of the struts in a manner described in US Patent Application Ser. No. 10/913,608, filed on Aug. 5, 2004, herein incorporated by reference in its entirety.

[00117] The hub 512 shown in FIGS. 10 and 11 may be connected to a non-traumatic support component 522. The support component 522 shown in FIGS. 10 and 11 has a stem 523 a plurality of pods or feet 524 extending radially away from the center line axis and the ends of the feet 524 are secured to struts 525 which extend between adjacent feet. A plane of material (not shown) may extend between adjacent feet 524 in a web-like fashion to provide further support in addition to or in lieu of the struts 525. The inner diameter of the stem 523 is threaded to secure the partitioning device 510 to a delivery catheter as shown in FIGS. 15-17.

[00118] As shown in FIG. 12, the distal ends 515 of the struts 514 are secured within the hub 512 and, as shown in FIG. 13, a transversely disposed connector bar 526 is secured within the hub which is configured to secure the hub 512 to the nontraumatic support component 522.

[00119] In FIGS. 12 and 13, the screw thread inside stem 523 allows the partitioning device 510 to be secured to the non-traumatic support component 522 and to be released from the delivery system within the patient's heart chamber. The distal ends 515 of the reinforcing struts 514 are secured within the hub 512 in a suitable manner or they may be secured to the surface defining the inner lumen or they may be disposed within channels or bores in the wall of the hub 512. The distal end of the struts 514 are preshaped so that when the struts are not constrained, other than by the membrane 511 secured thereto (as shown in FIGS. 8 and 9), the free proximal ends 516 thereof expand to a desired angular displacement away from the centerline axis which is about 20 degrees to about 90 degrees, preferably about 30 degrees to about 60 degrees. The unconstrained diameter of the partitioning device 510 should be greater than the diameter of the heart chamber at the deployed location of the partitioning device so that an outward force is applied to the wall of the heart chamber by the partially expanded struts 514 during systole and diastole so that the resilient frame 513 augments the heart wall movement.

[00120] FIG. 14 illustrates the curved free proximal ends 516 of struts 514 which are provided with sharp tip elements 527 configured to engage and preferably penetrate into the wall of the heart chamber and hold the partitioning device 510 in a deployed position within the patient's heart chamber so as to partition the ventricular chamber into a productive portion and a non-productive portion.

[00121] FIGS. 15-17 illustrate one variation of an applicator (delivery system) 530 that may be used for delivering the partitioning device 510 shown in FIGS. 8 and 9 into a patient's heart chamber and deploying the partitioning device to partition the heart chamber as shown in FIGS. 18A-18E. The applicator system 530 includes a guide catheter 531 and a delivery catheter 532.

[00122] The guide catheter 531 has an inner lumen 533 extending between the proximal end 534 and distal end 535. A hemostatic valve (not shown) may be provided at the proximal end 534 of the guide catheter 531 to seal about the outer shaft 537 of the delivery catheter 532. A flush port 536 on the proximal end 534 of guide catheter 531 is in fluid communication with the inner lumen 533.

[00123] The delivery catheter 532 in this variation includes an outer shaft 537 with an adapter 538 on the proximal end thereof having a proximal injection port 539 which is in fluid communication with the interior of the outer shaft 537. As shown in more detail in FIG. 16, the outer shaft 537 has an inner shaft 541 which is disposed within the interior thereof and is secured to the inner surface of the outer shaft 537 by webs 543 which extend along a substantial length of the inner shaft. The injection port 539 is in fluid communication with the passageways 542 between the inner and outer shafts 541 and 537 respectively and defined in part by the webs 542. A torque shaft 544, which is preferably formed of hypotubing (e.g. formed of stainless steel or superelastic NiTi), is disposed within the inner lumen 545 of the inner shaft 541 and has a proximal end 546 secured within the adapter 538. Balloon inflation port 547 is in fluid communication with the inner lumen 548 of the torque shaft 544. Torque shaft 544 is rotatably disposed within the inner lumen 545 of the inner shaft 541 and is secured to rotating knob 549. A helical coil screw 550 is secured to the distal end 551 of the torque shaft 544 and rotation of the torque knob 549 on the proximal end 546 of the torque shaft 544 rotates the screw 550 to facilitate deployment of a partitioning device 510. The proximal end 552 of inflatable balloon

553 is sealingly secured by adhesive 554) about the torque shaft 544 proximal to the distal end 551 of the torque shaft. The balloon 553 has an interior 555 in fluid communication with the inner lumen 548 of the torque shaft 544. Inflation fluid may be delivered to the balloon interior 555 through port 547 which is in fluid communication with the inner lumen 548 of the torque shaft 544. The distal end 556 of the balloon 553 is sealingly secured by adhesive 557 to the helical screw 550. The proximal and distal ends 552 and 556 of the balloon 553 are blocked by the adhesive masses 554 and 557 to prevent the loss of inflation fluid delivered to the interior 555 of the balloon 553. Delivery of inflation fluid through a fluid discharge port 558 in the distal end 551 of the torque shaft 544 inflates the balloon 553 which in turn applies pressure to the proximal surface of the partitioning component 510 (or device) to facilitate securing the partitioning component 510 to the wall 559 of heart chamber 560 as shown in FIGS. 18A-18E discussed below.

[00124] As shown in FIG. 18A, the partitioning component 510 is delivered through a delivery system 530 which includes a guide catheter 531 and a delivery catheter 532. The partitioning component 510 is collapsed in a first, delivery configuration which has small enough transverse dimensions to be slidably advanced through the inner lumen 533 of the guide catheter 531. Preferably, the guide catheter 531 has been previously percutaneously introduced and advanced through the patient's vasculature, such as the femoral artery, in a conventional manner to the desired heart chamber 560. The delivery catheter 532 with the partitioning component 510 attached is advanced through the inner lumen 533 of the guide catheter 531 until the partitioning component 510 is ready for deployment from the distal end of the guide catheter 531 into the patient's heart chamber 560 to be partitioned.

[00125] As shown in FIG. 18B-18C, the partitioning component 510 mounted on the screw 550 is urged further out of the inner lumen 533 of the guide catheter 532 until the support component 522 engages the heart wall 559. The guide catheter 531 is withdrawn while the delivery catheter 532 is held in place until the proximal ends 516 of the struts 514 exit the distal end 35 of the guide catheter. As shown in FIG. 18C, the free proximal ends 516 of struts 514 expand outwardly to press the sharp proximal tips 527 of the struts 514 against and preferably into the tissue lining the heart wall 559.

[00126] With the partitioning component 510 deployed within the heart chamber 560 and preferably partially secured therein, inflation fluid is introduced through the inflation port 558 in the distal end 551 torque shaft 544 where it is directed into the balloon interior 555 to inflate the balloon 553. The inflated balloon 553 presses against the pressure receiving surface 517 of the membrane 511 of the partitioning component 510 to ensure that the sharp proximal tips 527 are pressed well into the tissue lining the heart wall 559 as shown in FIG. 18D.

[00127] With the partitioning device 510 properly positioned within the heart chamber 560, the knob 549 on the torque shaft 544 (as shown in FIG. 15) is rotated counter-clockwise to disengage the helical coil screw 550 of the delivery catheter 532 from the stem 523 secured within hub 512. The counter-clockwise rotation of the torque shaft 544 rotates the helical coil screw 550 which rides on the screw thread inside the stem 523secured within the hub 512. Once the helical coil screw 550 disengages the screw thread inside the stem 523, the delivery system 530, including the guide catheter 531 and the delivery catheter 532, may then be removed from the patient.

[00128] The proximal end 534 of the guide catheter 531 is provided with a flush port 536 to inject fluids such as therapeutic, diagnostic or other fluids through the inner lumen 533 during the procedure. Similarly, the proximal injection port 539 of adapter 538 is in communication with passageways 542 if the delivery catheter 532 for essentially the same purpose.

[00129] The deployment of the partitioning component 510 in the patient's heart chamber 560 as shown in FIG. 18E divides the chamber into a main productive or operational portion 561 and a secondary, essentially non-productive portion 562. The operational portion 561 is smaller than the original heart chamber 560 and provides for an improved ejection fraction and an improvement in blood flow. Over time, the non-productive portion 562 fills first with thrombus and subsequently with cellular growth. Bio-resorbable fillers such as polylactic acid, polyglycolic acid, polycaprolactone and copolymers and blends may be employed to initially fill the non-productive portion 562. Fillers may be suitably supplied in a suitable solvent such as dimethylsulfoxide (DMSO). Other materials which accelerate tissue growth or thrombus may be deployed in the non-productive portion 562 as well as non-reactive fillers.

[00130] FIG. 19 is a top view of the deployed partitioning device shown in FIG. 18E schematically illustrating the sealed periphery of the membrane 511 against the ventricular wall.

[00131] Once the device is deployed, as shown in FIGS. 18E and 19, the device may be removed and/or repositioned. For example, in the implant variation shown in FIGS. 8 and 9, pulling the strand 519 may disengage the anchors or tip element 527 at the ends of the struts 514 from the heart wall. For example, the applicator 530 may be re-engaged with the implant (e.g., the hub region). An element on the applicator may engage the strand so that it can be pulled to collapse the implant. In some variations, one or more ends of the strand remain connected to the applicator during the insertion procedure, so that even when initially disengaged from the applicator, the strand is connected to the applicator until the position is confirmed.

[00132] Examples of applicators including members for grasping and/or manipulating a strand are described in greater detail below.

[00133] FIGS. 20A-20C illustrate the collapse and retrieval of an implant (partitioning device 510) by pulling on the ends 520 and 521 of an expansive strand 519 which extends around the periphery of the membrane 511. Typically, the partitioning device 510 may be secured to the delivery catheter 532, but the delivery catheter is not shown in this example to simplify the drawings. In FIG. 20A the partitioning device 510 is shown in a partially collapsed configuration. In FIG. 20B the partially collapsed partitioning device 510 is shown being withdrawn into the flared distal end 563 of retrieval catheter 564. FIG. 20C illustrates the completely collapsed partitioning device 510 pulled further into the retrieval catheter 564. The partitioning device 510 may be withdrawn by pulling the device through the inner lumen 565 of the retrieval catheter 564. Optionally, the partitioning device 510 and applicator (e.g., retrieval catheter) may be withdrawn from the patient together.

[00134] In this variation the applicator includes a flanged distal end on the catheter, so that the implant may more readily be inserted into the distal end of the applicator. This flanged distal end is optional, and is not necessarily present.

[00135] In general, the implantation, removal and/or repositioning of the impants described herein may be performed under direct or indirect visualization. For example, any of the procedures or methods described herein may be performed under fluoroscopy. To assist in properly locating the device during advancement and placement thereof into a patient's heart chamber, parts, e.g. the distal extremity, of one or more of the struts 14 and/or the hub 12 may be provided with markers at desirable locations that provide enhanced visualization by eye, by ultrasound, by X-ray, or other imaging or visualization means. Radiopaque markers may be made with, for example, stainless steel, platinum, gold, iridium, tantalum, tungsten, silver, rhodium, nickel, bismuth, other radiopaque metals, alloys and oxides of these metals.

[00136] FIG. 21 shows another variation of an applicator configured to apply and retrieve and/or reposition a cardiac implant. In some variations, an applicator such as the one illustrated in FIG. 21 is included as part of a system including an implant. In FIG. 21, the applicator includes a control handle 701 having a plurality of controls for controlling engaging and disengaging from an implant, as well as a flush port 703 and a balloon inflating port 705. In this variation, the applicator also includes an elongate shaft 707 comprising an inner shaft 709 and an outer shaft 711. The distal end of the applicator includes an everting balloon or inflatable sleeve 713 that is inflatable by applying fluid (e.g., air, liquid, etc.) through the inflation port 705. Inflating the everting balloon may cause it to extend, as illustrated in FIGS. 22A-22F. In

addition to the features illustrated in FIG. 21, other elements such as an implant stabilizing shaft and or a strand-grasping hook (not visible in FIG 21) may also be included within the inner shaft, and controlled proximally, e.g., using the handle. For example, the applicator may include a deployment member, as described above. The implant stabilizing shaft may be configured as a deployment member.

[00137] FIGS. 22A-22F illustrate operation of an applicator such as that shown in FIG. 21 to remove an implant (partitioning implant 720). FIG. 22A illustrates a cardiac implant 720 that has been deployed into a patient's heart, as shown. The implant 720 includes a strand, suture 724 that extends around the perimeter of the implant and has two ends 722, 722' which are knotted or otherwise prevented from pulling past the membrane surrounding the device. The strand 724 is threaded around the inner diameter of the implant.

[00138] In FIG. 22B, the applicator shown in FIG. 21 has been inserted into the heart so that the distal end of the applicator is positioned across from the deployed implant. The elongate catheter, including the inflatable distal portion 713 is positioned across from the implant so that an implant stabilizing shaft 726 may be extended from the distal end of the applicator to engage the implant. As previously described, the implant stabilizing shaft 726 (e.g., a deployment member) may engage with the implant at the hub or any other appropriate region (e.g., the foot, etc.). A strand hook 728 may also be extended from the distal end of the applicator as shown in FIG. 22B, so that it can extend from the applicator and engage at least a portion of the strand. In some variations, the strand hook is a grasper, jaw, or other strand-capturing element. As shown in FIG. 22C, the strand can then be drawn proximally by withdrawing the strand hook 728 proximally into the applicator while holding the device in position. Drawing the strand proximally while keeping the device distally positioned will constrict the strand and collapse the struts of the implant. In some variations, the method of collapsing the implant may include a step of pushing the implant distally (away from the applicator) to disengage the ends of the struts from the heart wall. As described in more detail below, the implant (e.g., the foot region) may also be configured to collapse or shorten to facilitate disengaging of the struts from the heart wall.

[00139] After collapse of the implant, as shown in FIG. 22C, the applicator may be extended over the implant. In one variation, illustrated in FIGS. 22D-22E, the inflatable everting balloon or cuff 713is inflated so that it extends and advances over the implant. In some variations, the cuff on the distal end of the applicator is not inflatable, but is otherwise extendable from the distal end to cover the device. For example, the distal end may include a toroidal region that can be "rolled" over the collapsed implant so that the implant is secured within the central lumen of the toroidal region. Once the implant has been secured within the applicator, it may be removed, along with the applicator, from the patient, or repositioned and deployed again.

[00140] FIG. 23A illustrates another variation of an applicator which may be used to apply and remove and/or reposition an implant. In FIG. 23A, the applicator includes a handle region 801 having one or more controls. In the variation shown in FIG. 23A the handle includes a control, shown as a knob 803 for extending an capture umbrella (described below), and a control for operating a suture hook (suture hook knob 805). The applicator also includes an elongate catheter region 807, and suture capture hook 822 as well as an implant capture umbrella 810.

[00141] FIG. 23B illustrates a cross-sectional view through the catheter region of the applicator shown in FIG. 23A along line A-A'. As shown in FIG. 23B, the applicator include an implant capture umbrella lumen 830 and a suture capture hook lumen 831. In some variations only a single lumen is used to house both the suture capture hook and the implant capture lumen. In some variations an implant stabilizing shaft is also included, similar to that described above in FIG. 21 and 22A-F. For example, an implant stabilizing shaft (not shown in FIGS. 23A-24F) may be positioned concentrically within the shaft connected to the implant capture umbrella. The implant stabilizing shaft may be operated independently of the implant capture umbrella 810.

[00142] FIGS. 24A-24F illustrate operation of an applicator as shown in FIG. 23A to remove an implant that has been deployed in a patient's heart. FIG. 24A shows an implant, similar to the implant shown and described for FIG. 22A, is shown implanted into the hleft ventricle 850 of a patient's heart. The implant 720 also includes a suture or strand 724, having two ends that have been jointed together or knotted 722. The implant may be removed from the deployed position in the heart as illustrated in FIGS. 24B-24. The stand capture hook 822 is extended distally from the applicator to capture or otherwise engage the strand 724 on the implant. In some variations an implant stabilization shaft 726 is also extended from the distal end of the applicator so that it engages the implant, as shown for FIG. 22B, above. After capture of the strand, the stand capture hook 822 is drawn proximally back using the applicator. For example, the applicator handle may be manipulated to draw the strand proximally, e.g., by operating the strand hook knob 805. This results in collapsing the implant, as illustrated in FIG. 24C. Thereafter, the implant capture umbrella 810 of the applicator is extended distally out of the catheter of the applicator. As shown in FIG. 24D, when the implant capture umbrella is extended from the applicator, it expands as it leaves the implant catheter region. For example, the implant capture umbrella may be formed of struts of Nitinol or other materials that are biased outwards. A membrane or netting may be present between the struts. In some variations, the umbrella does not include a membrane, but comprises only struts. The struts may be coated (e.g., with a polymeric material) to prevent damage to the tissue and/or the implant.

[00143] The implant capture umbrella may be extended over the collapsed device 720, as shown in FIG. 24D. The implant 720 may then be drawn into the applicator by retracting the capture umbrella 810 (and an implant stabilization shaft, if included) into the catheter region of the applicator, as shown in FIG. 24E. In some variations, the implant is only partially withdrawn into the applicator. FIG. 24F illustrates removal of the applicator and implant from the patient.

[00144] Although many of the applicator devices described herein are configured for both insertion and removal of an implant, it should be understood that an applicator can be configured as an implant removal device alone. For example, an implant removal device may otherwise resemble the applicators described above (including FIG. 23A), but may not be configured to release the implant in the patient's heart after it has been captured and removed. In some variations an implant removal device resembles the applicator of FIG. 23A, and does not include an implant stabilization shaft that is configured to release the implant.

[00145] In some variations, the applicator is configured so that the end or ends of the collapse or expansive strand extend proximally in the applicator and can be removed (e.g., withdrawn) from the implant or the applicator after it has been finally positioned. For example, FIG. 25A illustrates one variation of a system including an applicator 901 and an implant 903, in which the implant 903 includes a collapse strand 905 that extends around the perimeter of the implant and can collapse the struts of the implant if tensioned. The ends of the collapse strand 905 extend proximally into the applicator and extend from a port (e.g., on the handle at the proximal end of the applicator) 906, 906'. The applicator variation shown also includes an implant stabilization shaft (catheter) 909 which includes a balloon 907 for helping expand the implant once positioned, and an implant capture umbrella 920, within an outer cannula or guide catheter 915 of the applicator, similar to the applicator shown in FIG. 23A. In this example, the distal region of the applicator also includes a radiopaque marker 913 to aid in visualization. A balloon inflation port 927 is also present on the proximal end of the device. FIG. 25B illustrates the system of FIG. 25A in which the implant 903 has been detached from the applicator 901. In FIG. 25B the collapse strand 905 has been removed from the device. Presumably the device has been positioned in an acceptable position, and further adjustment is unnecessary. Until the strand is removed, the implant may be continuously collapsed and repositioned by pulling on the collapse strand 905, and using the implant capture umbrella 920 as previously described.

[00146] For example, FIGS. 26A-26D illustrate operation of the system of FIG. 25A. FIG. 26A shows a perspective view of the system of FIG. 25A, including an implant 903 that is attached to the distal end of an applicator 901. The very distal end of the implant includes a soft tip of foot 930. The implant may be inserted into the subject's heart (e.g., the left ventricle) as previously described. Once in position, it may be expanded as shown in FIG. 26A. The position or orientation of the implant may be confirmed or checked using visualization such as fluoroscopy. FIGS. 26B-26D illustrate retrieval of the implant after initially deploying it, but before removal of the collapse strand 905.

[00147] The implant 903 shown in FIGS. 25A-26D may be retrieved by pulling the free ends of the collapse wire 905 to collapse the implant, as shown in FIG. 26B. In this example, the passive anchors 935 can thus be disengaged from the heart wall. After at least partially collapsing the implant, the guide catheter 915 may be withdrawn to expose and expand the implant capture umbrella 920, as shown in FIG. 26C. In some variations, as described for FIG. 24C, above, the implant capture wire may be extended distally. Drawing the implant proximally and then pushing the guide catheter forward distally, as shown in FIG. 26D, will then capture the implant within the implant capture umbrella as it closes around the collapsed implant.

[00148] As mentioned briefly above, in some variations, the implant device includes a collapse element, such as the collapse strand described above, or a collapse sleeve. FIGS. 27A-27E illustrate operation of a system including an implant having a collapse sleeve and an applicator configured to operate the collapse sleeve.

[00149] In FIG. 27A, the implant 1001 is shown in an expanded state. For simplicity sake, the struts are not shown. The implant includes a collapse sleeve 1005 that is positioned distally (e.g., over the stem of the implant) when the implant struts and membrane are deployed, as shown in FIG. 27A. In this example, the implant is coupled to an applicator 1000, that includes a handle region having a collapse knob 1013, an active anchor knob 1015, and a detachment knob 1010. The applicator also includes a guide catheter 1007, within which an extendable/retractable collapse sleeve pullwire 1006 and an implant stabilization shaft 1009 reside. FIGS. 27B-27E illustrate use of the applicator to collapse the implant 1005. For example, in FIG. 27B, the collapse knob (or other appropriate control) on the handle may be operated to draw the collapse sleeve 1005 proximally. For example, turning the collapse knob may cause the pull wire to draw the collapse sleeve 1005 over the implant membrane/struts, collapsing it, as illustrate in FIG. 27C. After the implant is collapsed, it may be pulled inside the guide catheter and removed from the patient, or repositioned and redeployed (e.g., by extending the implant from the guide catheter and pushing on the collapse sleeve guidewire to expand the membrane/struts). The collapse sleeve pullwire may be a wire, a rod, a tube, etc., and may be used for pulling and/or pushing the collapse sleeve.

[00150] The collapse sleeve may be coupled with the collapse sleeve pullwire (or other collapse sleeve control on the applicator), using a configuration such as that illustrated in FIG. 28A and 28B. FIG. 28A shows a front view of an expanded implant including a centrally-located attachment mechanism 1101 for the collapse sleeve. This attachment mechanism can be a cross-bar or wire that extends across the central opening and connects to one or more points on the inner surface of the sleeve. In this example, both the hub region of the implant and the collapsible struts/membrane region include a track or slot along which this cross-bar or wire can move to allow the collapse sleeve to be moved proximally or distally. For example, two opposite struts 1107 shown in FIG. 28A include a slot or track 1105 along which the cross-bar or wire connected to the collapse sleeve may move. The applicator may include a shaft or wire that engages this attachment mechanism and pulls it proximally or pushes it distally. FIG. 28B shows a side view of the implant shown in FIG. 28A, including the collapse sleeve 1110.

[00151] Another variation of an implant delivery system is shown in FIGS. 29A-29E. FIG. 29A shows an applicator including a collapse line or lasso 1201 extending from a side port on an implant stabilizing shaft passing through a guide catheter 1207 on the device. The distal end of the implant stabilizing shaft includes a detachment screw 1205 that may be activated to detach an implant from the device. In this example, the collapse line may be drawn proximally (e.g., towards the handle of the applicator 1211) by manipulating a control on the handle such as a collapse line control knob 1209. The handle may also include one or more controls for detaching the implant 1213, or the like. In some variations the collapse line is connected to an implant prior to deployment of the implant, and may be released from the implant after it has been finally positioned. In other variations, the collapse line is not integral to the implant, but may be connected around the implant after it has been released.

[00152] FIGS. 29B-29E illustrate operation of the implant delivery system including the applicator and implant. For example, in FIG. 28B, the deployed implant is still attached to the applicator, but it is desired to collapse and reposition (or remove) the implant. In this variation the implant includes an implant stem, configured as an atraumatic foot 1220 extending from an expanded implant umbrella region 1222. In FIG. 29C the collapse line or lasso 1201 is contracted to collapse the implant until it is sufficiently collapsed to fit into the guide catheter 1207, as shown in FIG. 29D. Once it has collapsed sufficiently, the guide catheter may be moved distally to enclose the implant, as shown in FIG. 29E. FIGS. 30A and 30B illustrate side and front views, respectively, of an implant which may be used with the applicator shown in

FIG. 29A-29E. The implant is shown connected to a collapse line 1201 (or strand) that passes through two or more skives 1250 on the membrane 1240. The collapse line 1201 includes a push knot 1252. The implant also includes multiple struts 1245.

[00153] FIGS. 35A-35E illustrate another variation of a system for applying and removing a partitioning device (implant) that includes an applicator having a collapse line. For example, FIG. 35A shows a system including an applicator 1700 having a delivery cannula, and an implant 1701 including expandable struts with passive anchors at their ends. The system shown in FIG. 35A is in the undeployed state, and the distal end of the implant (including an atraumatic foot region extending distally). It can be deployed by pushing it from the delivery catheter region so that the struts can expand, as shown in FIG. 35B. In this example, a strand or lariat 1705 is pre-positioned around the device, and passes into a lariat guide tube 1707 that is within the delivery catheter. As the device is deployed, the lariat expands around it, and the lariat guide tube 1707 remains connected. If the position is correct, the lariat (string) may be withdrawn by pulling it from one end to remove it from around the device (not shown), and withdrawing both the lariat and the lariat guide tube with the applicator 1700. FIGS. 35C-35E illustrate one method of repositioning or removing the implant by pulling on one or both ends of the lariat and collapsing the implant (e.g., collapsing the expanded struts, as shown in FIG. 35C), until it can be either repositioned, as shown in FIG. 35D, or withdrawn into the delivery catheter and removed, as shown in FIG. 35E.

[00154] In some variations the implant is retrieved into the applicator after inverting the implant so that the membrane and/or struts may be collapsed as the implant is drawn into a catheter region of the applicator. One variation of this method and a system including this method is shown in FIGS. 31A-31D. For example, in FIG. 31A, the applicator includes a handle region 1401 having one or more controls 1403, 1405, an elongate catheter region 1408 including a guide catheter, and an implant stabilization shaft and a retrieval line 1410 that connects to the distal end (e.g., the foot region 1422) of the implant. FIGS. 31B-31D illustrate removal of a deployed implant using this applicator. Pulling on the retrieval line 1410 after deployment will disengage the implant 1420 from the walls of the left ventricle, as shown in FIG. 31C and invert the implant within the left ventricle (lv) as it is drawn towards the guide catheter in the applicator. In this example, the retrieval line 1410 is attached to a flexible foot region 1422. Withdrawing the inverted implant into the applicator collapses the implant, as shown in FIG. 31D.

[00155] FIGS. 32A and 32B illustrate another variation of an applicator 1500 configured to remove an implant by inverting the implant, and FIGS. 33A-33H illustrate the operation of the applicator 1500. In FIG. 32A, the system includes a handle region 1501 (control region) having a balloon inflation port 1503, an implant release port 1505, and an implant capture port 1507. The proximal control/handle region is connected to an elongate insertion cannula. An implant stabilization shaft 1509 configured to releaseably secure to an implant and an implant capture wire 1511 extend through the cannula, and are axially movable therein. Thus, the cannula may include one or more internal axial lumen through which these structures may move. The implant stabilization shaft may include a balloon 1515 or other deployment-aiding structure, and/or a screw 1513 that can be used to detach/reattach the implant. FIG. 33B shows the device of claim 33A in partial cross-section, so that the implant stabilization shaft 1509 and implant capture wire 1511 are visible. The proximal end of the implant stabilization shaft 1509 is shown withdrawn so that the implant stabilization shaft is completely within the cannula.

[00156] FIGS. 33A-33H illustrate operation of this system. In FIG. 33A, the applicator 1500 of FIGS. 32A and 32B is shown in partial cross-section with an implant 1520 pre-loaded on the distal end. The implant capture wire 1511 in this variation is pre-loaded through the implant, so that it extend from the implant release port, through the implant, and out of the implant capture port. For convenience, FIG. 33A shows the implant in an expanded (deployed) configuration, although it may also be contracted in a delivery configuration in which the struts and any membrane between them is collapsed and retracted at least partially into the delivery catheter.

[00157] FIG. 33B shows a cross-section through the distal region of the implant, showing a passageway through which the implant capture wire may pass. This passageway may be sized so that a retainer 1530 on the end of the implant capture wire cannot pass through the implant, so that it can be retrieved by pulling on the wire, as illustrated below. If the implant it positioned and deployed as desired, the implant capture wire may be completely withdrawn through the implant. For example, the retainer 1530 on the end of the implant capture wire may be removed or disengaged.

[00158] After deploying the device into a heart, e.g., into the left ventricle of the heart, the device may be withdrawn. For example, to remove the implant from the heart, one end of the implant capture wire 1511 may be withdrawn down the device, as illustrated in FIG. 33C. In this example, the implant capture wire is drawn proximally by pulling on the end of the implant capture wire extending from the implant capture port 1507. The opposite end of the implant capture wire is attached to a retainer 1530. The retainer is sized (or otherwise configured) so that it cannot pass through the implant hub 1533, as shown in FIG. 33D.

[00159] FIG. 33E shows the implant stabilization shaft disengaged from the implant 1520. With the implant stabilization shaft attached, the implant may partially withdrawn from the wall of the heart, to allow it space to move (e.g., within the ventricle) so that it has adequate room to be flipped, as illustrated in FIG. 33F. For example, pulling on the implant capture wire 1511 extending from the implant capture port 1507 will draw the foot (tip) of the implant to be drawn towards the applicator (the distal end of the cannula). In the example shown in FIG. 33F, the distal end of the catheter is marked with a radiopaque marker 1550, so that the position of the applicator can be observed. FIGS. 33G and 33H illustrate the steps of collapsing the implant into, by continuing to secure the implant at the distal end of the applicator (e.g., pulling on the implant capture wire 1511) while sliding a guide catheter, sheath, or collapsing catheter 1539 over the flipped implant. The guide catheter (or sheath, or collapsing catheter) 1539 moves axially over the delivery catheter 1561 to extend distally beyond the end of the guide catheter, and the distal end of the both may include a radiopaque marker 1550. Once collapsed, the implant and applicator may be removed from the patient.

[00160] In any of the variations described herein the implant may be removed after it has been at least partially secured or even anchored to the patient's heart wall. For example, an implant may include passive anchors at the ends of the ribs (struts), which may be pointed or sharp, and configured to partially penetrate the heart wall. Removal or re-positioning of the implant may therefore be simplified by disengaging the implant from the heart wall. In some variations a portion of the implant is axially shortenable (e.g., collapsible, compressable, etc.) after it has been deployed so that it can be disengaged. For example, the hub and/or foot region of the implant may be collapsible, as illustrated in FIGS. 34A-34D. In some variations the shortenable region is a telescoping region. In some variations the shortenable region includes a spring or other biasing element that holds the region is an extended (unshortened) position until it is allowed to compress or otherwise activated. Thus, the shortenable region may be activated by applying force to shorten it. In some variations, the shortenable region is lockable so that it cannot be shortened until the lock is disengaged. A lock may include a pin, a catch, or the like. The lock may be mechanically, electrically or magnetically activated.

[00161] FIG. 34A shows an implant having an elongated hub region 1601 that includes a collapse region 1601. The hub region 1601 of FIG. 34A is shown in more detail in FIG. 34B. In this variation, the collapsible region includes hinged arms. The hub region in this example may be foreshortened by pulling proximally on a string (or strings) 1605 attached distally to the collapse region 1601. This is illustrated in FIG. 34C, and in greater detail in FIG. 34D. In this example, the string passes from the proximal end of the implant (and may pass through or into an applicator), loops around a hole in the implant, and then back out proximally. After the device position is finalized, the string 1605 may be removed by withdrawing one end of the string while allowing the other end to be pulled through the implant and out again, as illustrated in FIGS. 34E and 34F.

[00162] In other variations, the foreshortening of the implant does not require a string, but may be activated by merely applying pressure or force to the device.

[00163] In addition to the devices and methods for collapsing an implant described above, other methods may also be applied, either separately or in combination with the methods described above. For example, the implant may be collapsed by changing the temperature of the implant. This method is particularly effective when the implant is made (at least partially) of a shape memory material, such as Nitinol. FIG. 36A shows a cross-section through one variation of an implant 3600 in which the device includes a frame (e.g., having struts 3601), and a centrally (and proximally) located tip 3603 that may be grasped by an applicator, as illustrated in FIGS. 36B and 36C, described below. The frame (e.g., struts 3601) may be formed in part from a shape-memory material that may transition between an expanded (Austentite) configuration into a collapsed (Martensite) configuration when exposed to cold.

[00164] FIGS. 36B and 36C illustrate this transition. In FIG. 36B the device 3600 has been inserted in to left ventricle 3612. An applicator 3609 including a pair of grabbing jaws 3615 (although any coupling means for securing the implant to the applicator may be used, including those described above) is brought near the implant, and the jaws 3615 may be secured to the tip 3603 of the implant. The applicator also includes a channel for applying chilled fluid 3621. For example, cooled saline (e.g., between 0 and 10 degrees C) may be applied from the channel 3621 to change the Nitinol of the implant from the austenite phase (expanded) to the martensite phase (collapsed). This is illustrated in FIG. 36C. The implant 3600 is shown in a collapsed configuration, disengaged from the wall. The implant is also shown being drawn into the applicator (which may include a catheter into which the implant may be withdrawn. In this example, the central region of the applicator, including the grasping jaws 3615 can be withdrawn into the outer cannula of the applicator.

[00165] To the extent not otherwise described herein, the various components of the implants, applicators, and delivery systems including any of them may be formed of conventional materials and in a conventional manner as will be appreciated by those skilled in the art.

[00166] While particular forms of the invention have been illustrated and described herein, it will be apparent that various modifications and improvements can be made to the invention.

Moreover, individual features of embodiments of the invention may be shown in some drawings and not in others, but those skilled in the art will recognize that individual features of one embodiment of the invention can be combined with any or all the features of another embodiment. Accordingly, it is not intended that the invention be limited to the specific embodiments illustrated. It is intended that this invention to be defined by the scope of the appended claims as broadly as the prior art will permit.

WHAT IS CLAIMED IS:

1. A method of deploying an implant comprising:
   advancing an implant into a patient's left ventricle chamber in a contracted configuration, wherein the implant comprises a plurality of struts formed of a shape memory material;
   expanding the implant into a deployed configuration at a first left ventricle location;
   changing the temperature of the implant to at least partially collapse the implant into the contracted configuration;
   retrieving the implant into a retrieval catheter; and
   withdrawing the implant from the first left ventricle location.

2. The method of claim 1, wherein the step of changing the temperature of the implant comprises exposing the implant to cooled saline.

3. A system for partitioning a patient's ventricle, the system comprising:
   an implant configured for deployment into the patient's ventricle, the implant including a plurality of struts, wherein the implant is configured to have a collapsed delivery configuration and an expanded deployed configuration; and
   an applicator configured to insert and retrieve the implant, comprising
      a control at the proximal end of the applicator for controlling release of the implant from the applicator;
      an elongate body extending from the proximal end to a distal end, wherein the distal end of the elongate body is configured to relasably secure the implant; and
      a capture wire extendable from the applicator's distal end and configured to draw the implant toward the applicator's distal end.

4. The system of claim 3, further wherein the applicator comprises a control at the proximal end for manipulating the capture wire.

5. The system of claim 3, wherein the capture wire is configured as a lariat.

6. The system of claim 3, wherein the implant comprises a strand that may be tensioned to collapse the implant from the expanded configuration, and further wherein the capture wire of the implant is configured as a hook that may engage the strand.

7. The system of claim 3, wherein the capture wire is connected to the implant.

8. The system of claim 3, wherein the applicator further comprises an inflatable sleeve configured to extend from the distal end of the applicator and collapse the implant.

9. The system of claim 3, wherein the applicator further comprises a capture umbrella configured to extend from the distal end of the applicator and collapse the implant.

10. The system of claim 3, wherein the implant further comprises a collapse sleeve configured to collapse the struts, wherein the system further comprises a collapse sleeve pullwire configured to engage the collapse sleeve on the implant.

11. A system for partitioning a patient's ventricle, the system comprising:
an implant configured for deployment into the patient's ventricle, the implant including:
a plurality of struts, wherein the implant is configured to have a collapsed delivery configuration and an expanded deployed configuration, and
a strand extending between the struts, wherein the strand may be tensioned to collapse the struts; and
an elongate applicator configured to insert and retrieve the implant, the applicator including:
a control at the proximal end of the applicator for controlling release of the implant from the applicator,
an implant stabilization shaft extending distally from the proximal end, wherein the implant stabilization shaft is configured to relasably secure to the implant, and
a strand capture element extending distally from the proximal end, wherein the strand capture element is configured to engage the strand on the implant and collapse the struts of the implant.

12. A device for partitioning a patient's ventricle into a main functional portion and a secondary non-functional portion, comprising:

a membrane having an expanded configuration and a collapsed configuration;

an expandable frame formed of a plurality of struts having a distal end secured to a hub, wherein the membrane is secured to the expandable frame;

a stem extending distally from the hub; and

a collapse sleeve configured to axially slide from the stem and to collapse the expandable frame and membrane into a collapsed configuration.

13. The device of claim 12, further comprising a passive anchor at the ends of each of the struts of the expandable frame.

14. The device of claim 12, further comprising a non-traumatic foot at the distal end of the device.

15. The device of claim 12, further comprising an attachment mechanism for a collapse sleeve pullwire.

16. A removable or repositionable implant for partitioning a chamber of a patient's heart into a main functional portion and a secondary non-functional portion, comprising:

a membrane;

a plurality of struts secured to a hub at a first end, wherein the membrane is secured to the plurality of struts, and the plurality of struts and membrane have a collapsed delivery configuration and an expanded deployed configuration for deployment within a heart chamber, wherein the membrane forms a recess when in the expanded configuration;

wherein end of each of the plurality of struts includes a passive anchor configured to secure to the wall of the patient's heart; and

a stem extending distally from the hub, wherein the stem comprises a shortenable region configured to be decreased in length and permit the passive anchors to disengage from the wall of the patient's heart.

17. The implant of claim 16 further comprising a trigger configured to shorten the shortenable region of the stem.

18. The device of claim 17, wherein the trigger comprises a wire or line extending distally through the stem portion.

19. The device of claim 16, wherein the shortenable region is a collapsible region.

20. The device of claim 16, wherein the shortenable region is a telescoping region.

21. The device of claim 16, further comprising a lock for locking the shortenable region.

22. A method of removing an implant that has been deployed at a first ventricle location, wherein the implant includes a plurality of struts each having a passive anchor at a first end and connected to a hub at a second end and a stem extending from the hub, the method comprising:

shortening a shortenable region of the stem to disengage the passive anchors from the heart wall;

at least partially collapsing the plurality of struts; and

withdrawing the implant from the first left ventricle location.

23. The method of claim 22, wherein the step of shortening the shortenable region comprises applying pulling on a wire or string to shorten the shortenable region.

24. The method of claim 22, further comprising unlocking the implant so that the shortenable region may be shortened.

25. The method of claim 22, wherein the step of at least partially collapsing the implant comprises pulling on a strand or collapse line to draw the struts together.

26. The method of claim 22, further comprising repositioning the implant within the left ventricle and expanding the struts into a deployed configuration at a second left ventricle location.

27. The method of claim 22, further comprising removing the implant from the patient.

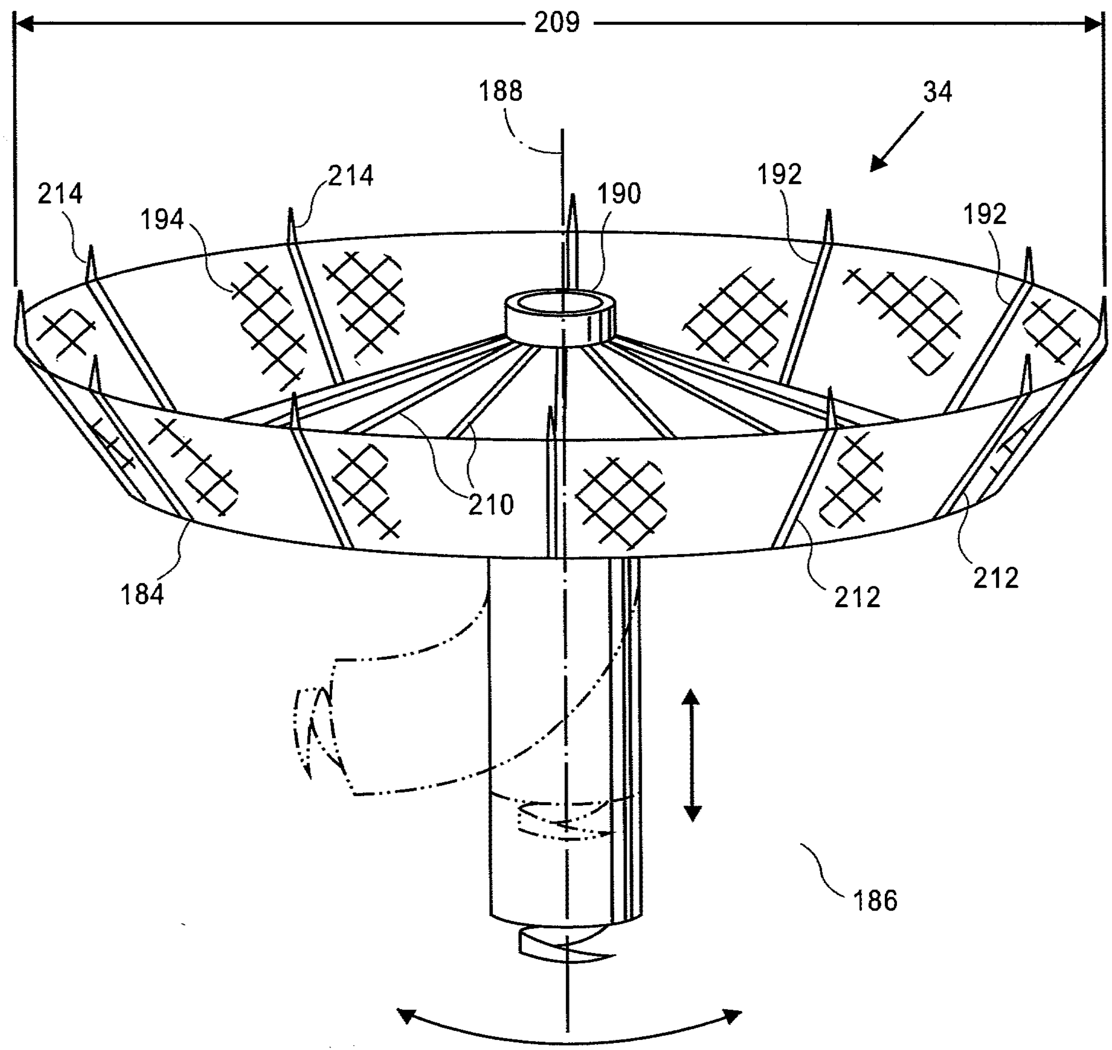

FIG. 1

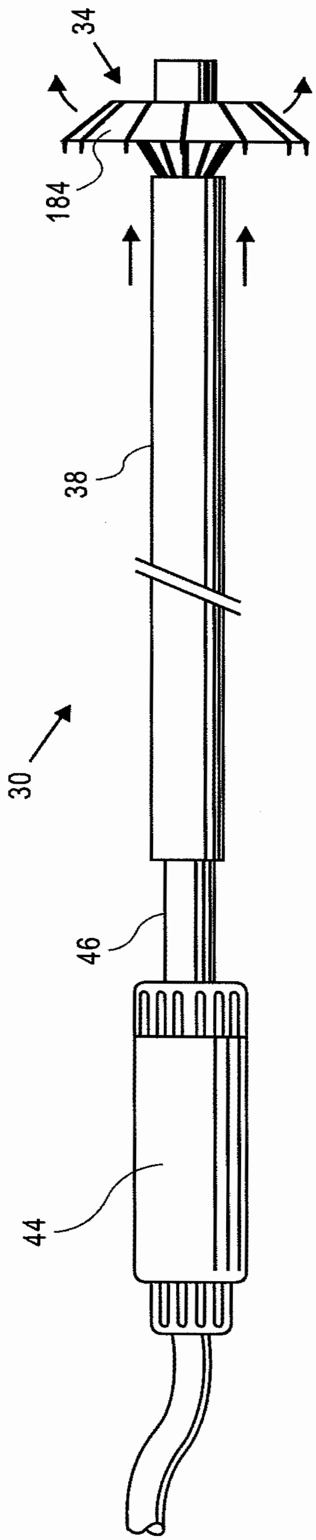

FIG. 2A

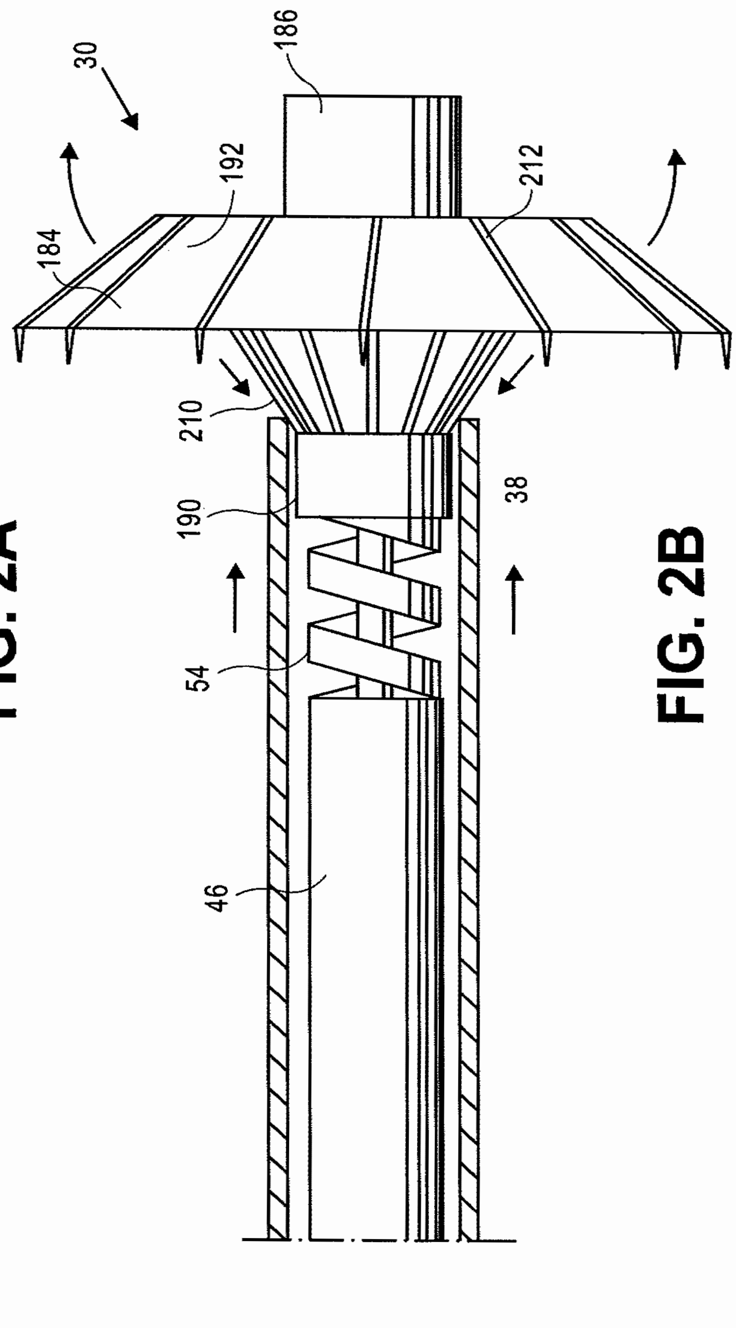

FIG. 2B

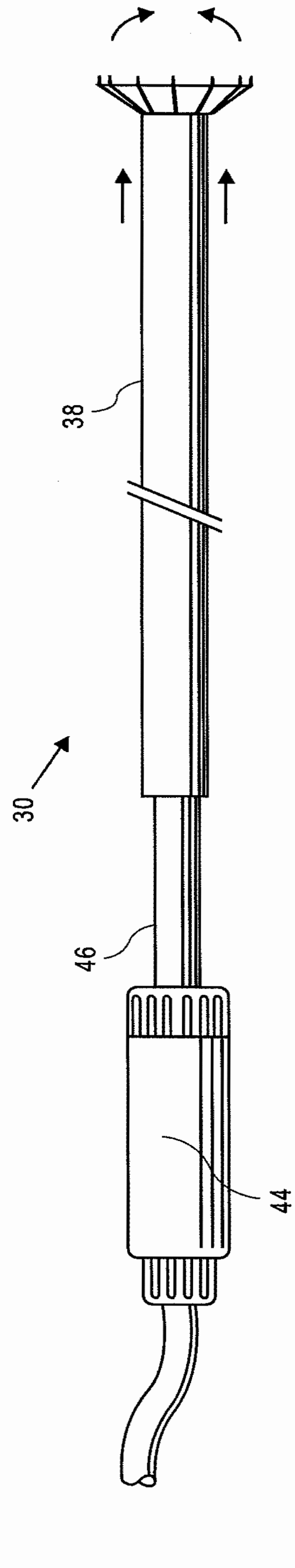

FIG. 3A

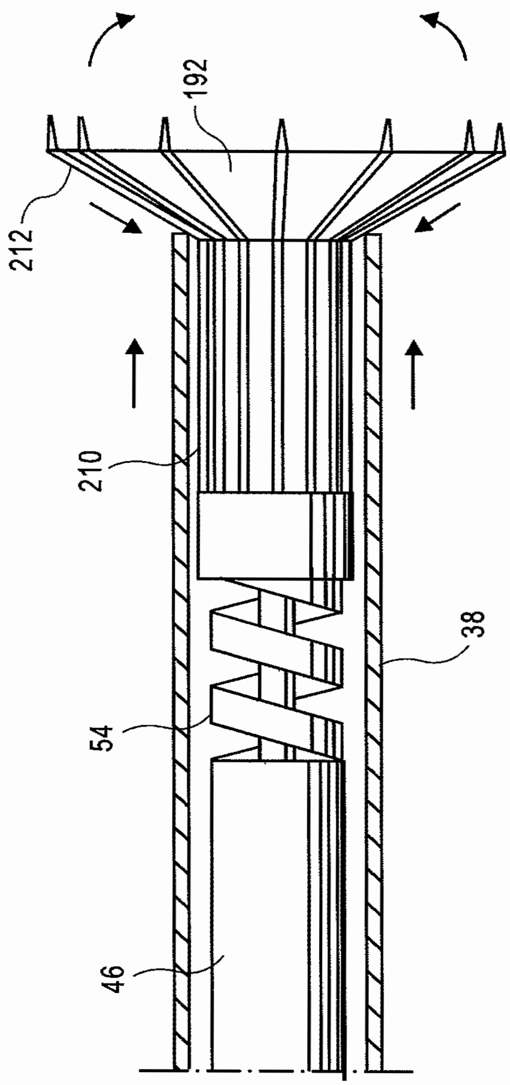

FIG. 3B

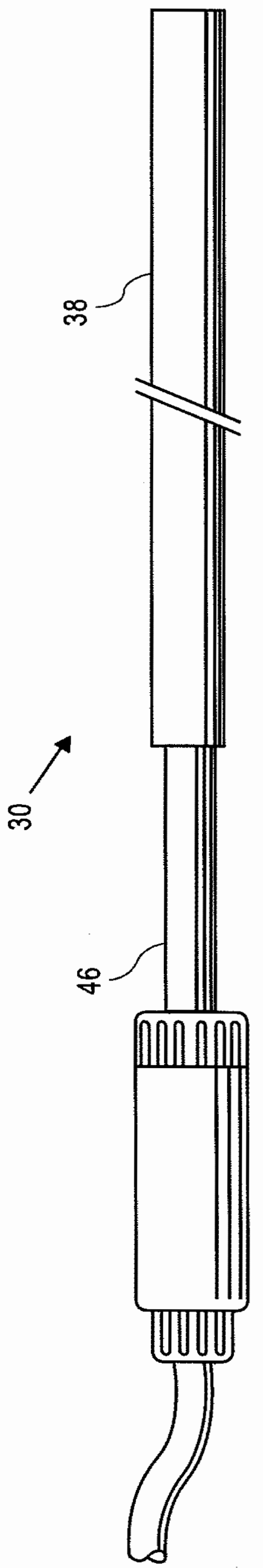

FIG. 4A

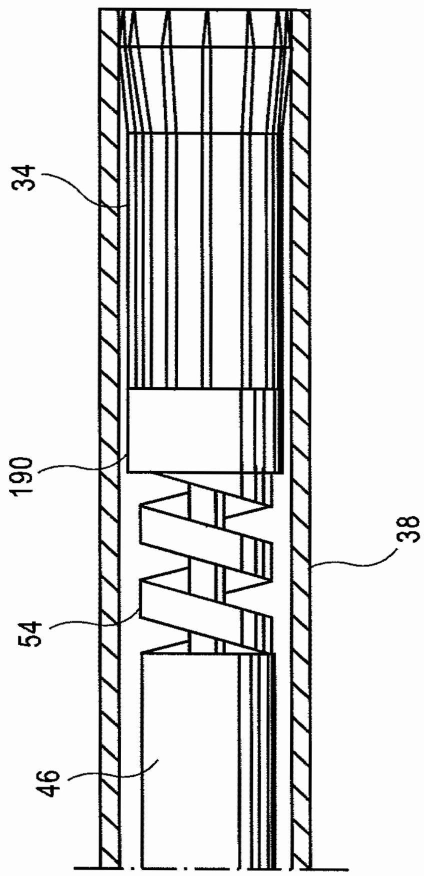

FIG. 4B

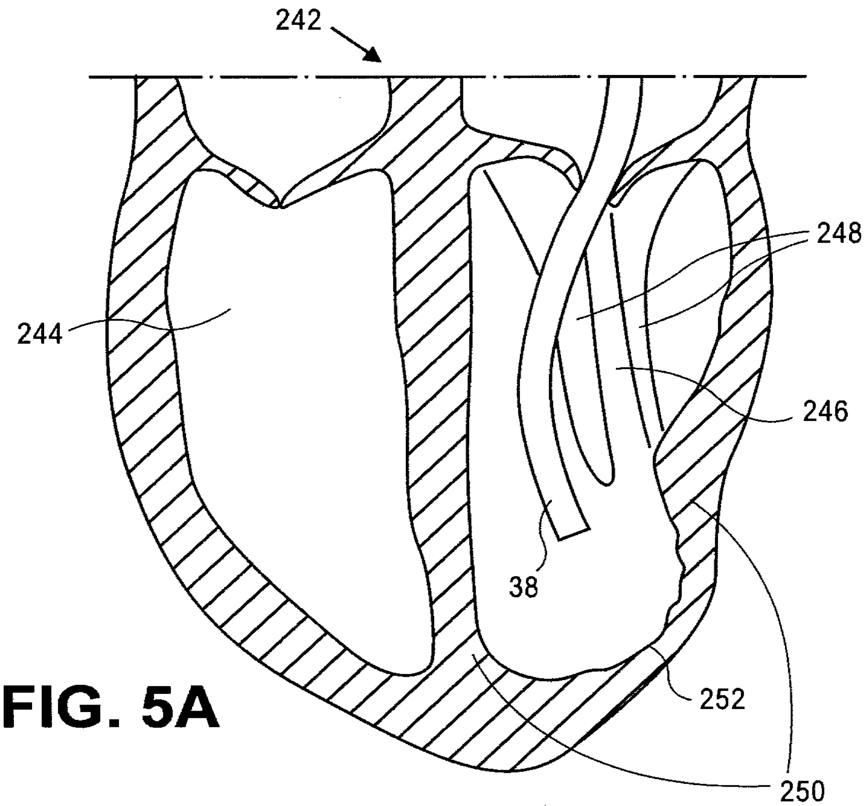

FIG. 5A

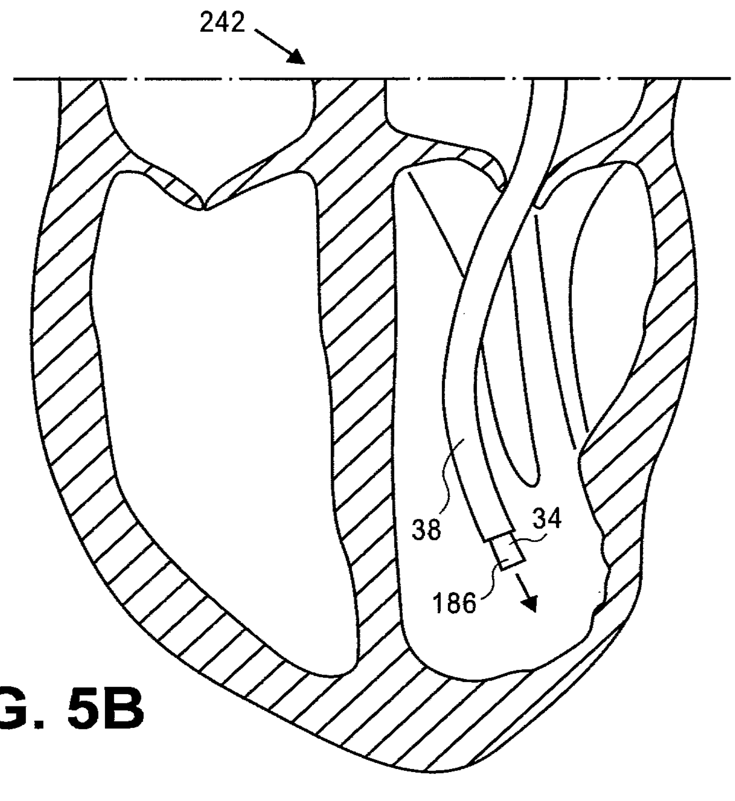

FIG. 5B

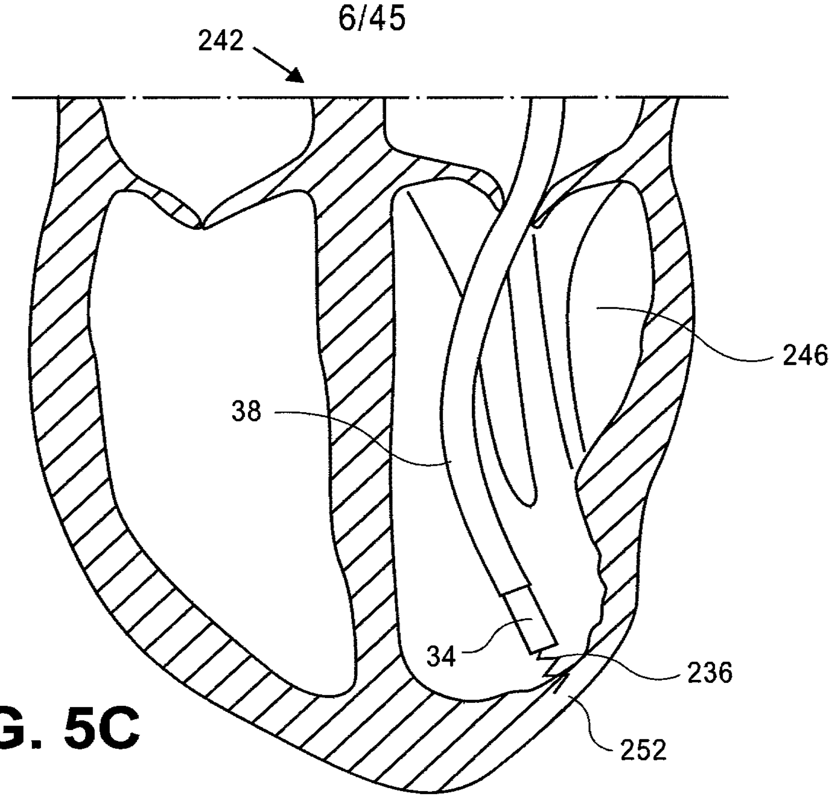

FIG. 5C

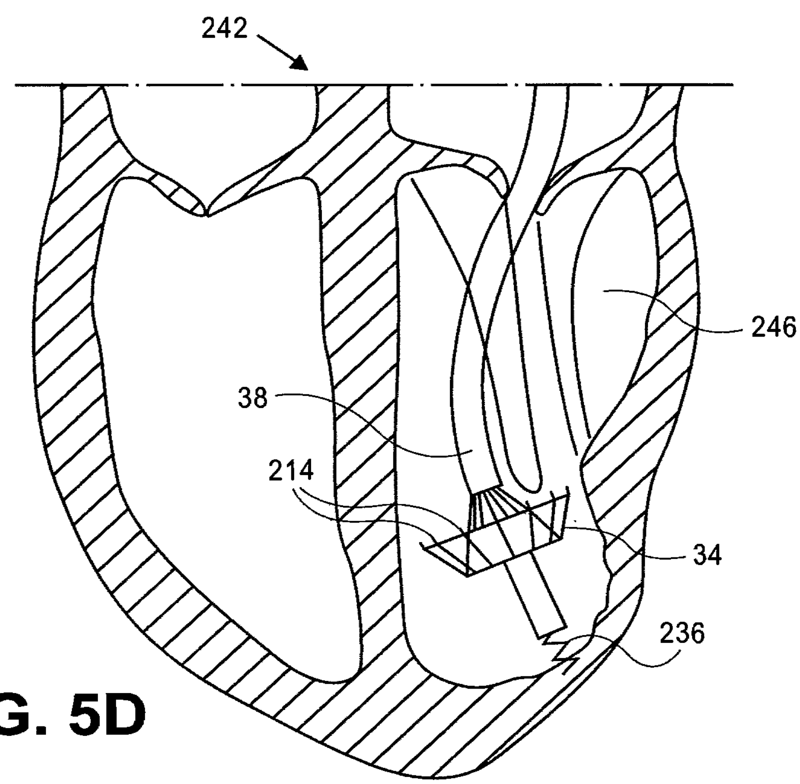

FIG. 5D

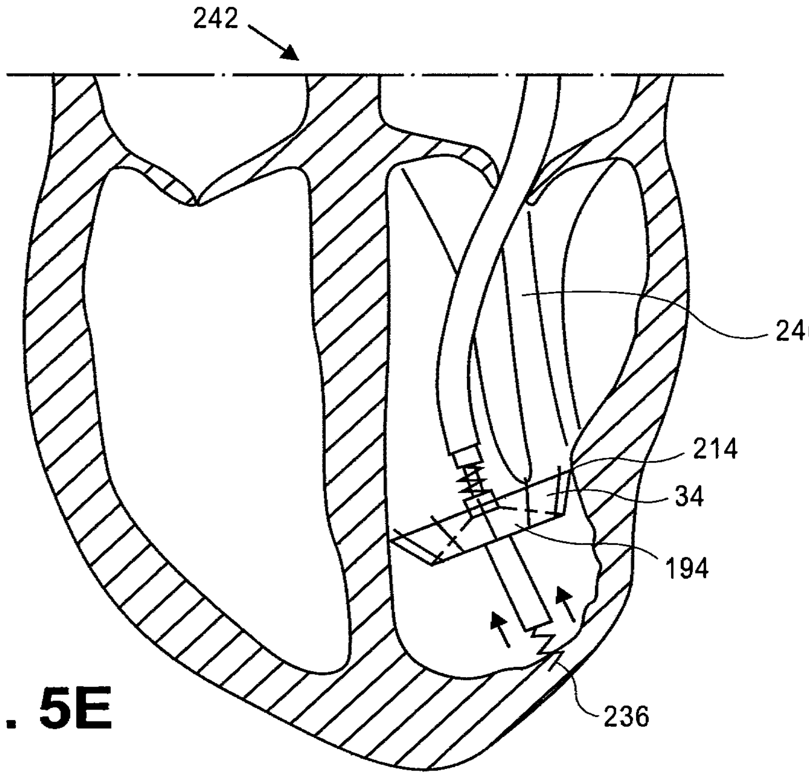

FIG. 5E

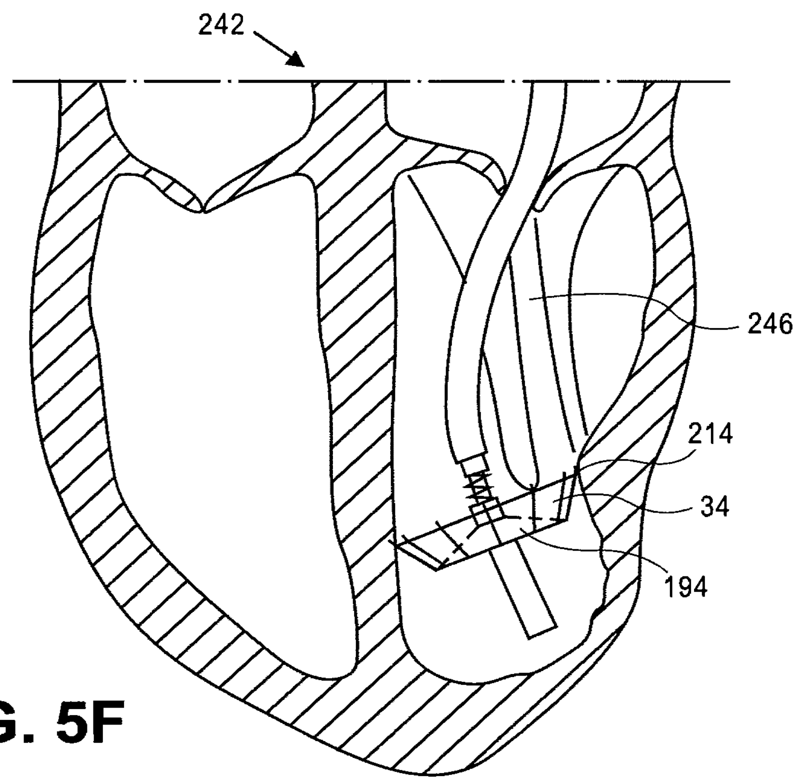

FIG. 5F

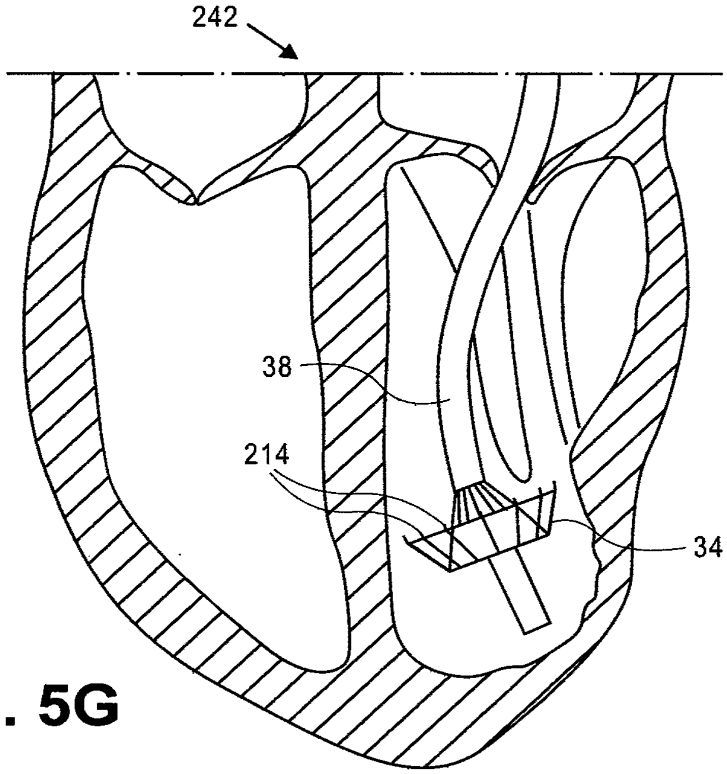

FIG. 5G

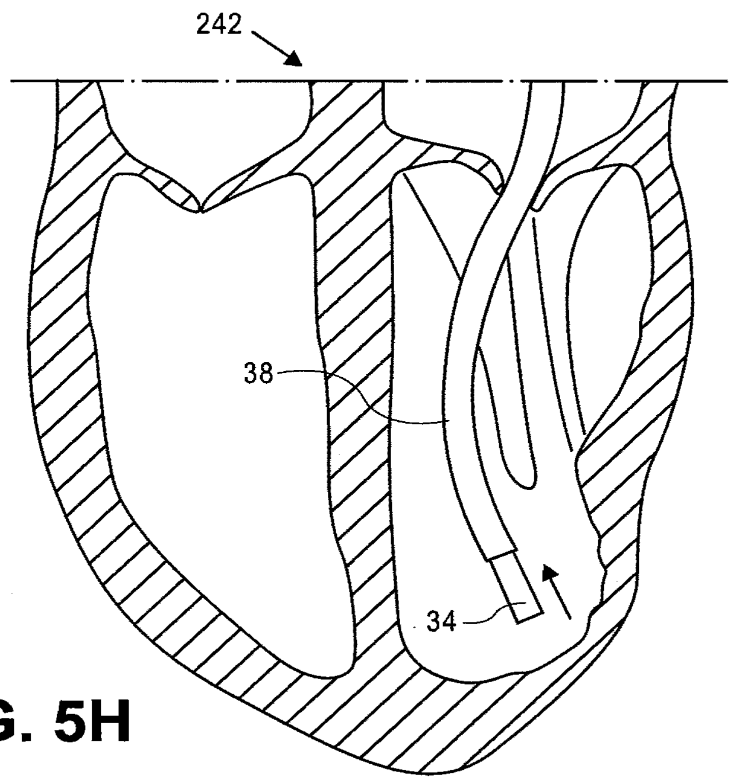

FIG. 5H

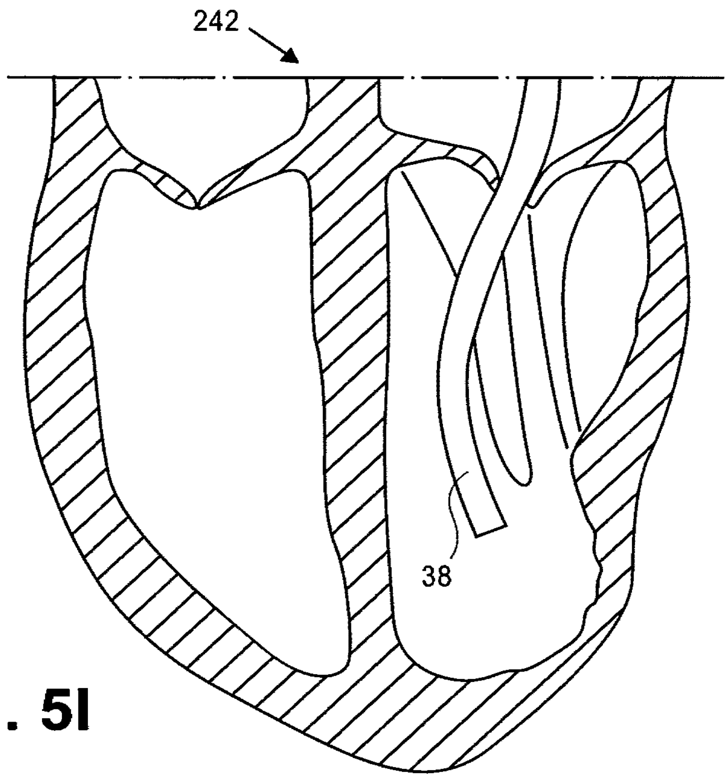

FIG. 5I

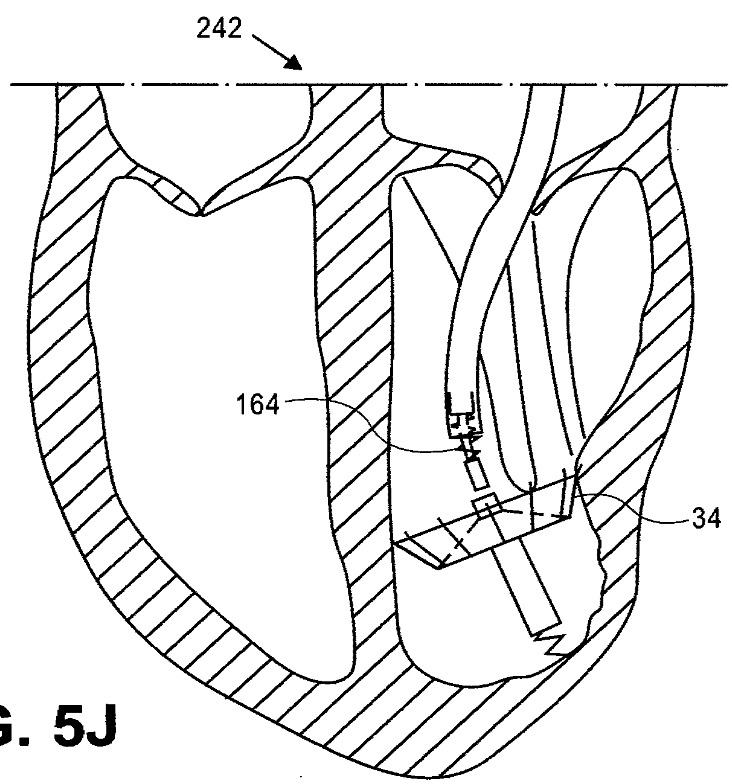

FIG. 5J

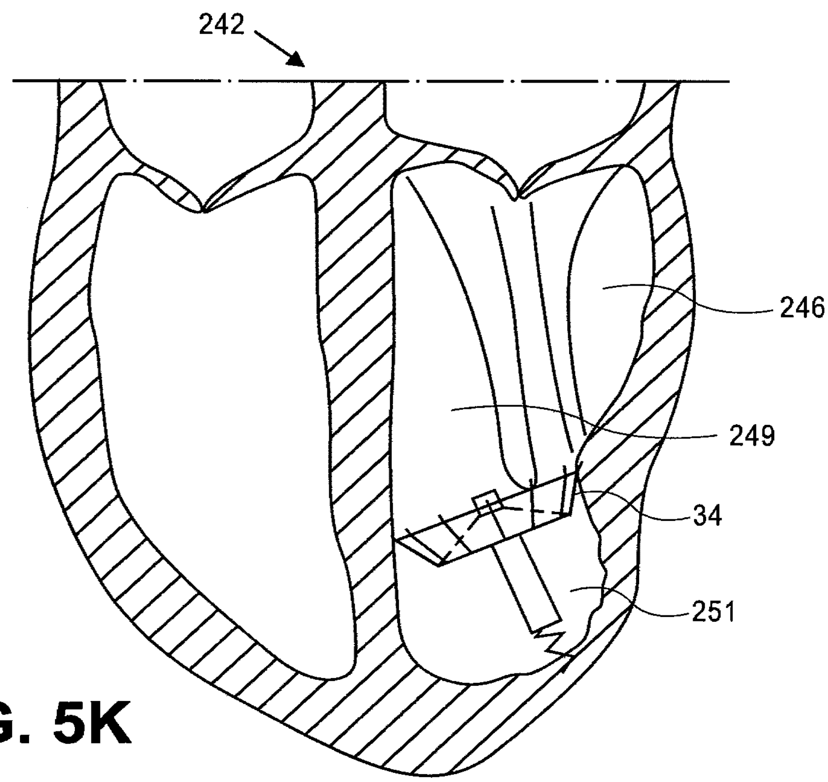

FIG. 5K

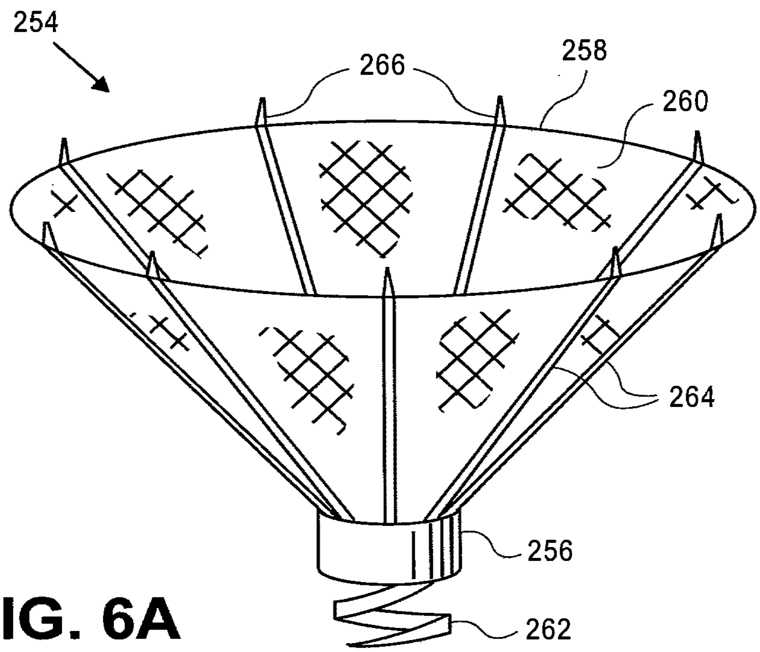

FIG. 6A

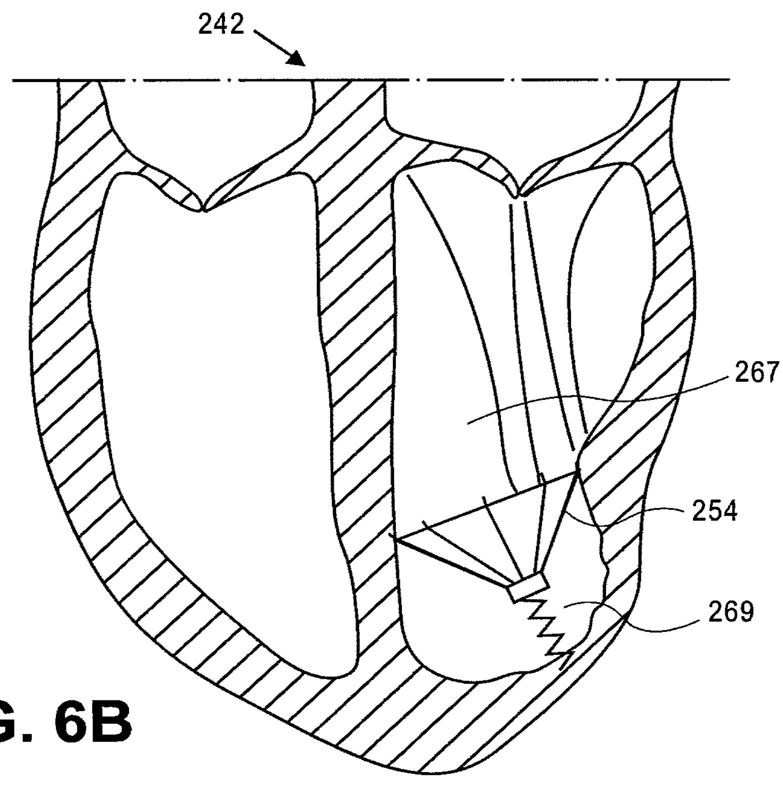

FIG. 6B

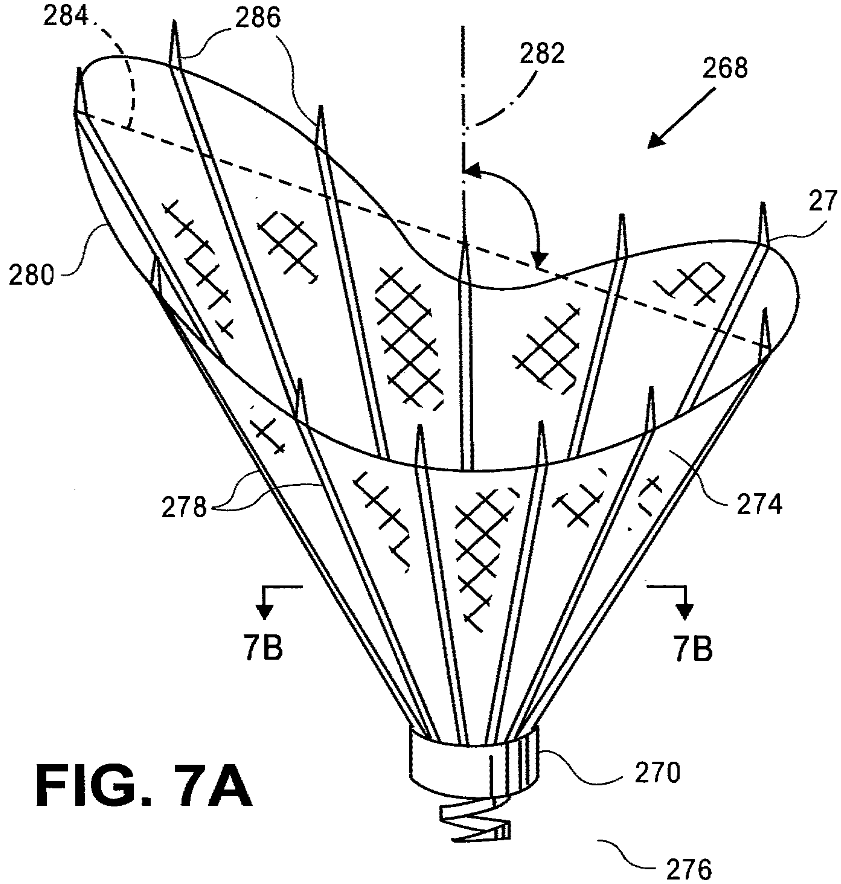

FIG. 7A

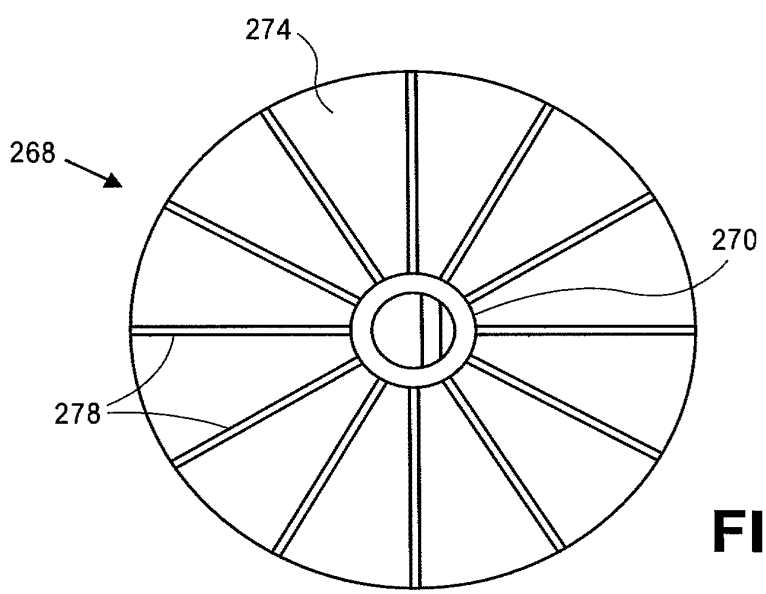

FIG. 7B

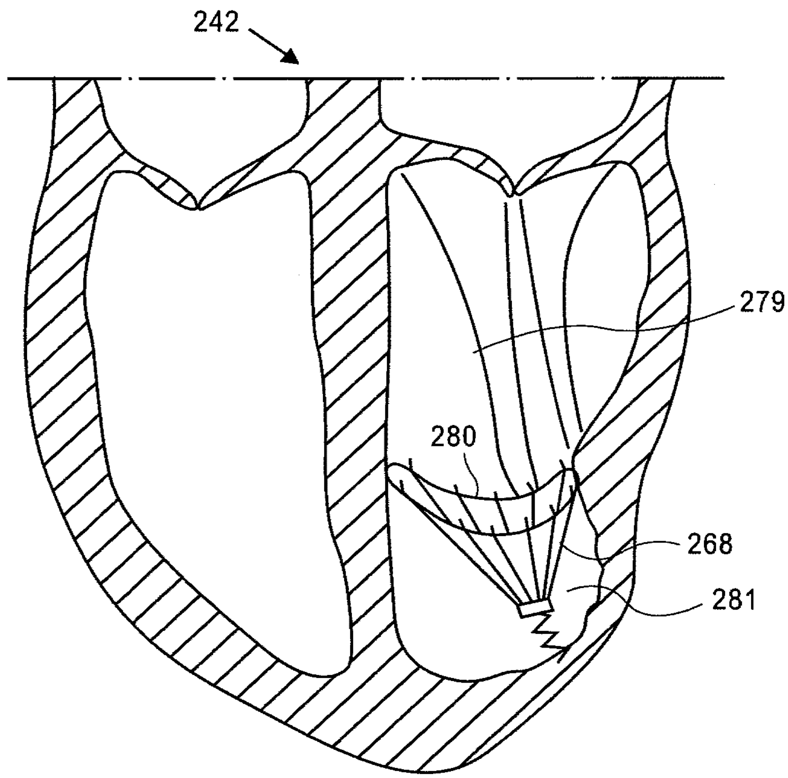

FIG. 7C

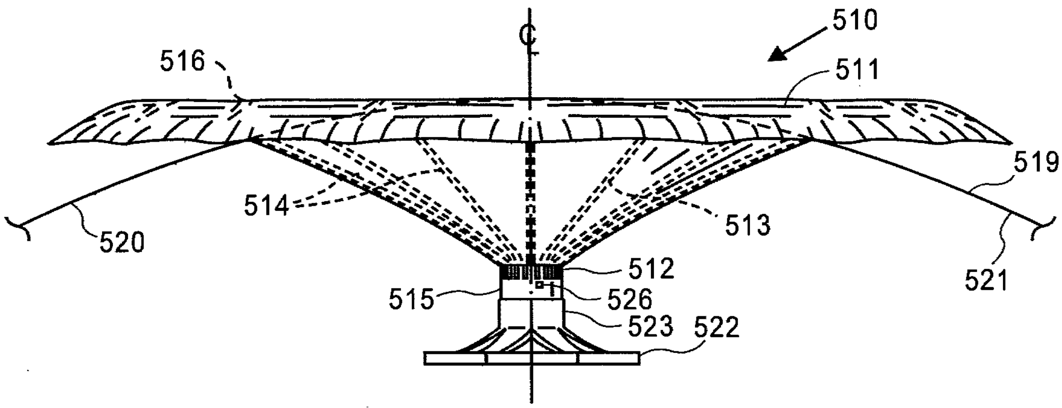
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FIG. 8

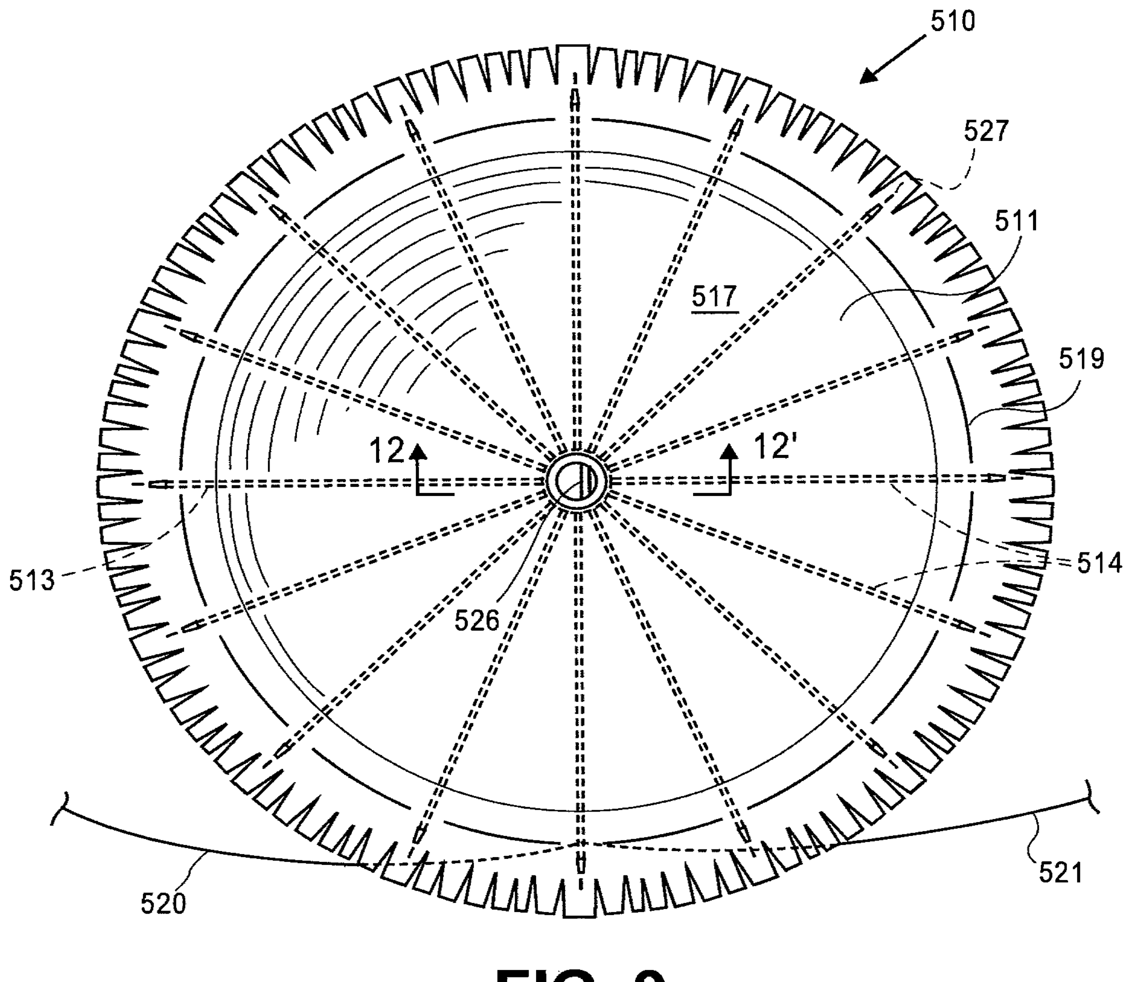
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FIG. 9

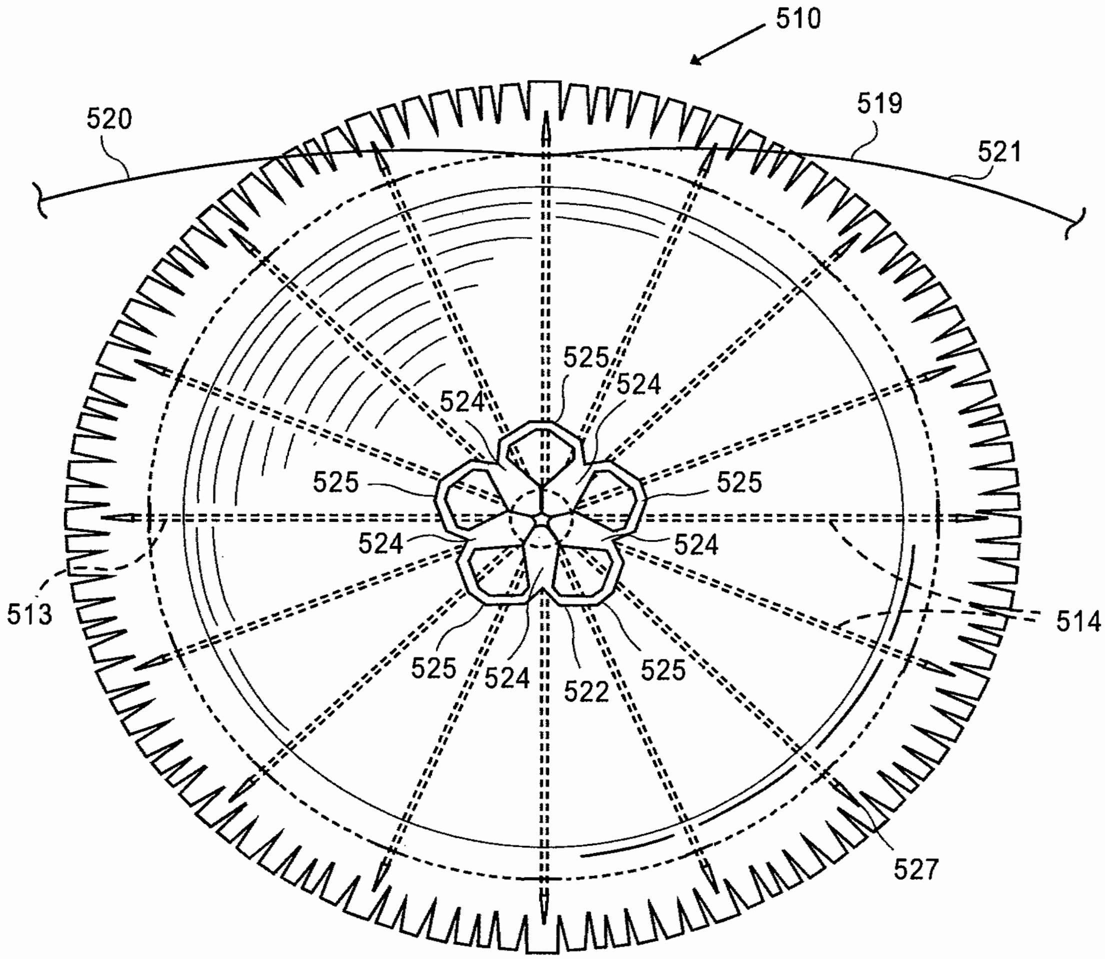
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FIG. 10

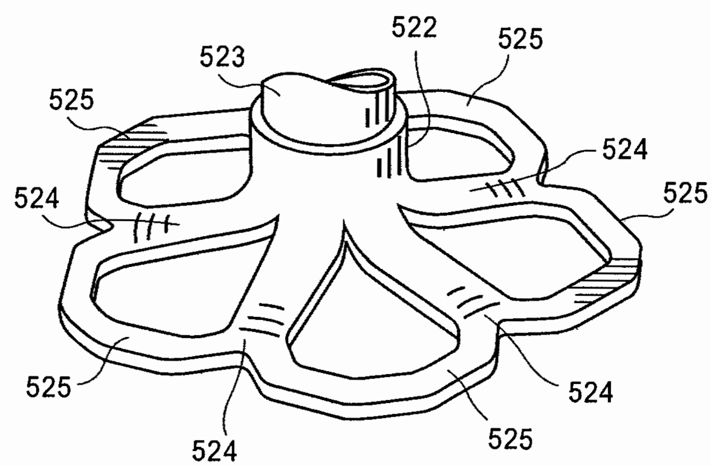
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FIG. 11

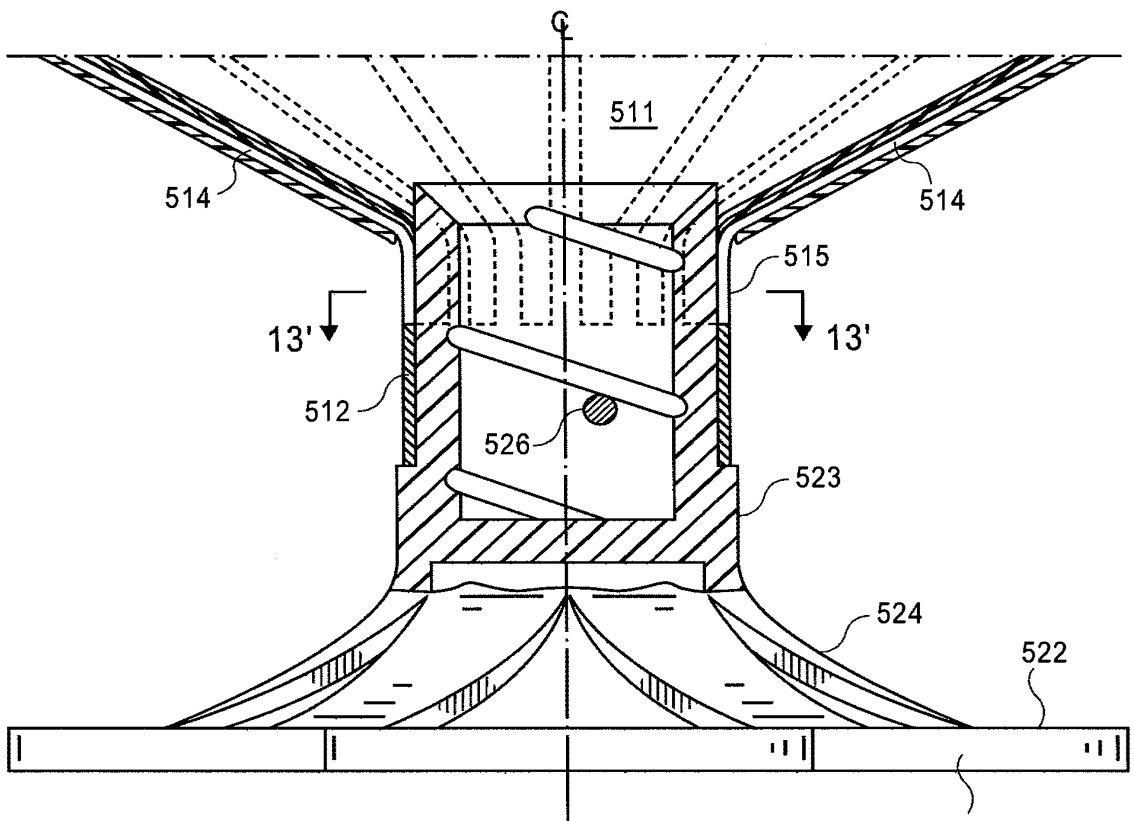

FIG. 12

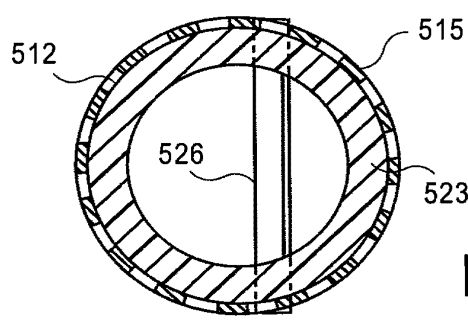

FIG. 13

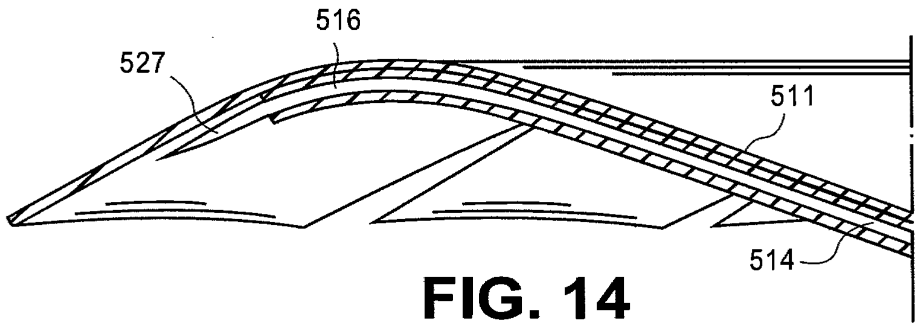

FIG. 14

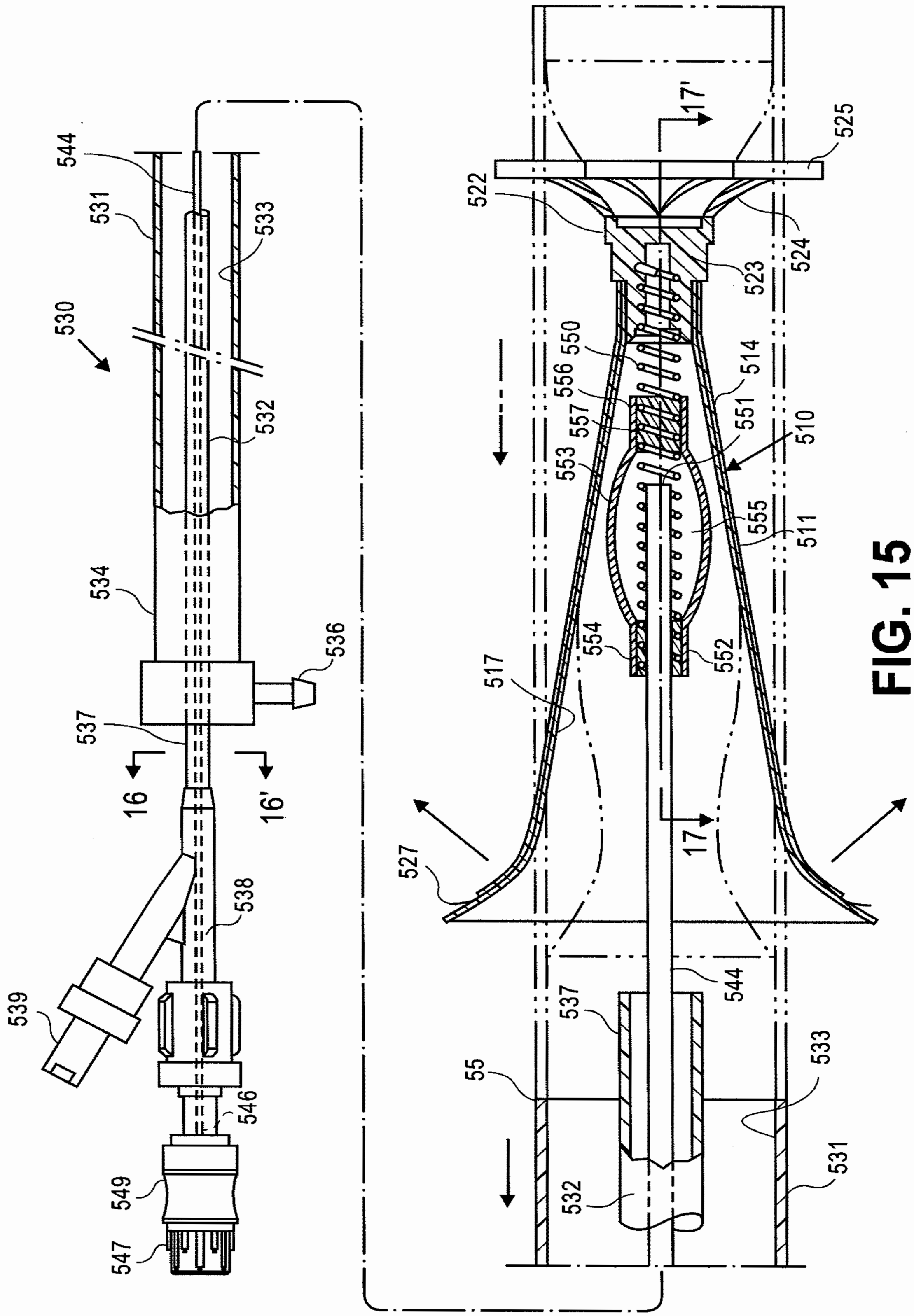

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FIG. 15

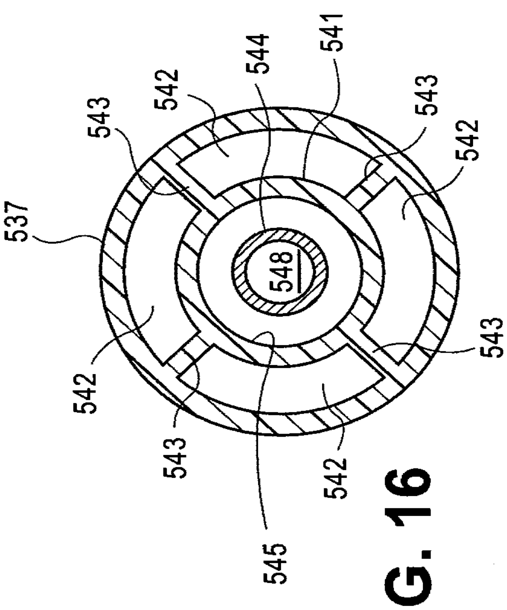
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FIG. 16

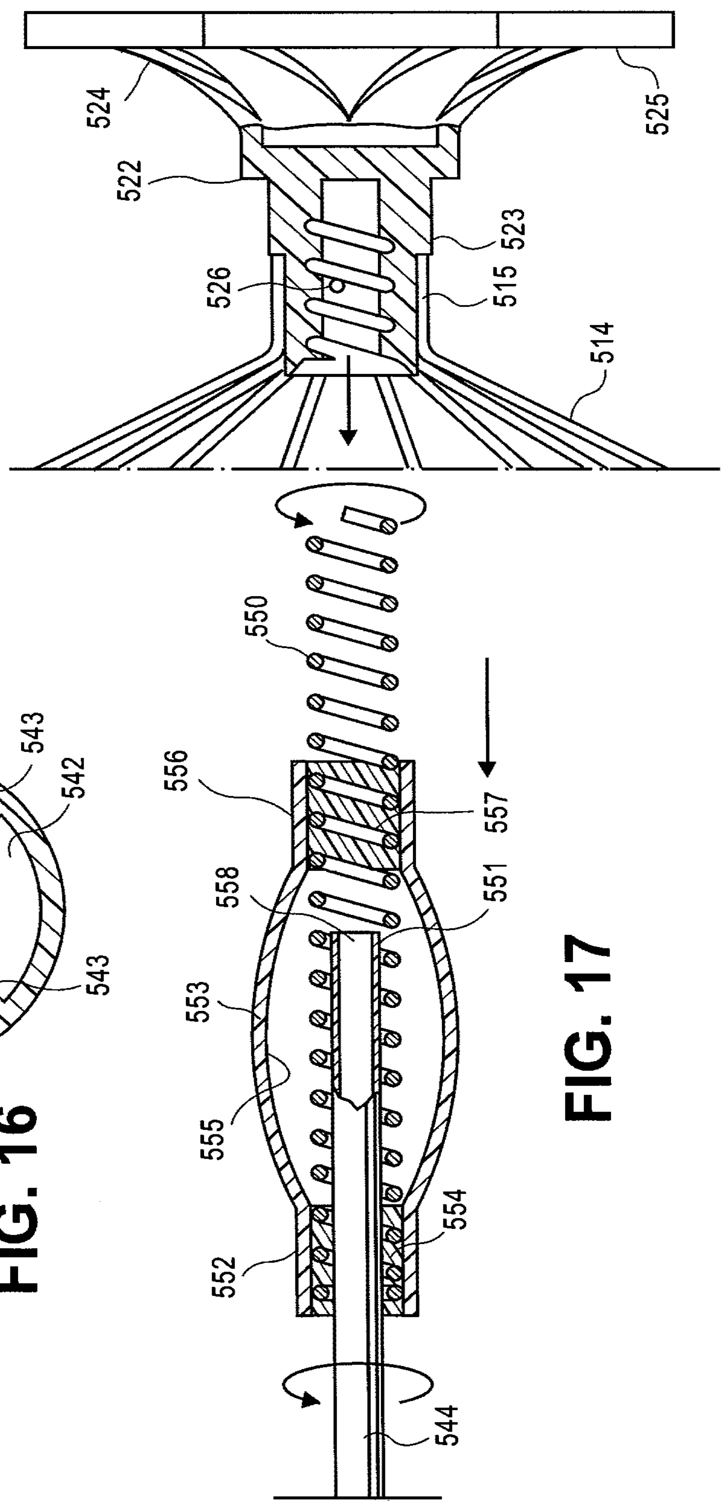
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FIG. 17

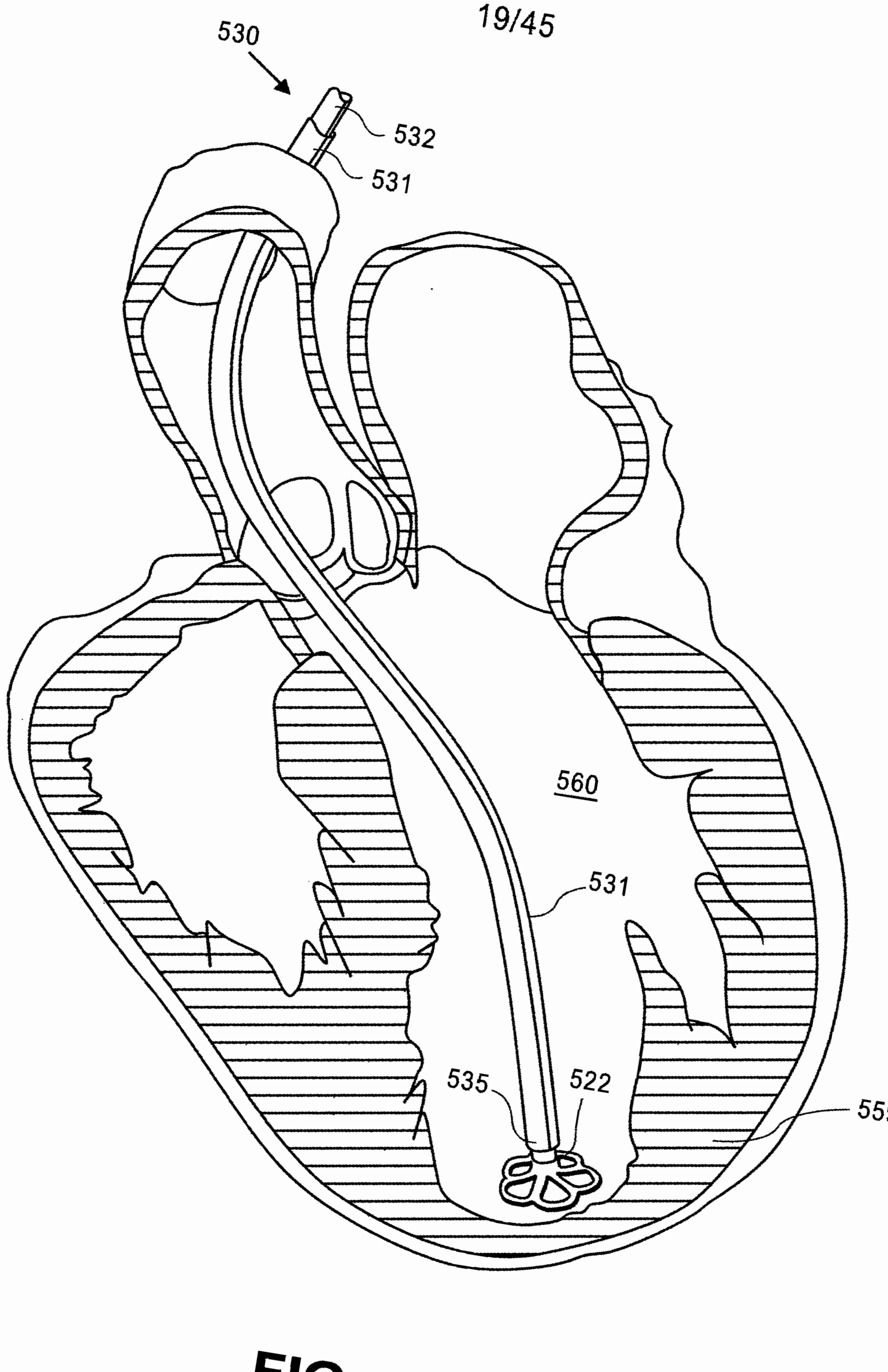


FIG. 18A

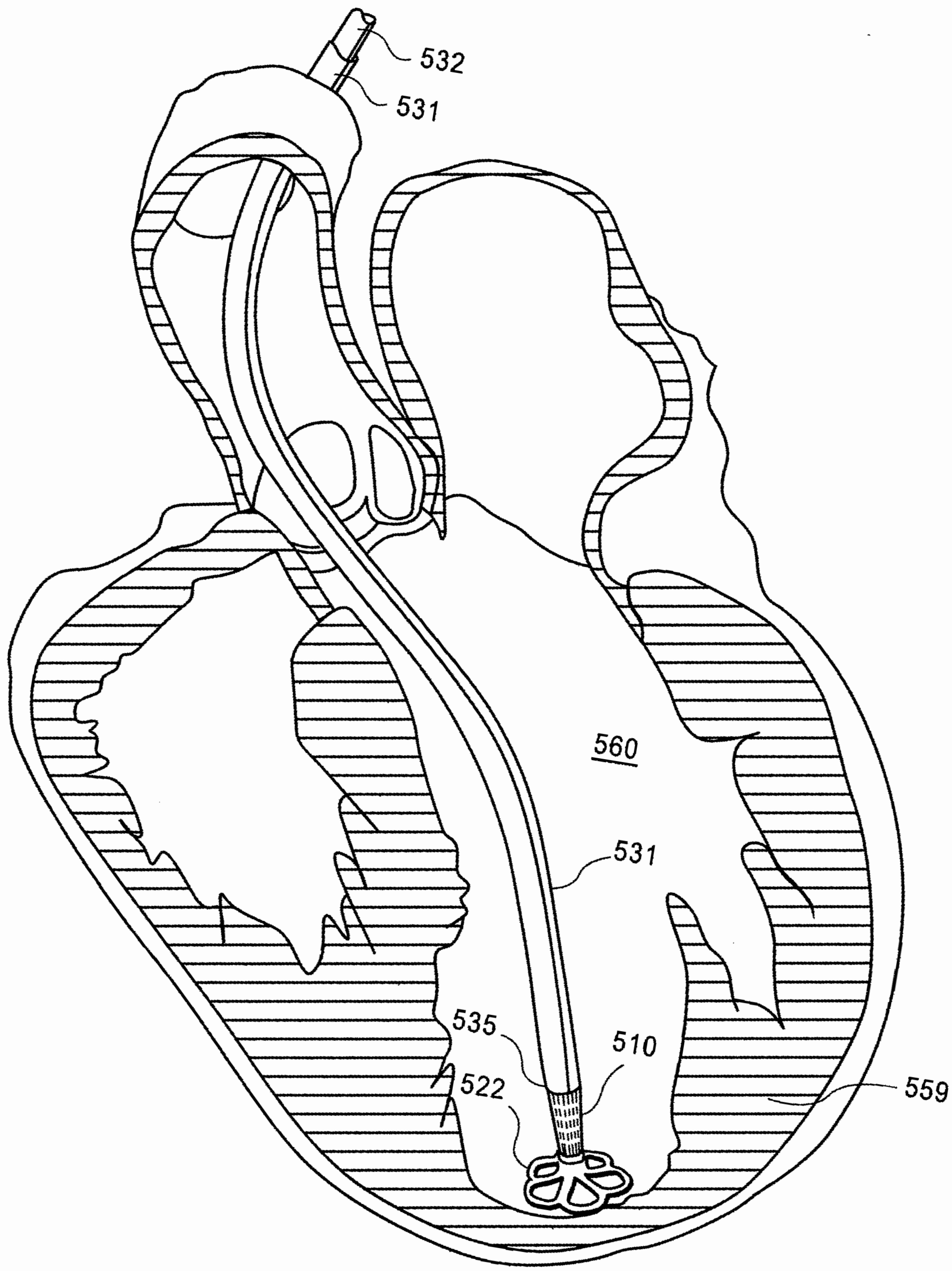


FIG. 18B

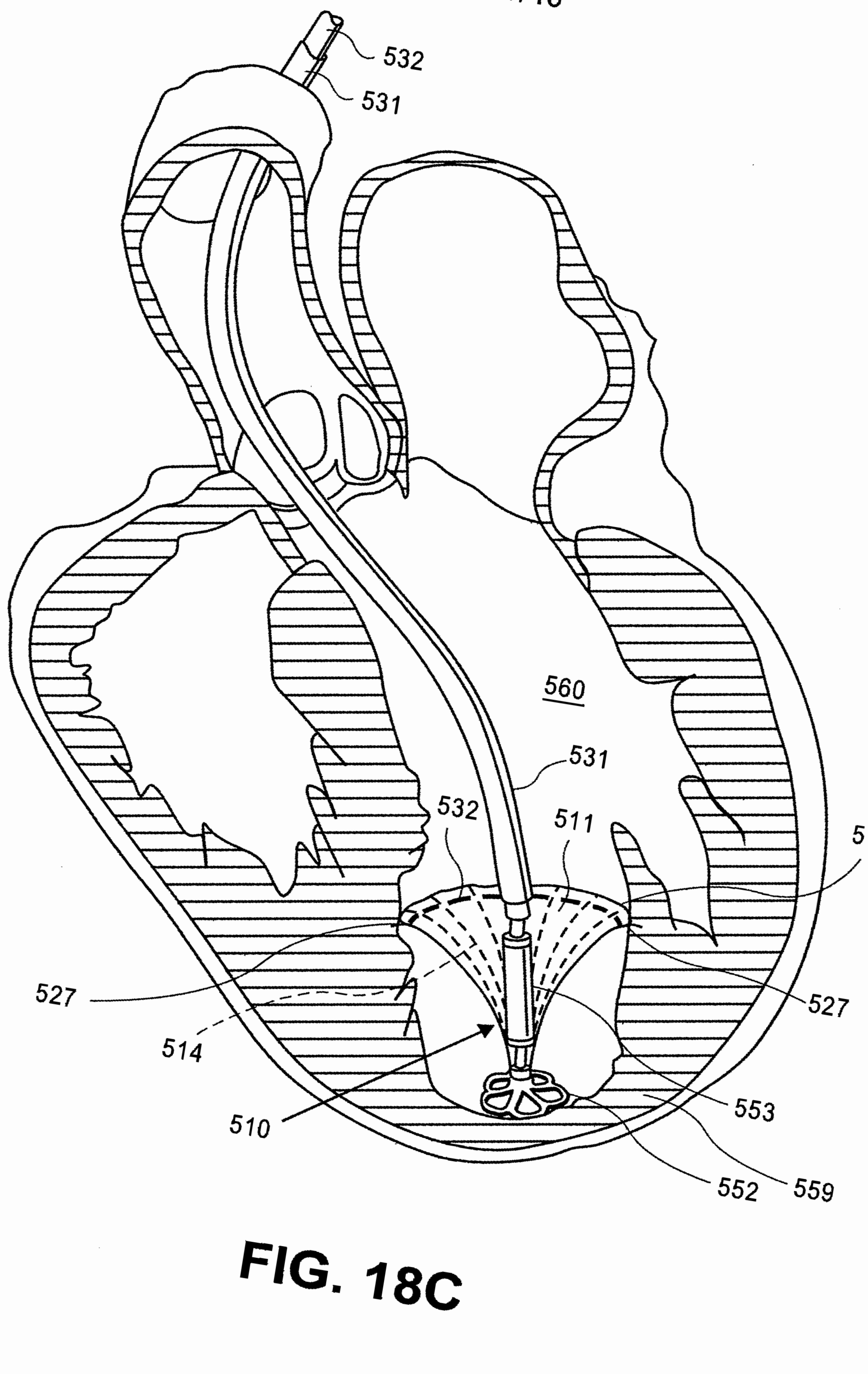


FIG. 18C

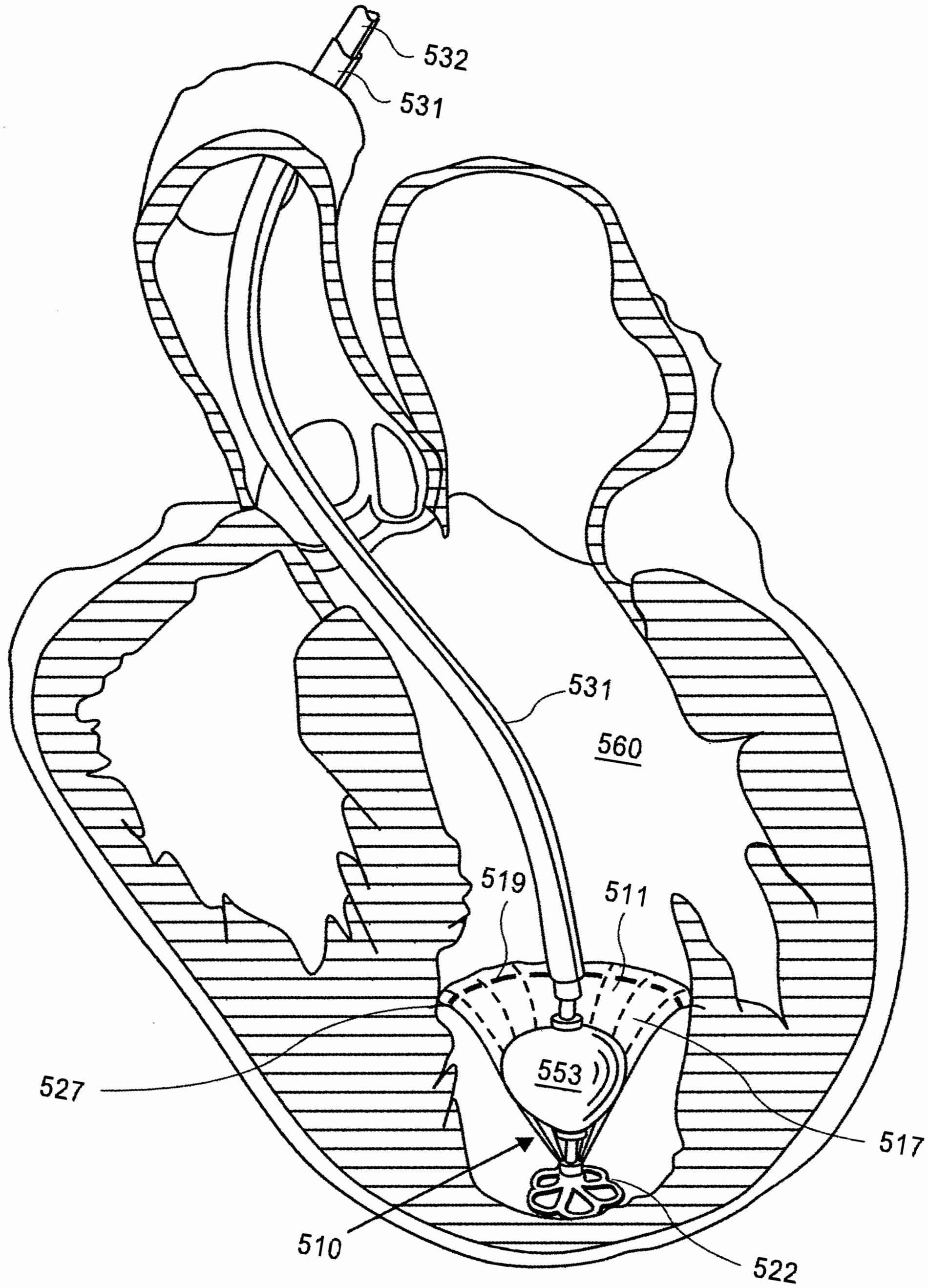


FIG. 18D

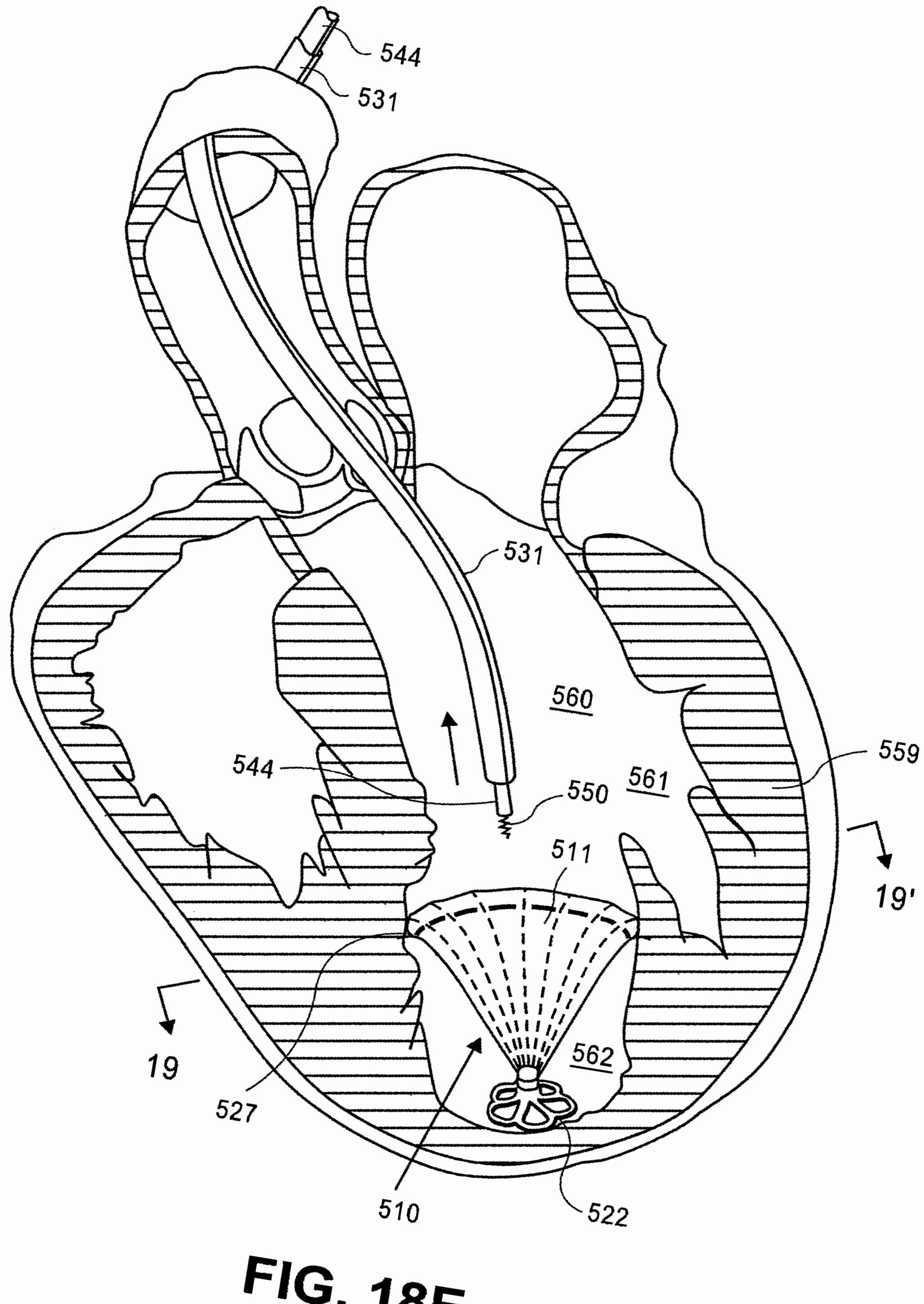


FIG. 18E

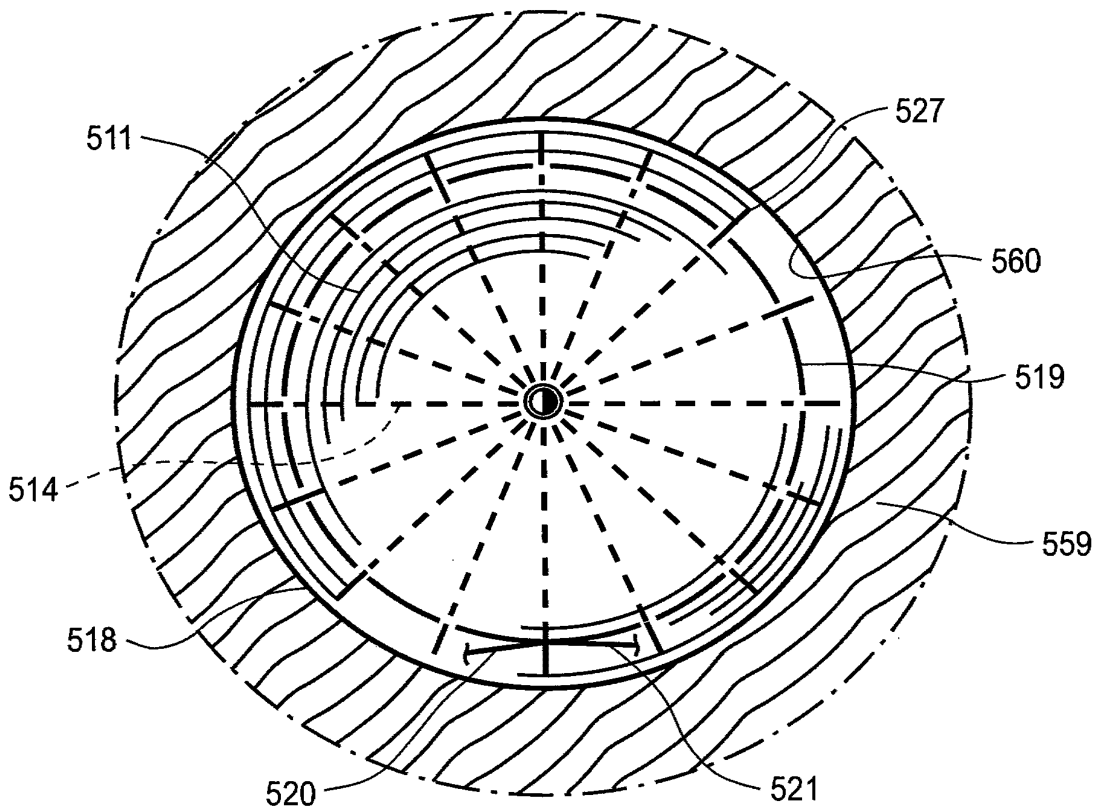


FIG. 19

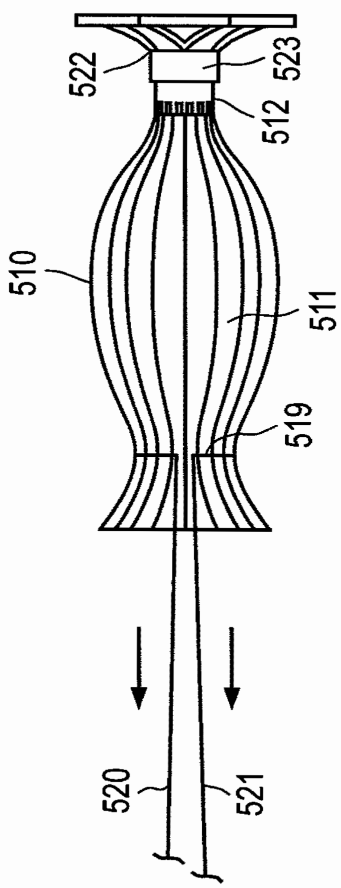


FIG. 20A

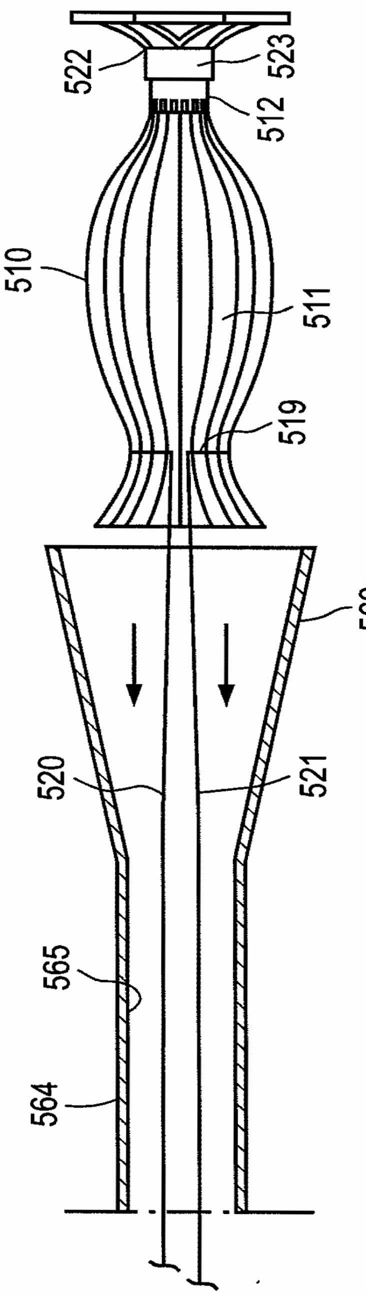


FIG. 20B

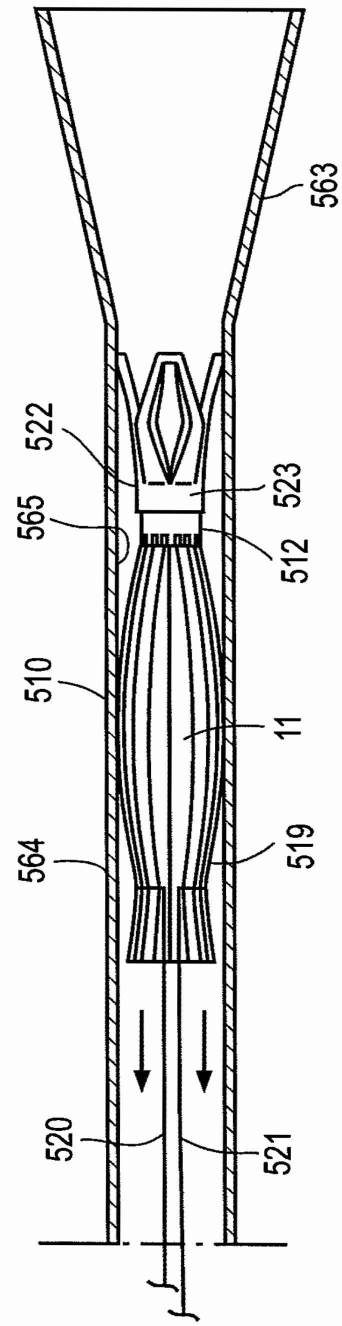


FIG. 20C

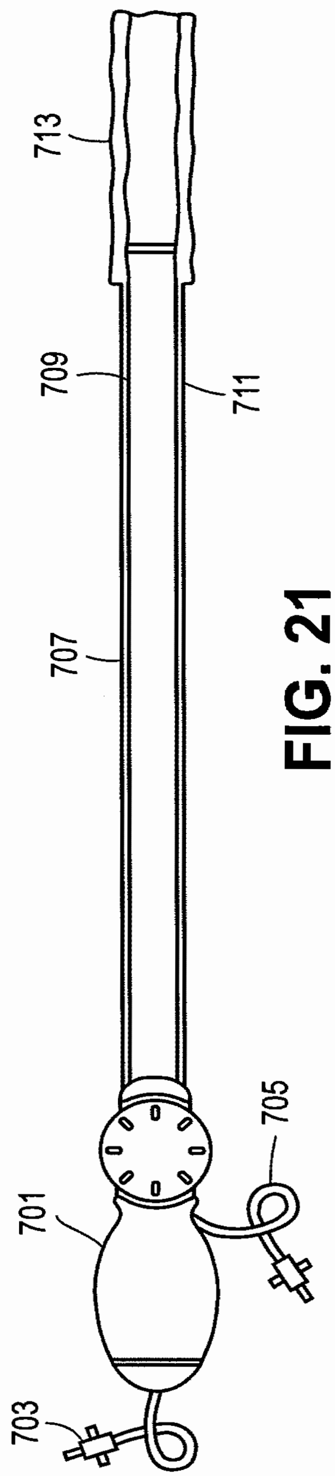


FIG. 21

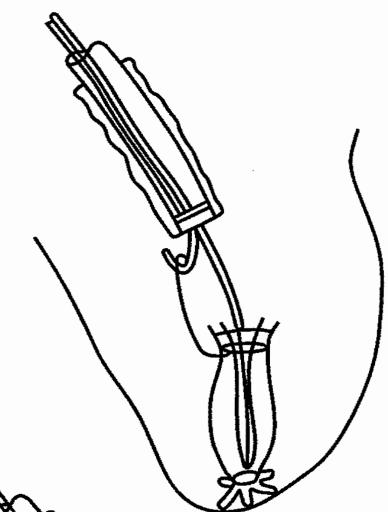


FIG. 22C

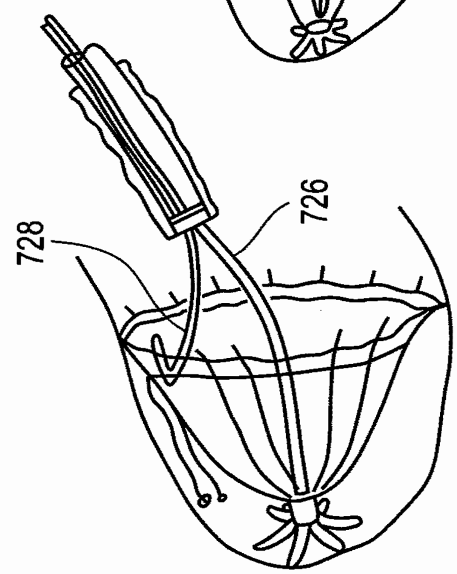


FIG. 22B

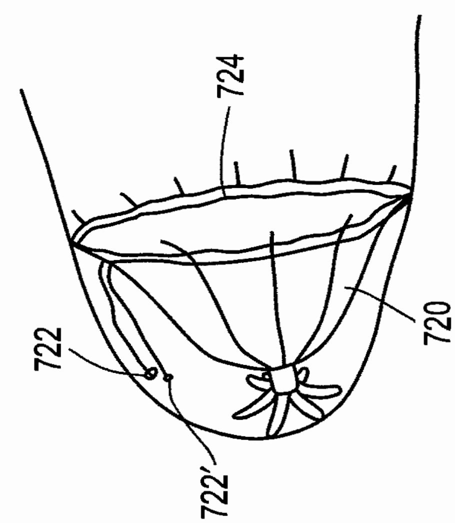


FIG. 22A

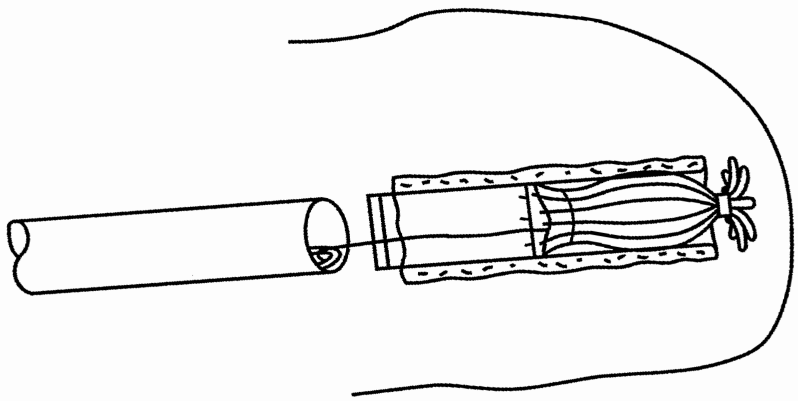


FIG. 22F

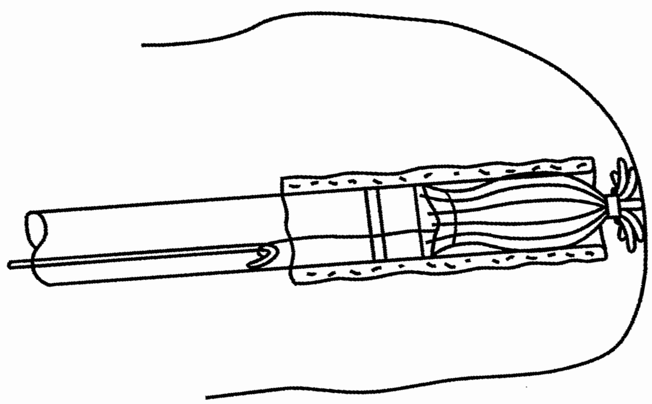


FIG. 22E

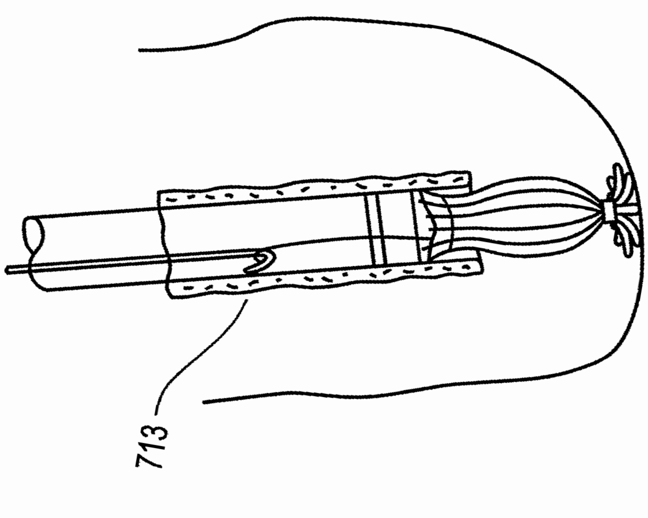


FIG. 22D

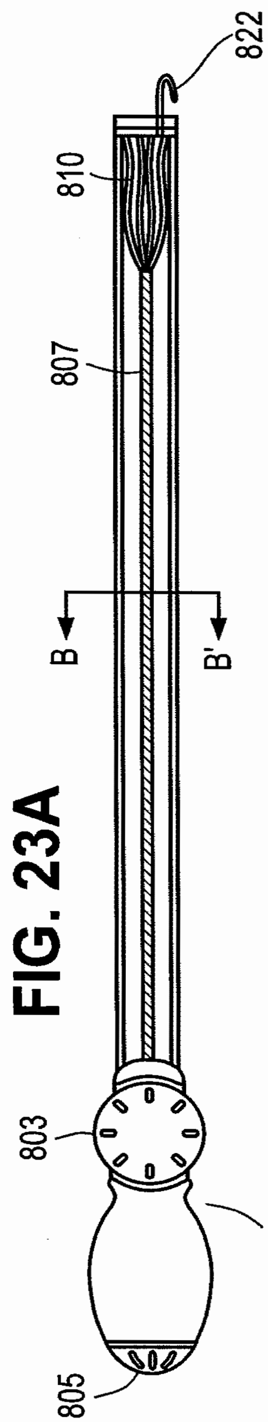


FIG. 23A

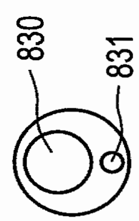


FIG. 23B

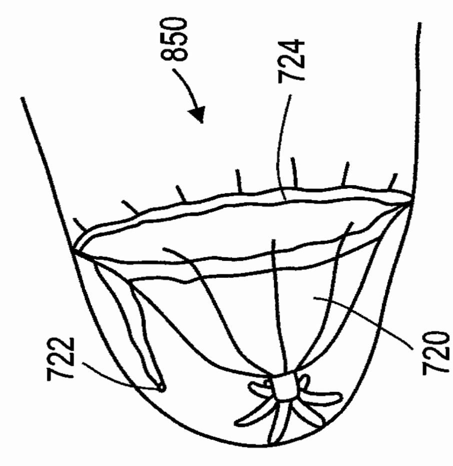


FIG. 24A

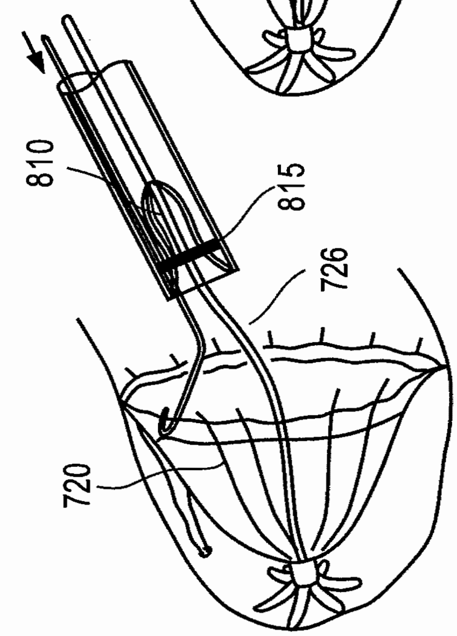


FIG. 24B

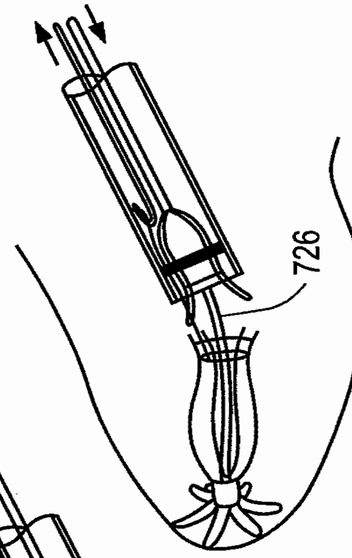


FIG. 24C

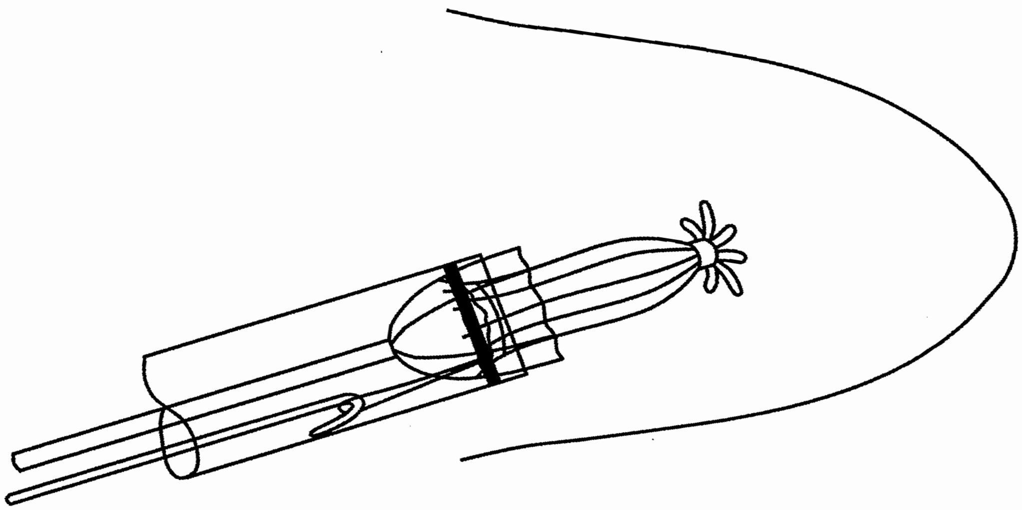


FIG. 24F

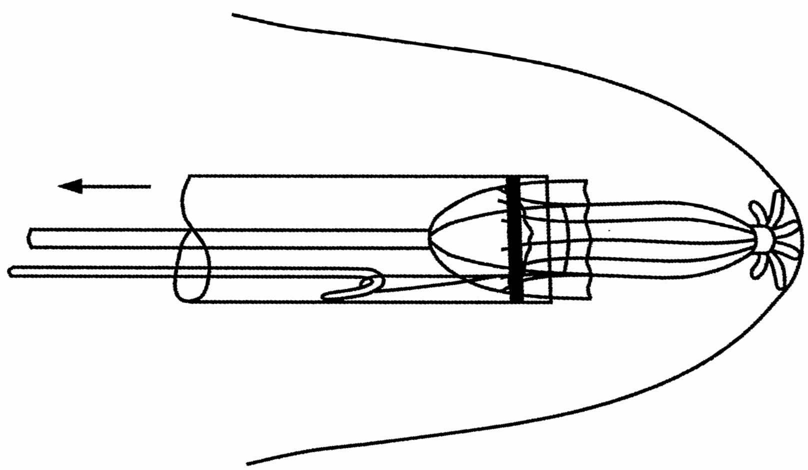


FIG. 24E

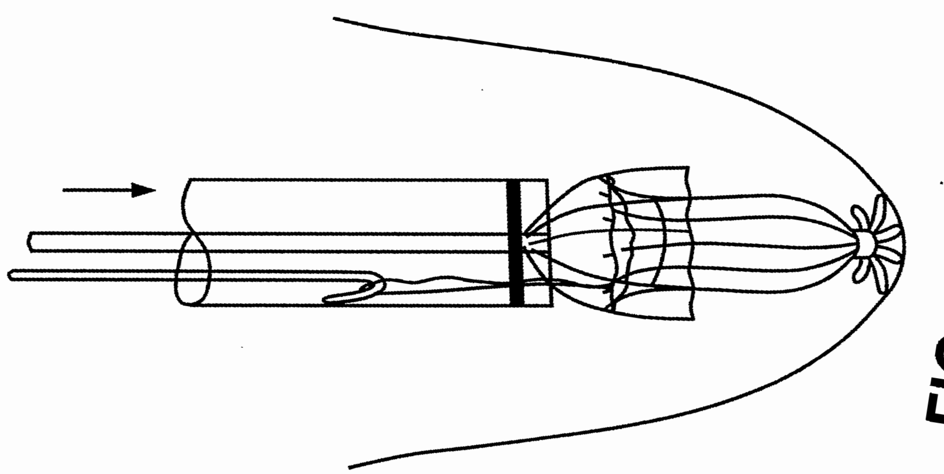


FIG. 24D

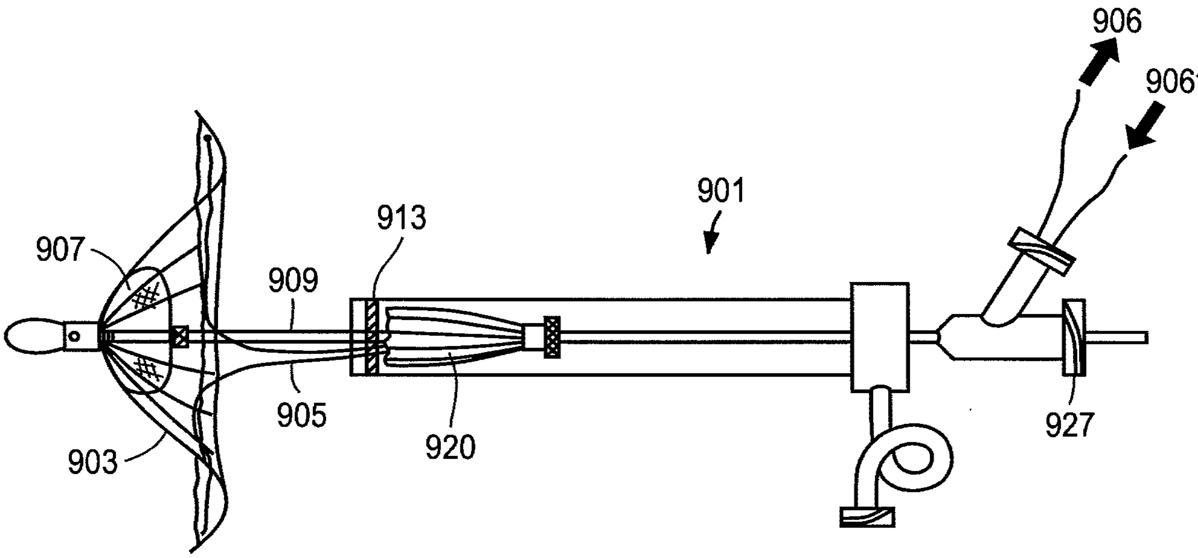


FIG. 25A

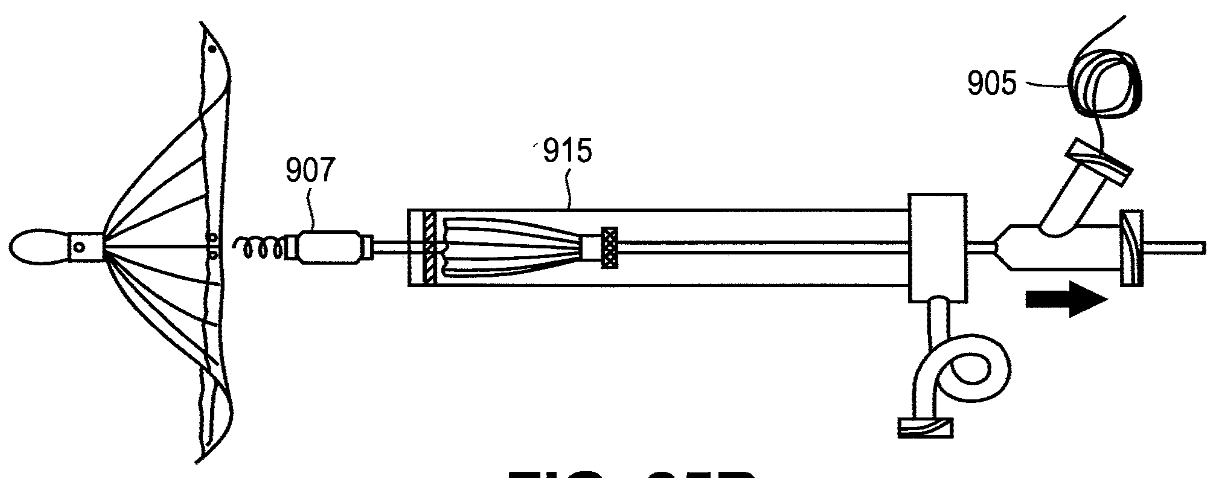


FIG. 25B

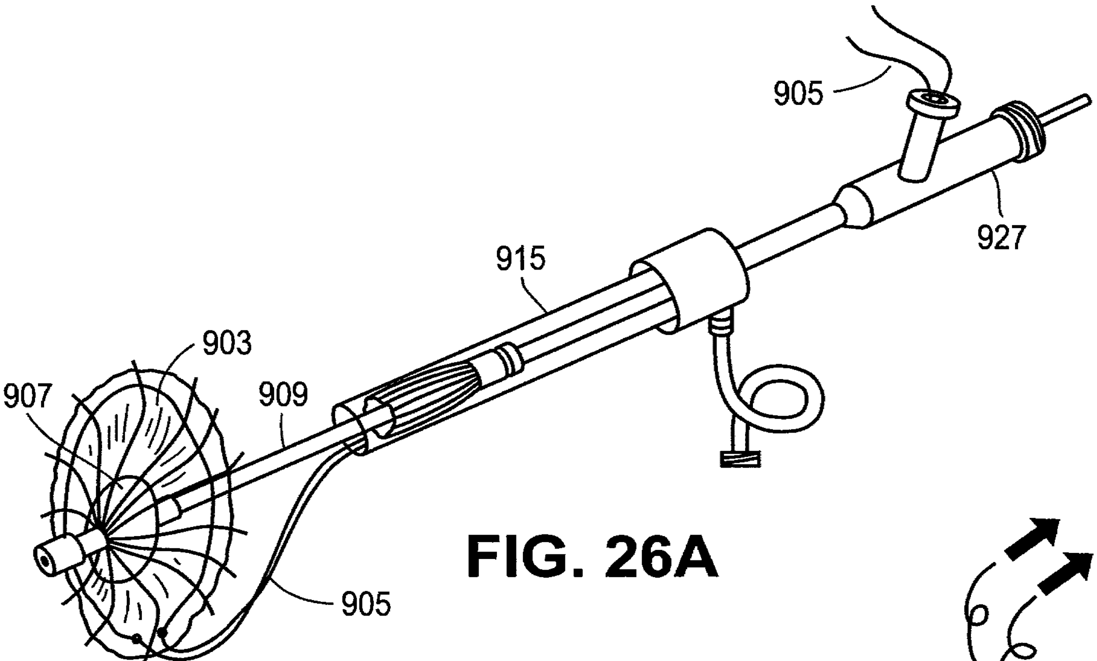


FIG. 26A

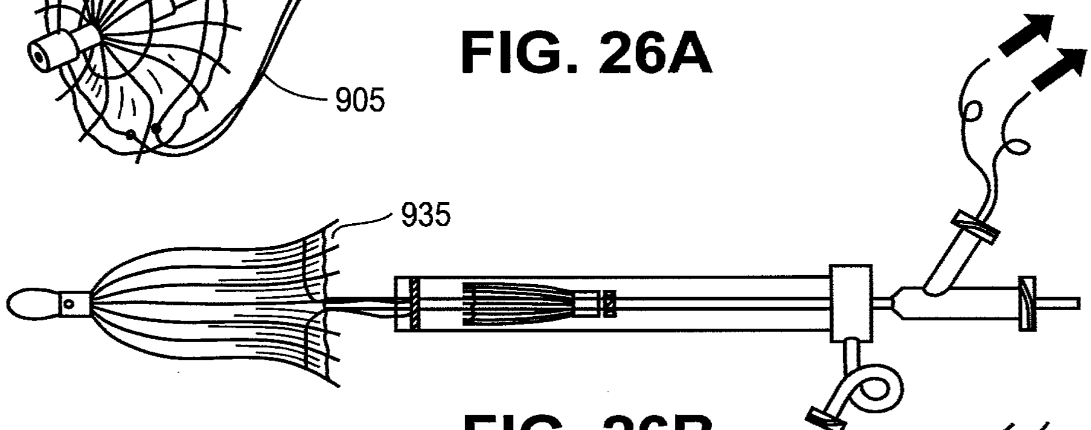


FIG. 26B

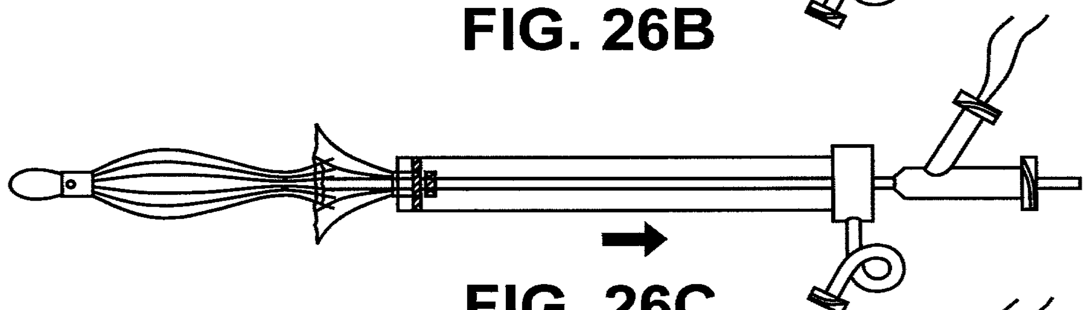


FIG. 26C

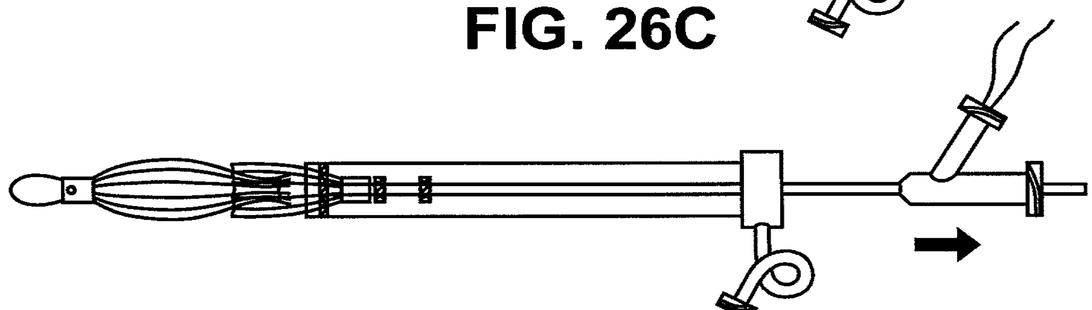


FIG. 26D

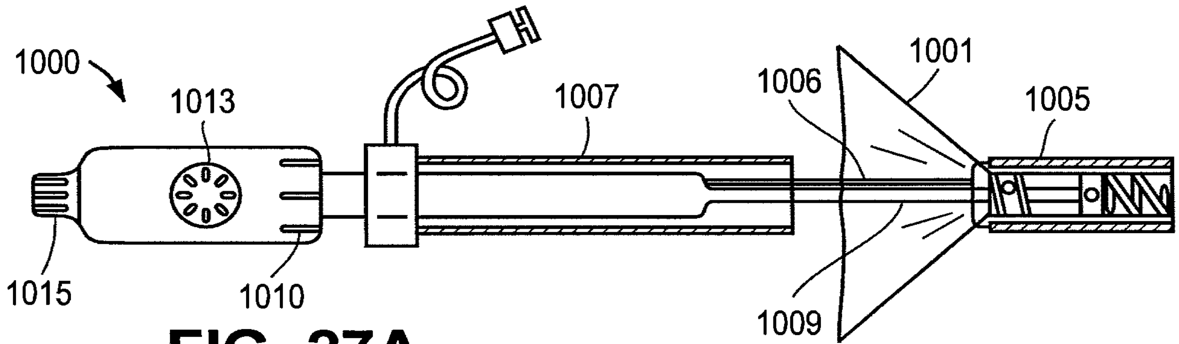


FIG. 27A

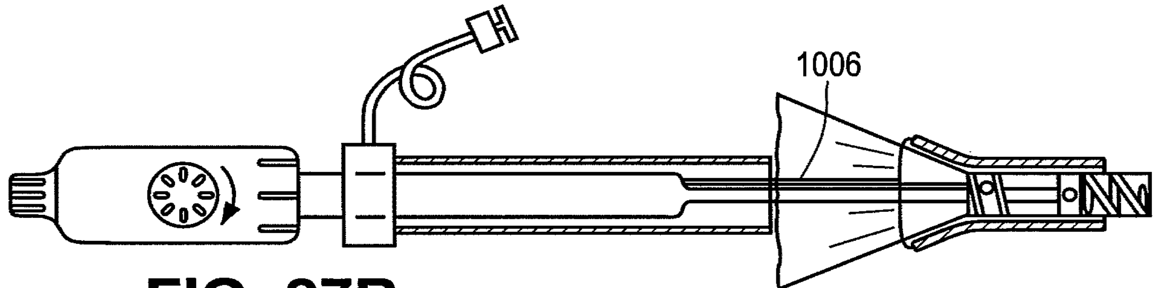


FIG. 27B

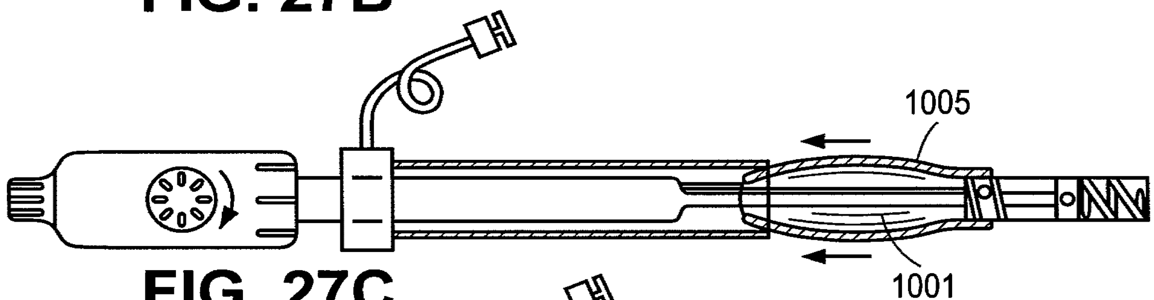


FIG. 27C

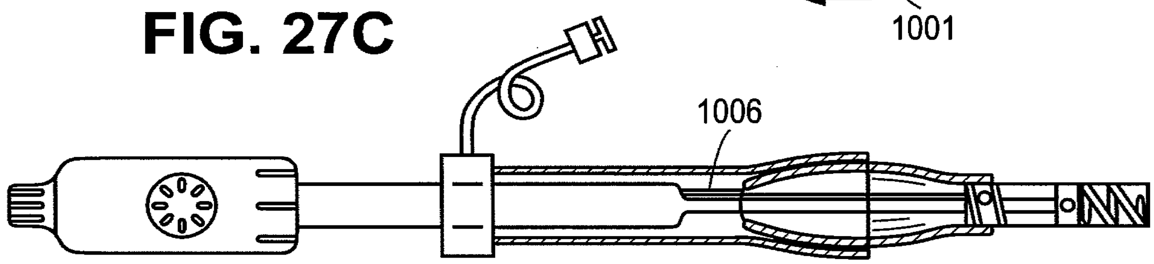


FIG. 27D

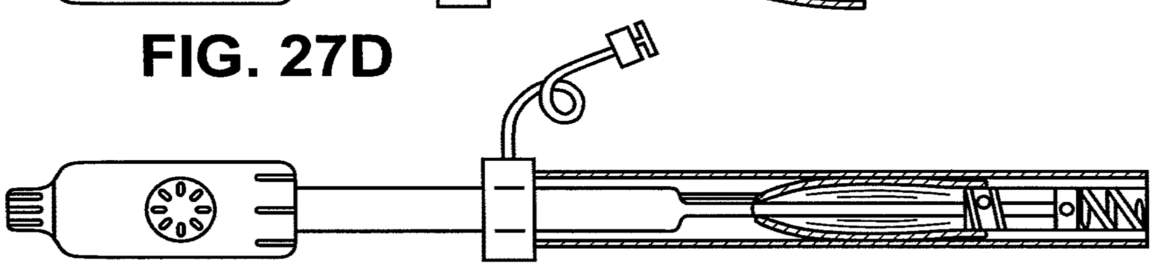


FIG. 27E

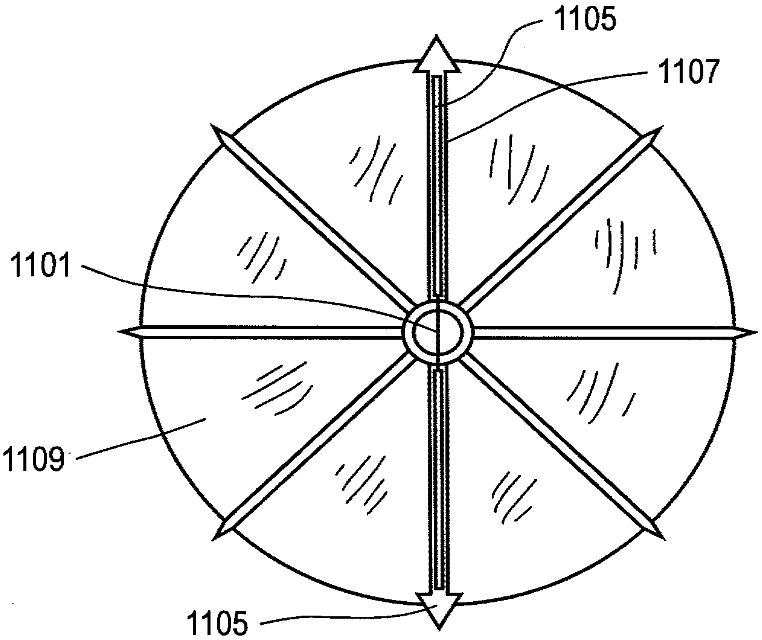


FIG. 28A

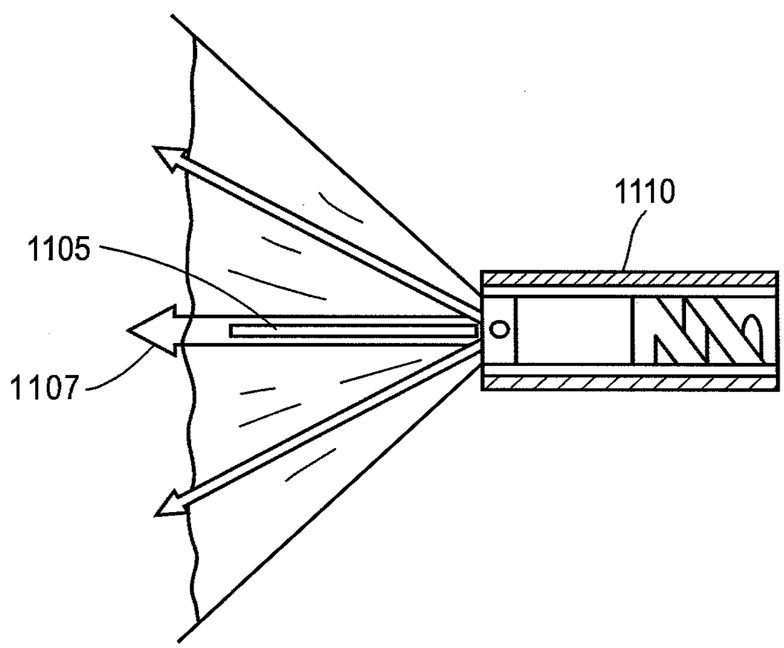


FIG. 28B

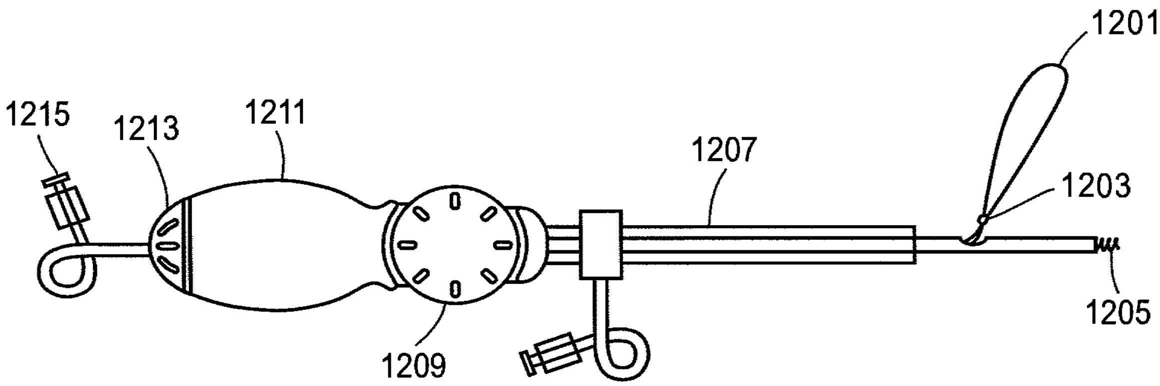


FIG. 29A

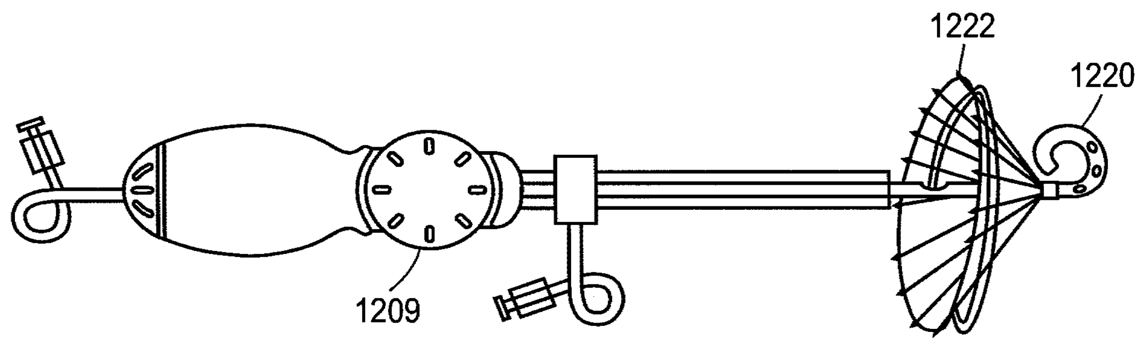


FIG. 29B

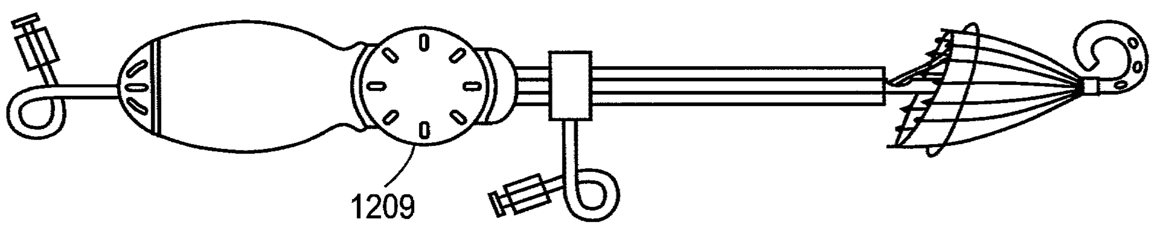


FIG. 29C

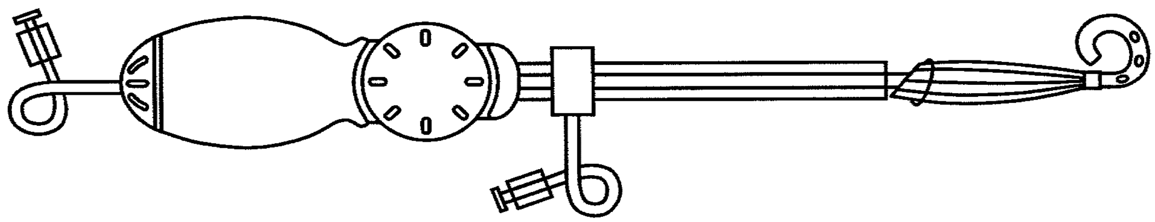


FIG. 29D

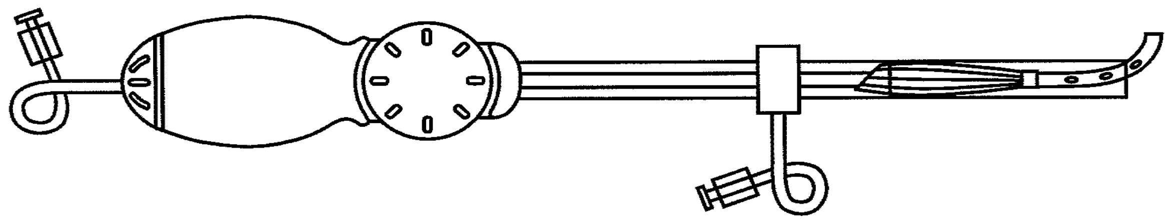


FIG. 29E

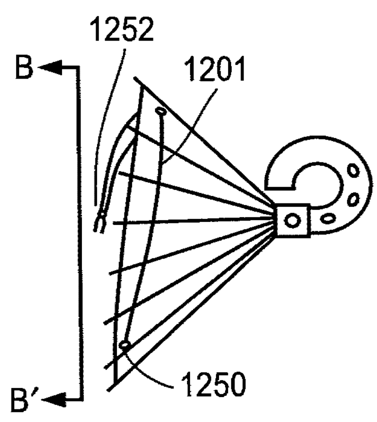
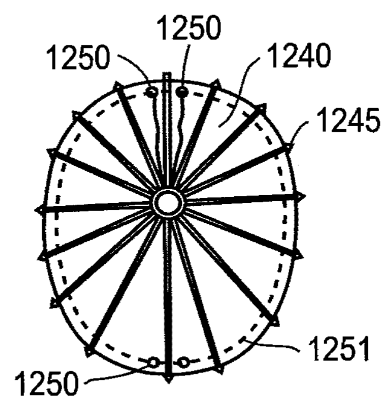


FIG. 30A



Section B – B′

FIG. 30B

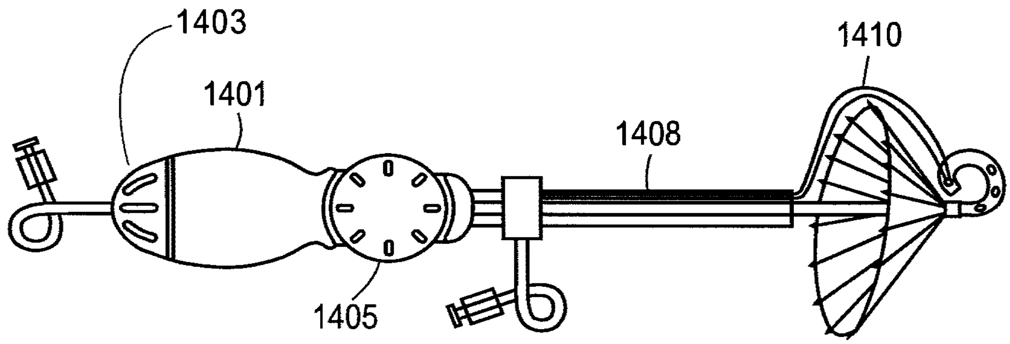


FIG. 31A

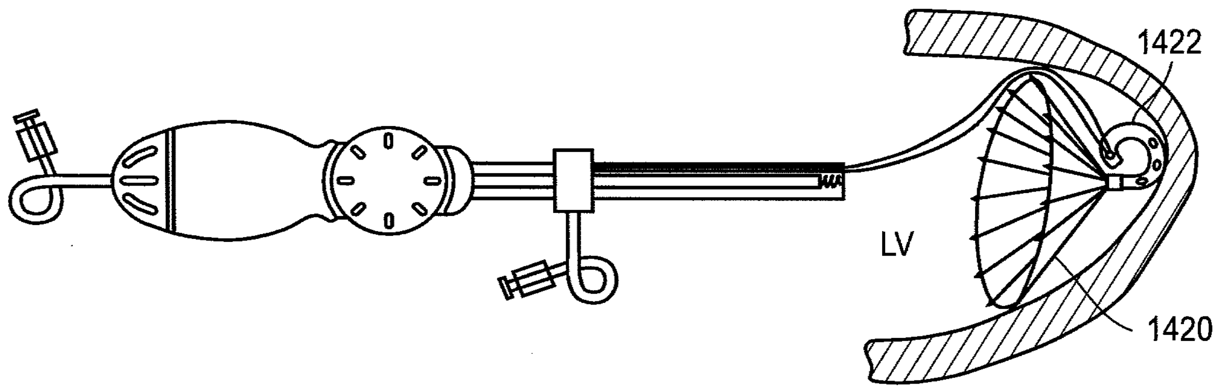


FIG. 31B

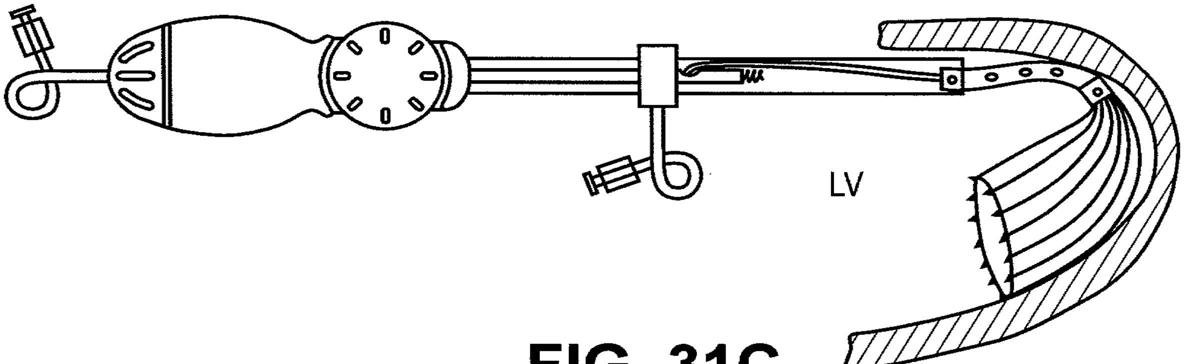


FIG. 31C

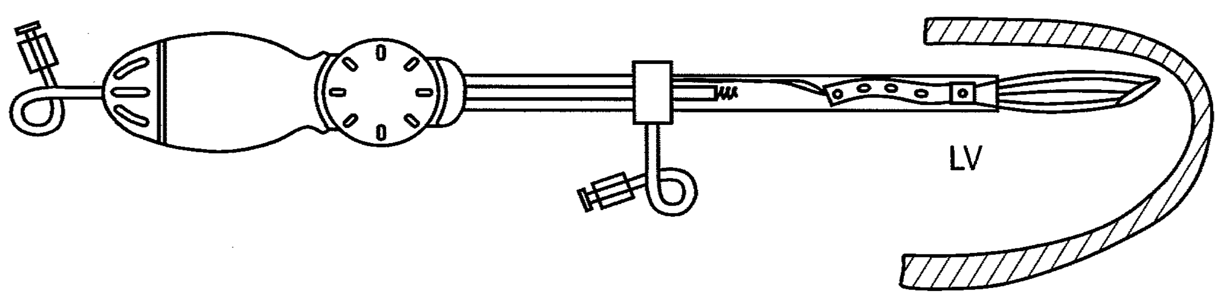


FIG. 31D

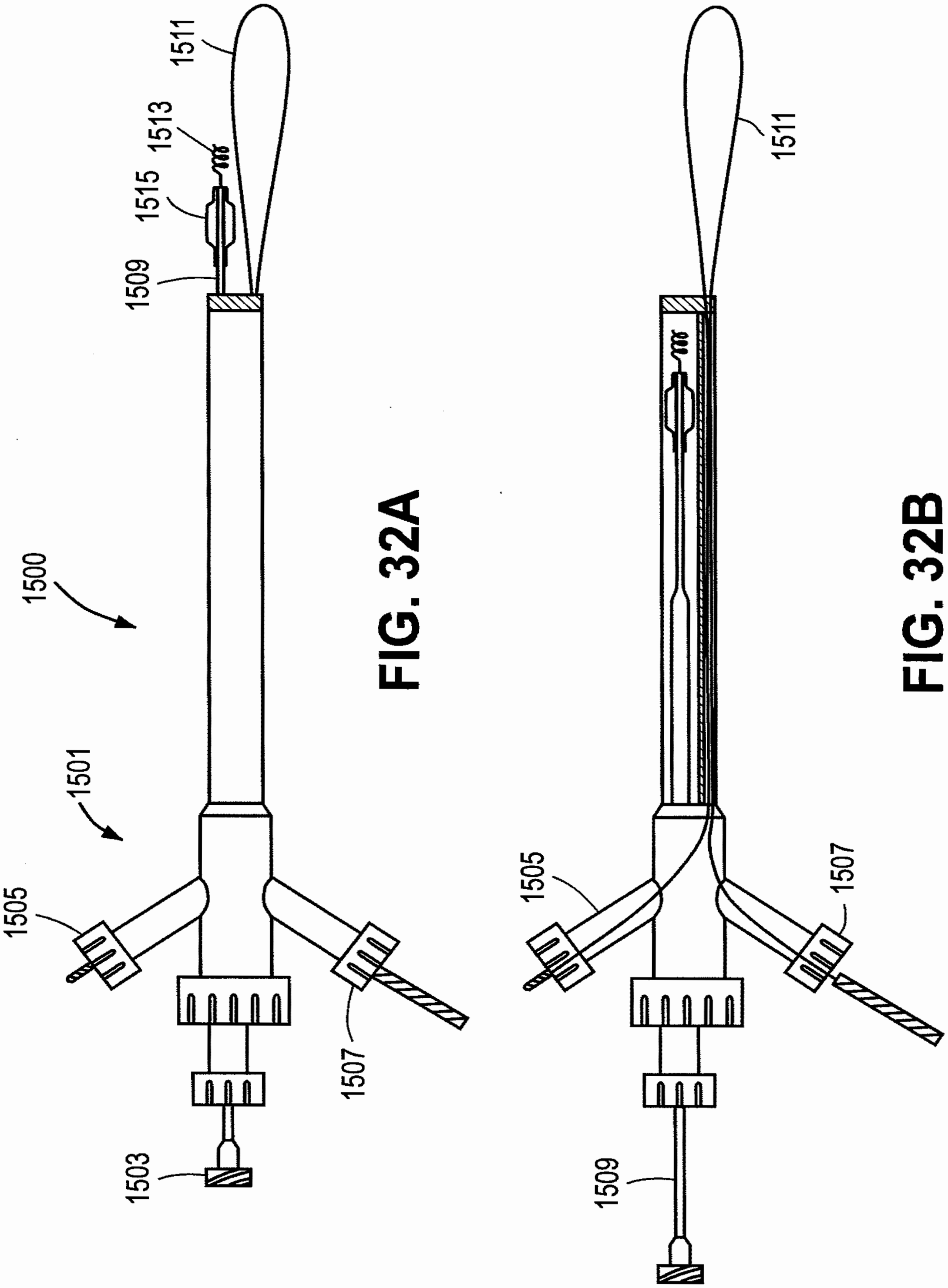


FIG. 32A

FIG. 32B

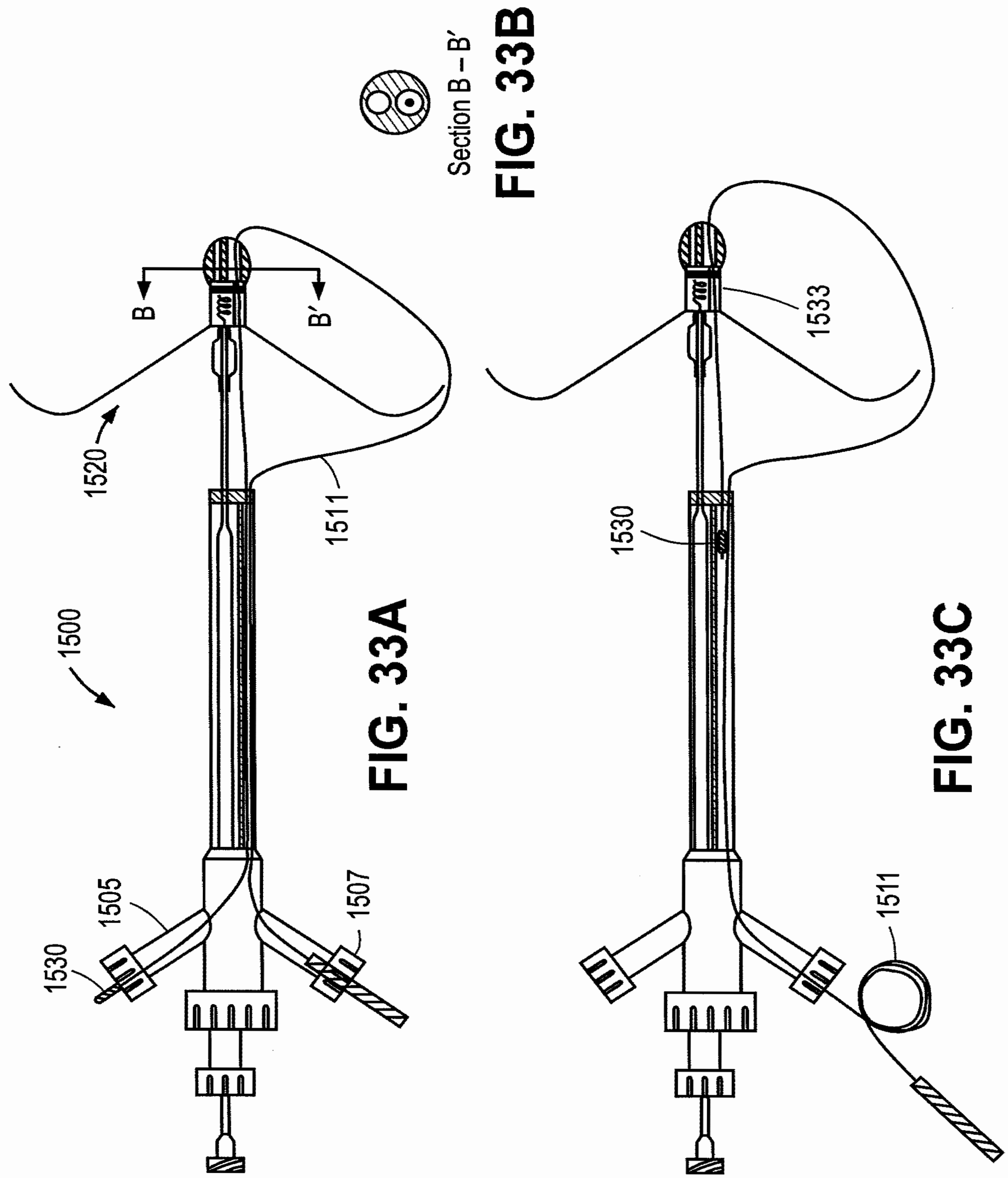


FIG. 33B

FIG. 33A

FIG. 33C

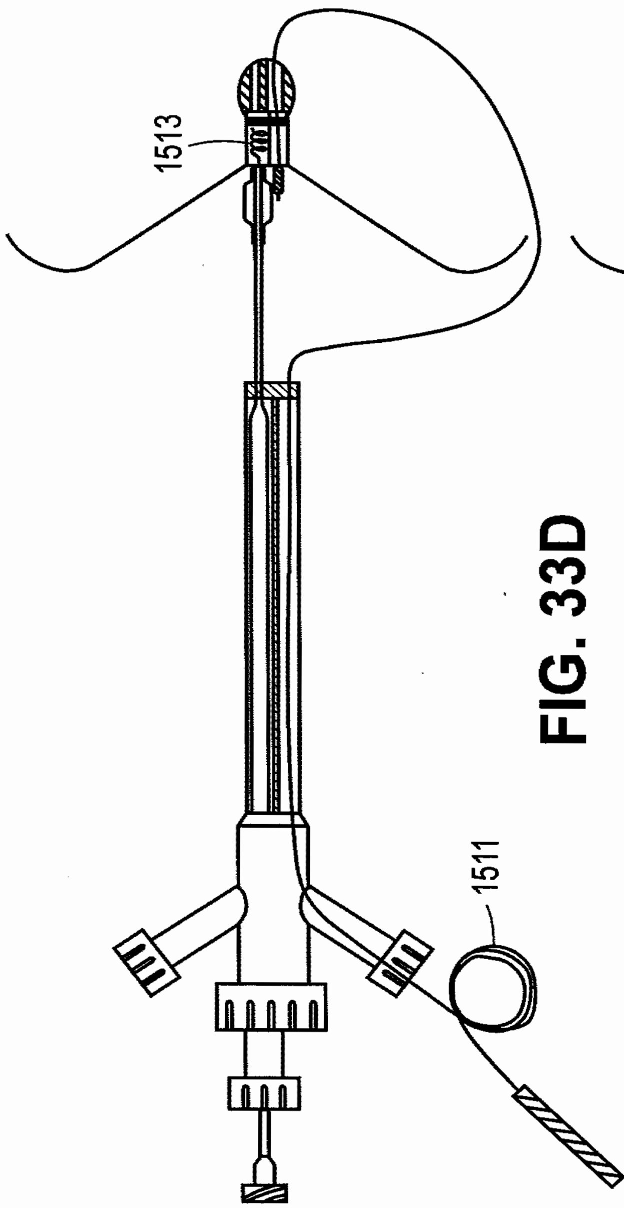


FIG. 33D

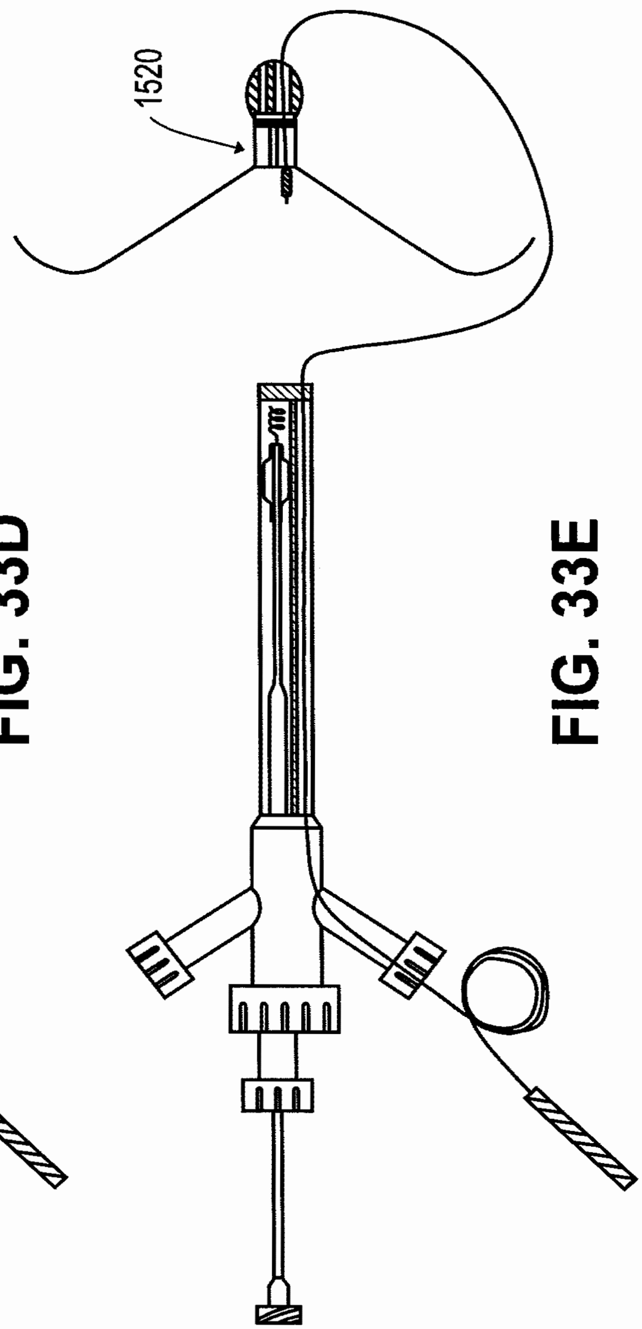


FIG. 33E

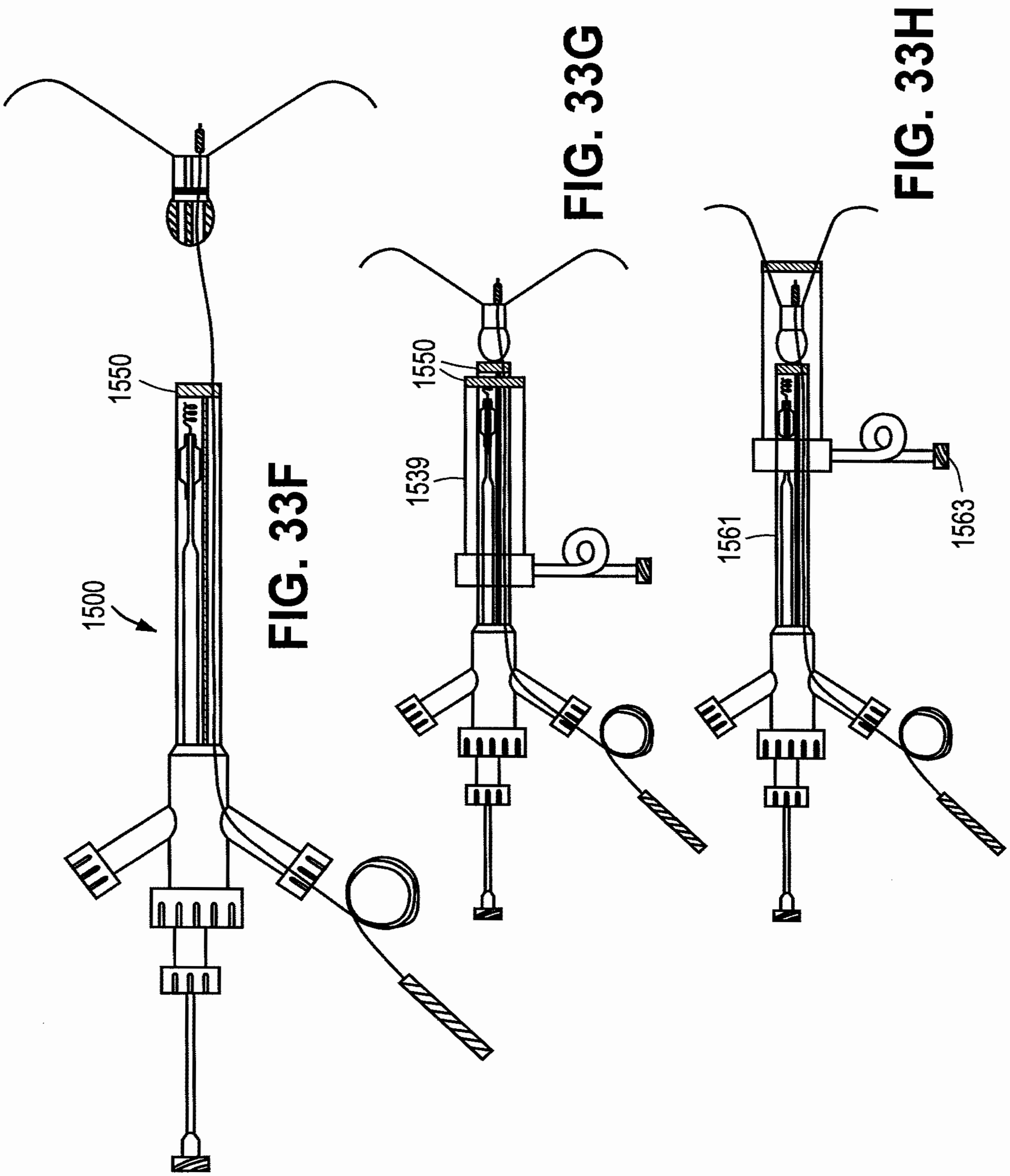


FIG. 33F

FIG. 33G

FIG. 33H

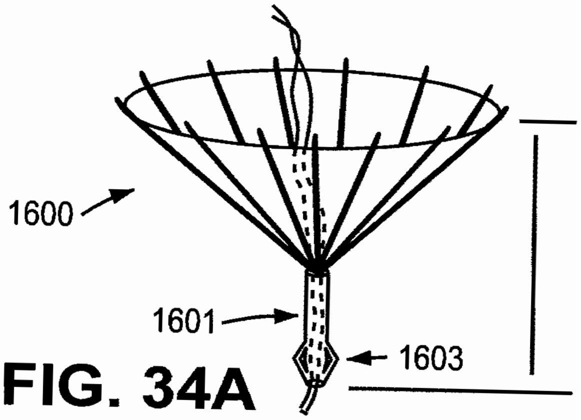


FIG. 34A

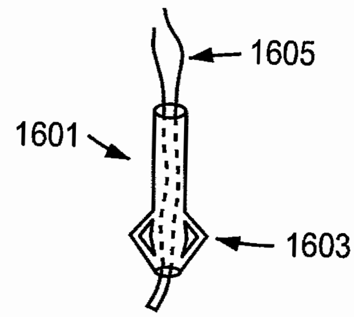


FIG. 34B

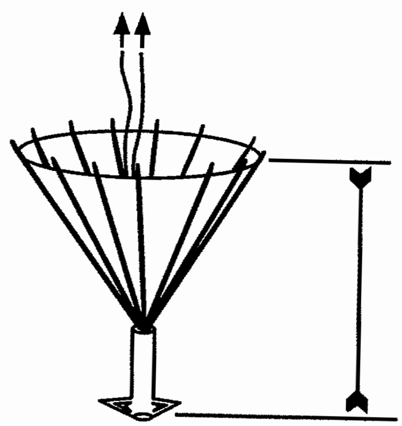


FIG. 34C

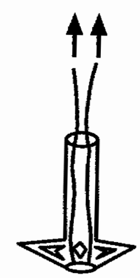


FIG. 34D

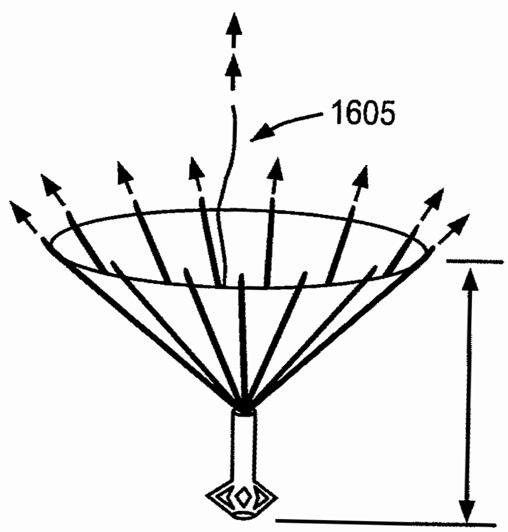


FIG. 34E

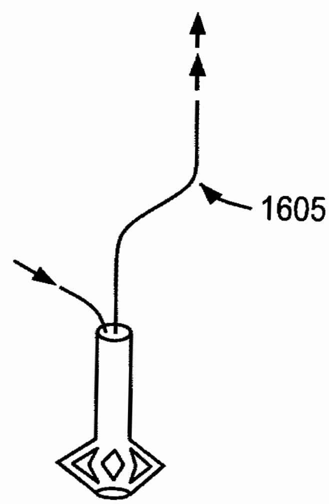
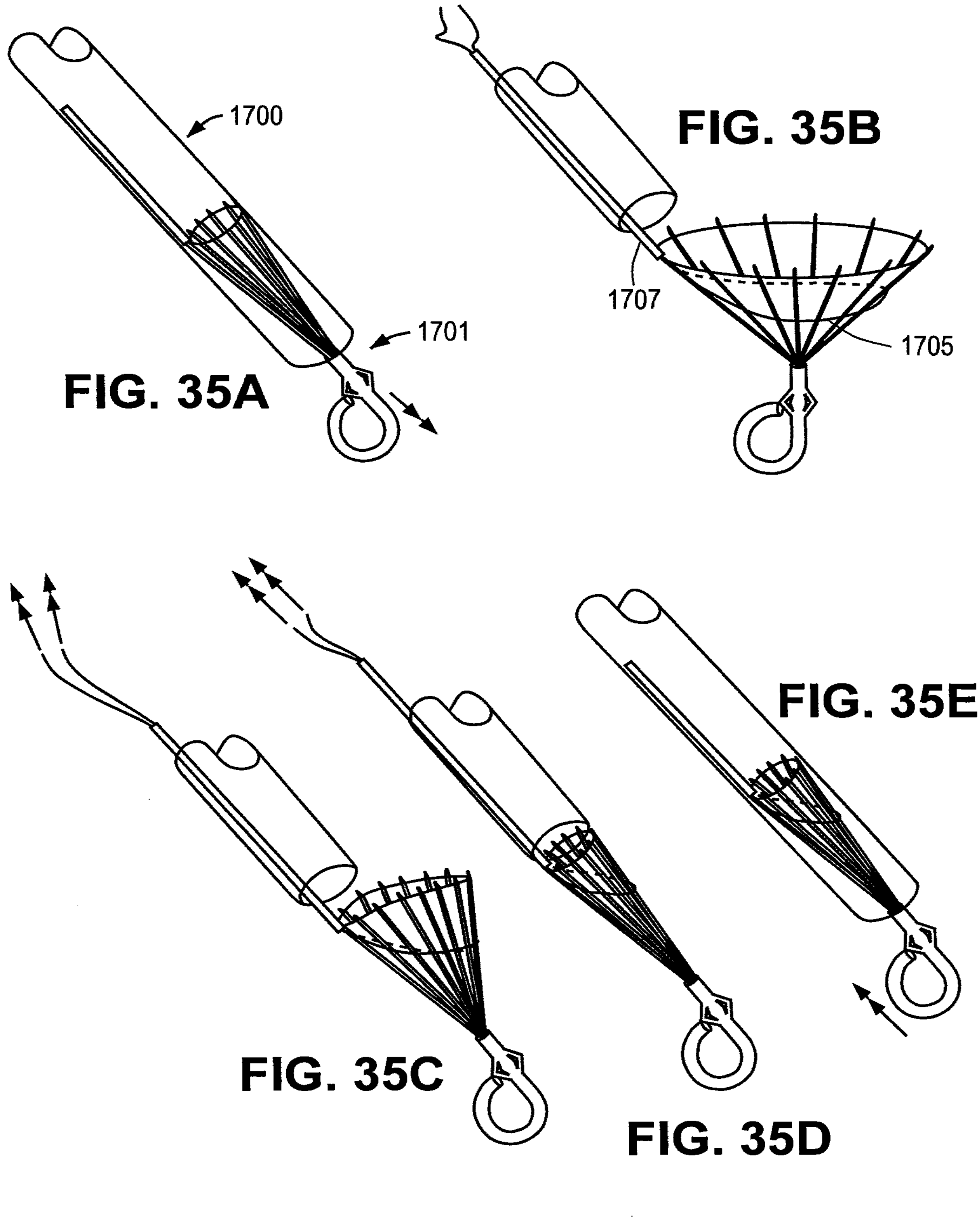


FIG. 34F


1700
1701
FIG. 35A
FIG. 35B
1707
1705
FIG. 35E
FIG. 35C
FIG. 35D

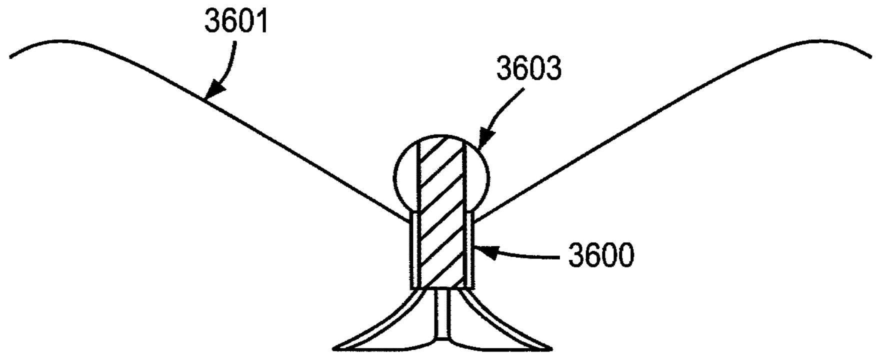


FIG. 36A

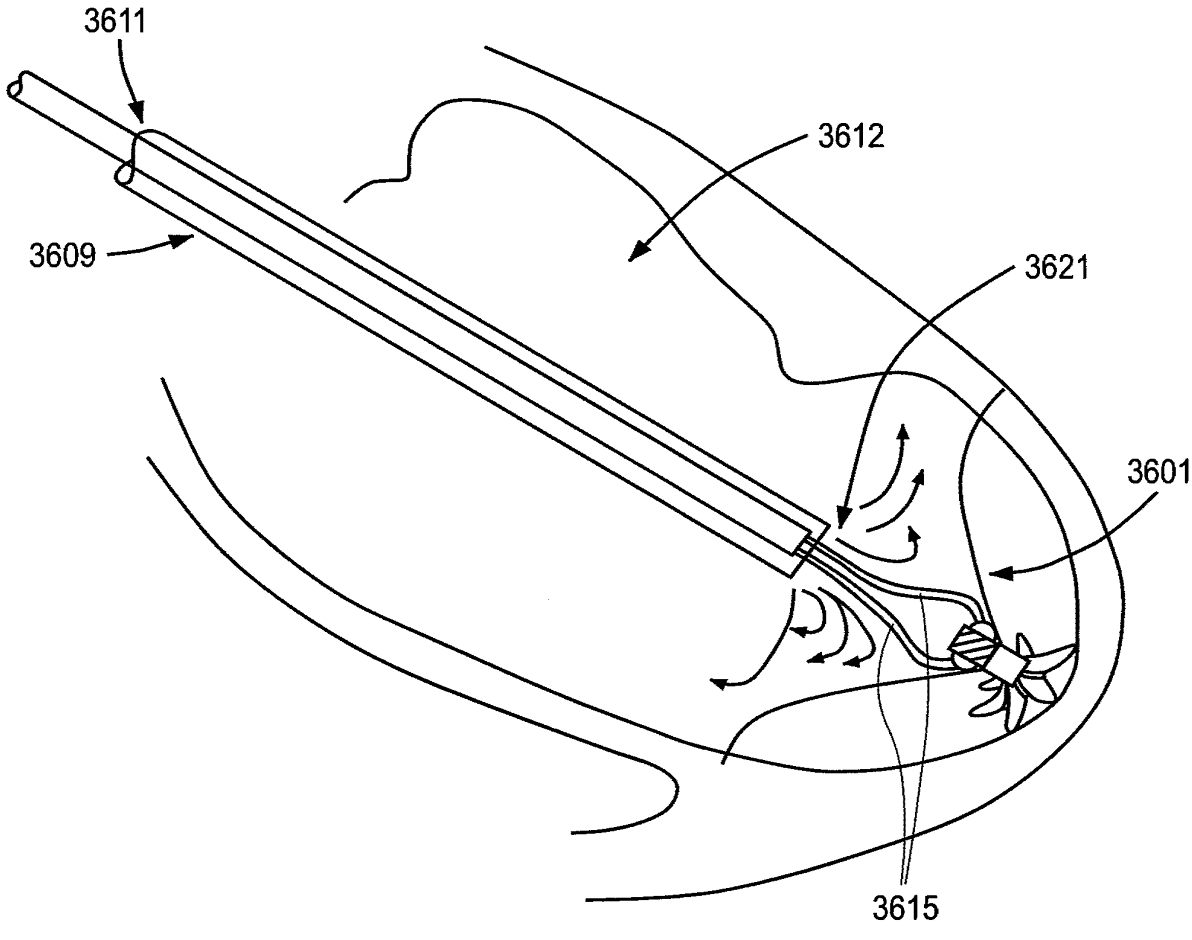


FIG. 36B

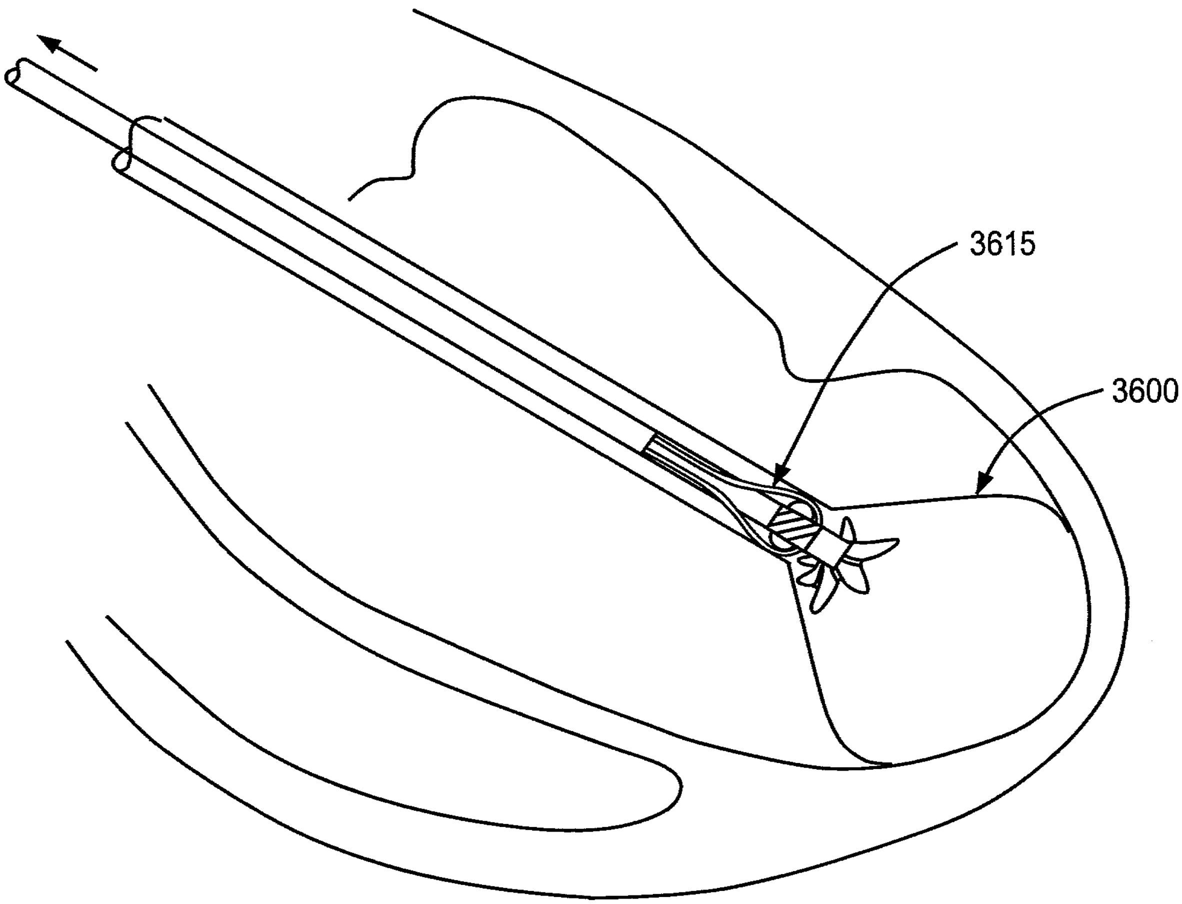


FIG. 36C

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/074217

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B17/12 A61F2/00 A61B17/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006/281965 A1 (KHAIRKHAHAN ET AL.) 14 December 2006 (2006-12-14) abstract; figures 1-4,8,13-13K,14-16 paragraphs [0049] - [0052], [0054], [0058]	3,4,7,11
Y		5,6,8,10
A		16
X	US 2007/129753 A1 (QUINN ET AL.) 7 June 2007 (2007-06-07) abstract; figure 11 paragraphs [0082] - [0088]	3,9
Y	WO 03/073961 A (SALVIAC LIMITED) 12 September 2003 (2003-09-12) abstract; figures 1,8-15,167-171,179-182,219-226,263,264	5,6

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 July 2009	17/07/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Giménez Burgos, R

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/074217

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2005/085826 A1 (NAIR ET AL.) 21 April 2005 (2005-04-21) paragraphs [0040] - [0042]; figures 10-12	8
X	WO 02/071977 A (ATRITECH, INC.) 19 September 2002 (2002-09-19) abstract; figures 3-7 page 17, line 1 - page 19, line 8	12-15
Y		10
A	US 2006/264980 A1 (KHAIRKHAHAN ET AL.) 23 November 2006 (2006-11-23) paragraphs [0125], [0141] - [0144], [0156], [0157]; figures 4,13A-13k	3,11
A	WO 2004/047679 A (CARDIOKINETIX, INC.) 10 June 2004 (2004-06-10) the whole document	3,11
A	US 2008/045778 A1 (LICHTENSTEIN ET AL.) 21 February 2008 (2008-02-21) the whole document	3
A	US 2007/162048 A1 (QUINN ET AL.) 12 July 2007 (2007-07-12) the whole document	3-5,7,10
A	US 2004/172042 A1 (SUON ET AL.) 2 September 2004 (2004-09-02) figures	3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/074217

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1,2,22-27
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[X] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 3-11

   An applicator configured to insert and retrieve an implant into a patient's ventricle.

   ---

2. claims: 12-21

   An expandable device for partitioning a patient's ventricle comprising means to facilitate the collapse of the expandable device into its reduced configuration.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/074217

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
US 2006281965	A1	14-12-2006	AU	2006257971	A1	21-12-2006
			CA	2613196	A1	21-12-2006
			EP	1893124	A2	05-03-2008
			JP	2008545509	T	18-12-2008
			WO	2006135747	A2	21-12-2006
US 2007129753	A1	07-06-2007	NONE			
WO 03073961	A	12-09-2003	AT	378019	T	15-11-2007
			AT	369088	T	15-08-2007
			AU	2003209965	A1	16-09-2003
			AU	2003209966	A1	16-09-2003
			DE	60315425	T2	26-06-2008
			DE	60317474	T2	02-10-2008
			EP	1482860	A1	08-12-2004
			EP	1482861	A1	08-12-2004
			ES	2295608	T3	16-04-2008
			WO	03073962	A1	12-09-2003
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			CA	2543211	A1	12-05-2005
			EP	1684647	A1	02-08-2006
			JP	2007508903	T	12-04-2007
			US	2007249998	A1	25-10-2007
			WO	2005041788	A1	12-05-2005
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			CN	1529571	A	15-09-2004
			EP	1365702	A2	03-12-2003
			JP	2005508201	T	31-03-2005
US 2006264980	A1	23-11-2006	US	2009062601	A1	05-03-2009
			US	2007213578	A1	13-09-2007
			US	2007213815	A1	13-09-2007
WO 2004047679	A	10-06-2004	AU	2003291569	A1	18-06-2004
US 2008045778	A1	21-02-2008	NONE			
US 2007162048	A1	12-07-2007	NONE			
US 2004172042	A1	02-09-2004	NONE			

Form PCT/ISA/210 (patent family annex) (April 2005)

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 March 2010 (11.03.2010)

PCT

(10) International Publication Number
WO 2010/027363 A1

(51) International Patent Classification:
A61F 2/06 (2006.01)

(21) International Application Number:
PCT/US2008/075504

(22) International Filing Date:
5 September 2008 (05.09.2008)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant *(for all designated States except US)*: **MERLIN MD PTE LTD** [SG/SG]; 29 Woodlands Industrial Park E1, #04-13/14 Northtech Lobby 3, Singapore 757716 (SG).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **RUDAKOV, Leon** [US/US]; 1797 Playa Vista, San Marcos, CA 92078 (US).

(74) Agent: **HILL, James, W.**; MCDERMOTT WILL & EMERY LLP, 18191 Von Karman, Suite 500, Irvine, CA 92612 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(54) **Title**: ENDOVASCULAR DEVICE

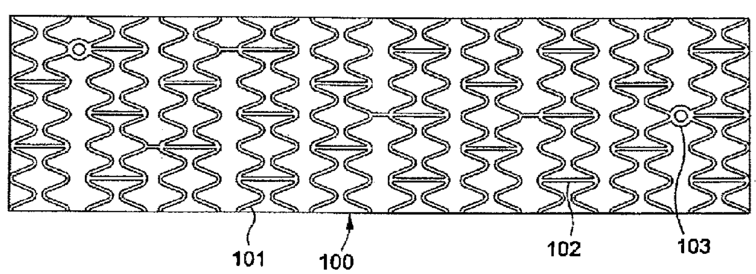


FIG. 1A

(57) **Abstract**: Embodiments of an endovascular device and of methods for treating an aneurysm therewith are described. In certain embodiments, an endovascular device includes a distal assembly coupled to a flow reducing member. In some embodiments, the distal assembly is composed of multiple engagement members that, when deployed within an aneurysm, engage an inner surface of the aneurysm. In certain embodiments, the engagements members are substantially parallel to a central axis of the distal assembly in a first position and shift away from the central axis to a second position, and the distal ends of some engagement members are substantially curled when in the second position. In certain embodiments, the flow-reducing member reduces blood flow from a blood vessel into the aneurysm. In certain embodiments the flow reducing member includes a membrane, which can include a porous section.

WO 2010/027363 A1

ENDOVASCULAR DEVICE

Field of the Invention

[0001] The invention concerns an endovascular device for insertion into a bodily vessel to treat a diseased, damaged, or weakened portion of a vessel.

Background of the Invention

[0002] Vascular diseases include aneurysms causing hemorrhage, atherosclerosis causing occlusion of blood vessels, vascular malformation, and tumors. Vessel occlusion or rupture of an aneurysm within the brain can result in stroke. Aneurysms fed by intracranial arteries can grow within the brain to a point where their size can also cause a stroke or the symptoms of a stroke, requiring surgery to remove the aneurysm, or other remedial intervention.

[0003] Occlusion of coronary arteries is a common cause of heart attack. Diseased and obstructed coronary arteries result in restricted blood flow in the heart which can lead to ischemia or necrosis. While the exact etiology of sclerotic cardiovascular disease is still in question, the treatment of narrowed coronary arteries is more defined. Surgical construction of coronary artery bypass grafts (CABG) is often the method of choice when there are several diseased segments in one or multiple arteries. Conventional open-heart surgery is of course highly invasive and traumatic for patients undergoing such procedures. Therefore, less invasive procedures that accomplish the same goals are highly desirable.

[0004] One alternative method of treatment involves the use of balloon angioplasty as a way in which to reopen the lumen of an occluded vessel. In this procedure a folded balloon is inserted via a catheter into a stenosed region that is either partially or fully occluding the vessel lumen. Inflation of the balloon physically expands the lumen, reopening the occluded region, and restoring normal or at least significantly improved blood flow through the vessel. Alternatively, occlusive atheromas may be cut from the inner surface, a procedure known as atherectomy. In both methods, a certain incidence of restenosis (resealing) occurs resulting in a loss of the benefit of the procedure, and potentially the need for additional rounds of therapy. Restenosis also results in reversion back to the original occluded condition, such that the vessel no longer conducts a normal flow volume, which can lead to ischemia or infarct depending on the particular location and function of the vessel in question.

[0005] A recent preferred therapy for repairing vascular occlusions involves placement of an expandable metal wire-frame (i.e. a stent) within the occluded region of a blood vessel in order to keep the lumen of the vessel open. Stents are generally delivered to the desired location within a vascular system by an intraluminal route, usually via a catheter. Advantages of the stent placement method over conventional vascular surgery include obviating the need for surgically exposing, removing, replacing, or by-passing the defective blood vessel, including heart-lung bypass, opening the chest and in some cases general anaesthesia.

[0006] When inserted and deployed in a vessel, duct or tract (all of which can be conveniently referred to as a vessel) of the body, for example, a coronary artery after dilation of the artery by balloon angioplasty, a stent acts as a prosthesis to maintain the vessel in an open state, thus providing a fluid pathway in the previously occluded vessel. The stent usually has an open-ended tubular form with interconnected struts as its sidewall to enable its expansion from a first outside diameter which is sufficiently small to allow the stent to traverse the vessel lumen and be delivered to a site where it is to be deployed, then expanded to a second outside diameter sufficiently large to engage the inner lining of the vessel for retention at that site. The stent may be expanded via the use of a mechanical device, for example a pressurizable balloon, or alternatively the stent may be self-expanding. Self-expanding stents can be manufactured at a to be deployed size, and then compressed to a smaller size to enable delivery, or may be manufactured from shape memory materials that are deformable to a memorized shape in response to an externally applied energy.

[0007] Usually a stent suitable for successful interventional placement should be hypoallergenic, or preferably non-allergenic, have good radio-opacity to permit radiographic visualization, free from distortion during magnetic resonance imaging (MRI), plastically deformable, resistant to vessel recoil, and be as thin as possible to minimize obstruction to blood flow (or other materials or fluids in vessels other than those of the cardiovascular system), and be relatively non-reactive in terms of eliciting thrombogenic responses.

[0008] The typical reaction when a foreign body is implanted in a body vessel is generally negative. Foreign bodies frequently cause an inflammatory response, and in the case of blood vessels, neointimal proliferation which results in narrowing and occlusion of the body vessel, obviating the benefit of the implant. As a result, both selection of the materials from which the stent is composed, as well as the design of the stent, play an important role in influencing the final suitability of the device in practice. Therefore, in addition to the structural requirements for a stent to maintain a previously occluded vessel in a substantially open conformation, stents must also be biologically compatible, and must be chemically stable when exposed to a biological environment.

[0009] A variety of materials have been tested and used in stents to address the issues of biocompatibility and material stability. For example, polyurethanes have been used in long term implants, but are not always suitable for use in endovascular treatments, especially in small blood vessels. Small blood vessels are considered to be those with an inner diameter of 2.0 to 5.0 mm. In addition, many commercially available polymers are with additives, or have impurities, that are surface-active and so reduce their usefulness in some biological applications.

[0010] More recently, polymers have been developed which can be further modified by the covalent attachment of various surface-modifying end groups, these end groups reducing the reactivity of the material with cells and other factors that function in the immune response. End groups can also be useful in providing greater chemical stability to the material, reducing degradation and improving the longevity of the prosthesis. For example, U.S. Patent No. 5,589,563 (Ward & White) discloses a series of biomedical base polymers with covalently attached end groups that give the polymer certain desirable properties. These modified polymers possess surface properties that improve the biocompatibility and overall performance of objects fashioned from them.

[0011] In addition to their biomechanical functionality, implantable medical devices like stents have been utilized for delivery of drugs or bioreagents for different biological applications. U.S. Patent 5,891,108 (Leone *et al.*) discloses a hollow tubular wire stent with holes through which an active substance can be delivered to a site in a vessel. In some cases the drugs or bioreagents can be coated directly onto the surface of the implantable medical devices or mixed with polymeric materials that are then applied to the surface of the devices. For example, U.S. Patent No. 5,599,352 (Dinh *et al.*) discloses a drug eluting stent comprising a stent body, a layer of a composite of a polymer combined with a therapeutic substance, overlaid by a second layer comprising fibrin.

[0012] However, each of these methods suffers from one or more problems including poor control of release or limitations of the form of drug or other reagent that can be applied. Also, these methods are unsuitable for situations where it would be desirable to maintain the bioactive molecule on the device rather than having it be released, in order to maintain a relatively high local activity of the reagent of interest.

[0013] As a result, in practice, the design and use of stents in the repair of aneurysms or other vessel defects or diseases typically represents a compromise among competing factors. First, the stent must adequately support the diseased or weakened region in order to prevent rupture of the aneurysm or vessel during and after stent placement, either of which could lead to serious complications including death, depending on the size, location and nature of the aneurysm or defect. Second, in the case of stents use in the repair of aneurysms, the stent must permit sufficient blood supply to maintain the patency of both the parent and perforator vessels, while at the same time limiting flow to the aneurysm proper. Generally speaking, flow of material through the framework of a stent is achieved by regulating the porosity of the stent.

[0014] Stent porosity can be managed in a number of ways. The simplest way is to manufacture the stent so that the framework itself defines the porosity of the device. However, in biological applications, regulating movement of materials on cellular or subcellular scale is required, and it is difficult and costly to manufacture stents that have such fine effective pore size. Other approaches have been to cover the stent framework for example with a membrane, where the membrane is either impermeable or porous as desired. U.S. Patent Application No. 2006/0217799 (Mailander *et al.*) discloses a stent comprising a grid or mesh structure in which one or more cells of the grid are covered with a membrane. Similarly, U.S. Patent Application No. 2006/0200230 (Richter) discloses a covering for an endoprosthetic device that comprises a sheath with holes of varying size and varying frequency disposed in different areas of the sheath.

[0015] However, a problem inherent with these designs is that they are not easily adapted for effecting vessel wall repairs where the area of disease, damage or weakness can vary in size. Thus, in order to optimally treat an aneurysm, it would be necessary to tailor the stent and its covering to more or less the precise size of the damaged area, in order to properly occlude the aneurysm site, while maintaining vessel patency in the parent vessel and any perforator vessels. Furthermore, these designs are not optimized such that they will generally provide flow to perforator vessels that are part of the collateral circulation in the area of the diseased, damaged, or weakened vessel, while blocking flow to an aneurysm.

Summary of the Invention

[0016] Some embodiments of the present invention provide an endovascular device, for treating an aneurysm of a body vessel, comprising a distal assembly, movable from a first position to a second position when the distal assembly is at least partially in an aneurysm; and a first flow-reducing member, coupled to the distal assembly, that reduces blood flow from the body vessel into the aneurysm when the distal assembly is in the second position; wherein the distal assembly comprises a plurality of engagement members, each of which extends, from a proximal portion to a distal portion, away from the flow-reducing member, and, when the distal assembly is in the first position, each of the plurality of engagement members is substantially parallel to a central axis of the distal assembly, and, when the distal assembly changes from the first to the second position, the distal portion of each of the plurality of engagement members moves away from the central axis, such that the distal portions of each of the plurality of engagement members: substantially curl; move closer to the first flow-reducing member; and engage an inner surface of the aneurysm.

[0017] In certain embodiments, an endovascular device of the invention comprises a mass and/or a volume less than a mass and/or a volume of known aneurysm "coil" devices, which provides such an endovascular device of the present invention with surprisingly improved properties in regard to aneurismal mass effects, in regard to pressure effects on nerve tissue at or near the aneurysm deployment site, and in regard to allowing for aneurysmal shrinkage over time. In certain embodiments, an endovascular device of the invention comprises a flow reducing member that resides entirely within the aneurysm and has no impact on branch vessels in a proximity of the aneurysm.

[0018] As used herein, the term "curl" encompasses forming a linear element into a curved two-dimensional or three-dimensional shape, or a curved element into a shape having a different curvature. The term "curl" also includes bending a structure such as a structure having a joint. The "curl" or bend can be at the joint or elsewhere in the structure.

[0019] In some embodiments, at least one of the plurality of engagement members comprises a polymer. In some embodiments, the polymer comprises at least one member selected from the group consisting of polyurethane, polyethylene terephthalate, expanded polytetrafluoroethylene (ePTFE), polyvinylchloride, nylon, polyimide, polyurethane ether, polyurethane ester, polyurethaneurea, polylactide, polyglycolide, poly-orthoester, polyphosphazene, polyanhydride, and polyphosphoester.

[0020] In some embodiments, at least one of the plurality of engagement members comprises a metal. In some embodiments, the metal comprises at least one member selected from the group consisting of NiTi, tungsten, stainless steel, iridium, platinum, alloys and/or joined combinations thereof.

[0021] In some embodiments, a distal end of at least one of the plurality of engagement members is blunt.

[0022] In some embodiments, when the distal assembly is in the second position, a distal end of each of the plurality of engagement members engages the inner surface of the aneurysm.

[0023] In some embodiments, when the distal assembly is in the second position, the first flow-reducing member resides in the body vessel.

[0024] In some embodiments, when the distal assembly is in the second position, the first flow-reducing member resides in the aneurysm.

[0025] In some embodiments, an endovascular device comprises a second flow-reducing member, coupled to the first flow-reducing member or to the distal assembly.

[0026] In some embodiments, the distal assembly is in the second position, the first flow-reducing member resides in the body vessel and the second flow-reducing member resides in the aneurysm.

[0027] In some embodiments, an endovascular device comprises a linking member that couples the second flow-reducing member to the first flow-reducing member or to the distal assembly.

[0028] In some embodiments, at least one of the linking member, the distal assembly, the first flow-reducing member, and the second flow-reducing member comprises a metal.

[0029] In some embodiments, at least one of the linking member, the distal assembly, the first flow-reducing member, and the second flow-reducing member comprises at least one metal selected from the group consisting of NiTi, tungsten, stainless steel, iridium, and platinum.

[0030] In some embodiments, the linking member comprises a wire.

[0031] In some embodiments, each of the linking member, the first flow-reducing member, the second flow-reducing member, and the distal assembly comprises a metal, and wherein a weld couples the linking member to at least one of the distal assembly, the first flow-reducing member, and the second flow-reducing member.

[0032] In some embodiments, the second flow-reducing member comprises a plug that substantially resides within a neck of the aneurysm and substantially inhibits blood flow through the neck.

[0033] In some embodiments, the first flow-reducing member comprises a membrane.

[0034] In some embodiments, when the distal assembly is in the second position within the aneurysm, a thickness of the membrane is between about 5 μm and about 500 μm.

[0035] In some embodiments, the membrane comprises at least one polymer selected from the group consisting of ePTFE, polyurethane, polyethylene terephthalate, polyvinylchloride, nylon, , polyimide, silicone, polyurethane ether, polyurethane ester, polyurethaneura, polylactide, polyglycolide, poly-orthoester, polyphosphazene, polyanhydride, and polyphosphoester.

[0036] In some embodiments, the first flow-reducing member is coupled to the distal assembly by suture or by interweaving.

[0037] In some embodiments, at least a portion of the membrane is non-porous.

[0038] In some embodiments, the membrane comprises a porous section having a porosity over a length extending from a proximal end of the porous section to a distal end of the porous section, wherein a pore spacing and a pore size of the porous section determine the porosity of the porous section, and wherein, when the distal assembly is in the second position, the membrane is effective to reduce blood flow into the aneurysm and to promote thrombosis at or in the aneurysm.

[0039] In some embodiments, a membrane porosity is selected such that, when the distal assembly is in the second position, the porous section of the membrane is effective to enhance endothelial cell migration and tissue growth onto the membrane and to substantially inhibit blood flow from the body vessel into the aneurysm.

[0040] In some embodiments, the pore size is between about 1 μm and about 150 μm. In some embodiments, the pore size is between about 10 μm and about 50 μm.

[0041] In some embodiments, the pore spacing is between about 40 μm and about 100 μm. In some embodiments, the pore spacing is between about 60 μm and about 75 μm.

[0042] In some embodiments, a material ratio of the porous section of the membrane comprises a ratio of a total area of an outer surface of the porous section of the membrane that comprises material to a total area of an outer surface of the porous section that comprises pores.

[0043] In some embodiments, when the distal assembly is in the second position, the material ratio is between about 25% and about 90%. In some embodiments, when the distal assembly is in the second position, the material ratio is between about 70% and about 80%. In some embodiments, when the distal assembly is in the second position within the aneurysm, the material ratio is about 75%.

[0044] In some embodiments, an endovascular device comprises at least one surface-modifying end group that, when the distal assembly is in the second position, promotes healing of the body vessel. In some embodiments, the at least one surface-modifying end group comprises at least one of a fluorocarbon and the combination of polyethylene glycol and silicon.

[0045] In some embodiments, an endovascular device comprises at least one agent, permanently attached to the membrane, that promotes healing of the aneurysm. In some embodiments, the healing agent comprises at least one of a peptide, a protein, an enzyme regulator, an antibody, a nucleic acid, and a polynucleotide. In some embodiments, an endovascular device comprises an endothelial cell inhibiting agent, such as L-PDMP. In some embodiments, an endovascular device comprises an endothelial cell inducing agent, such as D-PDMP.

[0046] Some embodiments of the present invention provide an endovascular device, for treating an aneurysm of a body vessel, comprising means for engaging an inner surface of an aneurysm, the means for engaging being movable from a first position to a second position when the means for engaging is at least partially within an aneurysm; and a first means for reducing blood flow into the aneurysm, the means for reducing blood flow coupled to the means for engaging such that, when the means for engaging is in the second position, the first means for reducing blood flow is effective to reduce blood flow from the body vessel into the aneurysm; wherein the means for engaging comprises a plurality of engagement members, each of which extends, from a proximal portion to a distal portion, away from the flow-reducing member, and wherein, when the means for engaging is in the first position, each of the plurality of engagement members is substantially parallel to a central axis of the distal assembly, and wherein, when the means for engaging changes from the first to the second position, the distal portion of each of the plurality of engagement members moves away from the central axis, such that the distal portions of each of the plurality of engagement members: substantially curl; move closer to the first flow-reducing member; and engage an inner surface of the aneurysm.

[0047] In some embodiments, an endovascular device comprises a second means for reducing blood flow into the aneurysm, coupled to the first flow-reducing member and effective to reduce blood flow into the aneurysm when the means for engaging is in the second position. In some embodiments, when the means for engaging is in the second position, the first flow-reducing means resides in the body vessel and the second flow-reducing means resides in the aneurysm.

[0048] Some embodiments of the present invention provide a method of treating an aneurysm of a body vessel comprising providing an endovascular device comprising a distal assembly, movable from a first position to a second position when the distal assembly is at least partially within an aneurysm, the distal assembly comprising a plurality of engagement members, each of which extends, from a proximal portion to a distal portion, away from the flow-reducing member and each of which, when the distal assembly is in the first position, is substantially parallel to a central axis of the distal assembly; and a first flow-reducing member, coupled to the distal assembly, that reduces blood flow from the body vessel into the aneurysm when the distal assembly is in the second position; positioning the distal assembly at least partially within the aneurysm; and changing the distal assembly from the first position to the second position such that the distal portion of each of the plurality of engagement members moves away from the central axis, whereby the distal portions of each of the plurality of engagement members: substantially curl; move closer to the first flow-reducing member; and engage an inner surface of the aneurysm.

[0049] Some embodiments of the present invention provide an endovascular device, for treating an aneurysm of a body vessel, comprising: a distal assembly, comprising an engagement member, the distal assembly being movable from a first position to a second position when the distal assembly is at least partially in the aneurysm; a flow-reducing assembly, coupled to the distal assembly and comprising a first flow-reducing member, the flow-reducing assembly reducing blood flow from the body vessel into the aneurysm when the distal assembly is in the second position; wherein the engagement member is elongate and curvilinear and extends, from a proximal to a distal end of the engagement member, along a path that originates from a point at the flow-reducing assembly and terminates at a point within the aneurysm when the first flow-reducing member resides in the body vessel; wherein the engagement member is coterminous with the path; wherein, when the distal assembly is in the second position in the aneurysm, the first flow-reducing member resides in the body vessel, a first portion of the engagement member engages a first region of an inner surface of the aneurysm, and a second portion of the engagement member engages a second region of the inner surface of the aneurysm; wherein the first and second regions are spaced at least 2 mm apart. In some embodiments, the flow-reducing assembly further comprises a second flow-reducing member; wherein, when the second flow-reducing member resides at least partially in the aneurysm, and the distal assembly is in the second position, the first flow-reducing member resides in the body vessel.

[0050] In some embodiments, a form of an engagement member comprises a curve. In some embodiments, a form of at least a portion of the engagement member is helical.

[0051] In some embodiments, the first and the second regions of the inner surface of the aneurysm are spaced at least 4 mm apart. In some embodiments, the first and second portions of the engagement member are spaced at least 2 mm apart. In some embodiments, the first portion and the second portion of the engagement member are spaced at least 4 mm apart.

[0052] Some embodiments of the present invention provide an endovascular device for insertion into a body vessel to treat an aneurysmal portion of the body vessel, the endovascular device comprises: an expandable member, expandable from a first position to a second position, said expandable member being expandable radially outwardly to the second position such that an outer surface of said expandable member engages with an inner surface of the vessel so as to maintain a fluid pathway in said vessel through a lumen in the expandable member; a membrane covering at least a portion of an outer surface of said expandable member; a plurality of pores in a porous section of the membrane, the porous section having a substantially uniform porosity over a length extending from a proximal end to a distal end of the porous section, porosity being determined by a pore spacing and a pore size; wherein the proportion of the total area of an outer surface of the porous section that consists of membrane material defines a material ratio; wherein the substantially uniform porosity is selected such that, when the expandable member is positioned in the body vessel, the membrane permits a flow of blood from within the lumen of the expandable member, through at least one of the pores, and into at least one branch vessel that branches off of the body vessel; and wherein the substantially uniform porosity is further selected such that, when the expandable member is positioned in the body vessel, the membrane reduces blood flow to the aneurysmal portion of the vessel, promoting thrombosis at or in the aneurysmal portion.

[0053] In some embodiments, the porosity of the porous section is selected such that it enables enhanced endothelial cell migration and tissue in-growth for endothelialization of the neck bridge while substantially preventing blood circulation to the diseased, damaged or weakened portion of the vessel wall.

[0054] In some embodiments, an endovascular device of the invention deployed within an aneurysm can be supported in that position by an endovascular device deployed in a body vessel at or near the aneurysm.

[0055] In some embodiments, the pore size is between about 1 μm and about 150 μm.

[0056] In some embodiments, the pore size is between about 10 μm and about 50 μm.

[0057] In some embodiments, the pore spacing is between about 40 μm and about 100 μm.

[0058] In some embodiments, the pore spacing is between about 60 μm and about 75 μm.

[0059] In some embodiments, the material ratio in an as-manufactured state is between about 85% and about 96%.

[0060] In some embodiments, the material ratio in a deployed state is between about 25% and about 90%.

[0061] In some embodiments, the material ratio in the deployed state is between about 70% and about 80%.

[0062] In some embodiments, the material ratio in the deployed state is about 75%.

[0063] In some embodiments, a diameter of the device in the deployed state is between about 2 mm and about 5 mm.

[0064] In some embodiments, a thickness of the membrane is between about 25 μm to about 125 μm.

[0065] In some embodiments, the thickness of the membrane is measured in an as-manufactured state.

[0066] In some embodiments, a thickness of the membrane is between about 5 μm to about 25 μm.

[0067] In some embodiments, the thickness of the membrane is measured in a deployed state.

[0068] In some embodiments, the device further comprises at least one surface-modifying end group that promotes healing of the body vessel after the device is inserted into the body vessel.

[0069] In some embodiments, the surface-modifying end group comprises at least one of a fluorocarbon and the combination of polyethylene glycol and silicon.

[0070] In some embodiments, the device further comprises at least one agent, permanently attached the membrane, that promotes healing of the aneurysm.

[0071] In some embodiments, at least one permanently attached agent comprises at least one of a peptide, a protein, an enzyme regulator, an antibody, a naturally occurring molecule, a synthetic molecule, a nucleic acid, a polynucleotide, L-PDMP, and D-PDMP.

[0072] In some embodiments, each pore has a diameter between about 30 μm and about 40 μm, and a distance between adjacent pores is between about 60 μm and about 70 μm.

[0073] In some embodiments, the aneurysmal portion of the vessel is located at or near at least one of an intracranial aneurysm, a saccular aneurysm, a wide-neck aneurysm, a fusiform aneurysm, a caroticocavernous fistula, an arteriovenous malformation, a carotid artery stenosis, a saphenous vein graft, a small vessel stenosis, and a renal artery repair.

[0074] In some embodiments, the porous section can be divided into n porous regions, and wherein an outer surface area of each of the n porous regions is substantially $1/n$ of a total outer surface area of the porous segment, and wherein each one of the n porous regions has substantially the same porosity as each of the other $n-1$ porous regions.

[0075] In some embodiments, $n = 2$.

[0076] In some embodiments, $n = 3$.

[0077] In some embodiments, $n = 4$.

[0078] In some embodiments, $n = 5$.

[0079] In some embodiments, the pore size is in a range between about 1 μm and about 150 μm, and pore spacing is between about 10 μm and about 50 μm.

[0080] In some embodiments, the pore size is between about 10 μm and about 50 μm, and the pore spacing is between about 60 μm and about 75 μm.

[0081] In some embodiments, an endovascular device system for insertion into a body vessel to treat an aneurysmal portion of the vessel, the endovascular device comprises: an expandable member, expandable from a first position to a second position, said expandable member being expandable radially outwardly to the second position such that an outer surface of said expandable member engages with an inner surface of the vessel so as to maintain a fluid pathway in said vessel through a lumen in the expandable member; a membrane covering at least a portion of an outer surface of said expandable member; a plurality of pores in a porous section of the membrane, the porous section having a substantially uniform porosity over a length extending from a proximal end to a distal end of the porous section, porosity being determined by a pore spacing and a pore size; wherein the proportion of the total area of an outer surface of the porous section that consists of membrane material defines a material ratio; wherein the substantially uniform porosity is selected such that, when the expandable member is positioned in the body vessel, the membrane permits a flow of blood from within the lumen of the expandable member, through at least one of the pores, and into at least one branch vessel that branches off of the body vessel; and wherein the substantially uniform porosity is further selected such that, when the expandable member is positioned in the body vessel, the membrane reduces blood flow to the aneurysmal portion of the vessel, promoting thrombosis at or in the aneurysmal portion; and a delivery device, operable to deliver the expandable member to the aneurysmal portion of the vessel, onto which the expandable member is loaded prior to delivery.

[0082] In some embodiments, the pore size is between about 1 μm and about 150 μm.

[0083] In some embodiments, the pore size is between about 10 μm and about 50 μm.

[0084] In some embodiments, the pore spacing is between about 40 μm and about 100 μm.

[0085] In some embodiments, the pore spacing is between about 60 μm and about 75 μm.

[0086] In some embodiments, the material ratio in an as-manufactured state is between about 85% and about 96%.

[0087] In some embodiments, the material ratio in a deployed state is between about 25% and about 80%.

[0088] In some embodiments, the material ratio in the deployed state is between about 70% and about 80%.

[0089] In some embodiments, the material ratio in the deployed state is about 75%.

[0090] In some embodiments, a diameter of the expandable member in the deployed state is between about 2 mm and about 5 mm

[0091] In some embodiments, a thickness of the membrane is between about 25 μm to about 125 μm.

[0092] In some embodiments, the thickness of the membrane is measured in an as-manufactured state.

[0093] In some embodiments, a thickness of the membrane is between about 5 μm to about 25 μm.

[0094] In some embodiments, the thickness of the membrane is measured in a deployed state.

[0095] In some embodiments, the system further comprises at least one surface-modifying end group that promotes healing of the body vessel after the device is inserted into the body vessel.

[0096] In some embodiments, the at least one surface-modifying end group is at least one of a fluorocarbon and the combination of polyethylene glycol and silicon.

[0097] In some embodiments, the system further comprises at least one permanently attached agent to promote healing of the aneurysmal portion.

[0098] In some embodiments, the at least one permanently attached agent comprises at least one of a peptide, a protein, an enzyme regulator, an antibody, a naturally occurring molecule, a synthetic molecule, a nucleic acid, a polynucleotide, L-PDMP, and D-PDMP.

[0099] In some embodiments, each pore has a diameter between about 10 μm and about 50 μm and the distance between adjacent pores is between about 60 μm and about 75 μm.

[0100] In some embodiments, the aneurysmal portion of the body vessel is located at or near at least one of an intracranial aneurysm, a saccular aneurysm, a wide-neck aneurysm, a fusiform aneurysm, a caroticocavernous fistula, an arteriovenous malformation, a carotid artery stenosis, a saphenous vein graft, a small vessel stenosis, and a renal artery repair.

[0101] In some embodiments, an endovascular device for insertion into a body vessel to treat an aneurysmal portion of a body vessel, the endovascular device comprises: means for maintaining a fluid pathway in the body vessel; means for covering at least part of the means for maintaining, the means for covering having a substantially uniform porosity in a porous segment of the means for covering; and wherein, when the means for maintaining is positioned in a body vessel, the means for covering permits blood flow from the fluid pathway to at least one branch vessel branching off the body vessel, while reducing blood flow to the aneurysmal portion, and the means for maintaining supports the body vessel in the region of the aneurysmal portion and provides a fluid pathway in the body vessel.

[0102] In some embodiments, a method of treating a body vessel having an aneurysmal portion comprises the steps of: providing an endovascular device, comprising: an expandable member, expandable from a first position to a second position, said expandable member being expandable radially outwardly to the second position such that an outer surface of said expandable member engages with an inner surface of the body vessel so as to maintain a fluid pathway in said body vessel through a lumen in the expandable member; a membrane covering at least a portion of an outer surface of said expandable member; a plurality of pores in a porous section of the membrane, the porous section having a substantially uniform porosity over a length extending from a proximal end to a distal end of the porous section, porosity being determined by a pore spacing and a pore size; wherein the proportion of the total area of an outer surface of the porous section that consists of membrane material defines a material ratio; wherein the substantially uniform porosity is selected such that, when the expandable member is positioned in the body vessel, the membrane permits a flow of blood from within the lumen of the expandable member, through at least one of the pores, and into at least one branch vessel that branches off of the body vessel; and wherein the substantially uniform porosity is further selected such that, when the expandable member is positioned in the body vessel, the membrane reduces blood flow to the aneurysmal portion of the body vessel, promoting thrombosis at or in the aneurysmal portion; and positioning the expandable member in the body vessel.

[0103] In some embodiments, the porosity of the membrane is selected such that it enhances endothelial cell migration and tissue in-growth.

[0104] In some embodiments, the pore size is between about 1 μm and about 150 μm.

[0105] In some embodiments, the pore size is between about 10 μm and about 50 μm.

[0106] In some embodiments, the pore spacing is between about 40 μm and about 100 μm.

[0107] In some embodiments, the pore spacing is between about 60 μm and about 75 μm.

[0108] In some embodiments, the material ratio in an as manufactured state is between about 85% and about 96%.

[0109] In some embodiments, the material ratio in a deployed state is between about 25% and about 80%.

[0110] In some embodiments, the material ratio in the deployed state is between about 70% and about 80%.

[0111] In some embodiments, the material ratio in the deployed state is about 75%.

[0112] In some embodiments, a diameter of the expandable member in the deployed state is between about 2 mm and about 5 mm.

[0113] In some embodiments, a thickness of the membrane is between about 25 μm to about 125 μm in the as-manufactured state.

[0114] In some embodiments, a thickness of the membrane is between about 5 μm to about 25 μm in the deployed state.

[0115] In some embodiments, the method further comprises providing a membrane having at least one surface-modifying end group that encourages healing of the body vessel after the device is inserted.

[0116] In some embodiments, the at least one surface-modifying end group is at least one of a fluorocarbon and the combination of polyethylene glycol and silicon.

[0117] In some embodiments, the membrane further comprises at least one permanently attached agent to promote healing of the aneurysm.

[0118] In some embodiments, the at least one permanently attached agent comprises at least one of a peptide, a protein, an enzyme regulator, an antibody, a naturally occurring molecule, a synthetic molecule, a nucleic acid, a polynucleotide, L-PDMP. and D-PDMP.

[0119] An endovascular device, for treating an aneurysm of a body vessel, comprising: a distal assembly comprising an engagement member, the distal assembly being movable from a first position to a second position when the distal assembly is at least partially in an aneurysm; a flow-reducing assembly comprising a first flow-reducing member and coupled to the distal assembly, the flow-reducing assembly reduces blood flow from the body vessel into the aneurysm when the distal assembly is in the second position; wherein the engagement member comprises an elongate and curvilinear form which follows a path originating from a point on the flow-reducing assembly and terminating at a point within the aneurysm; wherein the engagement member is coterminous with the path; wherein a space exists between the origination and termination points of the path; wherein, when the distal assembly is in the second position in the aneurysm, the first flow-reducing member resides in the body vessel, a first portion of the engagement member engages a first region of an inner surface of the aneurysm, and a second portion of the engagement member engages a second region of the inner surface of the aneurysm; wherein the first and second regions are spaced at least 2 mm apart.

[0120] In some embodiments, the flow-reducing assembly further comprises a second flow-reducing member, the first flow-reducing member resides in the aneurysm, and the second flow-reducing member resides in the body vessel.

[0121] In some embodiments, at least a portion of the form of the engagement member is helical.

[0122] In some embodiments, the first and the second regions of the engagement member are spaced at least 4 mm apart

[0123] In some embodiments, the first and the second portions of the engagement member are spaced at least 2 mm apart.

[0124] In some embodiments, the first portion and the second portions of the engagement member are spaced at least 4 mm apart.

[0125] In certain embodiments, an endovascular device of the invention that is positionable within an aneurysm can be used to treat a bifurcation aneurysm or a trifurcation aneurysm.

[0126] In certain embodiments, an endovascular device positionable within an aneurysm comprises a profile of about 0.018" to about 0.030" and may be delivered by microcatheter as a single unit. Delivery may comprise initial advancement and deployment followed by one or more retraction and repositioning events, if needed. In contrast, known coils are deployed by multiple delivery procedures and lack means for retraction and repositioning after being deployed.

[0127] Brief Description of the Drawings

[0128] Examples of embodiments of the invention will now be described with reference to the following drawings.

[0129] Fig. 1A illustrates an embodiment of a balloon expandable stent.

[0130] Fig. 1B illustrates another embodiment of a balloon expandable stent.

[0131] Fig. 2 illustrates a self-expanding stent.

[0132] Fig. 3 illustrates a delivery system with a stent expanded on a balloon.

[0133] Fig. 4A is a view of a stent disposed in the location of an aneurysm

[0134] Fig. 4B is a second diagrammatic view of a stent disposed in the location of an aneurysm.

[0135] Fig. 5 illustrates a membrane joining two stents for treating a bifurcation aneurysm.

[0136] Fig. 6 illustrates a stent with a membrane having a pattern of pores.

[0137] Fig. 7 illustrates a stent having polymer strips.

[0138] Fig. 8 illustrates a stent with a membrane having a mesh.

[0139] Fig. 9 illustrates a membrane secured to the struts of a stent.

[0140] Fig. 10 illustrates a membrane before the stent is deployed.

[0141] Fig. 11 illustrates a membrane flipping in side the vessel rather than staying close to the vessel wall.

[0142] Fig. 12 illustrates a stent partially covered by a membrane having pockets for release of therapeutically effective agents.

[0143] Fig. 13 illustrates a stent with a membrane secured at three different positions and with three different sizes.

[0144] Fig. 14 illustrates a sleeve as a membrane supported by two ring-like stents.

[0145] Fig. 15 illustrate one embodiments of a membrane showing pore positioning.

[0146] Fig. 16 illustrates equidistantly spaced pores.

[0147] Fig. 17 illustrates a macroporous membrane.

[0148] Fig. 18 illustrates a microporous membrane.

[0149] Fig. 19A is a graphical representation of a membrane as manufactured, (i.e. unexpanded) state.

[0150] Fig. 19B illustrates a membrane in the expanded (i.e. deployed) state.

[0151] Fig. 20 illustrates an experimental model for inducing aneurysms using elastase delivered by a catheter.

[0152] Fig. 21A illustrates a radiographic view of an aneurysm prior to treatment of an experimentally induced aneurysm.

[0153] Fig. 21B illustrates a radiographic view of the same aneurysm, 137 days after the start of treatment with an embodiment of a membrane-covered stent.

[0154] Fig. 21C is a histological section taken at the level of a thrombosed aneurysm.

[0155] Fig. 22 diagrams progressive remodeling of an aneurysm after implantation of a stent.

[0156] Fig. 23 is a graph of the relationship between coverage ratio and stent diameter.

[0157] Fig. 24A is a radiographic view of an aneurysm located in the subclavian artery of a rabbit.

[0158] Fig. 24B is the artery shown in Fig. 25A subsequent to treatment.

[0159] Fig. 25A is an image of a chronic angiograph of iliac arteries showing the patency of vessels implanted with the endovascular device having a solid membrane made from a polyurethane based material with fluorocarbon surface-modifying end groups.

[0160] Fig. 25B is an image of a chronic angiograph of iliac arteries showing the patency of vessels implanted with the endovascular device having a porous membrane made from a polyurethane based material with fluorocarbon surface-modifying end groups.

[0161] Fig. 26 illustrates an embodiment comprising a membrane having permanently attached agents.

[0162] Fig. 27 is a diagrammatic view of a stent with a membrane being used to treat a bifurcation aneurysm in a first example.

[0163] Fig. 28 is a diagrammatic view of a stent with a membrane being used to treat a bifurcation aneurysm in a second example.

[0164] Fig. 29 is a diagrammatic view of a stent with a membrane being used to treat a bifurcation aneurysm in a third example.

[0165] Fig. 30a illustrates an embodiment of a deployed endoprosthetic aneurysm occlusion device comprising a distal assembly, engagement members, and a flow-reducing member residing in a vessel, and a catheter useful for delivering the device to the aneurysm.

[0166] Figure 30b illustrates a cross section view of the embodiment of the device shown in figure 30a.

[0167] Figure 31 illustrates an embodiment of a deployed device comprising a distal assembly, engagement members, a flow-reducing member residing in the vessel, and a linking member.

[0168] Figure 32 illustrates an embodiment of a deployed device comprising a distal assembly, engagement members, a flow-reducing member comprising a membrane residing in the aneurysm, another flow-reducing member comprising a plug residing in the vessel, and two linking members.

[0169] Figure 33 illustrates an embodiment of a deployed device comprising a distal assembly, an engagement member comprising a curve, a flow-reducing member comprising a membrane, and a linking member.

[0170] Figure 34 illustrates an embodiment of a deployed device comprising a distal assembly, an engagement member comprising a helical shape, and a flow-reducing member residing in the vessel.

[0171] Figure 35 illustrates an embodiment of a deployed device together with certain forces that contribute to the secured positioning of the deployed device.

[0172] Detailed Description of the Invention

[0173] Implantable medical devices include physical structures for delivering drugs or reagents to desired sites within the endovascular system of a human body. These devices may take up diversified shapes and configurations depending upon specific applications. Common implantable medical devices include stents, vena cava filters, grafts and aneurysm coils.

[0174] The endovascular system of a human body includes blood vessels, cerebral circulation system, tracheo-bronchial system, the biliary hepatic system, the esophageal bowel system, and the urinary tract system. Although exemplary stents implantable in blood vessels are described, they are applicable to the remaining endovascular system. Embodiments of the invention, some of which are described herein are readily adaptable for use in the repair of a variety of vessels, including but not limited to, treatment or repair in cases of aneurysm, ischemic stroke, carotid artery stenosis, saphenous vein graft, small vessel stenosis, or renal artery repair.

[0175] Stents are expandable prostheses employed to maintain vascular and endoluminal ducts or tracts of the human body open and unoccluded. For example, stents are now frequently used to maintain the patency of a coronary artery after dilation by a balloon angioplasty procedure. A stent is a typically a tubular meshwork structure having an exterior surface defined by a plurality of interconnected struts and spaces between the struts. The tubular structure is generally expandable from a first position, wherein the stent is sized for intravascular insertion, to a second position, wherein at least a portion of the exterior surface of the stent contacts and engages the vessel wall where the stent has been placed.

[0176] The expanding of the stent is accommodated by flexing and bending of the interconnected struts throughout the structure. The force for expansion can be applied externally as from a inflated balloon onto which the stent is loaded prior to placement, or the stent itself may be self-expanding. A myriad of strut patterns are known for achieving various design goals such as enhancing strength, maximizing the expansion ratio or coverage area, enhancing longitudinal flexibility or longitudinal stability upon expansion, etc. One pattern may be selected over another in an effort to optimize those parameters that are of particular importance for a particular application.

[0177] Illustrated in Figs. 1A and 1B are two exemplary balloon expandable stent designs. Fig. 1A shows a tubular balloon expandable stent 100, further comprising end markers 103 to increase visibility of the stent 100 when viewed *in situ* using radiologic techniques. In some embodiments, the stent 100 is made of multiple circumstantial rings 101, where the ring connectors 102 connect two or three adjacent rings 101 and hold the rings in place. In Fig. 1A the end marker 103 is shown as a disc-shape. The shape of an end marker 103 is not critical to the function of the stent 100, and will be useful as long as the shape selected is effective to increase the radiographic visibility of the stent 100.

[0178] Fig. 1B illustrates a tubular balloon expandable stent 104, similar to the stent 100 shown in Fig 1A, with the exception that the stent 104 comprises center markers 105, 106. The center markers 105, 106 help to aid in placing the stent over an aneurysm opening during an implantation operation. The center markers 105, 106 can be of the same material and shape as the end markers 103.

[0179] Fig. 2 illustrates a self-expanding stent 107 made of wires or ribbons. While a self-expanding stent may have many designs, the stent 107 shown in Fig. 2 has a typical braided pattern 108 with welded ends 109. The stent 107 is designed to be relatively flexible along its longitudinal axis, to facilitate delivery through tortuous body lumens, but is still stiff and stable enough radially in the expanded state, such that it will serve to maintain the patency of a vessel lumen when implanted, for example in the lumen of an artery.

[0180] Illustrated in Fig. 3 is a delivery system and an expanded tubular stent 112, loaded over an expandable balloon 114. When the tubular stent 112 is fully expanded to its deployed diameter by inflation of the balloon 114, the latticework of struts takes on a shape in which adjacent crests undergo wide separation, and portions of the struts take on a transverse, almost fully lateral orientation relative to the longitudinal axis of the stent. Such lateral orientation of a plurality of the struts enables each fully opened cell to contribute to the firm mechanical support offered by the stent in its fully deployed condition, and insures a rigid structure that is highly resistant to recoil of the vessel wall following stent deployment.

[0181] While a stent 112 may be deployed by radial expansion under outwardly directed radial pressure exerted, for example, by active inflation of a balloon 114 of a balloon catheter on which the stent is mounted, the stent 112 may be self-expandable. In some instances, passive spring characteristics of a preformed elastic (i.e., self-opening) stent serve the purpose, while in others shape memory materials are used, such that upon activation by the appropriate energy source, the stent deforms into a pre-determined memorized shape. Regardless of design, in all cases the stent is expanded to engage the inner lining or inwardly facing surface of the vessel wall with sufficient resilience to allow some contraction, but also with sufficient stiffness to largely resist the natural recoil of the vessel wall following deployment.

[0182] Referring to the delivery system depicted in Fig. 3, there is included a guide wire lumen 110, a balloon inflating lumen 111, a connector 116, a balloon catheter shaft 113, and platinum marker bands 115 on the catheter shaft 113. The guide wire lumen 110 is used for introducing a guide wire in a balloon catheter, and the balloon inflating lumen 111 for inflating the balloon after the stent has been placed at a desired location. The connector 116 is used for separating the guide wire lumen 110 and the balloon inflating lumen 111. The balloon catheter shaft 113 carries the guide wire lumen 110 and the balloon inflating lumen 111 separately, with a typical length of about 135-170 cm. The ring markers 115 on the catheter shaft 113 are used so that the start of balloon tapers and the edges of the stent can be visualized by X-ray.

[0183] In Fig. 3, an expanded stent 112 is shown mounted onto an expanded balloon. Conveniently, the delivery catheter can be a conventional balloon dilation catheter used for angioplasty procedures. The balloon can be formed of suitable materials such as irradiated polyethylene, polyethylene terephthalate, polyvinylchloride, nylon, and copolymer nylons such as Pebax™. Other polymers may also be used. In order for the stent to remain in place on the balloon during delivery to the desired site within an artery, the stent is typically crimped onto the balloon. However, the precise design choices in delivery systems are not limiting to the scope of the disclosure.

[0184] In some embodiments, the delivery of the stent is accomplished as follows. The stent is first mounted onto an inflatable balloon on the distal extremity of the delivery catheter, and the stent is mechanically crimped onto the exterior of the folded balloon. The catheter/stent assembly is then introduced into the vasculature through a guiding catheter. A guide wire is disposed across the diseased arterial section and then the catheter/stent assembly is advanced over the guide wire that has been placed in the vessel until the stent is substantially located at the site of the diseased or damaged portion of the vessel. At this point, the balloon of the catheter is inflated, expanding the stent against the artery. The expanded stent engages the vessel wall, which serves to hold open the artery after the catheter is withdrawn.

[0185] Due to the formation of the stent from an elongated tube, the undulating component of the cylindrical elements of the stent is relatively flat in transverse cross-section, so that when the stent is expanded, the cylindrical elements are pressed into the wall of the vessel and as a result do not significantly interfere with the blood flow through the lumen. The cylindrical elements of the stent, which are pressed into the wall of the vessel, will eventually be overgrown with a layer of endothelial cells, further minimizing interference with blood flow that could be caused by the presence of the stent in the lumen. The closely spaced cylindrical elements, located at substantially regular intervals, provide uniform support for the wall of the artery, and consequently are well adopted to tack up and hold in place small flaps or dissections that may exists in the vessel wall.

[0186] Resilient or self-expanding prostheses can be deployed without dilation balloons. Self-expanding stents can be pre-selected according to the diameter of the blood vessel or other intended fixation site. While their deployment requires skill in stent positioning, such deployment does not require the additional skill of carefully dilating the balloon to plastically expand the prosthesis to the appropriate diameter, as the final diameter will be primarily a function of the stent design itself. Further, the size of the self-expanding stent is chosen such that when in place it remains at least slightly elastically compressed, and thus has a restoring force which facilitates acute fixation. By contrast, a plastically expanded stent must rely on the restoring force of deformed tissue, or on hooks, barbs, or other independent fixation elements included as part of the stent structure.

[0187] Self-expanding stents can be fashioned from resilient materials such as stainless steel, and the like, wherein the stent is loaded onto the delivery device in a compressed state, and upon placement at the desired location is allow to naturally elastically expand. Expandable stents can also be fashioned from shape memory materials such as nickel-titanium alloys and the like, wherein the stent is expanded from a first shape to a second shape by activation with an energy source such as heat, magnetic fields or an RF pulse for example.

[0188] The presence of a foreign object in a vessel, like a stent, can promote thrombus formation as blood flows through the vessel, and platelets contact the stent surface. This is a well-recognized problem in other areas of cardiovascular treatment, such as when artificial heart valves are implanted. In serious instances, clot formation can lead to acute blockage of the vessel. In addition, as the outward facing surface of the stent in contact or engagement with the inner lining of the vessel, tissue irritation can lead to an inflammatory reaction, further exacerbating restenosis due to localized hyperplasia. Stent design and use must take into account all these myriad factors.

[0189] In one embodiment, illustrated in Fig. 4A, and 4B, there is provided an intracranial stent 202 and for use in the repair of stenotic lesions and aneurysms 201. Due to the characteristics of intracranial blood vessels, the intracranial stents 202 are designed to be very flexible, low profile (diameter of 0.8 mm or less when crimped onto the delivery catheter) and having a thin wall (less than 0.1 mm). As they are used in small vessels, intracranial stents 202 do not necessarily possess, or need, the highest possible radial strength.

[0190] As shown in Fig. 4A, the intracranial stent 202 is located at the site of an aneurysm 201. A membrane 203 partially covers the stent 202 and is positioned to seal the neck, thus blocking blood flow to the aneurysm 201. Blocking blood flow is an important function of the stent, as it reduces the risk of aneurysm rupture, which can cause neurological deficit or even death if it occurs intracranially, and promotes the formation of a thrombus and resolution of the aneurysm. Radiopaque markers 204 can be located in the middle of the stent 202 to provide visibility of the stent 202 during operation and post-operation inspection.

[0191] In Fig. 4B, a portion of the stent 202 is shown to include open "cells" 205. This design avoids blocking perforator vessels (sometimes called perforators), small capillary vessels that have important and distinctive blood supply functions. It is possible that tubular stents can block perforators and inhibit important functions of these vessels, which may be related, but not limited the general health of the vessel and surrounding tissue. Moreover, stents covered with non-porous membranes suffer from the disadvantage that the membrane portion of the stent can block the perforators.

[0192] Stents may also be used to treat a number of different types of aneurysms, including bifurcation aneurysm, as shown in Fig. 5. For example, as illustrated, an intracranial aneurysm 201 can be treated with a stent 202 and membrane 203 to effectively prevent ischemic and hemorrhagic stroke. At least 30 to 35% of aneurysms are located at bifurcation sites of intracranial vessels. In this embodiment, the membrane 203 is one-sided and non-circumferential. In some embodiments the membrane may be circumferential and may cover substantially the entire stent. The stents 202 are joined by the membrane 203, which covers the aneurysm neck 201. The same pattern can be applicable to self-expandable (super-elastic) or balloon expandable (stainless steel, CoCr, PtIr alloys) stents. Thus, the intracranial stent 202 coupled with a membrane 203 acts as a scaffold to open clogged arteries, and the membrane provides a cover to prevent blood flow to the aneurysm 201. Obstructing blood supply to the aneurysm 201 isolates the aneurysm 201 from normal blood circulation, eventually resulting in thrombus formation within the aneurysm. Complete obstruction of the aneurysm 201 may not be necessary in order to achieve initiation of an aneurytic thrombus.

[0193] Table 1 provides a table with exemplary dimensions for an intracranial stent 202 designed for use with a membrane 203. The membrane 203 is biocompatible, has good adhesion to stent struts made from a variety of materials including, but not limited to stainless steel, titanium and nickel alloys and the like. The membrane forms an ultra-thin film that is porous as opposed to being a solid film, having holes or pores included during the process of manufacturing the membrane. In some embodiments, the pore size and material coverage area are selected to prevent blockage of perforator vessels, and while restricting blood flow to the aneurysm.

TABLE 1: Typical Dimensions of Manufactured Stents for Intracranial Use

Dimensions	**As Manufactured**	**Crimped**	**Expanded**
Strut Thickness	0.003" (0.076 mm)		
Outer Diameter	0.080" (2.03 mm)	0.040" (1.02 mm)	0.16" – 0.20" (4.0 – 5.0 mm)
Distance Between Struts	0.031" (0.80 mm)	0.016" (0.40 mm)	0.079" (2.0 mm)

[0194] In some embodiments, the membrane 203 is made from a thin film generally in a range of from about 25 μm to about 125 μm in thickness, measured in the as-manufactured state, and is from about 5 μm to about 25 μm thick, as measured in the deployed state (expanded state). The film has good expandability, and can be expanded up to about 400% using relatively low force. The membrane 203 also has good chemical stability at ambient conditions allowing for extended storage prior to use, and is stable under sterilization conditions (ethanol). Examples of physical properties of the membrane are a hardness of about 75A (measured with a Shore durometer), tensile strength up to about 7500 p.s.i., and elongation of up to about 500%.

[0195] Conveniently, membranes can be made porous, and if desired uniformly porous, by drilling holes into a solid film. In this way a stent 202 covered by a uniformly porous membrane 203 can be provided as illustrated in Fig. 6. The exploded view of Fig. 6 depicts an area of a membrane having uniformly spaced pores. The pore diameter is generally in the range of about 1-150 μm, while the distance between pores is generally less than about 100 μm. Porosity of a stent 202 covered by a membrane can be varied in other ways, including covering the stent 202 with membrane strips as shown in Fig. 7, or by providing a stent 202 covered with a mesh like membrane 203, as in Fig. 8.

Porosity can also be varied by changing pore diameter, or the number of pores per unit area of the membrane.

[0196] Where the stent is covered with membrane strips, as shown in Fig. 7, the strips of membrane 203 can be wrapped laterally around the stent 202. Securing the strips to the stent 202 may be accomplished by interlacing the strips above and below the struts of the stent (not shown). Typically the width of strips would be less than 0.075 mm, and the distance between adjacent strips would be less than about 100 μm.

[0197] Where a mesh or woven membrane is used, a sheet of woven membrane 203 can be wrapped circumferentially around the stent 202, as illustrated in Fig. 8. In one embodiment the mesh size is about 0.025 to 0.05 mm, while the width of the polymer is typically less than about 100 μm.

[0198] In some embodiments, the membrane 203 completely surrounds the stent struts, and forms a stable film between the struts, as shown in Fig. 9A and B. The film between struts can be disposed centrally between struts as in Fig. 9A, or outside struts as shown in Fig. 9B. Fig. 10 illustrates a membrane and stent in the unexpanded state, prior to deployment. Where the film is located outside the struts, as in Fig. 9B, there is a further advantage provided in that the membrane will tend to maintain closer contact with the vessel wall, and will avoid "flipping" toward the inside the vessel, as is depicted in Fig. 11.

[0199] Implantable medical devices can also be used to deliver drugs or reagents to specific locations within the vascular system of a human body. As shown in Fig. 12, a membrane 203 can comprise pockets 208 which serve as reservoirs for drugs or reagents intended for delivery into the region of a vessel wall or lumen. In certain embodiments, the membrane 203 comprises a first layer 206 attached to the outer surface of an implantable medical device such as a stent 202. An intermediate layer is attached to the first layer wherein the intermediate layer comprises at least two circumferential strips being separated from each other and a second layer covering the first layer and the intermediate layer.

[0200] The spaces surrounded by the first layer, and the circumferential strips and the second layer form the pockets 208 that serve as receptacles for drugs or reagents. In other embodiments, the intermediate layer includes at least one opening so that the pockets can be formed within the openings. The shapes and sizes of the openings can be varied in accordance with specific applications. The stent 202 can be partially covered by a membrane 203 that comprises a first layer 206 and a second layer 207.

[0201] In some embodiments, the membrane 203 can cover the entire stent, or portions of the stent 202 , as is shown in Fig. 13. Thus, the size of the membrane can be varied if desired to particularly suit the location where the stent is to be placed.

[0202] Many polymeric materials are suitable for making the layers of the membrane 203. Typically, one first layer is disposed onto the outer surface of a stent. The first layer has a thickness of about 50-125 μm, with pore sizes of about 20-30 μm as a nominal initial diameter. In certain embodiments, the first layer can serve as an independent membrane 203 to mechanically cover and seal the aneurysm 201. The first and/or second layers can be comprised of biodegradable material, and function as a drug or reagent carrier in order to provide sustained release functionality.

[0203] It is desirable that the intermediate layer be formed of a material which can fuse to the first and second layers or attached to the first layer in a different manner. In certain embodiments, the intermediate layer may be merged with the first layer to form a single layer with recessions within the outer surface of the merged layer. The second and intermediate layers can be made of biodegradable material that include drugs or other reagents for immediate or sustained release. After the biodegradable material is dissipated through the degradation process, the membrane 203 is still intact, providing vessel support. The second layer can also be composed of a polymeric material. In some embodiments, the second layer has a thickness of about 25-50 μm, with pore sizes ranging from about 70-100 μm.

[0204] The polymeric layers may be fashioned from a material selected from the group consisting of fluoropolymers, polyimides, silicones, polyurethanes, polyurethanes ethers, polyurethane esters, polyurethaneureas and mixtures and copolymers thereof. Biodegradable polymers can include polylactide, poly(lactide-co-glycolide), poly-orthoesters, polyphosphazenes, polyanhydrides, or polyphosphoesters. The fusible polymeric layers may be bonded by adhering, laminating, or suturing. The fusion of the polymeric layers may be achieved by various techniques such as heat-sealing, solvent bonding, adhesive bonding or the use of coatings.

[0205] Types of drugs or reagents that may prove beneficial include substances that reduce the thrombogenic, inflammatory or smooth muscle cell proliferation response due to the implanted device. For example, cell proliferation inhibitors can be delivered in order to reduce or inhibit smooth muscle cell proliferation. In intracranial or some other applications fibrin sealants can be used and delivered to seal aneurysm neck and provide fibroblasts and endothelial cells growth. Specific examples of drugs or reagents include heparin, phosporylcholine, albumin, dexamethasone, paclitaxel and vascular endothelial growth factor (VEGF). This list is not exhaustive, and other factors known to regulate inflammatory responses, cellular proliferation, thrombogenesis and other processes related to reaction to foreign bodies are contemplated to be useful within the scope of the disclosure.

[0206] The drug or reagents can be incorporated into the implantable medical devices in various ways. For example the drug or reagent can be injected in the form of a gel, liquid or powder into the pockets. Alternatively the drug or reagent can be supplied in a powder which has been formed into a solid tablet composition, positioned in receptacles placed in the device.

[0207] It is at times desirable to provide a stent that is highly flexible and of small profile in order to effect treat vessels of very small caliber, for example, intracranial vessels with lumen diameters ranging in size from about 1.5 mm to about 5.0 mm. High flexibility allows the stent to be advanced along the anatomy of the intracranial circulation.

[0208] In some embodiments, as illustrated in Fig. 14, a membrane 203 is embodied as a sleeve 301 supported by two ring-like short stents 302 at both ends of a device so that the membrane 203 covers the whole area of the device 302. There is no scaffold support in the middle of the device 302. Radiopaque markers 303 are located at both ends of the stent 302. Depending on the particular application, the rings can be balloon expandable and made from stainless steel or self-expandable and made from NiTi (memory shaped nickel- titanium alloy), and the like.

[0209] The membrane 203 is part of the stent structure and is effective to occlude the aneurysm neck and "recanalize" a diseased, damaged, or weakened vessel, leading to healing of the vessel and elimination of the aneurysm. The use of a stent as shown in Fig. 14, further obviates the need for coiling procedures, which are at times used in conjunction with stents to treat wide neck aneurysms. The present apparatus and methods are also a preferred treatment solution for cc fistula ruptured in cavernous sinus, pseudoaneurysms, saccular aneurysms.

[0210] In some embodiments, there is provided a porous membrane as part of the device. The membrane 203 has a system of holes or pores 25 with pore diameter 21 on the order of about 1 to 100 μm, and borders 23 between the pores have a width generally less than about 100 μm, as shown in Fig. 15. To provide a membrane of variable porosity, pore spacing and even pore size can be varied in different areas of the membrane.

[0211] It has been further discovered that a membrane having uniform porosity can be effective in blocking blood flow to an aneurysm while maintaining flow to perforator vessels.

[0212] In some embodiments, pore spacing (the distance between adjacent pores) can be in a range of from about 40 to 100 μm. To produce a membrane of uniform porosity, pore diameter 21, and interpore spacing 22, will be generally equidistant, as in Fig. 16, over substantially the entire area of the membrane. Depending on the size and number of pores in the membrane, the membrane can be described as being macroporous or microporous. For example, in a macroporous membrane, an schematic of which is shown in Fig. 17, pores 25, may range in size from about 10 to 100 μm, and are relatively equally spaced within the membrane material 20. Alternatively, in a microporous membrane, pore diameter may be on the order of about 1 to 10 μm, and again are generally equally spaced in a uniformly porous section of a membrane. The pore sizes shown in Fig. 17 and 18 are only examples, and a range of pore sizes are expected to be useful in an implantable device.

[0213] Furthermore, the characterization of a membrane as either macro-or microporous is not limiting to the disclosure. The functionality of the membrane is dependent on pore diameter and pore spacing, which are described in terms of physical measurement units, and how the particular physical dimensions of the membrane pores operate *in situ* to regulate blood flow. In either case, membranes having porous sections of uniform porosity can be fashioned by selecting a desired pore diameter and pore spacing combination. As is seen in the data presented below, various combinations of pore diameter and pore spacing are effective to provide a membrane of optimal porosity over a range of deployed sizes. Thus, a porous membrane 203 is able to significantly improve hemodynamics around the aneurysm 201, since it has a lower delivery profile and is more flexible, as compared to a stent 202 with a solid membrane.

[0214] One application for a device having a macroporous membrane is to treat aneurysms within close proximity of branches or perforators. Another specific application is the treatment of an intracranial saccular or wide neck aneurysm located above the ophthalmic artery where perforators extend from the parent artery within close proximity of the aneurysm. Microporous devices are suitable for use in areas where perfusion of perforators is of less immediate concern. Thus, the micro-porous device is used for conditions which require total coverage to immediately block blood flow, for example, a caroticocavernous fistula, or where there is little or no risk of blocking perforators, for example, below the ophthalmic artery.

[0215] The device may be used for the treatment of endovascular disease such as aneurysms, arteriovenous malformations (AVM's) and caroticocavernous fistulas. The device may also be useful in other vessel related applications such as treatment or repair in cases of ischemic stroke, carotid artery stenosis, saphenous vein graft, small vessel stenosis, or renal artery repair. The pore patterns are designed with consideration of factors such as specific flow conditions of blood vessels, and the location of the vessel being repaired.

[0216] The design of the porous section of a membrane is therefore initially determined according to the intended application of the device, and three main factors, pore size 21, bridge dimensions 22, 23, and material ratio of the membrane. Pore size 21 can be measured in the "as designed and manufactured" (i.e. unexpanded) and "as deployed" (i.e. expanded) states. Typically, pore size in the unexpanded state is about 1.5 to 2.5 times smaller than pore size after the membrane has been expanded to its deployed size. This is depicted in Fig. 19A and B.

[0217] Bridge dimensions 22, 23 refer to the shortest distance separating one pore 25 from its adjacent pores, as shown in Fig. 15. Each pore 25 may be spaced from adjacent pores at variable distances, or as shown in one embodiment depicted in Fig. 16, at generally equal distance. In a uniformly porous section of a membrane the pore spacing will be relatively equidistant throughout the membrane. Similar to pore size 21, bridge dimensions 22, 23 can also be measured in two states, as designed and manufactured, or as deployed. The as designed and manufactured bridge dimensions are typically larger than the as deployed bridge dimension 22, 23 by a factor of 1 to 2, since stretching of the membrane during deployment reduces the size of the bridge.

Membrane Porosity

[0218] The relative porosity of a porous section of a membrane will be dictated by the size of individual pores and the number of pores per unit area (i.e. pore density). As used herein, the term "porous section" refers to that area of a membrane that includes substantially all the pores of the membrane. Coverage and porosity can both be described in terms of a relationship between the area of the apparent area of the porous section of the membrane corresponding to membrane material, versus that corresponding to the pores. Thus, the material ratio is the fraction of a membrane area that corresponds to membrane material, or in other terms, total apparent area or the porous section (100%) – pore area (%) = material ratio (%). As used herein, the term "material ratio" refers in particular to the membrane material versus pore area in a porous section of a membrane.

[0219] As indicated, material ratio is conveniently expressed as a percentage. So, for example, a membrane lacking pores has a material ratio = 100%, while in a membrane with 20% of its total area encompassed by pores, the material ratio = 80%. Likewise, porosity can also be expressed as a percentage, where porosity (%) = total area of the porous section of the membrane (100%) – material ratio (%). A membrane having a material ratio of 75% would have a porosity of 25%. Both material ratio and porosity can be described in membranes in the "as manufactured" and "as deployed" stages. In some embodiments, the overall material ratio in the deployed state can range between about 25% to about 80%.

[0220] It has been discovered that a membrane of uniform porosity can be effective to promote healing of an aneurysm if the material ratio of the porous section of the membrane is within a certain range when the membrane is in the deployed state. Thus, in some embodiments the material ratio of the porous section of the membrane is preferably in a range between about 70% to 80%, with the optimal material ratio considered to be about 75%, when the membrane is deployed. Uniformity is achieved by maintaining the variance in the size of pores, as well as the spacing between pores in a porous section of the membrane, while an optimal material ratio is achieved on the basis of particular pore diameters and spacing.

[0221] The porous section can also be conceptually divided into a number (*n*) of porous regions, wherein the area of each of the *n* regions is substantially *1/n* of the total area of the porous section of the membrane. For example, in some embodiments, there can be 2, 3, 4, 5 or more porous regions, where each of the regions has substantially the same porosity as each of the other porous regions existing with the porous section of the membrane. The porosity of either a region or the porous section as a whole is determined by the combination of pore size and pore spacing.

[0222] While the interpore size variance will be substantially uniform over the area of a porous section within each individual membrane, it is to be recognized that it is possible to provide different membranes with different numbers of pores, or different pore spacing as a way in which to provide a set of membranes of varying porosity. In this way it is possible to have a set of membranes with a range of porosities, any one of which can be chosen based on the requirement in a particular application. Thus depending on a variety of factors, a membrane could be produced with properties that would make it particularly well-suited for use in aiding in the stabilization and repair of a particular vessel, while for another application a membrane of a different porosity might be preferable, and could be fashioned accordingly.

[0223] Porosity of the membrane is considered optimal when the membrane permits blood supply to perforators of main arteries while reducing blood circulation to the diseased, damaged or weakened portion of the vessel wall being repaired. In addition, a further benefit may be realized by selecting a membrane having a porosity that enables enhanced endothelial cell migration and tissue ingrowth for faster endothelialization. The membrane as disclosed may be used in devices designed for a variety of vessel repair applications other than aneurysms. These may include, but are not limited to, use in the treatment of ischemic stroke, carotid artery stenosis, saphenous vein graft, small vessel stenosis, or renal artery repair.

[0224] As indicated above, part of the novelty described in the present disclosure lies in the discovery that a stent having a uniformly porous membrane is capable of supporting a vessel wall at the site of an aneurysm, maintaining the patency of parent and perforator vessels, while restricting blood flow to the aneurysm itself. In prior art devices these functionalities were achieved using membranes with non-uniform porosity, or regions of varying porosity. By providing these features the device promotes more rapid and more effective healing of an aneurysm, while at the same time providing a device that is more universally adaptable for use in a wider variety of *in vivo* locations than previously possible, and simpler to manufacture and use.

[0225] This has been confirmed experimentally in an animal aneurysm model. In this model system, aneurysms are induced by infusion of elastase into the lumen of a vessel by way of a catheter, as diagrammed in Fig. 20 (See: Miskolczi, L. et al., Rapid saccular aneurysm induction by elastase application *in vitro*, Neurosurgery (1997) 41: 220-229; Miskolczi, L. et al., Saccular aneurysm induction by elastase digestion of the arterial wall, Neurosurgery (1997) 43: 595-600). An example aneurysm 200 produced by this method is shown in Fig. 21A.

[0226] In the illustrated experiment, a stent was deployed at the site of the aneurysm shown in Fig. 21A, in order to support the vessel wall and to aid in repair of the damaged area. As can be seen in Fig. 20B, after 137 days blood flow to the aneurysm had ceased, while the patency and flow in the parent vessel 210 and a nearby perforator vessel 220 was maintained. A histological section through the vessel at the site of the aneurysm, shown in Fig. 21C, reveals that a thrombus 240 formed at the site of the aneurysm, indicating that the aneurysm had become substantially occluded. Note that the parent vessel 210 is open and unobstructed. This process of remodeling of the aneurysm is diagrammed in Fig. 22.

[0227] Results from a series of studies like these have suggested that the material ratio of the membrane for optimal efficacy should be about 75%, or at least in the range of about 70-80%. In order to achieve this optimal porosity, several factors are considered. For example, the size as manufactured relative to the deployed size will be important, as the change in pore area occurs at a different rate than does the overall area of the membrane.

[0228] The material ratio has therefore been determined for membranes of varying pore diameter, pore spacing, and degree of expansion from the manufactured size to various deployment sizes, in order to evaluate what pore spacing and pore size can provide a material ratio in the range of about 70-80%, at deployed sizes ranging from 2.5-5.0 mm. In the examples described, material ratio in the unexpanded state ranged from 86-96% depending on the pore size and spacing. To determine the material ratio in the expanded state, membranes were expanded as they would be during deployment, and the pore diameter measured at selected areas. The material ratio was then determined as follows:

$$A = \text{total area of porous section of membrane};\ P = \text{total area of pores};$$

$$\text{Porosity} = (P \div A) \times 100\%;\ \text{Material Ratio} = (1 - (P \div A)) \times 100\%$$

[0229] In the data shown in Table 2, two membranes having porous sections with different pore size and pore spacing were evaluated. Porous 30/70 (30/70 membrane) refers to a membrane manufactured with 30 µm pores with an interpore spacing of 70 µm in the unexpanded state; likewise, Macroporous 40/60 (40/60 membrane) refers to a membrane with 40 µm pores and an interpore spacing of 60 µm, again, in the unexpanded state.

TABLE 2: Effect of Deployment Size on Material Ratio

Configuration	**Diameter of Stent**				
	2.0 mm (as made)	2.5mm	3.0mm	3.5mm	4.0mm
Macroporous 30/70 Pore Diameter: 30 µm Pore Spacing: 70 µm	92%	87%	80%	75%	69%

Macroporous 40/60 Pore Diameter: 40 μm Pore Spacing: 60 μm	86%	78%	72%	64%	56%

[0230] As the data in Table 2 shows, when a membrane is expanded from its manufactured size (here 2.0 mm) to various deployed sizes, ranging from 2.5 to 4.0 mm, the material ratio decreases. Thus, depending on the initial pore size and density, the optimal material ratio of about 70-80% will be achieved at different degrees of expansion, analogous to the various deployment diameters of the stent being covered by the membrane.

[0231] For example, in a 30/70 membrane, material ratios within the optimal desired range of about 70-80% are substantially achieved at deployment diameters of about 3.0 to about 4.0 mm, when starting with a manufactured size of 2.0 mm. For a 40/60 membrane the optimal material ratio is achieved at a point between 2.0 to 2.5 mm, up to about 3.0 to 3.5 mm.

[0232] By extending this analysis it is possible to determine the number of different stent pore patterns, the pattern being the combination of pore size and interpore spacing, necessary to provide about a 70-80% material ratio over wide range of stent diameters. The goal is to know beforehand, the combination of pore size and spacing that, when the membrane is expanded to its deployed size, will provide a material ratio within the desired range of about 70-80% and preferably about 75%.

[0233] For example, the calculations in Table 3 show that with three different membrane patterns, it is possible to achieve a material ratio in the range of about 70-80% using a stent with a manufactured size of 2.2 mm, expanded to deployment sizes ranging from 2.5-5.0 mm. In these cases, the material ratio of the membrane in the unexpanded state ranges from 86-96%.

TABLE 3: Relationship of Material Ratio and Stent Diameter

Final diameter of patch	Stent size	Pore diameter, μm	Interpore distance, μm	% coverage as	% coverage as manufactured at 2.2mm

				deployed	
2.5, 2.75, 3.0 mm	2.5/3.0mm	40	60	70-80%	86%
3.25, 3.5, 3.75, 4.0mm	3.5/4.0mm	30	70	70-80%	92%
4.25, 4.5, 4.75, 5.0mm	4.5/5.0mm	20	75	70-80%	96%

[0234] These results are further exemplified in Fig. 23, which shows a graphic analysis of the relationship between pore diameter, pore spacing and deployment size for three different pore patterns, and the material ratio that results upon deployment to various diameters. In each case the material ratio of the membrane is plotted as a function of diameter of the stent in the expanded state. In all cases, the stents are manufactured at a size of about 2.2 mm. A surgeon, simply by knowing the size of the vessel to be repaired, can readily select a stent and membrane combination optimized to provide a 70-80% material ratio within a porous section of the membrane when the device is deployed, and achieve effective healing and repair of an aneurysm.

[0235] As shown in Fig. 23, for a 40/60 membrane, deployment sizes ranging from about 2.7 mm to about 3.5 mm will provide a coverage area in the desired range of about 70-80%. For a 30/70 membrane, deployment diameters ranging from about 3.5 mm to about 4.5 mm will result in a coverage area in the desired range of about 70-80%, and for a 20/75 membrane (i.e. 20 μm pore diameter; 75 μm pore spacing) deployment sizes ranging from about 4.2 mm to about 5.4 mm will provide a coverage area in the desired range of about 70-80%. Thus, a material ratio in the range of about 70-80% can be achieved over deployment sizes of 2.7-5.4 mm by selecting the membrane from a set of only three membranes. It is contemplated that by varying pore spacing and pore diameter, as well as with membranes made from various materials, greater flexibility in obtaining optimum material ratio at the widest variety of deployed sizes is possible.

[0236] In practice, and as shown in Fig. 24A and B, an embodiment of a device 10 effectively reduces blood flow into an aneurysm 50. Reducing flow to the aneurysm induces intra-aneurysmal thrombosis. Fig. 24A shows an aneurysm 50 located in the subclavian artery of a rabbit. In Fig. 24B, the results show that within a few hours deployment of the device 10 in the vessel 5, blood supply to the body of the aneurysm 50 is effectively stopped. Significantly, the pore pattern of the membrane continues to allow an uninterrupted supply of blood through perforator vessels 55 located proximal to the deployed device 10. The device 10 uses the antagonistic relationship between the sufficient reduction of blood supply to disrupt and thus heal an aneurysm 50 and the maintenance of sufficient blood supply vital to keep the perforators 55 patent.

[0237] For example, consider an aneurysm 50 with aneurysm neck diameter of about 6 mm and height of about 10 mm. If the aneurysm neck is covered by a 25% material ratio macro-porous device 10, a reduction of 25% blood flow into the aneurysm sac is possible, with higher material ratios, for example 70-80%, or preferable 75%, even greater inhibition of blood flow to the aneurysm is achieved. It is expected that the percentage reduction in blood flow will exceed the simple percentage material ratio due to the viscosity of blood, as well as further reduction of blood flow due to flow disruption and dispersion. The geometry of the aneurysm can also play a role in the effectiveness and operation of the device.

<u>Chemical Properties of the Membrane</u>

[0238] The membrane is preferably made from biocompatible, highly elastomeric polymer. Polyether urethane (PEU) or polycarbonate urethane (PCU) may be used.

[0239] Trade names for PEU include Tecoflex, Tecothane, Hapflex, Cardiothane, Pellethane, and Biospan. Trade names for PCU include ChronoFlex, Carbothane, and Corethane.

[0240] In some embodiments the membrane is made from BioSpan F, a material developed by Polymer Technology Group (PTG), Berkeley, California, USA. BioSpan F is a polyurethane based material with fluorocarbon surface-modified end groups. In studies performed both *in vitro* and *in vivo*, this material has been shown to possess excellent compatibility properties matching the environment of small blood vessels. The selection of BioSpan F for the membrane of the device in treating small vessels is preferred due to resistance to thrombogenesis as compared with PET or e-PTFE membranes. Preferably, the membrane fashioned from BioSpan F will include a specific pore pattern as described earlier to obtain better resolution and healing of the aneurysm.

TABLE 4: Summary of Protein Adsorption Test

Test article	Concentration of protein found (μg/ml)	Amount of protein (μg)	Adsorbed protein (μg/cm^2)	Adsorbed protein (μg/g)
BioSpan	5.5	28	1.4	230
BioSpan F	3.5	18	0.88	160
ePTFE	16	80	4.0	4600

[0241] Table 4 shows initial results from *in vitro* biocompatibility tests comparing three materials; BioSpan, BioSpan F, and ePTFE. As can be seen, BioSpan F was the least thrombogenic of the three. The results of animal studies, shown in Fig. 25A and B, confirm the superior biocompatibility of BioSpan F. An endovascular device 76 with a membrane made from BioSpan F was placed in the right iliac artery 78 (left side of Fig. 25A). The angiographic study shows normal patency of the artery after healing of the implant. In contrast, an endovascular device 80, made from a different membrane material, and placed in the left iliac artery 74 of the same animal (right side of Fig. 25A), showed poor biocompatibility, such that after healing the vessel 74 became completely occluded in the region of the device 80.

[0242] Additional animal studies, shown in Fig. 25B, revealed that when BioSpan F was used as the membrane material, a stent covered with a porous membrane 78 had a lower degree of narrowing and thus had better healing properties than the stent covered with a solid membrane 79. With a porous membrane approximately 5% narrowing was observed (left side of Fig. 25B), while with a solid membrane 15-20% narrowing was seen (right side of Fig. 25B).

[0243] In some embodiments, membranes can be fashioned from materials of the BioSpan family using the same surface modifying end group technique, but with application of different end groups. BioSpan PS, for example, is a surface modified material with PEO and silicon end groups.

Membranes With Permanently-Attached Agents

[0244] In some embodiments, one of which is illustrated in Fig. 26, the device 1010 is a stent comprising struts 1011, covered by an ultra-thin membrane or coating 1015, and where the membrane 1015 is of substantially uniform porosity over its length. The membrane comprises two surfaces, a luminal surface and a vessel wall surface. On the luminal surface, agents 1020, 1021, 1022 are permanently attached to the membrane 1015. On the vessel wall surface, agents 1023, 1024, and 1025 are permanently attached to the membrane. At least one capture agent 1021 is permanently attached to the luminal surface of the membrane 1015 to capture a desired target component 1030 present in the fluid passing through the vessel. At least one signal agent 1022 is permanently attached to the luminal surface of the membrane 1015 to signal the captured target component 1030 to up regulate or down regulate a cell function of the captured target component 1030 to enhance endothelialization and healing.

[0245] The cell function being regulated can include, but is not limited to, proliferation, migration, maturation, and apoptosis. The desired target component 30 can include, but is not limited to, an endothelial progenitor cell, in which case the signal agent 22 could up regulate the rate of endothelialization, and reduce the time for inflammation and thrombosis. Conveniently it is possible to combine a membrane having uniform porosity, with one comprising agents, 1020, 1021, 1022, permanently attached to the membrane. A membrane configured in this way would thus be adapted to substantially prevent blood flow to an aneurysm, while maintaining blood flow to perforators, and in addition could provided various agents that would enhance the process of healing the aneurysm.

[0246] The pharmaceutical agents 1020, 1021. 1002, coated on the lumen side of the membrane 1015, prevent the occlusion of the original patent lumen. In some embodiments, the capture and agent 1021 is arranged in a first conformation of a single arm structure made of an organic linker anchored to the membrane 1015. The organic linker may be a short chain of organic molecules anchored on one end to the membrane 1015, and the other end bound to the agent molecule that captures specific endothelial cells from the blood to promote endothelialization. The capture and signal agents 1020, 1021, 1022 are arranged in a second conformation of a branched structure made up of an organic linker anchored to the membrane 1015. The capture agent 1021 specifically captures endothelial progenitor cells similar to the other capture agent 1020, while a signal agent 1022 enhances endothelial cell alignment and proliferation. Alternatively, the signal agent 1022 is arranged in a first conformation of a single arm structure made up of an organic linker anchored to the membrane 1015.

[0247] On the vessel wall side of the membrane 1015, a third pharmaceutical agent 1023 is permanently attached to the vessel wall surface of the membrane 1015 to enhance healing of the vessel wall 1005 from injury after the stent 1011 is deployed. Alternatively, the agents on the vessel wall side of the membrane 1015 also encourage proliferation of vessel wall components, for example, intima, elastic lamina, for enhancing the healing of the weakened, damaged or diseased portion of the vessel wall, for example, the aneurysm neck.

[0248] The agents can be effective to reduce, minimize, or prevent, immune reactions to foreign bodies. In some embodiments, agents can be effective to attract and capture endothelial cells, or endothelia progenitor cells, to aid in the formation of a healthy endothelium in the region of the aneurysm being treated. The lumen side of the membrane can be configured to generally discourage factors that are involved in thrombosis.

[0249] The capture and signal agents 1021, 1022, can include, but are not limited to, enzyme regulators tagged with antibodies or peptides, ceramides like L-PDMP, peptides, antibodies, naturally occurring molecules, and synthetic molecules, a nucleic acid, or even a polynucleotide, if desired. Specifically, the signal agent 1022 can be an endothelial cell specific L-PDMP or an smooth muscle cell-specific D-PDMP, that can bind specifically to target molecules on endothelial cells or progenitors. Peptide or antibodies have high binding affinity and specificity for endothelial cells and progenitors. Naturally occurring molecules (pure or synthesized) can mimic part of the basal lamina of the endothelium, so that endothelia cells or progenitors will preferentially bind and orient on the membrane. For example, laminin-mimetic pentapeptide immobilized on the lumen surface can be effective as a capture agent. The choice of capture agent is not considered to be a limitation of the disclosure. A number of molecules or moieties will be useful in preventing blood flow to an aneurysm, while maintaining flow to perforators, and which will promote healing and/or endothelialization, while reducing the risk of thrombosis or other injury to the vessel being treated are considered to be within the scope of the disclosure.

[0250] The signal agent 1022 can also be an anti-inflammatory agent in order to reduce recruitment and infiltration of white blood cells. Thus, through the choice of various signal agents it is possible to enhance attachment of endothelial cells to the membrane, while minimizing the inflammatory response. The capture agent 1021 and signal agent 1022 thus act cooperatively to increase the rate of endothelialization and decrease the during which thrombosis and restenosis might occur after the stent is expanded.

[0251] As shown in Figs. 27 through 29, in some embodiments the stent 202 can be used to treat a bifurcation or trifurcation aneurysm 201. It should be noted that the use of the device is not limited to those embodiments that are illustrated. The stent 202 is implanted to be partially located in a main artery extending to be partially located in a subordinate artery. For example, in Fig. 27, two vertebral arteries join to the basilar artery. The stent 202 is deployed such that it is located in the basilar artery and in a vertebral artery (right side) where the aneurysm 201 is formed. On the other vertebral artery (left side), blood continues to flow to the basilar artery without any obstruction since the membrane 203 is permeable to blood flow. Preferably, the membrane 203 covers the whole stent 202, and the permeability of the membrane 203 allows blood flow through the left vertebral artery (left side). Conveniently, radio-opaque markers 204 are provided in order to permit more accurate placement of the stent 202.

[0252] In Fig. 28, the middle cerebral artery divides into the superior trunk and the inferior trunk. The stent 202 is deployed such that it is located in the middle cerebral artery and in the inferior trunk. Again, the struts of the stent 202 do not inhibit blood flow to the superior trunk, and blood flows through the stent 202 to the inferior trunk.

[0253] In Fig. 29, the stent 202 is deployed in the vertebral artery. As the aneurysm 201 in this example is located in a middle portion of the vertebral artery, there is no need for the stent 202 to be located in more than one artery. When implanted, the stent 202 diverts blood flow away from the aneurysm 201. This leads to occlusion of the aneurysm 201 and keeps the arterial branches and the perforators patent. The stent 202 does not require precise positioning because it is uniformly covered with a porous membrane 203. Thus, most of the circumferential surface of the stent 202 is covered by the membrane 203, and thus the vessel wall will be uniformly contacted by the membrane in the area of the stent.

[0254] Due to the particular porosity and dimensions of the membrane 203, blood circulation to the aneurysm 201 is obstructed while blood supply to perforators and microscopic branches of main brain arteries as well as larger arteries is permitted. As described earlier, obstructing blood supply to the aneurysm 201 isolates the aneurysm 201 from normal blood circulation. The aneurysm in effect "dries out." The stent 202 and membrane 203 thus treats the aneurysm 201 by altering the hemodynamics in the aneurysm sac such that intra-aneurysmal thrombosis is initiated. At the same, blood flow into the arteries (branch, main, big or small) are not significantly affected by the implantation of the stent 202 or the membrane 203 due to the special porosity of the membrane 203. Although a bifurcation aneurysm has been described, it is envisaged that the stent 202 may be used to treat a trifurcation aneurysm, or other aneurysms, in a similar manner.

[0255] As used herein, the terms "secured to" and "coupled to" include direct and indirect means to secure and couple elements and/or components of endoprosthetic devices of the invention.

[0256] Fig. 30a illustrates an embodiment of a deployed endoprosthetic device 395. As shown, the distal assembly 400 of device 395 is made up of a plurality of engagement members 405, 410, 415, 420, coupled to flow-reducing member 425. While the embodiment illustrated in Fig. 30a comprises four engagement members 405, 410, 415, 420, some embodiments comprise one or more engagement members. Distal portions of the engagement members 405, 410, 415, 420 are curled and engage inner surfaces of an aneurysm 200. Flow reducing member 425 comprises a membrane 440, resides within the vessel 210, and reduces blood flow from the vessel 210 into the aneurysm 200. Device 395 can be delivered to the aneurysm by catheter 450 over a guide wire 452, and device 395 can be repositioned at or within the aneurysm 200, or entirely removed from the aneurysm as described herein.

[0257] In some embodiments, the delivery of an aneurysm occlusion device can be accomplished by advancing a guide wire through the vasculature and into the aneurysm, advancing a catheter over the guide wire, and withdrawing the guide wire. At this point, an aneurysm occlusion device can be advanced by a pusher, and pushed through the catheter until the device is positioned at least partially within the aneurysm (e.g. a neck of an aneurysm).

[0258] In some embodiments, the delivery of an aneurysm occlusion device can be achieved by a multilumenal catheter comprising a guide wire lumen and a pusher-device. The guidewire is advanced through the vasculature and into the aneurysm. The catheter is advanced through the vasculature and to the aneurysm by tracking over the guide wire, disposed within the guide wire lumen, with a pusher and a device loaded into the pusher-device lumen of the catheter. Upon deployment, the pusher can be used to advance the device into the aneurysm. In some embodiments, the pusher can be used to retract the initially advanced device so as to reposition the device within the aneurysm. In some embodiments, the device and the pusher can be reversibly coupled, and the device released from the pusher by breaking of a chemical bond and/or an electrical heating process.

[0259] In some embodiments, an aneurysm occlusion device can, alone or coupled with a catheter delivery device, have an outside diameter in a range of from about 0.017" to 0.035." In some embodiments, an aneurysm occlusion device can, alone or coupled with a catheter delivery device, have an outside diameter in a range of from about 0.022" tot 0.030."

[0260] In some embodiments, the device comprises a balloon (e.g. a flow reducing member), which is inflated once the device has been delivered to the aneurysm, thereby expanding the distal assembly of the device. The expanded device is released from the catheter, and the catheter is withdrawn from the vasculature. The expanded device engages an inner surface of the aneurysm, which secures the device at the aneurysm in a position in which the flow reducing member(s) reduces blood flow from the vessel into the aneurysm.

[0261] In some embodiments, the device comprises shape-memory elements that, upon the device being released from the catheter, provide movement to the distal assembly so that it engages an inner surface of the aneurysm, thereby securing the device in a position in which the flow reducing member(s) reduce blood flow from the vessel into the aneurysm.

[0262] In some embodiments, the device comprises one or more forming elements, the manipulation of which provide(s) movement to the distal assembly into a position in which it engages an inner surface reduces blood flow from the vessel into the aneurysm.

[0263] In certain embodiments, the size of device is chosen such that, when in place at the aneurysm, it remains at least slightly elastically compressed, and therefore has a restoring force which facilitates secure positioning. In certain embodiments, a device in place at the aneurysm can rely on the restoring force of deformed tissue for secure positioning, and/or on hooks, barbs, or other independent fixation elements included as part of the device structure.

[0264] In Fig. 30a, Engagement members 405, 410, 415, 420 of device 395 can be made of metals or polymers, such as NiTi, tungsten, stainless steel, iridium, platinum alloy, polyurethane, polyethylene terephthalate, polyvinylchloride, nylon, polyimide, polyurethane ether, polyurethane ester, polyurethaneurea, polylactide, polyglycolide, poly-orthoester, polyposphazene, poly anhydride, and polyphosphoester. The engagement members 405, 410, 415, 420 can have shape-memory properties that enable self expansion from a first, delivery position to the illustrated second, deployment position. Engagement member 405, 410, 415, 420 movement from a first position to the illustrated second position can be accomplished by assisted movement of the engagement members, either in the absence of or in combination with any degree of shape-memory properties that engagement members 405, 410, 415, 420 may have. Assisted engagement member movement can be accomplished by, for instance, inflating a balloon located at a central axis of the distal assembly 400.

[0265] Flow reducing member 425 can comprise a porous or nonporous membrane 440, as described herein, and can be expandable from a first, delivery position to a second, deployed position, in which at least a portion of the membrane 440 of the flow reducing member 425 is adjacent to an inner surface of the vessel 210. Flow reducing member 425 can comprise a frame, inflatable balloon, and/or thick plug. Frames of flow reducing members can comprise polymers and/or metals, such as such as NiTi, tungsten, stainless steel, iridium, platinum alloy, polyurethane, polyethylene terephthalate, polyvinylchloride, nylon, polyimide, polyurethane ether, polyurethane ester, polyurethaneurea, polylactide, polyglycolide, poly-orthoester, polyposphazene, poly anhydride, and polyphosphoester, and comprise struts. Flow reducing members can be coupled to a distal assembly and/or each other by weld, interweaving, suture, stitch, adhesive, combinations thereof, etc.

[0266] Fig. 30b illustrates a cross sectional view of device 395 shown in Fig. 30.

[0267] Fig. 31 illustrates a device 495 similar to the one shown in Fig. 30, but the engagement members 405, 410, 415, 420 of device 495 illustrated in Fig. 31 are curled in a different manner than those of device 395 of illustrated in Fig. 30. In addition, device 495 illustrated in Fig. 31 comprises a linking member 435, whereas device 395 shown in Fig. 30 does not have a linking member.

[0268] Fig. 32 illustrates a device 595 similar to device 495 shown in Fig. 31, but device 595 illustrated in Fig. 32 comprises three engagement members 405, 410, 415, whereas device 495 shown in Fig. 31 comprises four engagement members 405, 410, 415, 420. Device 495 shown in Fig. 31 has one flow reducing member 425, whereas device 595 illustrated in Fig. 32 further comprises a second flow-reducing member 430 that comprises a balloon, resides in the aneurysm 200, and reduces blood flow from the vessel 210 into the aneurysm 200. In addition, device 595 illustrated in Fig. 32 further comprises two linking members 436 and 437 that couple flow reducing members 425, 430 to each other and to the distal assembly 400, whereas device 495 illustrated in Fig. 31 comprises one linking member. A linking member can couple, directly or indirectly, itself to another linking member, a flow reducing member, and/or a distal assembly.

[0269] Fig. 33 illustrates a device 695 similar to device 495 shown in Fig. 31, but device 695 illustrated in Fig. 33 has one engagement member 505, whereas device 595 shown in Fig. 32 has three engagement members. As can be seen in Fig. 33, first and second portions of engagement member 505 engage first and second regions of the inner wall of the aneurysm 200, and the first and second portions of the engagement member can be separated by a space of at least 2 mm.

[0270] Fig. 34 illustrates a device 795 that comprises a flow reducing member 425 that comprises a membrane 440, a linking element 435, and a distal assembly 400 that engages an inner surface of an aneurysm in the illustrated, deployed position. The distal assembly is comprised of an engagement member 605 having a helical shape, first and second portions of which engage first and second regions of the inner wall of the aneurysm 200, and the first and second portions of the engagement member can be separated by a space of at least 2 mm.

[0271] Fig. 35 illustrates a device 895 that comprises a flow reducing member 425, positioned in the vessel 210 and comprising a membrane 440. The device 895 also comprises a distal assembly 400, within an aneurysm 200, having four engagement members 405, 407, 410, 415. Linking member 435 couples the flow reducing member 425 to the distal assembly 400. Also illustrated in Figure 35 are some forces that contribute to securing the device 895 in the deployed position within the aneurysm. For example, pull forces (FP) 421, 422, 423, 424 are established by the engagement of engagement members 405, 407, 410, 415 with the inner surfaces of the aneurysm 200. In addition, resistance forces (RF) 426, 427 are established by the interaction between the flow reducing member and blood pressure of the vessel 210. The FPs 421, 422, 423, 424 and the RFs 426, 427 contribute to a secure deployment of the device 895.

[0272] It will be appreciated by persons skilled in the art that certain embodiments of the devices illustrated in Figures 30a-35, and variants of those devices, can be used in combination with knows aneurysm occlusion devices, such as aneurysm coils. In addition, such devices can be useful in the treatment of different types of aneurysms, such as intracranial aneurysms, saccular aneurysms, wide-neck aneurysms, fusiform aneurysms, bifurcation aneurysms, and trifurcation aneurysms.

[0273] It will be also appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the specific embodiments disclosed herein, without departing from the scope or spirit of the disclosure as broadly described. The present embodiments are, therefore, to be considered in all respects illustrative and not restrictive of the invention, which is defined by the claims as presented herein.

What Is Claimed Is:

1. An endovascular device, for treating an aneurysm of a body vessel, comprising:

a distal assembly, movable from a first position to a second position when the distal assembly is at least partially in an aneurysm; and

a first flow-reducing member, coupled to the distal assembly, that reduces blood flow from the body vessel into the aneurysm when the distal assembly is in the second position;

wherein the distal assembly comprises a plurality of engagement members, each of which extends, from a proximal portion to a distal portion, away from the flow-reducing member;

wherein, when the distal assembly is in the first position, each of the plurality of engagement members is substantially parallel to a central axis of the distal assembly;

wherein, when the distal assembly changes from the first to the second position, the distal portion of each of the plurality of engagement members moves away from the central axis, such that the distal portions of each of the plurality of engagement members:

substantially curl;

move closer to the first flow-reducing member; and

engage an inner surface of the aneurysm.

2. The endovascular device of Claim 1, wherein at least one of the plurality of engagement members comprises a polymer selected from the group consisting of ePTFE, polyurethane, polyethylene terephthalate, polyvinylchloride, nylon, polyimide, polyurethane ether, polyurethane ester, polyurethaneurea, polylactide, polyglycolide, poly-orthoester, polyphosphazene, polyanhydride, and polyphosphoester.

3. The endovascular device of Claim 1, wherein at least one of the plurality of engagement members comprises a metal selected from the group consisting of NiTi, tungsten, stainless steel, iridium, and platinum.

4. The endovascular device of Claim 1, wherein a distal end of at least one of the plurality of engagement members is blunt.

5. The endovascular device of Claim 1, wherein, when the distal assembly is in the second position, a distal end of each of the plurality of engagement members engages the inner surface of the aneurysm.

6. The endovascular device of Claim 1, wherein, when the distal assembly is in the second position, the first flow-reducing member resides in the body vessel.

7. The endovascular device of Claim 1, wherein, when the distal assembly is in the second position, the first flow-reducing member resides in the aneurysm.

8. The endovascular device of Claim 1, further comprising a second flow-reducing member, coupled to the first flow-reducing member or to the distal assembly, that reduces blood flow from the body vessel into the aneurysm when the distal assembly is in the second position.

9. The endovascular device of Claim 8, wherein, when the distal assembly is in the second position, the first flow-reducing member resides in the body vessel and the second flow-reducing member resides in the aneurysm.

10. The endovascular device of Claim 8, further comprising a linking member that couples the second flow-reducing member to the first flow-reducing member or to the distal assembly.

11. The endovascular device of Claim 10, wherein at least one of the linking member, the distal assembly, the first flow-reducing member, and the second flow-reducing member comprises at least one metal selected from the group consisting of NiTi, tungsten, stainless steel, iridium, and platinum.

12. The endovascular device of Claim 10, wherein the linking member comprises a wire.

13. The endovascular device of Claim 10, wherein each of the linking member, the first flow-reducing member, the second flow-reducing member, and the distal assembly comprises a metal, and wherein a weld couples the linking member to at least one of the distal assembly, the first flow-reducing member, and the second flow-reducing member.

14. The endovascular device of Claim 10, wherein the second flow-reducing member comprises a plug, and wherein, when the distal assembly is in the second position, the plug substantially resides within a neck of the aneurysm and substantially inhibits blood flow through the neck of the aneurysm.

15. The endovascular device of Claim 14, wherein the plug comprises a balloon.

16. The endovascular device of Claim 8, wherein the first flow-reducing member comprises a membrane.

17. The endovascular device of Claim 16, wherein, when the distal assembly is in the second position, a thickness of the membrane is between about 5 μm and about 500 μm.

18. The endovascular device of Claim 16, wherein the membrane comprises at least one polymer selected from the group consisting of ePTFE, polyurethane, polyethylene terephthalate, polyvinylchloride, nylon, polyimide, silicone, polyurethane ether, polyurethane ester, polyurethaneura, polylactide, polyglycolide, poly-orthoester, polyphosphazene, polyanhydride, and polyphosphoester.

19. The endovascular device of claim 16, wher ein the first flow-reducing member is coupled to the distal assembly by suture or interweaving.

20. The endovascular device of Claim 16, wherein at least a portion of the membrane is non-porous.

21. The endovascular device of Claim 16, wherein the membrane comprises a porous section having a porosity over a length extending from a proximal end of the porous section to a distal end of the porous section;

wherein a pore spacing and a pore size of the porous section determine the porosity of the porous section;

wherein, when the distal assembly is in the second position, the membrane is effective to reduce blood flow into the aneurysm and to promote thrombosis at or in the aneurysm.

22. The endovascular device of Claim 21, wherein the porosity is selected such that, when the distal assembly is in the second position, the porous section of the

membrane is effective to enhance endothelial cell migration and tissue growth onto the membrane and to substantially inhibit blood flow from the body vessel into the aneurysm.

23. The endovascular device of Claim 21, wherein the pore size is between about 1 μm and about 150 μm.

24. The endovascular device of Claim 21, wherein the pore size is between about 10 μm and about 50 μm.

25. The endovascular device of Claim 21, wherein the pore spacing is between about 40 μm and about 100 μm.

26. The endovascular device of Claim 21, wherein the pore spacing is between about 60 μm and about 75 μm.

27. The endovascular device of Claim 21, wherein a material ratio of the porous section of the membrane comprises a ratio of a total area of an outer surface of the porous section of the membrane that comprises material to a total area of an outer surface of the porous section that comprises pores.

28. The endovascular device of Claim 27, wherein, when the distal assembly is in the second position, the material ratio is between about 25% and about 90%.

29. The endovascular device of Claim 16, further comprising at least one agent, permanently attached to the membrane, that, when the distal assembly is in the second position, promotes healing of the aneurysm.

30. The endovascular device of Claim 29, wherein the healing agent comprises at least one of a peptide, a protein, an enzyme regulator, an antibody, a naturally occurring molecule, a synthetic molecule, a nucleic acid, a polynucleotide, L-PDMP, and D-PDMP.

31. An endovascular device, for treating an aneurysm of a body vessel, comprising:

means for engaging an inner surface of an aneurysm, the means for engaging being movable from a first position to a second position when the means for engaging is at least partially within an aneurysm; and

first means for reducing blood flow into the aneurysm, the means for reducing blood flow being coupled to the means for engaging, such that when the means for engaging is in the second position, the first means for reducing blood flow is effective to reduce blood flow from the body vessel into the aneurysm;

wherein the means for engaging comprises a plurality of engagement members, each of which extends, from a proximal portion to a distal portion, away from the first means for reducing blood flow;

wherein, when the means for engaging is in the first position, each of the plurality of engagement members is substantially parallel to a central axis of the distal assembly;

wherein, when the means for engaging changes from the first to the second position, the distal portion of each of the plurality of engagement members moves away from the central axis, such that the distal portions of each of the plurality of engagement members:

substantially curl;

move closer to the first flow-reducing member; and

engage an inner surface of the aneurysm.

32. The endovascular device of claim 31, further comprising second means for reducing blood flow into the aneurysm, coupled to the first means for reducing blood flow and effective to reduce blood flow into the aneurysm when the means for engaging is in the second position.

33. The endovascular device of Claim 32, wherein, when the means for engaging is in the second position, the first flow-reducing means resides in the body vessel and the second flow-reducing means resides in the aneurysm.

34. A method of treating an aneurysm of a body vessel comprising:

providing an endovascular device comprising:

a distal assembly, movable from a first position to a second position when the distal assembly is at least partially within an aneurysm, the distal assembly comprising a plurality of engagement members, each of which extends, from a proximal portion to a distal portion, away from the flow-reducing member and each of which, when the distal assembly is in the first position, is substantially parallel to a central axis of the distal assembly; and a first flow-reducing member, coupled to the distal assembly, that reduces blood flow from the body vessel into the aneurysm when the distal assembly is in the second position;

positioning the distal assembly at least partially within the aneurysm; and

changing the distal assembly from the first position to the second position such that the distal portion of each of the plurality of engagement members moves away from the central axis, whereby the distal portions of each of the plurality of engagement members:

substantially curl;

move closer to the first flow-reducing member; and

engage an inner surface of the aneurysm.

35. The method of Claim 34, wherein at least one of the plurality of engagement members comprises a polymer selected from the group consisting of ePTFE polyurethane, polyethylene terephthalate, polyvinylchloride, nylon, polyimide, polyurethane ether, polyurethane ester, polyurethaneurea, polylactide, polyglycolide, poly-orthoester, polyphosphazene, polyanhydride, and polyphosphoester.

36. The method of Claim 34, wherein at least one of the plurality of engagement members comprises at least one metal selected from the group consisting of NiTi, tungsten, stainless steel, iridium, and platinum.

37. The method of Claim 34, wherein a distal end of at least one of the plurality of engagement members is blunt.

38. The method of Claim 34, wherein, when the distal assembly is in the second position, a distal end of each of the plurality engagement members engages the inner surface of the aneurysm.

39. The method of Claim 34, wherein, when the distal assembly is in the second position, the first flow-reducing member resides in the body vessel.

40. The method of Claim 34, wherein, when the distal assembly is in the second position, the first flow-reducing member resides in the aneurysm.

41. The method of Claim 34, wherein the endovascular device further comprises a second flow-reducing member, coupled to the first flow-reducing member or

to the distal assembly, that reduces blood flow from the body vessel into the aneurysm when the distal assembly is in the second position; and further comprising:

positioning the second flow-reducing member at least partially in the aneurysm.

42. The method of Claim 41, wherein, when the distal assembly is in the second position, the first flow-reducing member resides in the body vessel and the second flow-reducing member resides in the aneurysm.

43. The method of Claim 41, wherein the endovascular device further comprises a linking member that couples the second flow-reducing member to the first flow-reducing member or to the distal assembly.

44. The method of Claim 43, wherein the second flow-reducing member comprises a plug, and wherein, when the distal assembly is in the second position, the plug substantially resides within a neck of the aneurysm and substantially inhibits blood flow through the neck of the aneurysm.

45. The method of Claim 34, wherein the first flow-reducing member comprises a membrane.

46. An endovascular device, for treating an aneurysm of a body vessel, comprising:

a distal assembly, comprising an engagement member, the distal assembly being movable from a first position to a second position when the distal assembly is at least partially in the aneurysm;

a flow-reducing assembly, coupled to the distal assembly and comprising a first flow-reducing member, the flow-reducing assembly reducing blood flow from the body vessel into the aneurysm when the distal assembly is in the second position;

wherein the engagement member is elongate and curvilinear and extends, from a proximal to a distal end of the engagement member, along a path that originates from a point at the flow-reducing assembly and terminates at a point within the aneurysm when the first flow-reducing member resides in the body vessel;

wherein the engagement member is coterminous with the path;

wherein, when the distal assembly is in the second position in the aneurysm, the first flow-reducing member resides in the body vessel, a first portion of the engagement member engages a first region of an inner surface of the aneurysm, and a second portion of the engagement member engages a second region of the inner surface of the aneurysm;

wherein the first and second regions are spaced at least 2 mm apart.

47. The endovascular device of Claim 46, wherein the flow-reducing assembly further comprises a second flow-reducing member;

wherein, when the second flow-reducing member resides at least partially in the aneurysm, and the distal assembly is in the second position, the first flow-reducing member resides in the body vessel.

48. The endovascular device of Claim 46, wherein a form of at least a portion of the engagement member is helical.

49. The endovascular device of Claim 46, wherein the first and the second portions of the engagement member are spaced at least 2 mm apart.

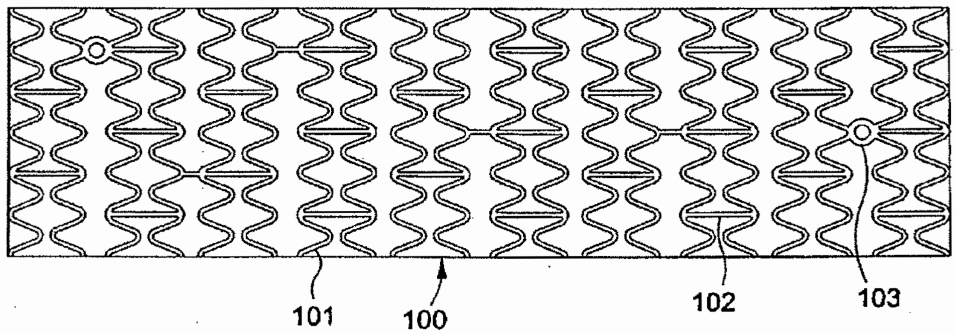


FIG. 1A

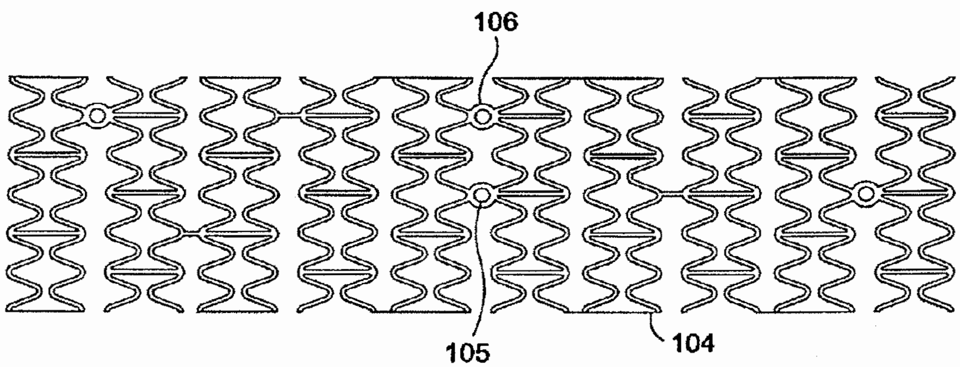


FIG. 1B

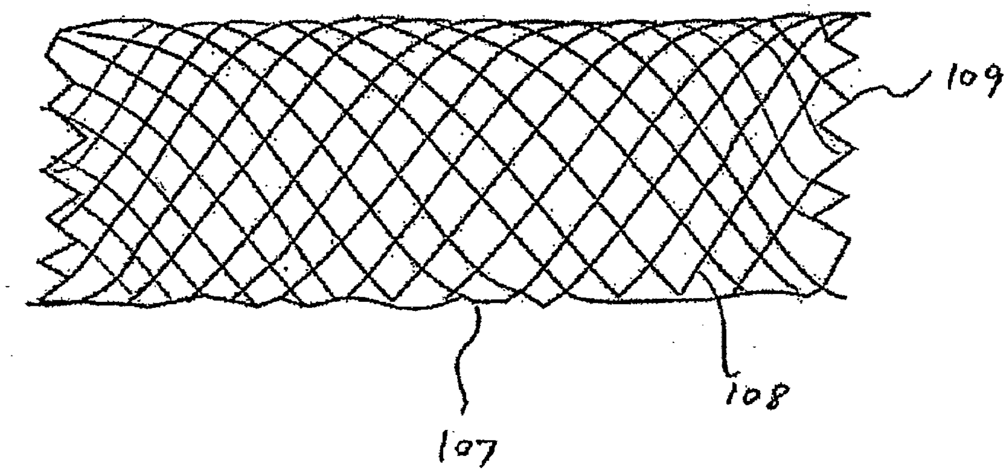


FIGURE 2

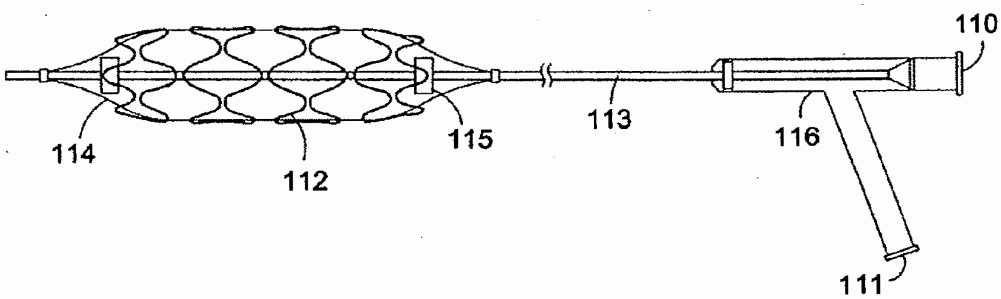


FIG. 3

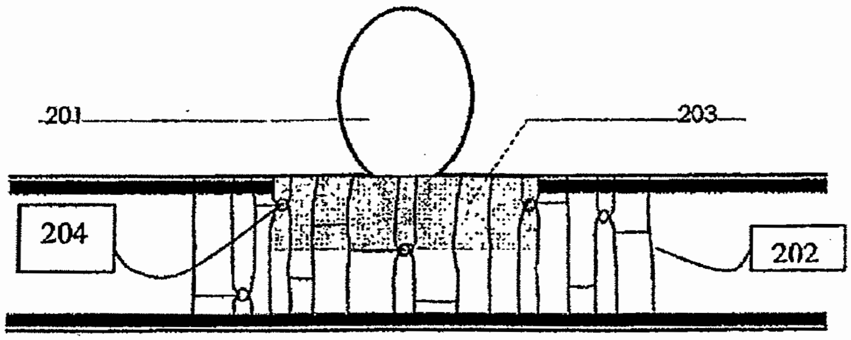


FIGURE 4A

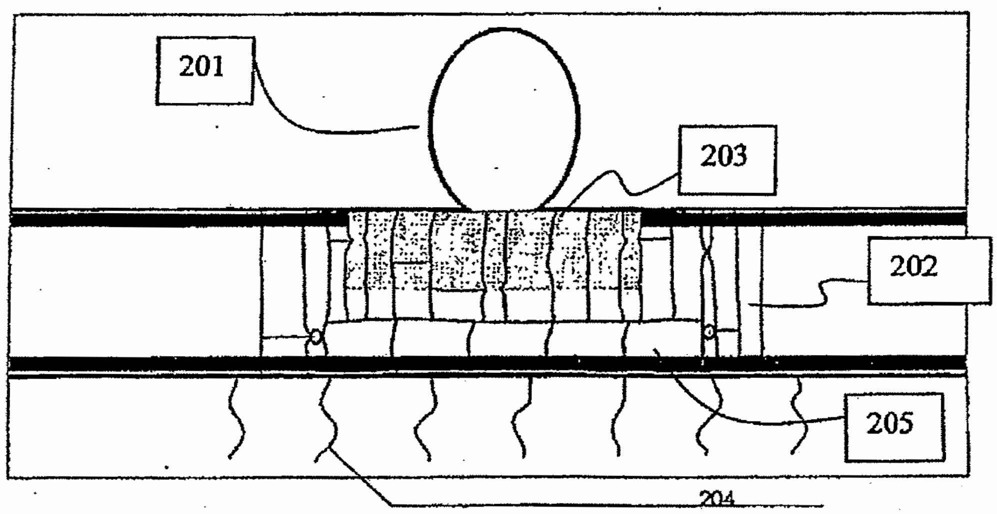


FIGURE 4B

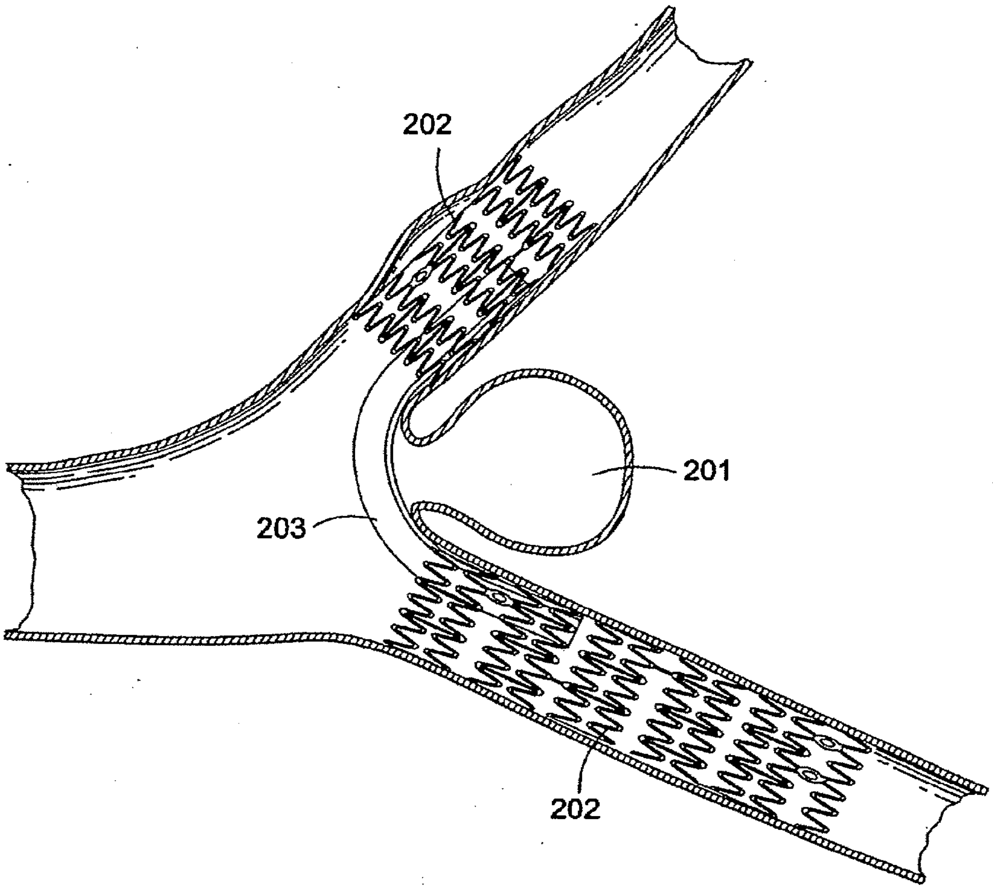


FIG. 5

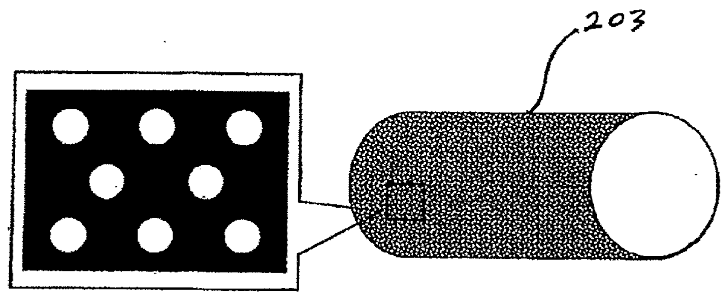


FIGURE 6

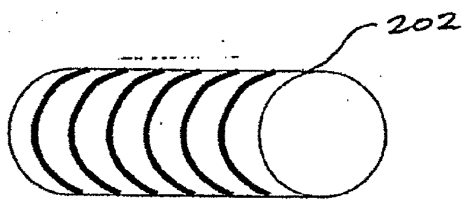


FIGURE 7

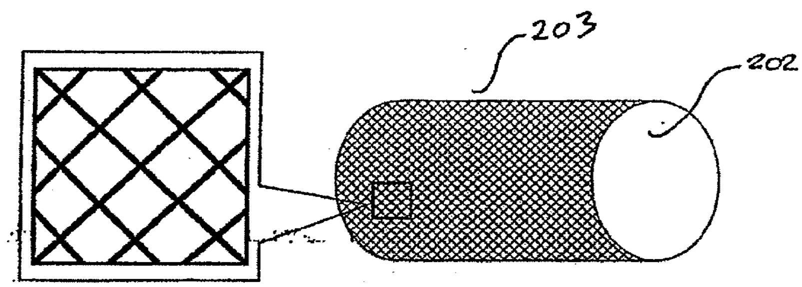


FIGURE 8

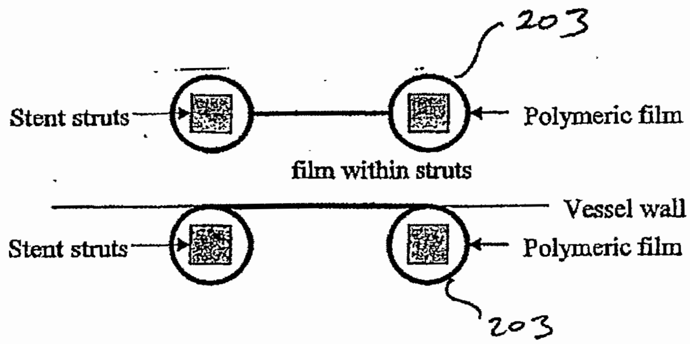


FIGURE 9

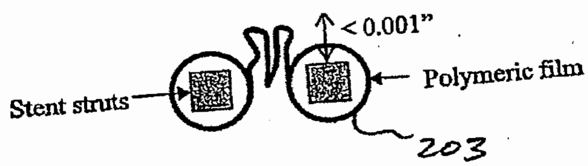


FIGURE 10

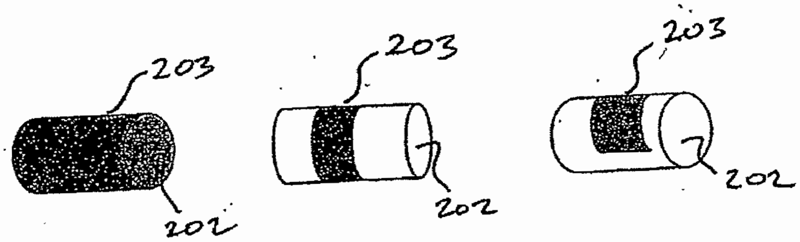


FIGURE 13

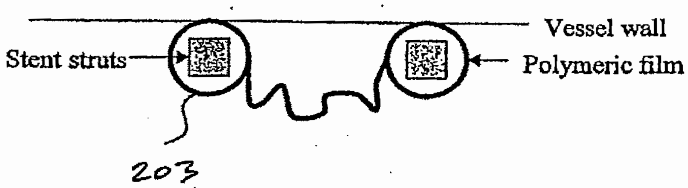


FIGURE 11

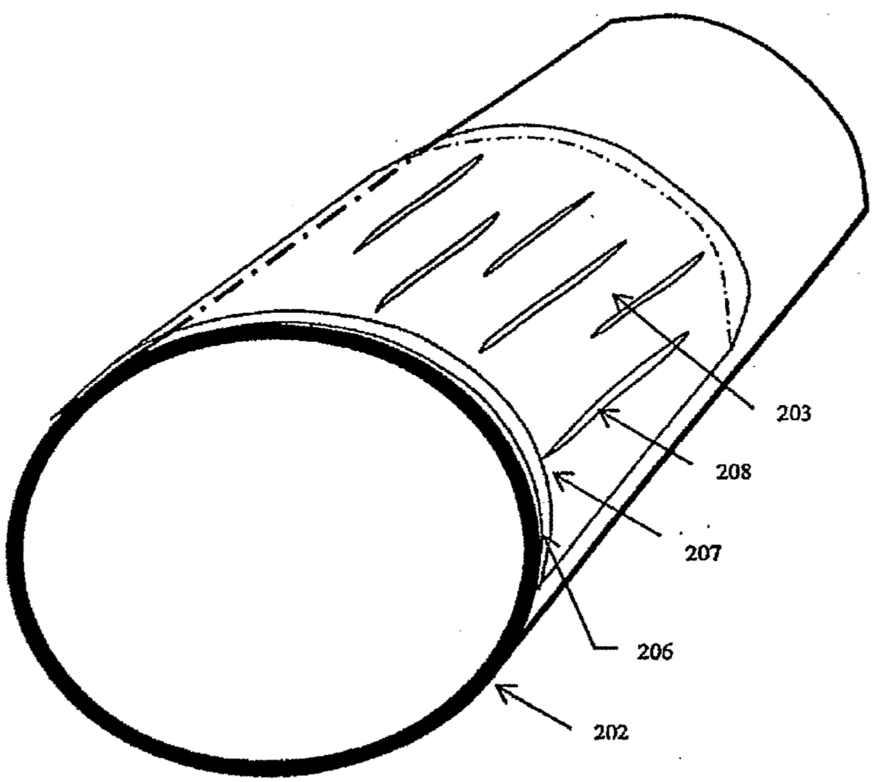


FIGURE 12

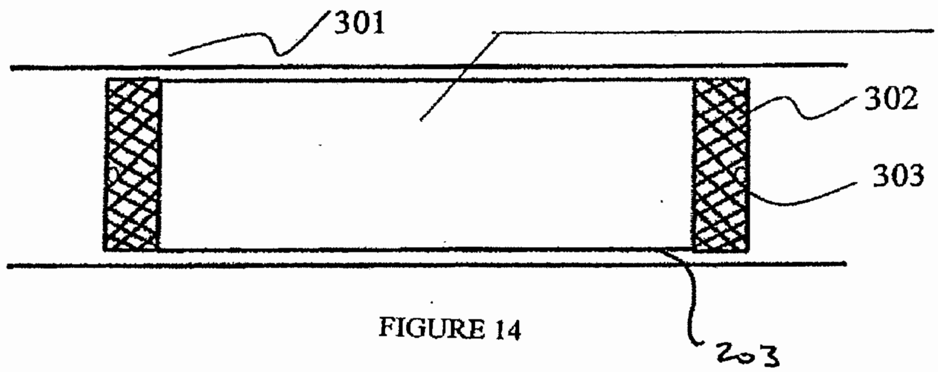


FIGURE 14

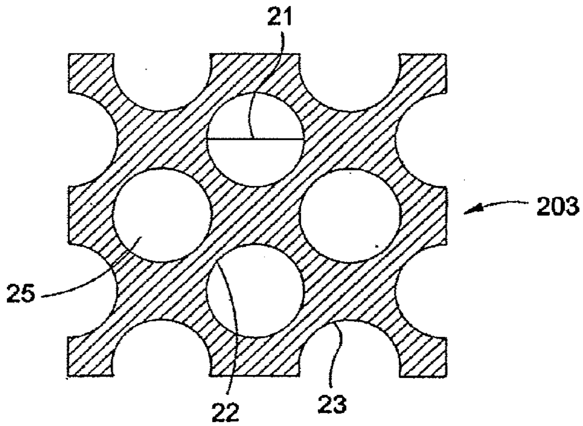


FIG. 15

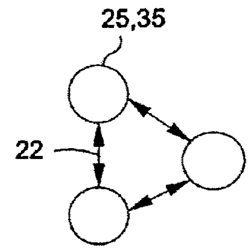


FIG. 16

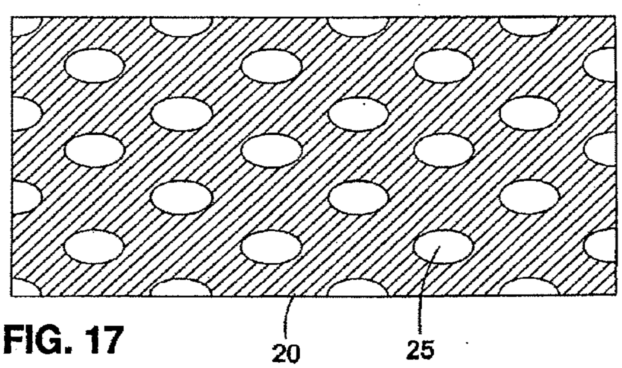


FIG. 17

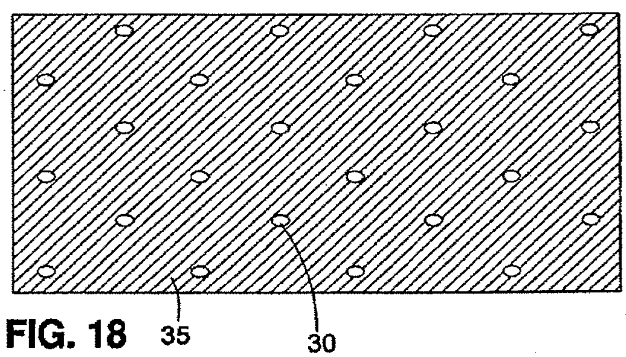


FIG. 18

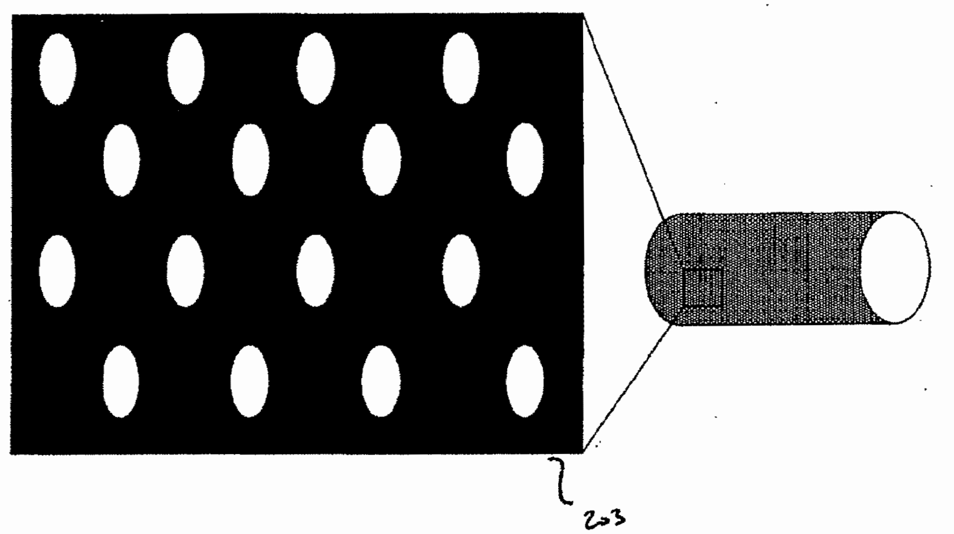


FIGURE 19B

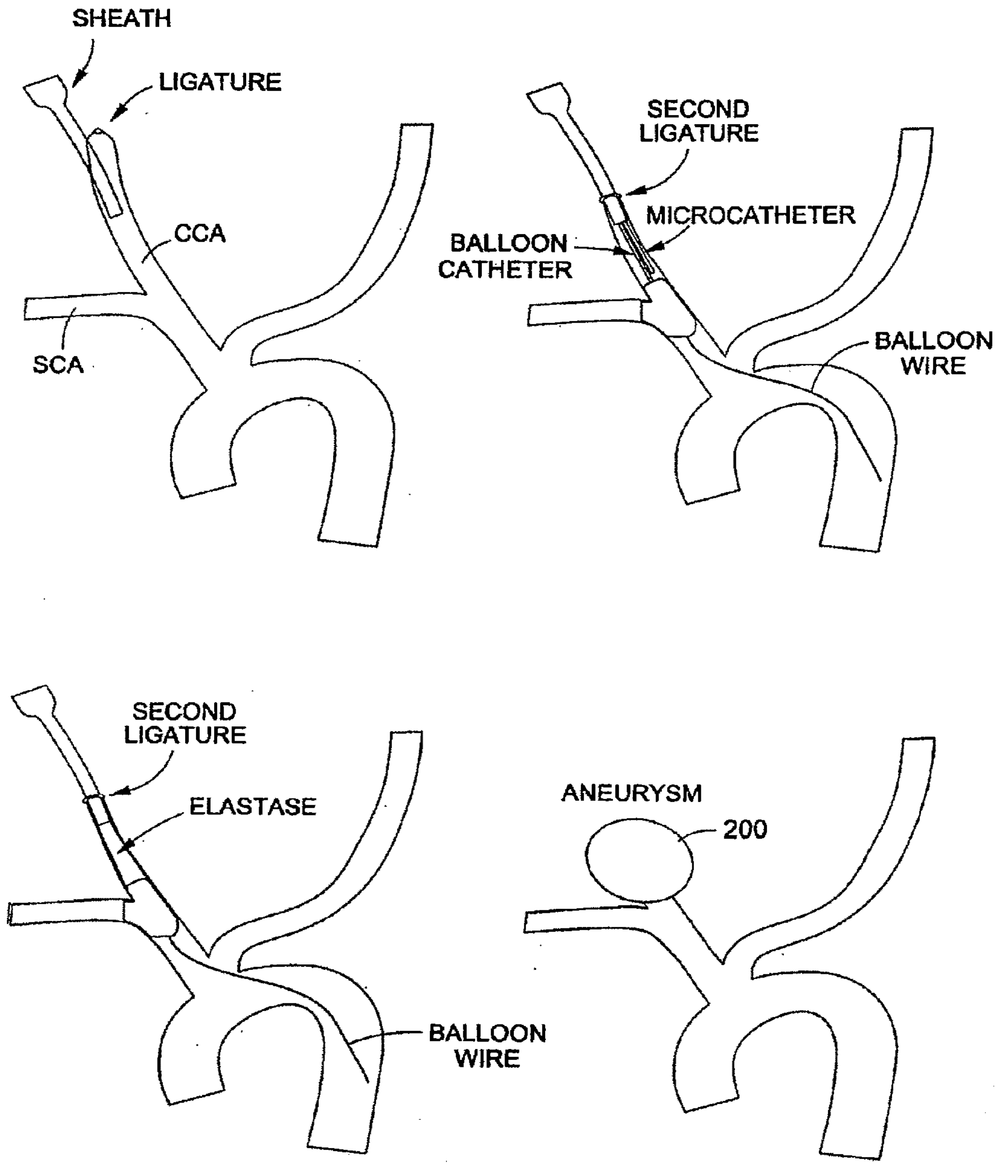

SHEATH
LIGATURE
CCA
SCA
SECOND LIGATURE
MICROCATHETER
BALLOON CATHETER
BALLOON WIRE
SECOND LIGATURE
ELASTASE
BALLOON WIRE
ANEURYSM
200

FIG. 20

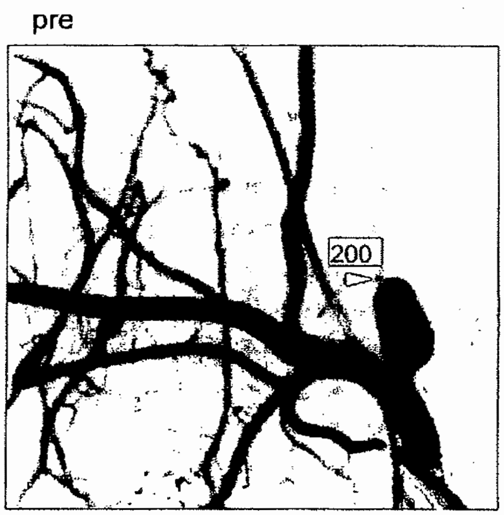


FIG. 21A

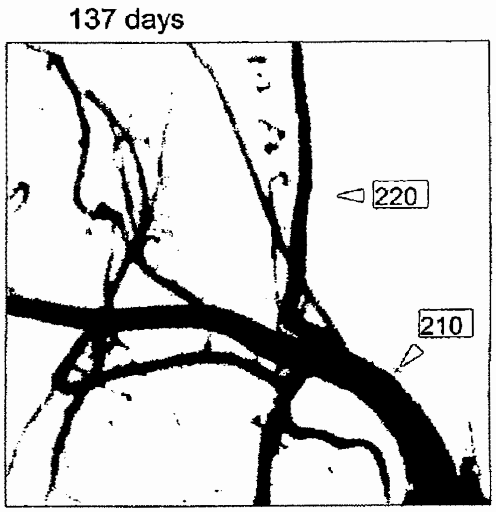


FIG. 21B

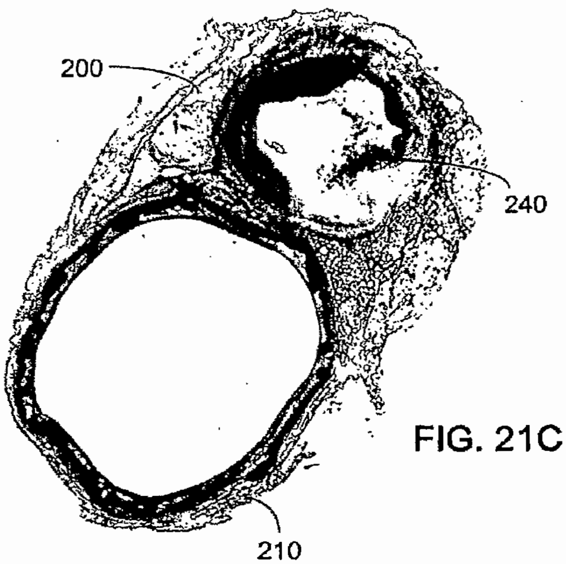


FIG. 21C

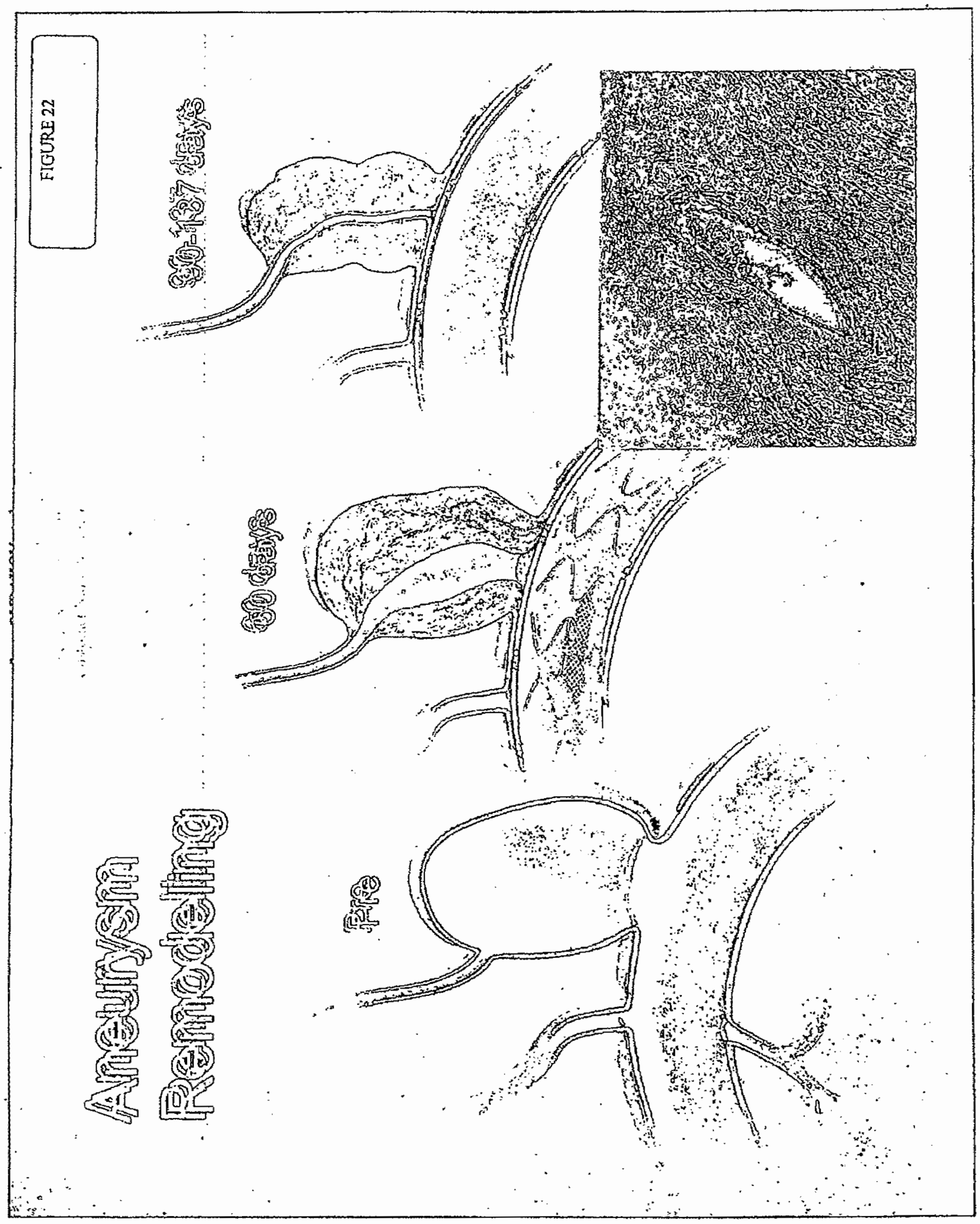


FIGURE 22

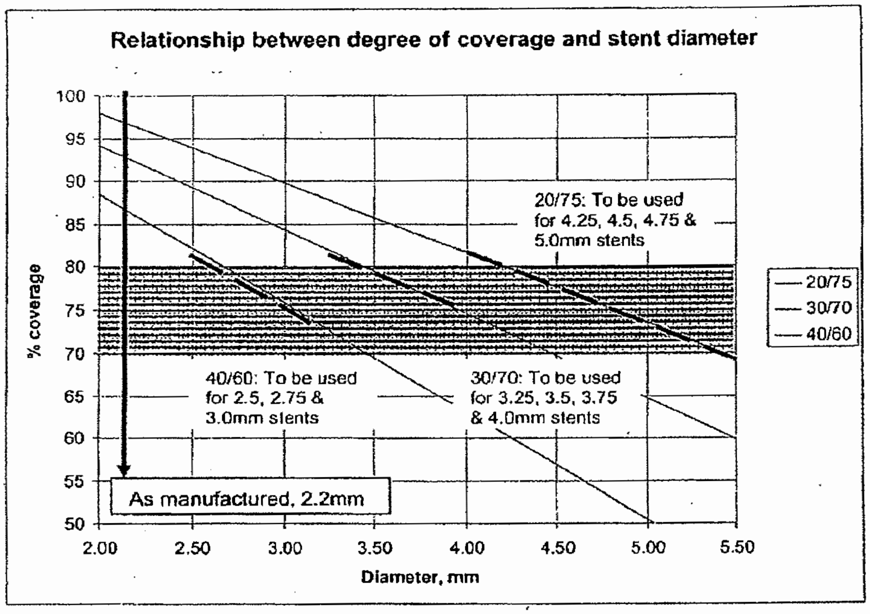


FIGURE 23

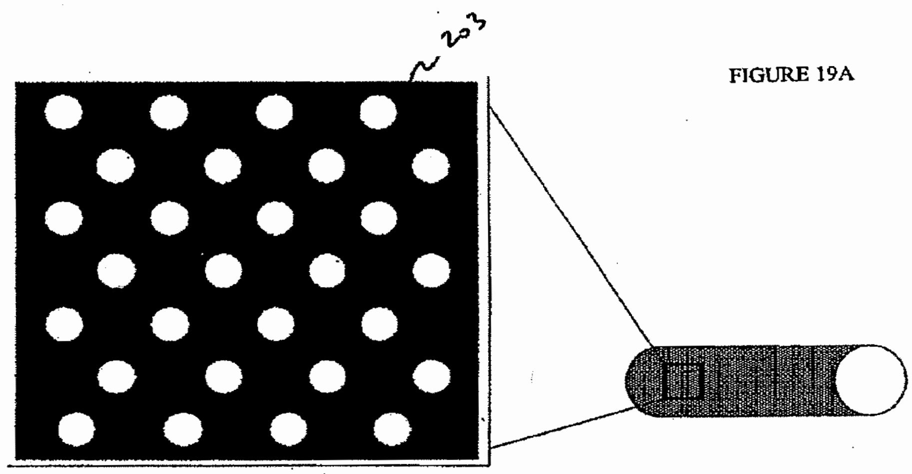


FIGURE 19A

FIGURE 24A

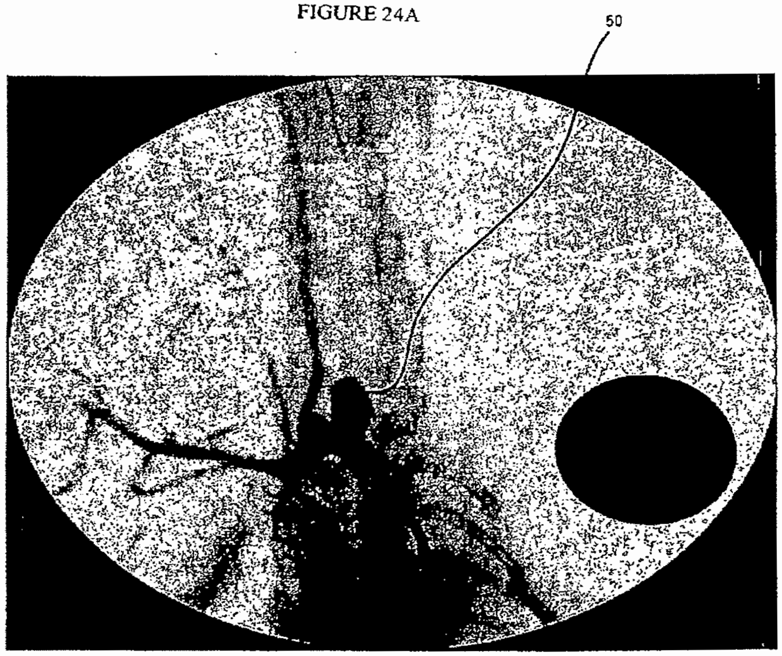


FIGURE 24B

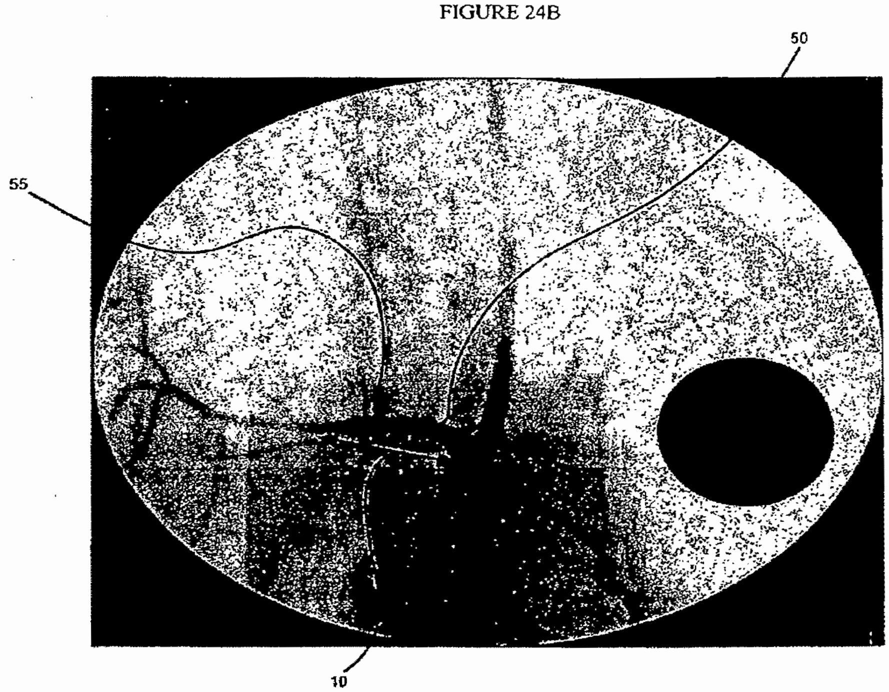


FIGURE 25A

FIGURE 25B

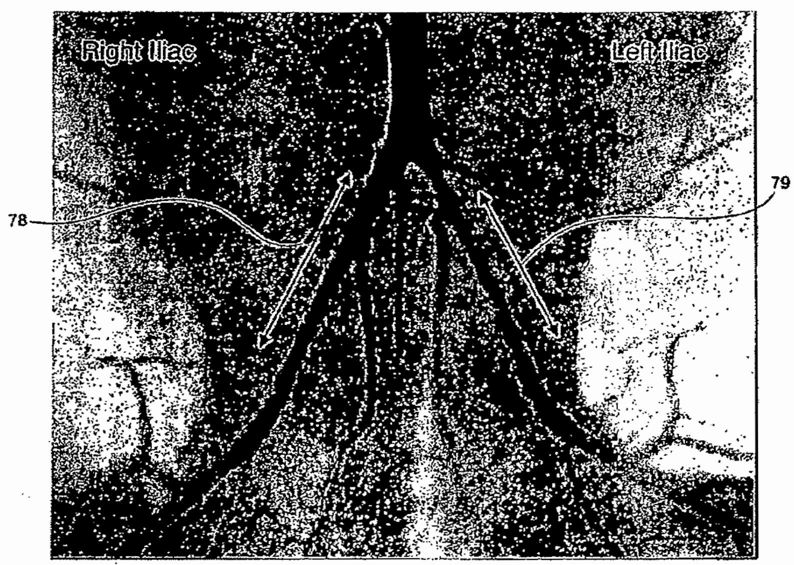


FIGURE 26

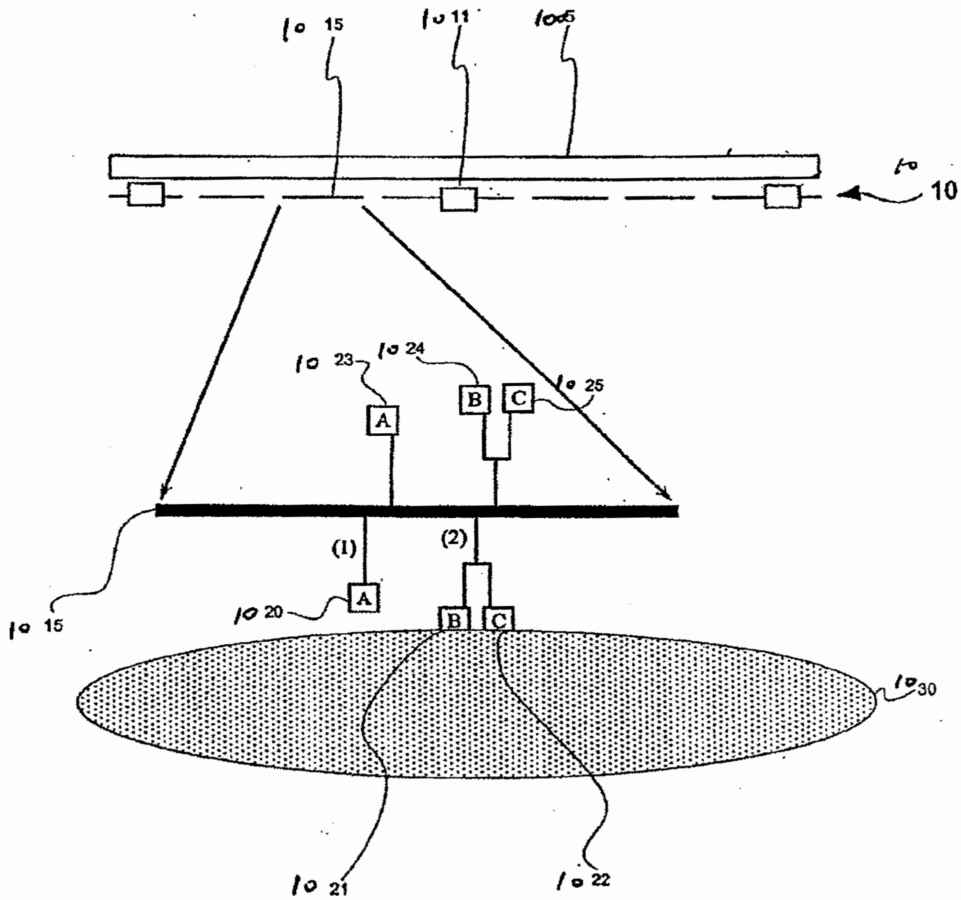

1015
1011
1005
10
1023
1024
1025
A
B
C
(1)
(2)
A
B
C
1020
1015
1030
1021
1022

FIGURE 27

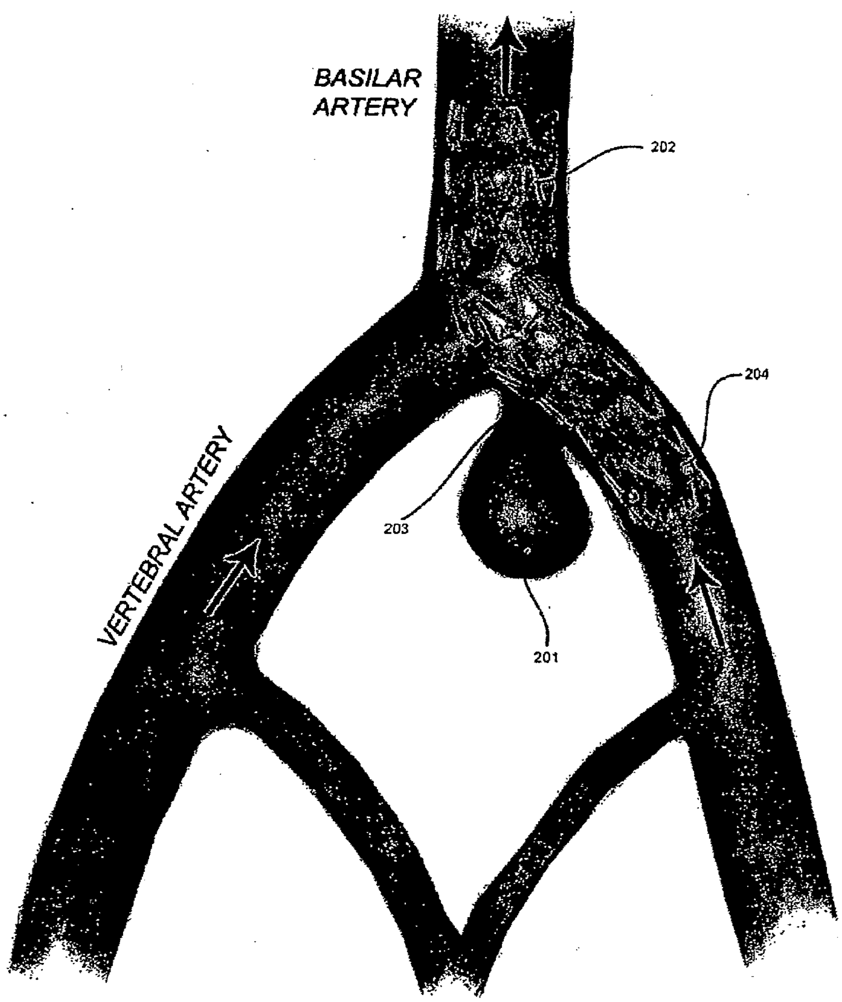


FIGURE 28

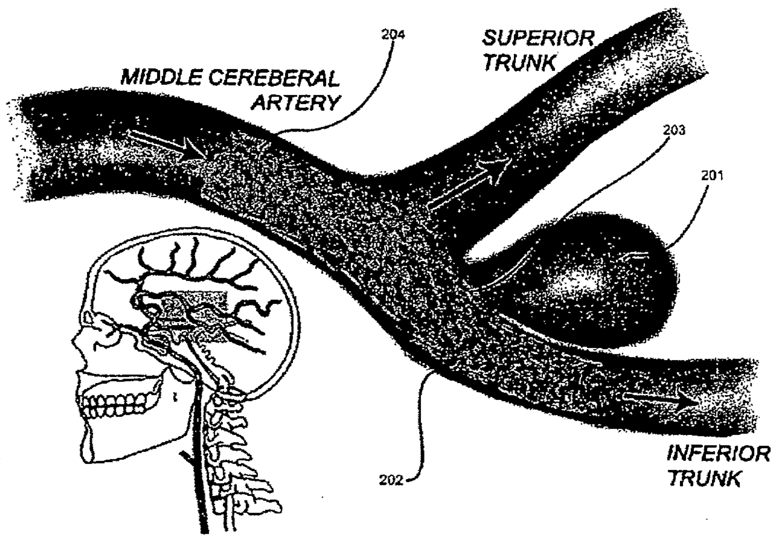
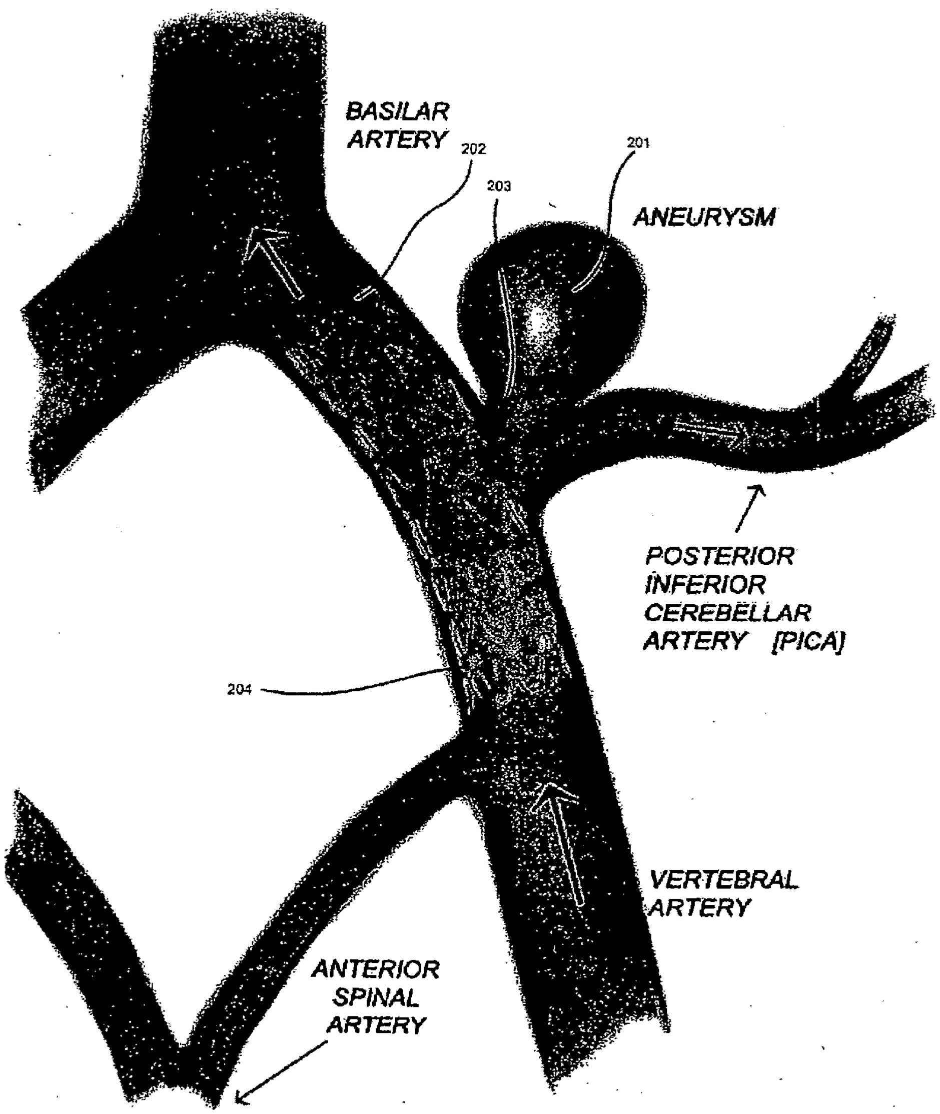

204
SUPERIOR TRUNK
MIDDLE CEREBERAL ARTERY
203
201
202
INFERIOR TRUNK

FIGURE 29


BASILAR
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201
203
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CEREBELLAR
ARTERY [PICA]
204
VERTEBRAL
ARTERY
ANTERIOR
SPINAL
ARTERY

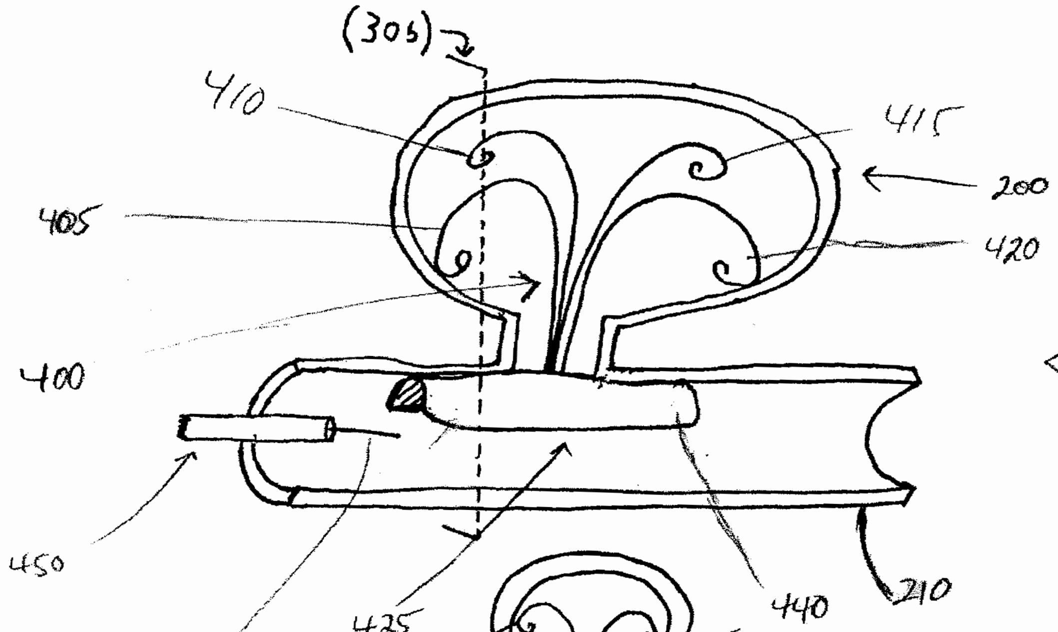


Fig. 30a

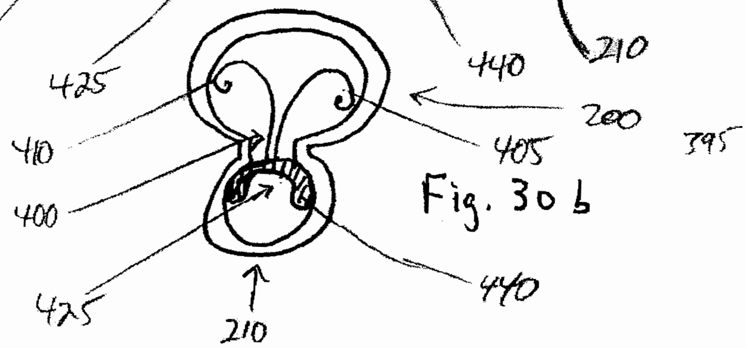


Fig. 30b

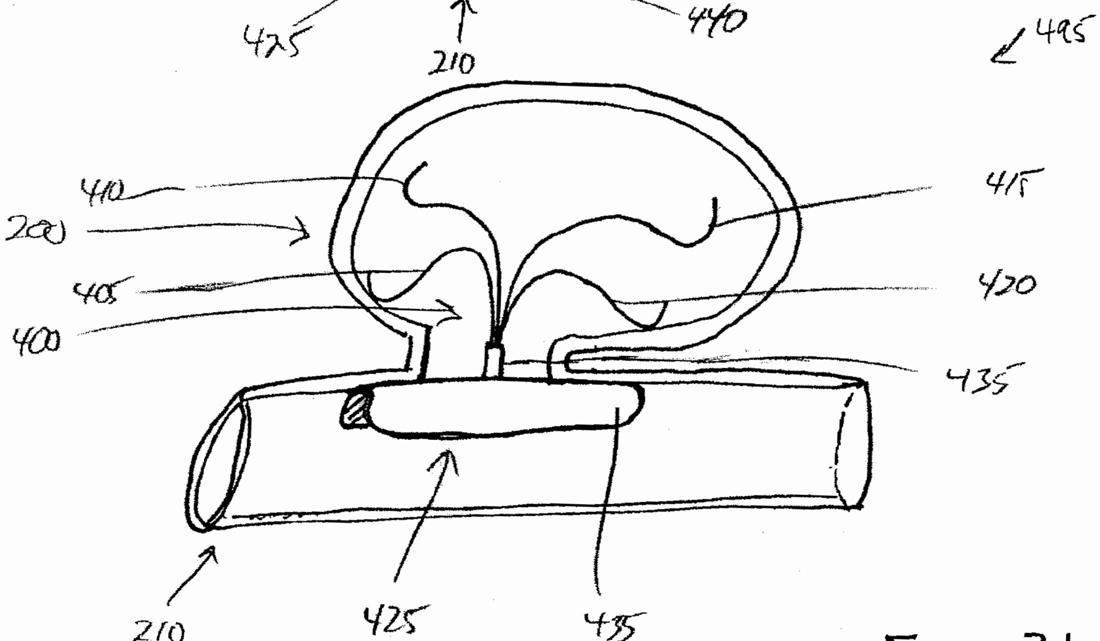


Fig. 31

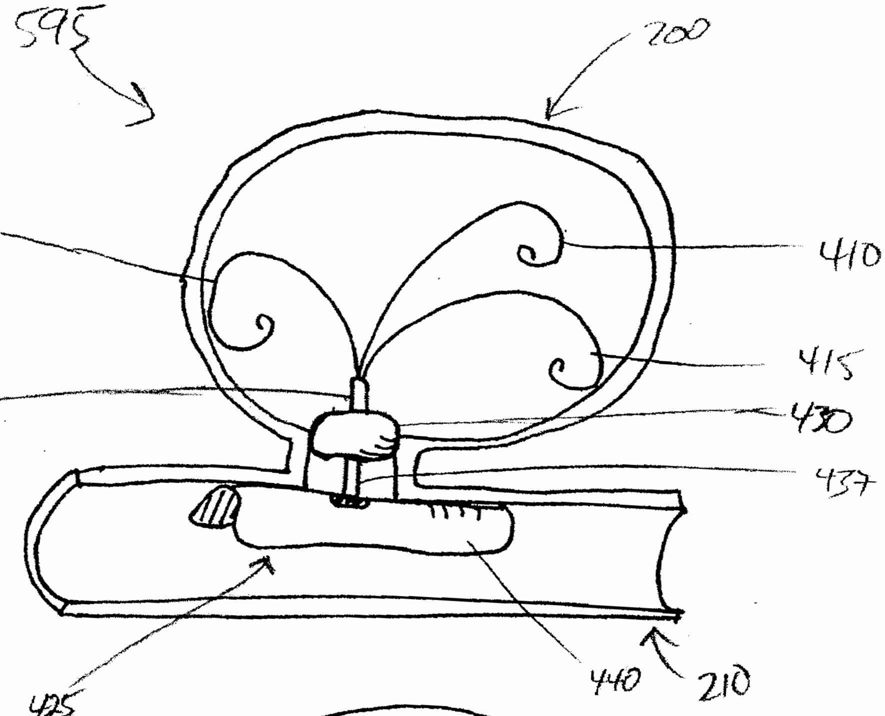
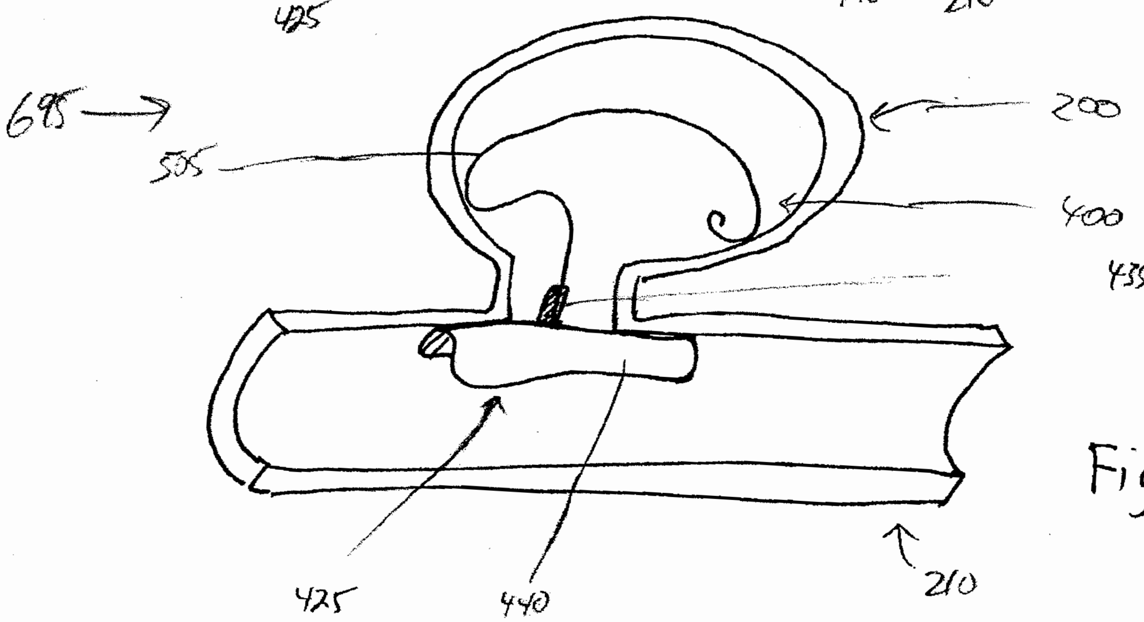

595
200
405
410
415
436
430
437
440
425
210

Fig. 32


695
200
505
400
435
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440
210

Fig. 33

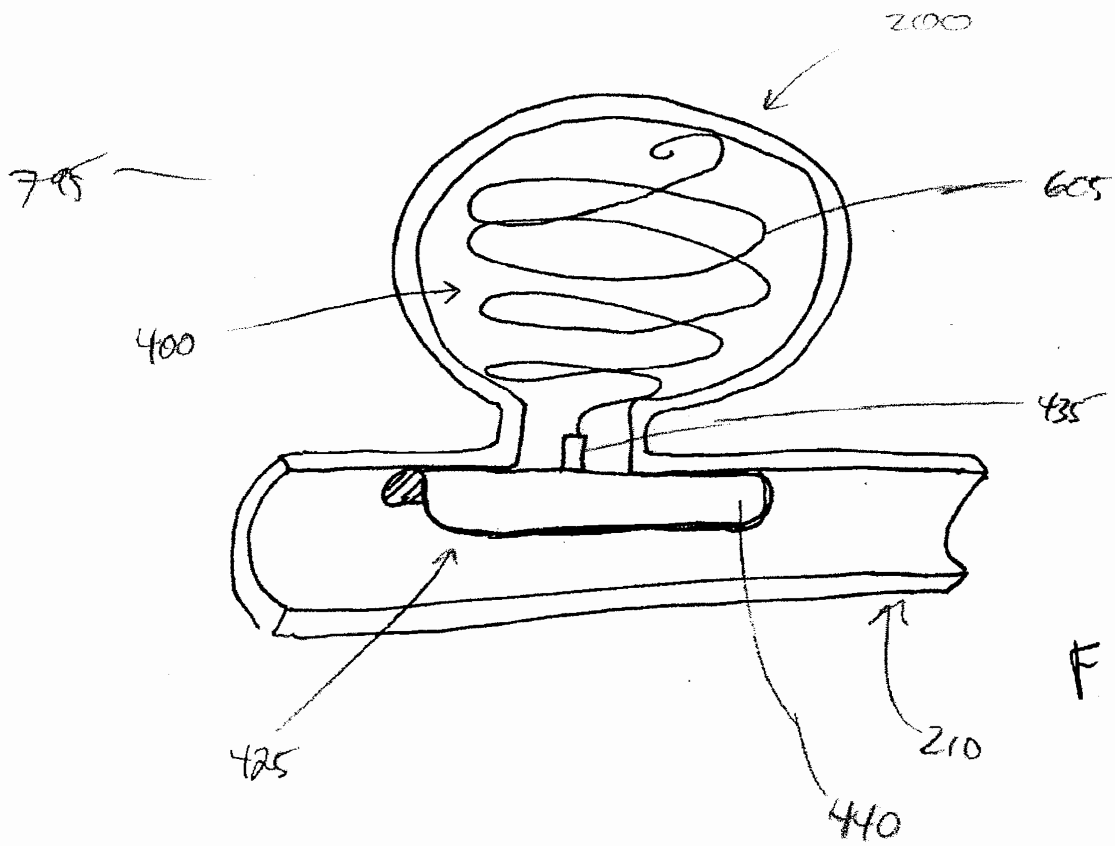

Fig. 34

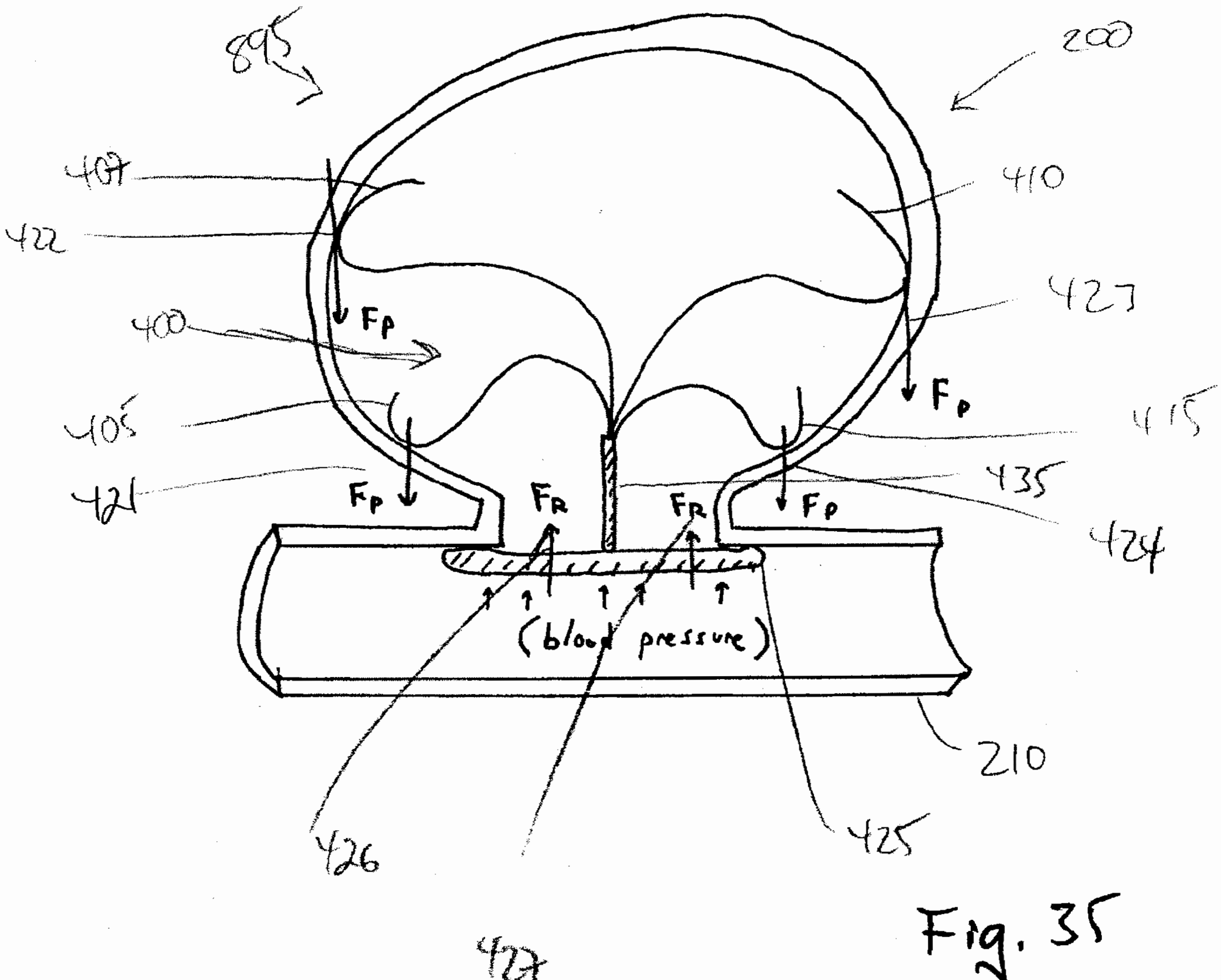
895
200
407
410
422
427
Fp
400
Fp
405
415
421
Fp
FR
FR
435
Fp
424
(blood pressure)
210
426
425
427

Fig. 35

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/75504

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61F 2/06 (2008.04)
USPC - 623/1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC 623/1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
All USPC; USPC 623/1, 623/1.36, 623/1.42, 623/1.46; IPC A61F 2/06

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); Google: @PD<20080509; aneurysm; engage; anchor; NiTi$; tungsten; stainless steel; iridium; platinum; graft; stent; pore size; pore spacing; non-porous; ePTFE; polyurethane; polyethylene terephthalate; polyvinylchloride; nylon; polyimide; polyurethane ether; polyurethane ester; etc.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007/0083258 A1 (Falotico, et. al.) 12 April 2007 (12.04.2007); para [0194], [0315]-[0320], [0364], [0368]-[0369], [0391], [0397]-[0399], [0404]-[0412], [0415]; Fig 27-29, 35-36	1-49
Y	US 2007/0038288 A1 (Lye, et. al.) 15 February 2007 (15.02.2007); Abstract; para [0012], [0027], [0053]; [0072]; Fig 3A, 4A, 5A, 6C, 13, 14	1-49
Y	US 2004/0186562 A1 (Cox) 23 September 2004 (23.09.2004); Abstract; para [0080]-[0081]; Fig 13-15, 22, 23	14, 15, 44, 48
Y	US 5,866,217 A (Stenoien, et. al.) 2 February 1999 (02.02.1999); Abstract; col 3, ln 15-40	21-28

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- "&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 November 2008 (03.11.2008)	13 NOV 2008

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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A61F 2/24 (2006.01) *A61M 39/22* (2006.01)
A61F 2/82 (2006.01) *A61M 29/00* (2006.01)

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61/139,398 19 December 2008 (19.12.2008) US
12/635,471 10 December 2009 (10.12.2009) US

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(72) Inventors; and
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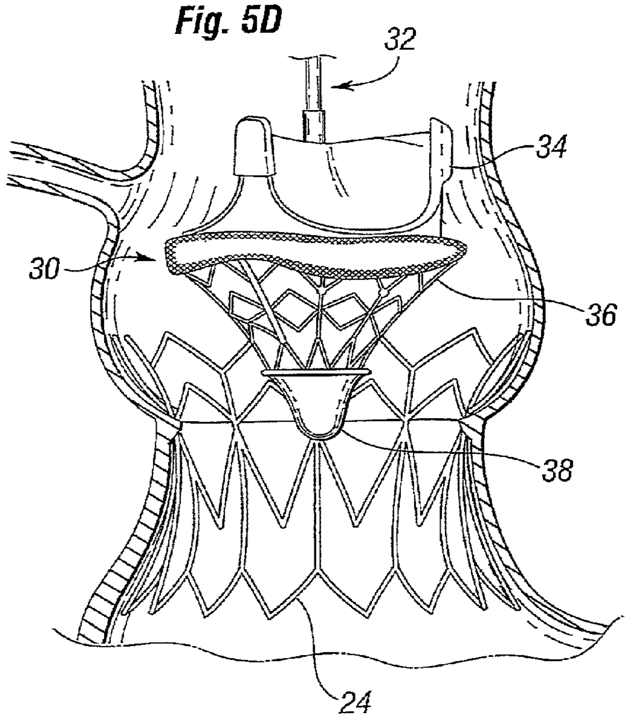
[Continued on next page]

(54) Title: QUIK-CONNECT PROSTHETIC HEART VALVE AND METHODS

Fig. 5D



(57) Abstract: A heart valve prosthesis that can be quickly and easily implanted during a surgical procedure is provided. The prosthetic valve has a base stent that is deployed at a treatment site, and a valve component configured to quickly connect to the base stent. The base stent may take the form of a self- or balloon-expandable stent that expands outward against the native valve with or without leaflet excision. The valve component has a non-expandable prosthetic valve and a self- or balloon-expandable coupling stent for attachment to the base stent, thereby fixing the position of the valve component relative to the base stent. The prosthetic valve may be a commercially available to valve with a sewing ring and the coupling stent attaches to the sewing ring. The system is particularly suited for rapid deployment of heart valves in a conventional open-heart surgical environment. A catheter-based system and method for deployment is provided.

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QUICK-CONNECT PROSTHETIC HEART VALVE AND METHODS

Field of the Invention

[0001] The present application claims priority under 35 U.S.C. §119(e) to U.S. provisional application number 61/139,398 filed December 19, 2008.

[0002] The present invention generally relates to prosthetic valves for implantation in body channels. More particularly, the present invention relates to prosthetic heart valves configured to be surgically implanted in less time than current valves.

Background of the Invention

[0003] In vertebrate animals, the heart is a hollow muscular organ having four pumping chambers as seen in Figure 1: the left and right atria and the left and right ventricles, each provided with its own one-way valve. The natural heart valves are identified as the aortic, mitral (or bicuspid), tricuspid and pulmonary, and are each mounted in an annulus comprising dense fibrous rings attached either directly or indirectly to the atrial and ventricular muscle fibers. Each annulus defines a flow orifice.

[0004] The atria are the blood-receiving chambers, which pump blood into the ventricles. The ventricles are the blood-discharging chambers. A wall composed of fibrous and muscular parts, called the interatrial septum separates the right and left atria (see Figures 2 to 4). The fibrous interatrial septum is a materially stronger tissue structure compared to the more friable muscle tissue of the heart. An anatomic landmark on the interatrial septum is an oval, thumbprint sized depression called the oval fossa, or fossa ovalis (shown in Figure 4).

[0005] The synchronous pumping actions of the left and right sides of the heart constitute the cardiac cycle. The cycle begins with a period of ventricular relaxation, called ventricular diastole. The cycle ends with a period of ventricular contraction, called ventricular systole. The four valves (see

Figures 2 and 3) ensure that blood does not flow in the wrong direction during the cardiac cycle; that is, to ensure that the blood does not back flow from the ventricles into the corresponding atria, or back flow from the arteries into the corresponding ventricles. The mitral valve is between the left atrium and the left ventricle, the tricuspid valve between the right atrium and the right ventricle, the pulmonary valve is at the opening of the pulmonary artery, and the aortic valve is at the opening of the aorta.

[0006] Figures 2 and 3 show the anterior (A) portion of the mitral valve annulus abutting the non-coronary leaflet of the aortic valve. The mitral valve annulus is in the vicinity of the circumflex branch of the left coronary artery, and the posterior (P) side is near the coronary sinus and its tributaries.

[0007] The mitral and tricuspid valves are defined by fibrous rings of collagen, each called an annulus, which forms a part of the fibrous skeleton of the heart. The annulus provides peripheral attachments for the two cusps or leaflets of the mitral valve (called the anterior and posterior cusps) and the three cusps or leaflets of the tricuspid valve. The free edges of the leaflets connect to chordae tendineae from more than one papillary muscle, as seen in Figure 1. In a healthy heart, these muscles and their tendinous chords support the mitral and tricuspid valves, allowing the leaflets to resist the high pressure developed during contractions (pumping) of the left and right ventricles.

[0008] When the left ventricle contracts after filling with blood from the left atrium, the walls of the ventricle move inward and release some of the tension from the papillary muscle and chords. The blood pushed up against the under-surface of the mitral leaflets causes them to rise toward the annulus plane of the mitral valve. As they progress toward the annulus, the leading edges of the anterior and posterior leaflet come together forming a seal and closing the valve. In the healthy heart, leaflet coaptation occurs near the plane of the mitral annulus. The blood continues to be pressurized in the left ventricle until it is ejected into the aorta. Contraction of the papillary muscles is simultaneous with the contraction of the ventricle and serves to keep healthy valve leaflets tightly shut at peak contraction pressures exerted by the ventricle.

[0009] Various surgical techniques may be used to repair a diseased or damaged valve. In a valve replacement operation, the damaged leaflets are excised and the annulus sculpted to receive a replacement valve. Due to aortic stenosis and other heart valve diseases, thousands of patients undergo surgery each year wherein the defective native heart valve is replaced by a prosthetic valve, either bioprosthetic or mechanical. Another less drastic method for treating defective valves is through repair or reconstruction, which is typically used on minimally calcified valves. The problem with surgical therapy is the significant insult it imposes on these chronically ill patients with high morbidity and mortality rates associated with surgical repair.

[0010] When the valve is replaced, surgical implantation of the prosthetic valve typically requires an open-chest surgery during which the heart is stopped and patient placed on cardiopulmonary bypass (a so-called "heart-lung machine"). In one common surgical procedure, the diseased native valve leaflets are excised and a prosthetic valve is sutured to the surrounding tissue at the valve annulus. Because of the trauma associated with the procedure and the attendant duration of extracorporeal blood circulation, some patients do not survive the surgical procedure or die shortly thereafter. It is well known that the risk to the patient increases with the amount of time required on extracorporeal circulation. Due to these risks, a substantial number of patients with defective valves are deemed inoperable because their condition is too frail to withstand the procedure. By some estimates, about 30 to 50% of the subjects suffering from aortic stenosis who are older than 80 years cannot be operated on for aortic valve replacement.

[0011] Because of the drawbacks associated with conventional open-heart surgery, percutaneous and minimally-invasive surgical approaches are garnering intense attention. In one technique, a prosthetic valve is configured to be implanted in a much less invasive procedure by way of catheterization. For instance, U.S. Patent No. 5,411,552 to Andersen et al. describes a collapsible valve percutaneously introduced in a compressed state through a catheter and expanded in the desired position by balloon inflation. Although these remote implantation techniques have shown great promise for treating certain patients, replacing a valve via surgical intervention is still the preferred treatment procedure. One hurdle to the acceptance of remote implantation is resistance from doctors who are understandably anxious about converting from an effective, if imperfect, regimen to a novel approach that promises great outcomes but is relatively foreign. In conjunction with the understandable caution exercised by surgeons in switching to new techniques of heart valve replacement, regulatory bodies around the world are moving slowly as well. Numerous successful clinical trials and follow-up studies are in process, but much more experience with these new technologies will be required before they are completely accepted.

[0012] Accordingly, there is a need for an improved device and associated method of use wherein a prosthetic valve can be surgically implanted in a body channel in a more efficient procedure that reduces the time required on extracorporeal circulation. It is desirable that such a device and method be capable of helping patients with defective valves that are deemed inoperable because their condition is too frail to withstand a lengthy conventional surgical procedure. The present invention addresses these needs and others.

Summary of the Invention

[0013] Various embodiments of the present application provide prosthetic valves and methods of use for replacing a defective native valve in a human heart. Certain embodiments are particularly well adapted for use in a surgical procedure for quickly and easily replacing a heart valve while minimizing time using extracorporeal circulation (i.e., bypass pump).

[0014] In one embodiment, a method for treating a native aortic valve in a human heart to replaces the function of the aortic valve, comprises: 1) accessing a native valve through an opening in a chest; 2) advancing an expandable base stent to the site of a native aortic valve, the base stent being radially compressed during the advancement; 3) radially expanding the base stent at the site of the native aortic valve; 4) advancing a valve component within a lumen of the base stent; and 5) expanding a coupling stent on the valve component to mechanically couple to the base stent in a quick and efficient manner.

[0015] In one variation, the base stent may comprise a metallic frame. In one embodiment, at least a portion of the metallic frame is made of stainless steel. In another embodiment, at least a portion of the metallic frame is made of a shape memory material. The valve member may take a variety of forms. In one preferred embodiment, the valve component comprises biological tissue. In another variation of this method, the metallic frame is viewed under fluoroscopy during advancement of the prosthetic valve toward the native aortic valve.

[0016] The native valve leaflets may be removed before delivering the prosthetic valve. Alternatively, the native leaflets may be left in place to reduce surgery time and to provide a stable base for fixing the base stent within the native valve. In one advantage of this method, the native leaflets recoil inward to enhance the fixation of the metallic frame in the body channel. When the native leaflets are left in place, a balloon or other expansion member may be used to push the valve leaflets out of the way and thereby dilate the native valve before implantation of the base stent. The native annulus may be dilated between 1.5-5 mm from their initial orifice size to accommodate a larger sized prosthetic valve.

[0017] In accordance with a preferred aspect, a prosthetic heart valve system comprises a base stent adapted to anchor against a heart valve annulus and defining an orifice therein, and a valve component connected to the base stent. The valve component includes a prosthetic valve defining therein a non-expandable, non-collapsible orifice, and an expandable coupling stent extending from an inflow end thereof. The coupling stent has a contracted state for delivery to an implant position and an expanded state configured for outward connection to the base stent. The base stent may also be expandable with a contracted state for delivery to an implant position adjacent a heart valve annulus and an expanded state sized to contact and anchor against the heart valve annulus. Desirably, the base stent and also the coupling stent are plastically expandable.

[0018] In one embodiment, the prosthetic valve comprises a commercially available valve having a sewing ring, and the coupling stent attaches to the sewing ring. The contracted state of the coupling stent may be conical, tapering down in a distal direction. The coupling stent preferably comprises a plurality of radially expandable struts at least some of which are arranged in rows, wherein the distalmost row has the greatest capacity for expansion from the contracted state to the expanded state. Still further, the strut row farthest from the prosthetic valve has alternating peaks and valleys, wherein the base stent includes apertures into which the peaks of the coupling stent may project to interlock the two stents. The base stent may include a plurality of radially expandable struts between axially-oriented struts, wherein at least some of the axially-oriented struts have upper projections that demark locations around the stent.

[0019] A method of delivery and implant of a prosthetic heart valve system is also disclosed herein, comprising the steps of:

advancing a base stent to an implant position adjacent a heart valve annulus;

anchoring the base stent to the heart valve annulus;

providing a valve component including a prosthetic valve having a non-expandable, non-collapsible orifice, the valve component further including an expandable coupling stent extending from an inflow end thereof, the coupling stent having a contracted state for delivery to an implant position and an expanded state configured for outward connection to the base stent;

advancing the valve component with the coupling stent in its contracted state to an implant position adjacent the base stent; and

expanding the coupling stent to the expanded state in contact with and connected to the base stent.

[0020] The base stent may be plastically expandable, and the method further comprises advancing the expandable base stent in a contracted state to the implant position, and plastically expanding the base stent to an expanded state in contact with and anchored to the heart valve annulus, in the process increasing the orifice size of the heart valve annulus by at least 10%, or by 1.5-5 mm. Desirably, the prosthetic valve of the valve component is selected to have an orifice size that matches the increased orifice size of the heart valve annulus. The method may also include mounting the base stent over a mechanical expander, and deploying the base stent at the heart valve annulus using the mechanical expander.

[0021] One embodiment of the method further includes mounting the valve component on a holder having a proximal hub and lumen therethrough. The holder mounts on the distal end of a handle having a lumen therethrough, and the method including passing a balloon catheter through the lumen of the handle and the holder and within the valve component, and inflating a balloon on the balloon catheter to expand the coupling stent. The valve component mounted on the holder may be packaged separately from the handle and the balloon catheter. Desirably, the contracted state of the coupling stent is conical, and the balloon on the balloon catheter has a larger distal expanded end than its proximal expanded end so as to apply greater expansion deflection to the coupling stent than to the prosthetic valve.

[0022] In the method where the coupling stent is conical, the coupling stent may comprise a plurality of radially expandable struts at least some of which are arranged in rows, wherein the row farthest from the prosthetic valve has the greatest capacity for expansion from the contracted state to the expanded state.

[0023] The method may employ a coupling stent with a plurality of radially expandable struts, wherein a row farthest from the prosthetic valve has alternating peaks and valleys. The distal end of the coupling stent thus expands more than the rest of the coupling stent so that the peaks in the row farthest from the prosthetic valve project outward into apertures in the base stent. Both the base stent and the coupling stent may have a plurality of radially expandable struts between axially-oriented struts, wherein the method includes orienting the coupling stent so that its axially-oriented struts are out of phase with those of the base stent to increase retention therebetween.

[0024] Another aspect described herein is a system for delivering a valve component including a prosthetic valve having a non-expandable, non-collapsible orifice, and an expandable coupling stent extending from an inflow end thereof, the coupling stent having a contracted state for delivery to an implant position and an expanded state. The delivery system includes a valve holder connected to a proximal end of the valve component, a balloon catheter having a balloon, and a handle configured to attach to a proximal end of the valve holder and having a lumen for passage of the catheter, wherein the balloon extends distally through the handle, past the holder and through the valve component. In the system, the prosthetic valve is preferably a commercially available valve having a sewing ring to which the coupling stent attaches.

[0025] The contracted state of the coupling stent in the delivery system may be conical, tapering down in a distal direction. Furthermore, the balloon catheter further may include a generally conical nose cone on a distal end thereof that extends through the valve component and engages a distal end of the coupling stent in its contracted state. Desirably, the handle comprises a proximal section and a distal section that may be coupled together in series to form a continuous lumen, wherein the distal section is adapted to couple to the hub of the holder to enable manual manipulation of the valve component using the distal section prior to connection with the proximal handle section. Preferably, the balloon catheter and proximal handle section are packaged together with the balloon within the proximal section lumen.

[0026] The system of claim 21, wherein the valve component mounted on the holder is packaged separately from the handle and the balloon catheter.A further understanding of the nature and advantages of the present invention are set forth in the following description and claims, particularly when considered in conjunction with the accompanying drawings in which like parts bear like reference numerals.

Brief Description of the Drawings

[0027] The invention will now be explained and other advantages and features will appear with reference to the accompanying schematic drawings wherein:

[0028] Figure 1 is an anatomic anterior view of a human heart, with portions broken away and in section to view the interior heart chambers and adjacent structures;

[0029] Figure 2 is an anatomic superior view of a section of the human heart showing the tricuspid valve in the right atrium, the mitral valve in the left atrium, and the aortic valve in between, with the tricuspid and mitral valves open and the aortic and pulmonary valves closed during ventricular diastole (ventricular filling) of the cardiac cycle;

[0030] Figure 3 is an anatomic superior view of a section of the human heart shown in Figure 2, with the tricuspid and mitral valves closed and the aortic and pulmonary valves opened during ventricular systole (ventricular emptying) of the cardiac cycle;

[0031] Figure 4 is an anatomic anterior perspective view of the left and right atria, with portions broken away and in section to show the interior of the heart chambers and associated structures, such as the fossa ovalis, coronary sinus, and the great cardiac vein;

[0032] Figures 5A-5H are sectional views through an isolated aortic annulus showing a portion of the adjacent left ventricle and aorta, and illustrating a number of steps in deployment of an exemplary prosthetic heart valve system of the present invention;

[0033] Figure 5A shows a deflated balloon catheter having a base stent thereon advanced into position at the aortic annulus;

[0034] Figure 5B shows the balloon on the catheter inflated to expand and deploy the base stent against the aortic annulus;

[0035] Figure 5C shows the deployed base stent in position within the aortic annulus;

[0036] Figure 5D shows a valve component mounted on a balloon catheter advancing into position within the base stent;

[0037] Figure 5E shows the valve component in a desired implant position at the aortic annulus and within the base stent, with the balloon catheter advanced farther to displace a nose cone out of engagement with a coupling stent;

[0038] Figure 5F shows the balloon on the catheter inflated to expand and deploy a valve component coupling stent against the base stent;

[0039] Figure 5G shows the deflated balloon on the catheter along with the nose cone being removed from within the valve component;

[0040] Figure 5H shows the fully deployed prosthetic heart valve of the present invention;

[0041] Figure 6 is an exploded view of an exemplary system for delivering the prosthetic heart valve of the present invention;

[0042] Figure 7 is an assembled view of the delivery system of Figure 6 showing a nose cone extending over a distal end of a valve component coupling stent;

[0043] Figure 8 is a view like Figure 7 but with a balloon catheter displaced distally to disengage the nose cone from the coupling stent;

[0044] Figure 9 is an assembled view of the delivery system similar to that shown in Figure 7 and showing a balloon inflated to expand the valve component coupling stent;

[0045] Figure 10 is an exploded elevational view of several components of the introducing system of Figure 9, without the balloon catheter, valve component and holder;

[0046] Figures 11A and 11B are perspective views of an exemplary valve component assembled on a valve holder of the present invention;

[0047] Figure 11C is a side elevational view of the assembly of Figures 11A and 11B;

[0048] Figures 11D and 11E are top and bottom plan views of the assembly of Figures 11A and 11B;

[0049] Figures 12A-12B illustrate an exemplary coupling stent in both a flat configuration (12A) and a tubular expanded configuration (12B);

[0050] Figures 13A-13B illustrate an alternative coupling stent having a discontinuous upper end in both flat and tubular expanded configurations;

[0051] Figure 14-17 are plan views of a still further alternative coupling stent;

[0052] Figure 18A-18B are flat and tubular views of an exemplary base stent with upper position markers and a phantom coupling stent superimposed thereover;

[0053] Figure 19 is a flat view of an alternative base stent with a coupling stent superimposed thereover;

[0054] Figure 20 is a sectional view of a coupling stent within a base stent illustrating one method of interlocking; and

[0055] Figure 21-23 is a perspective view of a device for delivering and expanding a base stent with mechanical fingers.

Detailed Description of the Preferred Embodiments

[0056] The present invention attempts to overcome drawbacks associated with conventional, open-heart surgery, while also adopting some of the techniques of newer technologies which decrease the duration of the treatment procedure. The prosthetic heart valves of the present invention are primarily intended to be delivered and implanted using conventional surgical techniques, including the aforementioned open-heart surgery. There are a number of approaches in such surgeries, all of which result in the formation of a direct access pathway to the particular heart valve annulus. For clarification, a direct access pathway is one that permits direct (i.e., naked eye) visualization of the heart valve annulus. In addition, it will be recognized that embodiments of the two-stage prosthetic heart valves described herein may also be configured for delivery using percutaneous approaches, and those minimally-invasive surgical approaches that require remote implantation of the valve using indirect visualization.

[0057] One primary aspect of the present invention is a two-stage prosthetic heart valve wherein the tasks of implanting a tissue anchor first and then a valve member are distinct and certain advantages result. The exemplary two-stage prosthetic heart valve of the present invention has an expandable base stent secured to tissue in the appropriate location using a balloon or other expansion technique. A hybrid valve member that has non-expandable and expandable portions then couples to the base stent in a separate or sequential operation. By utilizing an expandable base stent, the duration of the initial anchoring operation is greatly reduced as compared with a conventional sewing procedure utilizing an array of sutures. The expandable base stent may simply be radially expanded outward into contact with the implantation site, or may be provided with additional anchoring means, such as barbs. The operation may be carried out using a conventional open-heart approach and cardiopulmonary bypass. In one advantageous feature, the time on bypass is greatly reduced due to the relative speed of implanting the expandable base stent.

[0058] For definitional purposes, the term "base stent," refers to a structural component of a heart valve that is capable of attaching to tissue of a heart valve annulus. The base stents described herein are most typically tubular stents, or stents having varying shapes or diameters. A stent is normally formed of a biocompatible metal wire frame, such as stainless steel or Nitinol. Other base stents that could be used with valves of the present invention include rigid rings, spirally-wound tubes, and other such tubes that fit tightly within a valve annulus and define an orifice therethrough for the passage of blood, or within which a valve member is mounted. It is entirely conceivable, however, that the base stent could be separate clamps or hooks that do not define a continuous periphery. Although such devices sacrifice some dynamic stability, and speed and ease of deployment, these devices could be configured to work in conjunction with a particular valve member.

[0059] A distinction between self-expanding and balloon-expanding stents exists in the field. A self-expanding stent may be crimped or otherwise compressed into a small tube and possesses sufficient elasticity to spring outward by itself when a restraint such as an outer sheath is removed. In contrast, a balloon-expanding stent is made of a material that is substantially less elastic, and indeed must be plastically expanded from the inside out when converting from a compressed diameter to an expanded. It should be understood that the term balloon-expanding stents encompasses plastically-expandable stents, whether or not a balloon is used to actually expand it. The material of the stent plastically deforms after application of a deformation force such as an inflating balloon or expanding mechanical fingers. Both alternatives will be described below. Consequently, the term "balloon-expandable stent" should be considered to refer to the material or type of the stent as opposed to the specific expansion means.

[0060] The term "valve member" refers to that component of a heart valve that possesses the fluid occluding surfaces to prevent blood flow in one direction while permitting it in another. As mentioned above, various constructions of valve numbers are available, including those with flexible leaflets and those with rigid leaflets or a ball and cage arrangement. The leaflets may be bioprosthetic, synthetic, or metallic.

[0061] A primary focus of the present invention is a two-stage prosthetic heart valve having a first stage in which a base stent secures to a valve annulus, and a subsequent second stage in which a valve member connects to the base stent. It should be noted that these stages can be done almost simultaneously, such as if the two components were mounted on the same delivery device, or can be done in two separate clinical steps, with the base stent deployed using a first delivery device, and then the valve member using another delivery device. It should also be noted that the term "two-stage" refers to the two primary steps of anchoring structure to the annulus and then connecting a valve member, which does not necessarily limit the valve to just two parts.

[0062] Another potential benefit of a two-stage prosthetic heart valve, including a base stent and a valve member, is that the valve member may be replaced after implantation without replacing the base stent. That is, an easily detachable means for coupling the valve member and base stent may be used that permits a new valve member to be implanted with relative ease. Various configurations for coupling the valve member and base stent are described herein.

[0063] It should be understood, therefore, that certain benefits of the invention are independent of whether the base stent is expandable or not. That is, various embodiments illustrate an expandable base stent coupled to a hybrid valve member that has non-expandable and expandable portions. However, the same coupling structure may be utilized for a non-expandable base stent and hybrid valve member. Therefore, the invention should be interpreted via the appended claims.

[0064] As a point of further definition, the term "expandable" is used herein to refer to a component of the heart valve capable of expanding from a first, delivery diameter to a second, implantation diameter. An expandable structure, therefore, does not mean one that might undergo slight expansion from a rise in temperature, or other such incidental cause. Conversely, "non-expandable" should not be interpreted to mean completely rigid or a dimensionally stable, as some slight expansion of conventional "non-expandable" heart valves, for example, may be observed.

[0065] In the description that follows, the term "body channel" is used to define a blood conduit or vessel within the body. Of course, the particular application of the prosthetic heart valve determines the body channel at issue. An aortic valve replacement, for example, would be implanted in, or adjacent to, the aortic annulus. Likewise, a mitral valve replacement will be implanted at the mitral annulus. Certain features of the present invention are particularly advantageous for one implantation site or the other. However, unless the combination is structurally impossible, or excluded by claim language, any of the heart valve embodiments described herein could be implanted in any body channel.

[0066] Figures 5A-5H are sectional views through an isolated aortic annulus AA showing a portion of the adjacent left ventricle LV and ascending aorta with sinus cavities S. The two coronary sinuses CS are also shown. The series of views show snapshots of a number of steps in deployment of an exemplary prosthetic heart valve system of the present invention, which comprises a two-component system. A first component is a base stent that is deployed against the native leaflets or, if the leaflets are excised, against the debrided aortic annulus AA. A second valve component fits within the base stent and anchors thereto. Although two-part valves are known in the art, this is believed to be the first that utilizes a stent within a stent in conjunction with a non-expandable valve.

[0067] Figure 5A shows a catheter 20 having a balloon 22 in a deflated state near a distal end with a tubular base stent 24 crimped thereover. The stent 24 is shown in a radially constricted, undeployed configuration. The catheter 20 has been advanced to position the base stent 24 so that it is approximately axially centered at the aortic annulus AA.

[0068] Figure 5B shows the balloon 22 on the catheter 20 inflated to expand and deploy the base stent 24 against the aortic annulus AA, and Figure 5C shows the deployed base stent in position after deflation of the balloon 22 and removal of the catheter 20. The stent 24 provides a base within and against a body lumen (e.g., a valve annulus). Although a stent is described for purposes of illustration, any member capable of anchoring within and against the body lumen and then coupling to the valve component may be used. In a preferred embodiment, the base stent 24 comprises a plastically-expandable cloth-covered stainless-steel tubular stent. One advantage of using a plastically-expandable stent is the ability to expand the native annulus to receive a larger valve size than would otherwise be possible with conventional surgery. Desirably, the left ventricular outflow tract (LVOT) is significantly expanded by at least 10%, or for example by 1.5-5 mm, and the surgeon can select a valve component 30 with a larger orifice diameter relative to an unexpanded annulus. On the other hand, the present invention could also use a self-expanding base stent 24 which is then reinforced by the subsequently implanted valve component 30. Because the valve component 30 has a non-compressible part, the prosthetic valve 34, and desirably a plastically-expandable coupling stent 36, it effectively resists recoil of the self-expanded base stent 24.

[0069] With continued reference to Figure 5B, the stent 24 has a diameter sized to be deployed at the location of the native valve (e.g., along the aortic annulus). A portion of the stent 24 may expand outwardly into the respective cavity adjacent the native valve. For example, in an aortic valve replacement, an upper portion may expand into the area of the sinus cavities just downstream from the aortic annulus. Of course, care should be taken to orient the stent 24 so as not to block the coronary openings. The stent body is preferably configured with sufficient radial strength for pushing aside the native leaflets and holding the native leaflets open in a dilated condition. The native leaflets provide a stable base for holding the stent, thereby helping to securely anchor the stent in the body. To further secure the stent to the surrounding tissue, the lower portion may be configured with anchoring members, such as, for example, hooks or barbs (not shown).

[0070] As will be described in more detail below, the prosthetic valve system includes a valve component that may be quickly and easily connected to the stent 24. It should be noted here that the base stents described herein can be a variety of designs, including having the diamond/chevron-shaped openings shown or other configurations. The material depends on the mode of delivery (i.e., balloon- or self-expanding), and the stent can be bare strut material or covered to promote ingrowth and/or to reduce paravalvular leakage. For example, a suitable cover that is often used is a sleeve of fabric such as Dacron.

[0071] One primary advantage of the prosthetic heart valve system of the present invention is the speed of deployment. Therefore, the base stent 24 may take a number of different configurations as long as it does not require the time-consuming process of suturing it to the annulus. For instance, another possible configuration for the base stent 24 is one that is not fully expandable like the tubular stent as shown. That is, the base stent 24 may have a non-expandable ring-shaped orifice from which an expandable skirt stent or series of anchoring barbs deploy.

[0072] Figure 5D shows a valve component 30 mounted on a balloon catheter 32 advancing into position within the base stent 24. The valve component 30 comprises a prosthetic valve 34 and a coupling stent 36 attached to and projecting from a distal end thereof. In its radially constricted or undeployed state, the coupling stent 36 assumes a conical inward taper in the distal direction. The catheter 32 extends through the valve component 30 and terminates in a distal nose cone 38 which has a conical or bell-shape and covers the tapered distal end of the coupling stent 36. Although not shown, the catheter 32 extends through an introducing cannula and valve holder.

[0073] When used for aortic valve replacement, the prosthetic valve 34 preferably has three flexible leaflets which provide the fluid occluding surfaces to replace the function of the native valve leaflets. In various preferred embodiments, the valve leaflets may be taken from another human heart (cadaver), a cow (bovine), a pig (porcine valve) or a horse (equine). In other preferred variations, the valve member may comprise mechanical components rather than biological tissue. The three leaflets are supported by three commissural posts. A ring is provided along the base portion of the valve member.

[0074] In a preferred embodiment, the prosthetic valve 34 partly comprises a commercially available, non-expandable prosthetic heart valve, such as the Carpentier-Edwards PERIMOUNT Magna® Aortic Heart Valve available from Edwards Lifesciences of Irvine, California. In this sense, a "commercially available" prosthetic heart valve is an off-the-shelf (i.e., suitable for stand-alone sale and use) prosthetic heart valve defining therein a non-expandable, non-collapsible orifice and having a sewing ring capable of being implanted using sutures through the sewing ring in an open-heart, surgical procedure. The particular approach into the heart used may differ, but in surgical procedures the heart is stopped and opened, in contrast to beating heart procedures where the heart remains functional. To reiterate, the terms "non-expandable" and "non-collapsible" should not be interpreted to mean completely rigid and dimensionally stable, merely that the valve is not expandable/collapsible like some proposed minimally-invasively or percutaneously-delivered valves.

[0075] An implant procedure therefore involves first delivering and expanding the base stent 24 at the aortic annulus, and then coupling the valve component 30 including the valve 34 thereto. Because the valve 34 is non-expandable, the entire procedure is typically done using the conventional open-heart technique. However, because the base stent 24 is delivered and implanted by simple expansion, and then the valve component 30 attached thereto by expansion, both without suturing, the entire operation takes less time. This hybrid approach will also be much more comfortable to surgeons familiar with the open-heart procedures and commercially available heart valves.

[0076] Moreover, the relatively small change in procedure coupled with the use of proven heart valves should create a much easier regulatory path than strictly expandable, remote procedures. Even if the system must be validated through clinical testing to satisfy the Pre-Market Approval (PMA) process with the FDA (as opposed to a 510k submission), the acceptance of the valve component 30 at least will be greatly streamlined with a commercial heart valve that is already approved, such as the Magna® Aortic Heart Valve.

[0077] The prosthetic valve 34 is provided with an expandable coupling mechanism in the form of the coupling stent 36 for securing the valve to the base stent 24. Although the coupling stent 36 is shown, the coupling mechanism may take a variety of different forms, but eliminates the need for connecting sutures and provides a rapid connection means.

[0078] In Figure 5E the valve component 30 has advanced to a desired implant position at the aortic annulus AA and within the base stent 24. The prosthetic valve 34 may include a suture-permeable ring 42 that desirably abuts the aortic annulus AA. More preferably, the sewing ring 42 is positioned supra-annularly, or above the narrowest point of the aortic annulus AA, so as to allow selection of a larger orifice size than a valve placed intra-annularly. With the aforementioned annulus expansion using the base stent 24, and the supra-annular placement, the surgeon may select a valve having a size one or two increments larger than previously conceivable. As mentioned, the prosthetic valve 34 is desirably a commercially available heart valve having a sewing ring 42. The balloon catheter 32 has advanced relative to the valve component 30 to displace the nose cone 38 out of engagement with the coupling stent 36. A dilatation balloon 40 on the catheter 30 can be seen just beyond the distal end of the coupling stent 36.

[0079] Figure 5F shows the balloon 40 on the catheter 32 inflated to expand and deploy the coupling stent 36 against the base stent 24. The balloon 40 is desirably inflated using controlled, pressurized, sterile physiologic saline. The coupling stent 36 transitions between its conical contracted state and its generally tubular expanded state. Simple interference between the coupling stent 36 and the base stent 24 may be sufficient to anchor the valve component 30 within the base stent, or interacting features such as projections, hooks, barbs, fabric, etc. may be utilized.

[0080] Because the base stent 24 expands before the valve component 30 attaches thereto, a higher strength stent (self-or balloon-expandable) configuration may be used. For instance, a relatively robust base stent 24 may be used to push the native leaflets aside, and the absent valve component 30 is not damaged or otherwise adversely affected during the high-pressure base stent deployment. After the base stent 24 deploys in the body channel, the valve component 30 connects thereto by deploying the coupling stent 36, which may be somewhat more lightweight requiring smaller expansion forces. Also, the balloon 40 may have a larger distal expanded end than its proximal expanded end so as to apply more force to the coupling stent 36 than to the prosthetic valve 34. In this way, the prosthetic valve 34 and flexible leaflets therein are not subject to high expansion forces from the balloon 40. Indeed, although balloon deployment is shown, the coupling stent 36 may also be a self-expanding type of stent. In the latter configuration, the nose cone 38 is adapted to retain the coupling stent 36 in its constricted state prior to position in the valve component 30 within the base stent 24.

[0081] As noted above, the base stents described herein could include barbs or other tissue anchors to further secure the stent to the tissue, or to secure the coupling stent 36 to the base stent 24. Further, the barbs could be deployable (e.g., configured to extend or be pushed radially outward) by the expansion of a balloon. Preferably, the coupling stent 36 is covered to promote in-growth and/or to reduce paravalvular leakage, such as with a Dacron tube or the like.

[0082] Figure 5G shows the deflated balloon 40 on the catheter 32 along with the nose cone 38 being removed from within the valve component 30. Finally, Figure 5H shows the fully deployed prosthetic heart valve system of the present invention including the valve component 30 coupled to the base stent 24 within the aortic annulus AA.

[0083] Figure 6 is an exploded view, and Figures 7 and 8 are assembled views, of an exemplary system 50 for delivering the prosthetic heart valve of the present invention. Modified components of the delivery system 50 are also shown in Figures 9 and 10. The delivery system 50 includes a balloon catheter 52 having the balloon 40 on its distal end and an obturator 54 on a proximal end. The obturator 54 presents a proximal coupling 56 that receives a luer connector or other such fastener of a Y-fitting 58. The aforementioned nose cone 38 may attach to the distalmost end of the catheter 52, but more preferably attaches to a wire (not shown) inserted through the center lumen of the balloon catheter 52.

[0084] The catheter 52 and the nose cone 38 pass through a hollow handle 60 having a proximal section 62 and a distal section 64. A distal end of the distal handle section 64 firmly attaches to a hub 66 of a valve holder 68, which in turn attaches to the prosthetic heart valve component 30. Details of the valve holder 68 will be given below with reference to Figures 11A-11E.

[0085] The two sections 62, 64 of the handle 60 are desirably formed of a rigid material, such as a molded plastic, and coupled to one another to form a relatively rigid and elongated tube for manipulating the prosthetic valve component 30 attached to its distal end. In particular, the distal section 64 may be easily coupled to the holder hub 66 and therefore provide a convenient tool for managing the valve component 30 during pre-surgical rinsing steps. For this purpose, the distal section 64 features a distal tubular segment 70 that couples to the holder hub 66, and an enlarged proximal segment 72 having an opening on its proximal end that receives a tubular extension 74 of the proximal handle section 62. Figure 6 shows an O-ring 76 that may be provided on the exterior of the tubular extension 74 for a frictional interference fit to prevent the two sections from disengaging. Although not shown, the distal tubular segment 70 may also have an O-ring for firmly coupling to the holder hub 66, or may be attached with threading or the like. In one preferred embodiment, the balloon 40 on the catheter 52 is packaged within the proximal handle section 62 for protection and ease of handling. Coupling the proximal and distal handle sections 62, 64 therefore "loads" the system 50 such that the balloon catheter 52 may be advanced through the continuous lumen leading to the valve component 30.

[0086] Figures 9 and 10 illustrate a delivery system 50 similar to that shown in Figure 7, but with alternative couplers 77 on both the proximal and distal handle sections 62, 64 in the form of cantilevered teeth that snap into complementary recesses formed in the respective receiving apertures. Likewise, threading on the mating parts could also be used, as well as other similar expedients. Figure 9 shows the balloon 40 inflated to expand the valve component coupling stent 36.

[0087] In a preferred embodiment, the prosthetic valve component 30 incorporates bioprosthetic tissue leaflets and is packaged and stored attached to the holder 68 but separate from the other introduction system 50 components. Typically, bioprosthetic tissue is packaged and stored in a jar with preservative solution for long shelf life, while the other components are packaged and stored dry.

[0088] When assembled as seen in Figures 7-9, an elongated lumen (not numbered) extends from the proximal end of the Y-fitting 58 to the interior of the balloon 40. The Y-fitting 58 desirably includes an internally threaded connector 80 for attachment to an insufflation system, or a side port 82 having a luer fitting 84 or similar expedient may be used for insufflation of the balloon 40.

[0089] Figures 7 and 8 show two longitudinal positions of the catheter 52 and associated structures relative to the handle 60 and its associated structures. In a retracted position shown in Figure 7, the balloon 40 primarily resides within the distal handle section 64. Figure 7 illustrates the delivery configuration of the introduction system 50, in which the surgeon advances the prosthetic valve component 30 from outside the body into a location adjacent the target annulus. The nose cone 38 extends around and protects a distal end of the conical undeployed coupling stent 36. This configuration is also seen in Figure 5D, albeit with the holder 68 removed for clarity. Note the spacing **S** between the proximal coupling 56 and the proximal end of the handle 60.

[0090] As explained above with respect to Figures 5A-5H, the surgeon advances the prosthetic valve component 30 into its desired implantation position at the valve annulus, and then advances the balloon 40 through the valve component and inflates it. To do so, the operator converts the delivery system 50 from the retracted configuration of Figure 7 to the deployment configuration of Figure 8, with the balloon catheter 40 displaced distally as indicated by the arrow 78 to disengage the nose cone 38 from the coupling stent 36. Note that the proximal coupling 56 now contacts the proximal end of the handle 60, eliminating the space **S** indicated in Figure 7.

[0091] It should be understood that the prosthetic valve component 30 may be implanted at the valve annulus with a pre-deployed base stent 24, as explained above, or without. The coupling stent 36 may be robust enough to anchor the valve component 30 directly against the native annulus (with or without leaflet excision) in the absence of the base stent 24. Consequently, the description of the system 50 for introducing the prosthetic heart valve should be understood in the context of operating with or without the pre-deployed base stent 24.

[0092] Prior to a further description of operation of the delivery system 50, a more detailed explanation of the valve component 30 and valve holder 68 is necessary. Figures 11A-11E show a number of perspective and other views of the exemplary valve component 30 mounted on the delivery holder 68 of the present invention. As mentioned, the valve component 30 comprises the prosthetic valve 34 having the coupling stent 36 attached to an inflow end thereof. In a preferred embodiment, the prosthetic valve 34 comprises a commercially available off-the-shelf non-expandable, non-collapsible commercial prosthetic valve. Any number of prosthetic heart valves can be retrofit to attach the coupling stent 36, and thus be suitable for use in the context of the present invention. For example, the prosthetic valve 34 may be a mechanical valve or a valve with flexible leaflets, either synthetic or bioprosthetic. In a preferred embodiment, however, the prosthetic valve 34 includes bioprosthetic tissue leaflets 86 (Figure 11A). Furthermore, as mentioned above, the prosthetic valve 34 is desirably a Carpentier-Edwards PERIMOUNT Magna® Aortic Heart Valve (e.g., model 3000TFX) available from Edwards Lifesciences of Irvine, California.

[0093] The coupling stent 36 preferably attaches to the ventricular (or inflow) aspect of the valve's sewing ring 42 during the manufacturing process in a way that preserves the integrity of the sewing ring and prevents reduction of the valve's effective orifice area (EOA). Desirably, the coupling stent 36 will be continuously sutured to sewing ring 42 in a manner that maintains the outer contours of the sewing ring. Sutures may be passed through apertures or eyelets in the stent skeleton, or through a cloth covering that in turn is sewn to the skeleton. Other connection solutions include prongs or hooks extending inward from the stent, ties, Velcro, snaps, adhesives, etc. Alternatively, the coupling stent 36 may be more rigidly connected to rigid components within the prosthetic valve 34. During implant, therefore, the surgeon can seat the sewing ring 42 against the annulus in accordance with a conventional surgery. This gives the surgeon familiar tactile feedback to ensure that the proper patient-prosthesis match has been achieved. Moreover, placement of the sewing ring 42 against the outflow side of the annulus helps reduce the probability of migration of the valve component 30 toward the ventricle.

[0094] The coupling stent 36 may be a pre-crimped, tapered, 316L stainless steel balloon-expandable stent, desirably covered by a polyester skirt 88 to help seal against paravalvular leakage and promote tissue ingrowth once implanted within the base stent 24 (see Figure 5F). The coupling stent 36 transitions between the tapered constricted shape of Figures 11A-11E to its flared expanded shape shown in Figure 5F, and also in Figure 10.

[0095] The coupling stent 36 desirably comprises a plurality of sawtooth-shaped or otherwise angled, serpentine or web-like struts 90 connected to three generally axially-extending posts 92. As will be seen below, the posts 92 desirably feature a series of evenly spaced apertures to which sutures holding the polyester skirt 88 in place may be anchored. As seen best in Figure 5F, the stent 36 when expanded flares outward and conforms closely against the inner surface of the base stent 24, and has an axial length substantially the same as the base stent. Anchoring devices such as barbs or other protruberances from the coupling stent 36 may be provided to enhance the frictional hold between the coupling stent and the base stent 24.

[0096] It should be understood that the particular configuration of the coupling stent, whether possessing straight or curvilinear struts 90, may be modified as needed. There are numerous stent designs, as described below with reference to Figures 12-17, any of which potentially may be suitable. Likewise, although the preferred embodiment incorporates a balloon-expandable coupling stent 36, a self-expanding stent could be substituted with certain modifications, primarily to the delivery system. The same flexibility and design of course applies to the base stent 24. In a preferred embodiment, both the base stent 24 and the coupling stent 36 are desirably plastically-expandable to provide a firmer anchor for the valve 34; first to the annulus with or without native leaflets, and then between the two stents. The stents may be expanded using a balloon or mechanical expander as described below.

[0097] Still with reference to Figures 11A-11E, the holder 68 comprises the aforementioned proximal hub 66 and a thinner distal extension 94 thereof forming a central portion of the holder. Three legs 96a, 96b, 96c circumferentially equidistantly spaced around the central extension 94 and projecting radially outward therefrom comprise inner struts 98 and outer commissure rests 100. The prosthetic valve 34 preferably includes a plurality, typically three, commissures 102 that project in an outflow direction. Although not shown, the commissure rests 100 preferably incorporate depressions into which fit the tips of the commissures 102.

[0098] In one embodiment, the holder 68 is formed of a rigid polymer such as Delrin or polypropylene that is transparent to increase visibility of an implant procedure. As best seen in Figure 11E, the holder 68 exhibits openings between the legs 96a, 96b, 96c to provide a surgeon good visibility of the valve leaflets 86, and the transparency of the legs further facilitates visibility and permits transmission of light therethrough to minimize shadows. Although not described in detail herein, Figure 11E also illustrate a series of through holes in the legs 96a, 96b, 96c permitting connecting sutures to be passed through fabric in the prosthetic valve 34 and across a cutting guide in each leg. As is known in the art, severing a middle length of suture that is connected to the holder 68 and passes through the valve permits the holder to be pulled free from the valve when desired.

[0099] Figures 11C and 11D illustrate a somewhat modified coupling stent 36 from that shown in Figures 11A and 11B, wherein the struts 90 and axially-extending posts 92 are better defined. Specifically, the posts 92 are somewhat wider and more robust than the struts 90, as the latter provide the stent 36 with the ability to expand from the conical shape shown to a more tubular configuration. Also, a generally circular reinforcing ring 104 abuts the valve sewing ring 42. Both the posts 92 and the ring 104 further include a series of through holes 106 that may be used to secure the polyester skirt 88 to the stent 36 using sutures or the like. A number of variants of the coupling stent 36 are also described below.

[0100] Figures 12A-12B illustrate the exemplary coupling stent 36 in both a flat configuration (12A) and a tubular configuration (12B) that is generally the expanded shape. As mentioned, the web-like struts 90 and a reinforcing ring 104 connect three generally axially-extending posts 92. A plurality of evenly spaced apertures 106 provide anchors for holding the polyester skirt 88 (see Figure 11B) in place. In the illustrated embodiment, the web-like struts 90 also include a series of axially-extending struts 108. An upper end of the coupling stent 36 that connects to the sewing ring of the valve and is defined by the reinforcing ring 104 follows an undulating path with alternating arcuate troughs 110 and peaks 112. As seen from Figure 11C, the exemplary prosthetic valve 34 has an undulating sewing ring 42 to which the upper end of the coupling stent 36 conforms. In a preferred embodiment, the geometry of the stent 36 matches that of the undulating sewing ring 42. Of course, if the sewing ring of the prosthetic valve is planar, then the upper end of the coupling stent 36 will also be planar. It should be noted also that the tubular version of Figure 12B is an illustration of an expanded configuration, although the balloon 40 may over-expand the free (lower) end of the stent 36 such that it ends up being slightly conical.

[0101] Figures 13A and 13B show an alternative coupling stent 120, again in flattened and tubular configurations, respectively. As with the first embodiment, the coupling stent 120 includes web-like struts 122 extending between a series of axially-extending struts 124. In this embodiment, all of the axially-extending struts 124 are substantially the same thin cross-sectional size. The upper or connected end of the stent 120 again includes a reinforcing ring 126, although this version is interrupted with a series of short lengths separated by gaps. The upper end defines a plurality of alternating troughs 128 and peaks 130, with lengths of the reinforcing ring 126 defining the peaks. The axially-extending struts 124 are in-phase with the scalloped shape of the upper end of the stent 120, and coincide with the peaks and the middle of the troughs.

[0102] The gaps between the lengths making up the reinforcing ring 126 permit the stent 120 to be matched with a number of different sized prosthetic valves 34. That is, the majority of the stent 120 is expandable having a variable diameter, and providing gaps in the reinforcing ring 126 allows the upper end to also have a variable diameter so that it can be shaped to match the size of the corresponding sewing ring. This reduces manufacturing costs as correspondingly sized stents need not be used for each different sized valve.

[0103] Figure 14 is a plan view of a still further alternative coupling stent 132 that is very similar to the coupling stent 120, including web-like struts 134 connected between a series of axially-extending struts 136, and the upper end is defined by a reinforcing ring 138 formed by a series of short lengths of struts. In contrast to the embodiment of Figures 13A and 13B, the peaks of the undulating upper end have gaps as opposed to struts. Another way to express this is that the axially-extending struts 136 are out-of-phase with the scalloped shape of the upper end of the stent 132, and do not correspond to the peaks and the middle of the troughs.

[0104] Figure 15 illustrates an exemplary coupling stent 140 again having the expandable struts 142 between the axially-extending struts 144, and an upper reinforcing ring 146. The axially-extending struts 144 are in-phase with peaks and troughs of the upper end of the stent. The reinforcing ring 146 is a cross between the earlier-described such rings as it is continuous around its periphery but also has a variable diameter. That is, the ring 146 comprises a series of lengths of struts 148 of fixed length connected by thinner bridge portions 150 of variable length. The bridge portions 150 are each formed with a radius so that they can be either straightened (lengthened) or bent more (compressed). A series of apertures 152 are also formed in an upper end of the stent 142 provide anchor points for sutures or other attachment means when securing the stent to the sewing ring of the corresponding prosthetic valve.

[0105] In Figure 16, an alternative coupling stent 154 is identical to the stent 140 of Figure 15, although the axially-extending struts 156 are out-of-phase with the peaks and troughs of the undulating upper end.

[0106] Figure 17 shows a still further variation on a coupling stent 160, which has a series of expandable struts 162 connecting axially-extending struts 164. As with the version shown in Figures 12A and 12B, the web-like struts 162 also include a series of axially-extending struts 166, although these are thinner than the main axial struts 164. A reinforcing ring 168 is also thicker than the web-like struts 162, and features one or more gaps 170 in each trough such that the ring is discontinuous and expandable. Barbs 172, 174 on the axially extending struts 164, 166 may be utilized to enhance retention between the coupling stent 160 and a base stent with which it cooperates, or with annular tissue in situations where there is no base stent, as explained above.

[0107] As mentioned above, the two-component valve systems described herein utilize an outer or base stent (such as base stent 24) and a valve component having an inner or valve stent (such as coupling stent 36). The valve and its stent advance into the lumen of the pre-anchored outer stent and the valve stent expands to join the two stents and anchor the valve into its implant position. It is important that the inner stent and outer stent be correctly positioned both circumferentially and axially to minimize subsequent relative motion between the stents. Indeed, for the primary application of an aortic valve replacement, the circumferential position of the commissures of the valve relative to the native commissures is very important. A number of variations of coupling stent that attach to the valve component have been shown and described above. Figures 18-20 illustrate exemplary base stents and cooperation between the two stents.

[0108] Figures 18A and 18B show an exemplary embodiment of a base stent 180 comprising a plurality of radially-expandable struts 182 extending between a plurality of generally axially-extending struts 184. In the illustrated embodiment the struts 182 form chevron patterns between the struts 184, although other configurations such as serpentine or diamond-shaped could also be used. The top and bottom rows of the radially-expandable struts 182 are arranged in apposition so as to form a plurality of triangular peaks 186 and troughs 188. The axial struts 184 are in-phase with the troughs 188.

[0109] The flattened view of Figure 18A shows four axial projections 190 that each extend upward from one of the axial struts 184. Although four projections 190 are shown, the exemplary base stent 180 desirably has three evenly circumferentially spaced projections, as seen around the periphery in the tubular version of Figure 18B, providing location markers for the base stent. These markers thus make it easier for the surgeon to orient the stent 180 such that the markers align with the native commissures. Furthermore, as the valve component advances to within the base stent 180, the visible projections 190 provide reference marks such that the inner stent can be properly oriented within the base stent. In this regard the projections 190 may be differently colored than the rest of the stent 180, or have radiopaque indicators thereon.

[0110] The length of the projections 190 above the upper row of middle struts 182 may also be calibrated to help the surgeon axially position the stent 180. For example, the distance from the tips of the projections 190 to the level of the native annulus could be determined, and the projections 190 located at a particular anatomical landmark such as just below the level of the coronary ostia.

[0111] An undulating dashed line 192 in Figure 18A represents the upper end of the inner or coupling stent 140, which is shown in phantom superimposed over the base stent 180. As such, the dashed line 192 also represents an undulating sewing ring, and it bears repeating that the sewing ring could be planar such that the upper end of the coupling stent is also planar. The coupling stent 140 includes axially-extending struts that are in-phase with the respective peaks and troughs of the scalloped upper end of the stent. In the illustrated combination, the peaks of the scalloped upper end of the coupling stent (dashed line 192) correspond rotationally (are in-phase) with the axial struts 184 that have the projections 190. Therefore, because the coupling stent 140 axial struts are in-phase with the peaks of the upper end thereof, they are also in-phase with the axial struts 184 of the base stent 180. Conversely, a coupling stent may have axial struts out-of-phase with peaks of the upper end thereof, in which case the respective axial struts of the two stents are also out-of-phase.

[0112] Figure 19 shows an alternative base stent 200 that generally has the same components as the base stent 180 of Figure 18A, but the axial struts 184 extend between the peaks 186 of the outer rows of middle struts 182. In the earlier embodiment, the axial struts 184 extended between the troughs 188. The coupling stent 154 of Figure 16 is shown in phantom superimposed over the base stent 200 to illustrate how the axial struts of the two stents are now out-of-phase to increase interlocking therebetween.

[0113] The stent 200 also exhibits different rows of middle struts 182. Specifically, a first row 202a defines V's having relatively shallow angles, a second row 202b defines V's with medium angles, and a third row 202c defined V's with more acute angles. The different angles formed by the middle struts 182 in these rows helps shape the stent into a conical form when expanded. There is, the struts in the third row 202c which is farthest from the prosthetic valve have the greatest capacity for expansion to accommodate the transition from the collapsed conical shape of the stent to the expanded tubular shape.

[0114] Those of skill in the art will understand that there are many ways to increase retention between the two stents. For example, the peaks and troughs of the web-like expandable struts on the two stents could be oriented out-of-phase or in-phase. In a preferred embodiment the peaks and troughs of the two stents are out of phase so that expansion of the inner stent causes its peaks to deform outwardly into the troughs of the outer stent, and thereby provide interlocking structure therebetween. The variations described above provide a number of permutations of this cooperation.

[0115] Additionally, axial projections on one or both of stents could be bent to provide an interference with the other stent. For example, the lower ends of the axial struts 108 in the stent 36 shown in Figure 12A could be bent outward by expansion of a non-uniform shaped balloon such that they extend in voids within the outer stent. Likewise, the embodiment of Figure 17 illustrates barbs 172, 174 that can be bent outward into interference with the corresponding base stent. Strut ends or barbs that transition from one position to another to increase retention between the two stents can be actuated by mechanical bending, such as with a balloon, or through an automatic shape change upon installation within the body. Namely, some shape memory alloys such as Nitinol can be designed to undergo a shape change upon a temperature change, such that they assume a first shape at room temperature, and a second shape at body temperature.

[0116] Figure 20 illustrates a simplified means for increasing retention between the two stents. An inner valve stent 210 fits within an outer base stent 212 such that a lower end 214 thereof extends below the outer stent. By over-expansion of the balloon within the inner stent 210, the lower end 214 is caused to bend or wrap outward to prevent relative upward movement of the inner stent within the outer stent.

[0117] Figure 21 is a perspective view of a device 220 for delivering and expanding a base stent 222 with a mechanical expander 224. In the illustrated embodiment, the expander 224 includes a plurality of spreadable fingers 226 over which the base stent 22 is crimped. The device 220 includes a syringe-like apparatus including a barrel 230 within which a plunger 232 linearly slides. The fingers 226 are axially fixed but capable of pivoting or flexing with respect to the barrel 230. The distal end of the plunger 232 has an outer diameter that is greater than the diameter circumscribed by the inner surfaces of the spreadable fingers 226. Preferably there is a proximal lead-in ramp on the inside of the fingers 226 such that distal movement of the plunger

232 with respect to the barrel 230 gradually cams the fingers outward. The two positions of the plunger 232 are shown in Figures 21 and 23.

[0118] As an alternative to simple linear movement of the plunger 232, it may also be threadingly received within the barrel 230. Still further, the plunger 232 may be formed in two parts freely rotatable with respect to one another, with a proximal part threadingly received within the barrel 230 while a distal part does not rotate with respect to the barrel and merely cams the fingers 226 outward. Still further, a mechanical linkage may be used instead of a camming action whereby levers hinged together create outward movement of the fingers 226. And even further still, a hybrid version using an inflatable balloon with mechanical parts mounted on the outside of the balloon may be utilized. Those of skill in the art will understand that numerous variants on this mechanism are possible, the point being that balloon expansion is not only vehicle.

[0119] Desirably, the fingers 226 have a contoured exterior profile such that they expand the base stent 222 into a particular shape that better fits the heart valve annulus. For instance, the base stent 222 may be expanded into an hourglass shape with wider upper and lower ends and a smaller midsection, and/or an upper end may be formed with a tri-lobular shape to better fit the aortic sinuses. In the latter case, the tri-lobular shape is useful for orienting the base stent 222 upon implant, and also for orienting the coupling stent of the valve component that is received therewithin.

[0120] In another advantageous feature, the two-component valve system illustrated in the preceding figures provides a device and method that substantially reduces the time of the surgical procedure as compared with replacement valves that are sutured to the tissue after removing the native leaflets. For example, the stent 24 of Figures 5-9 may be deployed quickly and the valve component 30 may also be quickly attached to the stent. This reduces the time required on extracorporeal circulation and thereby substantially reduces the risk to the patient.

[0121] In addition to speeding up the implant process, the present invention having the pre-anchored stent, within which the valve and its stent mount, permits the annulus to be expanded to accommodate a larger valve than otherwise would be possible. In particular, clinical research has shown that the left ventricular outflow tract (LVOT) can be significantly expanded by a balloon-expandable stent and still retain normal functioning. In this context, "significantly expanding" the LVOT means expanding it by at least 10%, more preferably between about 10-30%. In absolute terms, the LVOT may be expanded 1.5-5 mm depending on the nominal orifice size. This expansion of the annulus creates an opportunity to increase the size of a surgically implanted prosthetic valve. The present invention employs a balloon-expandable base stent, and a balloon-expandable valve stent. The combination of these two stents permits expansion of the LVOT at and just below the aortic annulus, at the inflow end of the prosthetic valve. The interference fit created between the outside of the base stent and the LVOT secures the valve without pledgets or sutures taking up space, thereby allowing for placement of the maximum possible valve size. A larger valve size than would otherwise be available with conventional surgery enhances volumetric blood flow and reduces the pressure gradient through the valve.

[0122] It will be appreciated by those skilled in the art that embodiments of the present invention provide important new devices and methods wherein a valve may be securely anchored to a body lumen in a quick and efficient manner. Embodiments of the present invention provide a means for implanting a prosthetic valve in a surgical procedure without requiring the surgeon to suture the valve to the tissue. Accordingly, the surgical procedure time is substantially decreased. Furthermore, in addition to providing a base stent for the valve, the stent may be used to maintain the native valve in a dilated condition. As a result, it is not necessary for the surgeon to remove the native leaflets, thereby further reducing the procedure time.

[0123] It will also be appreciated that the present invention provides an improved system wherein a valve member may be replaced in a more quick and efficient manner. More particularly, it is not necessary to cut any sutures in order to remove the valve. Rather, the valve member may be disconnected from the stent (or other base stent) and a new valve member may be connected in its place. This is an important advantage when using biological tissue valves or other valves having limited design lives.

[0124] While the invention has been described in its preferred embodiments, it is to be understood that the words which have been used are words of description and not of limitation. Therefore, changes may be made within the appended claims without departing from the true scope of the invention.

WHAT IS CLAIMED IS:

1. A prosthetic heart valve system, comprising:

a base stent adapted to anchor against a heart valve annulus and defining an orifice therein; and

a valve component including a prosthetic valve defining therein a non-expandable, non-collapsible orifice, the valve component further including an expandable coupling stent extending from an inflow end thereof, the coupling stent having a contracted state for delivery to an implant position and an expanded state configured for outward connection to the base stent.

2. The system of claim 1, wherein the base stent is expandable and has a contracted state for delivery to an implant position adjacent a heart valve annulus and an expanded state sized to contact and anchor against the heart valve annulus.

3. The system of claim 2, wherein the base stent is plastically expandable.

4. The system of claim 1, wherein the coupling stent is plastically expandable.

5. The system of claim 1, wherein the prosthetic valve comprises a commercially available valve having a sewing ring, and wherein the coupling stent attaches to the sewing ring.

6. The system of claim 1, wherein the contracted state of the coupling stent is conical, tapering down in a distal direction.

7. The system of claim 6, wherein the coupling stent comprises a plurality of radially expandable struts at least some of which are arranged in rows, and wherein the distalmost row has the greatest capacity for expansion from the contracted state to the expanded state.

8. The system of claim 1, wherein the coupling stent comprises a plurality of radially expandable struts, and a row farthest from the prosthetic valve has alternating peaks and valleys, and wherein the base stent includes apertures into which the peaks of the coupling stent may project to interlock the two stents.

9. The system of claim 1, wherein the base stent includes a plurality of radially expandable struts between axially-oriented struts, and at least some of the axially-oriented struts have upper projections that demark locations around the stent.

10. A method of delivery and implant of a prosthetic heart valve system, comprising:

advancing a base stent to an implant position adjacent a heart valve annulus;

anchoring the base stent to the heart valve annulus;

providing a valve component including a prosthetic valve having a non-expandable, non-collapsible orifice, the valve component further including an expandable coupling stent extending from an inflow end thereof, the coupling stent having a contracted state for delivery to an implant position and an expanded state configured for outward connection to the base stent;

advancing the valve component with the coupling stent in its contracted state to an implant position adjacent the base stent; and expanding the coupling stent to the expanded state in contact with and connected to the base stent.

11. The method of claim 10, wherein the base stent is plastically expandable, and further comprising:

advancing the expandable base stent in a contracted state to the implant position; and

plastically expanding the base stent to an expanded state in contact with and anchored to the heart valve annulus, in the process increasing the orifice size of the heart valve annulus by at least 10%.

12. The method of claim 11, wherein the prosthetic valve of the valve component is selected to have an orifice size that matches the increased orifice size of the heart valve annulus.

13. The method of claim 11, further including mounting the base stent over a mechanical expander, and deploying the base stent at the heart valve annulus using the mechanical expander.

14. The method of claim 10, further including mounting the valve component on a holder having a proximal hub and lumen therethrough, and mounting the holder on the distal end of a handle having a lumen therethrough, the method including passing a balloon catheter through the lumen of the handle and the holder and within the valve component, and inflating a balloon on the balloon catheter to expand the coupling stent.

15. The method of claim 14, further including packaging the valve component mounted on the holder separately from the handle and the balloon catheter.

16. The method of claim 14, wherein the contracted state of the coupling stent is conical, and wherein the balloon on the balloon catheter has a larger distal expanded end than its proximal expanded end so as to apply greater expansion deflection to the coupling stent than to the prosthetic valve.

17. The method of claim 10, wherein the contracted state of the coupling stent is conical, and wherein the coupling stent comprises a plurality of radially expandable struts at least some of which are arranged in rows, and wherein the row farthest from the prosthetic valve has the greatest capacity for expansion from the contracted state to the expanded state.

18. The method of claim 10, wherein the coupling stent comprises a plurality of radially expandable struts, and a row farthest from the prosthetic valve has alternating peaks and valleys, and the method includes expanding the distal end of the coupling stent more than the rest of the coupling stent so that the peaks in the row farthest from the prosthetic valve project outward into apertures in the base stent.

19. The method of claim 10, wherein both the base stent and the coupling stent have a plurality of radially expandable struts between axially-oriented struts, and wherein the method includes orienting the coupling stent so that its axially-oriented struts are out of phase with those of the base stent to increase retention therebetween.

20. The method of claim 10, including increasing the orifice size of the heart valve annulus by 1.5-5 mm by plastically expanding the base stent.

21. A system for delivering a prosthetic heart valve, comprising:

a valve component including a prosthetic valve having a non-expandable, non-collapsible orifice, the valve component further including an expandable coupling stent extending from an inflow end thereof, the coupling stent having a contracted state for delivery to an implant position and an expanded state;

a valve holder connected to a proximal end of the valve component;

a balloon catheter having a balloon; and

a handle configured to attach to a proximal end of the valve holder and having a lumen for passage of the catheter, the balloon extending distally through the handle, past the holder and through the valve component.

22. The system of claim 21, wherein the prosthetic valve comprises a commercially available valve having a sewing ring, and wherein the coupling stent attaches to the sewing ring.

23. The system of claim 21, wherein the contracted state of the coupling stent is conical, tapering down in a distal direction.

24. The system of claim 21, wherein the contracted state of the coupling stent is conical and tapers down in a distal direction, and wherein the balloon catheter further includes a generally conical nose cone on a distal end thereof that extends through the valve component and engages a distal end of the coupling stent in its contracted state.

25. The system of claim 21, wherein the handle comprises a proximal section and a distal section that may be coupled together in series to form a continuous lumen, and wherein the distal section is adapted to couple to the hub of the holder to enable manual manipulation of the valve component using the distal section prior to connection with the proximal handle section.

26. The system of claim 25, wherein the balloon catheter and proximal handle section are packaged together with the balloon within the proximal section lumen.

27. The system of claim 21, wherein the valve component mounted on the holder is packaged separately from the handle and the balloon catheter.

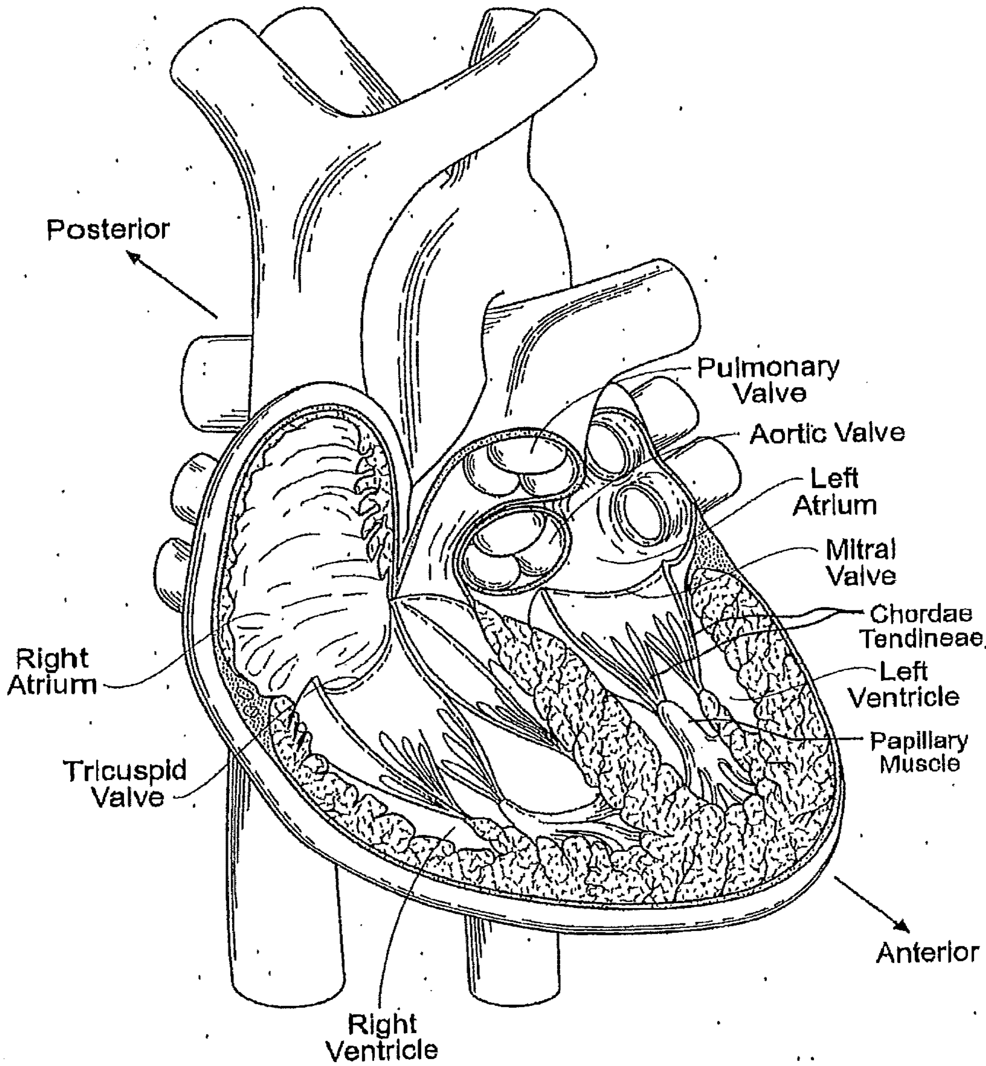
Posterior
Pulmonary Valve
Aortic Valve
Left Atrium
Mitral Valve
Chordae Tendineae
Left Ventricle
Papillary Muscle
Right Atrium
Tricuspid Valve
Anterior
Right Ventricle

Fig. 1

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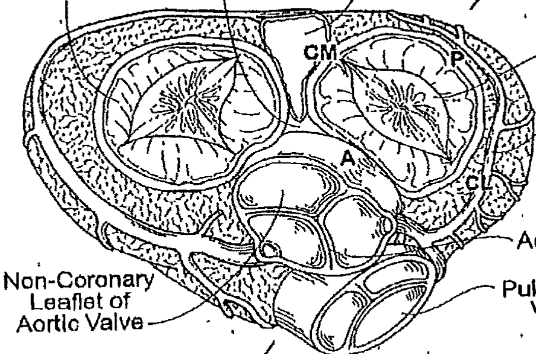

Fig. 2

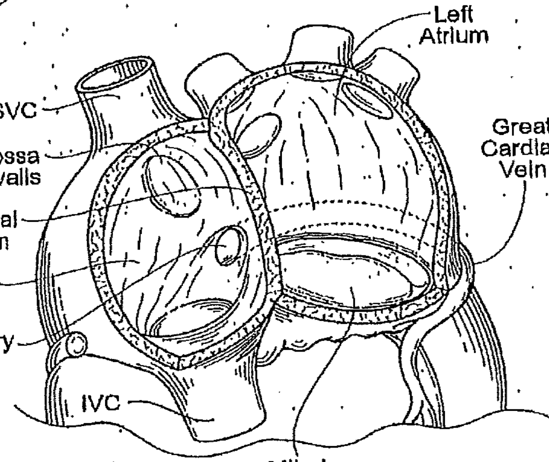

Fig. 4

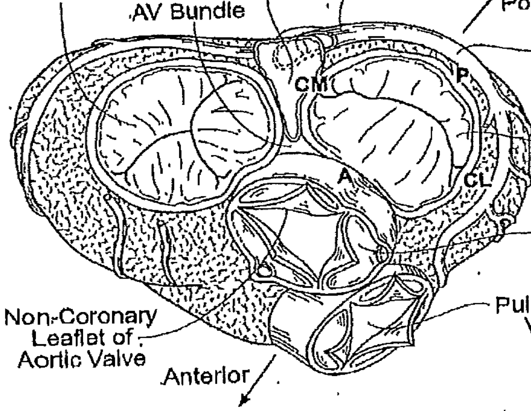

Fig. 3

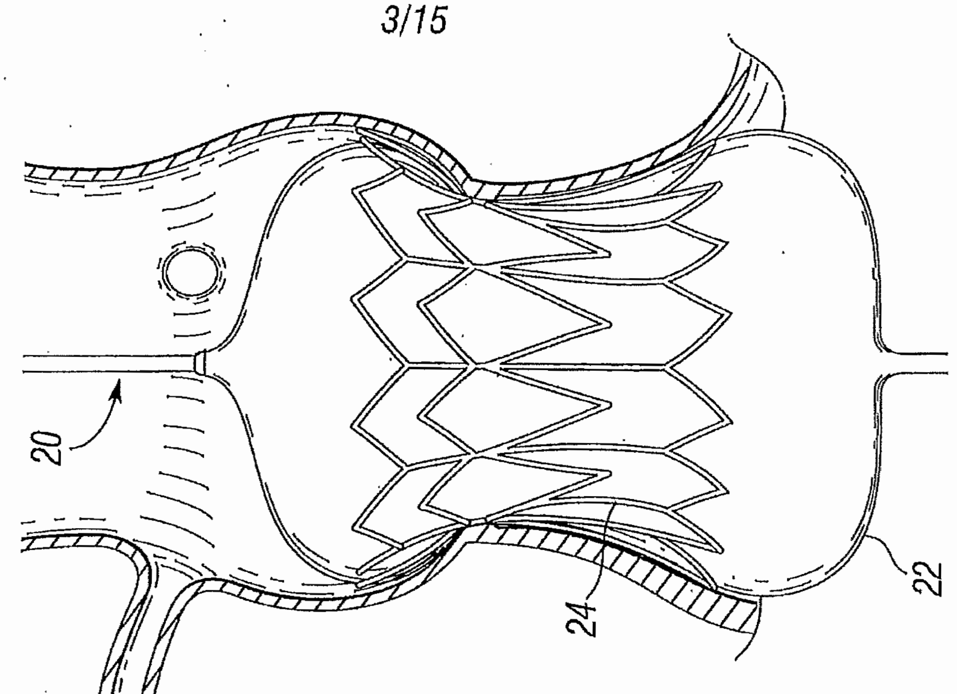

Fig. 5B

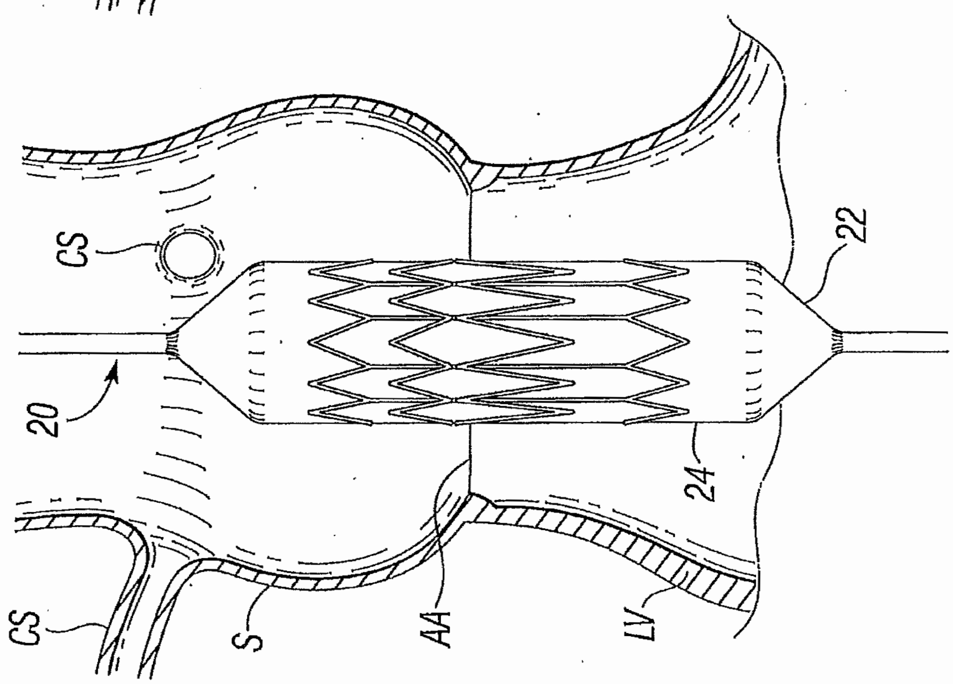

Fig. 5A

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Fig. 5D

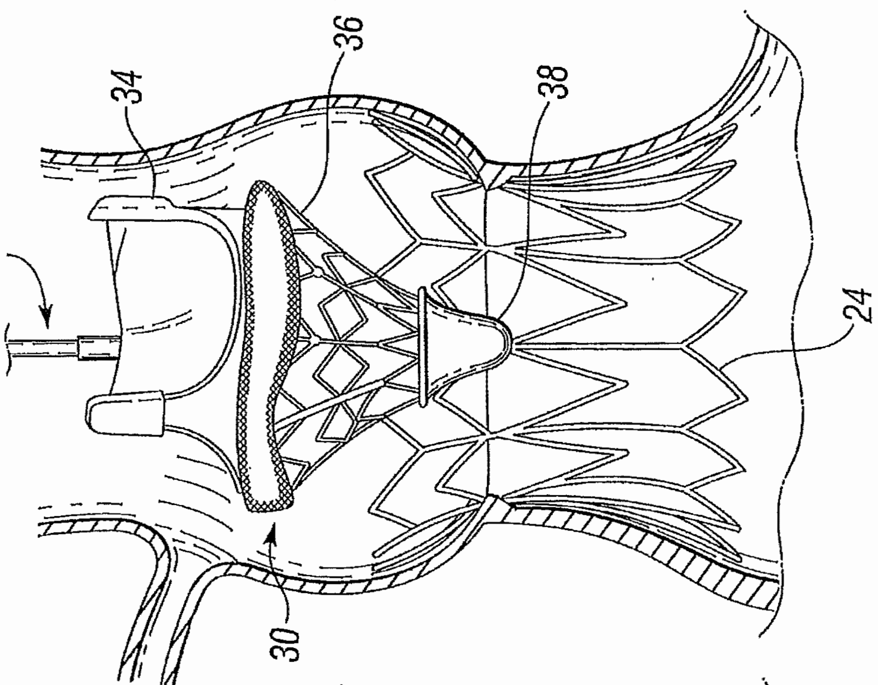
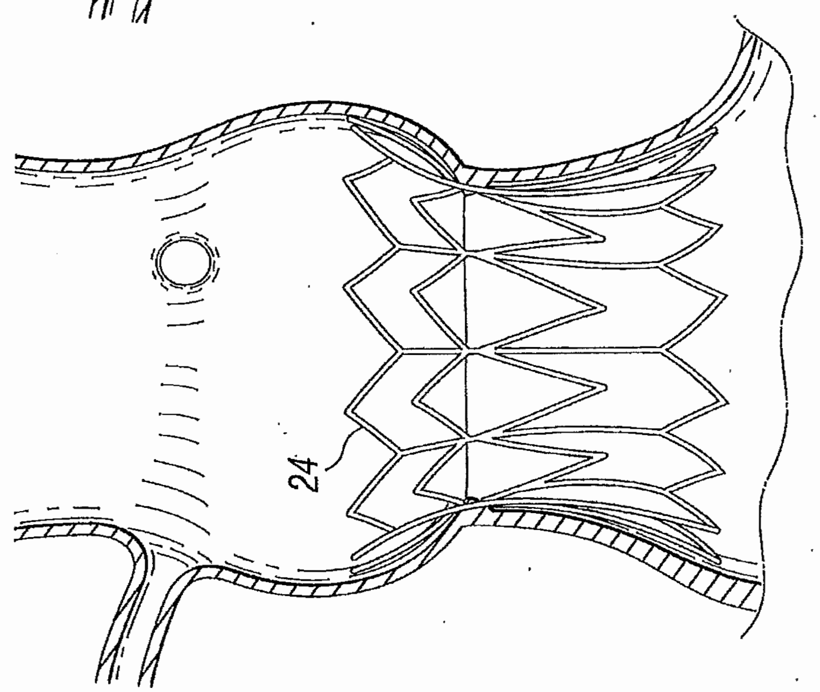


Fig. 5C



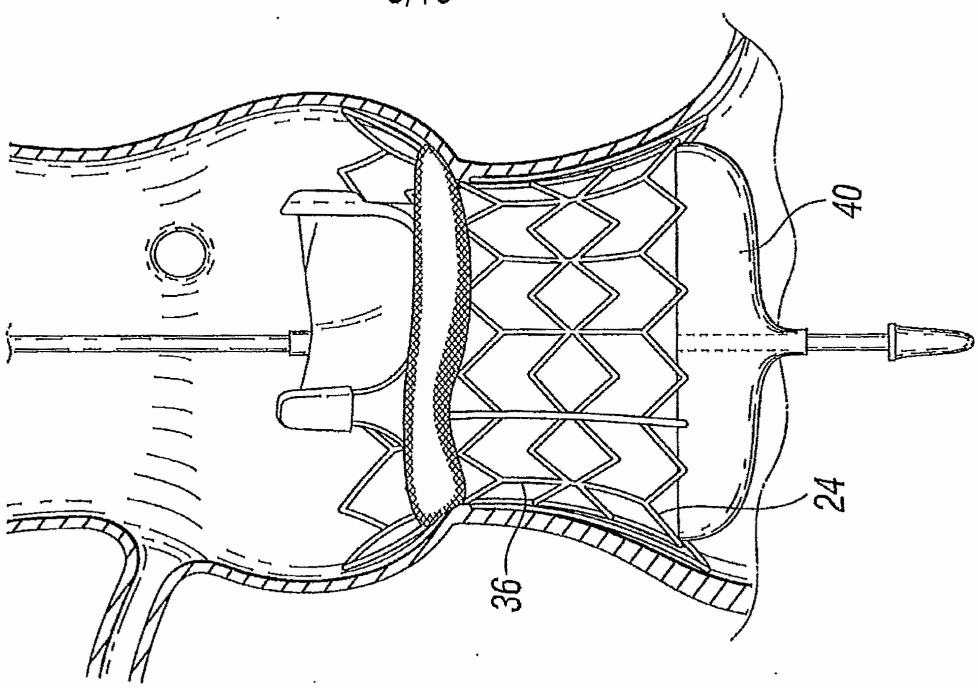


Fig. 5F

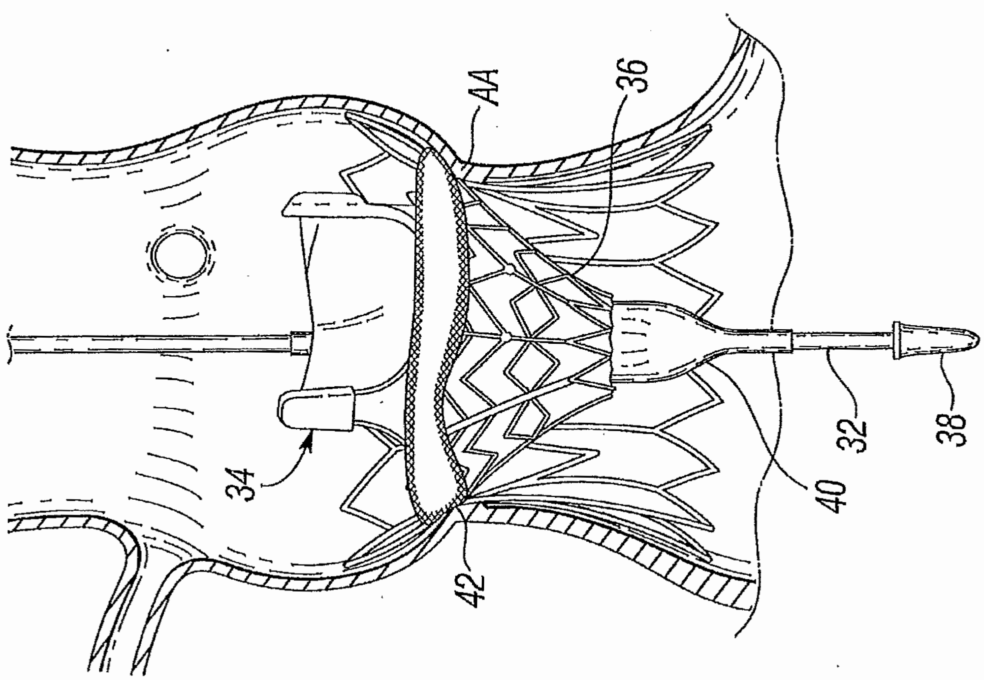


Fig. 5E

Fig. 5H

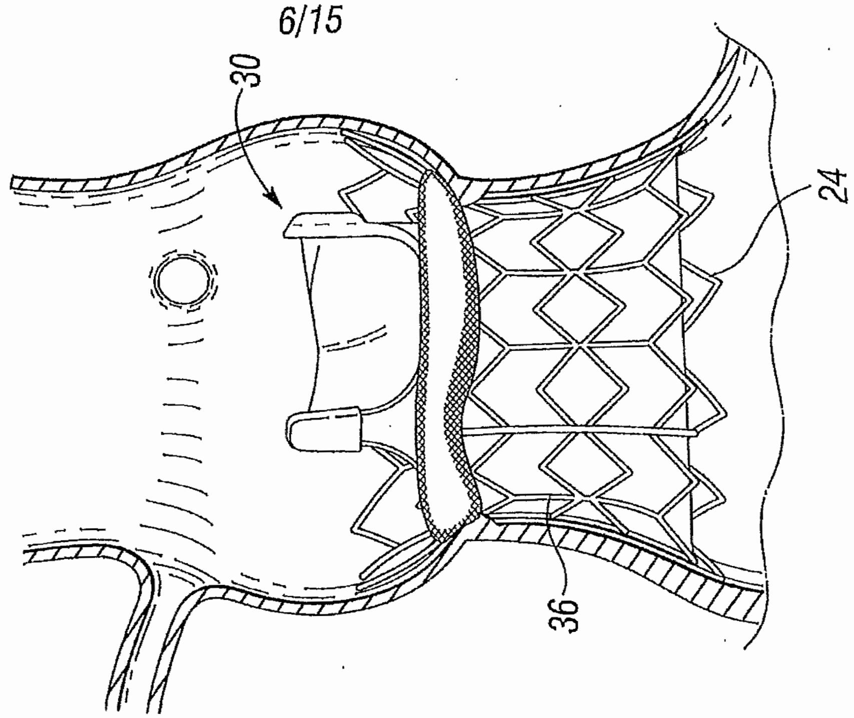
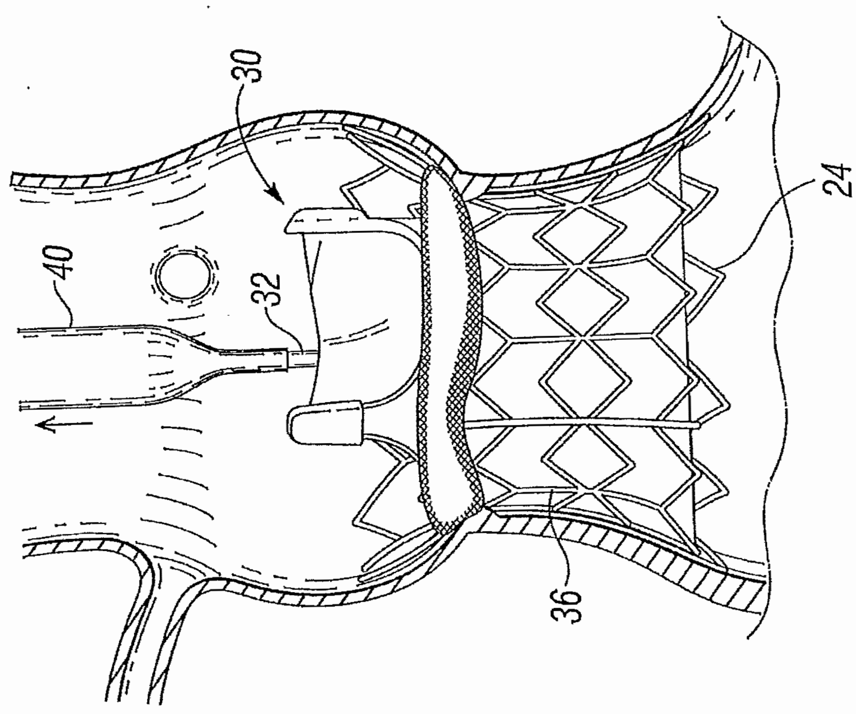


Fig. 5G



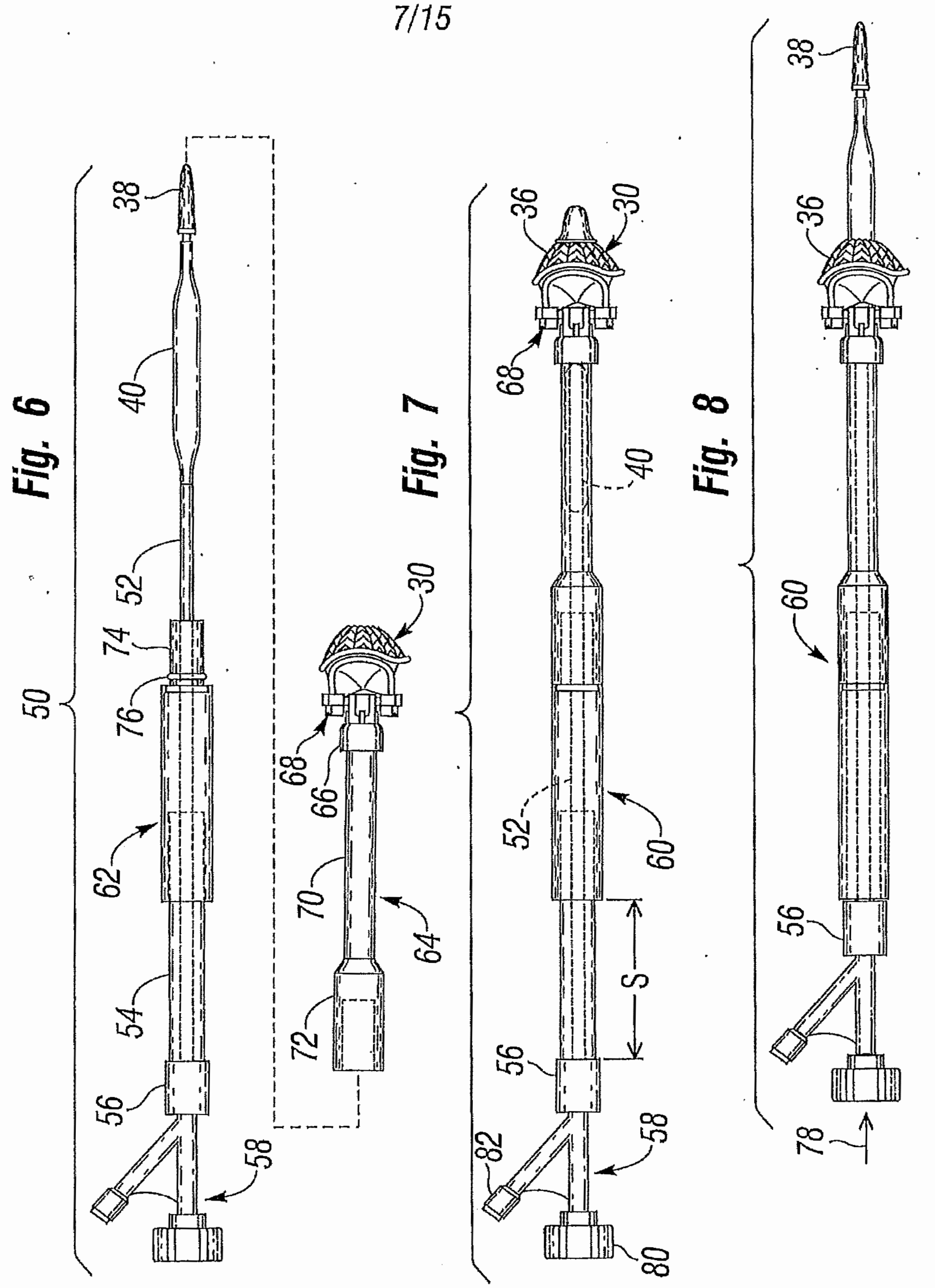


Fig. 6
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Fig. 7
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Fig. 8
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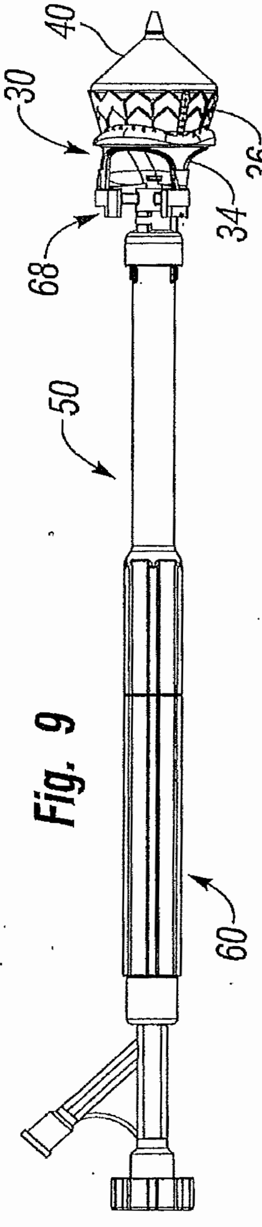


Fig. 9

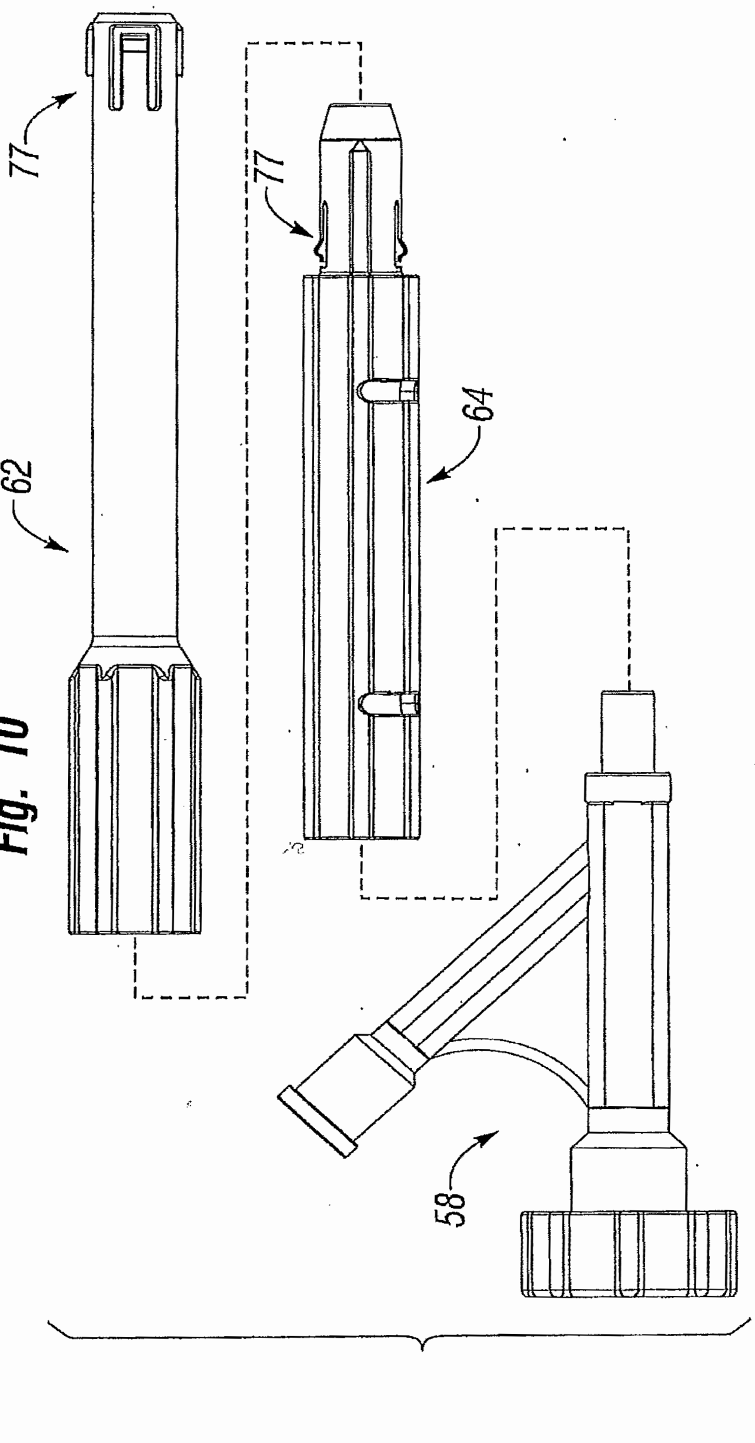


Fig. 10

Fig. 11A

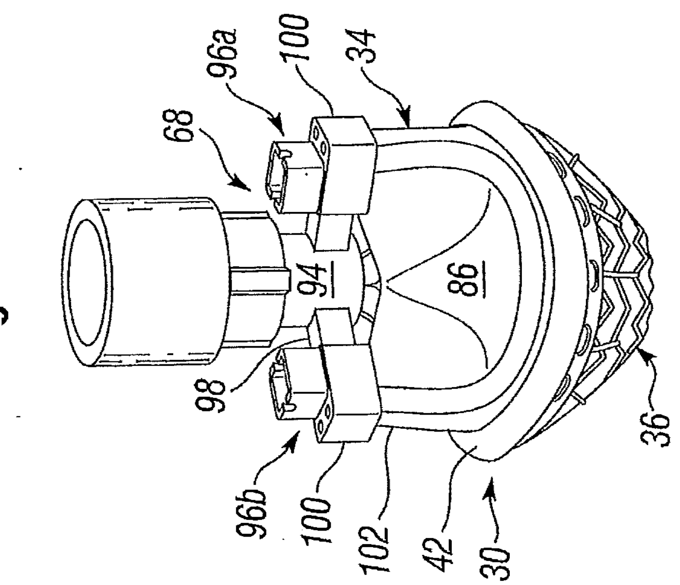


Fig. 11B

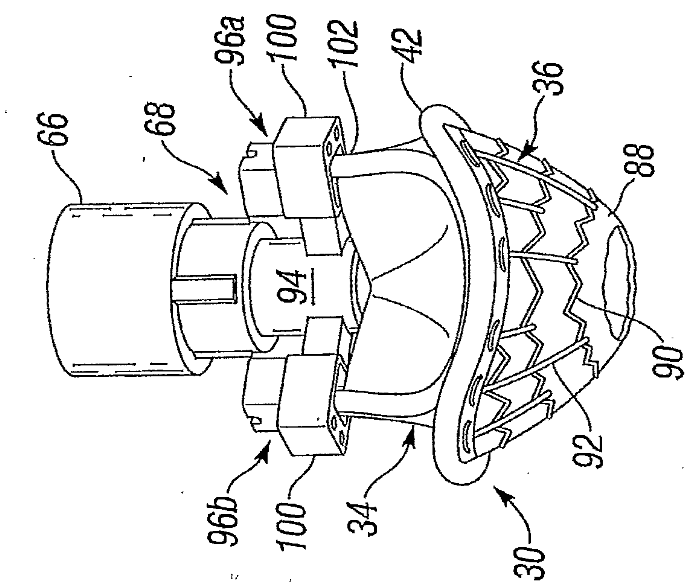


Fig. 11E

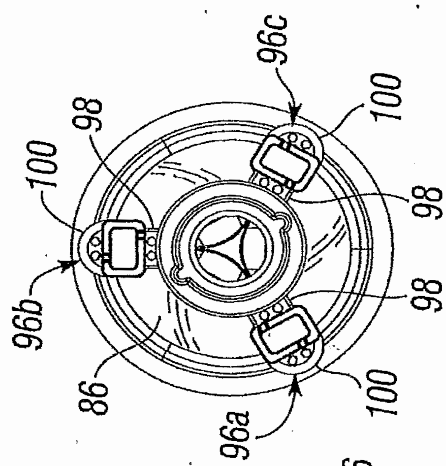


Fig. 11C

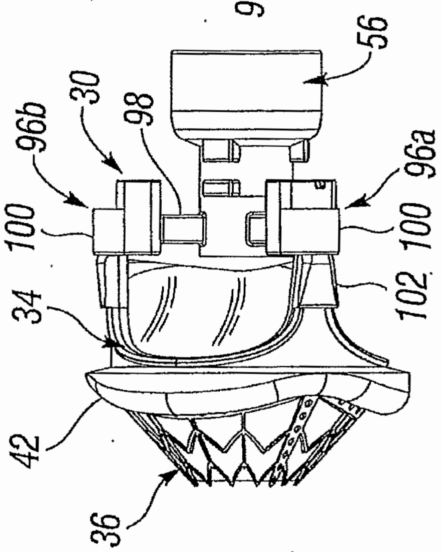


Fig. 11D

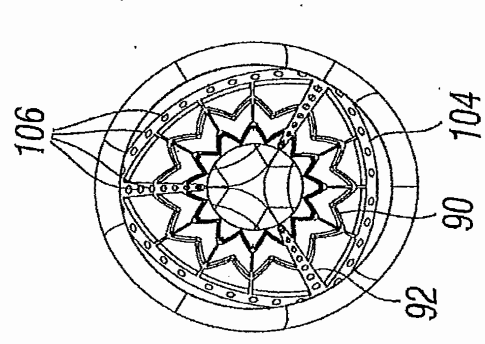


Fig. 12A

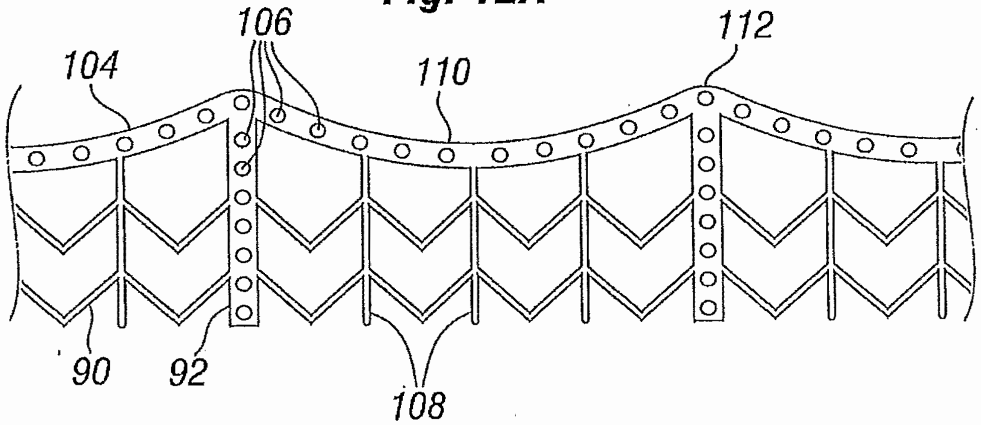


Fig. 12B

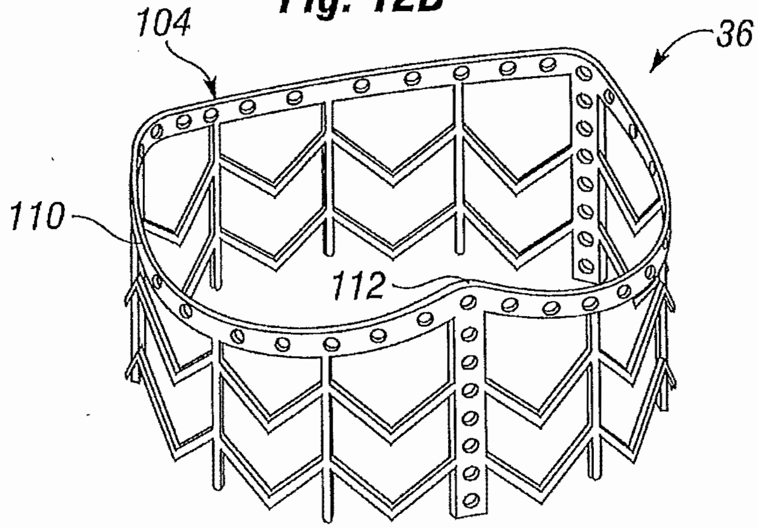


Fig. 13A

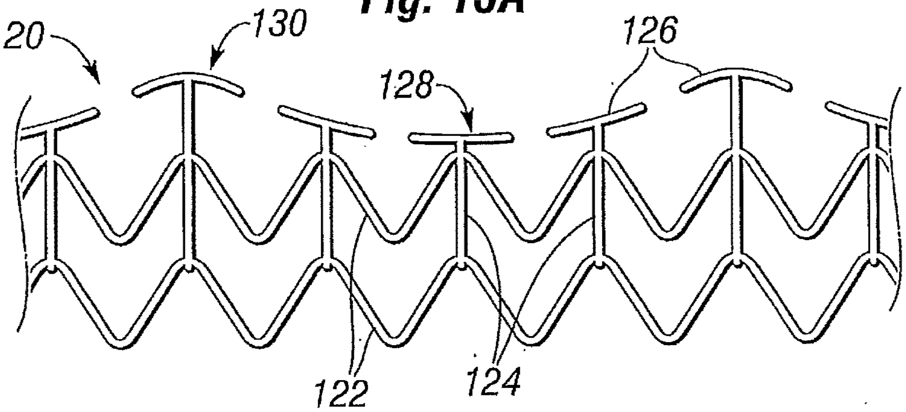


Fig. 13B

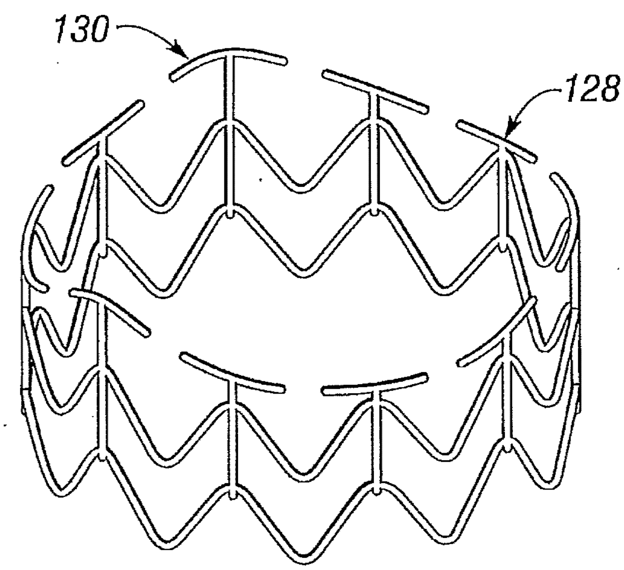


Fig. 14

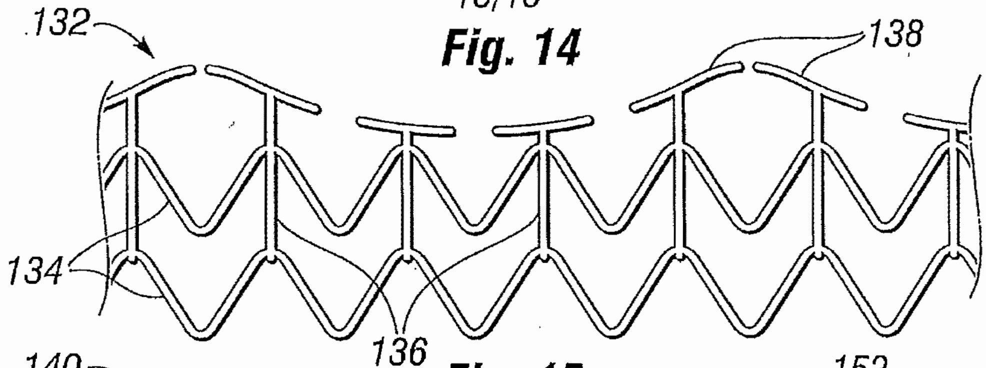


Fig. 15

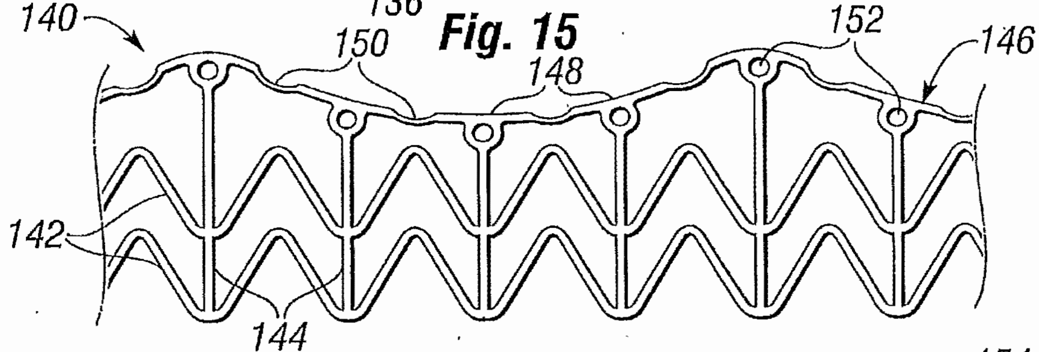


Fig. 16

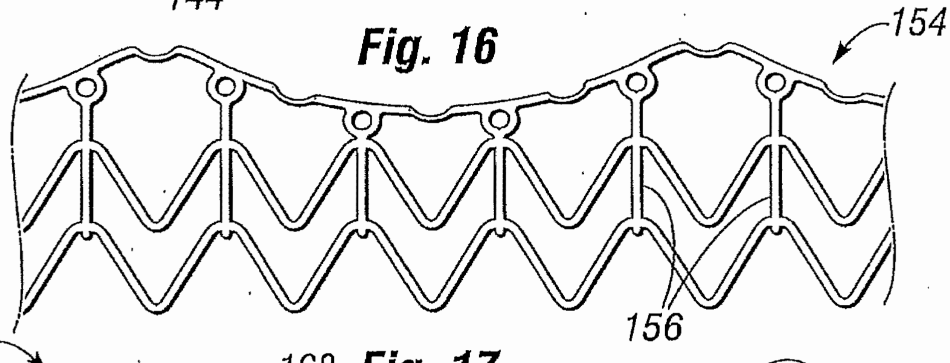


Fig. 17

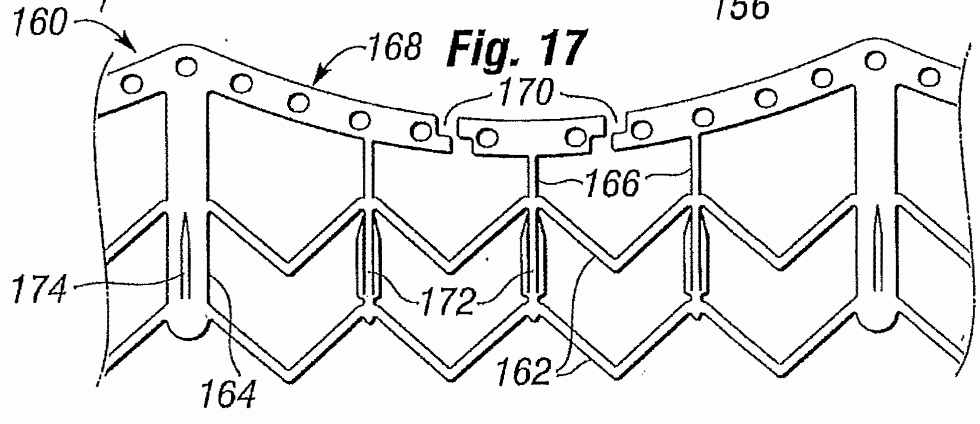


Fig. 18B

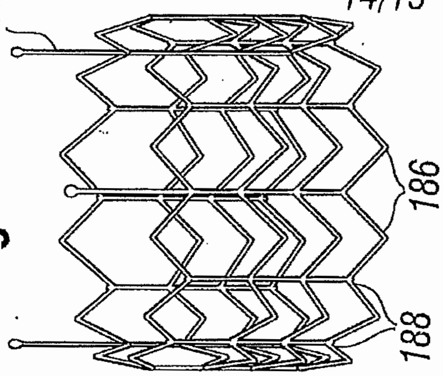


Fig. 20

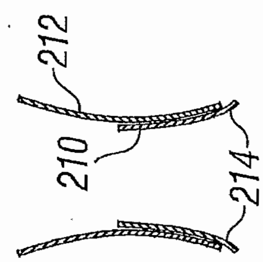


Fig. 18A

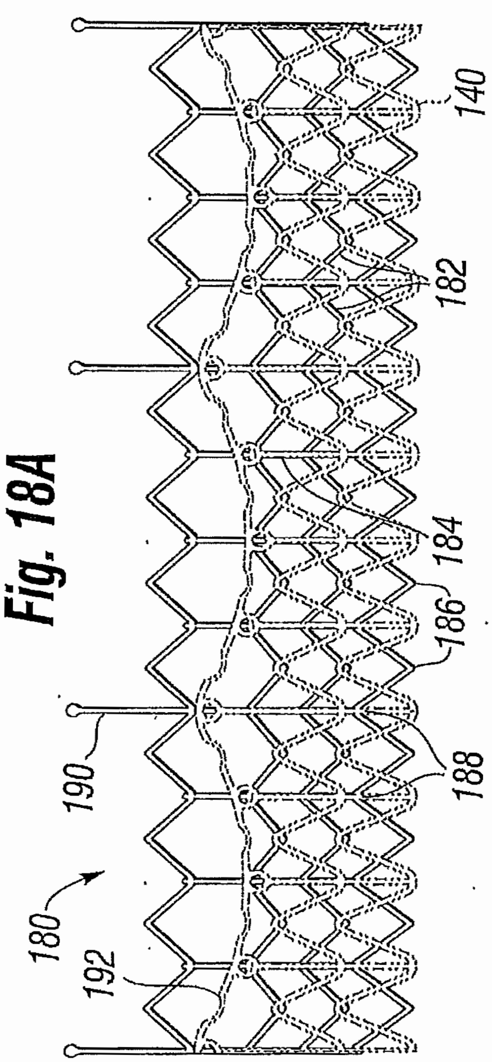


Fig. 19

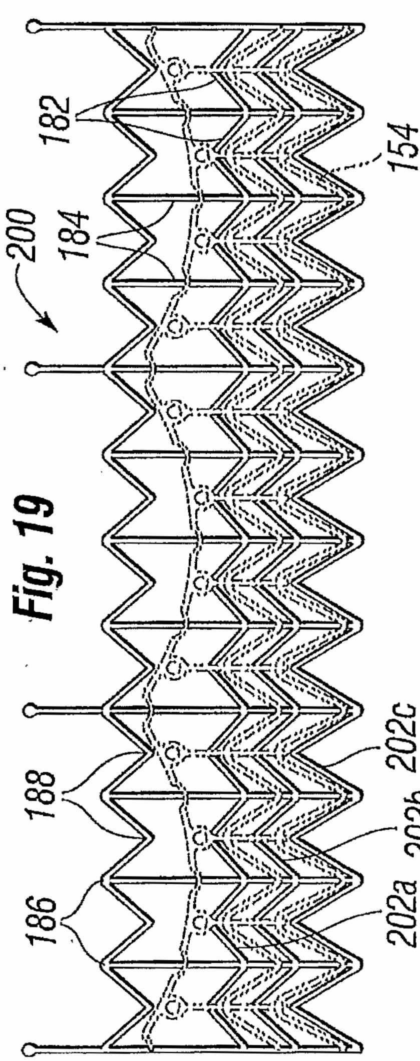


Fig. 21

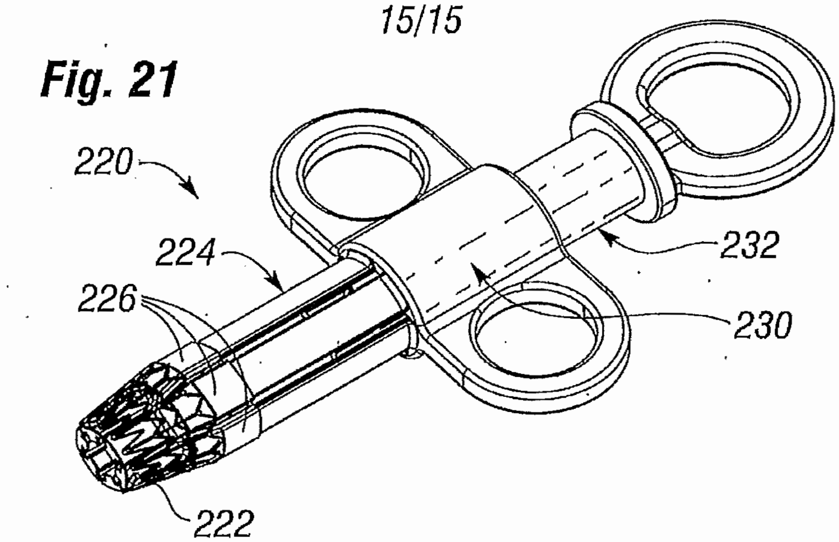


Fig. 22

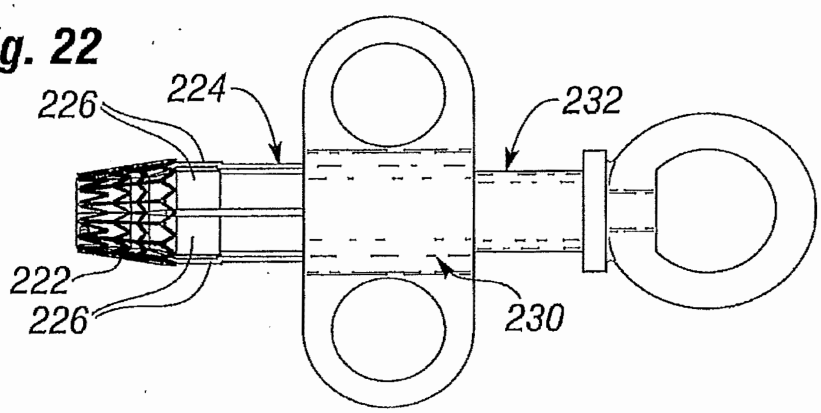
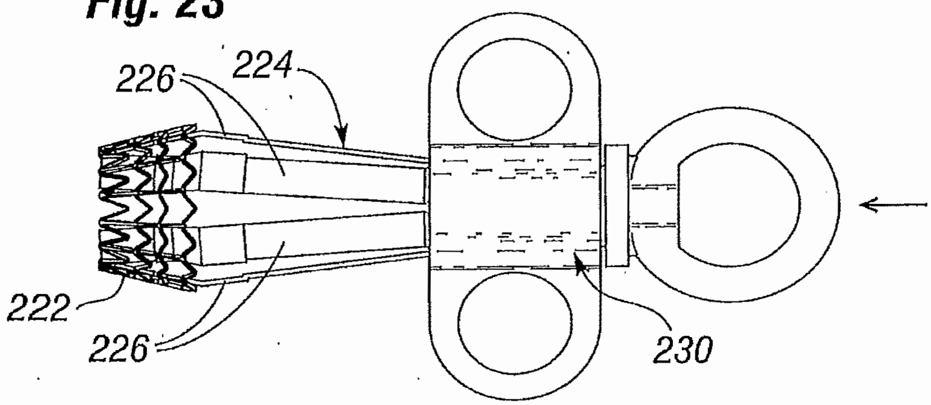


Fig. 23



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(54) **Title**: PACKAGING SYSTEMS FOR PERCUTANEOUSLY DELIVERABLE BIOPROSTHETIC VALVES

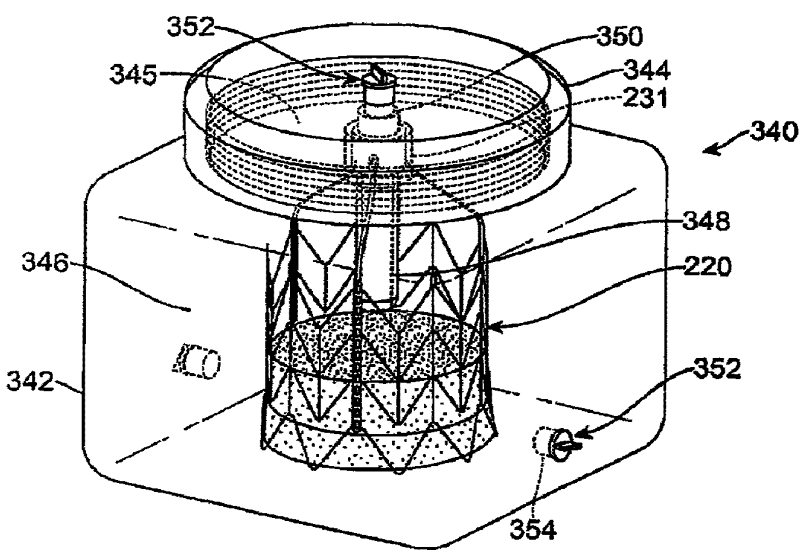

FIG. 3

(57) **Abstract**: A packaging system is disclosed for shipping a prosthetic tissue valve in a storage solution and preparing and loading of the bioprosthetic valve onto a catheter-based delivery system. The packaging system includes a fluid tight container filled with the storage solution attached to a delivery catheter, wherein the container surrounds the prosthetic tissue valve that is in a pre-loaded position on the delivery catheter during shipment and storage. The prosthetic tissue valve may include an attachment mechanism that attaches to the delivery catheter to properly position the tissue valve for loading within the delivery catheter. In another embodiment where the prosthetic tissue valve is not attached to the delivery catheter during shipment, the attachment mechanism may interact with the prosthetic tissue valve shipping container to prevent the bioprosthetic valve from moving during shipment.

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PACKAGING SYSTEMS FOR PERCUTANEOUSLY DELIVERABLE BIOPROSTHETIC VALVES

FIELD OF THE INVENTION

[0001] The invention relates generally to a packaging system for bioprosthetic valves. More specifically, the invention relates to packaging systems designed to protect a percutaneously deliverable bioprosthetic valve during shipping and/or to enable preparation and loading of the bioprosthetic valve onto a delivery catheter.

BACKGROUND OF THE INVENTION

[0002] Bioprosthetic heart valves include valve leaflets formed of flexible biological material. Bioprosthetic valves from human donors are referred to as homografts, whereas such valves from non-human animal donors are referred to as xenografts. These valves as a group are known as tissue valves. The tissue may include donor valve leaflets or other biological materials such as bovine or porcine pericardium, which are formed into the new valve structure. Depending on the method of implantation, the prosthetic valve structure may be sewn directly into place within a patient or attached to a second structure, such as a stent or other prosthesis, for implantation into a patient.

[0003] Conventional implantation of prosthetic tissue valves into the patient's body has been accomplished by invasive surgical procedures. Access to the heart valves (tricuspid, pulmonary, mitral, aortic), for instance, generally includes a thoracotomy or a sternotomy for the patient, and may include placing the patient on heart bypass to continue blood flow to vital organs, such as the brain, during the surgery. Thus, recovery from "open-heart" surgery often requires a great deal of time.

[0004] Recently percutaneous methods using catheter-based delivery mechanisms that traverse the vasculature to a treatment site have been developed allowing for minimally-invasive heart valve replacement and very short patient recovery times. Implantation of a prosthetic tissue valve percutaneously or by implantation using thoracic-microsurgery techniques is a far less invasive act than the surgical operation required for implanting traditional cardiac valve prostheses. Prosthetic tissue valves deliverable by these less invasive methods typically include an anchoring structure for supporting and fixing the valve prosthesis in the implantation position, to which the prosthetic valve leaflets are stably connected.

[0005] As mentioned above, some tissue valves are fashioned from xenografts taken from, for instance, a pig, horse, or cow, and others are fashioned from homografts taken from another human. The natural tissue for the replacement valves may be obtained from, for example, heart valves, aortic roots, aortic walls, aortic leaflets, pericardial tissue such as pericardial patches, bypass grafts, blood vessels, human umbilical tissue and the like. These natural tissues are typically soft tissues, and generally include collagen containing material. The tissue can be living tissue, decellularized tissue or recellularized tissue. The natural tissue can be fixed by crosslinking to provide mechanical stabilization, for example, by preventing enzymatic degradation of the tissue prior to implantation. A solution of glutaraldehyde or formaldehyde is typically used for fixation.

[0006] Preferably, the prosthetic tissue valves will be suspended in the glutaraldehyde storage solution until the surgical or percutaneous procedure is about to begin. As such when used in a catheter-based procedure, the clinician must prepare the fixed prosthetic tissue valve for insertion within the vasculature by removing the prosthetic tissue valve from the glutaraldehyde storage solution and rinsing the prosthetic tissue valve to remove the glutaraldehyde storage solution, followed by loading the prosthetic tissue valve onto or within the catheter-based delivery system. The clinician must take care during the preparation and loading steps not to contaminate or damage the prosthetic tissue valve. Such preparation adds time to the interventional procedure as well as risk that the tissue valve may not be properly loaded onto the catheter-based delivery system, which can lead to serious complications upon implantation of the prosthetic tissue valve at the treatment site. Due to the complexity and criticality of loading the prosthetic tissue valve onto the catheter-based delivery device, some vendors of replacement tissue valves actually provide representatives at the time of implantation to perform this aspect of the interventional procedure.

[0007] One solution to address proper loading concerns would be to “pre-load” the prosthetic tissue valve onto the catheter-based delivery system prior to shipment; however, prosthetic tissue valves heretofore have not been pre-loaded due to the sensitivity of the prosthetic tissue valves to prolonged crimping, as well as the necessity of maintaining the prosthetic tissue valve within a storage solution until just prior to implantation. Thus, there remains a need in the art for bioprosthetic valve packaging that can assure the sterility and integrity of a prosthetic tissue valve during shipment and ease loading of the prosthetic tissue valve onto a catheter-based delivery system by a clinician prior to performing the interventional procedure.

BRIEF SUMMARY OF THE INVENTION

[0008] Embodiments hereof are directed to a packaging and valve preparation system for shipping and preparing a prosthetic tissue valve having a natural tissue component in a storage solution and easing loading of the bioprosthetic valve onto a catheter-based delivery system. The packaging system includes a fluid tight shipping container or vessel filled with the storage solution, such as a glutaraldehyde solution, sealingly attached to a delivery catheter, wherein the container surrounds the prosthetic tissue valve that is in a pre-loaded position on the delivery catheter during shipment and storage. In an embodiment, the shipping container may be a bladder-type container. The prosthetic tissue valve may include an attachment mechanism that closes, crimps or otherwise attaches to the delivery catheter during shipment to properly position the bioprosthetic valve for loading within the delivery catheter by a clinician.

[0009] In another embodiment, a prosthetic tissue valve with an attachment mechanism may be unattached to the delivery catheter during shipment. In such an embodiment, the prosthetic tissue valve is disposed within a shipping container filled with a storage solution such that the attachment mechanism interacts with the shipping container to prevent the bioprosthetic valve from moving during shipment. In an embodiment, the shipping container may be a jar-like vessel with a threaded cap having a holding tube.

BRIEF DESCRIPTION OF DRAWINGS

[0010] The foregoing and other features and advantages of the invention will be apparent from the following description of embodiments hereof as illustrated in the accompanying drawings. The accompanying drawings, which are incorporated herein and form a part of the specification, further serve to explain the principles of the invention and to enable a person skilled in the pertinent art to make and use the invention. The drawings are not to scale.

[0011] FIG. 1 is a cross-sectional side view of a delivery catheter according to an embodiment hereof.

[0012] FIG. 2 is a side perspective view of a prosthetic tissue valve system according to an embodiment hereof.

[0013] FIG. 3 is a side perspective view of the prosthetic tissue valve system of FIG. 2 in a shipping container according to an embodiment hereof.

[0014] FIG. 4 is a side perspective view of the prosthetic tissue valve system of FIG. 2 being loaded onto the delivery catheter of FIG. 1.

[0015] FIGS 4A and 4B are perspective views of an attachment assembly according to another embodiment hereof.

[0016] FIG. 5 is a cross-sectional side view of the delivery catheter of FIG. 1 with the prosthetic tissue valve system of FIG. 2 in a delivery configuration.

[0017] FIG. 6 is a side view of a delivery catheter attached to a shipping bladder containing the prosthetic tissue valve of FIG. 2 in a shipping/storage configuration in accordance with another embodiment hereof, wherein the bioprosthetic valve is pre-loaded onto the delivery catheter.

[0018] FIG. 7 is a side view of a prosthetic tissue valve delivery system in partial section that is attached to an accordion-like shipping bladder containing the prosthetic tissue valve in a shipping/storage configuration in accordance with another embodiment hereof, wherein the bioprosthetic valve is pre-loaded onto the delivery catheter.

[0019] FIG. 8 is a side view of the delivery system and accordion-like shipping bladder of FIG. 7 with the prosthetic tissue valve collapsed for loading within the delivery catheter.

DETAILED DESCRIPTION OF THE INVENTION

[0020] Specific embodiments are now described with reference to the figures, wherein like reference numbers indicate identical or functionally similar elements. The terms "distal" and "proximal" are used in the following description with respect to a position or direction relative to the treating clinician. "Distal" or "distally" are a position distant from or in a direction away from the clinician. "Proximal" and "proximally" are a position near or in a direction toward the clinician.

[0021] The following detailed description is merely exemplary in nature and is not intended to limit the invention or the application and uses of the invention. Although the description of the invention is in the context of heart valve replacement via blood vessels such as the aorta, coronary, and carotid arteries, embodiments of the present invention may also be used to deliver tissue valves in any other vessel where it is deemed useful. Furthermore, there is no intention to be bound by any expressed or implied theory presented in the preceding technical field, background, brief summary or the following detailed description.

[0022] FIG. 1 is a cross-sectional side view of a delivery catheter 100 for percutaneously delivering a prosthetic tissue valve according to an embodiment of the present invention. Delivery catheter 100 includes an outer tubular component 102, a middle tubular component 104, and an inner component 106. Outer tubular component 102 defines a first lumen 108 from a proximal end 101 to a distal end 103 thereof through which middle tubular component 104 is slidably disposed, and may alternatively be referred to as a sheath component. Middle tubular component 104 defines a second lumen 110 from a proximal end 105 to a distal end 107 thereof through which inner component 106 is slidably disposed. Inner component 106 has a proximal end 111 and distal tip 112. In the embodiment of FIG. 1, distal tip 112 is a molded polymeric piece attached to a distal end 109 of an elongate shaft portion 114 of inner component 106. In another embodiment, distal end 109 of elongate shaft portion 114 may be coiled to provide a steerable tip, such that distal tip 112 is omitted. During an interventional procedure, proximal ends 101, 105, 111 of outer tubular component 102, middle tubular component 104, and inner component 106, respectively, each extend proximally outside of the patient's body such that they may be manipulated by a clinician and one or more of proximal ends 101, 105, 111 may include a handle or knob (not shown) in order to facilitate securing a longitudinal position or sliding movement thereof.

[0023] Outer and/or middle tubular components 102, 104 may be made from polymeric tubing, such as tubing formed from, for *e.g.*, polyethylene block amide copolymer, polyvinyl chloride, polyethylene, polyethylene terephthalate, polyamide, polyimide, polyetheretherketone (PEEK), nylon or copolymers thereof, as well as from metal tubing formed from stainless steel or nitinol, for example. In an embodiment, outer and/or middle tubular component 102, 104 may include a stainless steel hypotube, such as a hypotube of stainless steel 304 or 316, cut in a spiral or spring-like pattern to have high column strength with flexibility. In various other embodiments hereof, outer and/or middle tubular components 102, 104 may include a reinforced shaft segment, such as a shaft segment of a stainless steel braided polyimide, to provide columnar strength and pushability to delivery catheter 100 and/or multiple shaft components of varying flexibility to provide a gradual transition in flexibility as delivery catheter 100 extends distally. In another embodiment, outer and/or middle tubular components 102, 104 may be a composite shaft having an outer layer of polytetrafluoroethylene (PTFE) and an inner liner of fluorinated ethylene propylene (FEP). Inner component 106 may be a solid metallic core wire, and, in embodiments hereof, may be tapered at its distal end and/or include one or more core wire sections to provide a stiffness transition. In various other embodiments, inner component 106 may be a hollow polymeric or metallic tube that defines a guidewire lumen therethrough.

[0024] Delivery catheter 100 is depicted in FIG. 1 in a loading configuration with an annular distal stopper 116, which is attached to and surrounds inner component 106, positioned distal of distal ends 103, 107 of outer and middle tubular components 102, 104. In addition, distal tip 107 of middle tubular component 104 is positioned distal of distal end 103 of outer tubular component 102 so that middle tubular component distal end 107 acts as a proximal stopper during loading of a prosthetic valve, such as prosthetic tissue valve 220 depicted in FIG. 2 and described below. The operation of delivery catheter 100 during loading and delivery is also described in detail below. Alternatively, a proximal stopper may be attached to and surround inner component 106 an appropriate length proximal of distal stopper 116.

[0025] With reference to FIG. 2, prosthetic tissue valve system 220 includes a prosthetic tissue valve 221, having a stent-like frame 222 with valve leaflets 224 secured therein, and an attachment assembly 230. Stent-like frame 222 of prosthetic tissue valve 221 is a tubular structure having four sinusoidal rings 226 attached peak-to-peak and valley-to-valley by longitudinal connectors 228 and includes three bands 232, which may be slightly wider than longitudinal connectors 228, longitudinally extending from an outflow end of stent-like frame 222. Sinusoidal rings 226 may be attached to longitudinal connectors 228 and bands 232 by any attachment mechanism known to one of ordinary skill in the art of stent construction or may be formed pre-connected as a unitary structure, such as by laser cutting or etching the entire stent body from a hollow tube or sheet. Bands 232 may each include an eyelet 239, or in an alternate embodiment a broadened paddle-like area, at a proximal end thereof to aid in the releasable engagement of bands 232 with attachment assembly 230, as discussed in more detail below. Stent-like frame 222 is "self-expanding", which as used herein means that stent-like frame 222 has a mechanical memory to return to an expanded or deployed configuration as shown in

FIG. 2. Mechanical memory may be imparted to stent-like frame 222 by thermal treatment to achieve a spring temper in stainless steel, for example, or to set a shape memory in a susceptible metal alloy, such as nitinol. As such in embodiments hereof, sinusoidal rings 226 and longitudinal connectors 228 for producing stent-like frame 222 may be made from stainless steel, a pseudo-elastic metal such as nitinol, or a nickel-based super alloy. It would be understood by one of ordinary skill in the art that other self-expanding stent-like frames, with or without tubular structures having sinusoidal rings and/or connectors, may be utilized in embodiments of the present invention without departing from the scope hereof.

[0026] Valve leaflets 224 of prosthetic tissue valve 221 may be of xenograft or homograft natural tissue and may form a bicuspid, tricuspid, or tube replacement valve. The natural tissue for the replacement valve leaflets may be obtained from, for example, heart valves, aortic roots, aortic walls, aortic leaflets, pericardial tissue, such as pericardial patches, bypass grafts, blood vessels, human umbilical tissue and the like. Valve leaflets 224 may be sutured or otherwise securely attached to stent-like frame 222 as would be known to one of ordinary skill in the art of prosthetic tissue valve construction.

[0027] Attachment assembly 230 includes a locking collar 231 and a holding sleeve 460 (shown in FIG. 4). Locking collar 231 may be formed from a flexible material, such as nylon, polyethylene, polyurethane, silicone or other suitable polymer. In the embodiment of FIG. 2, locking collar 231 is c-shaped having cog-like projections 241 surrounding a distal end thereof with a plurality of slots 233 defined between projections 241. Slots 233 are sized to provide an interference or tight fit with bands 232 of stent-like frame 222 to substantially prevent longitudinal movement between attachment assembly 230 and prosthetic tissue valve 221 with eyelets 239 being wider than slots 233 to prevent bands 232 from sliding free thereof. Locking collar 231 is surrounded by holding sleeve 460 that fits tightly enough around locking collar 231, such as in an interference fit, to prevent radial movement and/or release of bands 232 from slots 233 and thereby secures prosthetic tissue valve 221 to attachment assembly 230.

[0028] In embodiments hereof, holding sleeve 460 is a thin-walled cylinder of a polymeric or elastomeric material that is slidable or stretchable over locking collar 231. In another embodiment, holding sleeve 460 may be of a material that is heat shrinkable around locking collar 231 to radially secure bands 232 therein. In one such embodiment, holding sleeve 460 may be a short, tubular component made from a thin, stretchable material, such as silicone or polyurethane, having an inner diameter slightly larger than the diameters of catheter tip 112 and outer tubular component 102, wherein the inner diameter may be stretched to a second, larger inner diameter when holding sleeve 460 contains the unlocked or open locking collar 231, such that holding sleeve 460 substantially returns to its reduced, original inner diameter when locking collar 231 is locked or closed onto inner component 106. In an embodiment where holding sleeve 460 is formed from a non-stretchable material, while snapping or closing locking collar 231 in place a clinician may maintain a position of holding sleeve 460 over locking collar 231 to retain band(s) 232 therein until outer tubular component 102 has been distally forward to capture band(s) 232 and retain prosthetic tissue valve 221. In each of the aforementioned embodiments, holding sleeve 460 is removed after the loading of bioprosthetic valve 221 is completed.

[0029] Locking collar 231 includes projections or posts 234 protruding from a first longitudinal end surface 237 thereof that align with and have an interference fit within holes 236 in a second longitudinal end surface 235 thereof. Each post 234 is fit within a respective hole 236 when locking collar 231 is closed or crimped onto delivery catheter 100 to pre-load prosthetic tissue valve 221 thereon, as discussed in more detail below.

[0030] In another embodiment shown in FIGS. 4A and 4B, attachment assembly 430 includes locking collar 431 having interlocking half-ring segments 431a, 431b and holding sleeve 460'. Half-ring segment 431a includes projections or posts 434 that fit or snap within corresponding holes 436 in half-ring segment 431b. Each half-ring segment 431a, 431b includes cog-like projections 441 radially extending from a distal end thereof between which slots 433 are defined for receiving bands 232. In an embodiment, slots 433 are sized to have an interference fit with bands 232 and/or to be narrower than eyelets 239. Locking collar 431 is surrounded by holding sleeve 460', which may be a thin-walled polymeric or elastomeric cylinder/tubular component as described above with reference to the embodiments of holding sleeve 460, that radially secures bands 232 within slots 433 in a manner as previously described with reference to the embodiments of holding sleeve 460. Locking collar 431 may be formed from a flexible material, such as nylon, polyethylene, polyurethane, silicone or other suitable polymer.

[0031] In FIG. 4A, attachment assembly 430 is shown holding prosthetic tissue valve 221 in a pre-loaded configuration over inner component 106 of delivery catheter 100, with unattached half-ring segments 431a, 431b encircling inner component 106 and positioned between distal stopper 116 and distal end 107, *viz.*, proximal stopper, of middle tubular component 104. In FIG. 4B, half-ring segments 431a, 431b have been closed or locked onto inner component 106 such that bands 232 are radially constrained within slots 433 by outer tubular component 102, which is drawn over locking collar 431 concurrent with the removal of holding sleeve 460'. With prosthetic tissue valve 221 secured in this manner to delivery catheter 100, a clinician is ready to load the bioprosthetic valve within the delivery catheter as described in more detail below.

[0032] In various other embodiments, attachment assemblies for securing prosthetic tissue valves to delivery systems in accordance herewith may include hooks, pigtails or cartridge-type connectors, such as those shown and described in patent application publications US 2008/0228254 A1 to Ryan and US 2008/0228263 A1 to Ryan, U.S. Appl. No. 12/357,958 to Bloom *et al.* (Atty. Dkt. No. P0027615.01) and/or U.S. Appl. No. 12/358,489 to Tabor *et al.* (Atty. Dkt. No. P0027615.04), each of which is incorporated by reference herein in its entirety.

[0033] FIG. 3 is a side perspective view of prosthetic tissue valve system 220 of FIG. 2 in a shipping container 340 according to an embodiment of the present invention. Shipping container 340 includes a jar-like vessel 342 having a threadably removable cap 344 for covering and uncovering a mouth 345 of vessel 342. Cap 344 has a centrally disposed holding tube 348 attached thereto that extends through locking collar 231, which is positioned within holding sleeve 460 (shown in FIG. 4), and into an interior of prosthetic tissue valve 221. With holding tube 348 so positioned, prosthetic tissue valve system 220 is prevented from moving during shipment and storage. In an embodiment, an upper or first end of the hollow holding tube 348 is accessible from an outside surface of cap 344 and defines an inflow port 350, which is fitted with a fluid-tight plug 352 during shipment and storage. Two outflow ports 354, which are apertures or holes, are shown in opposing walls of jar-like vessel 342, and are each fitted with a respective fluid-tight plug 352. Shipping container 340 holds prosthetic tissue valve 221 in a storage solution 346, such as a glutaraldehyde solution, during shipment and storage and is fluid-tight when cap 344 is threadably secured to jar-like vessel 342 and plugs 352 are in place within their respective ports 350, 354. Shipping container 340 may be made of glass or a suitable polymeric material, such as polyethylene, polyethylene terephthalate, polypropylene, acetal or nylon.

[0034] When a clinician is ready to use prosthetic tissue valve 221, plugs 352 are removed from inflow and outflow ports 350, 354 and a saline or other rinsing solution is introduced into jar-like vessel 342 via inflow port 350 to flush storage solution 346 out through outflow ports 352. As shown in FIG. 4, prosthetic tissue valve system 220 is then removed from vessel 342 and slipped/loaded over distal tip 112 of delivery catheter 100 until locking collar 231 surrounded by holding sleeve 460 is positioned around inner component shaft portion 114 between distal stopper 116 and distal end 107 of middle tubular component 104, which as mentioned above acts as a proximal stopper during loading and delivery. In FIG. 4, an optional radiopaque marker band 462 is shown surrounding distal end 103 of outer tubular component 102 to aid in fluoroscopic placement of delivery catheter 100 within a vessel. In order to secure prosthetic tissue valve system 220 to delivery catheter 100, locking collar 231 is crimped or otherwise closed down around inner component shaft portion 114 until male posts 234 are seated/snapped within holes 236, so that prosthetic tissue valve 221 is pre-loaded onto delivery catheter 100.

[0035] Once prosthetic tissue valve system 220 is properly locked onto delivery catheter 100 by snapping locking collar 231 in place, holding sleeve 460 is moved distally a short distance, for *e.g.*, approximately 5 – 10 mm, to expose stent eyelets 239 and locking collar 231 while maintaining stent bands 232 in slots 233 of locking collar 231. Outer tubular component 102 is moved distally to initially capture and cover stent bands/eyelets 232, 239 and locking collar 231 with continued distal movement of outer tubular component 102, relative to middle tubular component 104 and inner component 106, collapses and loads prosthetic tissue valve system 221 into the delivery system 100. Holding sleeve 460 is removed after completion of the loading process and stent bands/eyelets 232, 239 are held within slots 233 of locking collar 231 by outer tubular component 102 so that prosthetic tissue valve 221 remains attached to locking collar 231. In FIG. 5, prosthetic tissue valve 221 is shown fully collapsed and loaded in a delivery configuration within delivery catheter 100. During loading and delivery, proximal and distal stoppers 107, 116 aid in maintaining a longitudinal position of locking collar 231, and thus prosthetic tissue valve system 220, relative to delivery catheter inner component 106. In an alternate embodiment, proximal and distal stoppers may be omitted and locking collar 231 sized to have an interference or frictional fit with inner component 106 when closed thereon.

[0036] In an embodiment hereof, delivery catheter 100 with prosthetic tissue valve 221 loaded therein may be used in a heart valve replacement procedure, wherein prosthetic tissue valve 221 is to be used to replace an insufficient/incompetent aortic valve. Loaded delivery catheter 100, as shown in FIG. 5, may be introduced into the vasculature either via a percutaneous puncture, a.k.a the Seldinger technique, or via a surgical cut-down, to be positioned at the aortic treatment site via a retrograde approach. Delivery catheter 100 may achieve access to the vasculature through a branch of the femoral artery, a carotid artery, a subclavian artery, or a brachial artery. In another embodiment, access to the heart may be attained via a transapical, transaortic and/or other minimally-invasive surgical approach. Methods and apparatus for accessing the arterial system with catheters and navigating such catheters to the level of the aortic arch are generally known in the art. Once delivery catheter 100 is positioned as desired within the native aortic valve, outer tubular component 102 is proximally retracted relative to middle tubular component 104 and inner component 106 to release prosthetic tissue valve 221 from the collapsed, delivery configuration shown in FIG. 5. When outer tubular component 102 is retracted proximal of locking collar 231, self-expanding prosthetic tissue valve 221 will expand and bands 232 will be released from locking collar 231, which remains with delivery catheter 100 for removal from the patient therewith. In its fully deployed configuration, stent-like frame 222 of prosthetic tissue valve 221 radially displaces the native aortic valve leaflets to conform and seal to the aortic annulus, as would be understood by one of ordinary skill in the art of heart or venous valve replacement.

[0037] FIG. 6 is a side view of delivery catheter 600 attached to a shipping bladder 642 in a shipping/storage configuration in accordance with another embodiment hereof. Prosthetic tissue valve 221 is shown within shipping bladder 642 and attached/pre-loaded onto delivery catheter 600 by attachment assembly 631, which includes a collar component of metal or polymeric tubing having multiple slots around its circumference similar to slots 433 in the embodiment of FIG. 4. Attachment assembly 631 is pre-bonded onto inner tubular component 606, such that during shipment and storage the eyelet proximal ends 239 of stent bands 232 are held or "locked" in place between the collar component of attachment assembly 631 and outer tubular component 602, which is shown in FIG. 6 with a distal end positioned distal of the collar component and stent eyelets 239. In this manner, prosthetic tissue valve 221 is also maintained in a longitudinal position relative to delivery catheter 600 and shipping bladder 642. In addition, prosthetic tissue valve 221 is held in an expanded configuration within shipping bladder 642 and is not crimped or otherwise collapsed onto delivery catheter 600 during shipment, thereby preventing damage to or deformation of valve leaflets 224 that may occur during prolonged crimping. Shipping bladder 642 is a polymeric, fluid-tight vessel or sac-like container, which may or may not be distensible, with a neck portion 664 that is sealing attached around distal end 603 of outer tubular component 602 to contain storage solution 646 and prosthetic tissue valve 221 therein during shipment and storage. In order to prevent storage solution 646 from entering the guidewire lumen of delivery catheter 600, distal tip 612 is capped or otherwise sealed. In various other embodiments, shipping bladder 642 may be temporarily sealed around inner component 606 (not shown), distal tip 612 (not shown) and/or outer tubular component 602 using radial seals to prevent storage solution 646 from entering the lumens of delivery system 600. Shipping bladder 642 includes flushing ports 651, at least one of which is an inflow port 650 and at least one of which is an outflow port 652 that are weakened or thinned areas of shipping bladder 642. Shipping bladder 642 may be made of a suitable polymeric material, for *e.g.*, polyurethane, polypropylene, polyethylene terephthalate, or nylon.

[0038] When a clinician is ready to load prosthetic tissue valve 221 within delivery catheter 600 for delivery within the patient's vasculature, flushing ports 651 are punctured so that a rinsing solution may be introduced into shipping bladder 642 via inflow port(s) 650 to flush storage solution 646 out through outflow port(s) 652. As similarly described with reference to delivery catheter 100 in the embodiment of FIGS. 4 and 5, outer tubular component 602 is advanced distally relative to inner component 606 to thereby collapse prosthetic tissue valve 221 as the prosthetic valve is drawn within outer tubular component 602, wherein in the embodiment of FIG. 6, shipping bladder 642 surrounds and protects tissue valve 221 during the loading process. In another embodiment, a series of funnels may be used to help reduce the diameter of prosthetic tissue valve 221 to aid in retracting the prosthetic valve into delivery system 600. Shipping bladder 642 is then removed so that delivery catheter 600 with prosthetic tissue valve 221 loaded in a delivery configuration therein is ready for introduction into the patient's vasculature for tracking to a treatment site. In another embodiment, prosthetic tissue valve 221 may be rinsed, shipping bladder 642 removed and then the prosthetic valve may be retracted into or otherwise covered by outer tubular component 602.

[0039] In accordance with another embodiment hereof, FIG. 7 depicts a side view of a prosthetic tissue valve delivery system 700 in partial section that is attached to an accordion-like or pleated shipping bladder 742 containing prosthetic tissue valve 721 pre-loaded thereon in a shipping/storage configuration. Prosthetic tissue valve delivery system 700 includes an elongate outer sheath 702 defining a sheath lumen 708 through which slidably extends a balloon catheter 770. Outer sheath 702 is of a similar construction as outer tubular component 102, which was previously described in detail above. Balloon catheter 770 includes a dilatation balloon 772 along a distal portion of balloon catheter 770 that is connected via an inflation lumen to a source of inflation fluid at a proximal end (not shown) of balloon catheter 770. Balloon catheter 770 is of an over-the-wire construction and as such has a full-length guidewire lumen that extends from the proximal end (not shown) to a distal tip 712 thereof. In another embodiment, balloon catheter 770 may be of a rapid exchange configuration. In various embodiments, balloon catheters manufactured and/or sold by Medtronic Inc. of Minneapolis, MN under the trademarks SPRINTER LEGEND, NC SPRINTER and RELIANT may be adapted for use in embodiments hereof without departing from the scope of the present invention.

[0040] Prosthetic tissue valve 721 includes stent-like frame 722 with valve leaflets 724 secured therein, which are of a similar construction as stent-like frame 222 and valve leaflets 224 described above in detail with reference to prosthetic tissue valve 221. However in the embodiment of FIGS. 7 and 8, stent-like frame 722 is balloon-expandable rather than self-expanding and as such may be constructed of, for *e.g.*, platinum-iridium, cobalt chromium alloys (MP35N), stainless steel, tantalum or other stent materials.

[0041] Accordion-like shipping bladder 742 is a polymeric, fluid-tight vessel or container having a plurality of circumferential fold-lines or creases 775 longitudinally spaced along a length thereof that form pleats or accordion-like folds 776 when shipping bladder 742 is longitudinally compressed, as shown in FIG. 8. Shipping bladder 742 may be made of a suitable polymeric material, for *e.g.*, polyurethane, polypropylene, polyethylene terephthalate, or nylon. Shipping bladder 742 holds prosthetic tissue valve 721 in a storage solution 746 during shipment and storage and is fluid-tight, having a neck portion (not shown) that is sealed against outer sheath 702 by a sealing ring 774, which may be of silicone, polyurethane, or a medical grade rubber. In order to prevent storage solution 746 from entering balloon catheter 770, distal tip 712 is capped or otherwise sealed. An outer surface of stent-like frame 722 of prosthetic tissue valve 721 contacts an inner surface of shipping bladder 742 by which prosthetic tissue valve 721 is held in an expanded configuration over folded balloon 772 of balloon catheter 770 and otherwise prevented from longitudinal movement during shipment and storage. Shipping bladder 742 includes proximal flushing ports 750 and distal flushing port 752, wherein flushing ports 750, 752 include Luer fittings so that at least one port or ports may be connected to a source of rinsing solution and another port or ports may be connected/directed to a fluid waste receptacle. Flushing ports 750, 752 may be weakened or thinned areas of shipping bladder 742, which are punctured for use, or may be holes/apertures in shipping bladder 742 covered by removable caps, plugs or other covering (not shown).

[0042] When a clinician is ready to load prosthetic tissue valve 721 within delivery system 700 for delivery within the patient's vasculature, one or more flushing ports 750, 752 are uncapped or punctured so that a rinsing solution may be introduced into shipping bladder 742 to flush out storage solution 746. In an embodiment, an inlet flushing port may be connected to a source of sterile saline to properly rinse prosthetic tissue valve 721, wherein the storage solution is initially evacuated from shipping bladder 742 with the sterile saline "rinsing" solution subsequently introduced. In another embodiment, a large diameter syringe or a series of syringes filled with a volume of sterile saline sufficient to replace the volume of the storage solution within shipping bladder 742 may be used to effectively rinse the prosthetic tissue valve 721. Once prosthetic tissue valve 721 is sufficiently rinsed, a distal end 741 of shipping bladder 742 is pushed or slid proximally relative to delivery system 700 to longitudinally compress shipping bladder 742 and thereby form therein accordion-like folds 776 separated by reduced-diameter compression segments or rings 778. As the overall length of shipping bladder 742 is reduced during the compression process, distal tip 712 of balloon catheter 770 exits distal flushing port 752 and compression segments 778 function to collapse/crimp prosthetic tissue valve 721 onto balloon 772 of balloon catheter 770, as shown in FIG. 8. Although compression segments 778 are shown to have a longitudinal length in the embodiment of FIG. 8, in other embodiments compression segments 778 may be merely the reduced-diameter "valley" between adjacent accordion-like folds 776. Sealing ring 774 and shipping bladder 742 are then removed and delivery system outer sheath 702 is positioned over prosthetic tissue valve 721, such that delivery system 700 with prosthetic tissue valve 721 loaded therein are in a delivery configuration ready for introduction into the patient's vasculature for tracking to a treatment site. In alternate methods of use, outer sheath 702 may be slid over collapsed tissue valve 721 or collapsed tissue valve 721 may be drawn within outer sheath 702 prior to removal of shipping bladder 742 and sealing ring 774.

[0043] In another embodiment, a balloon-expandable prosthetic tissue valve may be used with shipping bladder 642 of FIG. 6 by utilizing an external crimper such that shipping bladder 642 acts as a sterile barrier during the crimping process. Following rinsing and crimping of the prosthetic tissue valve, shipping bladder 642 is removed and the balloon-expandable prosthetic tissue valve may be loaded within the delivery system as previously discussed.

[0044] Similar to prosthetic tissue valve 221 described above, prosthetic tissue valve 721 may be percutaneously or otherwise delivered to replace an insufficient/incompetent aortic valve. However as prosthetic tissue valve 721 is balloon-expandable, once delivery system 700 is positioned as desired within the native aortic valve, outer sheath 702 is proximally retracted and dilatation balloon 772 is expanded to deploy prosthetic tissue valve 721 into apposition with the native aortic valve. Accordingly, in its fully deployed configuration, stent-like frame 722 of prosthetic tissue valve 721 radially displaces the native aortic valve leaflets to conform and seal to the aortic annulus, as would be understood by one of ordinary skill in the art of heart or venous valve replacement.

[0045] It would be understood by one of ordinary skill in the art of prosthetic valve design that known tissue valve prosthesis, such as those disclosed in U.S. Patent No. 6,425,916 to Garrison et al., U.S. Patent Appl. Pub. No. 2006/0178740 to Stacchino et al., U.S. Patent Appl. Pub. No. 2006/0259136 to Nguyen et al., U.S. Patent No. 7,338,520 to Bailey et al., and U.S. Patent No. 7,347,869 to Hojeibane et al., each of which is incorporated by reference herein in its entirety, may be adapted for use in self-expanding and balloon expandable embodiments hereof without departing from the scope of the present invention. It will also be appreciated by one of ordinary skill in the art that the stent structures shown in the preceding embodiments are merely exemplary in nature and that either self-expanding or balloon-expandable stents of various forms may be adapted for use in accordance with the teaching hereof. Some examples of stent configurations that are suitable for use in embodiments hereof are shown in U.S. Patent No. 4,733,665 to Palmaz, U.S. Patent No. 4,800,882 to Gianturco, U.S. Patent No. 4,886,062 to Wiktor, U.S. Patent No. 5,133,732 to Wiktor, U.S. Patent No. 5,292,331 to Boneau, U.S. Patent No. 5,421,955 to Lau, U.S. Patent No. 5,776,161 to Globerman, U.S. Patent No. 5,935,162 to Dang, U.S. Patent No. 6,090,127 to Globerman, U.S. Patent No. 6,113,627 to Jang, U.S. Patent No. 6,663,661 to Boneau, and U.S. Patent No. 6,730,116 to Wolinsky *et al.*, each of which is incorporated by reference herein in its entirety.

[0046] Additionally it would be understood by one of ordinary skill in the art of medical device packaging that during shipment to the clinician, shipping container 340 and delivery catheter 100, as shown in FIGS. 1 and 3, and the delivery systems shown in FIGS. 6 and 7 would be enclosed within a suitable sterile protective packaging. In another embodiment, the protective packaging with the delivery systems therein may include insulation or be positioned within separate insulative packaging to prevent exposure of the prosthetic valve to extreme temperatures. In addition, temperature alert sensors may be incorporated into the protective packaging to ensure that a prosthetic valve damaged by exposure to extreme temperatures during shipment/storage is not used in an interventional procedure. In another embodiment, the protective packaging may include temperature sensors and/or thermal masses to protect the prosthetic valve by stabilizing its temperature when exposed during shipment/storage to extreme ambient temperatures.

[0047] While various embodiments according to the present invention have been described above, it should be understood that they have been presented by way of illustration and example only, and not limitation. It will be apparent to persons skilled in the relevant art that various changes in form and detail can be made therein without departing from the spirit and scope of the invention. Thus, the breadth and scope of the present invention should not be limited by any of the above-described exemplary embodiments, but should be defined only in accordance with the appended claims and their equivalents. It will also be understood that each feature of each embodiment discussed herein, and of each reference cited herein, can be used in combination with the features of any other embodiment. All patents and publications discussed herein are incorporated by reference herein in their entirety.

CLAIMS

What is claimed is:

1. A packaging system for a medical device, the system comprising:

a delivery catheter;

a shipping container sealingly attached to the delivery catheter and filled with a storage solution, wherein a component of the delivery catheter extends within the shipping container; and

a prosthetic tissue valve in an expanded configuration disposed in the storage solution within the shipping container and positioned to surround the component of the delivery catheter that extends within the shipping container.

2. The packaging system of claim 1, further comprising:

an attachment assembly for releasably attaching the prosthetic tissue valve to the delivery catheter.

3. The packaging system of claim 2, wherein the delivery catheter further comprises:

an outer tubular component having a distal end to which the shipping container is sealing attached; and

an inner component slidably disposed within the outer tubular component, wherein the component of the delivery catheter that extends within the shipping container is the inner component and the prosthetic tissue valve is secured to the inner component by the attachment assembly.

4. The packaging system of claim 3, wherein upon removal of the storage solution from the shipping container relative longitudinal movement between the inner component and the outer tubular component collapses and loads the prosthetic tissue valve within the outer tubular component.

5. The packaging system of claim 4, wherein upon removal of the shipping container the delivery catheter with the prosthetic tissue valve loaded therein are ready for delivery to a treatment site within the vasculature.

6. The packaging system of claim 1, wherein the shipping container is a bladder of a polymeric material.

7. The packaging system of claim 1, wherein the shipping container includes an inflow port for introducing a rinsing solution into an interior of the shipping container and an outflow port for draining the storage and rinsing solutions from the shipping container.

8. The packaging system of claim 1, wherein an outer surface of the prosthetic tissue valve touches an inner surface of the shipping container to thereby maintain a longitudinal position of the prosthetic tissue valve relative to the delivery catheter.

9. The packaging system of claim 8, wherein the delivery catheter further comprises:

an outer sheath having a distal end to which the shipping container is sealing attached; and

a balloon catheter slidably disposed within the outer sheath and having a dilatation balloon disposed along a distal portion thereof, wherein the component of the delivery catheter that extends within the shipping container includes the dilatation balloon of the balloon catheter such that the prosthetic tissue valve is positioned around the dilatation balloon.

10. The packaging system of claim 9, wherein upon removal of the storage solution from the shipping container longitudinally compressing the shipping container collapses the prosthetic tissue valve onto the dilatation balloon.

11. The packaging system of claim 10, wherein the shipping container forms accordion-like folds when longitudinally compressed and compression rings between the folds contact and collapse the prosthetic tissue valve.

12. The packaging system of claim 9, wherein upon removal of the shipping container the outer sheath is slidable over the prosthetic tissue valve and balloon catheter for delivery to a treatment site within the vasculature.

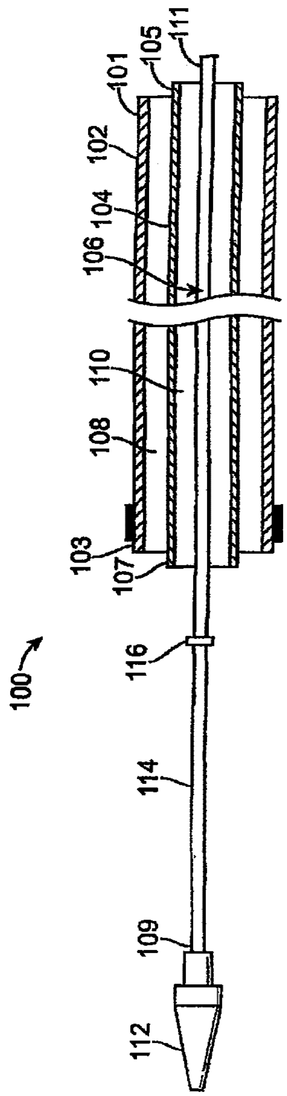
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FIG. 1

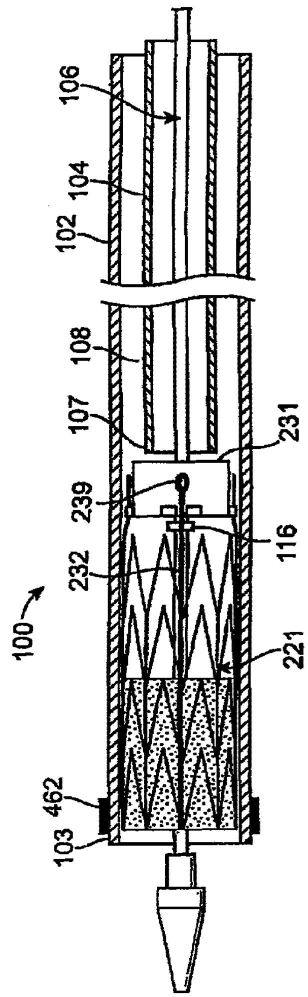
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FIG. 5

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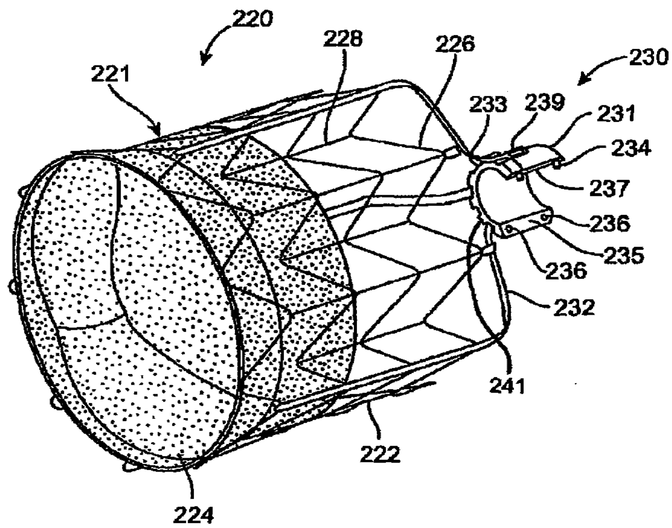
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FIG. 2

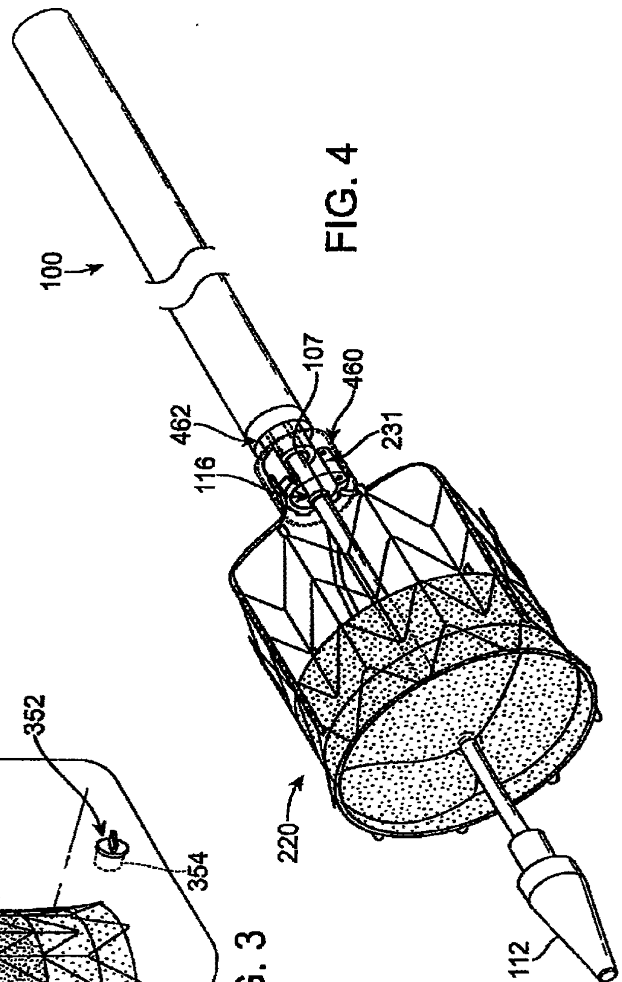
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FIG. 4

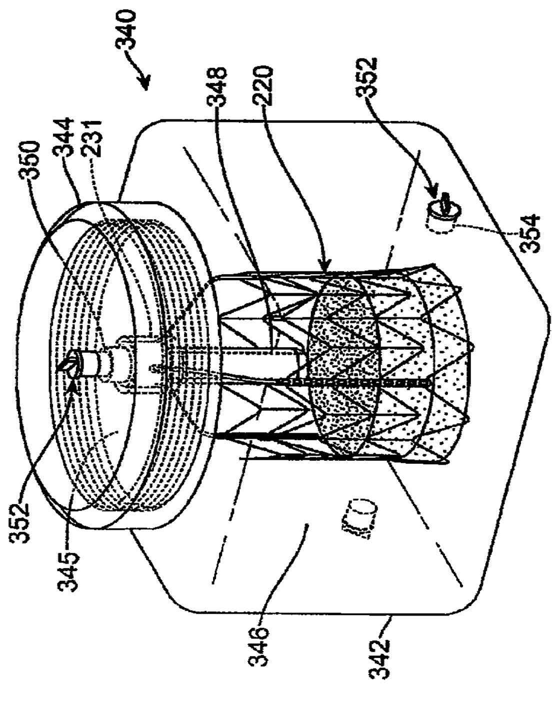
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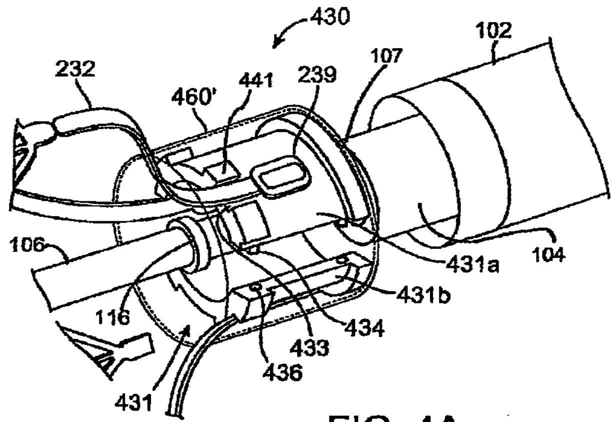
FIG. 3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106
431a
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431b
116
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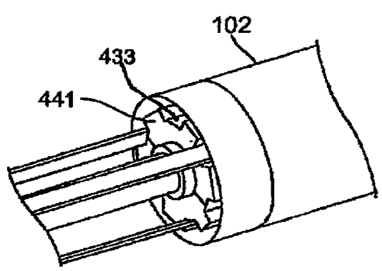
436
431

FIG. 4A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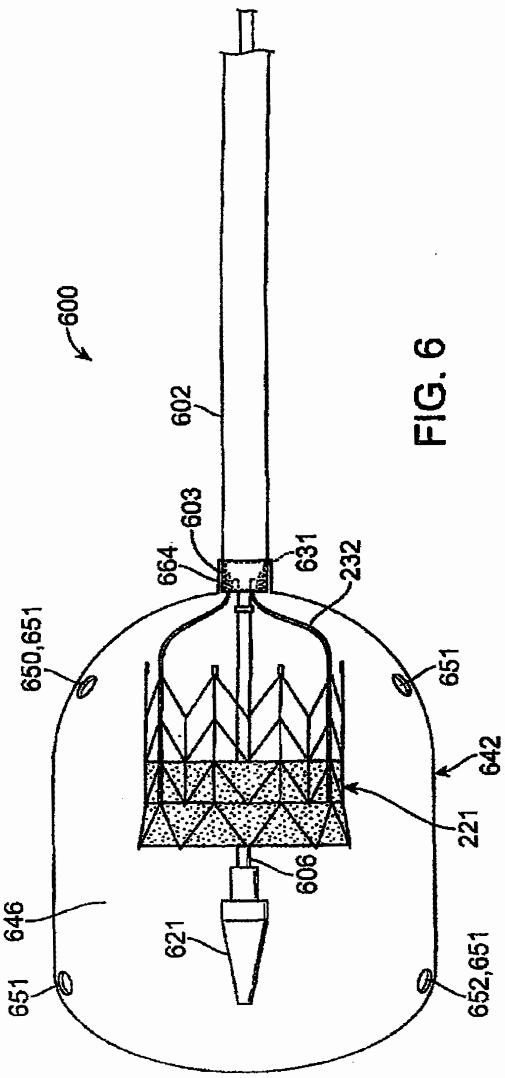
433
441

FIG. 4B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621
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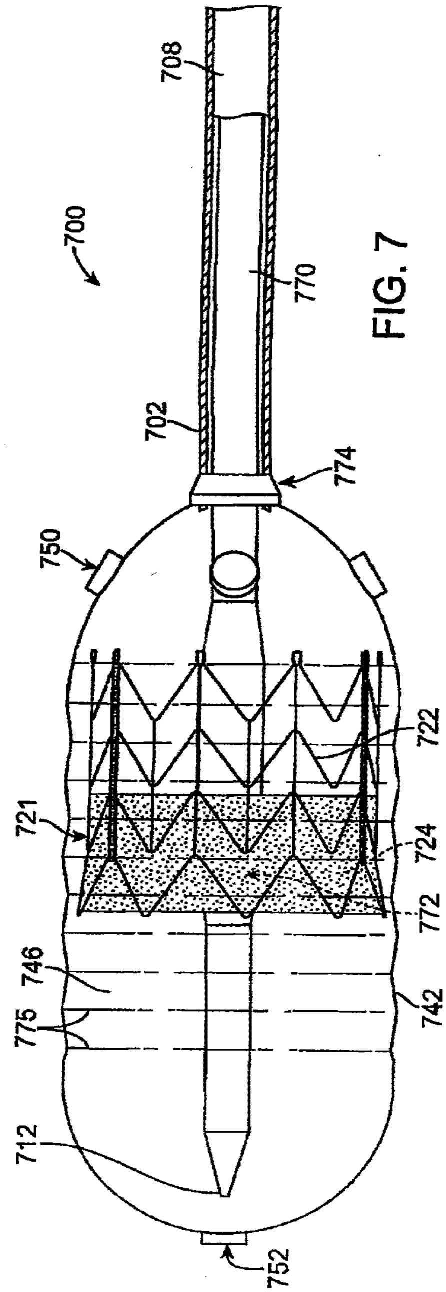
652,651

FIG. 6

6/6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750
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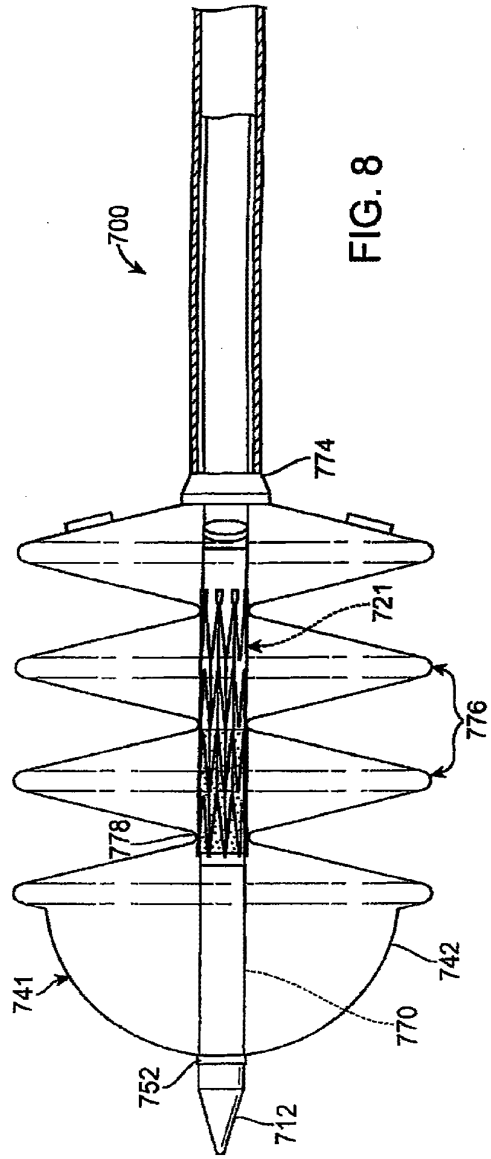
FIG. 7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742
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752
712
FIG. 8

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/026942

A. CLASSIFICATION OF SUBJECT MATTER
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ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/061008 A1 (SALAHIEH AMR [US] ET AL) 15 March 2007 (2007-03-15) paragraph [0044] - paragraph [0049]; figures	1,2,6-8
A	US 5 560 487 A (STARR STEPHEN [US]) 1 October 1996 (1996-10-01) column 2, line 50 - column 4, line 15; figures	1,2,8
A	WO 01/24730 A1 (EDWARDS LIFESCIENCES CORP [US]) 12 April 2001 (2001-04-12) abstract; figures	1,2,8

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 May 2010	28/05/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Neumann, Elisabeth

1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/026942

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		DE 60017158 T2	29-12-2005
		EP 1217966 A1	03-07-2002
		US 6416547 B1	09-07-2002

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(74) Agent: **YASKANIN, Mark, L.**; Holme Roberts & Owen LLP, 1700 Lincoln Street, Suite 4100, Denver, CO 80203 (US).

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(54) Title: TISSUE FOR PROSTHETIC IMPLANTS AND GRAFTS, AND METHODS ASSOCIATED THEREWITH

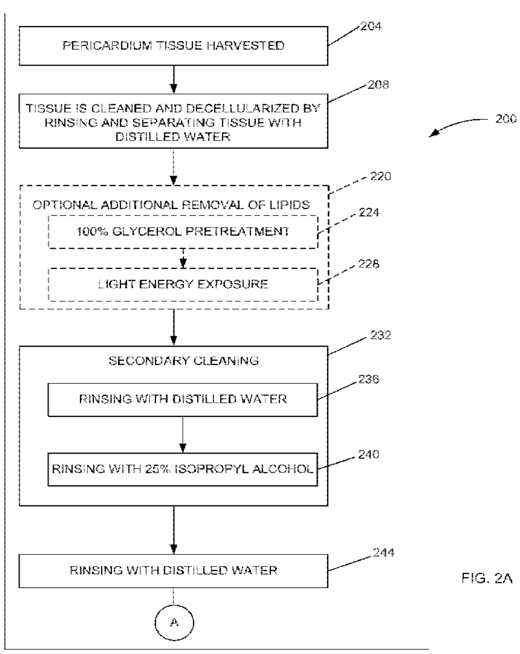


FIG. 2A

(57) Abstract: A prepared tissue for medical use with a patient is provided. Methods for preparing such tissue are also provided. Implantable tissue is provided by harvesting a tissue, such as but not limited to a pericardium tissue, and exposing the tissue to various cleaning, rinsing, treatment, separating, and fixation steps. The tissue of at least one embodiment is cleaned with distilled water, rinsed with isopropyl alcohol, and treated with a glutaraldehyde solution. The prepared tissue may be allowed to dry or partially hydrated prior to packaging and shipment. As such, the tissue can be implanted into the receiving patient in either a dry or wet state. The relatively thin yet strong tissue material is adapted for implanting within or grafting to human tissue. By way of example, the tissue may be used in a shunt, a valve, as graft material, as a patch, as a prosthetic tissue in a tendon and/or ligament, and a tissue product for wound management.

WO 2011/109433 A2

TISSUE FOR PROSTHETIC IMPLANTS AND GRAFTS, AND METHODS ASSOCIATED THEREWITH

FIELD

The present invention relates to the field of tissue engineering, and more particularly, to tissue for prosthetic implants and grafts.

BACKGROUND

Preparing tissue for medical use to treat a patient is common. These tissues are typically used for implanting with or grafting to a human tissue. Prepared tissue is often used in shunts, tissue grafts and patches, as a prosthetic tissue in valves, tendon and/or ligament, and as tissue product for wound management. Many of these medical applications typically employ tissues obtained from mammalian animals and are thus termed xenografts. As with allografts (from human sources), xenograft tissue in the raw state contains immunologically "foreign" proteins and antigenic chemistry provocative of patient host immune responses that would cause destruction of implanted tissue as well as potentially harmful immune-mediated reactions. Thus, tissue for implantation in patients requires a number of preparatory chemical treatments to become biocompatible enough for implantation. For the preparation of xenograft tissue for structural applications, these treatments are typically directed to specific goals to isolate and preserve the structural proteins such as collagen: 1) remove cells within the tissue matrix, 2) remove unwanted chemical constituents, especially lipid components, and 3) chemically fix (i.e., cause thorough cross-linking of) structural proteins. Numerous manipulations of these and other steps in tissue processing have been employed with varying success in the art to achieve durable and biocompatible xenograft tissues for human implant. Nevertheless, conventional tissue materials are plagued by a variety of problems. For example, often in such applications, long-term function and survival of the tissue implants have been compromised by destructive inflammation, loss of structural integrity, and reactive calcification.

When using xenograft tissue membrane for use as formed sheet material, the tissue is usually cleaned and sterilized *ex vivo*, as outlined above. The preparation process itself can deteriorate the strength and biocompatibility characteristics of the tissue, or be the cause of latent host reactions that ultimately cause failure within the body. Often, the prepared tissue must maintain a certain thickness in order to have the desired strength traits. As such, the tissue material may be produced to be relatively thick, which may limit the manner of its application, and may also limit its biocompatibility.

Furthermore, in certain functional forms, such as for prosthetic heart valves, the prepared tissue must be stored in a liquid (usually a preservative) solution, otherwise the tissue will dry out and become brittle and prone to damage. Maintaining the tissue in a "wet" state adds mass and bulk to the tissue product since the moisture content of the tissue is higher and the volume of the tissue is greater when hydrated. Because the tissue must be stored "wet," packaging must be robust to prevent leaks, the transportation environment must be carefully monitored and controlled, and once at the hospital or medical facility, significant efforts to rinse and prepare the tissue prior to use are needed.

By way of example and not limitation, when a surgeon is ready to use a bioprosthetic tissue heart valve, the valve and attached tissue must be rinsed, and in the case of transcatheter tissue heart valve devices, mounted onto a delivery system. In this example, if the tissue is associated with a percutaneously deliverable heart valve, the prosthetic heart valve is typically mounted to a balloon catheter in a catheterization lab. These steps extend procedure time, require manual manipulation of the tissue, and expose the tissue to harmful contaminants. Moreover, for the example of a percutaneously deliverable heart valve, human errors can be made in mounting and orienting catheters and sheaths.

Because the tissue has a relatively large profile, mass and volume, a surgeon's delivery options are often limited. For example, only patients having large enough vascular systems can use catheter-delivery procedures. Moreover, there is a need for tissue that can be used in a variety of medical indications unrelated to a percutaneously deliverable heart valves.

Accordingly, there is a need to address the shortcomings addressed above.

SUMMARY

It is to be understood that the present invention includes a variety of different versions or embodiments, and this Summary is not meant to be limiting or all-inclusive. This Summary provides some general descriptions of some of the embodiments, but may also include some more specific descriptions of other embodiments.

Embodiments of the one or more present inventions include methods of preparing or treating tissue for medical use, as well as the actual tissue itself. Accordingly, in at least one embodiment, implantable tissue is provided by first harvesting a tissue, and thereafter treating the tissue by: (a) cleaning and decellularizing the tissue by rinsing and separating the tissue with distilled water; (b) optionally treating the tissue to additionally remove lipids by a glycerol pretreatment and exposure to light energy; (c) a secondary cleaning that includes a distilled water rinse, and rinsing with isopropyl alcohol; (d) final rinsing with distilled water; (e) fixation treating for collagen cross-linking by at least one of (I) immersion in formalin, (II) immersion in glycerol, (III) immersion in glutaraldehyde, (IV) immersion in glutaraldehyde filtered to limit oligomeric content, or (V) any of I - IV above with addition to the fixative solution of free amino acids lysine and/or histidine; (f) post-fixation treating by distilled water rinsing then isopropyl alcohol; and (g) final rinsing in distilled water. In at least one embodiment, the implantable tissue is then allowed to dry and thereafter is associated with a package for

shipment. Alternatively, in at least one embodiment, the implantable tissue is then at least partially hydrated and associated with a package for shipment.

As noted above, one or more embodiments described herein are directed to one or more methods of preparing a section of tissue for medical use. By way of example and not limitation, the tissue may be used in a shunt, in a valve, as graft material, as a patch for repair of congenital heart defects, as a prosthetic tissue in tendon and/or ligament replacement, and a tissue product for wound management. Accordingly, a method of preparing a section of tissue for medical use is provided, the method comprising:

(a) cleaning and decellularizing the section of tissue by performing multiple rinses of the section of tissue with distilled water;

(b) rinsing the section of tissue with isopropyl alcohol for a first period of time of not less than about 7 days; and

(c) contacting the section of tissue with one of

(i) a formalin solution, or

(ii) a glutaraldehyde solution

for a second period of time of not less than about 6 days;

wherein step (b) occurs sometime after step (a), and wherein step (c) occurs sometime after step (b).

For the method directly above, in at least one embodiment, for step (c): if the formalin solution is used, then the formalin solution comprises a concentration of about 1-37.5% formalin, and more preferably, about 10% formalin; and if the glutaraldehyde solution is used, then the glutaraldehyde solution comprises a concentration of about 0.1-25% glutaraldehyde, and more preferably, about 0.25% glutaraldehyde.

In at least one embodiment, the method further comprises exposing the section of tissue to light energy for an exposure duration, the exposure duration extending until there is no further visible separation of lipid droplets from an exposed surface of the section of tissue. In at least one embodiment, the light energy is at least equivalent to exposing the section of tissue to a 25-100 watt light source, and more preferably, a 50 watt incandescent light source with a flat radiant face situated at a distance of about 10 centimeters from the exposed surface for about 15 minutes. In at least one embodiment, the method further comprises: (d) rinsing the section of tissue with distilled water and isopropyl alcohol for a post-fixation period of time of not less than about 7 days; wherein step (d) occurs after step (c). In at least one embodiment, the section of tissue comprises an ultimate tensile strength of greater than about 25 MegaPascals. In at least one embodiment, the section of tissue comprises a treated pericardium tissue.

In another embodiment, a method of preparing a tissue for medical use is provided, the method comprising: providing a section of tissue harvested from a mammalian organism; and causing osmotic shocking of the section of tissue by performing multiple rinses of the section of tissue with distilled water. In at least one embodiment, the method further comprises hydrating the section of tissue during a plurality of time intervals using distilled water. In at least one embodiment, the method further comprises not using saline for causing at least one of the osmotic shocking and the hydrating of the tissue. In at least one embodiment, the method further comprises pretreating the section of tissue with glycerol before contacting the section of tissue with one or more of isopropyl alcohol, glutaraldehyde and formalin. In at least one embodiment, the method further comprises contacting the section of tissue with a solution containing formalin after pretreating the section of tissue with glycerol. In at least one embodiment, the method further comprises contacting the section of tissue with a solution containing glutaraldehyde after pretreating the section of tissue with glycerol. In at least one embodiment, the method further comprises pretreating the section of tissue with isopropyl alcohol before contacting the section of tissue with either glutaraldehyde or formalin. In at least one embodiment, the method further comprises contacting the section of tissue with a solution containing formalin after pretreating the section of tissue with isopropyl alcohol. In at least one embodiment, the method further comprises contacting the section of tissue with a solution containing glutaraldehyde after pretreating the section of tissue with isopropyl alcohol. In at least one embodiment, the method further comprises exposing the section of tissue to light energy for a period of time, the period of time extending until there is no further visible separation of lipid droplets from an exposed surface of the section of tissue. In at least one embodiment, the light energy is at least equivalent to exposing the section of tissue to a 50 watt incandescent light source with a flat radiant face situated at a distance of about 10 centimeters from the exposed surface for about 15 minutes. In at least one embodiment, the section of tissue comprises a treated pericardium tissue.

Another embodiment of the one or more present inventions pertains to a method of preparing a section of tissue for medical use, comprising:

(a) contacting the section of tissue with distilled water;

(b) contacting the section of tissue with isopropyl alcohol for a pre-fixation period of time of not less than about 3 days; and

(c) contacting the section of tissue with one of

(i) a formalin solution, or

(ii) a glutaraldehyde solution

for a fixation period of time of not less than about 3 days; and

(d) contacting the section of tissue with isopropyl alcohol for a post-fixation period of time of not less than about 3 days;

wherein step (b) occurs sometime after step (a), wherein step (c) occurs sometime after step (b), and wherein step (d) occurs sometime after step (c).

In at least one embodiment, for step (c): if the formalin solution is used, then the formalin solution comprises a concentration of about 1 - 37.5% formalin; and if the glutaraldehyde solution is used, then the glutaraldehyde solution comprises a concentration of about 0.1 - 25% glutaraldehyde. In at least one embodiment, for step (c): if the formalin solution is used, then the formalin solution comprises a concentration of about 8-12% formalin; and if the glutaraldehyde solution is used, then the glutaraldehyde solution comprises a concentration of about 0.1 - 0.5% glutaraldehyde. In at least one embodiment, the section of tissue comprises a treated pericardium tissue.

As mentioned above, one or more embodiments are directed to a tissue for medical use. Accordingly, a prepared tissue for medical use is provided, comprising: a section of treated tissue harvested from a mammalian organism, the section of tissue including an ultimate tensile strength of greater than about 15 MegaPascals. In at least one embodiment, the section of treated tissue has a thickness of between about 50 to 500 micrometers. In at least one embodiment, the section of treated tissue comprises a water content of less than about 60% by weight of the section of tissue. In at least one embodiment, the section of treated tissue comprises a water content of less than about 50% by weight of the section of treated tissue. In at least one embodiment, the section of treated tissue comprises a water content of less than about 40% by weight of the section of treated tissue. In at least one embodiment, the section of treated tissue is attached to a frame *ex vivo* for at least one of: (a) surgical use; or (b) percutaneous implantation. In at least one embodiment, the section of treated tissue does not include a matrix that has been exposed to a polymer infiltrate. In at least one embodiment, the section of treated tissue is unbraided and uncompounded (as used herein, "unbraided an uncompounded" means the tissue comprises a single layer and is not overlapped or otherwise intertwined). In at least one embodiment, the section of treated tissue comprises an ultimate tensile strength of greater than about 25 MegaPascals. In at least one embodiment, the section of treated tissue has been exposed to isopropyl alcohol before contacting the section of tissue with either glutaraldehyde and formalin. In at least one embodiment, the section of treated tissue has been exposed to a solution containing formalin after pretreatment with isopropyl alcohol. In at least one embodiment, the section of treated tissue has been exposed to a solution containing glutaraldehyde after pretreatment with isopropyl alcohol. In at least one embodiment, the section of treated tissue comprises a pericardium tissue.

In at least one embodiment, a prepared tissue for medical use with a patient is provided, comprising: a section of tissue harvested from a mammalian organism, wherein the section of tissue is prepared *ex vivo* for future grafting or implantation in the patient, the section of tissue including a thickness of about 50 to 500 micrometers and an ultimate tensile strength of greater than about 25 MegaPascals. In at least one embodiment, the section of tissue is unbraided and uncompounded. In at least one embodiment, the section of tissue comprises a water content of less than about 40% by weight of the section of tissue. In at least one embodiment, the section of tissue is attached to a frame *ex vivo* for at least one of: (a) surgical use; or (b) percutaneous implantation in the patient. In at least one embodiment, the section of tissue does not include a matrix that has been exposed to a polymer infiltrate. In at least one embodiment, the section of tissue comprises a treated pericardium tissue.

One or more embodiments described herein are directed to one or more articles comprising a treated tissue. Accordingly, an article is provided, comprising: a section of tissue harvested from an organism, the section of tissue residing within packaging, wherein the section of tissue is adapted for at least one of implanting within or grafting to a human tissue, and wherein the section of tissue comprises a water content of less than about 40% by weight of the section of tissue.

As used herein, the term “dry” (or “substantially dry”) when referring to the state of the tissue means a moisture content less than the water moisture content of the tissue when the tissue is allowed to fully rehydrate in the body of a patient. Typically, 70% by weight of the fully hydrated tissue membrane is water. Drying to a constitution of less than 40% by weight of water usefully alters the handling properties for purposes of folding, sewing or otherwise manipulating the tissue. As those skilled in the art will appreciate, the moisture content of the tissue may vary when dry. For example, the moisture content of the tissue when being folded and dry may be different than the moisture content of the tissue when dry and being shipped, for example, in a premounted state within a catheter delivery system.

With regard to delivery characteristics, another significant advantage of a prosthetic implant using a relatively thin tissue component described herein is that the prosthetic implant offers a relatively low packing volume as compared to commercially available prosthetic implants. In accordance with one or more embodiments, a dry tissue membrane has substantially less mass than a wet membrane. By way of example, a substantially dry pericardium tissue prepared by one or more of the present embodiments has approximately 30% of the mass of a wet pericardium tissue, and a marked reduction in profile and packing volume, thereby achieving a relatively low profile and making it suitable for implantation in greater number of patients.

Various components are referred to herein as "operably associated." As used herein, "operably associated" refers to components that are linked together in operable fashion, and encompasses embodiments in which components are linked directly, as well as embodiments in which additional components are placed between the two linked components.

As used herein, "at least one," "one or more," and "and/or" are open-ended expressions that are both conjunctive and disjunctive in operation. For example, each of the expressions "at least one of A, B and C," "at least one of A, B, or C," "one or more of A, B, and C," "one or more of A, B, or C" and "A, B, and/or C" means A alone, B alone, C alone, A and B together, A and C together, B and C together, or A, B and C together.

As used herein, "sometime" means at some indefinite or indeterminate point of time. So for example, as used herein, "sometime after" means following, whether immediately following or at some indefinite or indeterminate point of time following the prior act.

Various embodiments of the present inventions are set forth in the attached figures and in the Detailed Description as provided herein and as embodied by the claims. It should be understood, however, that this Summary does not contain all of the aspects and embodiments of the one or more present inventions, is not meant to be limiting or restrictive in any manner, and that the invention(s) as disclosed herein is/are understood by those of ordinary skill in the art to encompass obvious improvements and modifications thereto.

Additional advantages of the present invention will become readily apparent from the following discussion, particularly when taken together with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

To further clarify the above and other advantages and features of the one or more present inventions, a more particular description of the one or more present inventions is rendered by reference to specific embodiments thereof which are illustrated in the appended drawings. It is appreciated that these drawings depict only typical embodiments of the one or more present inventions and are therefore not to be considered limiting of its scope. The one or more present inventions is described and explained with additional specificity and detail through the use of the accompanying drawings in which:

Fig. 1 is a generalized flow chart illustrating preparation of tissue for use in an implantable construct or for use as a graft material;

Figs. 2A-2B are flow charts illustrating elements of the tissue preparation;

Fig. 3 is a flow chart illustrating elements of the drying and sizing;

Fig. 4 is an elevation view of a piece of tissue; and

Fig. 5 is a graph that shows actual stress-strain test results for five tissue samples prepared in accordance with at least one embodiment.

The drawings are not necessarily to scale.

DETAILED DESCRIPTION

Embodiments of the one or more inventions described herein include tissue for prosthetic implants and/or methods relating to preparation of tissue for prosthetic implants. A prosthetic implant made at least partially from tissue in accordance with at least one embodiment described herein can be surgically implanted or otherwise grafted to a patient. One or more embodiments of the prosthetic implant described herein have application for at least aortic and pulmonary valves, as well as in forming prosthetic ligaments and tendons.

Referring now to Fig. 1, preparation of tissue for use in an implantable construct or as a graft is generally shown in method 100. Method 100 generally includes preparing the tissue at 200 and then, optionally, drying the tissue at 300 in preparation of manipulating the tissue for forming an implantable construct, such as a braided or folded structure. Further detail of the tissue preparation is provided below.

At least one or more embodiments described herein include a relatively thin tissue component. By way of example and not limitation, in at least one embodiment the tissue has a thickness of approximately 50 - 150 μm, and further possesses characteristics of pliability and resistance to calcification after implantation. The relatively thin nature of the tissue used in the implantable prosthetic implant assists with biocompatibility. In addition, the relatively thin tissue component thereby provides for a relatively low mass.

With reference now to Fig. 2A, the process associated with preparation of a biocompatible tissue consistent with the above-noted characteristics is described. In at least one embodiment, pericardium tissue, such as porcine or bovine pericardium tissue, is harvested at 204 and then processed to serve as biocompatible tissue. Accordingly, subsequent to the harvesting at 204, the pericardium tissue is cleaned and decellularized at 208. More particularly, in at least one embodiment the tissue is initially cleaned with distilled water using gentle rubbing and hydrodynamic pressure at 208 in order to remove adherent non-pericardial and non-collagenous tissue. In at least one embodiment, the hydrodynamic pressure at 208 is provided by spraying the tissue with a relatively weak stream of liquid to remove at least some of the non-collagenous material associated with the tissue. The rinsing at 208 is to achieve effective decellularization of the pericardium tissue through osmotic shock. Typically, the thickness of the tissue in the cleaned condition varies from about 50 to 500 micrometers, depending on the source of raw tissue. Cleaning preferably continues until there is no visible adherent non-pericardial or non-collagenous tissue.

With continued reference to Fig. 2A, after the tissue has been cleaned and decellularized at 208, the tissue then undergoes optional additional removal of lipids at 220 to further treat the tissue for preventing immunologic response and calcification. More particularly, the tissue first optionally undergoes a 100% glycerol pretreatment at 224 while being positioned on a flat surface (e.g., an acrylic plate), after which the tissue becomes nearly transparent.

At 228, the tissue optionally undergoes a "thermophotonic" process. In at least one embodiment, the tissue is optionally exposed to light energy for additional removal of lipids and for initial cross-linking of the collagen. By way of example and not limitation, in at least one embodiment a 25-100 watt incandescent light source, and more preferably, a 50 watt incandescent light source with a flat radiant face is employed at a distance of about 10 centimeters from the tissue surface, typically requiring 15 minutes of exposure before further visible separation of lipid droplets from the tissue stops.

Still referring to Fig. 2A, the tissue is then cleaned again in secondary cleaning at 232. More particularly, at 236 the tissue is again rinsed with distilled water. Thereafter, at 240 the tissue is rinsed with 25% isopropyl alcohol for periods of several hours to several days and weeks, depending on the desired tissue properties of pliability and tensile strength. By way of example, tissue prepared by the methods described herein has been successfully prepared by rinsing with 25% isopropyl alcohol for a period of 7 days, and after the further treatment steps described herein, provided an ultimate tensile strength of greater than 25 MegaPascals. In at least one embodiment where isopropyl alcohol is described as a rinsing agent, ethanol may be used in its place as an alternative, although resulting tissue properties may vary. Referring back to Fig. 2A, after the tissue is rinsed with isopropyl alcohol at 240, the tissue is then rinsed with distilled water at 244 as a final cleaning step and for rehydration.

Referring now to Fig. 2B, following the rinse with distilled water at 244, treatment of the tissue continues. More particularly, fixation for collagen cross-linking at 248 is achieved by performing at least one of the following:

a. At 248a, immersion of the tissue in 1-37.5% formalin, ideally a buffered solution, for between about 3 days to 5 weeks, and more preferably, for between about 3 days to 4 weeks, and more preferably yet, for between about 3 weeks to 4 weeks, at a temperature of between about 4 to 37°C, and more preferably, 10% formalin for 6 days at 20°C; or

b. At 248b, immersion of the tissue in 100% glycerol for up to 6 weeks at between 4 to 37°C, and more preferably, immersion of the tissue in 100% glycerol for about 3 weeks at 20°C; or

c. At 248c, immersion of the tissue in 0.1 - 25% glutaraldehyde for between about 3 days to 5 weeks, and more preferably, for between about 3 days to 4 weeks, and more preferably yet, for between about 3 weeks to 4 weeks, at 0 to 37°C, and more preferably, immersion of the tissue in 0.25% glutaraldehyde for 7 days at 4°C; or

d. At 248d, immersion of the tissue in 0.1 - 25% glutaraldehyde (filtered to limit oligomeric content) for between about 3 days to 5 weeks, and more preferably, for between about 3 days to 4 weeks, and more preferably yet, for between about 3 weeks to 4 weeks, at 0 to 37°C, and more preferably, 0.25% glutaraldehyde for 7 days at 4°C; or

e. At 248e, immersion in the tissue in one of the above formalin, glutaraldehyde, or oligomeric filtered glutaraldehyde solutions together with added amino acids, lysine and/or histidine, wherein the concentration of the amino acids, L-lysine or histidine, used as an additive to the fixative is in the range of about 100 - 1000 milliMolar, with a preferred value of about 684 mM.

In addition to the foregoing, combinations of the processes listed above may be performed, including: step a followed by step b; step a followed by step c; and step a followed by step d.

As those skilled in the art will appreciate, heat-shrink testing may be conducted on tissue samples to correlate the effectiveness of protein cross-linking. Here, results of heat-shrink testing performed on one or more samples of tissue prepared in accordance with at least one embodiment using formalin showed that the tissue had a shrink temperature of 90°C. This compares favorably with samples prepared using glutaraldehyde, wherein the shrink temperature was 80°C. Accordingly, formalin is a suitable variant of fixation. It is noted that formalin was generally abandoned by the field, largely because of material properties that were unfavorable and because of inadequate or unstable protein cross-linking. Such problems have been overcome through the pretreatments described herein, allowing production of tissue with strength, pliability, and durability in a relatively thin membrane. When used in a prosthetic implant, such as a heart valve, the tissue characteristics imparted by the tissue preparation process facilitate formation of a construct having a relatively low-profile, which also thereby facilitates dry packaging of the prosthetic implant. The same advantages are also achieved using the pretreatments when using a glutaraldehyde process.

Referring still to Fig. 2B, after fixation for collagen cross-linking at 248, an alcohol post-fixation treatment at 252 is preferably performed by rinsing the tissue in distilled water at 256, and then at 260 rinsing the tissue in 25% isopropyl alcohol for between about 30 minutes to 14 days or more at between about 0 to 37°C, and more preferably, for at least about 7 days at 20°C. At 264, the tissue undergoes a rinsing with distilled water.

In accordance with at least one embodiment, treatment of the tissue, including from the time of harvest to the time of implantation or grafting, does not include contact and/or exposure to a polymer to infiltrate and/or encapsulate tissue fibers of the tissue.

Referring now to Fig. 3, the drying process at 300 is performed after the tissue preparation at 200. Thus, in accordance with at least one embodiment, the tissue is dried under a load. More particularly, for the tissue drying at 304, the tissue is placed minimally stretched flat (that is, stretched just enough to eliminate visible wrinkles and bubbles) on a flat surface (e.g., a polymer or acrylic sheet) at 308, and held fixed at its edges at 312. Optionally, the joined tissue and underlying sheet are then set in a slight curve. The tension maintains the substantially flat structure of the tissue as it dries, thereby mitigating or preventing excessive shrinkage, wrinkling, and/or curling at the edges, and also making the rate of drying more uniform across the surface of the tissue because of the surface tension between the plate and the tissue. Alternatively, the tissue is dried while compressed between acrylic plates. When drying the tissue, the temperature is held at between about 4 to 37°C, and more preferably, between about 20 to 37°C (i.e., approximately room temperature to normal human body temperature), and more preferably, at about 20°C. At 314, the drying process is performed in substantially dark conditions (i.e., substantially no visible light) for between about 6 hours to 5 days, and more preferably, for about 72 hours. By way of example, the tissue is dried in dark conditions at a temperature of about 20°C for between about 6 hours to 5 days, and more preferably, for about 72 hours. As those skilled in the art will appreciate, drying the tissue while the tissue is compressed between plates requires a longer period of time.

In at least one embodiment, after drying, the tissue lots are inspected at 316, such as by stereomicroscopy, to identify and discard those with defects or discontinuities of the fiber matrix. If desired, the preferential fiber direction for each piece may be identified to determine a particular orientation, for example, to determine the free edge of the pieces that will form valve leaflets for a heart valve. Depending upon the size (i.e., the area) of the tissue being prepared and the size of tissue needed for a given implant, the tissue may be trimmed or otherwise sized in optional sizing at 320, such as by cutting the tissue into an appropriately sized and shaped sheet for implant formation and/or manipulation. Preferably, cutting of the tissue membrane is oriented so that the resulting free edge is parallel to the preferential fiber direction of the tissue membrane. Optionally, the free edge may also be cut with a parabolic or other curved profile to compensate for any attachment angles in order to increase the total contact surface between the tissue membrane and any associated frame or other structure. This approach minimizes weaknesses in the operating margins of the tissue assembly and advantageously distributes the principal loading forces of the operating implant along the long axis of the collagen fibers. As a result, the tissue is resistant to surface fracture and fraying.

As shown in Fig. 3, optional sizing at 320 is performed after the drying at 304 and inspection at 316. A rectangular shaped piece of tissue 400 is shown in Fig. 4. The tissue 400 may be manipulated for use in a variety of prosthetic implants and grafts.

As mentioned above, tissue prepared by the methods described herein has been successfully prepared by rinsing with 25% isopropyl alcohol for a period of 7 days, and after the further treatment steps described herein, provided an ultimate tensile strength of greater than 25 MegaPascals. Here, the combination of tissue pliability and tensile strength is sought for purposes of producing a material having property characteristics suitable for being physically manipulated to form prosthetic implants, such as a tissue leaflet assembly for a heart valve or a ligament, while providing a tissue material that will operate properly once implanted. These techniques are intended to conserve and preserve collagen fibers, minimize damage to the tissue and improve tissue characteristics. The preparation and fixation techniques produce tissue membrane material that may be rendered and used at lesser thicknesses than typically rendered in the prior art. Thinner membranes are more pliable, but with conventional tissue preparation techniques the tensile strength of the tissue is sacrificed. Advantageously, the preparation techniques described herein have produced membranes that have as much as three times the tensile strength of a commercial product of the prior art. This achieved strength is thus desirable for providing a tissue assembly having a low profile with appropriate durability, even in a substantially dry state. More particularly, the tissue possesses a relatively high tensile strength. By way of example and not limitation, testing has shown that embodiments of tissue prepared as described herein provide a tissue having a tensile strength of approximately three times the tensile strength of current pericardial valve tissue, such as on the order of approximately 25 MegaPascals, thereby providing about 2,000 times the physiologic load strength for valve tissue. Moreover, testing of an embodiment of an implantable prosthetic heart valve made with tissue prepared as described herein and under a static load of greater than approximately 250 mmHg showed less than approximately 14% leakage, wherein such results are generally considered superior to surgical tissue valve prostheses.

With reference to Fig. 5, stress-strain curve results for five different tissue samples prepared in accordance with an embodiment are shown. For the testing results shown, the yield stress or ultimate tensile strength was obtained by attaching strips of tissue fixed at the ends in a linear force tester and increasing the length by 0.3 mm/sec while recording resultant force (tension) until the material ruptured or separated entirely; these measurements were then used to calculate the stress-strain curves depicted in Fig. 5. As illustrated in the graph, the yield stress or ultimate tensile strength of the various tissue samples varied from about 30 to about 50 MegaPascals. More particularly, for each curve shown in Fig. 5, the testing procedures were the same. That is, each of the curves shown pertain to separate pieces of tissue that were subjected to the same test. The results show a minimum ultimate tensile strength of 30 MegaPascals, with a range up to 50 MegaPascals. Accordingly, the illustrated test results demonstrate consistency of the ultimate tensile strength results for the tissue treatment process.

It is to be understood that the tissue generated from one or more of the tissue preparation procedures described herein may be used for a variety of devices or uses, and that use in a prosthetic heart valve is but one possible application for utilizing the tissue. For example, the tissue may be used in a shunt, or as graft material for repair or modification of one or more human organs, including the heart and its blood vessels. By way of further example, the tissue may be used as a pericardial membrane patch for repair of congenital heart defects. The tissue also has application as a prosthetic tissue in tendon and ligament replacement, and as a tissue product for wound management. Moreover, for use in a prosthetic heart valve, the tissue may be configured in a variety of ways and attached to a frame in a variety of ways. In addition, a plurality of separate tissue pieces may each be connected together, such as by suturing, to form a larger composite of treated tissue material. Thereafter, whether the prosthetic implant or graft is made of a folded tissue assembly or a plurality of separate tissue pieces, the resulting prosthetic implant or graft may then be further manipulated for treatment of a patient.

In at least one embodiment, tissue generated from one or more of the tissue preparation procedures described herein may be used to form a prosthetic implant that includes a stent, frame, bone screw or other fastening or anchoring mechanism. In yet other embodiments, tissue generated from one or more of the tissue preparation procedures described herein may be used to form a prosthetic implant or graph that does not include a stent, frame, bone screw or other fastening or anchoring mechanism. Tissue generated from one or more of the tissue preparation procedures described herein may be may be packaged for delivery in a substantially dry, partially hydrated or hydrated ("wet") state. For example, a prosthetic implant utilizing a prepared tissue described herein may be packaged for delivery as a hydrated prosthetic implant. Accordingly, while a portion of the tissue preparation process may include drying the tissue so that it may be manipulated more easily, the tissue may then be hydrated at a later point in time prior to implantation, and it may be maintained in a hydrated condition up to and including packaging, delivery and implantation into a patient. Hydration of the tissue membrane portion occurs rapidly and begins with simple preparatory flushing of the tissue. Those skilled in the art will appreciate that one or more embodiments described herein provide a tissue 400 suitable for implanting in a human, wherein the implantable tissue may be allowed to dry prior to implanting and effectively rehydrated at the time of implanting, such as by flushing of the tissue at the time of implanting using saline or water.

All embodiments described herein are described for use in human patients. However, all embodiments described herein have application for use in veterinary medicine, such as equine medicine.

The present invention may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

The one or more present inventions, in various embodiments, include components, methods, processes, systems and/or apparatuses substantially as depicted and described herein, including various embodiments, subcombinations, and subsets thereof. Those of skill in the art will understand how to make and use the present invention after understanding the present disclosure.

The present invention, in various embodiments, includes providing devices and processes in the absence of items not depicted and/or described herein or in various embodiments hereof, including in the absence of such items as may have been used in previous devices or processes (e.g., for improving performance, achieving ease and/or reducing cost of implementation).

The foregoing discussion of the invention has been presented for purposes of illustration and description. The foregoing is not intended to limit the invention to the form or forms disclosed herein. In the foregoing Detailed Description for example, various features of the invention are grouped together in one or more embodiments for the purpose of streamlining the disclosure. This method of disclosure is not to be interpreted as reflecting an intention that the claimed invention requires more features than are expressly recited in each claim. Rather, as the following claims reflect, inventive aspects lie in less than all features of a single foregoing disclosed embodiment. Thus, the following claims are hereby incorporated into this Detailed Description, with each claim standing on its own as a separate preferred embodiment of the invention.

Moreover, though the description of the invention has included descriptions of one or more embodiments and certain variations and modifications, other variations and modifications are within the scope of the invention (e.g., as may be within the skill and knowledge of those in the art, after understanding the present disclosure). It is intended to obtain rights which include alternative embodiments to the extent permitted, including alternate, interchangeable and/or equivalent structures, functions, ranges or acts to those claimed, whether or not such alternate, interchangeable and/or equivalent structures, functions, ranges or acts are disclosed herein, and without intending to publicly dedicate any patentable subject matter.

CLAIMS

What is claimed is:

1. A prepared tissue for medical use, comprising:

a section of treated tissue harvested from a mammalian organism, the section of treated tissue including an ultimate tensile strength of greater than about 15 MegaPascals.

2. The prepared tissue of Claim 1, wherein the section of treated tissue has a thickness of between about 50 to 500 micrometers.

3. The prepared tissue of Claim 1, wherein the section of treated tissue comprises a water content of less than about 60% by weight of the section of treated tissue.

4. The prepared tissue of Claim 1, wherein the section of treated tissue comprises a water content of less than about 50% by weight of the section of treated tissue.

5. The prepared tissue of Claim 1, wherein the section of treated tissue comprises a water content of less than about 40% by weight of the section of treated tissue.

6. The prepared tissue of Claim 1, wherein the section of treated tissue is attached to a frame ex vivo for at least one of: (a) surgical use; or (b) percutaneous implantation.

7. The prepared tissue of Claim 1, wherein the section of treated tissue does not include a matrix that has been exposed to a polymer infiltrate.

8. The prepared tissue of Claim 1, wherein the section of treated tissue is unbraided and uncompounded.

9. The prepared tissue of Claim 1, wherein the section of treated tissue comprises an ultimate tensile strength of greater than about 25 MegaPascals.

10. The prepared tissue of Claim 9, wherein the section of treated tissue is unbraided and uncompounded.

11. The prepared tissue of Claim 1, wherein the section of treated tissue has been exposed to isopropyl alcohol before contacting the section of treated tissue with either glutaraldehyde or formalin.

12. The prepared tissue of Claim 1, wherein the section of treated tissue has been exposed to a solution containing formalin after pretreatment with isopropyl alcohol.

13. The prepared tissue of Claim 1, wherein the section of treated tissue has been exposed to a solution containing glutaraldehyde after pretreatment with isopropyl alcohol.

14. The prepared tissue of Claim 1, wherein the section of treated tissue comprises a pericardium tissue.

15. A prepared tissue for medical use with a patient, comprising:

a section of tissue harvested from a mammalian organism, wherein the section of tissue is prepared ex vivo for future grafting or implantation in the patient, the section of tissue including a thickness of about 50 to 500 micrometers and an ultimate tensile strength of greater than about 25 MegaPascals.

16. The prepared tissue of Claim 15, wherein the section of tissue is unbraided and uncompounded.

17. The prepared tissue of Claim 15, wherein the section of tissue comprises a water content of less than about 40% by weight of the section of tissue.

18. The prepared tissue of Claim 15, wherein the section of tissue is attached to a frame ex vivo for at least one of: (a) surgical use; or (b) percutaneous implantation in the patient.

19. The prepared tissue of Claim 15, wherein the section of tissue does not include a matrix that has been exposed to a polymer infiltrate.

20. The prepared tissue of Claim 15, wherein the section of tissue comprises a treated pericardium tissue.

21. A method of preparing a tissue for medical use, comprising:

providing a section of tissue harvested from a mammalian organism; and

causing osmotic shocking of the section of tissue by performing multiple rinses of the section of tissue with distilled water.

22. The method of Claim 21, further comprising hydrating the section of tissue during a plurality of time intervals using distilled water.

23. The method of Claim 22, further comprising not using saline for causing at least one of the osmotic shocking and the hydrating of the section of tissue.

24. The method of Claim 21, further comprising pretreating the section of tissue with glycerol before contacting the section of tissue with one or more of isopropyl alcohol, glutaraldehyde and formalin.

25. The method of Claim 24, further comprising contacting the section of tissue with a solution containing formalin after pretreating the section of tissue with glycerol.

26. The method of Claim 24, further comprising contacting the section of tissue with a solution containing glutaraldehyde after pretreating the section of tissue with glycerol.

27. The method of Claim 21, further comprising pretreating the section of tissue with isopropyl alcohol before contacting the section of tissue with either glutaraldehyde or formalin.

28. The method of Claim 27, further comprising contacting the section of tissue with a solution containing formalin after pretreating the section of tissue with isopropyl alcohol.

29. The method of Claim 27, further comprising contacting the section of tissue with a solution containing glutaraldehyde after pretreating the section of tissue with isopropyl alcohol.

30. The method of Claim 21, further comprising exposing the section of tissue to light energy for a period of time, the period of time extending until there is no further visible separation of lipid droplets from an exposed surface of the section of tissue.

31. The method of Claim 30, wherein the light energy is at least equivalent to exposing the section of tissue to a 50 watt incandescent light source with a flat radiant face situated at a distance of about 10 centimeters from the exposed surface for about 15 minutes.

32. The method of Claim 21, wherein the section of tissue comprises a treated pericardium tissue.

33. A method of preparing a section of tissue for medical use, comprising:

(a) cleaning and decellularizing the section of tissue by performing multiple rinses of the section of tissue with distilled water;

(b) rinsing the section of tissue with isopropyl alcohol for a first period of time of not less than about 7 days; and

(c) contacting the section of tissue with one of

(i) a formalin solution, or

(ii) a glutaraldehyde solution

for a second period of time of not less than about 6 days;

wherein step (b) occurs sometime after step (a), and wherein step (c) occurs sometime after step (b).

34. The method of Claim 33, wherein for step (c):

if the formalin solution is used, then the formalin solution comprises a concentration of about 1 - 37.5% formalin; and

if the glutaraldehyde solution is used, then the glutaraldehyde solution comprises a concentration of about 0.1 - 25% glutaraldehyde.

35. The method of Claim 33, further comprising exposing the section of tissue to light energy for an exposure duration, the exposure duration extending until there is no further visible separation of lipid droplets from an exposed surface of the section of tissue.

36. The method of Claim 35, wherein the light energy is at least equivalent to exposing the section of tissue to a 50 watt incandescent light source with a flat radiant face situated at a distance of about 10 centimeters from the exposed surface for about 15 minutes.

37. The method of Claim 33, further comprising:

(d) rinsing the section of tissue with distilled water and isopropyl alcohol for a post-fixation period of time of not less than about 7 days;

wherein step (d) occurs sometime after step (c).

38. The method of Claim 33, wherein the section of tissue comprises an ultimate tensile strength of greater than about 25 MegaPascals.

39. The method of Claim 33, wherein the section of tissue comprises a treated pericardium tissue.

40. A method of preparing a section of tissue for medical use, comprising:

(a) contacting the section of tissue with distilled water;

(b) contacting the section of tissue with isopropyl alcohol for a pre-fixation period of time of not less than about 3 days; and

(c) contacting the section of tissue with one of

(i) a formalin solution, or

(ii) a glutaraldehyde solution

for a fixation period of time of not less than about 3 days; and

(d) contacting the section of tissue with isopropyl alcohol for a post-fixation period of time of not less than about 3 days;

wherein step (b) occurs sometime after step (a), wherein step (c) occurs sometime after step (b), and wherein step (d) occurs sometime after step (c).

41. The method of Claim 40, wherein for step (c):

if the formalin solution is used, then the formalin solution comprises a concentration of about 1 - 37.5% formalin; and

if the glutaraldehyde solution is used, then the glutaraldehyde solution comprises a concentration of about 0.1 - 25% glutaraldehyde.

42. The method of Claim 40, wherein for step (c):

if the formalin solution is used, then the formalin solution comprises a concentration of about 8-12% formalin; and

if the glutaraldehyde solution is used, then the glutaraldehyde solution comprises a concentration of about 0.1-0.5% glutaraldehyde.

43. The method of Claim 40, wherein the section of tissue comprises a treated pericardium tissue.

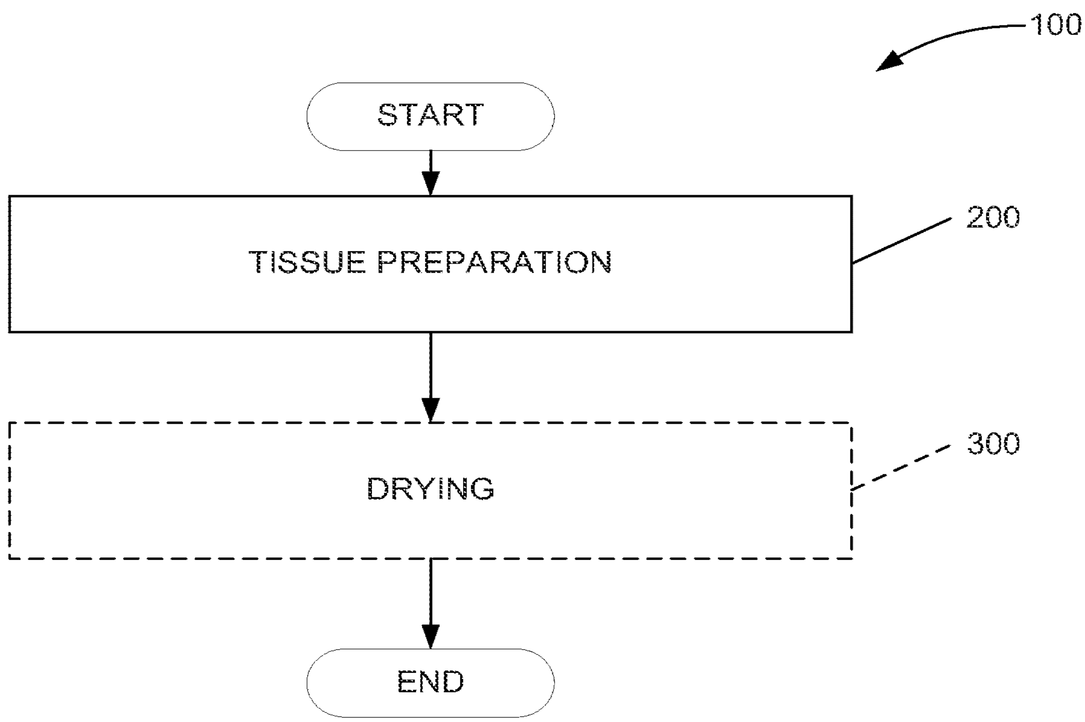


FIG. 1

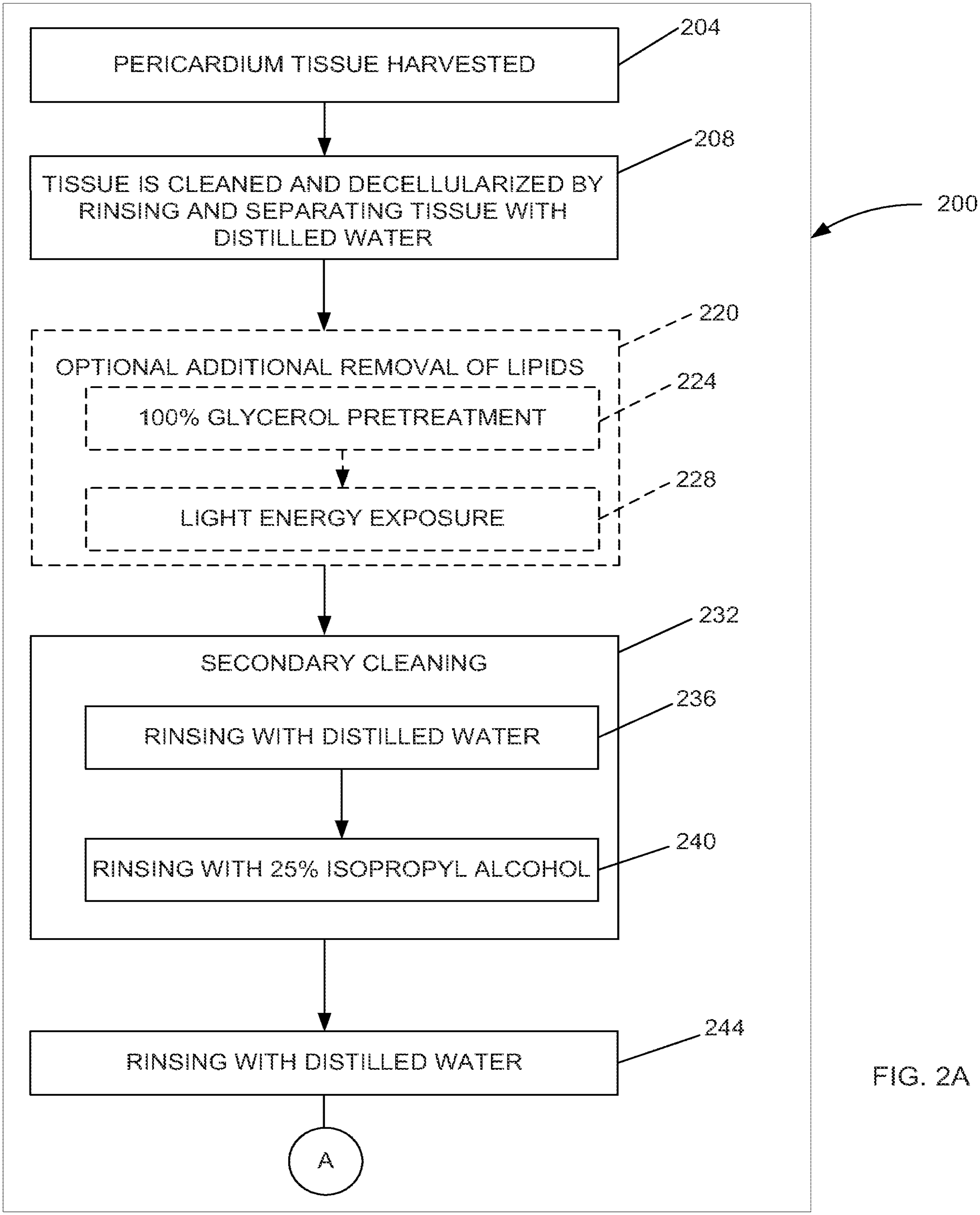

PERICARDIUM TISSUE HARVESTED
204
TISSUE IS CLEANED AND DECELLULARIZED BY RINSING AND SEPARATING TISSUE WITH DISTILLED WATER
208
200
OPTIONAL ADDITIONAL REMOVAL OF LIPIDS
220
100% GLYCEROL PRETREATMENT
224
LIGHT ENERGY EXPOSURE
228
SECONDARY CLEANING
232
RINSING WITH DISTILLED WATER
236
RINSING WITH 25% ISOPROPYL ALCOHOL
240
RINSING WITH DISTILLED WATER
244
A

FIG. 2A

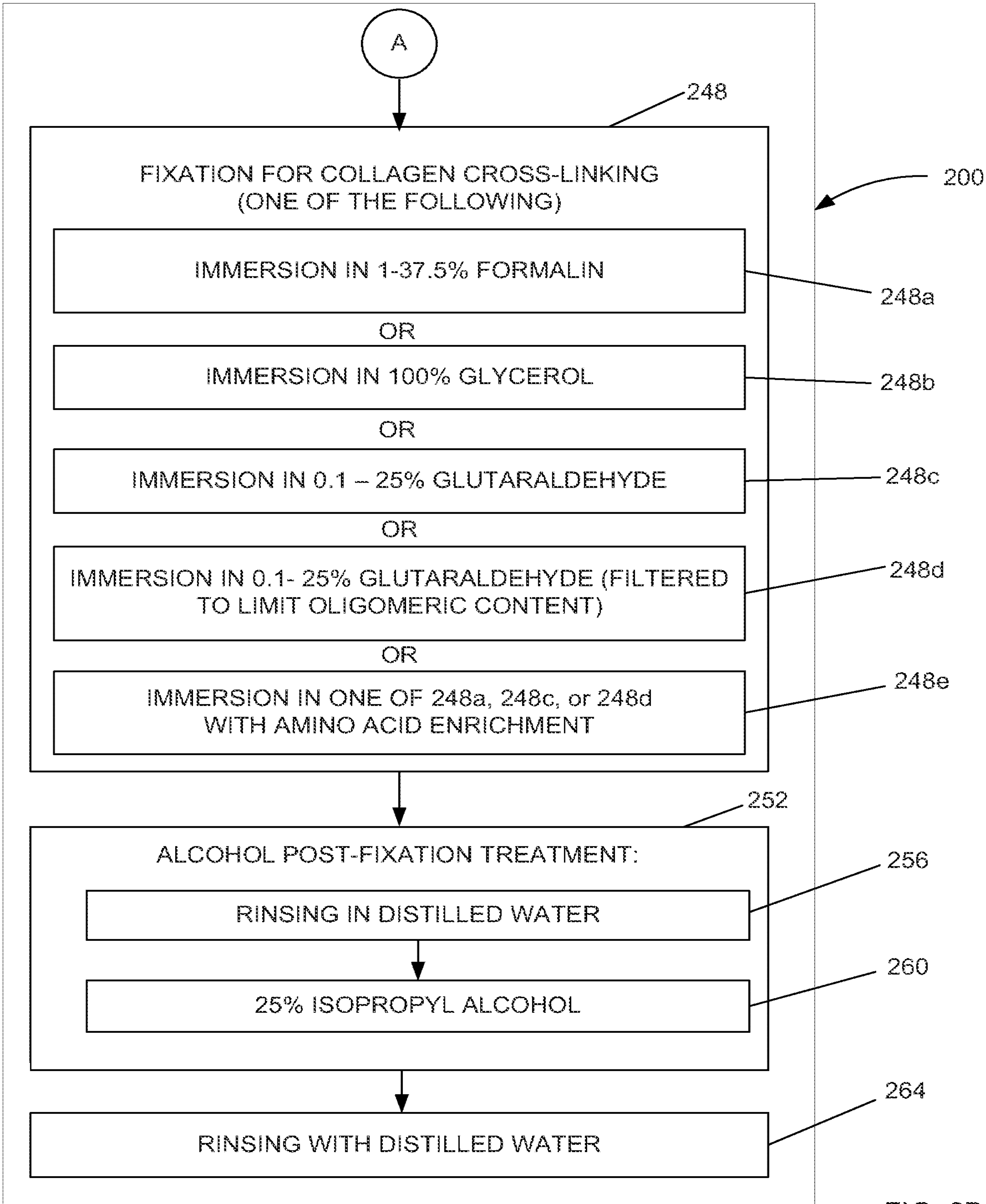

A
248
FIXATION FOR COLLAGEN CROSS-LINKING (ONE OF THE FOLLOWING)
IMMERSION IN 1-37.5% FORMALIN
248a
OR
IMMERSION IN 100% GLYCEROL
248b
OR
IMMERSION IN 0.1 – 25% GLUTARALDEHYDE
248c
OR
IMMERSION IN 0.1- 25% GLUTARALDEHYDE (FILTERED TO LIMIT OLIGOMERIC CONTENT)
248d
OR
IMMERSION IN ONE OF 248a, 248c, or 248d WITH AMINO ACID ENRICHMENT
248e
200
252
ALCOHOL POST-FIXATION TREATMENT:
RINSING IN DISTILLED WATER
256
25% ISOPROPYL ALCOHOL
260
RINSING WITH DISTILLED WATER
264

FIG. 2B

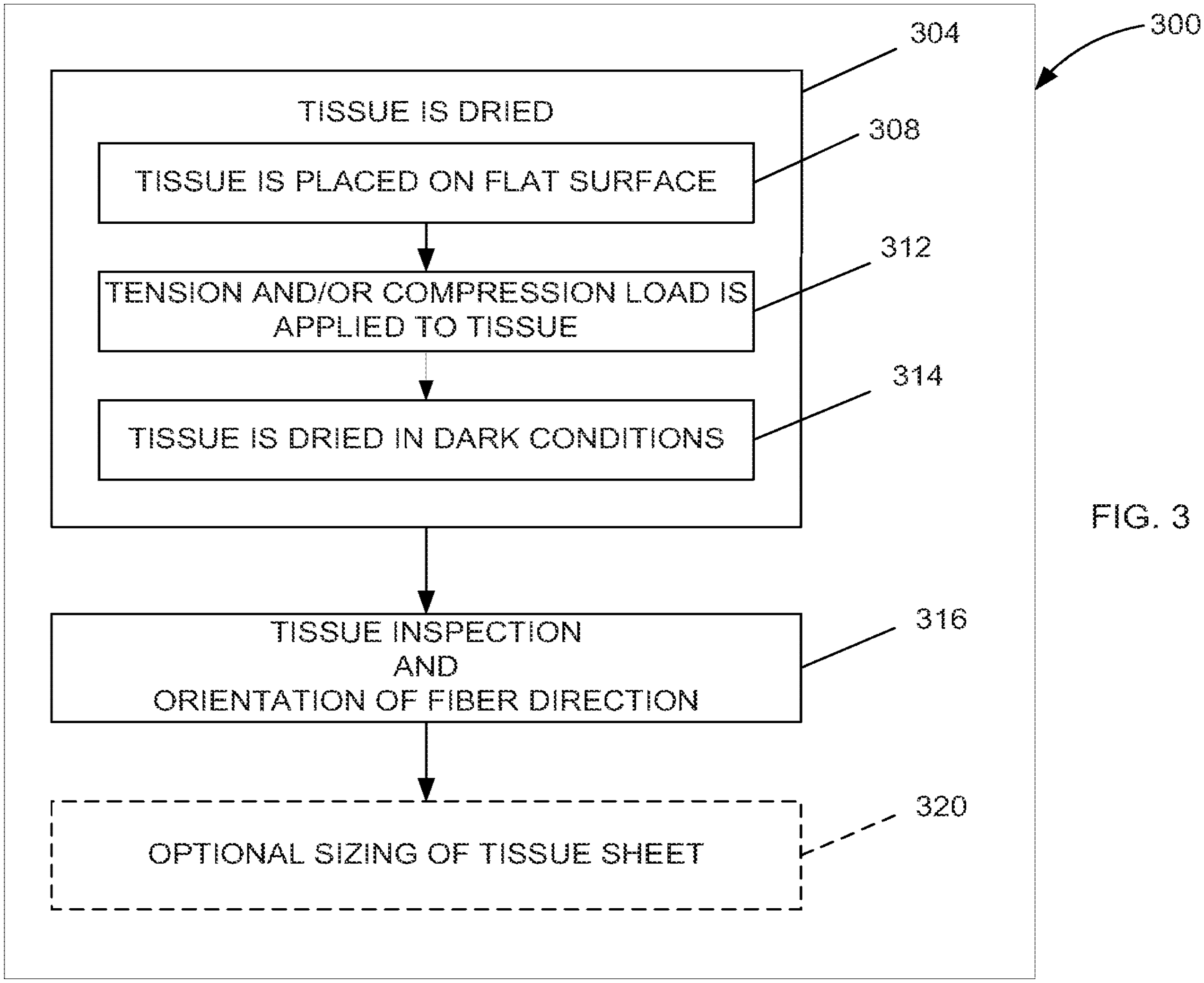

300
304
TISSUE IS DRIED
308
TISSUE IS PLACED ON FLAT SURFACE
312
TENSION AND/OR COMPRESSION LOAD IS APPLIED TO TISSUE
314
TISSUE IS DRIED IN DARK CONDITIONS
316
TISSUE INSPECTION AND ORIENTATION OF FIBER DIRECTION
320
OPTIONAL SIZING OF TISSUE SHEET

FIG. 3

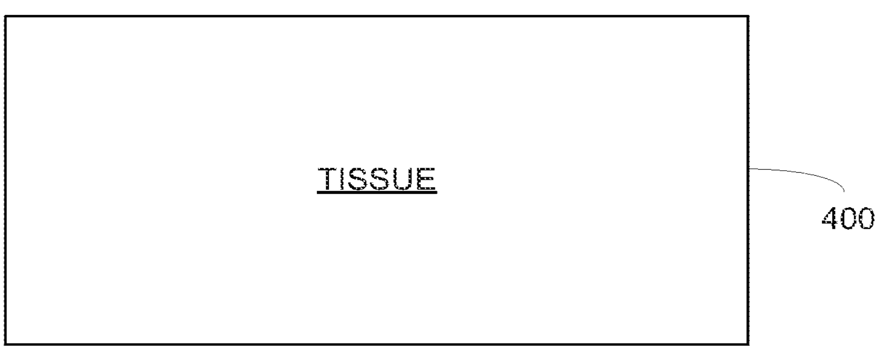
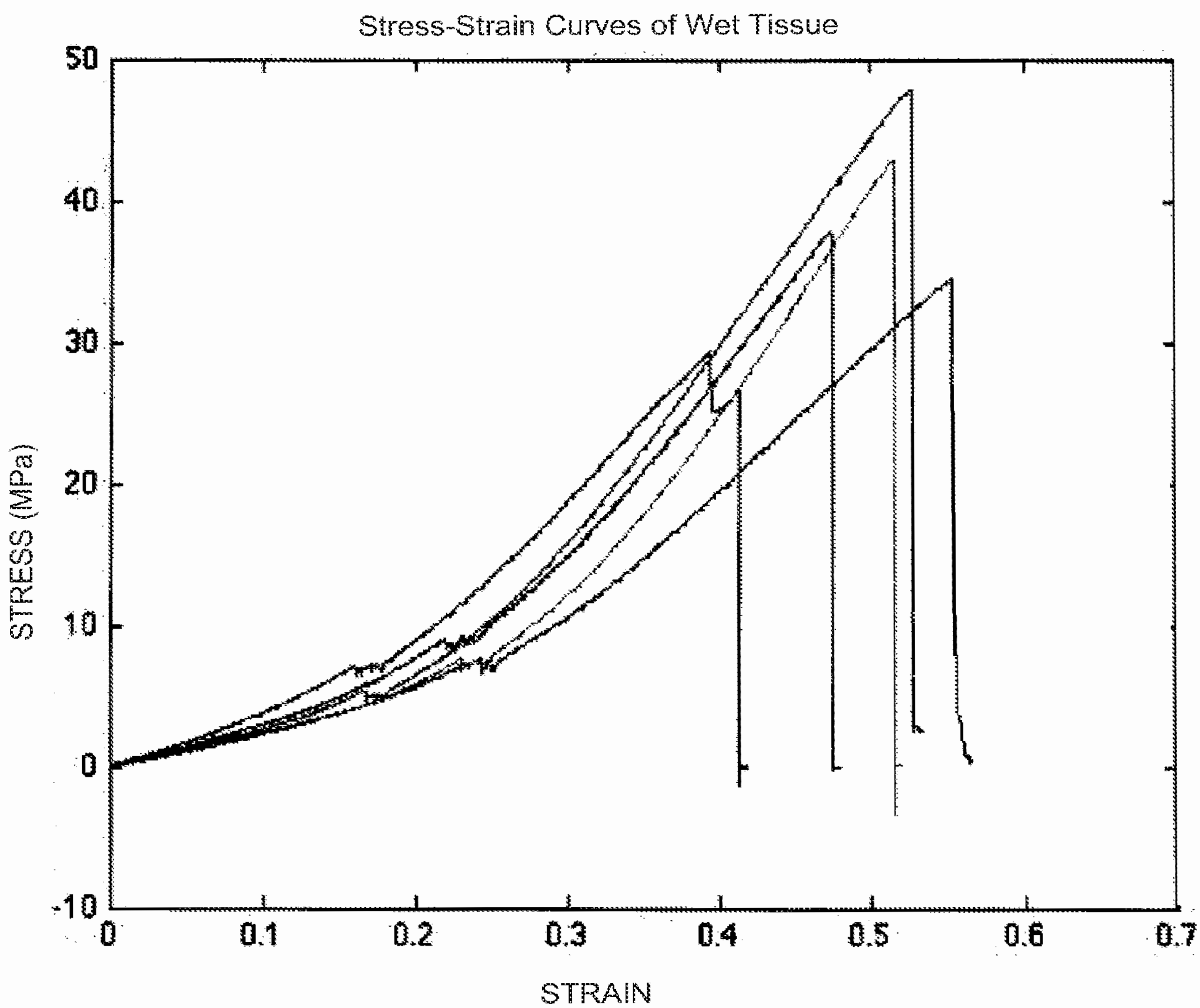

TISSUE
400

FIG.4



Stress-strain curves in wet or hydrated state of five samples. Each curve corresponds to a separate sample.

FIG. 5

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[Continued on next page]

(54) Title: PERCUTANEOUSLY DELIVERABLE HEART VALVE AND METHODS ASSOCIATED THEREWITH

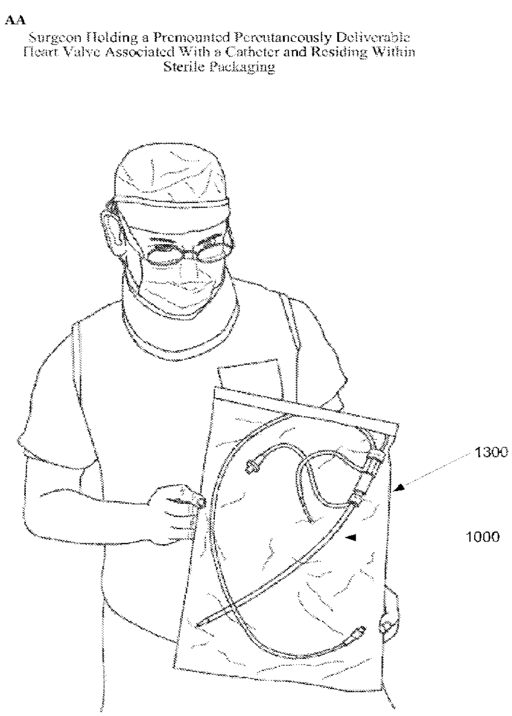

FIG.13

(57) Abstract: A prosthetic heart valve implantable by catheter without surgery includes a substantially "dry" membrane or tissue material. In at least one embodiment, the tissue is folded in a dry state to form a tissue leaflet assembly that is then attached to a frame to form an implantable prosthetic heart valve. Alternatively, one or more tissue leaflets are operatively associated with a frame to form an implantable prosthetic heart valve. The implantable prosthetic heart valve is subsequently pre-mounted on an integrated catheter delivery system. The catheter delivery system that includes the implantable prosthetic heart valve is then packaged and transported while the tissue remains dry. The implantable prosthetic heart valve, while remaining substantially dry, can then be implanted into the receiving patient.

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PERCUTANEOUSLY DELIVERABLE HEART VALVE AND METHODS ASSOCIATED THEREWITH

FIELD

The present invention relates to the field of medical devices, and more particularly, to a percutaneously deliverable heart valve and a method of making a percutaneously deliverable heart valve.

BACKGROUND

Heart valve disease is a common degenerative condition that compromises physiologic function and causes limiting symptoms and threat to life in millions of patients all over the world. There are various underlying causes, but malfunction of heart valves is ultimately expressed as insufficient conduction of blood through the plane of the valve due to narrowing of the anatomic pathway (stenosis), or as incompetent closure that allows blood to return back through the valve again, thereby reducing the effective forward conduction of blood through the valve (insufficiency or regurgitation). These hemodynamic states lead to 1) deficiency of cardiac output and 2) adverse loads on the pumping chambers of the heart, both of which in turn lead to functional compromise of the patient and often premature death unless effectively corrected.

Definitive corrective treatment of heart valve disease is conventionally performed by open-chest surgical techniques, wherein the valve is manipulated, repaired, or replaced with a prosthetic valve under direct vision. Heart valve surgery is performed in hundreds of thousands of cases yearly world-wide, but carries a high burden of cost, morbidity, and mortality, especially in susceptible patients who may be elderly or otherwise physiologically compromised by collateral disease. Further, the costs and resource requirements of the surgical enterprise restrict the availability of heart valve replacement to many more patients all over the world.

In pursuit of alternatives to heart valve surgery, over the last ten years a number of development programs have brought percutaneous, trans-catheter implantation of prosthetic heart valves into commercial use in the European Union (EU) and into pivotal clinical trials in the United States of America. Initial clinical experience in the EU was directed toward patients who had critical aortic valve stenosis, but were deemed to be at unacceptably high risk for open-heart surgical valve replacement. In several thousand such cases, utilizing both balloon-expandable and self-expanding designs in two separate programs, percutaneous heart valve replacement (PHVR) was shown to be feasible and possibly competitive with surgery in selected patients with 12-18 month mortality rates of about 25%. Grube E., et al., *Progress and Current Status of Percutaneous Aortic Valve Replacement: Results of Three Device Generations of the CoreValve Revalving System*, Circ. Cardiovasc Intervent. 2008;1:167-175.

The application of PHVR thus far has been challenged by the technical difficulties of the implantation sequence—especially in the aortic valve position. The technique for available devices is limited by the large caliber of the devices and their delivery catheters; often, if it can be done at all in some smaller arteries, open surgical exposure and management of the femoral artery is required to insert the 18 – 24 French (6 – 8 mm diameter) systems, and their bulkiness inside the central arteries can threaten the safety of the delivery sequence. Further, access site bleeding complications form a significant part of the adverse events of the procedures.

Typically, the current PHV designs comprise a biological membrane forming the operating leaflets of the valve, attached within a metal frame, that is then collapsed onto a delivery catheter or balloon, and then constrained within an outer sheath. After an initial dilation of the diseased valve with a large balloon, this assembly is then advanced to the plane of the valve and deployed by self-expansion or by balloon expansion.

The effective caliber of the valve delivery system is determined by the total bulk of each coaxially mounted component. The bulk of the PHV itself is determined by the diameter of the frame and by the thickness, stiffness, and particular arrangement of the inner membrane forming the operating leaflets of the valve. The characteristic thickness of current PHV membranes is thus a limiting factor in the ultimate delivery profile of the PHV. Such characteristic membrane thickness is, in turn, a result of the methods by which it is processed and ultimately delivered for use. Typically, glutaraldehyde fixation (for protein cross-linking) of animal tissue is employed to produce suitable biological membranes for incorporation. Requirements for strength and durability have determined the most useful ranges for tissue thickness and cross-linking while typically imposing countervailing stiffness and brittleness. Subsequent hydration in suitable solutions improves these characteristics, but the hydrated membrane by this means also gains thickness.

One of the evident requirements for a PHV design is that the valve functions with a high degree of competence immediately on deployment, since the patient's hemodynamic survival depends on it. To this end, in part, like surgical valve prostheses, current PHV designs are completed, transported, and delivered for use in a hydrated state in a jar of solution. In use, commercially available surgical and percutaneously implanted bioprosthetic heart valves are rinsed and prepared before use in a "wet" state. More particularly, commercially available prosthetic heart valves are rinsed, crimped, and mounted in the catheterization lab. Accordingly, problems with current commercially available prosthetic heart valves include the time, cost and variability associated with the necessity to rinse, crimp, and mount the valve in the catheterization lab. That is, current mounting of prosthetic heart valves in the catheterization lab imposes one or more of delay, cost, technical burdens and possible errors. Avoiding one or more of these problems would be advantageous. In addition, current "wet" valve designs impose additional profile on the collapsed valve. The hydrated membrane, while having desirable and necessary flexibility for reliable operation immediately on deployment, also imposes a large part of the thickness of the assembled and mounted valve that compromises its deliverability.

Expanding on some of the problems described above, the use of current PHVs in the catheter lab requires a number of preparatory acts that are potentially troublesome and can prolong the delivery sequence during a critical phase of the procedure. Since PHVs are delivered for use "wet" in a preservative solution, they have to be treated prior to insertion with a series of cleansing and hydrating solutions. Once this is completed, the PHVs have to be mounted on their delivery catheters. Special crimping and mounting tools are needed in the case of the balloon-expandable Edwards Sapien valve, for example. Accordingly, there is a need to address the shortcomings discussed above.

SUMMARY

It is to be understood that the present invention includes a variety of different versions or embodiments, and this Summary is not meant to be limiting or all-inclusive. This Summary provides some general descriptions of some of the embodiments, but may also include some more specific descriptions of other embodiments.

In at least one embodiment, a substantially "dry" membrane PHV system is provided wherein a tissue material is prepared and folded in a dry state to form a tissue leaflet assembly. Thereafter, the tissue leaflet assembly is attached to a frame to form an implantable prosthetic heart valve that is subsequently pre-mounted in an integrated catheter delivery system. The catheter delivery system that includes the prosthetic heart valve is then packaged and transported while the tissue leaflet assembly remains substantially dry. The prosthetic heart valve is available for use directly out of its package envelope. Accordingly, it can be inserted into the body without need of hydration, crimping or mounting tools, or other preparatory acts. That is, the tissue forming the tissue leaflet assembly of the prosthetic heart valve can be treated and dried, then while remaining dry, folded into a tissue leaflet assembly. Thereafter, the tissue leaflet assembly is at least partially rehydrated and then attached within a frame, such as a stent, to form an implantable prosthetic heart valve. The tissue leaflet assembly of the prosthetic heart valve is then allowed to dry. The prosthetic heart valve can thereafter be subsequently packaged, delivered, and shipped while the tissue leaflet assembly of the prosthetic heart valve remains in a dry condition. The prosthetic heart valve can then be implanted into the receiving patient. Accordingly, the PHV system simplifies arterial insertion, and, as the dry condition also confers lower bulk and profile, procedural manipulation and associated complications may be reduced if not eliminated. In addition, one or more embodiments of the present invention widen the candidacy of patients with smaller arteries for the PHV procedure. As an added advantage, at least one embodiment of the present invention allows the implantation to take place under shorten elapsed times at the most critical phase of the procedure.

In at least one embodiment, a membrane PHV system is provided wherein a tissue material is prepared and folded in a dry state to form a tissue leaflet assembly, and further wherein the tissue leaflet assembly is thereafter at least partially hydrated and attached to a frame that is subsequently pre-mounted in an integrated catheter delivery system.

In at least one embodiment, a membrane PHV system is provided wherein a tissue material is prepared and folded in a dry state to form a tissue leaflet assembly, and further wherein the tissue leaflet assembly is at least partially hydrated and attached to a frame to form the prosthetic heart valve. Thereafter, the prosthetic heart valve is allowed to dry and subsequently pre-mounted in an integrated catheter delivery system after which the tissue leaflet assembly of the prosthetic heart valve remains dry, and wherein the system is then associated with a package for shipment while the tissue leaflet assembly remains dry.

In at least one embodiment, a membrane PHV system is provided wherein a tissue material is prepared and then folded in a dry state to form a tissue leaflet assembly, and further wherein the tissue leaflet assembly is at least partially hydrated and attached to a frame to form the prosthetic heart valve. Thereafter, the prosthetic heart valve is allowed to dry and subsequently pre-mounted in an integrated catheter delivery system after which the tissue leaflet assembly of the prosthetic heart valve is then at least partially hydrated and associated with a package for shipment.

In at least one embodiment, an article adapted for trans-catheter delivery into a patient is provided, comprising: a prosthetic heart valve further comprising a treated tissue attached to a frame, wherein the treated tissue comprises a thickness of about 50 to 500 micrometers and an ultimate tensile strength of greater than about 15 MegaPascals when at a water content of less than about 50% by weight of the section of treated tissue. Here it is noted that the tensile strength of the treated tissue described herein is higher than the tensile strength of other known prepared tissues, whether hydrated or dry. In at least one embodiment, the water content of the treated tissue is less than about 40% by weight of the treated tissue. In at least one embodiment, the ultimate tensile strength is greater than about 20 MegaPascals. In at least one embodiment, the treated tissue does not include a matrix that has been exposed to a polymer infiltrate. In at least one embodiment the treated tissue comprises a treated pericardium tissue.

In at least one embodiment, the method further comprises exposing the section of tissue to light energy for an exposure duration, the exposure duration extending until there is no further visible separation of lipid droplets from an exposed surface of the section of tissue. In at least one embodiment, the light energy is at least equivalent to exposing the section of tissue to a 25-100 watt light source, and more preferably, a 50 watt incandescent light source with a flat radiant face situated at a distance of about 10 centimeters from the exposed surface for about 15 minutes. In at least one embodiment, the method further comprises: (d) rinsing the section of tissue with distilled water and isopropyl alcohol for a post-fixation period of time of not less than about 7 days; wherein step (d) occurs after step (c).

In at least one embodiment, an article adapted for implantation in a patient is provided, comprising: a prosthetic heart valve further comprising a treated tissue attached to a frame, wherein the treated tissue comprises a water content of less than about 60% by weight of the treated tissue. In at least one embodiment, the treated tissue comprises a section of pericardium tissue having an ultimate tensile strength of greater than about 12 MegaPascals. In at least one embodiment, the section of treated tissue comprises a thickness of between about 50 to 300 micrometers. In at least one embodiment, the water content of the treated tissue is less than about 40% by weight of the treated tissue.

As used herein, the term "dry" (or "substantially dry") when referring to the state of the tissue that forms the heart valve of the percutaneous heart valve means a moisture content less than the water moisture content of the tissue when the tissue is allowed to fully rehydrate in the body of a patient. Typically, pericardium tissue treated in accordance with one or more embodiments described herein is about 70% by weight water when fully hydrated. Drying to a constitution of less than 40% by weight of water usefully alters the handling properties for purposes of folding and sewing the tissue. As those skilled in the art will appreciate, the moisture content of the tissue may vary when dry. For example, the moisture content of the tissue when being folded and dry may be different than the moisture content of the tissue when dry and being shipped in a premounted state within a catheter delivery system.

Advantageously, at least one embodiment of the one or more present inventions is directed to a prosthetic heart valve that is mounted onto a valve delivery system and stored in a sterile package. Accordingly, in at least one embodiment, an assembly is provided, comprising:

a prosthetic heart valve including:

a frame; and

a tissue leaflet assembly attached to the frame;

a percutaneously insertable valve delivery mechanism, wherein the prosthetic heart valve is releasably mounted onto the percutaneously insertable valve delivery mechanism; and

sterile packaging containing the prosthetic heart valve releasably mounted onto the percutaneously insertable valve delivery mechanism.

In at least one embodiment, the percutaneously insertable valve delivery mechanism comprises a balloon catheter. In at least one embodiment, the balloon catheter is a 12 to 14 French balloon catheter. In at least one embodiment, the balloon catheter is less than about 12 French. In at least one embodiment, the balloon catheter is between about 5 to 12 French. In at least one embodiment, the percutaneously insertable valve delivery mechanism comprises a mandrel. In at least one embodiment, tissue forming the tissue leaflet assembly within the sterile packaging is at least one of hydrated and not substantially dry. In at least one embodiment, tissue forming the tissue leaflet assembly within the sterile packaging is substantially dry. In at least one embodiment, the frame comprises a stent. In at least one embodiment, tissue forming the tissue leaflet assembly comprises treated pericardium tissue.

At least one embodiment of the one or more present inventions includes a prosthetic heart valve for implantation in a patient. Accordingly, a pre-packaged percutaneous, trans-catheter deliverable prosthetic heart valve ready for implantation in a patient is provided, comprising:

a frame; and,

a tissue leaflet assembly attached to the frame, the tissue leaflet assembly comprising a substantially dry tissue.

In at least one embodiment, the substantially dry tissue comprises treated pericardium tissue. In at least one embodiment, the frame and tissue leaflet assembly attached thereto are operably associated with a 12 to 14 French balloon catheter. In at least one embodiment, the frame and tissue leaflet assembly attached thereto are operably associated with a balloon catheter having a size of less than about 12 French. In at least one embodiment, the frame and tissue leaflet assembly attached thereto are operably associated with a balloon catheter having a size of between about 5 to 12 French. In at least one embodiment, the substantially dry tissue comprises a water moisture content of less than about 40% by weight of the substantially dry tissue.

In at least another embodiment, an assembly for use with a patient is provided, comprising:

a sealed sterile package containing a delivery system for percutaneously deploying a heart valve in the patient, the heart valve including:

a frame releasably mounted on the delivery system within the sealed sterile package; and

a tissue leaflet assembly attached to the frame.

In at least one embodiment, the tissue leaflet assembly comprises pericardium tissue.

In at least one embodiment, a method is provided, comprising:

partially compressing and mounting a prosthetic heart valve upon a delivery catheter, the prosthetic heart valve comprising a tissue;

allowing the tissue to at least partially dry;

further compressing and mounting the prosthetic heart valve upon the delivery catheter; and

sterilizing and packaging the prosthetic heart valve and delivery catheter.

In at least one embodiment, the method further comprises transporting the sterilized and packaged prosthetic heart valve and delivery catheter. In at least one embodiment, the tissue comprises treated pericardium tissue. In at least one embodiment, prior to partially compressing and mounting the prosthetic heart valve upon the delivery catheter, the tissue is at least one of (a) not substantially dry, and (b) at least partially hydrated.

For the various embodiments described herein, the prosthetic heart valve, including the tissue leaflet assembly, comprises membrane tissue other than pericardium tissue.

In at least one embodiment, a method is provided, comprising:

attaching pericardium tissue to a frame;

partially compressing and mounting the frame, with the tissue attached thereto, upon a delivery catheter;

allowing the tissue to at least partially dry;

further compressing and mounting the frame, with the tissue attached thereto, upon the delivery catheter; and

sterilizing and packaging the frame and delivery catheter, with the tissue attached thereto.

In at least one embodiment, prior to partially compressing and mounting the frame, the tissue is at least one of (a) not substantially dry, and (b) at least partially hydrated. In at least one embodiment, the method further comprises transporting the sterilized and packaged frame, with the tissue attached thereto, mounted upon the delivery catheter, to a surgical or medical procedure facility. In at least one embodiment, prior to attaching the tissue to the frame the tissue is folded to form a tissue leaflet assembly. In at least one embodiment, the tissue leaflet assembly comprises at least one cuff and at least one pleat.

In at least one embodiment, a method of preparing a percutaneous, trans-catheter prosthetic heart valve is provided, the method comprising:

providing a membrane tissue from an organism;

treating the membrane tissue with at least one chemical to produce a treated membrane tissue;

drying the treated membrane tissue until it is a substantially dry tissue;

attaching the substantially dry tissue in a frame;

rehydrating the substantially dry tissue that is attached within the frame to form a rehydrated tissue;

collapsing the frame with the rehydrated tissue attached thereto; and

drying the rehydrated tissue within the collapsed frame until it is a substantially dry tissue.

In at least one embodiment the method further comprises compressing and mounting the frame, with the substantially dry tissue attached thereto, upon a delivery catheter. In at least one embodiment the method further comprises sterilizing and packaging the frame, with the substantially dry tissue attached thereto, mounted upon the delivery catheter. In at least one embodiment, the treating comprises sterilizing the frame with the substantially dry tissue attached thereto with exposure to at least one of ethylene oxide, a proton beam, and gamma radiation. In at least one embodiment, the method further comprises shipping the sterilized and packaged frame with the substantially dry tissue attached thereto, mounted upon the delivery catheter, to a surgery or medical procedure facility. In at least one embodiment, prior to the attaching step the dry tissue is not folded to provide a cuff and/or a pleat. In at least one embodiment, prior to the attaching step the dry tissue is folded to form a tissue leaflet assembly. In at least one embodiment, the tissue leaflet assembly comprises at least one cuff and at least one pleat.

In at least one embodiment, the method of preparing a percutaneous, trans-catheter prosthetic heart valve further comprises implanting the frame with the substantially dry tissue attached thereto into a patient. In at least one embodiment, the frame comprises a stent. In at least one embodiment, the method further comprises mounting the frame and the tissue leaflet assembly attached thereto upon a 12 to 14 French balloon catheter. In at least one embodiment, the method further comprises mounting the frame and the tissue leaflet assembly attached thereto upon a balloon catheter having a size of less than about 12 French. In at least one embodiment, the method further comprises mounting the frame and the tissue leaflet assembly attached thereto upon a balloon catheter having a size of between about 5 to 12 French. In at least one embodiment, the method further comprises mounting the frame and the tissue leaflet assembly attached thereto on a mandrel. In at least one embodiment, the method of preparing a percutaneous, trans-catheter prosthetic heart valve further comprises immersion of the membrane tissue in buffered or unbuffered 1-37.5% formalin for between about 3 days to 3 weeks. In at least one embodiment, the method of preparing a percutaneous, trans-catheter prosthetic heart valve further comprises immersion of the membrane tissue in buffered or unbuffered 1-37.5% formalin for between about 3 days to 5 weeks. In at least one embodiment the treating comprises immersion of the membrane tissue in 100% glycerol for greater than 3 weeks. In at least one embodiment the treating comprises immersion of the membrane tissue in 0.1 - 25% glutaraldehyde for between about 3 days to 3 weeks. In at least one embodiment the treating comprises immersion of the membrane tissue in 0.1 - 25% glutaraldehyde for between about 3 days to 5 weeks. In at least one embodiment the treating comprises immersion of the membrane tissue in oligomeric filtered 0.1 - 25% glutaraldehyde for between about 3 days to 3 weeks. In at least one embodiment the treating comprises immersion of the membrane tissue in oligomeric filtered 0.1 - 25% glutaraldehyde for between about 3 days to 5 weeks. In at least one embodiment the treating comprises immersion of the membrane tissue in the aforementioned formalin, glutaraldehyde, or oligomeric filtered glutaraldehyde solutions with the added free amino acids lysine and/or histidine. In at least one embodiment the treating does not include contact and/or exposure to a polymer to infiltrate and/or encapsulate tissue fibers of the tissue.

In at least one embodiment, a method of preparing a percutaneous, trans-catheter prosthetic heart valve is provided, the method comprising:

providing a section of tissue harvested from a mammalian organism; and

causing osmotic shocking of the section of tissue by performing multiple rinses of the section of tissue with distilled water. In at least one embodiment, the method further comprises hydrating the section of tissue during a plurality of time intervals using distilled water. In at least one embodiment the section tissue comprises pericardium tissue. In at least one embodiment, the method further comprises not using saline for causing at least one of the osmotic shocking and the hydrating of the tissue. In at least one embodiment, the method further comprises pretreating the section of tissue with glycerol before contacting the section of tissue with one or more of isopropyl alcohol, glutaraldehyde and formalin. In at least one embodiment, the method further comprises contacting the section of tissue with a solution containing formalin after pretreating the section of tissue with glycerol. In at least one embodiment, the method further comprises contacting the section of tissue with a solution containing glutaraldehyde after pretreating the section of tissue with glycerol. In at least one embodiment, the method further comprises pretreating the section of tissue with isopropyl alcohol before contacting the section of tissue with either glutaraldehyde and formalin. In at least one embodiment, the method further comprises contacting the section of tissue with a solution containing formalin after pretreating the section of tissue with isopropyl alcohol. In at least one embodiment, the method further comprises contacting the section of tissue with a solution containing glutaraldehyde after pretreating the section of tissue with isopropyl alcohol. In at least one embodiment, the method further comprises exposing the section of tissue to light energy for a period time, the period of time extending until there is no further visible separation of lipid droplets from an exposed surface of the section of tissue. In at least one embodiment, the light energy is at least equivalent to exposing the section of tissue to a 50 watt incandescent light source with a flat radiant face situated at a distance of about 10 centimeters from the exposed surface for about 15 minutes.

With regard to delivery characteristics, another significant advantage of an implantable prosthetic heart valve using a relatively thin tissue component described herein is that the implantable prosthetic heart valve offers a relatively low packing volume as compared to commercially available prosthetic heart valves. As a result, the implantable prosthetic heart valve provides a relatively low catheter delivery profile, thereby enabling implantation in patients possessing relatively small diameter vascular systems.

In accordance with one or more embodiments, a dry tissue membrane has substantially less mass than a wet membrane. By way of example, a substantially dry pericardium tissue prepared by one or more of the present embodiments has approximately 30% of the mass of a wet pericardium tissue, and marked reduction in profile and packing volume, thereby achieving a relatively low profile and making it suitable for implantation in greater number of patients, especially those having small diameter vascular systems. In addition, a dry prosthetic heart valve does not require storage and transport in preservative. A dry prosthetic heart valve can be mounted on a delivery catheter at its location of manufacture, which allows for pre-packaging of an integrated delivery system. Together with a relatively low profile, embodiments of the prosthetic heart valves thereby offer reliability and convenience because the implantable prosthetic heart valve is pre-mounted upon a delivery catheter and forms part of a pre-packaged delivery system. In addition, a dry prosthetic heart valve does not require rinsing, rehydration, or mounting upon a delivery catheter in a catheterization lab. Therefore, a dry prosthetic heart valve can be inserted directly from package into the body at a critical time during the procedure. Advantageously, this avoids procedure time, manipulation, and errors of mounting, crimping, and orienting catheters and sheaths. Once at the surgical facility/location, the dry prosthetic heart valve is inserted and delivered by balloon catheter expansion in the plane of the diseased valve in the standard way and the dry prosthetic heart valve begins to function immediately, even in its dry state or not fully rehydrated state (because some rehydration will occur upon flushing of the catheter with the prosthetic heart valve residing therein), with rehydration of the tissue membrane subsequently completing naturally in the body.

Various components are referred to herein as “operably associated.” As used herein, “operably associated” refers to components that are linked together in operable fashion, and encompasses embodiments in which components are linked directly, as well as embodiments in which additional components are placed between the two linked components.

As used herein, "at least one," "one or more," and "and/or" are open-ended expressions that are both conjunctive and disjunctive in operation. For example, each of the expressions "at least one of A, B and C," "at least one of A, B, or C," "one or more of A, B, and C," "one or more of A, B, or C" and "A, B, and/or C" means A alone, B alone, C alone, A and B together, A and C together, B and C together, or A, B and C together.

As used herein, “sometime” means at some indefinite or indeterminate point of time. So for example, as used herein, “sometime after” means following, whether immediately following or at some indefinite or indeterminate point of time following the prior act.

Various embodiments of the present inventions are set forth in the attached figures and in the Detailed Description as provided herein and as embodied by the claims. It should be understood, however, that this Summary does not contain all of the aspects and embodiments of the one or more present inventions, is not meant to be limiting or restrictive in any manner, and that the invention(s) as disclosed herein is/are understood by those of ordinary skill in the art to encompass obvious improvements and modifications thereto.

Additional advantages of the present invention will become readily apparent from the following discussion, particularly when taken together with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

To further clarify the above and other advantages and features of the one or more present inventions, a more particular description of the one or more present inventions is rendered by reference to specific embodiments thereof which are illustrated in the appended drawings. It is appreciated that these drawings depict only typical embodiments of the one or more present inventions and are therefore not to be considered limiting of its scope. The one or more present inventions is described and explained with additional specificity and detail through the use of the accompanying drawings in which:

Fig. 1 is a flow chart of a method associated with at least of one embodiment of the present invention;

Figs. 2A-2B are a flow chart illustrating elements of the tissue preparation;

Fig. 3 is a flow chart illustrating elements of the drying and sizing;

Fig. 4 is a flow chart illustrating elements of the valve construction with attachment of tissue membrane leaflets to a frame;

Fig. 5 is a flow chart illustrating elements of the mounting of the valve into a delivery system;

Fig. 6 is a flow chart illustrating elements of the ensheathing, sterilization, and packaging;

Fig. 7 is a flow chart illustrating elements of the delivery of the valve into a patient;

Fig. 8A is a view of a one-piece section of tissue prior to being folded;

Fig. 8B is a view of two (of three) separate pieces of tissue after folding (detailed below);

Fig. 8C is a view of the two pieces of tissue shown in Fig. 8B after being sutured together at the pleat formed after folding (detailed below);

Fig. 8D is a view of a tissue blank with the line of primary fold shown using a dashed line;

Fig. 8E is a perspective view of the tissue blank being folded along the primary fold line;

Fig. 8F is a 2-part figure showing the pleats fold lines and pleats after folding;

Fig. 8G is a detail perspective view of a single pleat shown in Fig. 8F;

Fig. 8H is a perspective schematic view of a folded and seamed tissue leaflet assembly;

Fig. 8I is a perspective schematic view of a frame;

Fig. 8J is a perspective schematic view of the frame of Fig. 8I with the tissue leaflet assembly of Fig. 8H attached thereto;

Fig. 8K is side elevation schematic view of the device shown in Fig. 8J;

Fig. 8L is an end schematic view of the frame and tissue leaflet assembly attached thereto;

Fig. 9 is a graph that shows actual stress-strain test results for five tissue samples prepared in accordance with at least one embodiment;

Fig. 10 is a schematic of a portion of a catheter with a percutaneously deliverable heart valve mounted thereto;

Fig. 11A is a photo of an implantable prosthetic heart valve, including a tissue leaflet assembly attached within a frame, wherein the tissue is situated in a partially open orientation;

Fig. 11B is a drawing of an implantable prosthetic heart valve, including a tissue leaflet assembly attached within a frame, wherein the tissue is situated in a closed orientation;

Fig. 11C is a side cutaway view of an implantable prosthetic heart valve, including a tissue leaflet assembly attached within a frame, wherein the tissue is situated in a closed orientation;

Fig. 11D is another side cutaway view of an implantable prosthetic heart valve, including a tissue leaflet assembly attached within a frame, wherein the tissue is situated in a closed orientation;

Fig. 12 is a photo of valve tissue after testing through 30,000,000 cycles of pumping used to model human heart conditions, wherein the photo shows a smooth uniform surface;

Fig. 13 is a drawing of a surgeon holding a premounted percutaneously deliverable heart valve associated with a catheter and residing within sterile packaging;

Fig. 14 is a schematic of a simplified cutaway view of a human heart, including heart valves that may be targeted for receiving an embodiment of an implantable prosthetic heart valve;

Fig. 15 is a schematic of a human aorta receiving a catheter with an implantable prosthetic heart valve mounted thereto; and

Fig. 16 is a schematic of a human aorta with the implanted prosthetic heart valve implanted at the site of the original diseased aortic valve.

The drawings are not necessarily to scale.

DETAILED DESCRIPTION

Embodiments of the one or more inventions described herein include one or more devices, assemblies and/or methods related to a prosthetic heart valve. A prosthetic heart valve in accordance with at least one embodiment described herein can be surgically implanted, such as by percutaneous, trans-catheter delivery, to the implantation site within the patient. One or more embodiments of the prosthetic heart valves described herein have application for at least aortic and pulmonary valve positions, including for structural defects and diseased valves.

In at least one embodiment, biocompatible material is attached within a frame to form an implantable prosthetic heart valve, and then at a later time, the implantable prosthetic heart valve is implanted within a patient, such as by way of a percutaneous, trans-catheter delivery mechanism. Once implanted, the prosthetic heart valve serves to regulate the flow of blood associated with the patient's heart by allowing forward blood flow and substantially preventing backflow or valvular regurgitation.

Referring now to Fig. 1, a flow chart illustrates at least one embodiment of a prosthetic heart valve preparation and delivery method 100. The prosthetic heart valve preparation and delivery method 100 generally includes a plurality of procedures to include tissue preparation at 200, drying at 300, tissue leaflet assembly construction and attachment to frame at 400 to form an implantable prosthetic heart valve, mounting of the prosthetic heart valve (that is, the frame with the tissue leaflet assembly) into a delivery system at 500, ensheathing, sterilizing and packaging the delivery system including the prosthetic heart valve at 600, and finally, delivering the prosthetic heart valve into the patient at 700. Further detail of the prosthetic heart valve preparation and delivery method 100 is provided below.

At least one or more embodiments described herein include a relatively thin tissue component. By way of example and not limitation, in at least one embodiment the tissue has a thickness of approximately 50 - 150 μm, and further possesses characteristics of pliability and resistance to calcification after implantation. The relatively thin nature of the tissue used in the implantable prosthetic heart valve assists with biocompatibility. In addition, the relatively thin tissue component thereby provides for a relatively low mass. As a result, an implantable prosthetic heart valve using the tissue can accelerate to a relatively high heart rate in beats per minute with competent function.

Tissue suitable for use in the one or more prosthetic heart valves and/or one or more assemblies described herein is relatively thin and can generally be considered to be a membrane. Those skilled in the art will appreciate that both natural and synthetic types of materials may be used to form a leaflet assembly of a prosthetic heart valves. Accordingly, it is to be understood that although treated pericardium tissue is described as a suitable material for use in the leaflet assembly of a prosthetic heart valve of one or more embodiments described herein, material other than xenograft tissue membrane can be used, and indeed, xenograft tissue membrane other than pericardium tissue can be used. More specifically, synthetic materials may include, but are not limited to, PTFE, PET, Dacron, and nylon. In addition, other than pericardium tissue, xenograft tissue membrane may include, but is not limited to, membrane material from the intestine, lung and brain. Suitable material may also comprise allograft material, that is, material from human sources. The listing of possible materials is for exemplary purposes and shall not be considered limiting.

With reference now to Fig. 2A, the process associated with preparation of a biocompatible tissue consistent with the above-noted characteristics is described. In at least one embodiment, pericardium tissue, such as porcine or bovine pericardium tissue, is harvested at 204 and then processed to serve as the biocompatible tissue for association with a frame, such as by attaching within a frame. Accordingly, subsequent to the harvesting at 204, the pericardium tissue is cleaned and decellularized at 208. More particularly, in at least one embodiment the tissue is initially cleaned with distilled water using gentle rubbing and hydrodynamic pressure at 208 in order to remove adherent non-pericardial and non-collagenous tissue. In at least one embodiment, the hydrodynamic pressure at 208 is provided by spraying the tissue with a relatively weak stream of liquid to remove at least some of the non-collagenous material associated with the tissue. The rinsing at 208 is to achieve effective decellularization of the pericardium tissue through osmotic shock. Typically, the thickness of the tissue in the cleaned condition varies from about 50 to 500 micrometers, depending on the source of raw tissue. Cleaning preferably continues until there is no visible adherent non-pericardial or non-collagenous tissue.

With continued reference to Fig. 2A, after the tissue has been cleaned and decellularized at 208, the tissue then undergoes optional additional removal of lipids at 220 to further treat the tissue for preventing immunologic response and calcification. More particularly, the tissue first optionally undergoes a 100% glycerol pretreatment at 224 while being positioned on a flat surface (e.g., an acrylic plate), after which the tissue becomes nearly transparent.

At 228, the tissue optionally undergoes a "thermophotonic" process. In at least one embodiment, the tissue is optionally exposed to light energy for additional removal of lipids and for initial cross-linking of the collagen. By way of example and not limitation, in at least one embodiment a 25-100 watt incandescent light source, and more preferably, a 50 watt incandescent light source with a flat radiant face is employed at a distance of about 10 centimeters from the tissue surface, typically requiring 15 minutes of exposure before further visible separation of lipid droplets from the tissue stops.

Still referring to Fig. 2A, the tissue is then cleaned again in secondary cleaning at 232. More particularly, at 236 the tissue is again rinsed with distilled water. Thereafter, at 240 the tissue is rinsed with 25% isopropyl alcohol for periods of several hours to several days and weeks, depending on the desired tissue properties of pliability and tensile strength. By way of example and not limitation, tissue has been successfully prepared by rinsing with 25% isopropyl alcohol for a period of 7 days, and after further treatment steps described herein, provided an ultimate tensile strength of greater than 25 MegaPascals. Here, the combination of tissue pliability and tensile strength is sought for purposes of producing a material having property characteristics suitable for being physically manipulated to form a tissue leaflet assembly or other configuration appropriate for attaching with a frame, while providing a tissue material that will operate properly once implanted. These techniques are intended to conserve and preserve collagen fibers, minimizing damage to the tissue and improving tissue characteristics. The preparation and fixation techniques produce tissue membrane material that may be rendered and used at lesser thickness than typically rendered in the prior art. Thinner membranes are more pliable, but with conventional preparation techniques the tensile strength of the tissue is sacrificed. Advantageously, the preparation techniques described herein have produced membranes that have as much as three times the tensile strength of a commercial product of the prior art. This achieved strength is thus enabling for providing a tissue leaflet assembly having a low profile with appropriate durability, even in a substantially dry state. More particularly, the tissue possesses a relatively high tensile strength. By way of example and not limitation, testing has shown that embodiments of tissue prepared as described herein provide a tissue with a tensile strength of approximately three times the tensile strength of current pericardial valve tissue, such as on the order of approximately 25 MegaPascals, thereby providing about 2000 times the physiologic load strength for valve tissue. Moreover, testing of an embodiment of an implantable prosthetic heart valve made with tissue prepared as described herein and under a static load of greater than approximately 250 mmHg showed less than approximately 14% leakage, wherein such results are generally considered superior to surgical tissue valve prostheses.

In at least one embodiment where isopropyl alcohol is described as a rinsing agent, ethanol may be used in its place as an alternative, although resulting tissue properties may vary.

With reference to Fig. 9, stress-strain curve results for five different tissue samples prepared in accordance with an embodiment are shown. For the testing results shown, the yield stress or ultimate tensile strength was obtained by mounting strips of tissue fixed at the ends in a linear force tester and increasing the length by 0.3 mm/sec while recording resultant force (tension) until the material ruptured or separated entirely; these measurements were then used to calculate the stress-strain curves depicted in Fig. 9. As illustrated in the graph, the yield stress or ultimate tensile strength of the various tissue samples varied from about 30 to about 50 MegaPascals. More particularly, for each curve shown in Fig. 9, the testing procedures were the same. That is, each of the curves shown pertain to separate pieces of tissue that were subjected to the same test. The results show a minimum ultimate tensile strength of 30 MegaPascals, with a range up to 50 MegaPascals. Accordingly, the illustrated test results demonstrate consistency of the ultimate tensile strength results for the tissue treatment process.

With reference back to Fig. 2A, the tissue is rinsed with distilled water at 244 as a final cleaning step and for rehydration.

Referring now to Fig. 2B, following the rinse with distilled water at 244, treatment of the tissue continues. More particularly, fixation for collagen cross-linking at 248 is achieved by performing at least one of the following:

a. At 248a, immersion of the tissue in 1-37.5% formalin, ideally a buffered solution, for between about 3 days to 5 weeks, and more preferably, for between about 3 days to 4 weeks, and more preferably yet, for between about 3 weeks to 4 weeks, at a temperature of between about 4 to 37°C, and more preferably, 10% formalin for 6 days at 20°C; or

b. At 248b, immersion of the tissue in 100% glycerol for up to 6 weeks at between 4 to 37°C, and more preferably, immersion of the tissue in 100% glycerol for about 3 weeks at 20°C; or

c. At 248c, immersion of the tissue in 0.1 - 25% glutaraldehyde for between about 3 days to 5 weeks, and more preferably, for between about 3 days to 4 weeks, and more preferably yet, for between about 3 weeks to 4 weeks, at 0 to 37°C, and more preferably, immersion of the tissue in 0.25% glutaraldehyde for 7 days at 4°C; or

d. At 248d, immersion of the tissue in 0.1 - 25% glutaraldehyde (filtered to limit oligomeric content) for between about 3 days to 5 weeks, and more preferably, for between about 3 days to 4 weeks, and more preferably yet, for between about 3 weeks to 4 weeks, at 0 to 37°C, and more preferably, 0.25% glutaraldehyde for 7 days at 4°C; or

e. At 248e, immersion in the tissue in one of the above formalin, glutaraldehyde, or oligomeric filtered glutaraldehyde solutions together with added amino acids, lysine and/or histidine, wherein the concentration of the amino acids, L-lysine or histidine, used as an additive to the fixative is in the range of about 100 - 1000 milliMolar, with a preferred value of about 684 mM.

In addition to the foregoing, combinations of the processes listed above may be performed, including: step a followed by step b; step a followed by step c; and step a followed by step d.

As those skilled in the art will appreciate, heat-shrink testing may be conducted on tissue samples to correlate the effectiveness of protein cross-linking. Here, results of heat-shrink testing performed on one or more samples of tissue prepared in accordance with at least one embodiment using formalin showed that the tissue had a shrink temperature of 90°C. This compares favorably with samples prepared using glutaraldehyde, wherein the shrink temperature was 80°C. Accordingly, formalin is a suitable variant of fixation. It is noted that formalin was generally abandoned by the field, largely because of material properties that were unfavorable and because of inadequate or unstable protein cross-linking. Such problems have been overcome through the pretreatments described herein, allowing production of tissue with strength, pliability, and durability in a relatively thin membrane. When used in a percutaneous deliverable heart valve (also referred to herein as "prosthetic heart valve"), the tissue characteristics imparted by the tissue preparation process facilitate formation of a construct having a relatively low-profile, which also thereby facilitates dry packaging of the prosthetic heart valve. The same advantages are also achieved using the pretreatments when using a glutaraldehyde process.

Referring still to Fig. 2B, after fixation for collagen cross-linking at 248, an alcohol post-fixation treatment at 252 is preferably performed by rinsing the tissue in distilled water at 256, and then at 260 rinsing the tissue in 25% isopropyl alcohol for between about 30 minutes to 14 days or more at between about 0 to 37°C, and more preferably, for at least about 7 days at 20°C. At 264, the tissue undergoes a rinsing with distilled water.

In accordance with at least one embodiment, treatment of the tissue, including from the time of harvest to the time of implantation or grafting, does not include contact and/or exposure to a polymer to infiltrate and/or encapsulate tissue fibers of the tissue.

Referring now to Figs. 1 and 3, the drying process at 300 is performed after the tissue preparation at 200. Thus, in accordance with at least one embodiment, the tissue is dried under a load. More particularly, for the tissue drying at 304, the tissue is placed minimally stretched flat (that is, stretched just enough to eliminate visible wrinkles and bubbles) on a flat surface (e.g., a polymer or acrylic sheet) at 308, and held fixed at its edges at 312. Optionally, the joined tissue and underlying sheet are then set in a slight curve. The tension maintains the substantially flat structure of the tissue as it dries, thereby mitigating or preventing excessive shrinkage, wrinkling, and/or curling at the edges, and also making the rate of drying more uniform across the surface of the tissue because of the surface tension between the plate and the tissue. Alternatively, the tissue is dried while compressed between acrylic plates. When drying the tissue, the temperature is held at between about 4 to 37°C, and more preferably, between about 20 to 37°C (i.e., approximately room temperature to normal human body temperature), and more preferably, at about 20°C. At 314, the drying process is performed in substantially dark conditions (i.e., substantially no visible light) for between about 6 hours to 5 days, and more preferably, for about 72 hours. By way of example, the tissue is dried in dark conditions at a temperature of about 20°C for between about 6 hours to 5 days, and more preferably, for about 72 hours. As those skilled in the art will appreciate, drying the tissue while the tissue is compressed between plates requires a longer period of time.

In at least one embodiment, after drying, the tissue lots are inspected at 316, such as by stereomicroscopy, to identify and discard those with defects or discontinuities of the fiber matrix. In addition, the preferential fiber direction for each piece is identified to determine the necessary orientation of the free edge of the pieces that will form the valve leaflets. Depending upon the size (i.e., the area) of the tissue being prepared and the size of tissue needed for a given valve, the tissue may be trimmed or otherwise sized in optional sizing at 320, such as by cutting the tissue into an appropriately sized and shaped sheet for valve formation. Preferably, cutting of the tissue membrane is oriented so that the resulting free edge of the leaflet is parallel to the preferential fiber direction of the tissue membrane. Optionally, the free edge of the leaflets may also be cut with a parabolic or other curved profile to compensate for the downward angle from the commissural leaflet attachment point to the central coaptation point and to increase the total contact surface between the coapting leaflets. This approach minimizes focal weaknesses in the operating margins of the leaflet assembly and advantageously distributes the principal loading forces of the operating valve along the long axis of the collagen fibers. As a result, the tissue is resistant to surface fracture and fraying. As shown in Fig. 3, optional sizing at 320 is performed after the drying at 304 and inspection at 316.

With reference now to Fig. 4, an embodiment associated with forming a tissue leaflet assembly and attachment to a frame to form a prosthetic heart valve at 400 is further described. It is to be understood that the tissue generated from one or more of the tissue preparation procedures described herein may be used for a variety of devices or uses, and that use in a prosthetic heart valve is but one possible application for utilizing the tissue. For example, the tissue may be used in a shunt, or as graft material for repair or modification of one or more human organs, including the heart and its blood vessels. By way of further example, the tissue may be used as a pericardial membrane patch for repair of congenital heart defects. The tissue also has application as a prosthetic tissue in tendon and ligament replacement, and as a tissue product for wound management. Moreover, for use in a prosthetic heart valve, the tissue may be configured in a variety of ways and attached to a frame in a variety of ways. By way of example and not limitation, in at least one embodiment, the prepared tissue is formed into a tissue leaflet assembly at 404 by folding the tissue at 408, preferably while the tissue is in a dry state, to form at least a portion of the tissue leaflet assembly. Here, those skilled in the art will appreciate that a completed tissue leaflet assembly may be formed of a single monolithic piece of tissue 800, such as that shown in Fig. 8A, or alternatively, as shown in Figs. 8B and 8C, it may be formed of a plurality of tissue pieces 802 that are operatively connected, such as by gluing or sewing the tissue pieces together along seams 804. As seen in Fig. 8C, the seams 804 are preferably situated at overlapping portions of pleats 832 of the plurality of tissue pieces 802.

As those skilled in the art will further appreciate, a single monolithic piece of tissue 800 or a plurality of tissue pieces 802 may be used to form a prosthetic heart valve, wherein the tissue leaflet assembly is not a folded construct. By way of example and not limitation, a plurality of separate tissue pieces may each be attached to a frame (such as by suturing) to form a prosthetic heart valve. Thereafter, whether the prosthetic heart valve is made of a folded tissue leaflet assembly or a plurality of separate tissue pieces attached to a frame, the resulting prosthetic heart valve may then be further manipulated for delivery as a dry prosthetic heart valve.

In an alternative embodiment, tissue generated from one or more of the tissue preparation procedures described herein may be used to form a prosthetic heart valve that includes a frame, and that may be implanted by a “trans-apical” approach in which the prosthetic heart valve is surgically inserted through the chest wall and the apex of the heart.

In yet another alternative embodiment, tissue generated from one or more of the tissue preparation procedures described herein may be used to form a prosthetic heart valve that does not include a frame, and is not delivered via a catheter, but rather, is implanted via a surgical opening through the patient’s chest. In such a case, the prosthetic heart valve may be packaged for delivery as a dry prosthetic heart valve.

In still yet another alternative embodiment, tissue generated from one or more of the tissue preparation procedures described herein may be used to form a prosthetic heart valve that includes a frame, but that is not delivered via a catheter, but rather, is implanted via a surgical opening through the patient’s chest. In such a case, the prosthetic heart valve may be packaged for delivery as a dry prosthetic heart valve.

As a further alternative to the embodiments described herein, tissue may be implanted in a "wet" or hydrated state. For example, a prosthetic heart valve utilizing a prepared tissue described herein may be packaged for delivery as a hydrated prosthetic heart valve. Accordingly, while a portion of the tissue preparation process may include drying the tissue so that it may be manipulated more easily, the tissue may then be hydrated at a later point in time prior to implantation, and it may be maintained in a hydrated condition up to and including packaging, delivery and implantation into a patient. Advantages associated with using a folded tissue leaflet assembly include that a folded structure allows a relatively thin membrane to be used by avoiding suture lines in loaded, dynamically active surfaces. Accordingly, a sutureless leaflet assembly preserves long-term integrity. However, it is to be understood that a prosthetic heart valve that does not include a folded tissue leaflet assembly is encompassed by one or more embodiments described herein.

With reference now to Figs. 8D-8L, and in accordance with at least one embodiment, for a prosthetic heart valve that includes a tissue leaflet assembly formed of a folded tissue membrane, the folding sequence for the tissue is shown for configuring the tissue into a completed tissue leaflet assembly. More particularly, a tissue blank 808 is shown in Fig. 8D, wherein the tissue blank 808 is a single monolithic piece of tissue 800. Depending upon the size requirements for a given tissue leaflet assembly, a line of primary fold or fold line 812 (shown as a dashed line) is visualized for the tissue blank 808. As shown in Fig. 8D, the primary fold 814 is achieved along the fold line 812 by folding the bottom edge 816 of the tissue blank 808 toward the top edge 820, but leaving a cuff portion 824 along the upper portion 828 of the tissue blank 808. Here, it is noted that the direction of top and bottom are relative to each other and are used as a convenience for describing the folding sequence, wherein such directions correspond to the orientation of the page illustrating the drawings. Advantageously, the folding geometry of Figs. 8D-8L forms cuffs 824 that are continuous with the leaflets, thereby reducing the risk of aortic insufficiency or leakage.

With reference now to Fig. 8F, after folding the tissue blank 808 along fold line 812 to form primary fold 814, pleats are formed by folding the tissue along its length. For the embodiment shown in Fig. 8F, three pleats 832a, 832b, and 832c are shown. Fig 8G illustrates a detail drawing of a single pleat 832 representative of one of pleats 832a-c. In Fig. 8G, the inner leaflet layer free edge 836 is shown, as is the valve sinus 840 and the commissure folds 844.

Referring again to Fig. 4 as well as Fig. 8H, at 412 the folded tissue is seamed to form a folded tissue leaflet assembly. More particularly, Fig. 8H shows a schematic perspective drawing of tissue leaflet assembly 848, wherein the pleated tissue construct shown in the bottom half of Fig. 8F is seamed, such as along seam 850, to form a substantially tubular construct. At

416, the folded tissue leaflet assembly 848 is maintained dry or is partially hydrated prior to mounting the tissue leaflet assembly in a frame. At 420, the tissue leaflet assembly 848 is then attached within a frame, such as frame 852 shown in Fig. 8I. The tissue leaflet assembly 848 attached within a frame 852 forms an implantable prosthetic heart valve 860, such as that shown in the schematic perspective drawing of Fig. 8J, side elevation view Fig. 8K, as well as that shown in the photo of Fig. 11A, and drawing of Fig. 11B. Fig. 8K illustrates possible suture points 864 where the tissue leaflet assembly 848 can be sutured to the frame 852. That is, the tissue leaflet assembly 848 may be attached within the frame 852, such as by suturing the outer layer of the tissue leaflet assembly 848 to the frame. In the foregoing sentence, and as used herein, it is noted that the term "attached" means that the tissue leaflet assembly 848 is secured to the frame 852, although the inner leaflet layer free edges 836 are able to readily move during operation of the prosthetic heart valve 860.

Referring now to Fig. 11C, a cutaway side elevation view of a prosthetic heart valve 860 that includes a frame 852 with a tissue leaflet assembly 848 attached therein is shown. The tissue membrane leaflet assembly 848 is disposed coaxially within the frame 852. As shown in Fig. 11C, the valve 860 is illustrated in the closed position with the leaflet free edges 836 in at least partial contact with each other. An arc 1112 of the leaflet free edges 836 (out of plane of the cutaway view) is continuous with pleats 832 at the radial edge of the tissue leaflet assembly 848, and may be seen in the alternate view shown in Fig. 8L. The tissue membrane leaflet assembly 848 is attached to the frame 852 along the axially oriented membrane pleats 832, as illustrated again in Fig. 8L. The extended cuff layer is attached circumferentially at the distal edge 1104 of the frame 852. By way of example and not limitation, continuous suture attachment 1108 may be used to attach the extended cuff layer to the distal edge 1104.

Referring now to Fig. 11D, an embodiment is shown wherein the cuff layer is not extended distally to the distal edge 1104 of the frame 852. As shown in Fig. 11D, the distal edge of the cuff layer is attached circumferentially to an inner aspect of the frame 852, such as along those possible suture points 864 illustrated in Fig. 8K. As a result, a distal portion 1116 of the frame 852 does not include any portion of the tissue leaflet assembly 848, such as the cuff layer. However, with the valve 860 in the closed position the leaflet free edges 836 still at least partially contact each other.

With reference now to Fig. 8L, an end view of the prosthetic heart valve is shown. As depicted in Fig. 8L, the pleats 832 are used as the portion of the tissue leaflet assembly 848 to attach to the frame 852. As can be seen in Fig. 8L, the outer cuff layer is attached to the frame members of frame 852. When the prosthetic heart valve 860 is closed, the cusps 868 formed by the inner leaflet layer are generally situated as depicted in Fig. 8L. Fig. 12 is a photo of the tissue leaflets of a prosthetic heart valve after 30,000,000 cycles of testing to model performance if associated with a human heart. In testing, the prosthetic heart valve 860 has demonstrated a natural opening gradient of approximately 5 mmHg.

It will be appreciated by one of ordinary skill in the art that the tissue leaflet assembly 848 described and shown herein is but one possible construct for forming a flow control mechanism that can be attached to a frame to regulate the flow of blood in a patient's vascular system upon deployment. That is, the illustrated tissue leaflet assembly 848 is provided by way of example and not limitation, and in no way should be interpreted to limit the geometries of membrane leaflet assemblies that can be used to regulate fluid flow. Accordingly, other leaflet configurations and constructs are considered encompassed by claims directed to or otherwise including premounted percutaneously deliverable valves.

As those skilled in the art will appreciate, the frame 852 may be a stent or a structure having similarities to a stent. The frame 852 essentially serves as a holding mechanism for the tissue leaflet assembly 848 that can then be inserted percutaneously into a patient, wherein the frame 852 serves as a way to anchor the folded tissue leaflet assembly 848 to a vascular portion (e.g., *in situ* arterial tissue) of the patient. Thus, at 424 the tissue leaflet assembly 848 is inserted into a frame 852. More particularly, at 424a the frame 852 may comprise a balloon-expandable frame, or alternatively, at 424b a self-expanding frame may be used. After the tissue leaflet assembly is inserted into the frame, at 428 the folded tissue leaflet assembly 848 is attached to the frame 852, such as by suturing the tissue leaflet assembly 848 to the frame 852 to form an implantable prosthetic heart valve 860, such as that shown in Fig. 8L. In at least one embodiment, after attaching the tissue leaflet assembly 848 within the frame 852 and connecting the tissue leaflet assembly 848 to the frame 852 to form an implantable prosthetic heart valve 860, at 432 the prosthetic heart valve 860 is fully hydrated for inspection and testing. Thereafter, the fully constructed implantable prosthetic heart valve 860 may be dried and maintained in a substantially dry condition. Accordingly, as those skilled in the art will appreciate, one or more embodiments described herein provide a tissue 800 suitable for implanting in a human, wherein the implantable tissue may be allowed to dry prior to implanting, or it may be hydrated prior to implanting. In addition, the tissue 800 is suitable for use in forming a tissue leaflet assembly 848 for use in a prosthetic heart valve, including an implantable prosthetic heart valve 860 that can be implanted with its tissue leaflet assembly in a dry state, or with its tissue leaflet assembly in a partially or fully hydrated state.

One or more of the embodiments of the tissue leaflet assemblies described herein may be implanted into the patient using a balloon-expandable frame or a self-expanding frame. Expandable frames are generally conveyed to the site of the target valve on balloon catheters.

For insertion, the expandable frame is positioned in a compressed configuration along the delivery device, for example crimped onto the balloon of a balloon catheter that is part of the delivery device intended for coaxial mounting on a guidewire. After the expandable frame is positioned across the plane of the valve, the expandable frame is expanded by the delivery device. For a self-expanding frame, commonly a sheath is retracted, allowing expansion of the self-expanding frame.

In at least one embodiment, the frame comprises a metal alloy frame possessing a high strain design tolerance that is compressible to a relatively small diameter. By providing a device with a low profile, the implantable prosthetic heart valve 860 allows standard retrograde arterial aortic delivery via femoral artery insertion, without surgical cutdown or general anesthesia. This is achieved by providing the prosthetic heart valve on a premounted delivery system with the tissue leaflet assembly or tissue membrane construct in a substantially dry condition.

In accordance with one or more embodiments, a dry tissue membrane has substantially less mass than a wet membrane. By way of example, a substantially dry pericardium tissue prepared by one or more of the present embodiments has approximately 30% of the mass of a wet pericardium tissue, and marked reduction in profile and packing volume, thereby achieving a relatively low profile and making it suitable for implantation in greater number of patients, especially those having small diameter vascular systems. In addition, a dry prosthetic heart valve does not require storage and transport in preservative. A dry prosthetic heart valve can be mounted on a delivery catheter at its location of manufacture, which allows for pre-packaging of an integrated delivery system. In the foregoing sentence, it is noted that the term "mounted" means that the prosthetic heart valve 860 is temporarily associated with the delivery catheter. Together with a relatively low profile, embodiments of the prosthetic heart valve thereby offer reliability and convenience because the implantable prosthetic heart valve 860 is pre-mounted upon its delivery catheter and forms part of a pre-packaged delivery system. In addition, a dry prosthetic heart valve does not require rinsing, rehydration, or mounting in a catheterization lab. Therefore, a dry prosthetic heart valve can be inserted directly from package into the patient's body at a critical time during the procedure. Advantageously, this avoids procedure time, manipulation, and errors of mounting, crimping, and orienting catheters and sheaths. Once at the surgical facility/location, the dry prosthetic heart valve is inserted and delivered by balloon catheter expansion in the plane of the target valve in the standard way and the dry prosthetic heart valve begins to function immediately, even without specific steps to rehydrate the tissue membrane portion of the heart valve from its dry state, with hydration of the tissue membrane subsequently occurring rapidly and naturally in the body. More particularly, hydration of the tissue membrane portion occurs rapidly and begins with simple preparatory flushing of catheter lumens with saline. Thereafter, hydration continues with device insertion and dwelling into the central blood vessels, and completes naturally after deployment in the patient's body.

The low profile of the implantable prosthetic valve is particularly advantageous for patient's having relatively small diameter vascular systems. Table 1 provides aortic and pulmonary valve prosthesis sizing.

Table 1: Aortic and Pulmonary Valve Prosthesis Sizing

Aorta/Pulmonary Valve Diameter	**Collapsed Implantable Prosthetic Heart Valve Size (French)**	**Collapsed Implantable Prosthetic Heart Valve Diameter**
19 - 21 mm	12 French	4.0 mm
22 - 26 mm	14 French	4.7 mm
27 - 30 mm	16 French	5.3 mm

For most human patients, the femoral artery has a diameter of between about 5-8 mm. Accordingly, it is apparent that embodiments of the collapsed implantable prosthetic heart valves 860 described herein offer a low profile that enables a larger group of patients to qualify for receiving an implantable prosthetic heart valve 860. As a result of the sizing advantages offered by one or more embodiments of implantable prosthetic heart valves 860 described herein, virtually no candidate patients would be excluded from treatment with an implantable prosthetic heart valve 860 without open heart surgery and without general anesthesia on the basis of inadequate femoral blood vessel access caliber. In addition, one or more embodiments of the implantable prosthetic heart valve 860 described herein feature a scalable construct, wherein the implantable prosthetic heart valves 860 can be produced to accommodate target valve diameters ranging between 6 - 35 mm, and wherein the implantable prosthetic heart valves 860 offer consistent function using fundamentally a single design.

Referring now to Fig. 5, the mounting of the implantable prosthetic heart valve 860 into a delivery system at 500 is further described. More particularly, at 504 an implantable prosthetic heart valve 860 (also referred to herein as a percutaneously deliverable heart valve) is collapsed. The initial phase of collapsing the percutaneously deliverable heart valve is executed with the tissue membrane in a hydrated condition. That is, since the percutaneously deliverable heart valve 860 includes the frame 852 with the tissue leaflet assembly 848 attached within the frame 852, the percutaneously deliverable heart valve 860 is collapsed down as an integral unit. If a balloon-expandable frame is used, then an axial puller may be utilized to collapse down the frame 852 of the percutaneously deliverable heart valve 860 without the application of force directly to the sides of the frame 852. This procedure offers the advantage of preserving the cell structure of the frame 852 while also maintaining the orientation of the leaflets of the tissue leaflet assembly 848 as the percutaneously deliverable heart valve 860 is compressed. The proper orientation and disposition of the leaflets is facilitated by the hydrated state of the leaflets. This assists in preventing tissue prolapse or bulging of the tissue 800 or 802 through the frame 852. In addition, this technique reduces recompression strain on the metal frame 852 (e.g., a stent) that can tend to compromise fatigue life of the frame 852. This technique also tends to promote the circumferentially uniform collapsing of cells in the frame 852, thereby mitigating bunching of the tissue that forms the tissue leaflet assembly 848 of the percutaneously deliverable heart valve 860. For a self-expanding frame, the sides are forced to collapse by providing a radial compression force to the frame and may be assisted by axial traction force.

With further reference to Fig. 5, the percutaneously deliverable heart valve 860 (i.e., the frame 852 with the tissue leaflet assembly 848 attached thereto) is collapsed in an initially hydrated state. At 508 the delivery mandrel or balloon is inserted into a delivery sheath, and the mounting segment is then extended out the end of the sheath. Thereafter, at 512 the sheath and frame are coaxially mounted and then compressed with initial crimping onto the mounting segment with the tissue leaflet assembly 848 still in a hydrated state. At 516, the tissue leaflet assembly 848 of the percutaneously deliverable heart valve 860 is then allowed to dry, which further reduces the volume and profile of the tissue membrane leaflets, permitting further compression by radial force. Accordingly, in the final compression step, the percutaneously deliverable heart valve 860 is then further crimped with a circumferential crimping tool at 520 to finally mount the compressed valve/frame onto the delivery mandrel or balloon catheter.

Referring now to Fig. 6, the ensheathing, sterilization and packaging at 600 is described. More particularly, once the percutaneously deliverable heart valve 860 is coaxially mounted and crimped on a delivery mandrel or balloon catheter as described above and shown in Fig. 5, the assembly is then inserted at 604 into a distal end of a delivery sheath, such as by "backloading" the assembly into position with a distal end of the percutaneously deliverable heart valve 860 contained within the delivery sheath proximate the end of the sheath. Reference here is made to Fig. 10 that schematically illustrates catheter 1000 with an implantable prosthetic heart valve 860 mounted thereto.

With further reference to Fig. 6, at 608 the percutaneously deliverable heart valve 860 and delivery catheters are sterilized, such as by using by one or more of ethylene oxide, proton beam, or gamma radiation. At 612, the assembly is then optionally packaged in a sterile package. Additional elements are optionally shipped with the assembly, wherein, by way of example, such elements may include any necessary delivery tools and documentation. In at least one embodiment, the package may optionally contain a device to control the water vapor content within the sealed volume of the package. Fig. 13 depicts a surgeon holding a sterile package 1300 containing a premounted percutaneously implantable prosthetic heart valve.

Referring now to Fig. 7, a flow chart illustrating the general procedure associated with implantation of the percutaneously deliverable heart valve 860 is provided. More particularly, at 704, catheter access is gained to the patient's femoral artery and a guidewire is placed through the plane of the diseased valve that is targeted to receive the implant. Fig. 14 is a schematic of a simplified cutaway view of a human heart, including heart valves that may be targeted for receiving an embodiment of an implantable prosthetic heart valve. Fig. 15 illustrates the aorta with the guidewire placed through the diseased aortic valve. At 708, the percutaneously deliverable heart valve 860 in the form of a prepackaged assembled dry prosthetic heart valve is removed from the sterile packaging. The dry prosthetic heart valve assembly, including its lumens, are preferably flushed and prepared in the usual fashion for standard balloons and catheters that do not contain a biocompatible tissue. Advantageously, implantation of the dry prosthetic heart valve assembly can be conducted without specific maneuvers for rehydration of the tissue leaflet assembly 848 of the percutaneously deliverable heart valve 860. Some rehydration of the tissue leaflets may occur as a consequence of the routine flushing of the catheter lumens in preparation for use as with any other catheters. Additionally, implantation of the dry prosthetic heart valve assembly can proceed without additional cleaning steps, such as by having to use alcohol or water rinsing solutions. In addition, further mounting of the dry tissue leaflet assembly 848 that resides in the frame 852 of the percutaneously deliverable heart valve 860 is not needed, thereby obviating the need for another mounting step. Accordingly, the percutaneously deliverable heart valve 860 can essentially be implanted percutaneously in its dry state. At 712, the carrier catheter or balloon catheter is then coaxially mounted and advanced over the guidewire, such as under fluoroscopic vision initially to the level of the great vessel where it can be inspected under fluoroscopy. At 716, and after the nominal position and configuration is confirmed, the delivery system is advanced through the plane of the diseased valve under fluoroscopy, and the covering sheath is withdrawn, either at this point or during the advance prior to it, thus exposing the mounted implantable prosthetic heart valve 860 in place. At 720, in the case of a balloon expandable frame, and assuming the delivery approach involving the pre-mounting of the percutaneously deliverable heart valve 860 on the expansion balloon, the balloon is then inflated, deploying the percutaneously deliverable heart valve 860 in the plane of the valve. At 724, the leaflets of the percutaneously deliverable heart valve 860 operate immediately. The deployed prosthetic heart valve 860 is shown in Fig. 16, wherein the tissue leaflet assembly 848 serves to properly control the flow blood.

The present invention may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

The one or more present inventions, in various embodiments, include components, methods, processes, systems and/or apparatus substantially as depicted and described herein, including various embodiments, subcombinations, and subsets thereof. Those of skill in the art will understand how to make and use the present invention after understanding the present disclosure.

The present invention, in various embodiments, includes providing devices and processes in the absence of items not depicted and/or described herein or in various embodiments hereof, including in the absence of such items as may have been used in previous devices or processes (e.g., for improving performance, achieving ease and/or reducing cost of implementation).

The foregoing discussion of the invention has been presented for purposes of illustration and description. The foregoing is not intended to limit the invention to the form or forms disclosed herein. In the foregoing Detailed Description for example, various features of the invention are grouped together in one or more embodiments for the purpose of streamlining the disclosure. This method of disclosure is not to be interpreted as reflecting an intention that the claimed invention requires more features than are expressly recited in each claim. Rather, as the following claims reflect, inventive aspects lie in less than all features of a single foregoing disclosed embodiment. Thus, the following claims are hereby incorporated into this Detailed Description, with each claim standing on its own as a separate preferred embodiment of the invention.

Moreover, though the description of the invention has included description of one or more embodiments and certain variations and modifications, other variations and modifications are within the scope of the invention (e.g., as may be within the skill and knowledge of those in the art, after understanding the present disclosure). It is intended to obtain rights which include alternative embodiments to the extent permitted, including alternate, interchangeable and/or equivalent structures, functions, ranges or acts to those claimed, whether or not such alternate, interchangeable and/or equivalent structures, functions, ranges or acts are disclosed herein, and without intending to publicly dedicate any patentable subject matter.

CLAIMS

What is claimed is:

1. An assembly, comprising:

a prosthetic heart valve including:

a frame; and

a tissue leaflet assembly attached to the frame;

a percutaneously insertable valve delivery mechanism, wherein the prosthetic heart valve is releasably mounted onto the percutaneously insertable valve delivery mechanism; and

sterile packaging containing the prosthetic heart valve releasably mounted onto the percutaneously insertable valve delivery mechanism.

2. The assembly of Claim 1, wherein the percutaneously insertable valve delivery mechanism comprises a balloon catheter.

3. The assembly of Claim 2, wherein the balloon catheter is a 12 to 14 French balloon catheter.

4. The assembly of Claim 2, wherein the balloon catheter is less than about 12 French.

5. The assembly of Claim 2, wherein the balloon catheter is between about 5 to 12 French.

6. The assembly of Claim 1, wherein the percutaneously insertable valve delivery mechanism comprises a mandrel.

7. The assembly of Claim 1, wherein tissue forming the tissue leaflet assembly within the sterile packaging is at least one of hydrated and not substantially dry.

8. The assembly of Claim 1, wherein tissue forming the tissue leaflet assembly within the sterile packaging is substantially dry.

9. The assembly of Claim 1, wherein the frame comprises a stent.

10. The assembly of Claim 1, wherein tissue forming the tissue leaflet assembly comprises treated pericardium tissue.

11. A pre-packaged percutaneous, trans-catheter deliverable prosthetic heart valve ready for implantation in a patient, comprising:

a frame; and

a tissue leaflet assembly attached to the frame, the tissue leaflet assembly comprising a substantially dry tissue.

12. The pre-packaged percutaneous, trans-catheter deliverable prosthetic heart valve of Claim 11, wherein the substantially dry tissue comprises treated pericardium tissue.

13. The pre-packaged percutaneous, trans-catheter deliverable prosthetic heart valve of Claim 11, wherein the substantially dry tissue comprises a water moisture content of less than about 40% by weight of the substantially dry tissue.

14. The pre-packaged percutaneous, trans-catheter deliverable prosthetic heart valve of Claim 11, wherein the frame and the tissue leaflet assembly attached thereto are operably associated with a 12 to 14 French balloon catheter.

15. The pre-packaged percutaneous, trans-catheter deliverable prosthetic heart valve of Claim 11, wherein the frame and the tissue leaflet assembly attached thereto are operably associated with a balloon catheter having a size of less than about 12 French.

16. The pre-packaged percutaneous, trans-catheter deliverable prosthetic heart valve of Claim 11, wherein the frame and the tissue leaflet assembly attached thereto are operably associated with a balloon catheter having a size of between about 5 to 12 French.

17. An assembly for use with a patient, comprising:

a sealed sterile package containing a delivery system for percutaneously deploying a heart valve in the patient, the heart valve including:

a frame releasably mounted on the delivery system within the sealed sterile package; and

a tissue leaflet assembly attached to the frame.

18. The assembly of Claim 17, wherein the tissue leaflet assembly comprises a treated pericardium tissue.

19. The assembly of Claim 17, wherein the delivery system includes a percutaneously insertable balloon catheter.

20. The assembly of Claim 19, wherein the balloon catheter is a 12 to 14 French balloon catheter.

21. The assembly of Claim 19, wherein the balloon catheter is less than about 12 French.

22. The assembly of Claim 19, wherein the balloon catheter is between about 5 to 12 French.

23. The assembly of Claim 17, wherein the delivery system includes a percutaneously insertable mandrel.

24. The assembly of Claim 17, wherein the tissue leaflet assembly within the sealed sterile package is at least one of partially hydrated and not substantially dry.

25. The assembly of Claim 17, wherein the tissue leaflet assembly within the sealed sterile package is substantially dry.

26. The assembly of Claim 17, wherein the frame comprises a stent.

27. An article adapted for implantation in a patient, comprising:

a prosthetic heart valve further comprising a treated tissue attached to a frame, wherein the treated tissue comprises a water content of less than about 60% by weight of the treated tissue.

28. The article of Claim 27, wherein the treated tissue comprises a section of treated pericardium tissue having an ultimate tensile strength of greater than about 12 MegaPascals.

29. The article of Claim 28, wherein the section of pericardium tissue comprises a thickness of between about 50 to 300 micrometers.

30. The article of Claim 27, wherein the water content of the treated tissue is less than about 40% by weight of the treated tissue.

31. An article adapted for trans-catheter delivery into a patient, comprising:

a prosthetic heart valve further comprising a treated tissue attached to a frame, wherein the treated tissue comprises a thickness of about 50 to 500 micrometers and an ultimate tensile strength of greater than about 15 MegaPascals when at a water content of less than about 50% by weight of the treated tissue.

32. The article of Claim 31, wherein the treated tissue comprises a treated pericardium tissue.

33. The article of Claim 31, wherein the water content of the treated tissue is less than about 40% by weight of the treated tissue.

34. The article of Claim 31, wherein the ultimate tensile strength is greater than about 20 MegaPascals.

35. The article of Claim 31, wherein the treated tissue does not include a matrix that has been exposed to a polymer infiltrate.

36. A method, comprising:

partially compressing and mounting a prosthetic heart valve upon a delivery catheter, the prosthetic heart valve comprising a tissue;

allowing the tissue to at least partially dry;

further compressing and mounting the prosthetic heart valve upon the delivery catheter; and

sterilizing and packaging the prosthetic heart valve and delivery catheter.

37. The method of Claim 36, further comprising transporting the sterilized and packaged prosthetic heart valve and delivery catheter.

38. The method of Claim 36, wherein the tissue comprises a treated pericardium tissue.

39. The method of Claim 36, wherein prior to partially compressing and mounting the prosthetic heart valve upon the delivery catheter, the tissue is at least one of (a) not substantially dry, and (b) at least partially hydrated.

40. A method, comprising:

attaching a tissue to a frame;

partially compressing and mounting the frame, with the tissue attached thereto, upon a delivery catheter;

allowing the tissue to at least partially dry;

further compressing and mounting the frame, with the tissue attached thereto, upon the delivery catheter; and

sterilizing and packaging the frame and delivery catheter, with the tissue attached thereto.

41. The method of Claim 40, wherein prior to partially compressing and mounting the frame, the tissue is at least one of (a) not substantially dry, and (b) at least partially hydrated.

42. The method of Claim 40, further comprising transporting the sterilized and packaged frame, with the tissue attached thereto, mounted upon the delivery catheter, to a surgical or medical procedure facility.

43. The method of Claim 40, wherein prior to attaching the tissue to the frame the tissue is folded to form a tissue leaflet assembly.

44. The method of Claim 43, wherein the tissue leaflet assembly comprises at least one cuff and at least one pleat.

45. The method of Claim 40, wherein the tissue comprises a treated pericardium tissue.

46. A method of preparing a percutaneous, trans-catheter prosthetic heart valve, comprising:

providing a membrane tissue from an organism;

treating the membrane tissue with at least one chemical to produce a treated membrane tissue;

drying the treated membrane tissue until it is a substantially dry tissue;

attaching the substantially dry tissue to a frame;

rehydrating the substantially dry tissue that is attached to the frame to form a rehydrated tissue;

collapsing the frame with the rehydrated tissue attached thereto; and

drying the rehydrated tissue attached to the collapsed frame until it is a substantially dry tissue.

47. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, further comprising compressing and mounting the frame, with the tissue attached thereto, upon a delivery catheter.

48. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 47, further comprising sterilizing and packaging the frame, with the substantially dry tissue attached thereto, mounted upon the delivery catheter.

49. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 48, further comprising at least one of transporting and shipping the sterilized and packaged frame with the substantially dry tissue attached thereto, mounted upon the delivery catheter, to a surgical or medical procedure facility.

50. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 49, further comprising implanting the frame with the substantially dry tissue attached thereto into a patient.

51. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein the frame comprises a stent.

52. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein prior to the attaching step the dry tissue is not folded with a cuff and a pleat.

53. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein prior to the attaching step the dry tissue is folded to form a tissue leaflet assembly.

54. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 53, wherein the tissue leaflet assembly comprises at least one cuff and at least one pleat.

55. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 53, further comprising mounting the frame and the tissue leaflet assembly attached thereto upon a 12 to 14 French balloon catheter.

56. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 53, further comprising mounting the frame and the tissue leaflet assembly attached thereto upon a balloon catheter having a size of less than about 12 French.

57. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 53, further comprising mounting the frame and the tissue leaflet assembly attached thereto upon a balloon catheter having a size of between about 5 to 12 French.

58. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 53, further comprising mounting the frame and the tissue leaflet assembly attached thereto on a mandrel.

59. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, further comprising sterilizing the frame with the substantially dry tissue attached thereto with exposure to at least one of ethylene oxide, a proton beam, and gamma radiation.

60. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in a buffered or unbuffered 1 – 37.5% formalin solution for between about 3 days to 3 weeks.

61. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in a buffered or unbuffered 1 – 37.5% formalin solution for between about 3 days to 5 weeks.

62. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in a buffered or unbuffered 1 - 37.5% formalin solution containing at least one of free amino acids (a) lysine and (b) histidine, for between about 3 days to 3 weeks.

63. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in a buffered or unbuffered 1 - 37.5% formalin solution containing at least one of free amino acids (a) lysine and (b) histidine, for between about 3 days to 5 weeks.

64. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in 100% glycerol for greater than about 3 weeks.

65. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in a 0.1 - 25% glutaraldehyde solution for between about 3 days to 3 weeks.

66. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in a 0.1 - 25% glutaraldehyde solution for between about 3 days to 5 weeks.

67. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in a 0.1 - 25% glutaraldehyde solution containing at least one of free amino acids (a) lysine and (b) histidine, for between about 3 days to 3 weeks.

68. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in a 0.1 - 25% glutaraldehyde solution containing at least one of free amino acids (a) lysine and (b) histidine, for between about 3 days to 5 weeks.

69. The met ous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in an oligomeric filtered 0.1 - 25% glutaraldehyde solution for between about 3 days to 3 weeks.

70. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in an oligomeric filtered 0.1 - 25% glutaraldehyde solution for between about 3 days to 5 weeks.

71. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in an oligomeric filtered 0.1 - 25% glutaraldehyde solution containing at least one of free amino acids (a) lysine and (b) histidine, for between about 3 days to 3 weeks.

72. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in an oligomeric filtered 0.1 - 25% glutaraldehyde solution containing at least one of free amino acids (a) lysine and (b) histidine, for between about 3 days to 5 weeks.

73. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein the membrane tissue comprises a treated pericardium tissue.

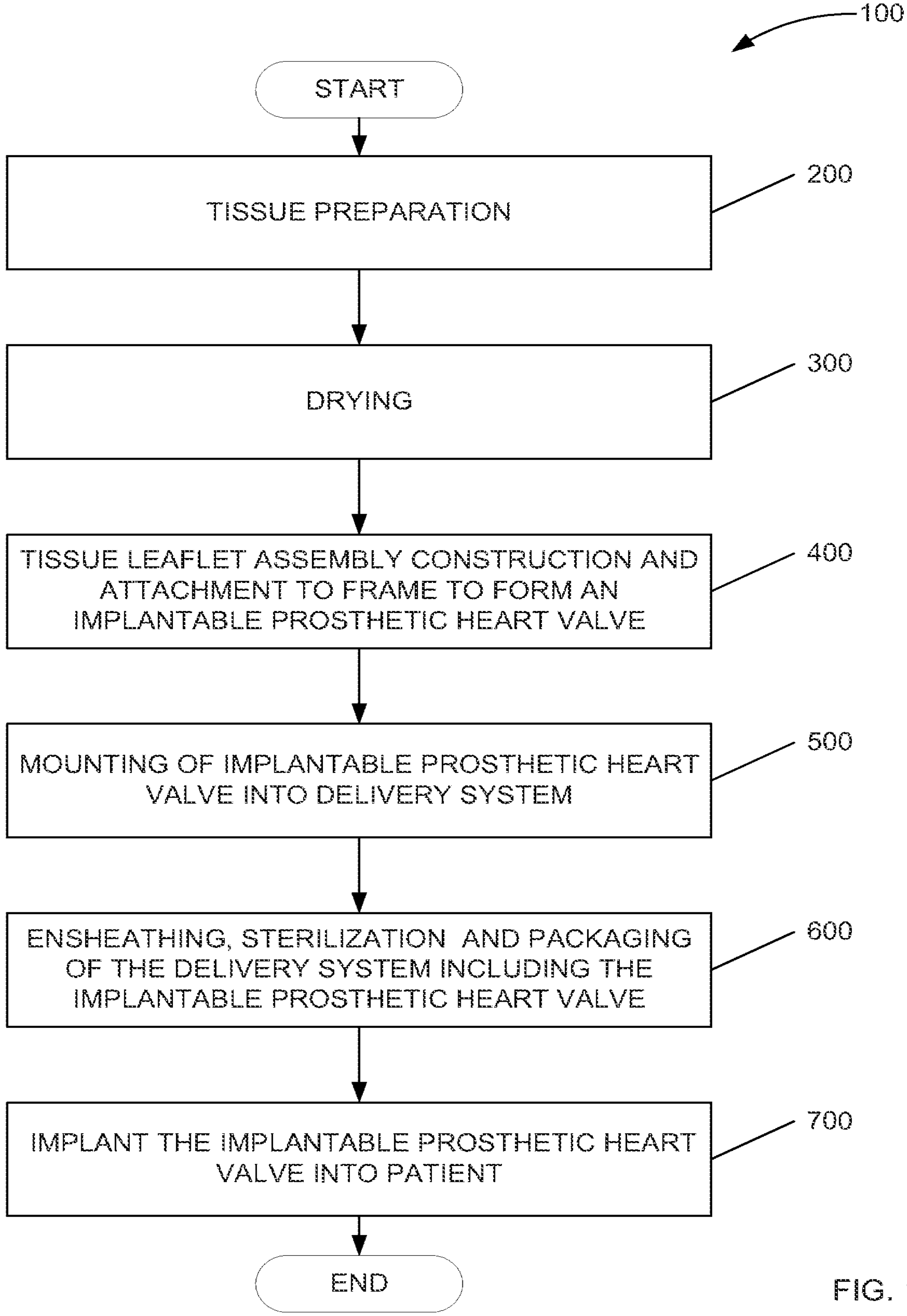

100
START
TISSUE PREPARATION
200
DRYING
300
TISSUE LEAFLET ASSEMBLY CONSTRUCTION AND ATTACHMENT TO FRAME TO FORM AN IMPLANTABLE PROSTHETIC HEART VALVE
400
MOUNTING OF IMPLANTABLE PROSTHETIC HEART VALVE INTO DELIVERY SYSTEM
500
ENSHEATHING, STERILIZATION AND PACKAGING OF THE DELIVERY SYSTEM INCLUDING THE IMPLANTABLE PROSTHETIC HEART VALVE
600
IMPLANT THE IMPLANTABLE PROSTHETIC HEART VALVE INTO PATIENT
700
END

FIG. 1

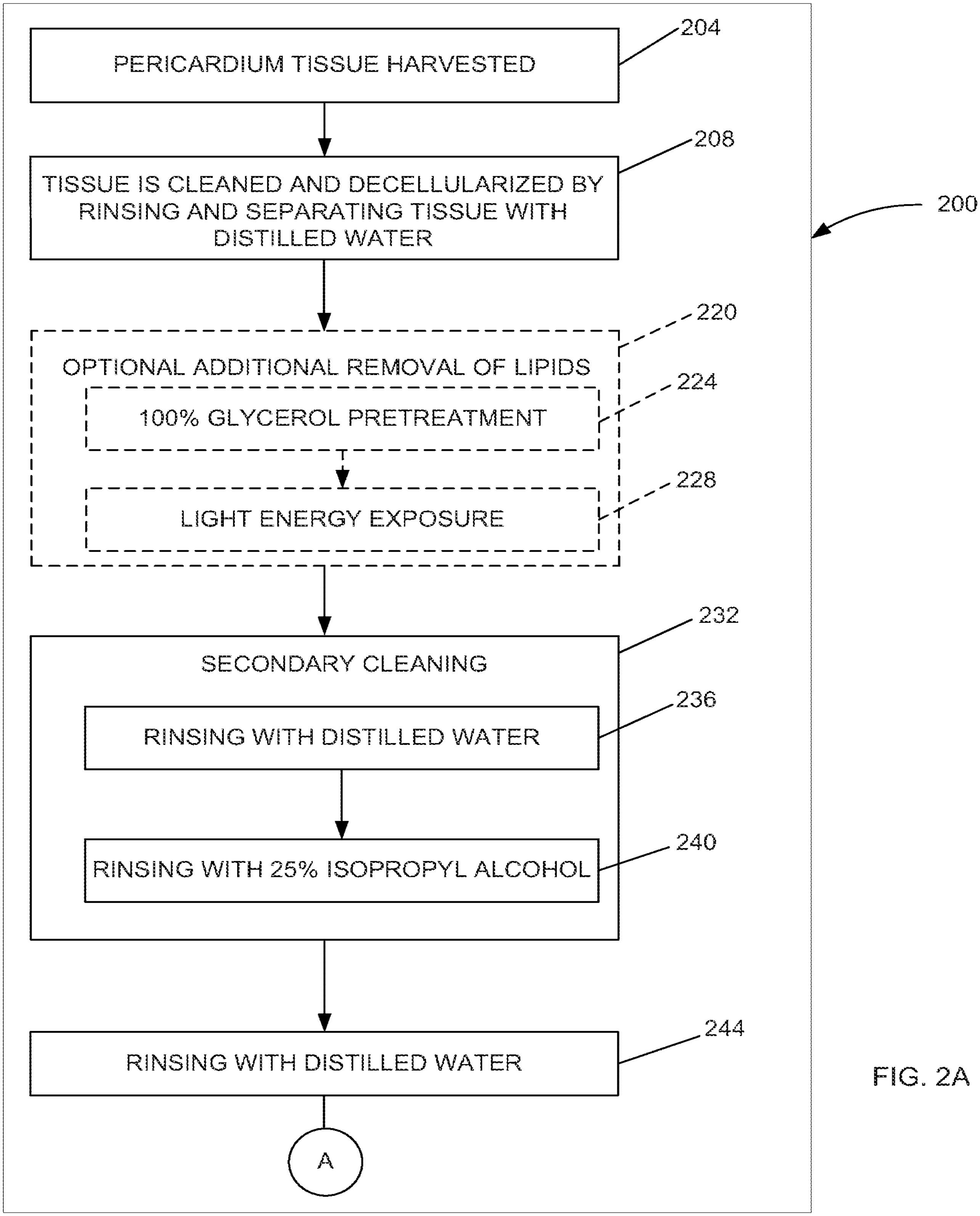

204
PERICARDIUM TISSUE HARVESTED
208
TISSUE IS CLEANED AND DECELLULARIZED BY RINSING AND SEPARATING TISSUE WITH DISTILLED WATER
200
220
OPTIONAL ADDITIONAL REMOVAL OF LIPIDS
224
100% GLYCEROL PRETREATMENT
228
LIGHT ENERGY EXPOSURE
232
SECONDARY CLEANING
236
RINSING WITH DISTILLED WATER
240
RINSING WITH 25% ISOPROPYL ALCOHOL
244
RINSING WITH DISTILLED WATER
A

FIG. 2A

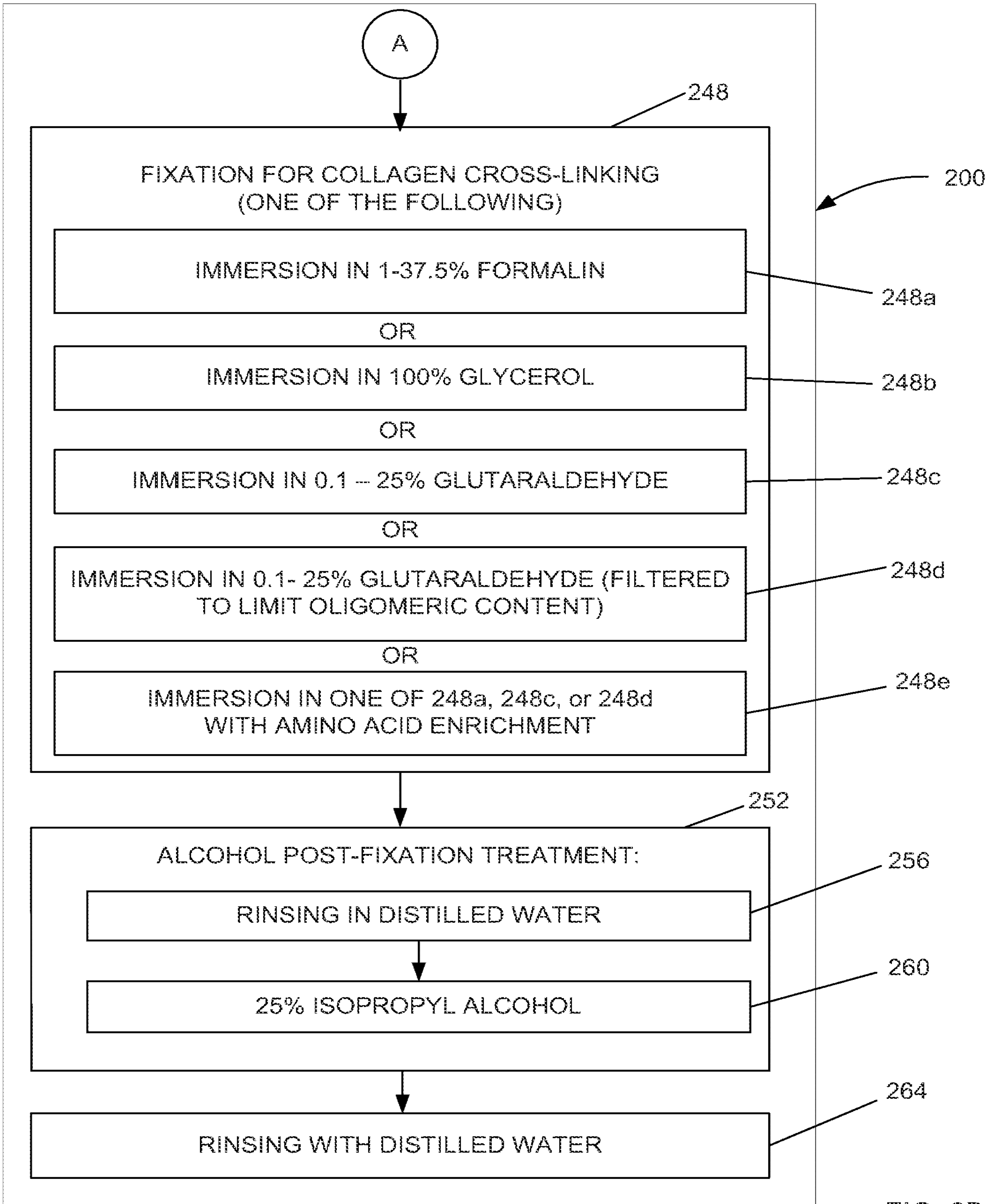

A
248
FIXATION FOR COLLAGEN CROSS-LINKING (ONE OF THE FOLLOWING)
IMMERSION IN 1-37.5% FORMALIN
248a
OR
IMMERSION IN 100% GLYCEROL
248b
OR
IMMERSION IN 0.1 – 25% GLUTARALDEHYDE
248c
OR
IMMERSION IN 0.1- 25% GLUTARALDEHYDE (FILTERED TO LIMIT OLIGOMERIC CONTENT)
248d
OR
IMMERSION IN ONE OF 248a, 248c, or 248d WITH AMINO ACID ENRICHMENT
248e
200
252
ALCOHOL POST-FIXATION TREATMENT:
RINSING IN DISTILLED WATER
256
25% ISOPROPYL ALCOHOL
260
RINSING WITH DISTILLED WATER
264

FIG. 2B

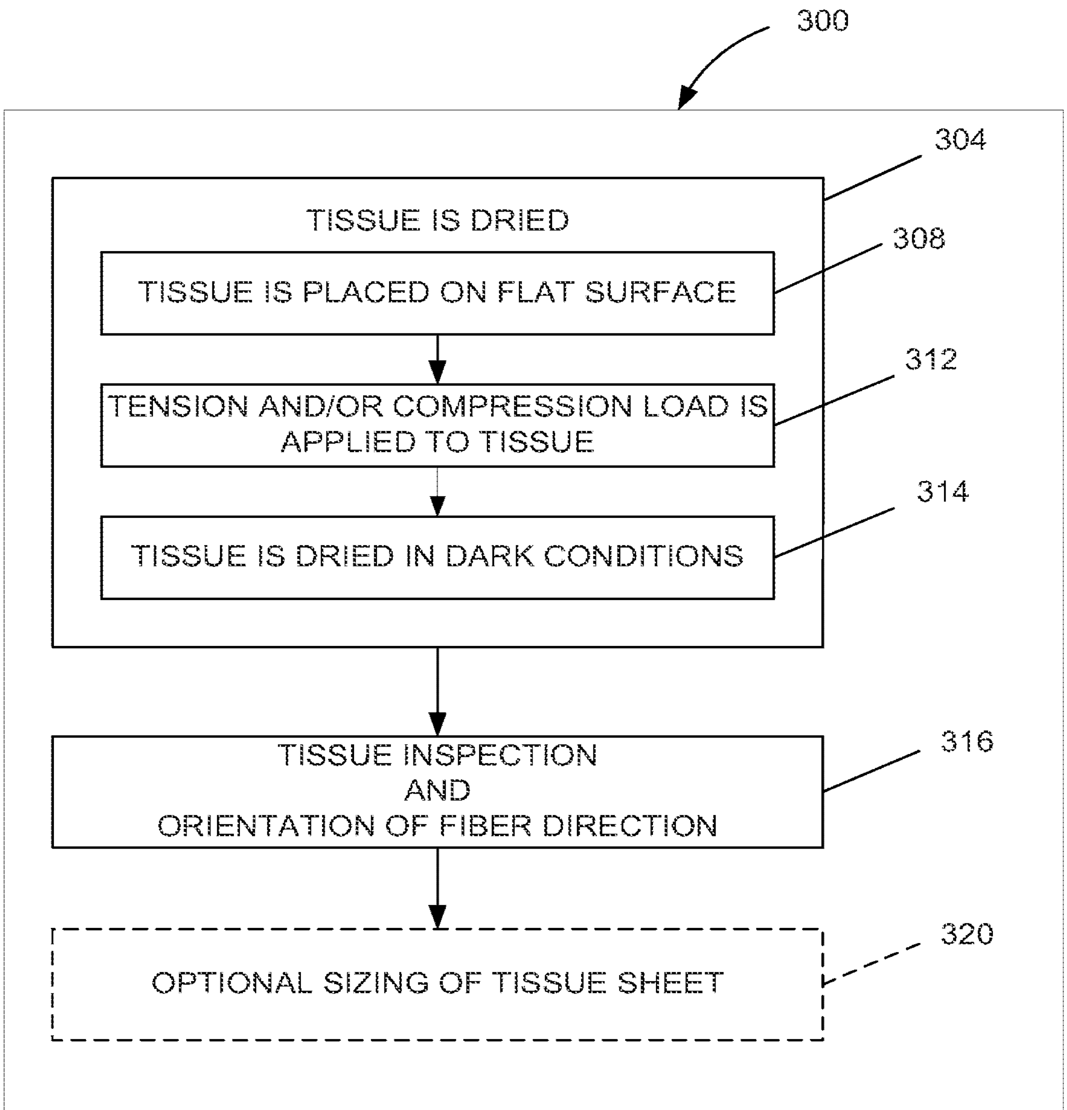

300
304
TISSUE IS DRIED
308
TISSUE IS PLACED ON FLAT SURFACE
312
TENSION AND/OR COMPRESSION LOAD IS APPLIED TO TISSUE
314
TISSUE IS DRIED IN DARK CONDITIONS
316
TISSUE INSPECTION AND ORIENTATION OF FIBER DIRECTION
320
OPTIONAL SIZING OF TISSUE SHEET

FIG. 3

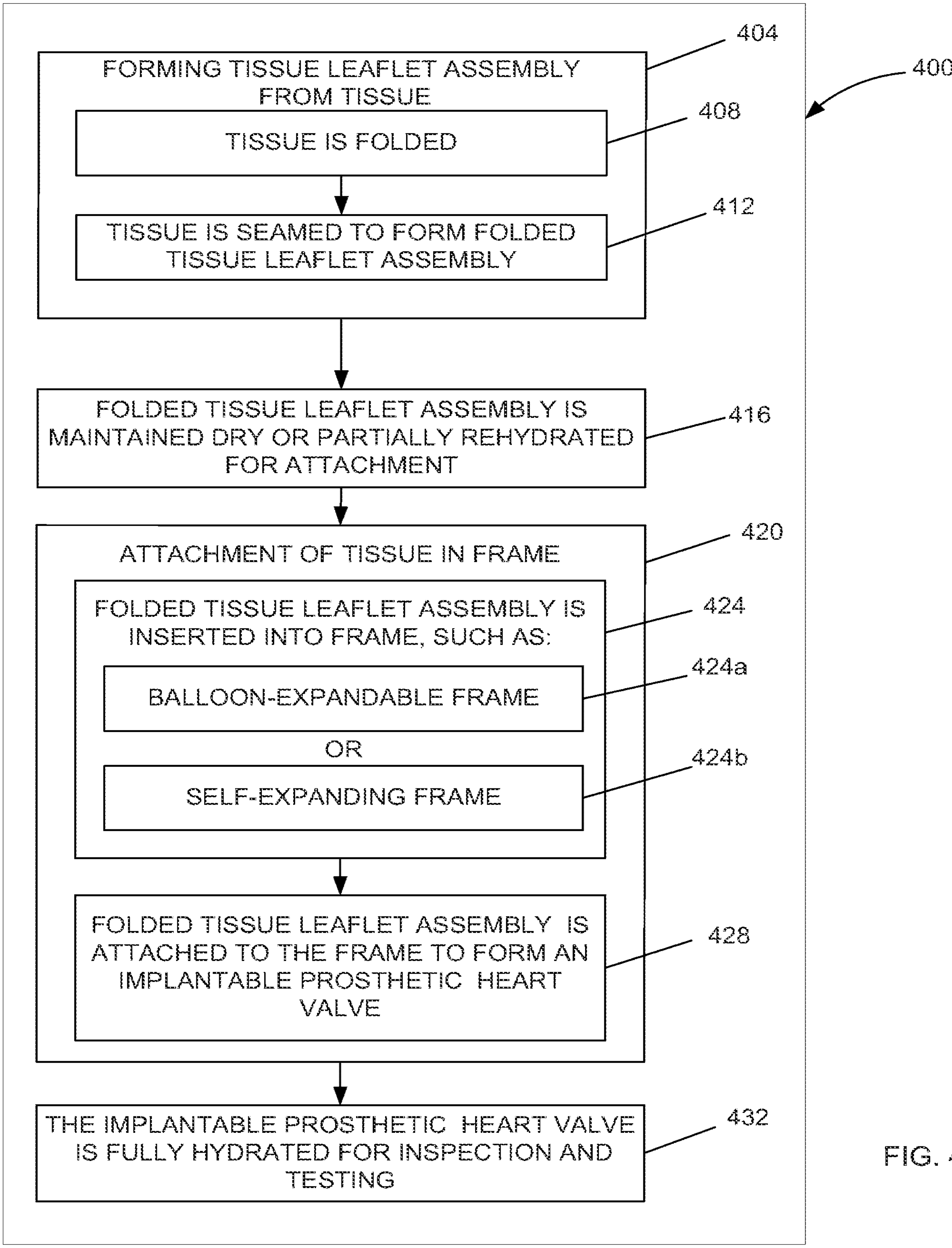

404
400
FORMING TISSUE LEAFLET ASSEMBLY FROM TISSUE
408
TISSUE IS FOLDED
412
TISSUE IS SEAMED TO FORM FOLDED TISSUE LEAFLET ASSEMBLY
FOLDED TISSUE LEAFLET ASSEMBLY IS MAINTAINED DRY OR PARTIALLY REHYDRATED FOR ATTACHMENT
416
420
ATTACHMENT OF TISSUE IN FRAME
FOLDED TISSUE LEAFLET ASSEMBLY IS INSERTED INTO FRAME, SUCH AS:
424
424a
BALLOON-EXPANDABLE FRAME
OR
424b
SELF-EXPANDING FRAME
FOLDED TISSUE LEAFLET ASSEMBLY IS ATTACHED TO THE FRAME TO FORM AN IMPLANTABLE PROSTHETIC HEART VALVE
428
THE IMPLANTABLE PROSTHETIC HEART VALVE IS FULLY HYDRATED FOR INSPECTION AND TESTING
432

FIG. 4

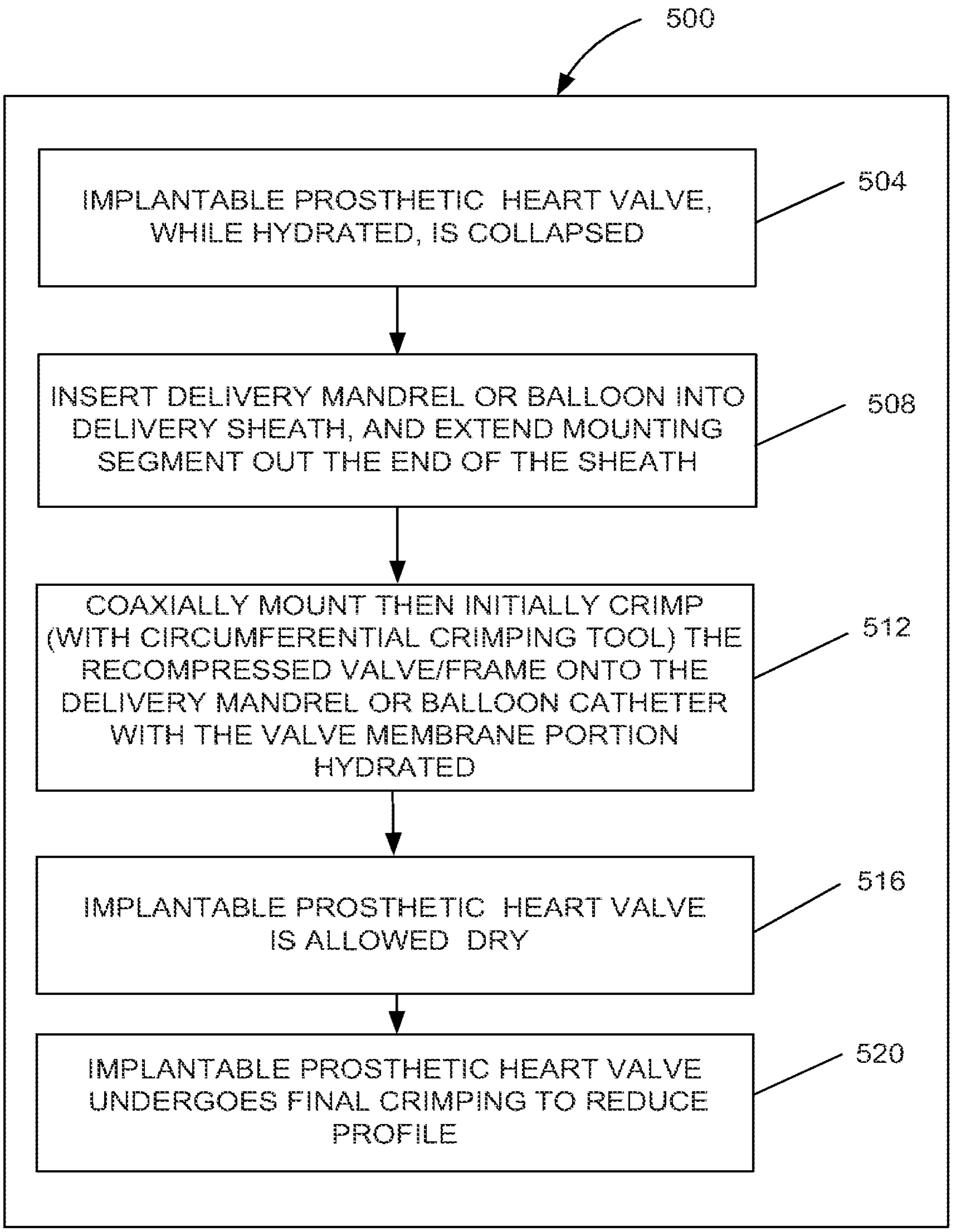

500
IMPLANTABLE PROSTHETIC HEART VALVE, WHILE HYDRATED, IS COLLAPSED
504
INSERT DELIVERY MANDREL OR BALLOON INTO DELIVERY SHEATH, AND EXTEND MOUNTING SEGMENT OUT THE END OF THE SHEATH
508
COAXIALLY MOUNT THEN INITIALLY CRIMP (WITH CIRCUMFERENTIAL CRIMPING TOOL) THE RECOMPRESSED VALVE/FRAME ONTO THE DELIVERY MANDREL OR BALLOON CATHETER WITH THE VALVE MEMBRANE PORTION HYDRATED
512
IMPLANTABLE PROSTHETIC HEART VALVE IS ALLOWED DRY
516
IMPLANTABLE PROSTHETIC HEART VALVE UNDERGOES FINAL CRIMPING TO REDUCE PROFILE
520

FIG. 5

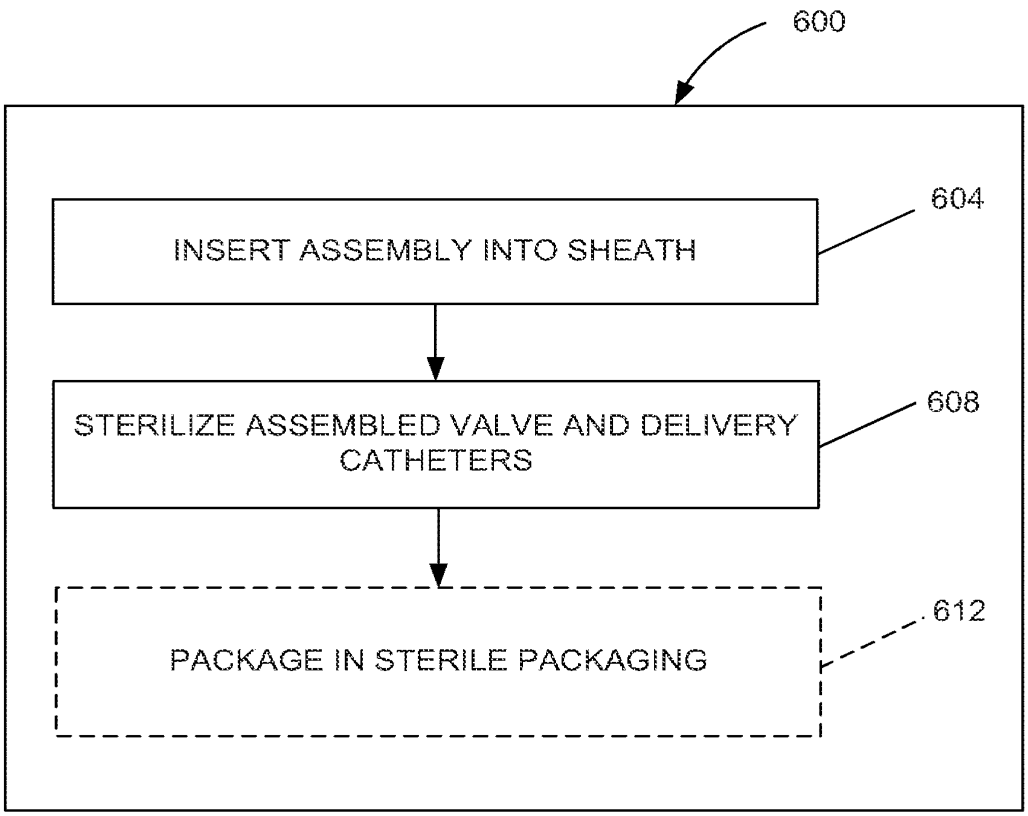

600
INSERT ASSEMBLY INTO SHEATH
604
STERILIZE ASSEMBLED VALVE AND DELIVERY CATHETERS
608
PACKAGE IN STERILE PACKAGING
612

FIG. 6

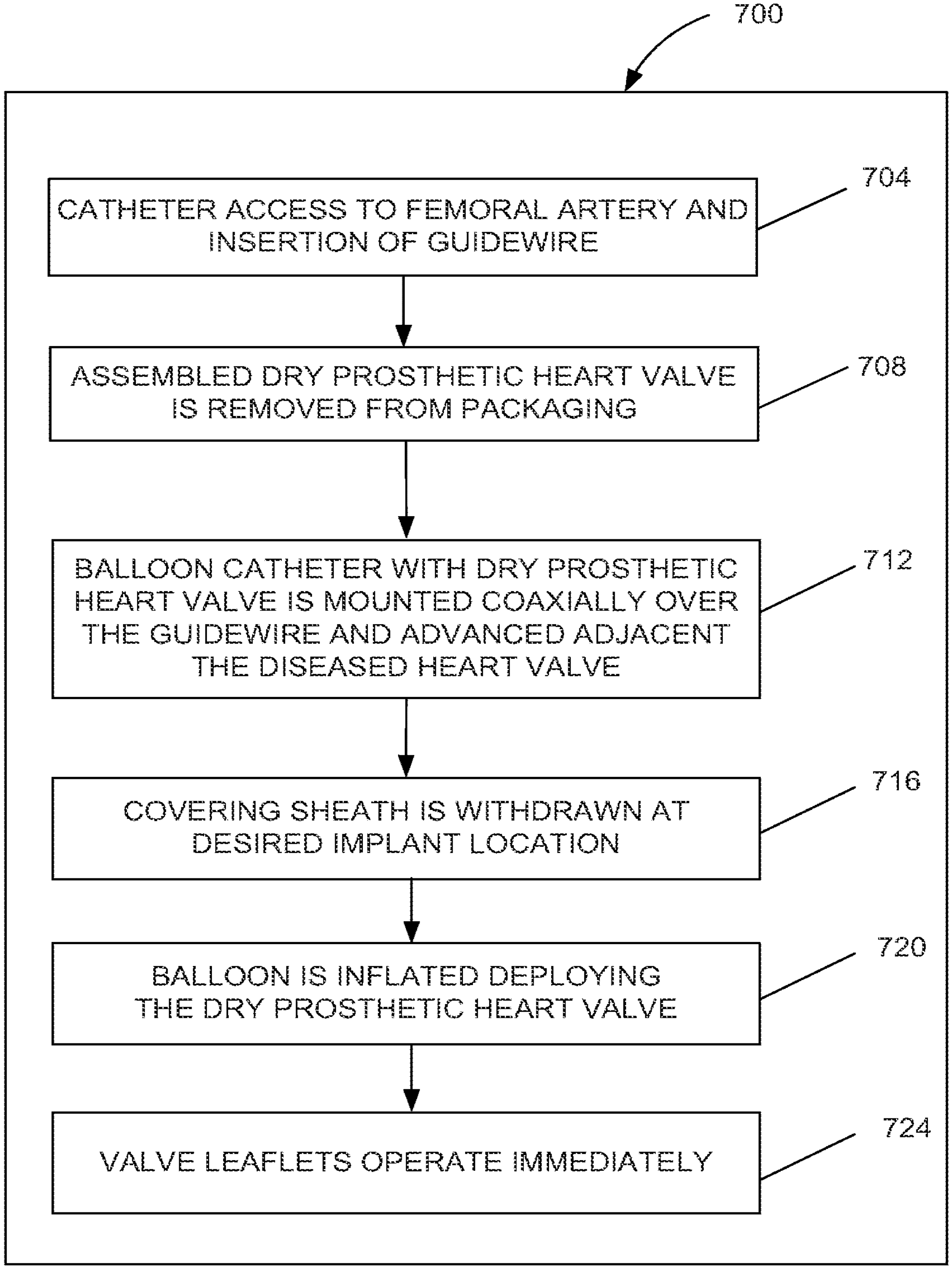

700
CATHETER ACCESS TO FEMORAL ARTERY AND INSERTION OF GUIDEWIRE
704
ASSEMBLED DRY PROSTHETIC HEART VALVE IS REMOVED FROM PACKAGING
708
BALLOON CATHETER WITH DRY PROSTHETIC HEART VALVE IS MOUNTED COAXIALLY OVER THE GUIDEWIRE AND ADVANCED ADJACENT THE DISEASED HEART VALVE
712
COVERING SHEATH IS WITHDRAWN AT DESIRED IMPLANT LOCATION
716
BALLOON IS INFLATED DEPLOYING THE DRY PROSTHETIC HEART VALVE
720
VALVE LEAFLETS OPERATE IMMEDIATELY
724

FIG.7

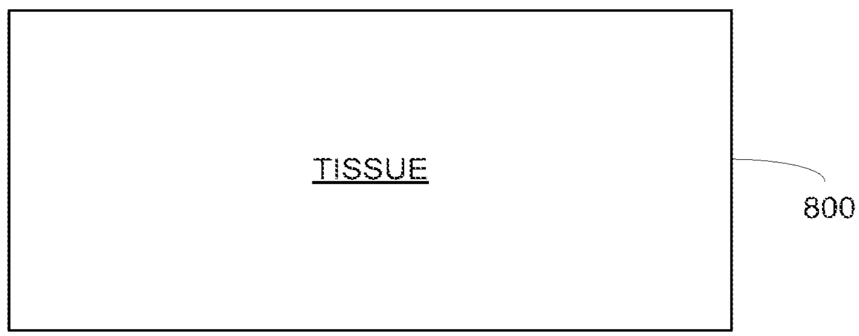


FIG.8A

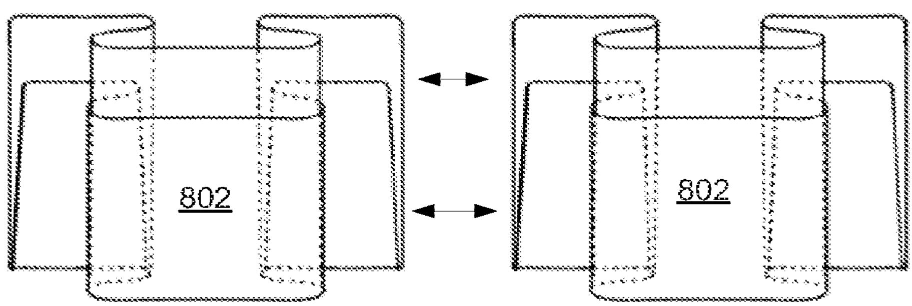


FIG.8B

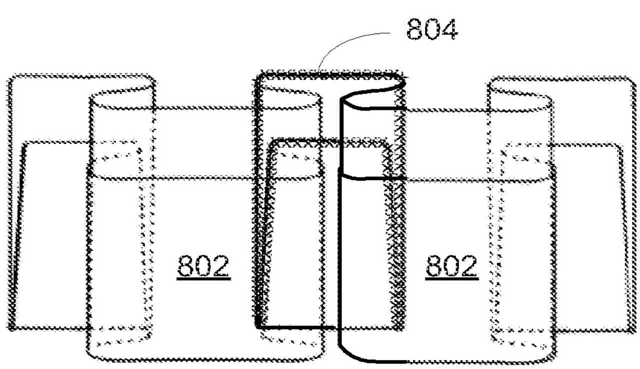


FIG.8C

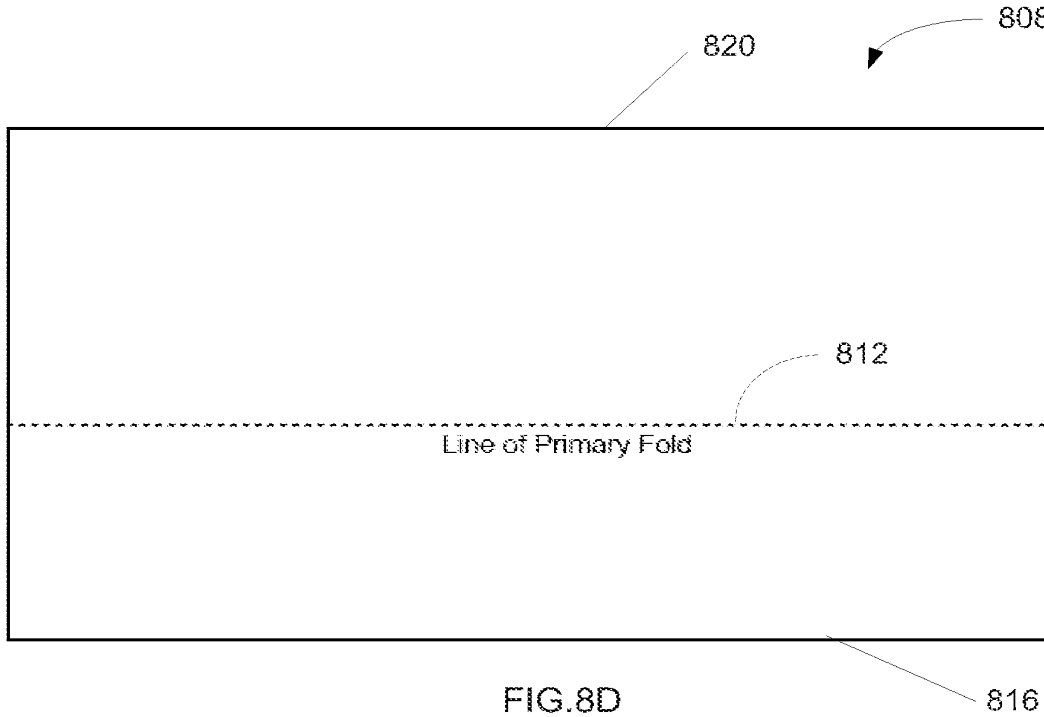

820
808
812
Line of Primary Fold
816

FIG.8D

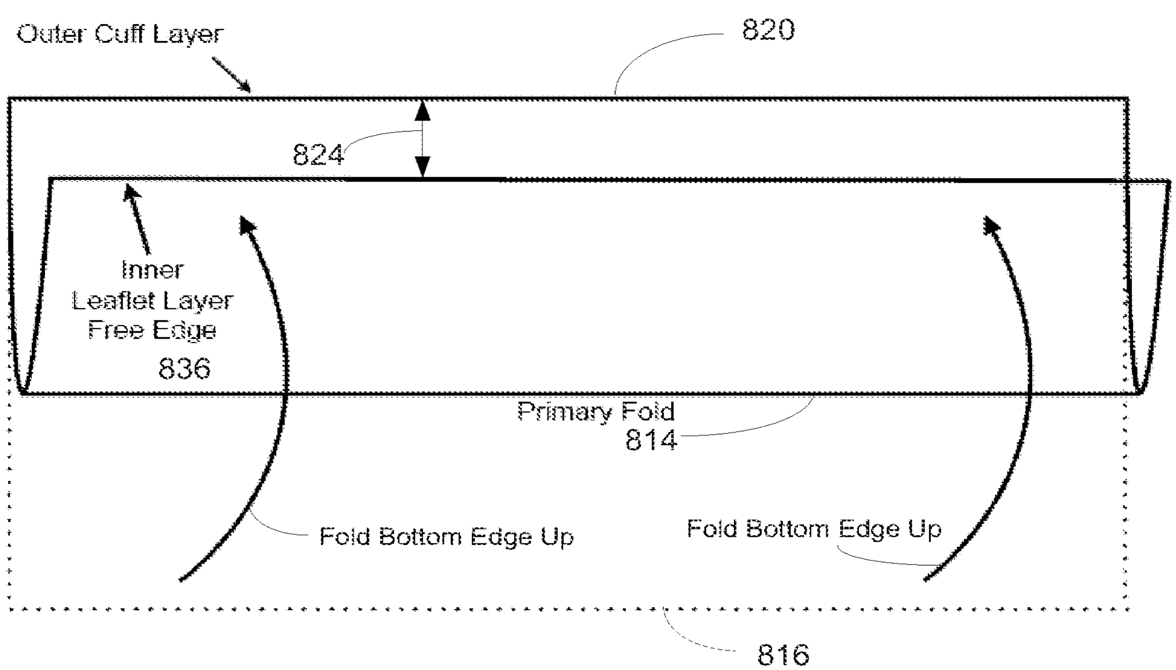
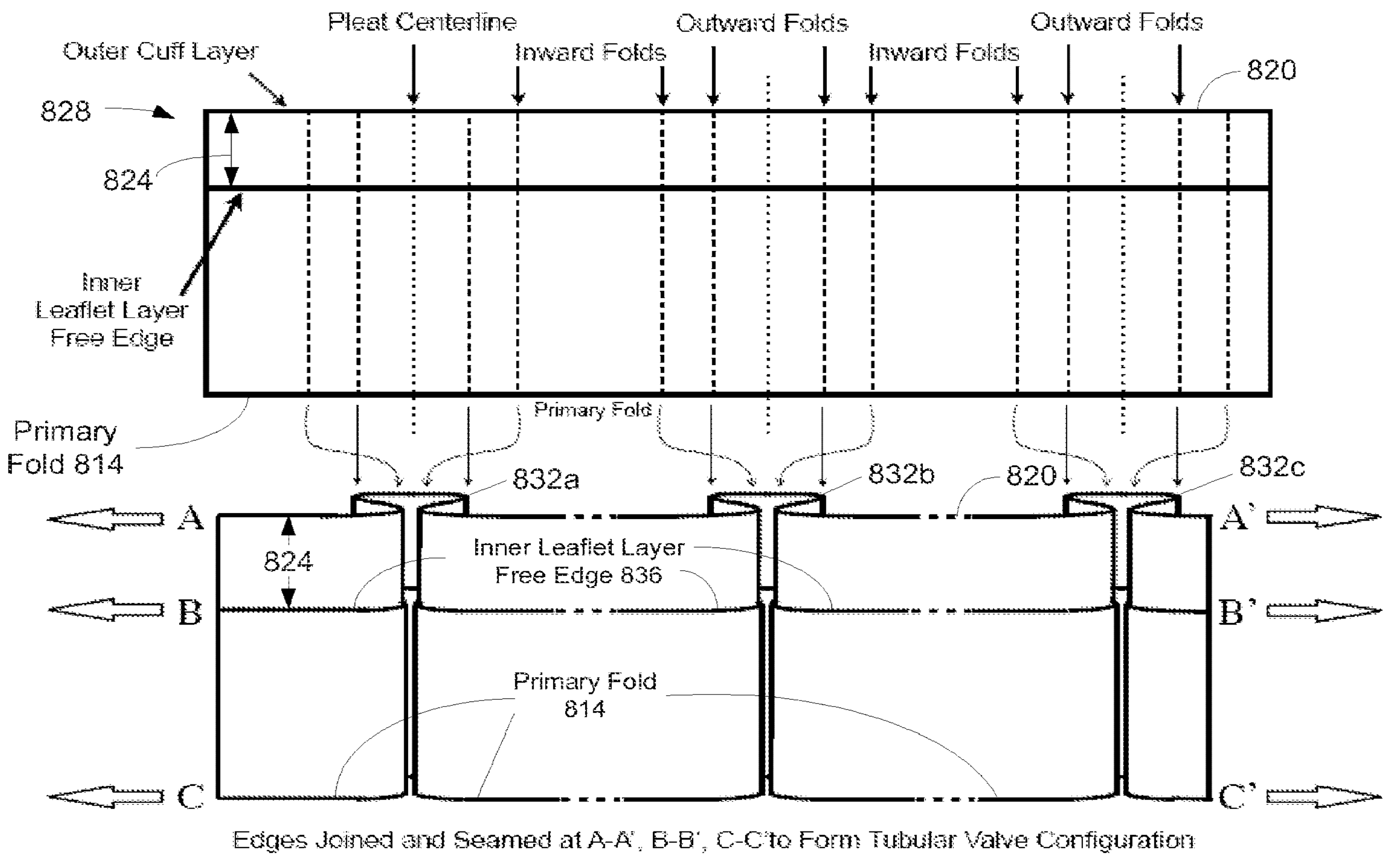

Outer Cuff Layer
820
824
Inner
Leaflet Layer
Free Edge
836
Primary Fold
814
Fold Bottom Edge Up
Fold Bottom Edge Up
816

FIG.8E



Pleat Centerline
Outward Folds
Outward Folds
Outer Cuff Layer
Inward Folds
Inward Folds
820
828
824
Inner
Leaflet Layer
Free Edge
Primary Fold
Primary
Fold 814
832a
832b
820
832c
A
A'
824
Inner Leaflet Layer
Free Edge 836
B
B'
Primary Fold
814
C
C'
Edges Joined and Seamed at A-A', B-B', C-C'to Form Tubular Valve Configuration

FIG.8F

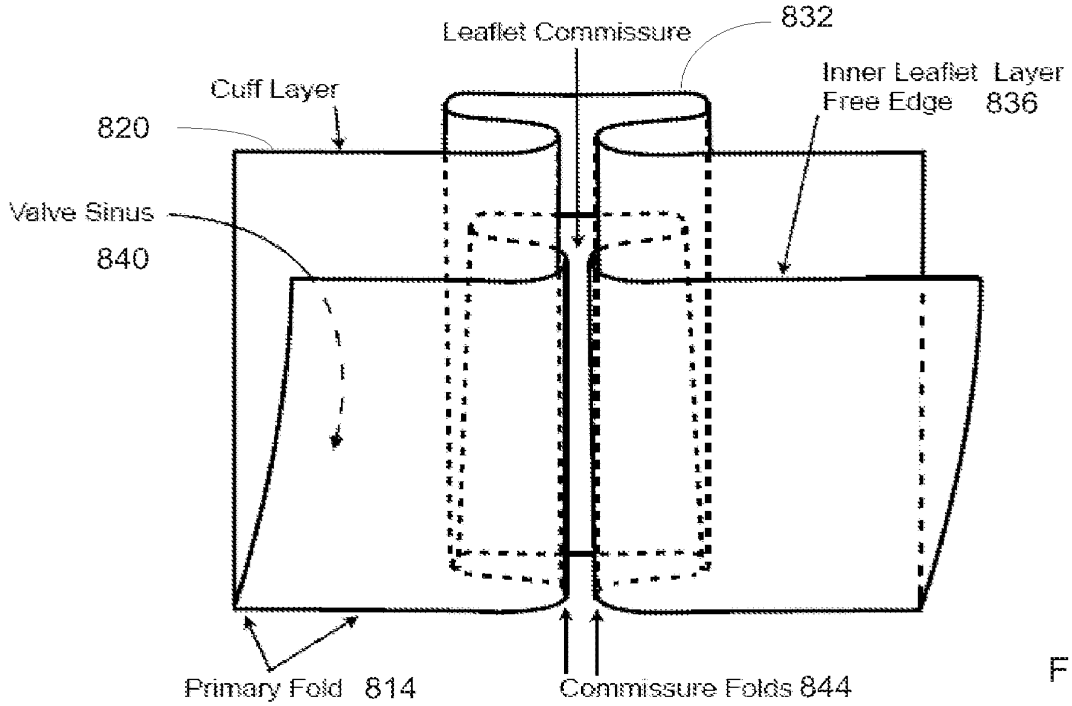


FIG.8G

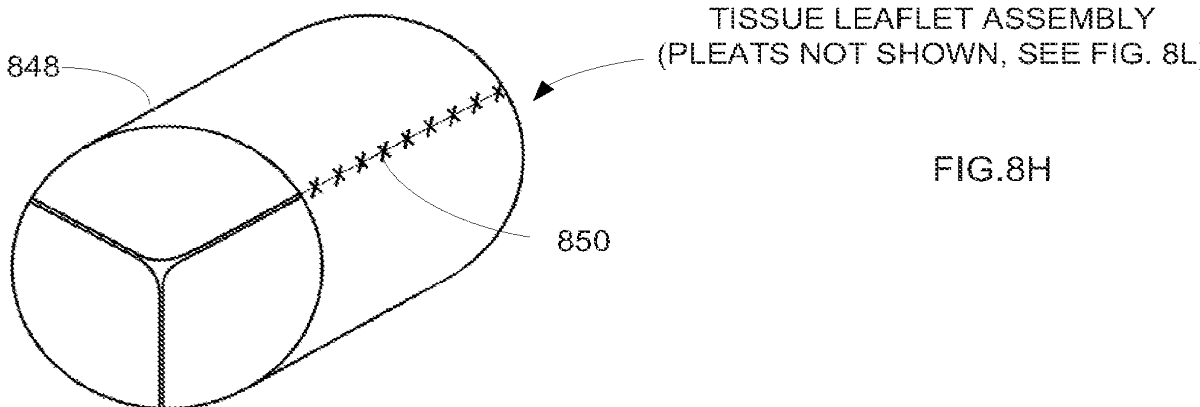


FIG.8H

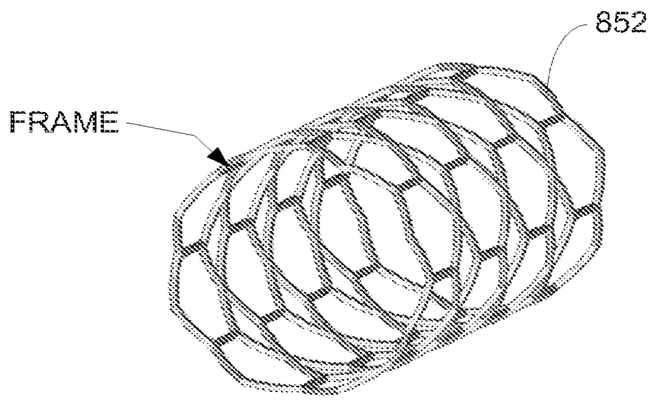


FIG.8I

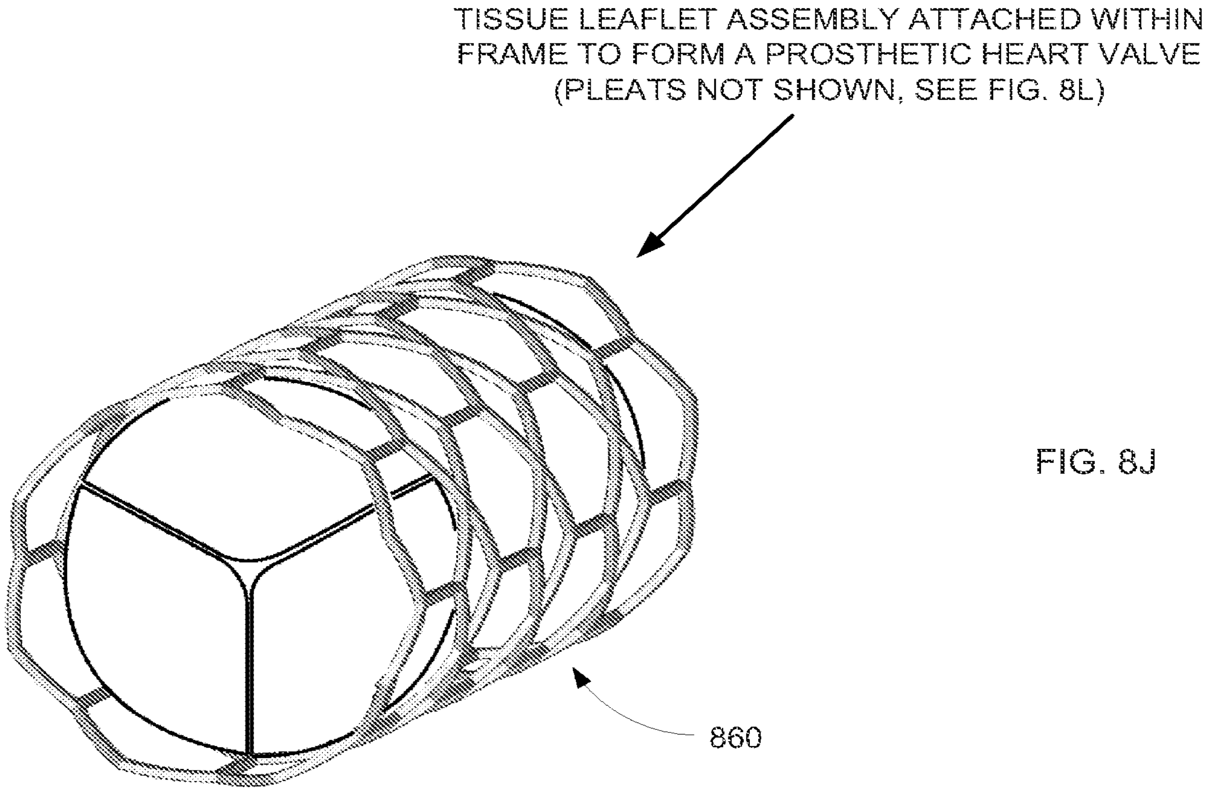

TISSUE LEAFLET ASSEMBLY ATTACHED WITHIN
FRAME TO FORM A PROSTHETIC HEART VALVE
(PLEATS NOT SHOWN, SEE FIG. 8L)
860

FIG. 8J

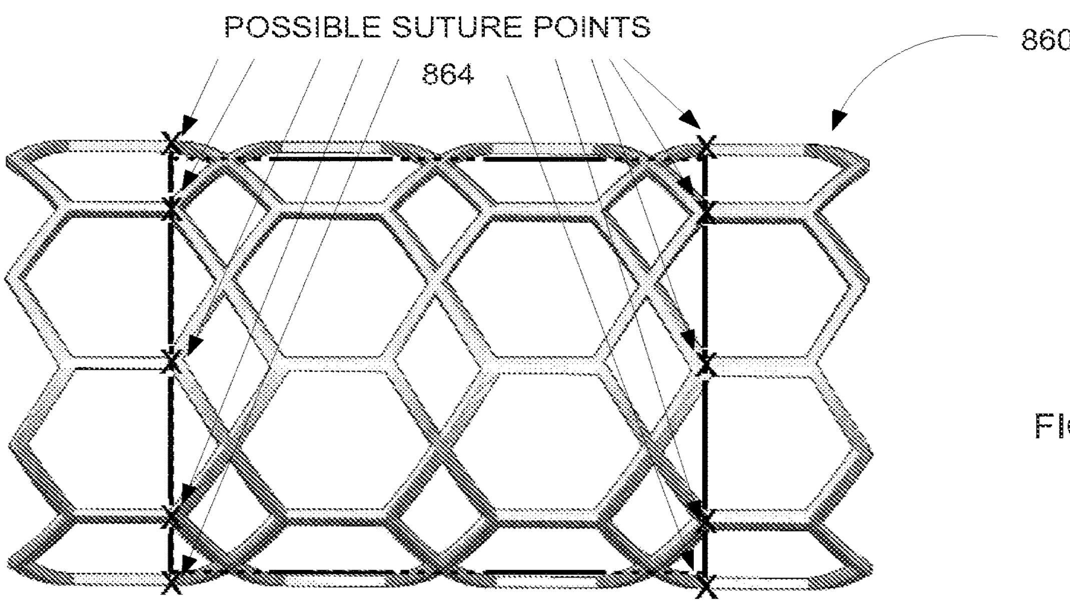

POSSIBLE SUTURE POINTS
864
860

FIG. 8K

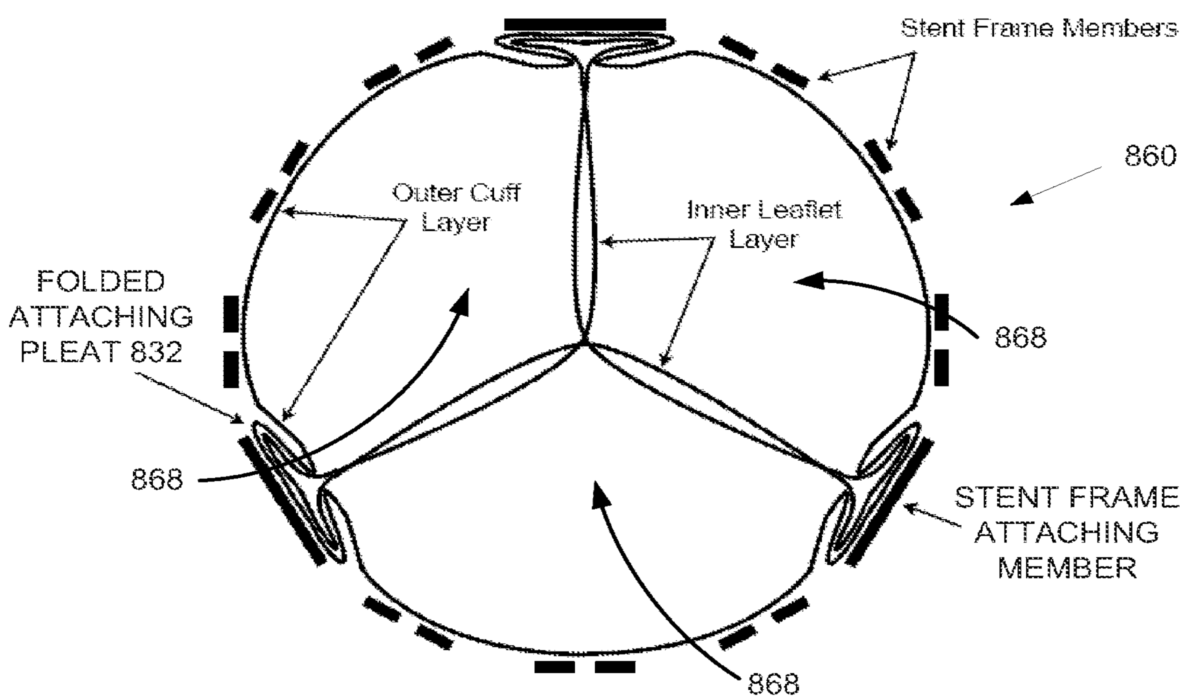
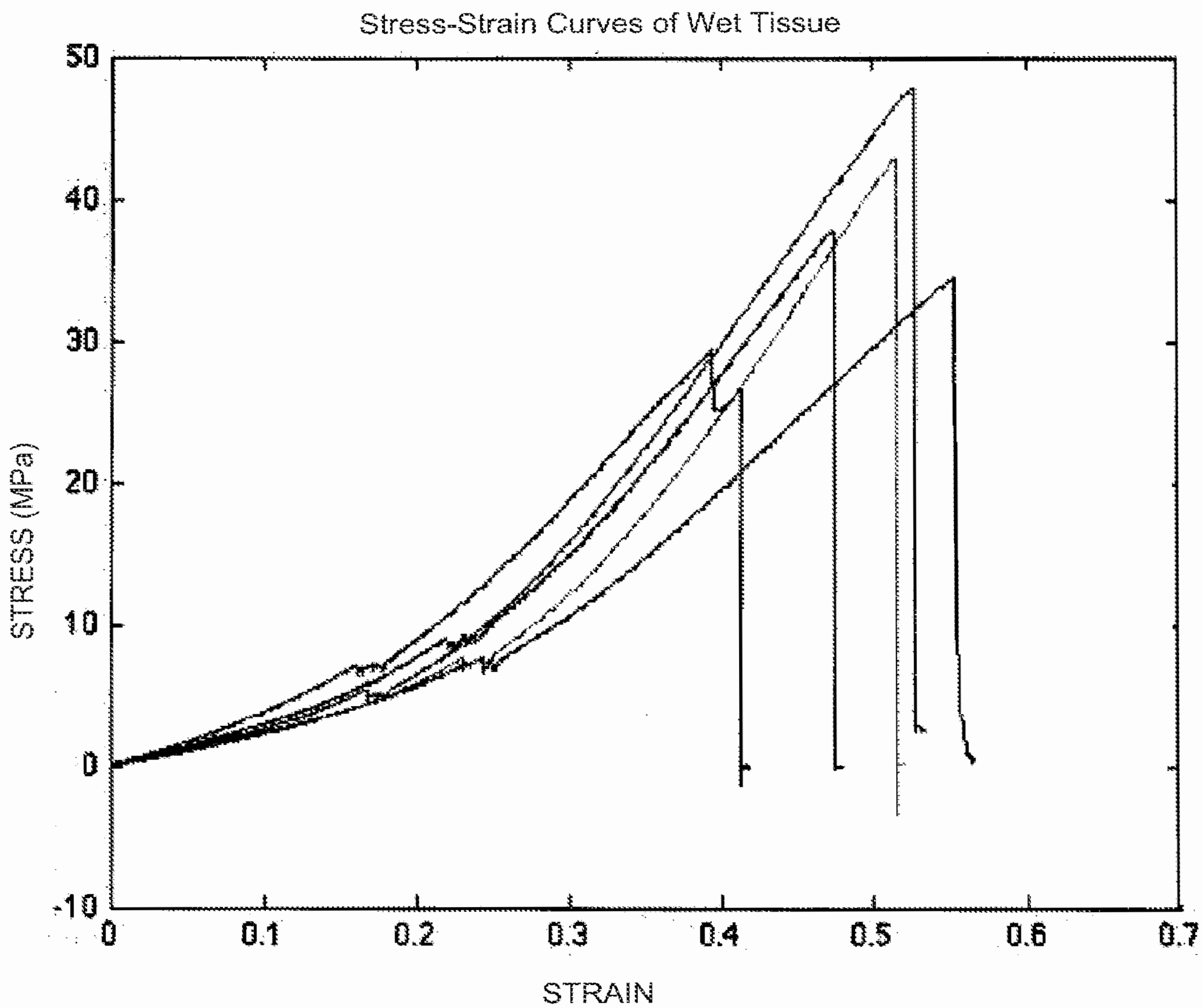

Stent Frame Members
860
Outer Cuff Layer
Inner Leaflet Layer
FOLDED ATTACHING PLEAT 832
868
868
STENT FRAME ATTACHING MEMBER
868

FIG.8L



Stress-strain curves in wet or hydrated state of five samples. Each curve corresponds to a separate sample.

FIG. 9

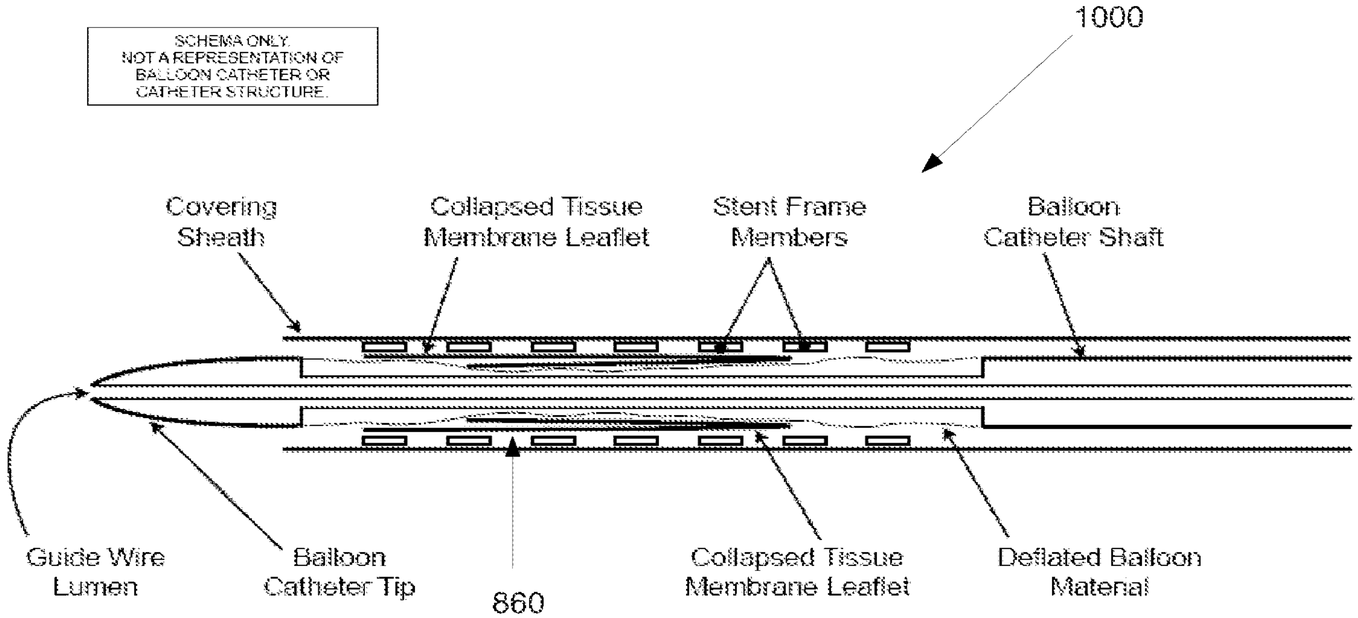

SCHEMA ONLY.
NOT A REPRESENTATION OF BALLOON CATHETER OR CATHETER STRUCTURE.
1000
Covering Sheath
Collapsed Tissue Membrane Leaflet
Stent Frame Members
Balloon Catheter Shaft
Guide Wire Lumen
Balloon Catheter Tip
860
Collapsed Tissue Membrane Leaflet
Deflated Balloon Material

FIG.10

Photo of Tissue Leaflet Assembly Attached in Frame to Form Implantable Prosthetic Heart Valve

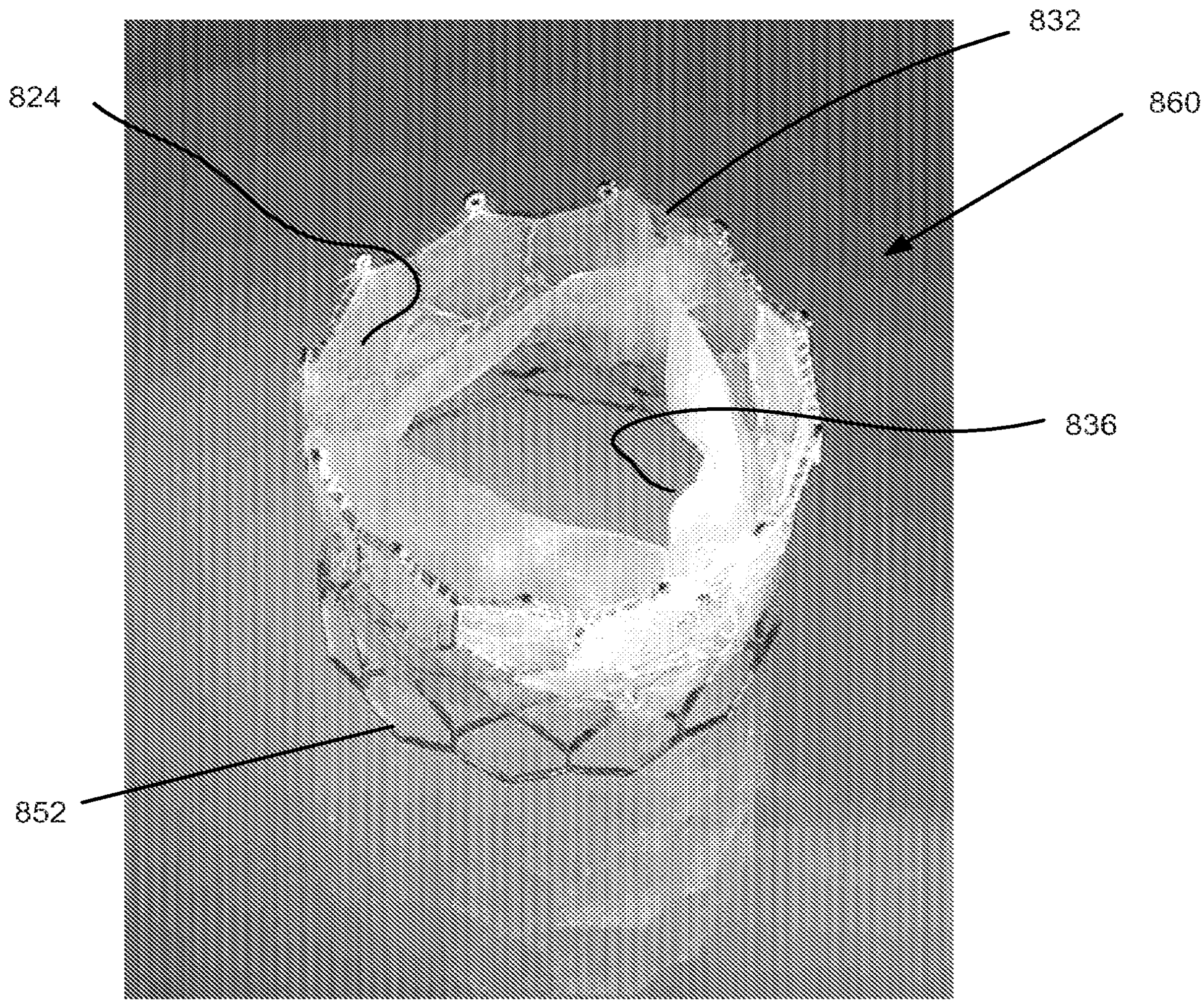


FIG.11A

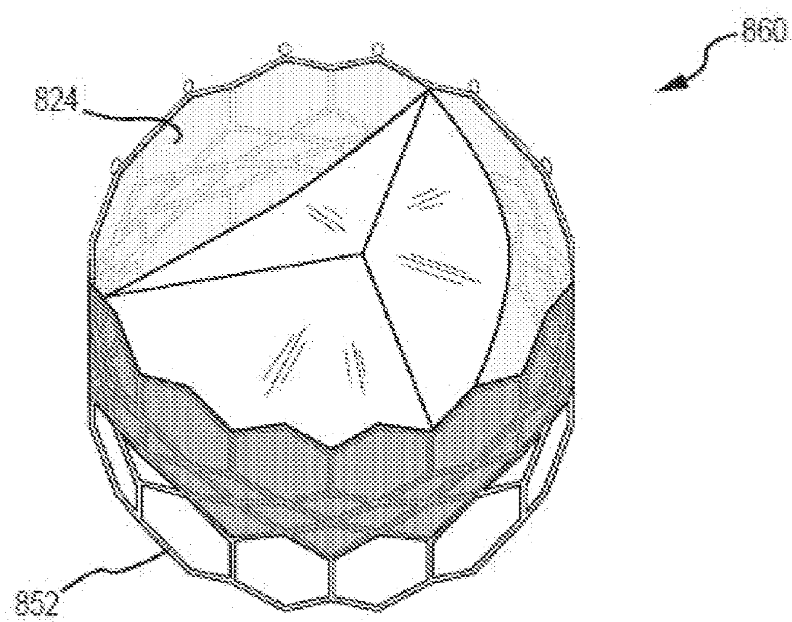


FIG. 11B

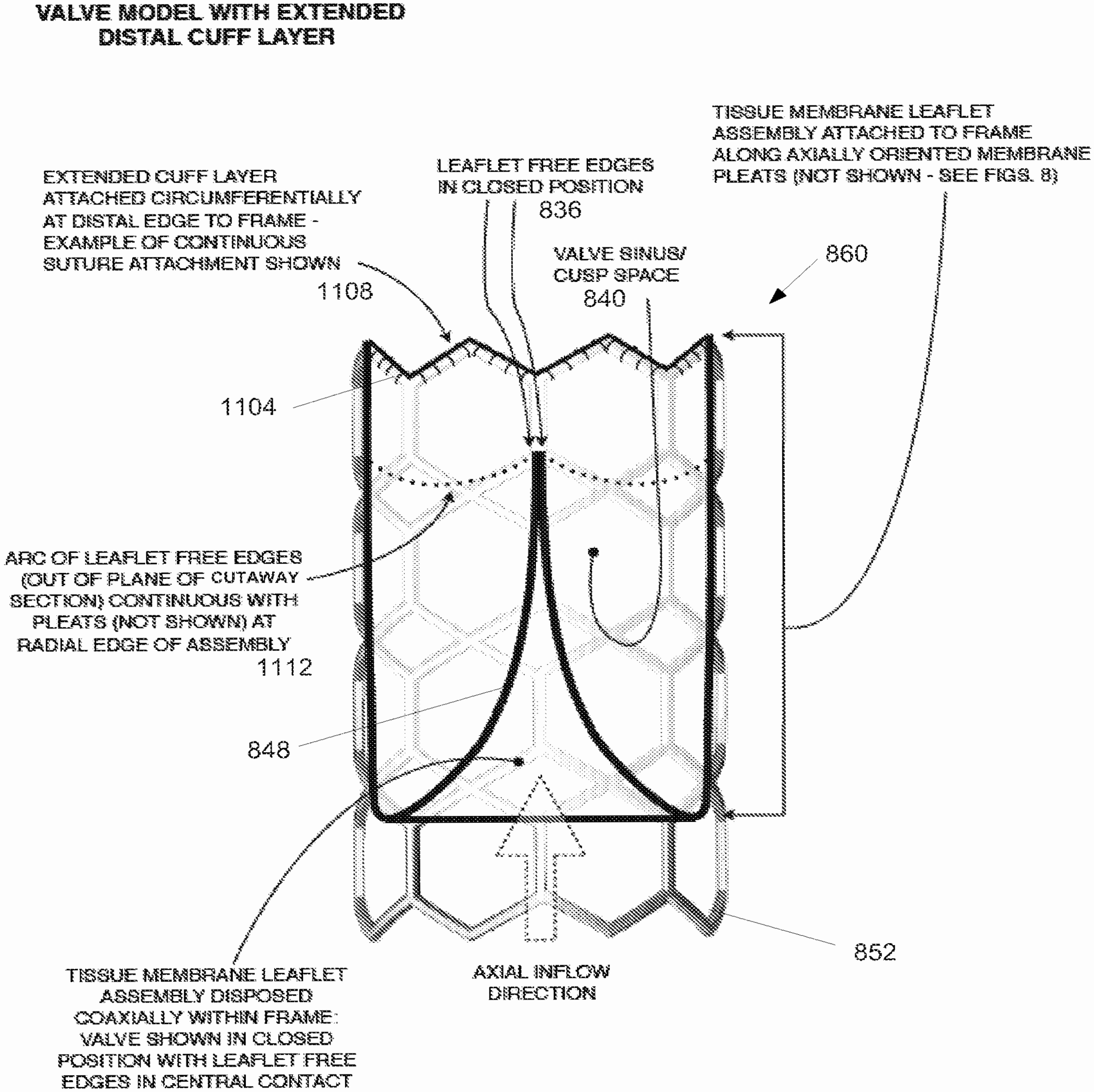

VALVE MODEL WITH EXTENDED
DISTAL CUFF LAYER
EXTENDED CUFF LAYER
ATTACHED CIRCUMFERENTIALLY
AT DISTAL EDGE TO FRAME -
EXAMPLE OF CONTINUOUS
SUTURE ATTACHMENT SHOWN
1108
LEAFLET FREE EDGES
IN CLOSED POSITION
836
VALVE SINUS/
CUSP SPACE
840
TISSUE MEMBRANE LEAFLET
ASSEMBLY ATTACHED TO FRAME
ALONG AXIALLY ORIENTED MEMBRANE
PLEATS (NOT SHOWN - SEE FIGS. 8)
860
1104
ARC OF LEAFLET FREE EDGES
(OUT OF PLANE OF CUTAWAY
SECTION) CONTINUOUS WITH
PLEATS (NOT SHOWN) AT
RADIAL EDGE OF ASSEMBLY
1112
848
852
TISSUE MEMBRANE LEAFLET
ASSEMBLY DISPOSED
COAXIALLY WITHIN FRAME:
VALVE SHOWN IN CLOSED
POSITION WITH LEAFLET FREE
EDGES IN CENTRAL CONTACT
AXIAL INFLOW
DIRECTION

FIG. 11C

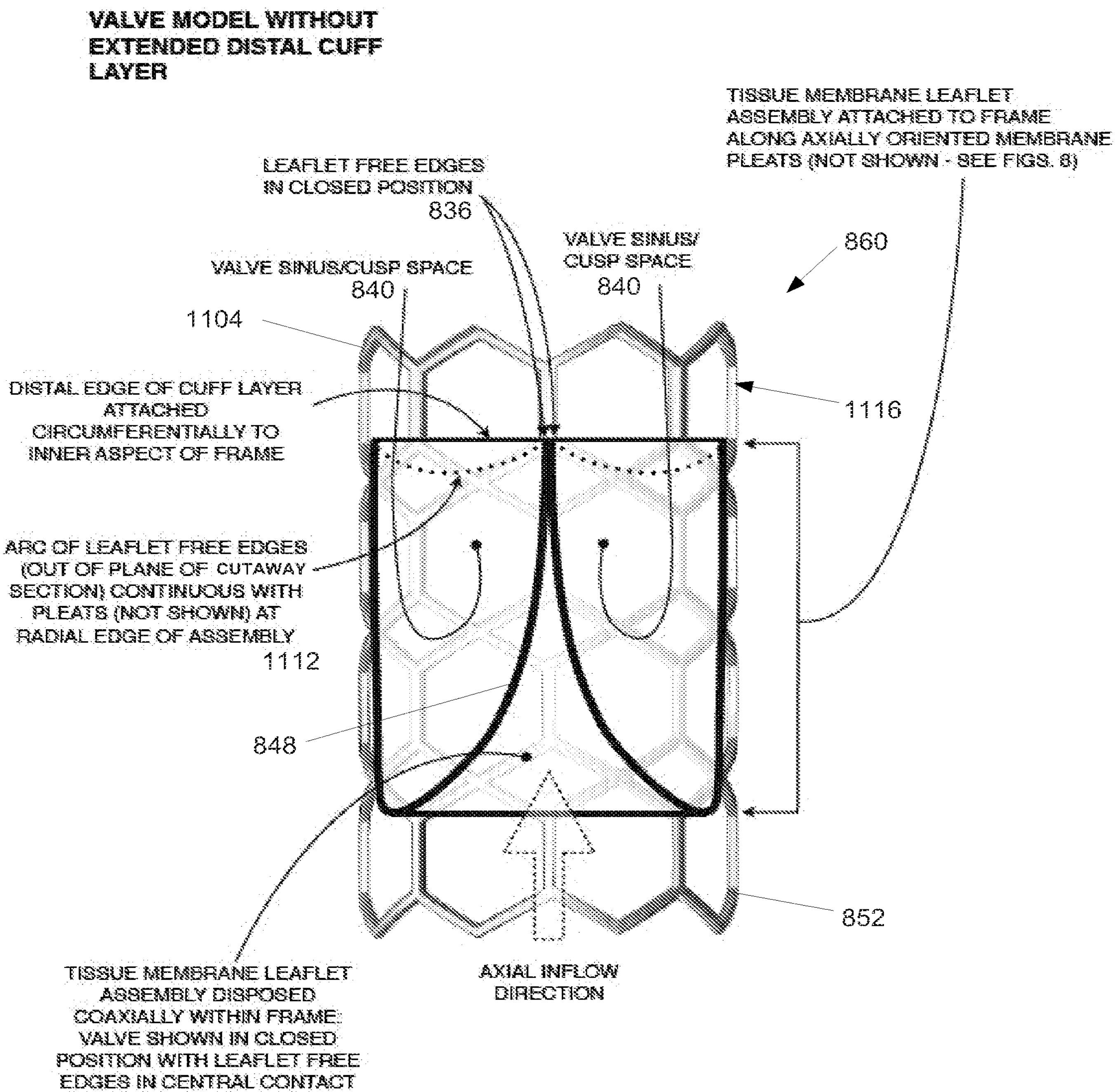

VALVE MODEL WITHOUT EXTENDED DISTAL CUFF LAYER
TISSUE MEMBRANE LEAFLET ASSEMBLY ATTACHED TO FRAME ALONG AXIALLY ORIENTED MEMBRANE PLEATS (NOT SHOWN - SEE FIGS. 8)
LEAFLET FREE EDGES IN CLOSED POSITION
836
VALVE SINUS/CUSP SPACE
840
VALVE SINUS/ CUSP SPACE
840
860
1104
1116
DISTAL EDGE OF CUFF LAYER ATTACHED CIRCUMFERENTIALLY TO INNER ASPECT OF FRAME
ARC OF LEAFLET FREE EDGES (OUT OF PLANE OF CUTAWAY SECTION) CONTINUOUS WITH PLEATS (NOT SHOWN) AT RADIAL EDGE OF ASSEMBLY
1112
848
852
TISSUE MEMBRANE LEAFLET ASSEMBLY DISPOSED COAXIALLY WITHIN FRAME: VALVE SHOWN IN CLOSED POSITION WITH LEAFLET FREE EDGES IN CENTRAL CONTACT
AXIAL INFLOW DIRECTION

FIG. 11D

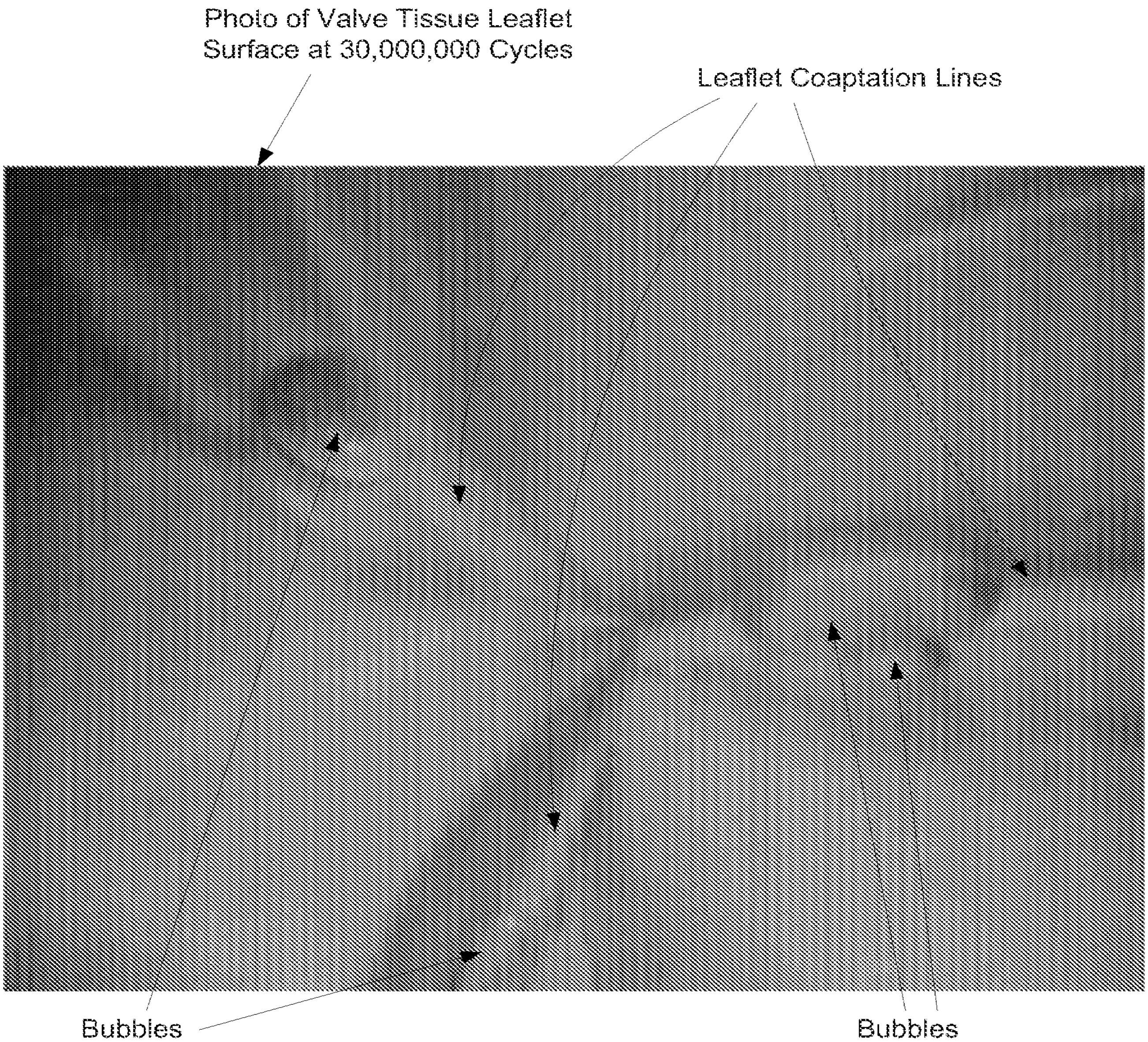


Photo of Valve Tissue Leaflet Surface at 30,000,000 Cycles
Leaflet Coaptation Lines
Bubbles
Bubbles

FIG.12

Surgeon Holding a Premounted Percutaneously Deliverable
Heart Valve Associated With a Catheter and Residing Within
Sterile Packaging

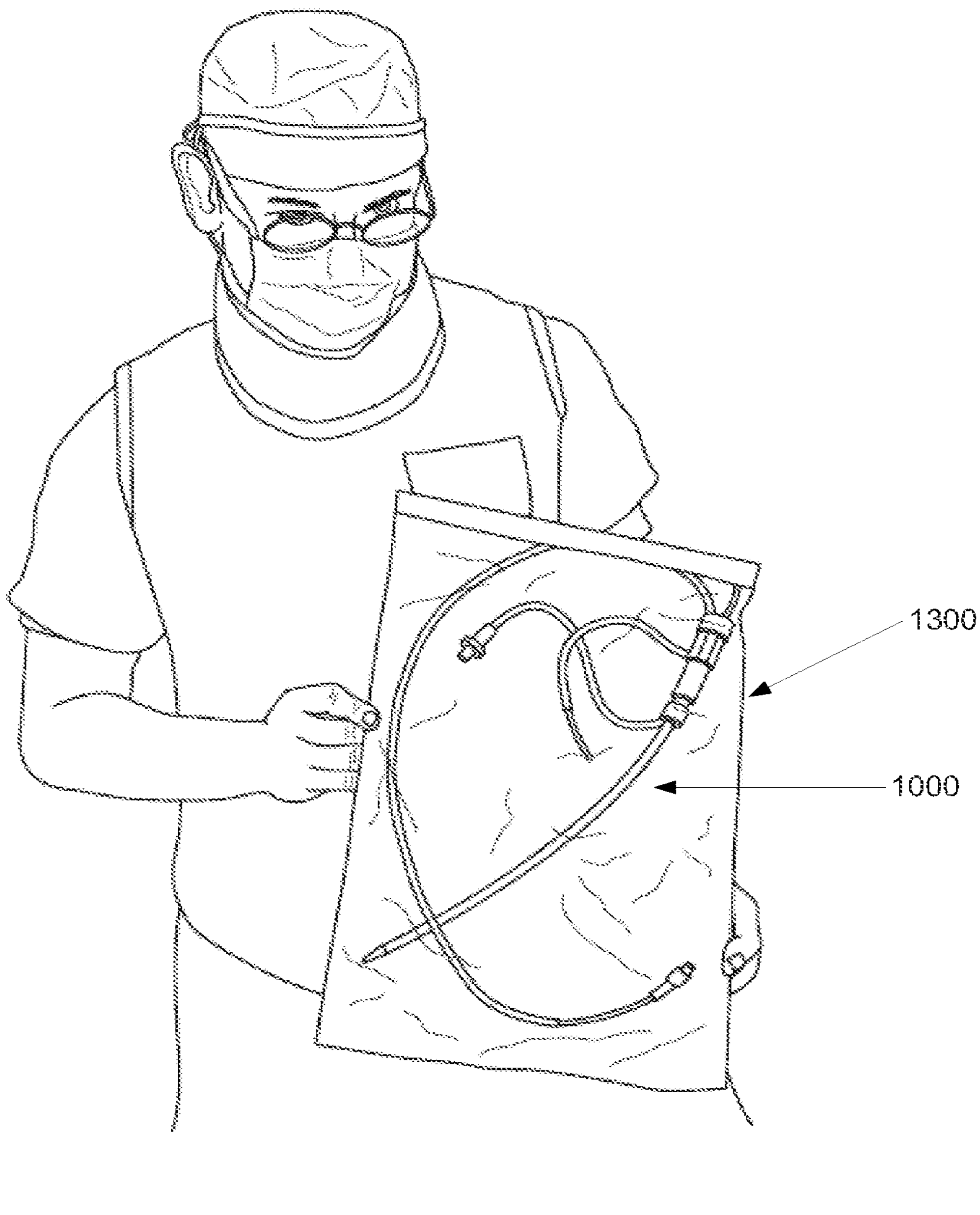


FIG.13

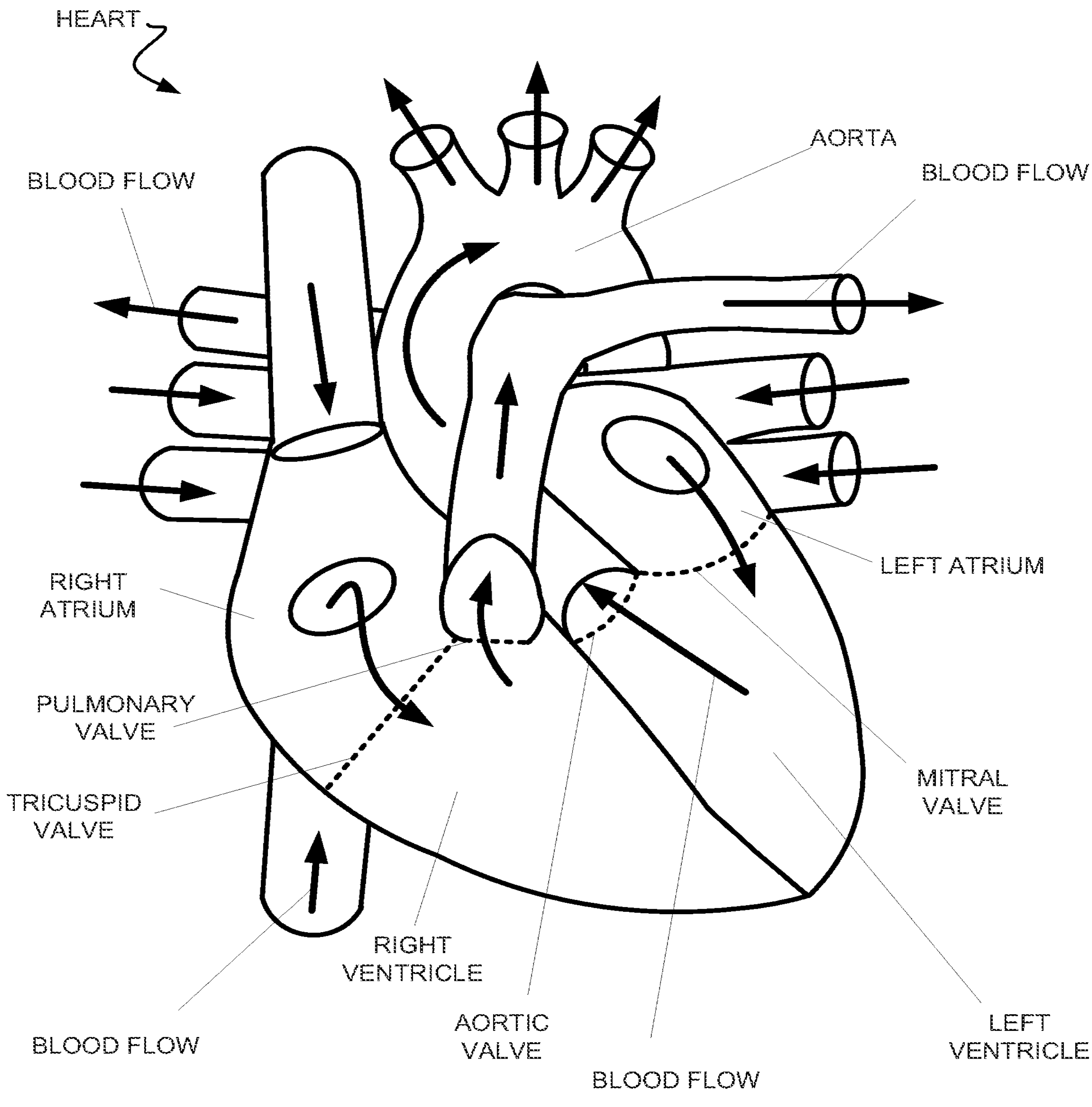

HEART
AORTA
BLOOD FLOW
BLOOD FLOW
LEFT ATRIUM
RIGHT ATRIUM
PULMONARY VALVE
TRICUSPID VALVE
MITRAL VALVE
RIGHT VENTRICLE
BLOOD FLOW
AORTIC VALVE
BLOOD FLOW
LEFT VENTRICLE

FIG.14

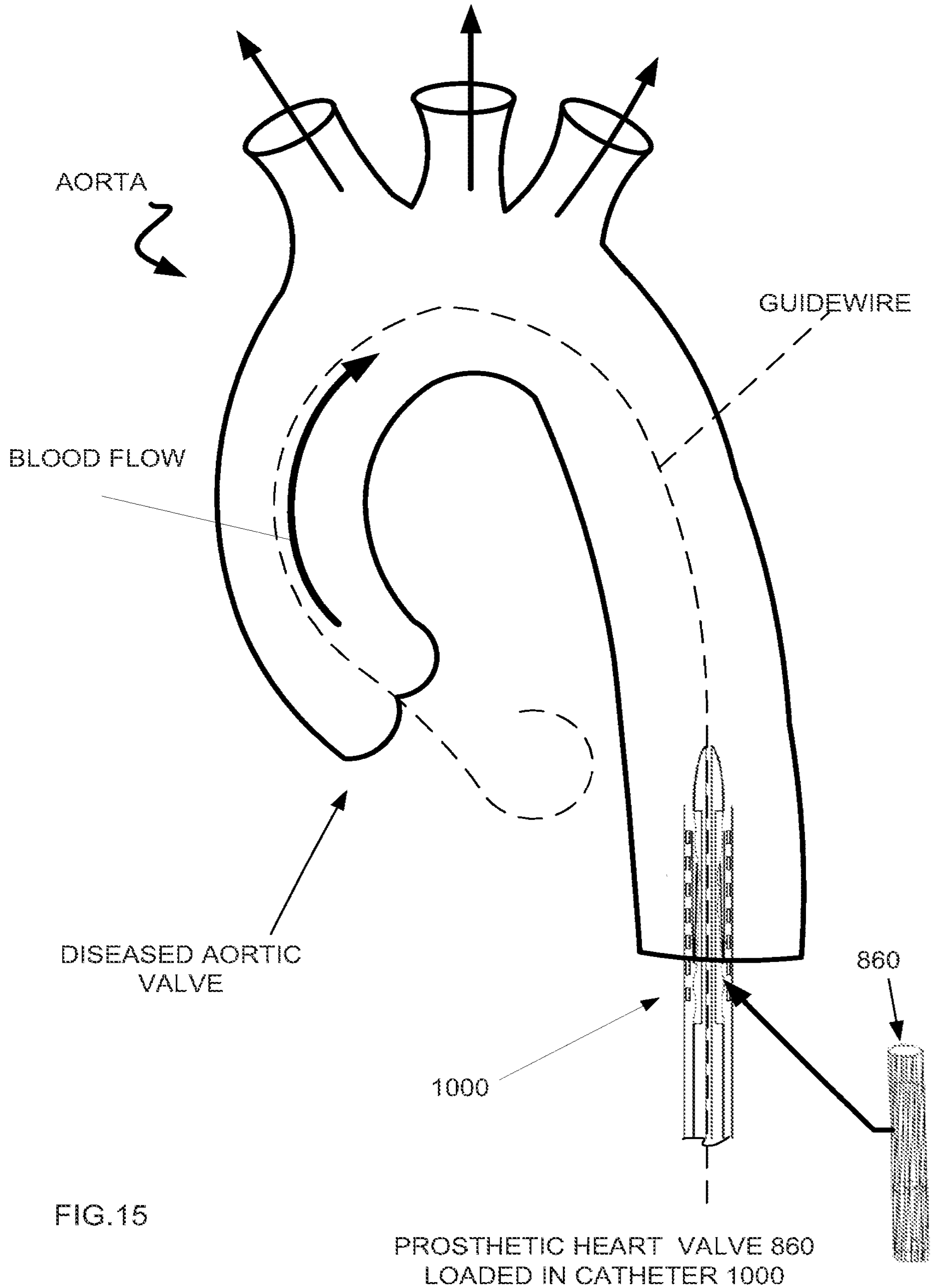

AORTA
GUIDEWIRE
BLOOD FLOW
DISEASED AORTIC VALVE
860
1000
PROSTHETIC HEART VALVE 860 LOADED IN CATHETER 1000

FIG.15

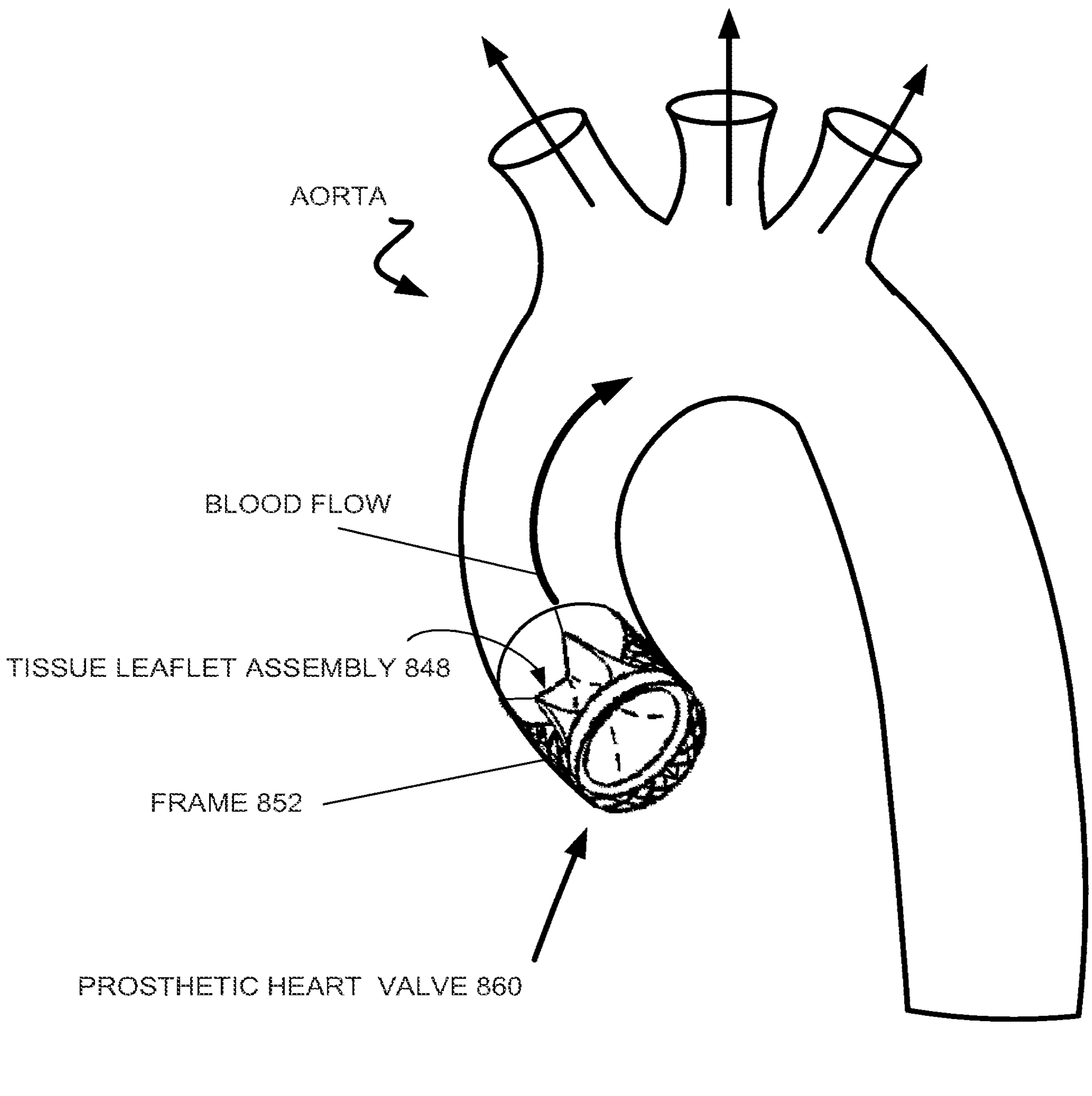

AORTA
BLOOD FLOW
TISSUE LEAFLET ASSEMBLY 848
FRAME 852
PROSTHETIC HEART VALVE 860

FIG. 16

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(54) **Title**: METHOD AND APPARATUS FOR THE ENDOLUMINAL DELIVERY OF INTRAVASCULAR DEVICES

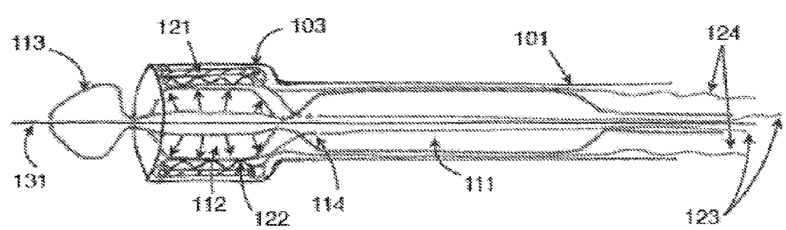


FIG. 4B

(57) **Abstract**: A dual-balloon delivery catheter system includes a carrier segment that is a lead/carrier balloon or mandrel at a distal portion of a catheter. The carrier segment is sequentially arrayed with a more proximally positioned delivery segment, wherein the delivery segment is a delivery balloon or mandrel. The first carrier segment expands the stent-valve a sufficient amount to receive the delivery segment after the carrier segment is moved away from the sent-valve. The delivery segment is then positioned at the target site and the stent-valve is then deployed.

WO 2012/006124 A2

METHOD AND APPARATUS FOR THE ENDOLUMINAL DELIVERY OF INTRAVASCULAR DEVICES

FIELD

Embodiments of the one or more present inventions relate to surgical methods and apparatus in general, and more particularly to surgical methods and apparatus for the endoluminal delivery of intravascular devices to a site within the body.

For the purposes of illustration but not limitation, embodiments of the one or more present inventions will hereinafter be discussed in the context of delivering a percutaneous heart valve to a valve seat located within the heart; however, it should be appreciated that at least one embodiment of the one or more present inventions is also applicable to other endoluminal delivery applications.

BACKGROUND

Percutaneous aortic valves, such as those available from Edwards Lifesciences LLC (Irvine, CA) under the tradename SAPIEN® typically utilize an expandable frame having valve leaflets attached thereto. This expandable frame essentially comprises a stent, with the valve leaflets (preferably in the form of tissue membrane) attached to a portion thereof. For this reason, these percutaneous aortic valves are commonly referred to as "stent-valves". Typically, the percutaneous aortic stent-valve is compressed down upon a deflated balloon catheter, the combined assembly is then inserted into the femoral artery through a covering sheath, and then the combined assembly is delivered endoluminally through the iliac artery and aorta to the valve seat. At the valve seat, the balloon is used to expand the stent so that the stent-valve is set at the valve seat, then the balloon is deflated, and finally the balloon catheter is withdrawn, whereupon the leaflets of the stent-valve act in place of the natural leaflets of the diseased aortic valve.

Percutaneous heart valves of the sort described above currently show great promise, particularly for elderly and/or otherwise infirm patients who cannot tolerate the trauma of conventional open heart valve replacement procedures.

Unfortunately, current percutaneous heart valve systems require the use of relatively large delivery/deployment apparatus. More particularly, since the internal balloon must be capable of expanding the stent portion of the stent-valve to the full size of the natural valve seat, and since the deflated size of a balloon having this full-expansion capability is relatively large, and since the stent-valve must be disposed circumferentially outboard of the balloon, the overall size of the delivery/deployment apparatus is necessarily large. By way of example but not limitation, the Edwards SAPIEN® delivery/deployment apparatus is typically approximately 7 to 8 mm in diameter.

Clinically, this can present a significant problem for the surgeon, since the preferred access to the vascular system of the patient is via the femoral artery, with subsequent delivery to the aortic valve seat via the iliac artery and aorta. However, the femoral artery is typically only about 5 to 8 mm in diameter, and this 5-8 mm range is for the general population as a whole - elderly female patients, who are expected to make up a substantial percentage of the candidate population for percutaneous aortic valve replacement, are on the smaller end of this range (e.g., perhaps 5-6 mm in diameter). Thus, it can be difficult or even impossible to pass the 7-8 mm (diameter) SAPIEN® device through the 5-6 mm (diameter) femoral artery of an elderly female patient, particularly where the femoral artery is tortuous, stenotic and/or occluded. Surgical incision has sometimes been required in order to gain access to a higher level of the ilio-femoral artery (e.g., within the pelvis) that is large enough to accommodate the stent-valve assembly. However, this approach is generally more invasive, and often leads to complications such as substantial bleeding and artery obstruction.

Referring now to Fig. 1, a schematic side view of a catheter-deliverable device, or stent-valve, known in the prior art is shown. The stent-valve may have an expanded diameter of approximately 25 mm. However, the stent-valve can be compressed to approximately 4 mm in diameter. As shown in Fig. 2, to achieve expansion of the stent-valve, it may be mounted on a typical prior art large-diameter delivery balloon catheter that is inflatable to a diameter of 25 mm. However, the combined diameter of the stent-valve mounted on to the large-diameter delivery balloon catheter is perhaps 18 Fr or 6 mm, which is too large to insert into some patient's femoral artery.

For the foregoing reasons, there is a substantial need for a new and improved method and apparatus for the endoluminal delivery of intravascular devices to a site within the body.

SUMMARY

It is to be understood that embodiments of the one or more present inventions include a variety of different versions or embodiments, and this Summary is not meant to be limiting or all-inclusive. This Summary provides some general descriptions of some of the embodiments, but may also include some more specific descriptions of other embodiments.

When first considered, a solution associated with the difficulty of placing a stent-valve in a relatively small femoral artery appears to be use of a small delivery device. Accordingly, a small-diameter delivery balloon initially appears to address the problem. However, and with reference now to Fig. 3, if a small diameter delivery balloon catheter is used, then while the stent-valve can be compressed to a relatively small diameter, the small-diameter delivery balloon is incapable of fully expanding the stent-valve to 25 mm; that is, a small diameter delivery balloon may only be capable of expanding the stent-valve to approximately 10 mm in diameter, for example.

At least one embodiment of the one or more present inventions addresses the aforementioned problems associated with the prior art by providing a novel method and apparatus for the endoluminal delivery of intravascular devices to a site within the body, at least one embodiment of the one or more present inventions takes advantage of the principle of dividing the volume of the stent-valve delivery apparatus into smaller diameter parts for separate insertion into the vascular system of a patient (e.g., into a relatively small diameter access vessel such as the femoral artery) and then re-assembling those parts within another portion of the vascular system of the patient (e.g., in a larger diameter vessel such as the aorta) which can accommodate the full size of the assembled components. By dividing the balloon expansion task into two serially-deployed balloons, activated in a staged fashion, the stent-valve can be delivered with a smaller profile, yet full stent-valve expansion at the valve seat can be ensured. Accordingly, novel devices and methods are proposed that involve transfer of a deliverable device, such as a stent-valve, after insertion into the body from its "carrier segment" to another "delivery segment" which may reside on the same or separate catheters, and deployment of the stent-valve from that "delivery segment" that is capable of expansion to suitable diameter for the stent-valve.

In at least one embodiment of the one or more present inventions, the stent-valve can be pre-mounted within a packaged pre-assembled delivery system for ready transport and clinical use.

In a first preferred form of the one or more present inventions, the first "carrier" balloon and second "delivery" balloon are mounted on separate inserter elements for independent delivery to the larger blood vessel, such as the aorta, where the second "delivery" balloon is united with the then-partially-expanded stent-valve – in this form, each balloon is independently advanced to the aorta via its own inserter element.

In a second preferred form of the one or more present inventions, the first and second balloons are serially disposed on a single inserter element, with the first "carrier" balloon being mounted to the inserter element distal to (or, optionally, more proximal to) the second "delivery" balloon – in this form, a single inserter element is used to sequentially position the first "carrier" balloon and second "delivery" balloon relative to the stent-valve.

In a third preferred form of the one or more present inventions, the first "carrier" balloon and second "delivery" balloon are mounted on separate inserter elements, but these inserter elements are arranged in a co-axial fashion so as to permit a telescoping action between the two inserter elements (and hence a telescoping action between the first "carrier" balloon and the second "delivery" balloon). In this form, the first "carrier" balloon shaft, being coaxially mounted upon a leading guide wire, can act as something of a firmer guidewire for the second "delivery" balloon.

In addition to the foregoing, after initial expansion of the stent-valve via the first "carrier" balloon, the first "carrier" balloon catheter can be removed and replaced by a shaped catheter element in order to provide guidance and assistance in traversing the central arteries and crossing the plane of (and, optionally, preparing) the native valve seat. This shaped catheter element can be disposed on an inserter element distal to the second "delivery" balloon or to the first carrier balloon, if desired.

If desired, the first "carrier" balloon can alternatively be another expandable device, e.g., the first "carrier" balloon (which constitutes the mounting segment for the stent-valve) can be an expandable mandrel. Alternatively, the stent-valve may be initially mounted on a non-expanding element, that is, simply a low-profile mandrel or other segment of the delivery catheter.

It should be appreciated that while at least one embodiment of the one or more present inventions has sometimes been discussed in the context of delivering a stent-valve to the aortic valve seat, it may also be used to deliver other valves to other valve seats, and/or for delivering other intravascular devices to other sites within the body.

It should also be appreciated that while at least one embodiment of the one or more present inventions is sometimes discussed in the context of advancing the stent-valve through the arterial system of the body, it may also be used to advance the stent-valve through the venous system of the body, or to endoluminally advance a device through some other luminal system of the body.

In at least one embodiment of the one or more present inventions, the covering sheath (through which the various components are advanced into the blood vessel) can be flexible and expandable so as to allow initial expansion of the stent-valve, and the exchange of the first "carrier" balloon and the second "delivery" balloon within the covering sheath, so that the apparatus is continuously protected.

It will be seen that at least one embodiment of the one or more present inventions provides a novel method and apparatus for the endoluminal delivery of an intravascular device to a site within the body.

Accordingly, at least one embodiment described herein is directed to a stent-valve and delivery system that is inserted separately into the femoral artery, then assembled inside the aorta, and thereafter advanced for deployment at the valve plane. This means that the limiting size of the artery (or vein, for the pulmonary valve) access diameter is determined by the largest single piece of the system - effectively the stent/valve itself. When the stent/valve is compressed without the balloon catheter, it is possible to deliver a valve into the circulation in as small as 14 French sheath rather than an 18 to 24 French, as has previously been achieved.

In at least one embodiment, an in-line dual-balloon delivery catheter system includes a carrier segment that is a lead/carrier balloon or mandrel at the distal portion of a catheter with the carrier segment arrayed in-line on a catheter shaft with a more proximally positioned delivery segment together at the distal portion of the catheter shaft. In essence, since the first "carrier" balloon only needs to expand the stent-valve a sufficient amount to receive the deflated second "delivery" balloon, the first "carrier" balloon can be quite small in its deflated condition. Moreover, the stent-valve, unrestricted by the traditional need for mounting on a single, relatively large deployment balloon, can be compressed to its minimum structural diameter for mounting on the relatively small first "carrier" balloon. As a result, the combined assembly (i.e., of carrier balloon catheter and stent-valve) can be much smaller in diameter than previous delivery devices at the time of accessing the vascular system of the patient. At the same time, by thereafter uniting the stent-valve with the second, larger "delivery" balloon, sufficient stent expansion can be provided to ensure secure valve seating.

In at least one embodiment, a woven wire "stent" with or without sheath investment is provided wherein its length is coupled to diameter. Nitinol or another alloy wire is formed in an expanded sheath shape and compressed by traction on trailing wire ends. At the point of the procedure requiring distal sheath expansion, the traction is released to allow expansion to a mechanically biased open position. Alternatively, traction wires may be attached to a distal end of the wire weave within the sheath and a traction force, there applied, causes simultaneous expansion and shortening of the distal end of the sheath, thereby advantageously releasing the underlying mounted stent-valve and exposing it for deployment.

In at least one embodiment a mechanism is provided for retaining a stent-valve frame on a delivery balloon by magnetic or electromagnetic means. The frame is preferably constituted of or contains ferrous metal elements. By such means, a stent-valve can be securely advanced through the vascular system without need for a covering sheath, thereby simplifying the delivery procedure and the system. The stent-valve is retained on the balloon segment by magnetic force.

In at least one embodiment, a device that utilizes magnetic force to deploy and, if desired, later retrieve a stent-valve is provided, the device using a magnetic force set at a level to permit ready balloon expansion of a stent-valve at a plane of the diseased native valve. As the frame of the stent-valve is pushed away from the magnet, retention force weakens, thereby allowing unimpeded final device expansion. A stronger magnet/electromagnet mounted on a separate catheter can be used to retrieve or reposition the stent-valve. In addition, a strong magnet mounted on a retrieval catheter can be used to retract the stent-valve frame from the native valve seat.

For the purposes of illustration but not limitation, embodiments of the one or more present inventions are hereinafter discussed in the context of delivering a prosthetic stent-valve to the aortic valve seat; however, it should be appreciated that at least one embodiment of the one or more present inventions is also applicable to other endoluminal delivery applications.

Accordingly, in at least one embodiment, a system for providing endoluminal delivery of a deliverable device through vasculature of a patient to a delivery site within the patient is provided, the system comprising:

an outer delivery sheath including a distal section, wherein at least a portion of the outer delivery sheath is sized for insertion into the vasculature of the patient;

a carrier segment located at a distal portion of a catheter shaft, the carrier segment having an outer surface sized to temporarily hold the deliverable device in the distal section of the outer delivery sheath, wherein at least a portion of the catheter shaft is located within and coaxial to the outer delivery sheath; and

a delivery segment located coaxial to the outer delivery sheath, the delivery segment having an outer surface sized to radially fit within the deliverable device after detaching the deliverable device from the carrier segment when the deliverable device resides within the distal section of the outer delivery sheath, wherein the delivery segment is configured to deploy the deliverable device at the delivery site.

In addition to the foregoing, in at least one embodiment at least a portion of the distal section of the outer delivery sheath is expandable. In at least one embodiment, the at least a portion of the distal section of the outer delivery sheath comprises one or more electrically activated elements. In at least one embodiment, the at least a portion of the distal section of the outer delivery sheath comprises one or more piezo-ceramic elements. In at least one embodiment, the at least a portion of the distal section of the outer delivery sheath comprises a passively expandable material that is expandable upon application of an outward radial force applied by at least one of the carrier segment and the delivery segment. In at least one embodiment, the at least a portion of the distal section of the outer delivery sheath expands upon application of a tensile force to the at least a portion of the distal section.

In at least one embodiment, the distal section includes at least one of an internal projection and a narrowed area extending radially inward from an interior surface of the distal section.

In at least one embodiment, a portion of an internal surface of the outer delivery sheath further comprises a guide for retaining at least a portion of a longitudinally extending element configured to selectively manipulate at least a part of the outer delivery sheath or a structure coaxial to the outer delivery sheath. In at least one embodiment, a portion of an internal surface of the outer delivery sheath further comprises a guide, the guide comprising at least one of:

(a) a lumen; and

(b) a grommet;

wherein the guide retains at least one control line for selective retention of the deliverable device.

In at least one embodiment, the carrier segment and the delivery segment are both situated upon the catheter shaft. In at least one embodiment, the carrier segment is situated upon the catheter shaft, and wherein the delivery segment is associated with a delivery segment shaft that is coaxial to the catheter shaft and axially moveable relative to the catheter shaft. In at least one embodiment, the carrier segment is an expandable balloon having an expanded diameter smaller than an expanded diameter for the delivery segment. In at least one embodiment, the delivery segment is an expandable balloon having an expanded diameter larger than an expanded diameter for the carrier segment. In at least one embodiment, at least one of the carrier segment and the delivery segment is a mandrel. In at least one embodiment, the mandrel is expandable by mechanical or electromechanical means. In at least one embodiment, the mandrel is not expandable.

In at least one embodiment, the delivery segment is located axially proximal to the carrier segment. In at least one embodiment, the delivery segment is located axially distal to the carrier segment.

In at least one embodiment, one or both of the carrier segment and the delivery segment include at least one magnet or electromagnet to aid manipulation of the deliverable device.

In at least one embodiment an assembly for intravascular delivery of a deliverable device to a delivery site within a patient is provided, comprising:

a first catheter including a first catheter shaft;

a carrier segment situated along the first catheter shaft, the carrier segment configured to receive the deliverable device prior to inserting the first catheter within the patient; and

a delivery segment sequentially positioned in an axial orientation relative to the carrier segment, wherein the delivery segment is configured to engage the deliverable device within the patient while the deliverable device is coaxial to at least a portion of the first catheter, and wherein the delivery segment is configured to thereafter deploy the deliverable device at the delivery site.

[0037] In at least one embodiment, the delivery segment is also situated along the first catheter. In at least one embodiment, the delivery segment is situated along a second catheter, the second catheter comprising a coaxial lumen through which passes the first catheter. In at least one embodiment, at least one of the first catheter and the second catheter comprise a curved distal portion.

One or more embodiments of the one or more present inventions also pertain to methods of delivering a device, such as a stent-valve, within a patient. Accordingly, in at least one embodiment, a method of delivering a deliverable device through vasculature of a patient to a target site within the patient is provided, comprising:

mounting the deliverable device on a selectively expandable carrier segment located along a catheter shaft, wherein at least a portion of the catheter shaft is located within and coaxial to an outer delivery sheath;

inserting the outer delivery sheath and catheter shaft into the patient;

moving the outer delivery sheath within the patient to position the selectively expandable carrier segment and the deliverable device near the target site;

partially expanding the deliverable device using the selectively expandable carrier segment while the deliverable device remains at least partially within the outer delivery sheath;

positioning a delivery segment radially within the deliverable device and partially expanding the delivery segment to facilitate engagement of the delivery segment with the deliverable device;

moving the delivery segment and deliverable device to the target site; and

deploying the deliverable device at the target site by further expanding the delivery segment.

Various components are referred to herein as “operably associated.” As used herein, “operably associated” refers to components that are linked together in operable fashion, and encompasses embodiments in which components are linked directly, as well as embodiments in which additional components are placed between the two linked components.

As used herein, “at least one,” “one or more,” and “and/or” are open-ended expressions that are both conjunctive and disjunctive in operation. For example, each of the expressions “at least one of A, B and C,” “at least one of A, B, or C,” “one or more of A, B, and C,” “one or more of A, B, or C” and “A, B, and/or C” means A alone, B alone, C alone, A and B together, A and C together, B and C together, or A, B and C together.

Various embodiments of the present inventions are set forth in the attached figures and in the Detailed Description as provided herein and as embodied by the claims. It should be understood, however, that this Summary does not contain all of the aspects and embodiments of the one or more present inventions, is not meant to be limiting or restrictive in any manner, and that the invention(s) as disclosed herein is/are understood by those of ordinary skill in the art to encompass obvious improvements and modifications thereto.

Additional advantages of at least one embodiment of the one or more present inventions will become readily apparent from the following discussion, particularly when taken together with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

To further clarify the above and other advantages and features of the one or more present inventions, a more particular description of the one or more present inventions is rendered by reference to specific embodiments thereof which are illustrated in the appended drawings. It should be appreciated that these drawings depict only typical embodiments of the one or more present inventions and are therefore not to be considered limiting of its scope. The one or more present inventions are described and explained with additional specificity and detail through the use of the accompanying drawings in which:

Fig. 1 is a schematic side view of a catheter-deliverable device frame (or stent-valve) known in the prior art;

Fig. 2 is a schematic side view of a typical prior art large-diameter delivery balloon catheter in a deflated state;

Fig. 3 is a schematic side view of a small-diameter delivery balloon catheter in a deflated state;

Fig. 4A is a side view of an in-line dual balloon delivery system in accordance with at least one embodiment of the one or more present inventions;

Fig. 4B is a side view of the system shown in Fig. 4A, wherein the carrier balloon is dilated to partially expand a stent-valve to accommodate the larger delivery balloon (catheter inflation ports, lumens, wire lumens not shown for clarity);

Fig. 4C is a side view of the system shown in Fig. 4B, wherein the deflated carrier balloon is advanced out of the partially expanded valve device as the delivery balloon is advanced into the stent-valve to “capture” or “dock” with the stent-valve;

Fig. 4D is a side view of the system shown in Fig. 4C, wherein the carrier balloon is optionally inflated to facilitate crossing the plane of the diseased heart valve with the delivery system, and wherein the delivery balloon is positioned astride the stent-valve to capture and subsequently deploy the stent-valve;

Fig. 4E is a side view of the system shown in Fig. 4D, wherein after the stent-valve is positioned in the plane of the heart valve, the sheath is withdrawn to expose the stent-valve in place at the heart valve seat and to allow for deployment if the stent-valve by expansion;

Fig. 4F is a side view of the system shown in Fig. 4E, wherein with the stent-valve is positioned at the valve seat and the sheath withdrawn, and wherein the delivery balloon then expanded to deploy the stent-valve;

Fig. 5A is a side view of a catheter delivery system in accordance with another embodiment of the one or more present inventions, wherein a carrier balloon shaft passes through a central coaxial lumen of a delivery balloon (wherein the wall of central lumen is omitted for clarity);

Fig. 5B is a side view of the system shown in Fig. 5A, wherein partial inflation of the leading carrier balloon may be used as a "nose cone" to facilitate insertion of the delivery catheter into a patient's artery;

Fig. 5C is a side view of the system shown in Fig. 5B, wherein full inflation of the leading carrier balloon partially expands the stent-valve within an expandable sheath segment;

Fig. 5D is a side view of the system shown in Fig. 5C, wherein at "(1)" the leading carrier balloon is deflated and advanced out of the stent-valve, and wherein at "(2)" the delivery balloon is advanced into position within stent-valve to "dock" with or "capture" the stent-valve;

Fig. 5E is a side view of the system shown in Fig. 5D, wherein the leading carrier balloon and guidewire are first advanced into the left ventricle (in the case of implantation in the native aortic valve seat), and wherein the leading carrier balloon shaft then acts as a guide rail for delivery of the balloon catheter;

Fig. 6A is a side view of an embodiment of a sheath, wherein traction elongates the sheath weave and reduces its diameter, and wherein release of the traction shortens/retracts the sheath weave and expands its diameter;

Fig. 6B is a side view of an embodiment of a cut shape memory alloy stent (nitinol) within a sheath wall investment that expands as a contained balloon and/or stent-valve (omitted for clarity) is expanded therein and self-contracts as the balloon is deflated;

Fig. 6C is a side view of an embodiment of a plastic material sheath that passively expands;

Fig. 6D is a side view of an embodiment of electrically actuated piezo-ceramic (p-c) elements sealed within an elastic sheath wall, wherein each p-c element is connected by a conductor pair to a voltage controlled power source, wherein a switch engages a power source, and wherein p-c elements expand the sheath when electrically energized;

Fig. 6E is a perspective view of an embodiment of actuator elements that utilize differential alloy laminates, wherein an application of current induces bend in the actuator;

Fig. 7 is a side view of an embodiment of a device for retaining a stent-valve on a delivery balloon by magnetic or electromagnetic means (for Figs. 7-8B, conductors and a power source for electromagnet are not shown; the valve membrane or other valve mechanism is not shown; the balloon inflation lumen and optional control lines/harness are omitted for clarity);

Fig. 8A is a side view of an embodiment of a retrieval catheter device that utilizes magnetic force to retrieve a stent-valve;

Fig. 8B is a side view of a stent-valve wherein the stent-valve is contracted by magnetic force and thereafter can be retracted from the native valve seat by optional control lines or a harness;

Fig. 8C is a side perspective view of an embodiment of a multipolar magnetic retrieval catheter system; and

Fig. 8D is an end view of the system shown in Fig. 8C positioned radially within a stent-valve.

For the figures presented herein, balloons in a collapsed state are depicted as partially expanded to emphasize the difference in sizes. In addition, balloon catheter wire lumen and inflation lumens are omitted for clarity.

The drawings are not necessarily to scale.

DETAILED DESCRIPTION

Overview

In general, at least one embodiment of the one or more present inventions uses a serial approach for delivering and deploying the percutaneous aortic valve at the valve seat. This serial approach allows various components of the combined assembly (i.e., the various components of the balloon catheter and the stent-valve) to be separately introduced into the vascular system of the patient, each with its own minimized profile, so as to facilitate a low-profile endoluminal delivery of the system components into the large central blood vessels (e.g. the aorta) where, in a preferred sequence, these components are co-axially re-assembled prior to advancement to the target valve seat. As a result, at least one embodiment of the one or more present inventions facilitates femoral artery access to the aortic valve seat, even with patients having small femoral artery diameters (e.g., elderly female patients). In other words, since the various components of the system are not fully assembled at the time of insertion into the vascular system of the patient, and are only fully assembled at some point subsequent to insertion (e.g., within a larger diameter blood vessel upstream (farther inward) of the insertion site), a relatively large access vessel is no longer necessary - thereby making percutaneous heart valve therapy available for a larger patient population and with a lower risk of access site and blood vessel complications. By way of example but not limitation, where the intravascular device comprises an aortic stent-valve, the various components of the system can be easily introduced into a relatively narrow femoral artery and thereafter assembled in a larger upstream (farther inward) vessel (e.g., in the relatively wide aorta) before being advanced to and seated at the native aortic valve seat.

More particularly, at least one embodiment of the one or more present inventions preferably utilizes two separate balloons for a staged deployment of the stent-valve: a first, smaller-diameter "carrier" balloon for initial stent expansion (e.g., for preliminarily expanding the stent while the stent-valve is disposed in the descending aorta), and a second, larger-diameter "delivery" balloon for ultimate stent seating at the native valve seat. In one preferred form of at least one embodiment of the one or more present inventions, the stent-valve is mounted on the deflated first, smaller-diameter "carrier" balloon, then this relatively small assembly is introduced (within a covering sheath) into the relatively small femoral artery, advanced through the femoral artery, up through the iliac artery, and then into the relatively large descending aorta. The first, smaller-diameter "carrier" balloon is then inflated so as to expand the stent-valve to an intermediate diameter configuration that is large enough in diameter to receive the deflated second, larger-diameter "delivery" balloon. The first "carrier" balloon is then deflated, the first "carrier" balloon is withdrawn and replaced by the deflated second "delivery" balloon which, by partial inflation or other means, captures the stent-valve, and the assembly is then advanced up the descending aorta, ascending aorta, etc. to the native valve seat. The second "delivery" balloon is then inflated so as to set the stent-valve at the valve seat. Finally, the second "delivery" balloon is deflated and withdrawn from the surgical site.

<u>In-line Dual-Balloon Catheter Delivery System</u>

With reference now to Figs. 4A-4F, a stent-valve 120 may be advanced upon a first, smaller-diameter "carrier" balloon to the aorta and initially deployed (using the first, smaller-diameter "carrier" balloon) to an intermediate size, followed by co-axial exchange for the second, larger-diameter "delivery" balloon for advancement to the valve seat, and then further expansion of the stent-valve 120 at the valve seat. Alternatively, the stent-valve 120 may be advanced upon the carrier balloon all the way to the target valve seat and initially deployed before coaxial exchange for the delivery balloon and subsequent final expansion.

Referring now to Fig. 4A, an integrated system is shown in the form of an in-line dual-balloon delivery catheter system 100 that features an in-line dual-balloon catheter configuration. The configuration shown in Fig. 4A illustrates the in-line dual-balloon delivery catheter system 100 as it is being translated through the patient's body toward the target valve seat, such as the aortic valve. For the in-line dual-balloon delivery catheter system 100 described herein, the carrier segment 112 is a lead/carrier balloon or mandrel at the distal portion of a catheter with the carrier segment 112 arrayed in-line on a catheter shaft with a more proximally positioned delivery segment 111 together at the distal portion of the catheter shaft. Alternatively, the delivery segment may be positioned distal to the carrier segment. The carrier segment 112 and delivery segment 111 are, for the case of the balloon-expandable stent-valve 120 example in this discussion, expandable balloons, for example, but may also be mandrels or expandable mandrels.

Here, it is noted that, in at least one embodiment (including both the in-line dual-balloon delivery catheter system 100 and the telescoping delivery system 200), a delivery segment comprising a delivery mandrel can be non-expanding. By way of example and not limitation, the means by which the delivery segment retains the stent-valve may vary. For example, in addition to friction, the delivery segment may retain the stent-valve by use of magnetic force. For such an assembly, if the stent-valve (or other deliverable device) is self-expanding or actuated to expansion and retained on the delivery segment for release by some other means (electronic, heat, e.g.), then the delivery mandrel can be non-expanding.

For the configuration shown in Fig. 4A, an outer delivery sheath 101 having, for example, a lengthwise body 104 that is 14 French inside diameter, is coaxially situated over a guidewire 131, for example, a 0.035 inch diameter wire, whereupon the integrated pair of expandable balloons reside. It is noted that all sizes and material types presented herein are exemplary and are not intended to be limiting, nor should they be interpreted as limiting, unless otherwise claimed. Although not required, an optional nose cone 113 may be positioned distally of the carrier segment 112 to assist with insertion of the catheter into the artery and subsequent traverse through it. In the embodiment wherein the delivery segment is disposed distal to the carrier segment, said nose cone is positioned immediately distal to the delivery segment and approximated to the tip of the sheath. The carrier segment 112 is used to hold the stent-valve 120 in place within the outer delivery sheath 101 and provide initial expansion of the stent-valve 120. Thereafter, the delivery segment 111 is used to provide final expansion of the stent-valve 120 for deployment of the stent-valve 120 at the valve seat.

The in-line dual-balloon delivery catheter system 100 is assembled external to the body by passing the delivery catheter with its linearly arrayed carrier segment 112 and delivery segment 111 within the central coaxial lumen of the delivery sheath 101 such that the carrier segment 112 of the catheter extends and is fully exposed beyond the distal terminal opening of the delivery sheath 101. The catheter-deliverable device, such as the stent-valve 120 in this example, is then coaxially mounted upon the carrier segment 112 by collapsing and compressing it onto the carrier segment 112 such that friction between the two retains the device 120 upon the carrier segment 112. The carrier segment 112 with the catheter-deliverable device (stent-valve 120) mounted upon it is then retracted back (proximally) into the distal portion of the delivery sheath 101 so that the device is completely covered within the sheath 101. In some cases the tip of the carrier segment 112 may be extended beyond the end of the sheath. In such a case, partial expansion of the leading tip 113 of the carrier segment 112 (balloon or expandable mandrel) may be used to form the tapered "nose cone" as noted above, to facilitate advancement or insertion of the delivery system into the blood vessel. Alternatively, the carrier segment may be fabricated with a soft plastic tapered tip for this purpose.

In the example of retrograde (in relation to blood flow) passage of the delivery system carrying the catheter-deliverable device, initial guidance for passage of the delivery system is established by advancement of the guidewire 131 across the heart valve seat 141 into the upstream anatomic chamber, such as the left ventricle, there acting as a guiding rail for the coaxial advancement of the delivery system catheters. Then, at a point external to the body, by inserting the guide wire 131 into the distal tip of the carrier segment 112 of the delivery catheter, the assembled in-line dual-balloon delivery catheter system 100 with sheath 101 is then advanced into the body coaxially over the guidewire 131 to a position proximate to but short of the target anatomic site--in this case, the diseased heart valve seat 141.

Referring now to Fig. 4B, when in the aorta, the leading carrier segment 112 is expanded as by balloon inflation, thus partially expanding the catheter-deliverable device (stent-valve 120) within the expandable distal segment 103 of the delivery sheath 101. That is, the carrier segment 112 is used to pre-dilate the stent-valve 120 so that the diameter of the stent-valve 120 is sufficient to accept the delivery segment 111 when the delivery segment 111 is at least partially deflated or not fully expanded. The outer delivery sheath may include an expandable and flexible distal segment to accommodate the partially expanded stent-valve 120 and hold the partially expanded stent-valve 120 in place. The carrier segment 112 is then contracted as by balloon deflation and advanced by advancing the delivery catheter out of the catheter-deliverable device (stent-valve 120) that is retained within the expanded distal segment 103 of the sheath 101. Optional shallow flanges 102 on the internal surface of the sheath 101 immediately proximal and/or distal to the mounted position of the device 120 can be used to assist in retention of the device during movement relating to the exchange of the carrier segment 112 for the delivery segment 111 with the advance of the delivery catheter. Alternatively, retention or control lines 123, 124 of wire or suture material may be attached to the device 120, as on the frame 121 of the stent-valve 120. Other forms of retaining force may be advantageously applied, such as by incorporating magnetic or electromagnetic elements within the delivery catheter shaft or within the sheath wall.

Referring now to Fig. 4C, as the delivery catheter 110 is thus advanced, the delivery segment 111 integrated thereupon thus is also advanced within the sheath 101 to a position astride the catheter-deliverable device (stent-valve 120) within the delivery sheath 101, with the tip of the delivery catheter extended beyond the tip of the delivery sheath 101. More particularly, the delivery segment 111 is advanced axially to a position radially interior to the stent-valve 120. The delivery segment 111 is then partially expanded to contact the stent-valve 120.

Referring to Fig. 4D, with the delivery segment 111 positioned within the stent-valve 120, in at least one embodiment the carrier segment 112 is positioned at the valve seat and may be further expanded to facilitate advancement of the stent-valve 120 within the plane of the aortic valve. That is, if deemed desirable by the surgeon, the carrier segment 112 is temporarily expanded and then contracted or deflated within the plane of the valve seat to facilitate subsequent axial advancement of the delivery segment 111 that carries the stent-valve 120.

With the projected tip of the delivery segment, and beyond that the carrier segment leading, the delivery catheter, catheter-deliverable device (stent-valve 120), and delivery sheath 101 are advanced together as a unit across the target anatomic plane (native heart valve seat 141, for example) to a position astride the target plane deemed suitable for deployment of the catheter-deliverable device (stent-valve 120). In the embodiment wherein the carrier segment is disposed proximal to the delivery segment this advancement occurs with the tip of the delivery segment leading the catheter assembly, and the carrier segment further proximal within the sheath. Referring now to Fig. 4E, after the delivery segment 111 is positioned in the plane of the target valve seat, the outer delivery sheath of the delivery system is withdrawn (as shown by the arrows in Fig. 4E) to expose the stent-valve 120; however, the stent-valve 120 remains undeployed because it continues to remain attached to the delivery segment 111. That is, the delivery sheath 101 is coaxially retracted with the delivery catheter held in place so as to expose the catheter-deliverable device (stent-valve 120) retained upon the delivery segment 111 at the site of deployment. The catheter-deliverable device (stent-valve 120) is then deployed by expansion of the delivery segment 111, such as by balloon inflation. Accordingly, and referring now to Fig. 4F, after the stent-valve 120 is exposed at the plane of the aortic valve, the delivery segment 111 is expanded to deploy the stent-valve 120. With full expansion and deployment of the catheter-deliverable device (stent-valve 120) the device is retained within the target anatomic plane (native heart valve seat 141). The delivery segment 111 is then contracted as by balloon deflation, function of the deployed device is confirmed, and the delivery catheter, delivery sheath 101, and guidewire 131 are retracted from the anatomic target area and removed from the body to complete the procedure.

In at least one embodiment, optional retention/control lines 123, 124 are released from valve frame 121 after successful deployment of stent-valve 120 is confirmed. Then balloon catheter 110 and guidewire 131 are removed from the valve seat 141 and withdrawn into sheath 101 for removal from the body.

In at least one embodiment, the carrier segment 112 is located axially proximal to the delivery segment 111. For such a configuration, the delivery segment 111 is advanced outside the sheath 101 and leads the assembly until the point the exchange is made. Then after the stent-valve 120 is partially expanded by the carrier segment 112, the delivery segment 111 is pulled back into the sheath 101 where the stent-valve 120 is retained, and the delivery segment 111 then captures the stent-valve 120. In this case, the tip of the delivery segment 111 at the tip of the sheath 101 will lead the further advance while the carrier segment 112 is sequestered more proximally in the sheath 101.

Telescoping Catheter Delivery System

Referring now to Figs. 5A-5E, in an alternative embodiment, a telescoping delivery system 200 for a stent-valve 120 is provided wherein a delivery balloon catheter 210 is co-axially situated or "threaded" over a carrier balloon catheter shaft 224 associated with a carrier segment 221. Accordingly, the carrier segment 221 can be advanced axially independent of the axial position of the delivery balloon 211. As a result, the carrier segment shaft 224 acts as a guide rail for the delivery balloon catheter 210 and the stent-valve 120 that is then radially positioned exterior to the delivery balloon 211. Step-by-step illustrations are provided in the drawings and are described in the following paragraphs.

Referring now to Fig. 5A, an outer delivery sheath 101 having, for example, a proximal shaft body with a 14 French inside diameter, is coaxially situated over a guidewire 131, whereupon a carrier segment shaft 224 and a delivery balloon shaft 214 are also co-axially situated. For the embodiment of the telescoping delivery system 200 described, the carrier segment 221 is a carrier balloon or mandrel at a distal portion of a carrier catheter 220 that is passed within the central lumen of a larger delivery catheter 210 that has a delivery segment 211 at its distal portion. By way of example and not limitation, the carrier segment shaft has a 0.035 inch outer diameter and is connected to the carrier segment 221 that is expandable to between 5-10 mm in diameter. The delivery segment 211 is, for the case of the balloon-expandable stent-valve 120 example, an expandable delivery balloon, for example. Accordingly, the delivery balloon may have an outside diameter of, for example, approximately 12-14 French when uninflated, and, in separate embodiments, is located axially either proximal or distal to the carrier segment 221.

The system is assembled external to the body by passing the carrier catheter 220 within the central coaxial lumen of the larger delivery catheter 210 such that the carrier segment 221 extends and is fully exposed beyond the tip 212 of the delivery catheter. These two catheters thus joined are then passed together through the delivery sheath 101 such that the carrier segment 221 of the carrier catheter 220 again extends and is fully exposed beyond the tip of the delivery sheath 101. The catheter-deliverable device, such as the stent-valve 120 in this example, is then coaxially mounted upon the carrier segment 221 by collapsing and compressing it onto the carrier segment 221 such that friction between the two retains the device 120 upon the carrier segment 221. The carrier segment 221 with the catheter-deliverable device (stent-valve 120) mounted upon it is then retracted back (proximally) into the delivery sheath 101 so that the device is completely covered within the sheath 101.

Referring now to Fig. 5B, the lead carrier segment balloon 221 optionally may be partially expanded to hold the stent-valve 120 within the outer delivery sheath 101. In addition, in some cases the tip 222 of the carrier catheter and carrier segment 221 may be extended beyond the end of the sheath 101. In such a case, partial expansion of the leading tip 223 of the carrier segment 221 (balloon or expandable mandrel) may be used to form a tapered "nose cone" to facilitate advancement or insertion of the delivery system into the blood vessel. Alternatively, and as previously noted for the in-line dual-balloon delivery catheter system 100, the carrier catheter 220 for the telescoping delivery system 200 may be fabricated with a soft plastic tapered tip for this purpose.

In the example of retrograde (in relation to blood flow) passage of the delivery system carrying the catheter-deliverable device, initial guidance for passage of the delivery system is established by advancement of the guidewire 131 across the heart valve seat 141 into the upstream anatomic chamber, such as the left ventricle, there acting as a guiding rail for the coaxial advancement of the delivery system catheters. Then, at a point external to the body, by inserting the guide wire 131 into the distal tip of the carrier catheter 220, the assembled delivery catheter system 200 with carrier catheter 220, delivery catheter 210 and sheath 101 is then advanced into the body coaxially over the guidewire 131 to a position proximate to but short of the target anatomic site--in this case, the diseased heart valve seat 141.

Referring now to Fig. 5C, in at least one embodiment, when in the aorta the carrier segment 221 is further expanded to effect expansion of the stent-valve 120 within the outer delivery sheath so that the delivery balloon can be advanced axially and positioned radially to the interior of the stent-valve 120. That is, when in the aorta, the leading carrier segment 221 is expanded, such as by balloon inflation, thus partially expanding the catheter-deliverable device (stent-valve 120) within the expandable distal segment 103 of the delivery sheath 101. In at least one embodiment, the outer delivery sheath 101 includes an expandable, flexible distal segment 103 that allows partial expansion of the stent-valve 120 within the outer delivery sheath, such as to a sufficient diameter to receive the unexpanded delivery balloon 211. Although the distal segment of the outer delivery sheath may be expandable, the outer delivery sheath shaft 104 located axially proximal to the carrier segment 221 preferably remains relatively small in diameter, that is, at its original unexpanded diameter, such as having a 14 French inside diameter at the entry point of the body and blood vessel.

With reference now to Fig. 5D, after partial expansion of the stent-valve 120 within the distal portion 103 of the outer delivery sheath 101, the carrier segment 221 is contracted as by balloon deflation and is then advanced axially beyond the outer delivery sheath 101 and out of the catheter-deliverable device (stent-valve 120) leaving it retained within the expanded distal segment 103 of the sheath 101.

The delivery segment balloon 211 is then axially advanced to a position radially to the interior of the stent-valve 120. With the delivery segment 211 of the delivery catheter 210 then coaxially advanced over the shaft 224 of the carrier catheter to a position astride the catheter-deliverable device (stent-valve 120) within the delivery sheath 101, the delivery segment balloon 211 is then partially expanded to dock or capture the stent-valve 120.

Referring now to Fig. 5E, the leading carrier segment balloon 221 of the carrier catheter 220 is then advanced across the target anatomic plane (native heart valve seat 141) coaxially following the guide wire 131 there in place, where it then provides additional mechanical guidance and support for the further coaxial advancement of the larger delivery catheter 210 upon the shaft 224 of the carrier catheter 220. Alternatively, the carrier catheter 220 may be coaxially withdrawn from the system and the body leaving the guide wire in place , then a shaped catheter (one with specifically designed terminal curves, such as "pig tail" or Amplatz type curves commonly found on angiographic catheters, to facilitate its being properly situated relative to the anatomy) may then be advanced over the guide wire to the upstream anatomic chamber, its shaft then substituting for the shaft 224 of the carrier catheter. Accordingly, Fig. 5E illustrates the guidewire 131 and carrier segment 221 as having passed the aortic valve such that the guidewire and carrier segment reside within the patient's left ventricle. Axial advancement of the carrier segment 221 and the carrier catheter shaft 224 can be done independent of the location of the delivery balloon 211. Thereafter, the delivery segment balloon 211 and the delivery catheter shaft 214 are axially advanced co-axially over the carrier catheter shaft 224 that acts as a guide rail for the delivery segment balloon 211. More particularly, with the projected tip 212 of the delivery catheter 211 leading beyond the tip of the sheath, the delivery segment 211, catheter-deliverable device (stent-valve 120), and delivery sheath 101 are advanced together as a unit across the target anatomic plane (native heart valve seat 141, for example) to a position astride the target plane deemed suitable for deployment of the catheter-deliverable device (stent-valve 120).

Once positioned at the plane of the valve seat of the patient's aortic valve, the delivery sheath 101 is coaxially retracted with the delivery catheter held in place so as to expose the catheter-deliverable device (stent-valve 120) retained upon the delivery segment 211 at the site of deployment. Thereafter, the final delivery balloon is expanded to deploy the stent-valve 120.

With full expansion and deployment of the catheter-deliverable device (stent-valve 120) the device is retained within the target anatomic plane (native heart valve seat 141). The delivery segment 211 is then contracted as by balloon deflation, function of the deployed device is confirmed, and the delivery catheter, carrier catheter, delivery sheath 101, and guide wire 131 are retracted from the anatomic target area and removed from the body to complete the procedure.

Expandable Outer Delivery Sheath

As described herein, at least one embodiment of the endoluminal delivery system includes an outer delivery sheath that further comprises a distal segment that is expandable. Several different ways of providing an expandable distal segment are described in the following paragraphs.

Referring now to Fig. 6A, the distal segment of the outer delivery sheath 310 may comprise a woven alloy wire portion 311. By way of example and not limitation, the distal segment may be similar in design to the IDEV TECHNOLOGIES SUPERA® stent that includes woven nitinol wire. Alternatively, in at least one embodiment, the woven wire portion 311 may further comprise a flexible plastic investment; that is, a configuration wherein the woven wire portion resides within a flexible plastic matrix forming a tubular portion of the outer delivery sheath. In typical operation, the wire weave is formed in expanded configuration and elongated by longitudinal traction force on the wire elements with resulting contraction of the tubular form to a decreased diameter. Thereafter, the release of traction force effects self-expansion of the weave. In at least one embodiment, a distal portion of the distal segment of the outer delivery sheath 310 may be widened by using control lines to pull on control ends of the woven wire portion of the distal segment.

Referring now to Fig. 6B, in an alternative embodiment, the distal segment of the outer delivery sheath 320 includes a cut nitinol stent 321 residing within the sheath investment. More particularly, the distal segment of the outer delivery sheath includes a nitinol stent 321 embedded within the distal segment, wherein the nitinol stent 321 provides shape-memory functionality for the distal segment. As a result, when the balloon catheter is inflated within the distal segment with the stent-valve 120 mounted on it, the distal segment expands to accommodate the inflated balloon catheter and stent-valve. Thereafter, when the balloon catheter is pushed out of the outer delivery sheath 320, the distal segment then retracts because of the shape-memory functionality associated with the nitinol stent 321 residing with the distal segment.

Referring now to Fig. 6C, in at least one embodiment the distal segment of the outer delivery sheath 330 comprises an elastic material that can passively expand and optionally retract. That is, when a balloon catheter is expanded within the distal segment, the elastic material accommodates the expansion. Thereafter, with deflation of the balloon catheter the elastic material forming the distal segment retracts. Alternatively, the sheath material, such as PTFE (polytetrafluoroethylene) may expand but not contract. In such case, the thin-walled sheath material folds inward along longitudinal lines when retracted through a proximally disposed entry sheath or the vascular entry point itself, permitting ready removal from the body, even in a persistently expanded condition.

Referring now to Fig. 6D, in an alternative embodiment, the distal segment of the outer delivery sheath 340 includes a plurality of electrically actuated piezo-ceramic elements 341. Electrical wiring or conductors 342 extend to the proximal end of the outer delivery sheath 340 to facilitate application of an electrical current to the piezo-ceramic elements 341. When desired, the surgeon closes a circuit to engage a power source 343 and apply the electrical current to the piezo-ceramic elements 341 via the electrical wiring or conductors 342. Upon being energized, the piezo-ceramic elements 341 expand the distal segment of the outer delivery sheath 340. Contraction of the distal segment is achieved by terminating the electrical current to the piezo-ceramic elements 341. Further reference here is made to U.S. Patent No. 5,415,633, the content of which is incorporated by reference in its entirety.

Referring now to Fig. 6E, a variation of the use of electrically charged elements comprises the use of active elements featuring differential alloy sandwiches or laminates 344 that bend when a current is applied. The bending of the active elements causes the distal segment to expand. As with the piezo-ceramic elements 341 described above, contraction of the distal segment is achieved by terminating the application of electrical current to the differential alloy sandwiches or laminates 344.

In another alternative embodiment, a magnetic or electromagnetic force is used to retain a stent-valve 120 on a delivery segment balloon for advancement to the target valve plane and subsequent deployment. More particularly, and with reference now to Fig. 7, an alternative endoluminal magnetic delivery system 400 is shown that utilizes a magnetic or electromagnetic force to maintain the position of the stent-valve 120 on the delivery segment balloon 411, wherein the delivery segment balloon 411 is located at or near the distal portion of a delivery catheter shaft 414. The magnet or electromagnet 416 are preferably incorporated into the balloon catheter shaft 414 co-axial to and axially centered along the delivery segment balloon 411 so as to align with the axial position of the mounted stent-valve. As one of skill in the art will appreciate, the stent-valve 120 must incorporate a material susceptible to magnetism in a sufficient quantity and distribution to facilitate attraction of the stent-valve 120 to the magnet or electromagnet 416 incorporated into the balloon catheter shaft 414. A guidewire 131 serves to guide the co-axially situated delivery balloon catheter 410. The delivery balloon may be partially expanded to: (a) provide a nose cone for facilitating insertion of the delivery system into, and traverse through the patient's blood vessel; and/or (b) to provide further frictional force for securing the stent-valve 120. Since the stent-valve 120 is held in place by a magnetic or electromagnetic force as well as any further frictional force due to partial expansion of the delivery balloon, the stent-valve 120 can be securely advanced through the patient's vascular system without need of an outer delivery sheath, thereby simplifying and reducing the profile of the delivery system. Once the target valve plane is reached, the delivery balloon 411 is expanded, thereby overcoming the magnetic or electromagnetic force (of course, an electromagnetic force may be terminated by stopping current to the electromagnet), to deploy the stent-valve 120 at the plane of the diseased native valve. Similarly, the magnet of the magnetic delivery catheter 410 may be incorporated into the delivery segment balloons of the in-line dual balloon system 100 and/or the telescoping catheter delivery system 200 in a similar manner to facilitate capture and retention of the stent-valve upon the delivery segment balloon in its traverse through the anatomic structures.

In addition to endoluminal delivery of a stent-valve 120, at least one embodiment of the one or more present inventions is directed to a retrieval and/or repositioning system 500 that can be used to remove a deployed stent-valve 120 from a patient, or otherwise reposition the stent-valve 120 within the patient. With reference now to Figs. 8A and 8B, an embodiment of a retrieval and/or repositioning system 500 is shown. The retrieval and/or repositioning system comprises a retrieval catheter 510 on a distal portion of which is integrated a magnet 511, and more preferably, an electromagnet of sufficient strength to at least partially collapse and secure a previously deployed stent-valve 120. With reference to Fig. 8B, the partially collapsed valve is then either withdrawn (that is, retrieved from the patient), for example as by traction on optional control lines 124 as shown, or repositioned and then redeployed.

Referring now to Figs. 8C and 8D, in a separate embodiment, a multipolar magnetic retrieval catheter system 520 is provided in which multiple magnetic elements 522 are circumferentially arrayed and disposed at a distal portion of a retrieval catheter 521 in a manner that allows the radially outward movement of the magnets 522, and the portions of the underlying catheter elements 523 to which they are attached, into contact with the radially interior surface of the deployed stent-valve 120. In at least one embodiment, the underlying portions 523 of the catheter to which the magnets 522 are attached are longitudinally separate from each other so that they are free to move independently from each other as the attached magnets 522 move radially outward. In at least one embodiment, the magnets 522 are of like polarity and are initially restrained into proximity with each other by an overlying sheath mechanism. When said sheath 524 is retracted the distal catheter portions 523 with their attached magnets 522 move radially outward under repulsive magnetic force into contact with the stent-valve 120. The close proximity if not complete contact of the magnets 522 to the stent-valve frame 121 advantageously maximizes the retention force facilitating the traction force applied in the removal of the device from the valve plane. The sheath 524 may be re-advanced over the magnetic distal portions 523 of the catheter, thus applying radially inward force on the device frame that serves to contract it and facilitate its removal under axial traction.

<u>Shaped Catheter</u>

The various sheath and catheter shafts described herein for the various embodiments may include a “shaped” distal portion. More particularly, a “shaped” catheter may be used to assist in crossing anatomic resistance or provide guidance for recrossing the valve plane in the event the guide wire is displaced from the ventricle. This problem occurs when the stent-valve and the delivery system are advanced around the aorta. In such a situation, the traction forces, not uncommonly, will pull the guide wire out of the ventricle. If this happens—with the delivery system already in the aorta—it requires the delivery system be removed from the patient’s body and the sequence started over from the beginning. Advantageously, one or more embodiments described herein can assist with avoiding this problem. That is, a catheter can be used that includes a distal portion with one or more curved shapes, such as “pig tail” or Amplatz type curves commonly found on angiographic catheters, and including a central coaxial lumen through which is passed the guidewire. The shaped catheter is used to “steer” the guide wire across the very narrowed valve orifice. Thus, in one embodiment, a “shaped” catheter is passed within the central lumen of the delivery catheter. In such a configuration, the guide wire can be re-crossed through the valve plane more readily, and the shaped catheter—advantageously, a relatively firm catheter—can be advanced to the ventricle and left to act as an enhanced support rail for the delivery catheter.

To assist in the understanding of the present invention the following list of components and associated numbering found in the drawings is provided herein:

Number	Component
100	In-Line Dual Balloon Catheter Delivery System
101	Delivery Sheath
102	Optional Flange Of Internal Sheath
103	Expandable, Flexible Sheath Segment
104	Sheath Body
110	Dual In-Line Balloon Catheter Assembly
111	Delivery Segment Is Delivery Balloon
112	Carrier Segment Is In-Line Leading Carrier Balloon
113	Optional Nose Cone
114	Exit Of Distal Control Lines From Catheter Shaft
120	Stent-Valve Assembly
121	Valve Frame
122	Collapsed Valve Membrane
123	Optional Control Lines Attached To Distal End Of Valve Frame (Passed Within Catheter Shaft)
124	Optional Control Lines Attached To Proximal End Of Valve Frame
130	Guide Wire Assembly
131	Guide Wire
140	Native Heart Valve
141	Native Heart Valve Seat
200	Telescoping Balloon Catheter Delivery System
210	Delivery Balloon Catheter Assembly
211	Delivery Segment Is Delivery Balloon
212	Tip Of Delivery Segment Balloon
213	Partially Inflated Leading Tip Of Delivery Segment Balloon
214	Delivery Balloon Catheter Shaft
220	Carrier Balloon Catheter Assembly
221	Carrier Segment Is Leading Balloon That Coaxially Telescopes Within Central Lumen Of Delivery Segment Balloon
222	Tip Of Carrier Segment Balloon
223	Inflated Leading Tip Of Carrier Segment Balloon
224	Shaft Of Carrier Catheter

300	Expandable Sheath System
310	Woven Wire Sheath
320	Sheath With Embedded Nitinol Stent
321	Nitinol Stent
330	Flexible Plastic Sheath
340	Electronically Actuated Sheath
341	Piezo-Ceramic Elements
342	Conductors
343	Power Source
344	Alloy Laminates
400	Magnetic Balloon Catheter Delivery System
410	Magnetic Balloon Delivery Catheter
411	Delivery Balloon
412	Tip Of Magnetic Balloon Delivery Catheter
413	Partially Inflated Tip Of Delivery Balloon
414	Shaft Of Magnetic Balloon Delivery Catheter
415	Guide Wire Lumen Of Magnetic Balloon Delivery Catheter
416	Magnet Or Electromagnet
500	Magnetic Retrieval Catheter System
510	Magnetic Retrieval Catheter Assembly
511	Magnet Or Electromagnet
520	Multipolar Magnetic Retrieval Catheter Assembly
521	Multipolar Magnetic Retrieval Catheter
522	Magnets – Circumferentially Arrayed
523	Distal Mobile Catheter Elements Attaching To Magnets
524	Sheath

The one or more present inventions may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the one or more present inventions is, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

The one or more present inventions, in various embodiments, includes components, methods, processes, systems and apparatus substantially as depicted and described herein, including various embodiments, subcombinations, and subsets thereof. Those of skill in the art will understand how to make and use the one or more present inventions after understanding the present disclosure.

The one or more present inventions, in various embodiments, includes providing devices and processes in the absence of items not depicted and/or described herein or in various embodiments hereof, including in the absence of such items as may have been used in previous devices or processes (e.g., for improving performance, achieving ease and/or reducing cost of implementation).

The foregoing discussion of the one or more present inventions has been presented for purposes of illustration and description. The foregoing is not intended to limit the one or more present inventions to the form or forms disclosed herein. In the foregoing Detailed Description for example, various features of the one or more present inventions are grouped together in one or more embodiments for the purpose of streamlining the disclosure. This method of disclosure is not to be interpreted as reflecting an intention that the claimed one or more present inventions requires more features than are expressly recited in each claim. Rather, as the following claims reflect, inventive aspects lie in less than all features of a single foregoing disclosed embodiment. Thus, the following claims are hereby incorporated into this Detailed Description, with each claim standing on its own as a separate preferred embodiment of the one or more present inventions.

Moreover, though the description of the one or more present inventions has included description of one or more embodiments and certain variations and modifications, other variations and modifications are within the scope of the one or more present inventions (e.g., as may be within the skill and knowledge of those in the art, after understanding the present disclosure). It will be understood that many changes in the details, materials, steps and arrangements of elements, which have been herein described and illustrated in order to explain the nature of the invention, may be made by those skilled in the art without departing from the scope of embodiments of the one or more present inventions. It is intended to obtain rights which include alternative embodiments to the extent permitted, including alternate, interchangeable and/or equivalent structures, functions, ranges or steps to those claimed, whether or not such alternate, interchangeable and/or equivalent structures, functions, ranges or steps are disclosed herein, and without intending to publicly dedicate any patentable subject matter.

CLAIMS

What Is Claimed Is:

1. A system for providing endoluminal delivery of a deliverable device through vasculature of a patient to a delivery site within the patient, comprising:

an outer delivery sheath including a distal section, wherein at least a portion of the outer delivery sheath is sized for insertion into the vasculature of the patient;

a carrier segment located at a distal portion of a catheter shaft, the carrier segment having an outer surface sized to temporarily hold the deliverable device in the distal section of the outer delivery sheath, wherein at least a portion of the catheter shaft is located within and coaxial to the outer delivery sheath; and

a delivery segment located coaxial to the outer delivery sheath, the delivery segment having an outer surface sized to radially fit within the deliverable device after detaching the deliverable device from the carrier segment when the deliverable device resides within the distal section of the outer delivery sheath, wherein the delivery segment is configured to deploy the deliverable device at the delivery site.

2. The system of Claim 1, wherein at least a portion of the distal section of the outer delivery sheath is expandable.

3. The system of Claim 2, wherein the at least a portion of the distal section of the outer delivery sheath comprises one or more electrically activated elements.

4. The system of Claim 2, wherein the at least a portion of the distal section of the outer delivery sheath comprises one or more piezo-ceramic elements.

5. The system of Claim 2, wherein the at least a portion of the distal section of the outer delivery sheath comprises a passively expandable material that is expandable upon application of an outward radial force applied by at least one of the carrier segment and the delivery segment.

6. The system of Claim 2, wherein the at least a portion of the distal section of the outer delivery sheath expands upon application of a tensile force to the at least a portion of the distal section.

7. The system of Claim 1, wherein the distal section includes at least one of an internal projection and a narrowed area extending radially inward from an interior surface of the distal section.

8. The system of Claim 1, wherein a portion of an internal surface of the outer delivery sheath further comprises a guide for retaining at least a portion of a longitudinally extending element configured to selectively manipulate at least a part of the outer delivery sheath or a structure coaxial to the outer delivery sheath.

9. The system of Claim 1, wherein a portion of an internal surface of the outer delivery sheath further comprises a guide, the guide comprising at least one of:

(a) a lumen; and

(b) a grommet;

wherein the guide retains at least one control line for selective retention of the deliverable device.

10. The system of Claim 1, wherein the carrier segment and the delivery segment are both situated upon the catheter shaft.

11. The system of Claim 1, wherein the carrier segment is situated upon the catheter shaft, and wherein the delivery segment is associated with a delivery segment shaft that is coaxial to the catheter shaft and axially moveable relative to the catheter shaft.

12. The system of Claim 1, wherein the carrier segment is an expandable balloon having an expanded diameter smaller than an expanded diameter for the delivery segment.

13. The system of Claim 1, wherein the delivery segment is an expandable balloon having an expanded diameter larger than an expanded diameter for the carrier segment.

14. The system of Claim 1, wherein at least one of the carrier segment and the delivery segment is a mandrel.

15. The system of Claim 14, wherein the mandrel is expandable by mechanical or electromechanical means.

16. The system of Claim 14, wherein the mandrel is not expandable.

17. The system of Claim 1, wherein the delivery segment is located axially proximal to the carrier segment.

18. The system of Claim 1, wherein the delivery segment is located axially distal to the carrier segment.

19. The system of Claim 1, wherein the delivery segment includes a magnet to aid in capture and retention of the deliverable device on the delivery segment.

20. An assembly for intravascular delivery of a deliverable device to a delivery site within a patient, comprising:

a first catheter including a first catheter shaft;

a carrier segment situated along the first catheter shaft, the carrier segment configured to receive the deliverable device prior to inserting the first catheter within the patient; and

a delivery segment sequentially positioned in an axial orientation relative to the carrier segment, wherein the delivery segment is configured to engage the deliverable device within the patient while the deliverable device is coaxial to at least a portion of the first catheter, and wherein the delivery segment is configured to thereafter deploy the deliverable device at the delivery site.

21. The assembly of Claim 20, wherein the delivery segment is also situated along the first catheter.

22. The assembly of Claim 20, wherein the delivery segment is situated along a second catheter, the second catheter comprising a coaxial lumen through which passes the first catheter.

23. The assembly of Claim 22, wherein at least one of the first catheter and the second catheter comprise a curved distal portion.

24. The assembly of Claim 20, wherein the carrier segment is an expandable balloon.

25. The assembly of Claim 20, wherein the carrier segment is a mandrel.

26. The assembly of Claim 25, wherein the mandrel is expandable by mechanical or electromechanical means.

27. The assembly of Claim 25, wherein the mandrel is non-expandable.

28. The assembly of Claim 20, wherein the delivery segment is an expandable balloon.

29. The assembly of Claim 20, wherein the delivery segment is a mandrel.

30. The assembly of Claim 29, wherein the mandrel is expandable by mechanical or electromechanical means.

31. The assembly of Claim 29, wherein the mandrel is non-expandable.

32. The assembly of Claim 20, wherein the delivery segment includes a magnet to aid in capture and retention of the deliverable device on the delivery segment.

33. The assembly of Claim 20, wherein the delivery segment includes an electromagnet to aid in capture and retention of the deliverable device on the delivery segment.

34. A method of delivering a deliverable device through vasculature of a patient to a target site within the patient, comprising:

mounting the deliverable device on a selectively expandable carrier segment located along a catheter shaft, wherein at least a portion of the catheter shaft is located within and coaxial to an outer delivery sheath;

inserting the outer delivery sheath and catheter shaft into the patient;

moving the outer delivery sheath within the patient to position the selectively expandable carrier segment and the deliverable device near the target site;

partially expanding the deliverable device using the selectively expandable carrier segment while the deliverable device remains at least partially within the outer delivery sheath;

positioning a delivery segment radially within the deliverable device and partially expanding the delivery segment to facilitate engagement of the delivery segment with the deliverable device;

moving the delivery segment and deliverable device to the target site; and

deploying the deliverable device at the target site by further expanding the delivery segment.

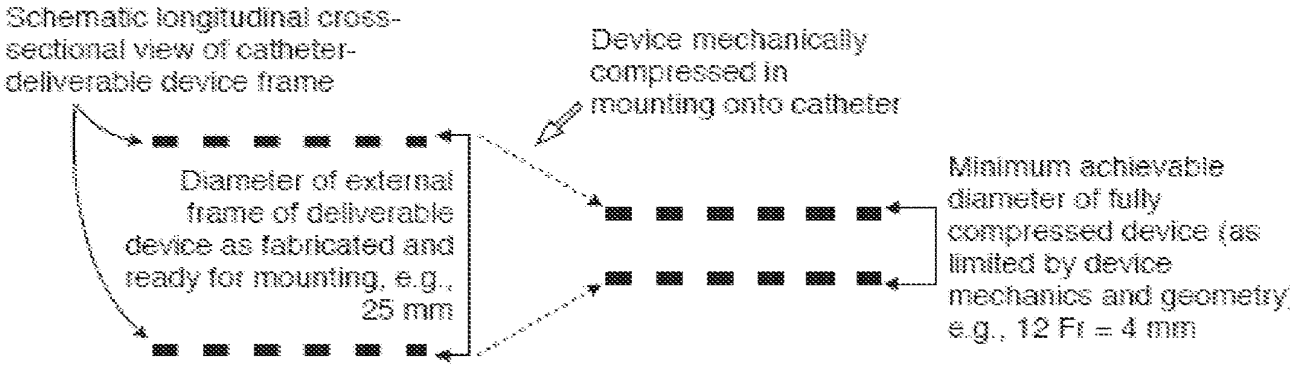


FIG. 1
(PRIOR ART)

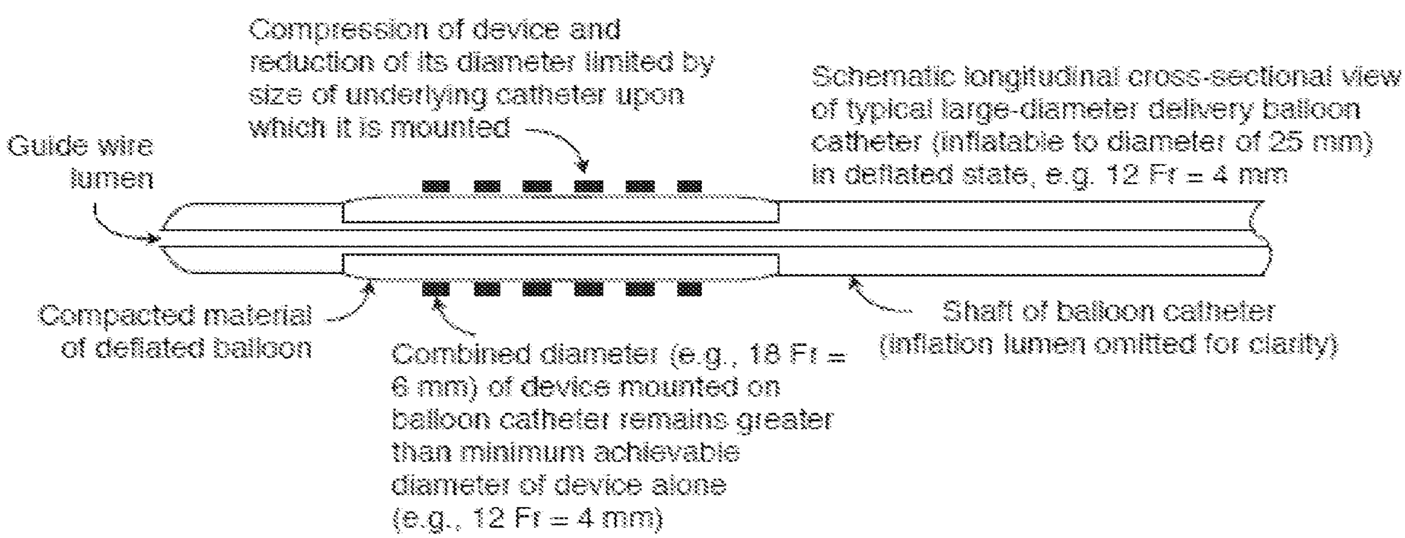


FIG. 2
(PRIOR ART)

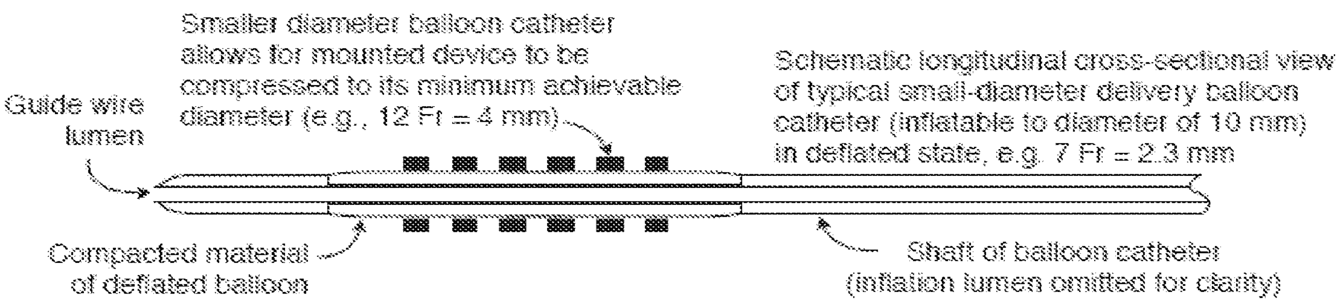
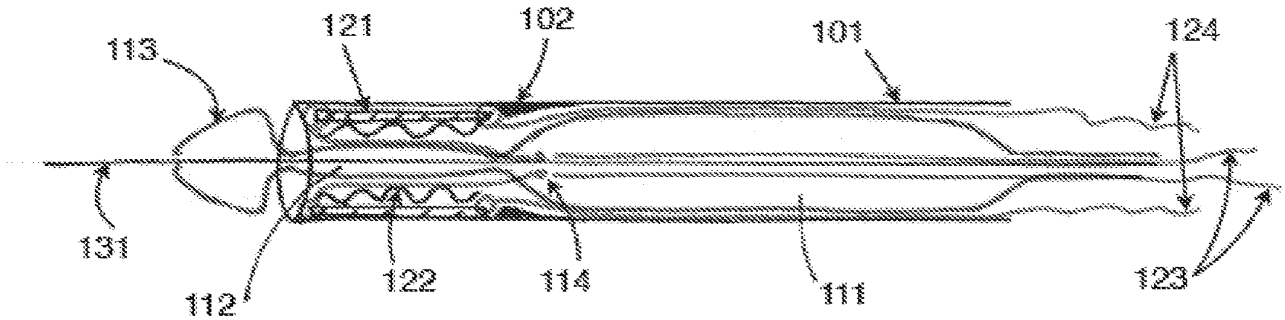

Smaller diameter balloon catheter allows for mounted device to be compressed to its minimum achievable diameter (e.g., 12 Fr = 4 mm)
Schematic longitudinal cross-sectional view of typical small-diameter delivery balloon catheter (inflatable to diameter of 10 mm) in deflated state, e.g. 7 Fr = 2.3 mm
Guide wire lumen
Compacted material of deflated balloon
Shaft of balloon catheter (inflation lumen omitted for clarity)

FIG. 3

FIG. 4A



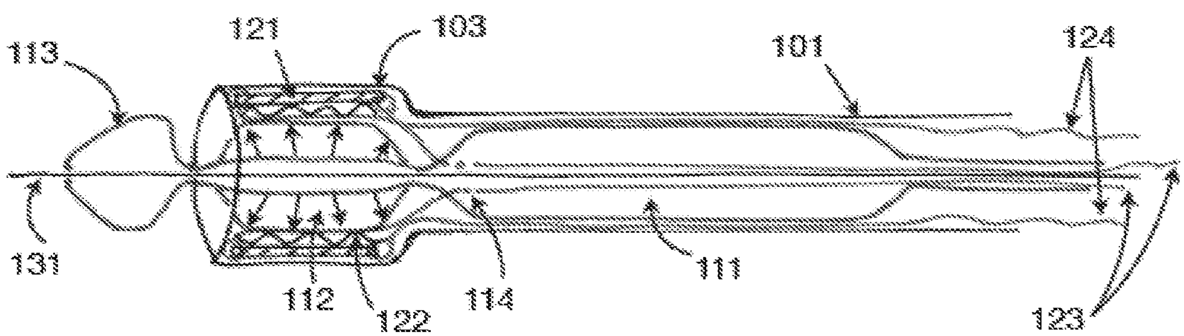


FIG. 4B

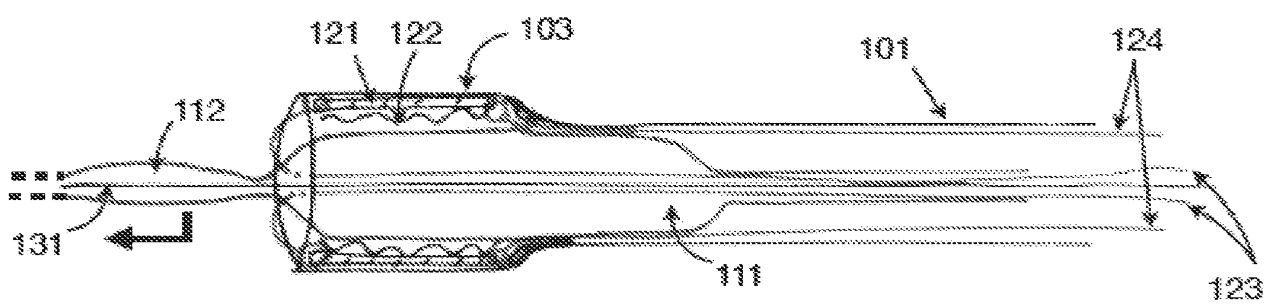
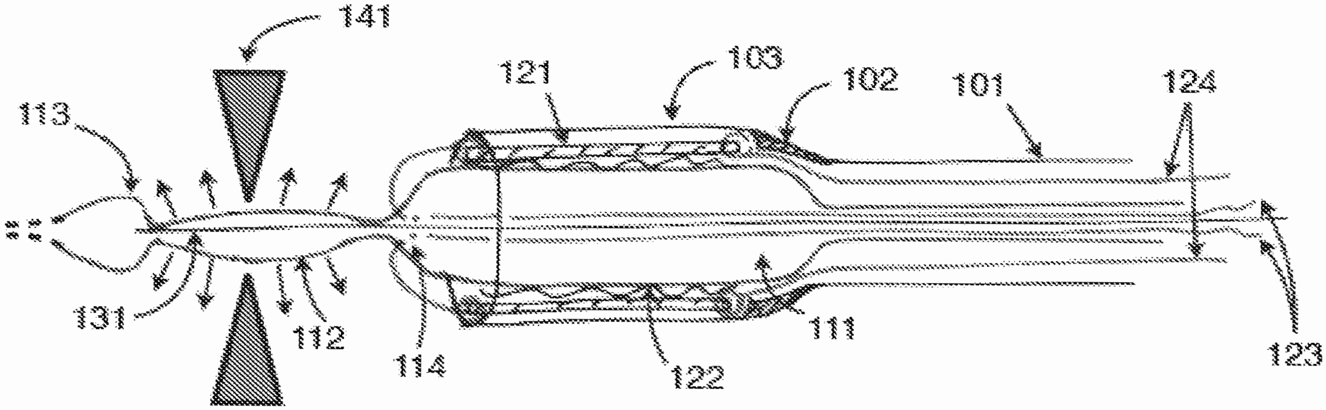


FIG. 4C

FIG. 4D



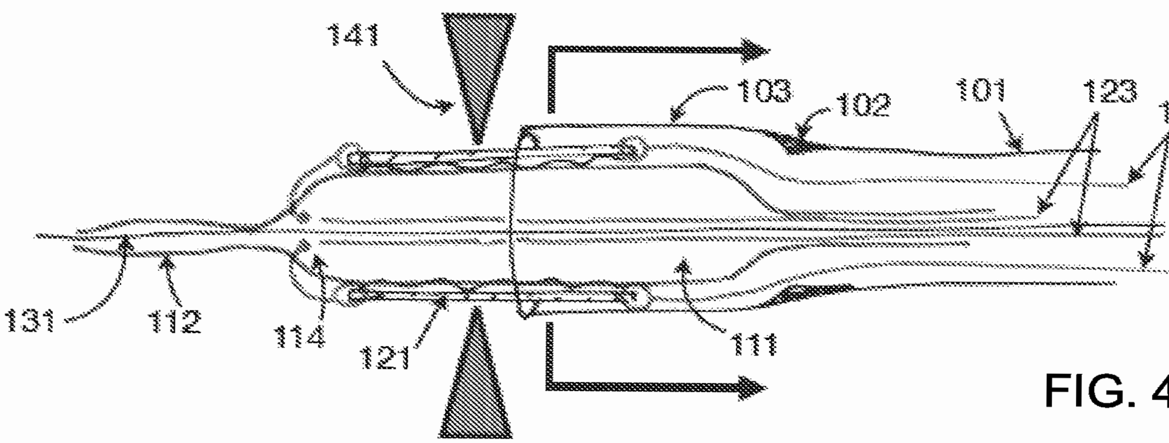


FIG. 4E

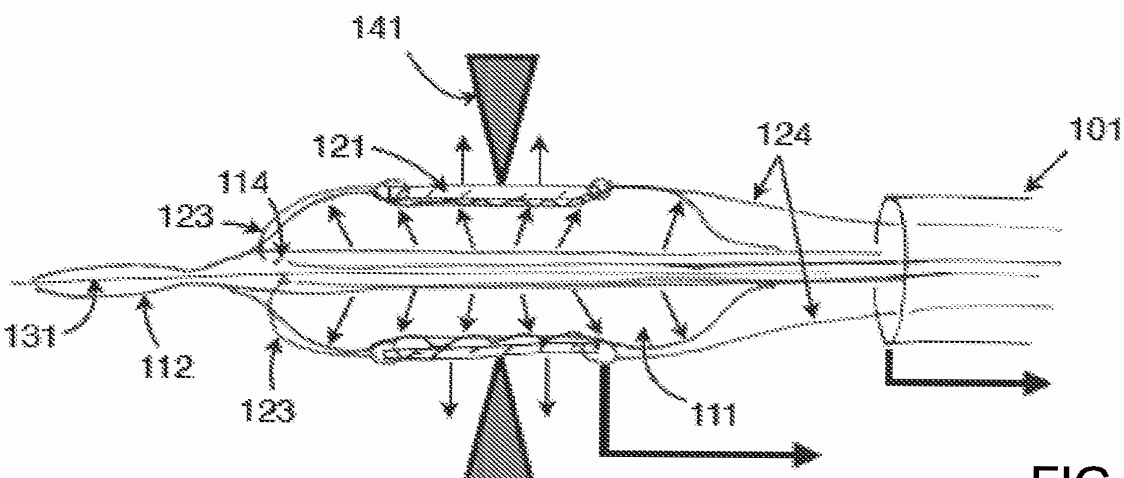


FIG. 4F

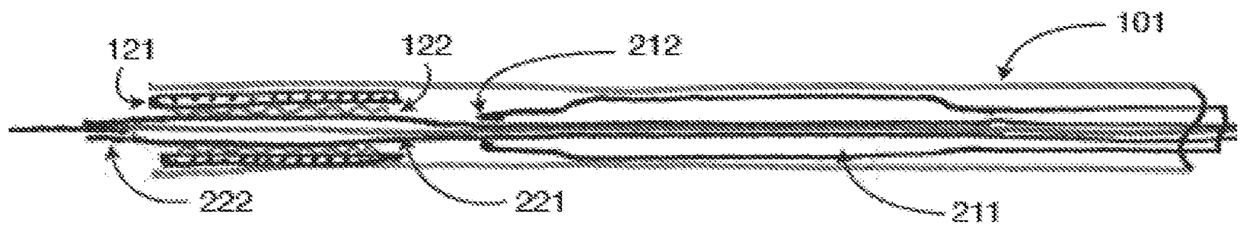


FIG. 5A

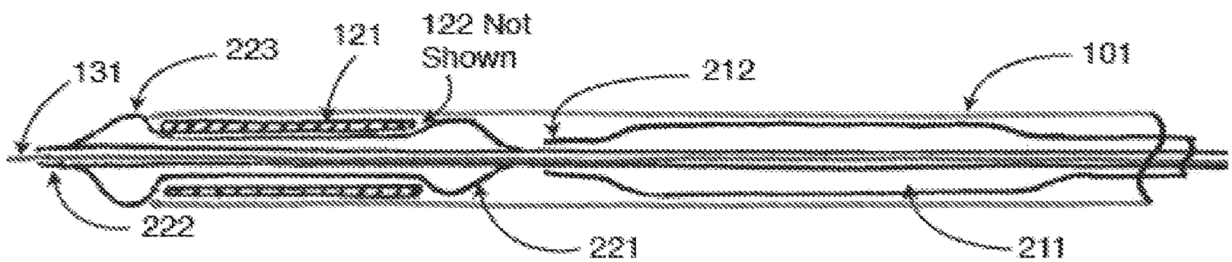


FIG. 5B

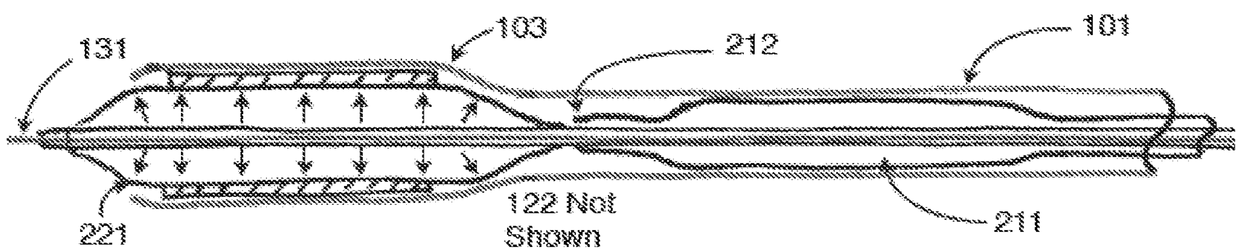


FIG. 5C

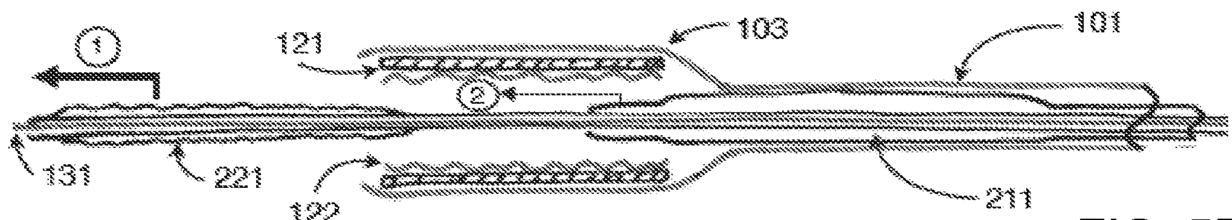


FIG. 5D

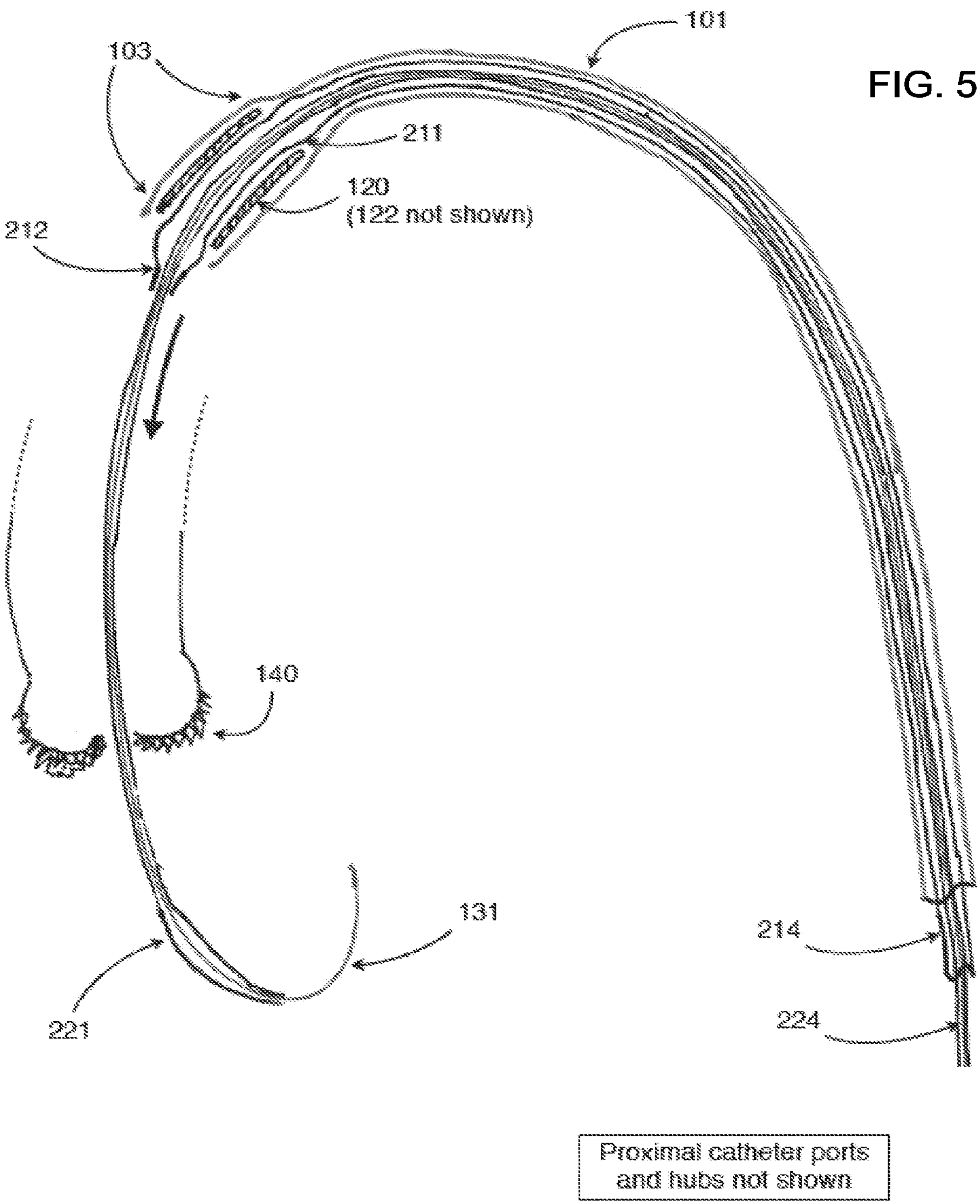
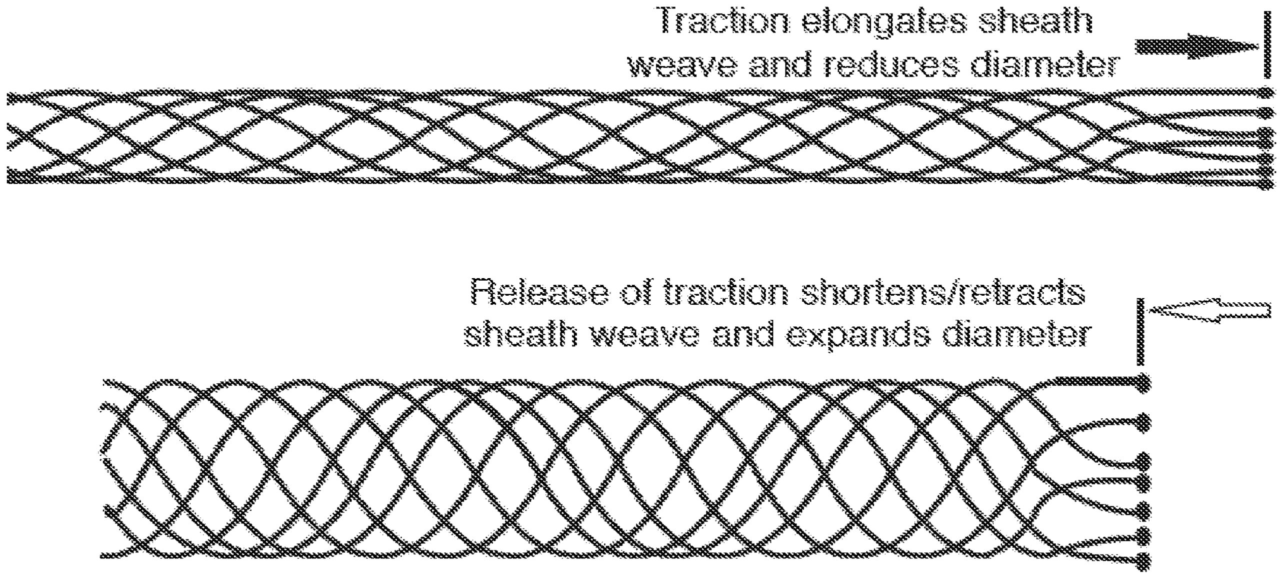

101
103
211
120
(122 not shown)
212
140
131
214
221
224
Proximal catheter ports
and hubs not shown

FIG. 5E

FIG. 6A



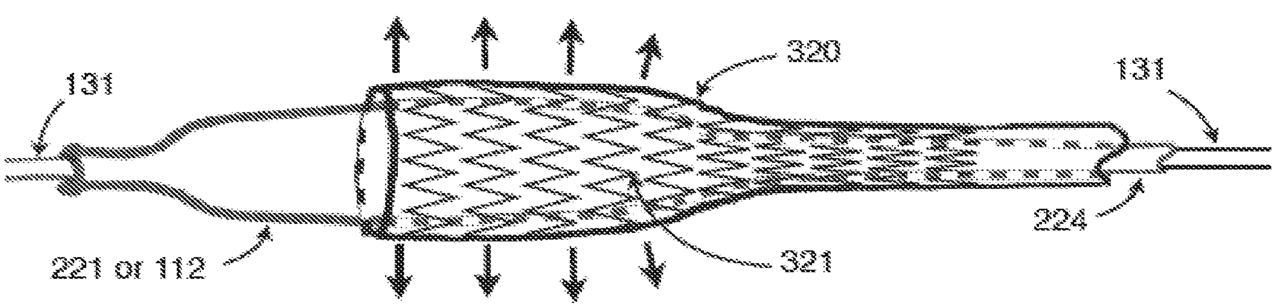


FIG. 6B

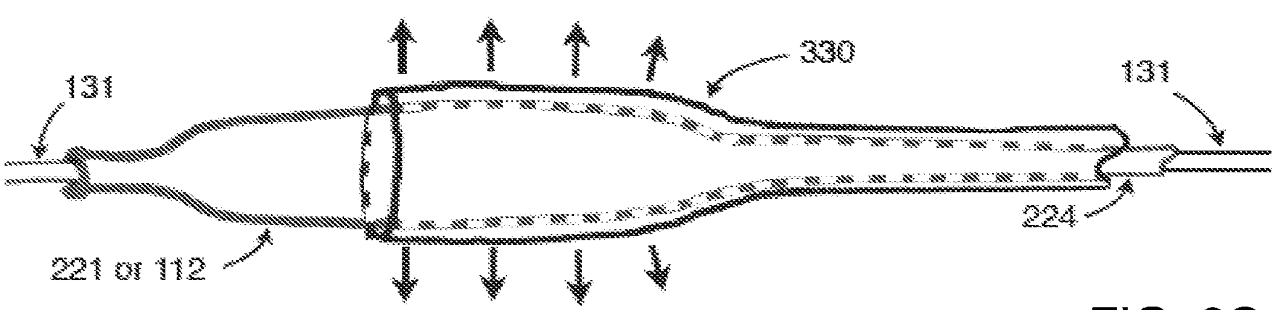
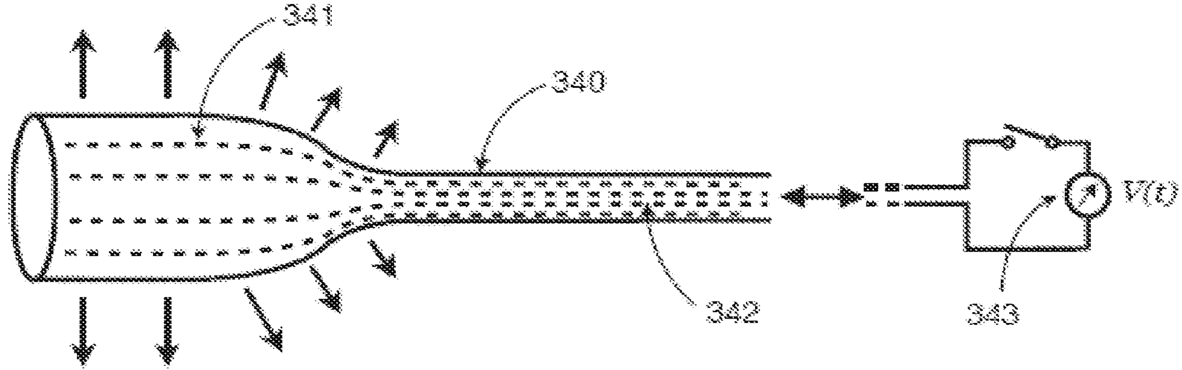


FIG. 6C

FIG. 6D



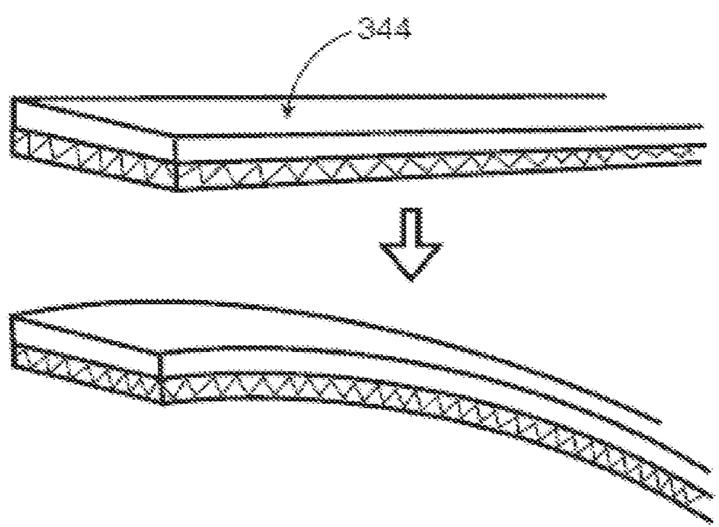


FIG. 6E

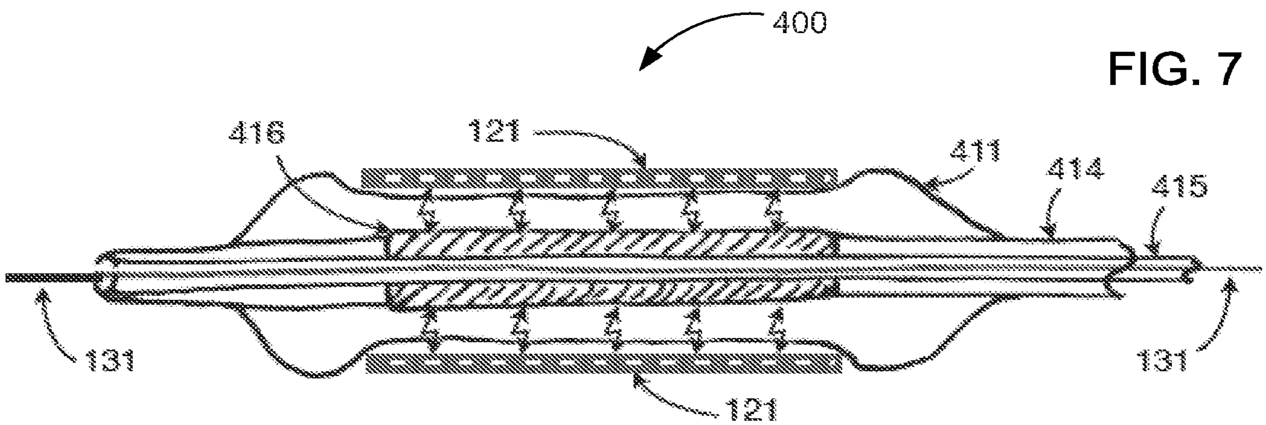


FIG. 7

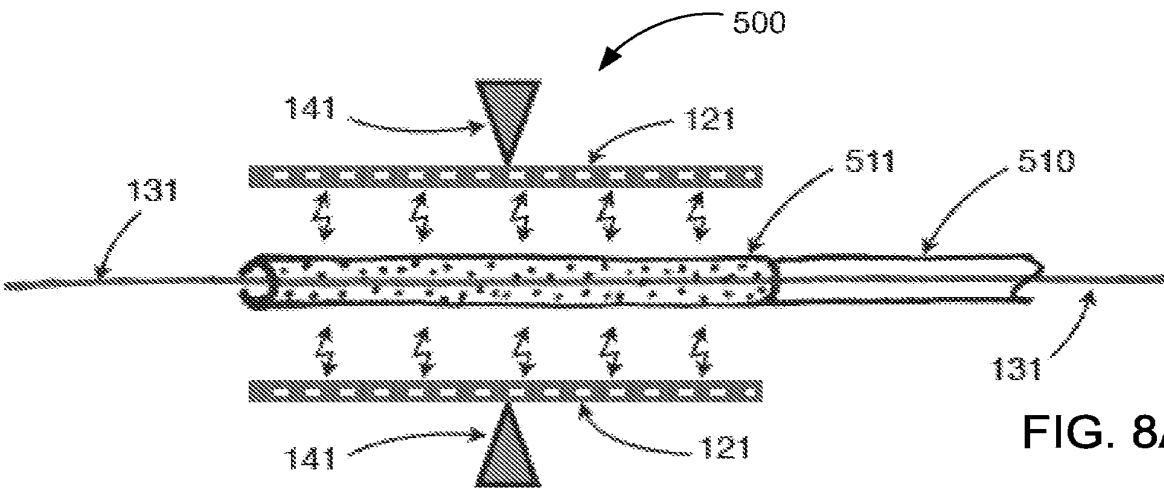


FIG. 8A

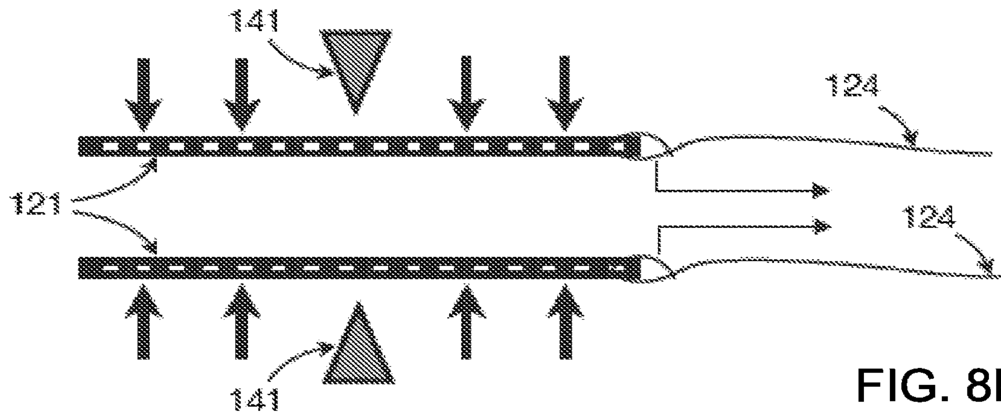


FIG. 8B

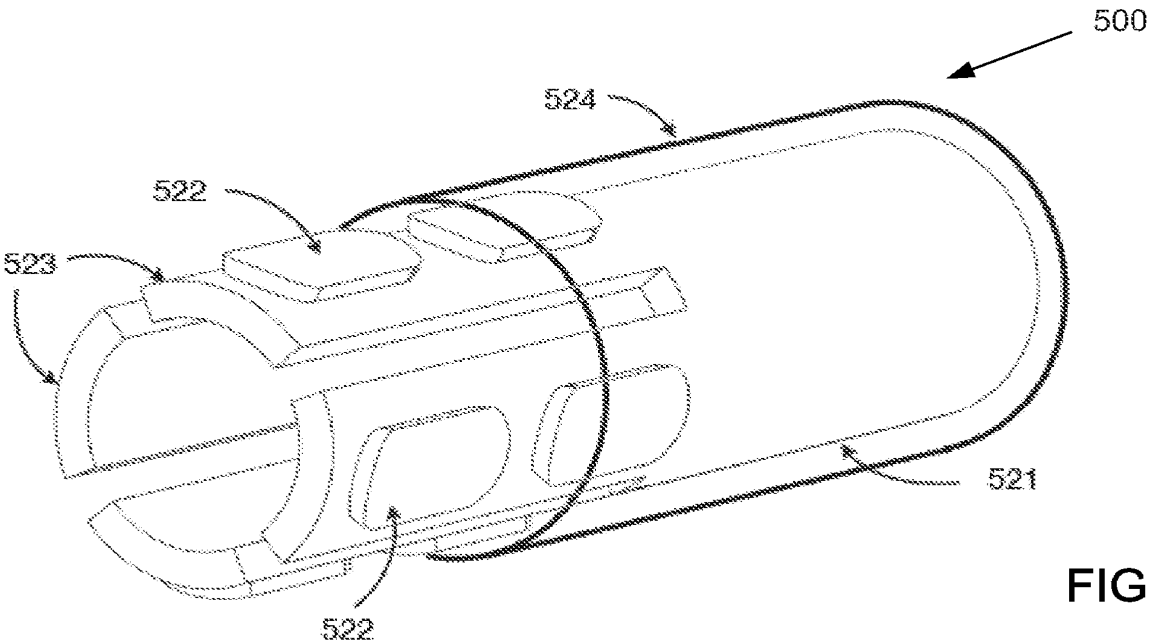

500
524
522
523
521
522

FIG. 8C

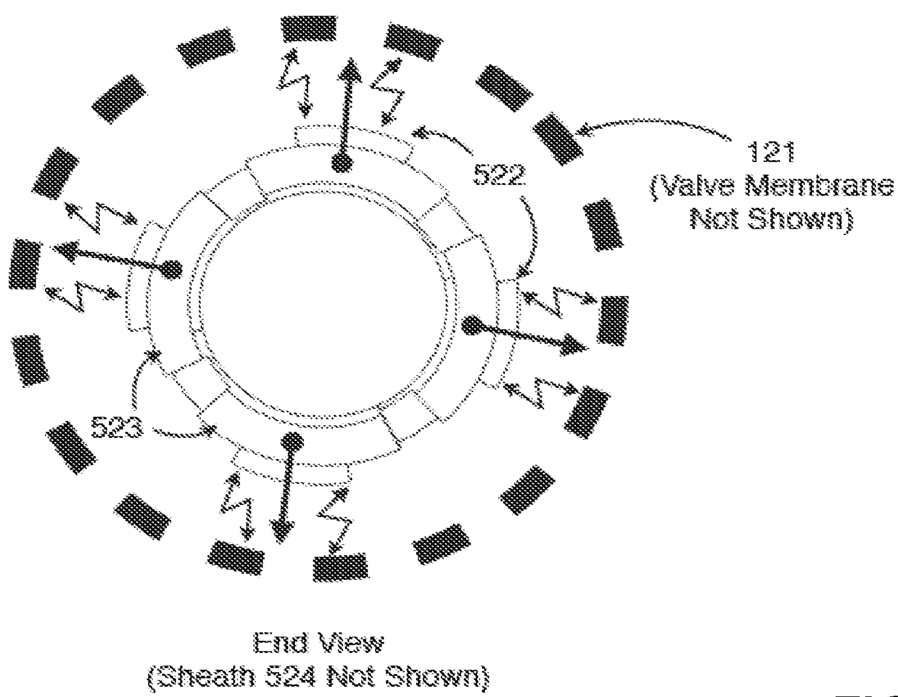

522
121
(Valve Membrane
Not Shown)
523
End View
(Sheath 524 Not Shown)

FIG. 8D

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A61L 27/28 (2006.01) *A61M 25/01* (2006.01)

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(54) Title: PERCUTANEOUSLY DELIVERABLE HEART OR BLOOD VESSEL VALVE WITH FRAME HAVING ABLUMINALLY SITUATED TISSUE MEMBRANE

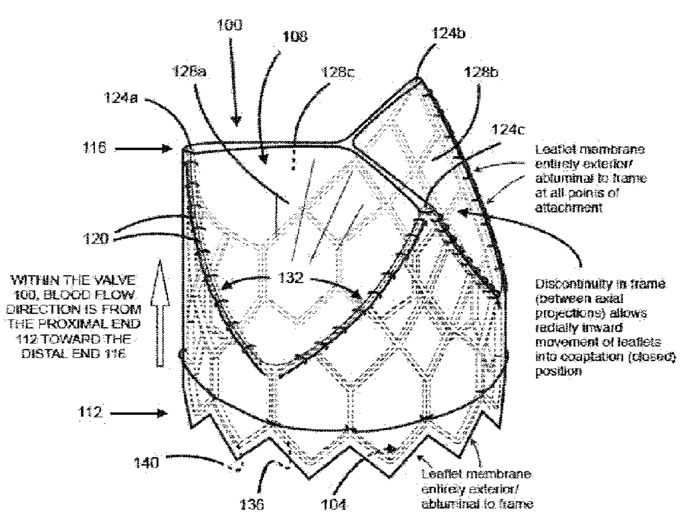

Figure 1A

(57) Abstract: A prosthetic valve implantable by catheter without surgery includes a frame with an abluminal surface extending between a proximal end of the frame and a distal end of the frame, and a single layer of a biocompatible membrane material mounted to the abluminal surface of the frame. The single layer of biocompatible membrane is located such that an interior surface of the membrane sheet extends between the proximal end of the frame and the distal end of the frame, and resides radially exterior the abluminal surface of the frame. In at least one embodiment, the disposition of membrane sheet at all points of attachment is entirely exterior/ab luminal to the frame, such that no part of the abluminal surface of the membrane sheet contacts the frame.

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PERCUTANEOUSLY DELIVERABLE HEART OR BLOOD VESSEL VALVE WITH FRAME HAVING ABLUMINALLY SITUATED TISSUE MEMBRANE

FIELD

The present invention relates to the field of medical devices, and more particularly, to a percutaneously deliverable heart valve and to a percutaneously deliverable blood vessel valve.

BACKGROUND

Heart valve disease is a common degenerative condition that compromises physiologic function and causes limiting symptoms and threat to life in millions of patients all over the world. There are various underlying causes, but malfunction of heart valves is ultimately expressed as insufficient conduction of blood through the plane of the valve due to narrowing of the anatomic pathway (stenosis), or as incompetent closure that allows blood to return back through the valve again, thereby reducing the effective forward conduction of blood through the valve (insufficiency or regurgitation). These hemodynamic states lead to 1) deficiency of cardiac output and 2) adverse loads on the pumping chambers of the heart, both of which in turn lead to functional compromise of the patient and often premature death unless effectively corrected.

Definitive corrective treatment of heart valve disease is conventionally performed by open-chest surgical techniques, wherein the valve is manipulated, repaired, or replaced with a prosthetic valve under direct vision. Heart valve surgery is performed in hundreds of thousands of cases yearly world-wide, but carries a high burden of cost, morbidity, and mortality, especially in susceptible patients who may be elderly or otherwise physiologically compromised by collateral disease. Further, the costs and resource requirements of the surgical enterprise restrict the availability of heart valve replacement to many more patients all over the world.

In pursuit of alternatives to heart valve surgery, over the last ten years a number of development programs have brought percutaneous, trans-catheter implantation of prosthetic heart valves into commercial use in the European Union (EU) and into pivotal clinical trials in the United States of America. Initial clinical experience in the EU was directed toward patients who had critical aortic valve stenosis, but were deemed to be at unacceptably high risk for open-heart surgical valve replacement. In several thousand such cases, utilizing both balloon-expandable and self-expanding designs in two separate programs, percutaneous heart valve replacement (PHVR) was shown to be feasible and possibly competitive with surgery in selected patients with 12-18 month mortality rates of about 25%. Grube E., et al., *Progress and Current Status of Percutaneous Aortic Valve Replacement: Results of Three Device Generations of the CoreValve Revalving System*, Circ. Cardiovasc Intervent. 2008;1:167-175.

Typically, the current percutaneous heart valve (PHV) designs, including the commercialized Medtronic CoreValve and the Edwards Lifesciences Sapien valves, comprise a biological membrane forming the operating leaflets of the valve, mounted within the interior of a metal frame, that is then collapsed onto a delivery catheter or balloon, and then constrained within an outer sheath. After an initial dilation of the diseased valve with a large balloon, this assembly is then advanced to the plane of the valve and deployed by self-expansion or by balloon expansion.

PHV designs are confronted by several central challenges. More particularly, the functioning valve leaflets are typically constructed of flexible and compressible tissue membrane valve members attached by sutures to a surrounding stent frame that together must be durable, yet of sufficiently low mass to allow for passage in collapsed form into the patient's body through an anatomic pathway—a peripheral artery, for example—of limited diameter, leading to the implantation site within the central circulation system. This condition favors simple, yet robust design geometries.

Secondly, the PHV in its implanted operating configuration must emulate both the opening mechanics and the closing mechanics of the native heart valve—two differing geometries and mechanical forms afforded by the native anatomy of the aortic valve, for example, but with the limitation that the PHV must effectively embody both within its physical and operational envelope without the benefit of the grossly different anatomical forms native to the aortic valve.

As a practical matter, the measures of effective function are simple—the pressure gradient during forward passage of blood across the valve must be as low as possible, typically 5 - 10 mmHg or less. While achieving this, the “success” of operation in the closed configuration, wherein the leaflets are pressed together along lines of apposition by the pressure of the blood pumped beyond the valve, would also appear to be simply measured by the amount of retrograde blood passage back into the pumping chamber—the “regurgitation” or “leakage.”

However, since this closed phase of valve function is the phase in which the principal force loads are applied to the valve membrane leaflets, and since the manner in which the design of the valve distributes these forces determines the durability of the valve, the real measure of the valve's closing function is best understood by how well the design minimizes and distributes the force loads on the valve leaflets. To date, this problem has not been sufficiently addressed.

In the field of blood vessel diseases certain conditions may be advantageously treated by insertion of valves into an affected patient’s blood vessels. Currently no such valve devices are available, though investigation of this approach has suggested potential clinical utility for blood vessel valves, and in particular for valves to be inserted into the vein system for particular conditions. In the first example, insufficiency of the inlet (atrioventricular) tricuspid valve to the right ventricle of the heart results in regurgitation of blood back into the right atrium, which, serving to receive blood flow returning in the veins from the entire body, then results in turn in suffusion and swelling (edema) of all the organs, most notably in the abdomen and extremities, insufficient forward conduction of blood flow from the right ventricle into the lungs causing compromise of pulmonary function, and ultimately pump failure of the right heart. Collectively these conditions are termed right heart failure, a condition that leads to incapacity and possibly to death if progressive and uncorrected. Often, the remedy is surgical repair or replacement of the tricuspid valve, but results are uncertain, damage to the right ventricle being often irreversible, and progressive heart failure may supervene despite technically successful valve surgery.

In a yet a further example, insufficiency of vein function due to the incompetence or destruction of intrinsic valves within the vein system leads to acute then chronic swelling of the veins and their dependent lymphatics and tissues. This condition can affect the deep veins of the body, commonly the lower extremities or pelvis, or the superficial veins of the lower extremities in particular, leading to progressive expansion of the veins and further valvular incompetence, a condition known as varicose veins. Millions of people worldwide suffer from these conditions and enormous funds are expended on procedures to destroy or remove these dilated incompetent veins. It has long been hoped that some form of implantable valve for the vein system could alleviate these conditions.

Several references of interest have been reviewed in preparation of the present disclosure. The applicants do not admit that the any one or more of the following references constitute citable prior art.

U.S. Patent No. 7,758,632 to Hojeibane discloses a valve construct wherein all embodiments include stent portions that act as proximal and distal anchors that are interconnected by connecting members, and further include a "cantilever valve strut" that acts as a biasing arm to "facilitate the opening and closing of the membrane assembly." Such structures may disrupt the flow channel and potentially interfere with membrane integrity when crimping the valve to mount it on an expandable balloon. In addition, at the point of engagement of the tissue against the connecting members, there is relatively intense focal stress along the straight connecting member – especially at the free edge of the leaflet. Hojeibane further utilizes flaps 403 and cusps 404 that may be independent components attached to the tubular membrane to form the membrane assembly 102. Accordingly, Hojeibane does not appear to use a flat sheet of membrane.

U.S. Patent No. 7,025,780 to Gabbay discloses two separate uses of a device referred to as a "stent." The first use is that of the stent in a surgical valve wherein it is a supportive structure to give shape and mechanical support to the tissue leaflets formed upon it. This device in Gabbay is like a surgical tissue valve. As shown in Figs. 5 and 6 of Gabbay, the stent is disposed outside of at least an inner tissue leaflet layer. In the second use, as shown in Figs. 1 and 2 of Gabbay, a tissue valve of some type is disposed within an outer frame of the vascular stent type. In this case, the tissue layer is not disposed upon the abluminal surface of the outer stent frame. The reader is directed to column 1, lines 61-63 of Gabbay that state "The prosthesis includes a valve apparatus located within a stent apparatus to form a stented valve." Gabbay further references only a "valve apparatus comprising an animal pulmonic heart valve." Accordingly, Gabbay fails to disclose a valve formed of flat tissue membrane wherein the tissue membrane is attached to the abluminal surface of a frame.

U.S. Patent Application Publication No. 2006/0190074 to Hill is directed to venous valves, and as such, the structural embodiments shown in Hill do not appear robust enough for application as prosthetic heart valves, such as in the aortic valve position. The valve material is referred to as a "cover" comprising a matrix and "integrated flexible support members 124" — essentially a reinforcing layer applied to the matrix. While tissue sources of "extracellular membrane" are cited as possible sources for the matrix, the use of a single layer tissue membrane for the leaflets is not disclosed in Hill.

With further reference to U.S. Patent Application Publication No. 2006/0190074, Hill also does not describe how the cover material is attached to the frame to achieve a sufficiently robust construct for utilization as a prosthetic heart valve. That is, while Hill generally discusses attachment of the cover to the frame at Paragraph [0072] using a variety of possible fasteners, none are shown and described relative to the frame. Of particular relevance is that while Hill mentions coupling the cover 108 to the frame 102 at connection regions 132 and 134, there is no mention of coupling the cover 108 to the arcuate portions of the frame members 126 that lead to the connection regions 132 and 134.

Accordingly, there is a need to address the shortcomings discussed above.

SUMMARY

It is to be understood that the present invention includes a variety of different versions or embodiments, and this Summary is not meant to be limiting or all-inclusive. This Summary provides some general descriptions of some of the embodiments, but may also include some more specific descriptions of other embodiments.

As noted above, the real measure of the valve's closing function is best understood by how well the design minimizes and distributes the force loads on the valve leaflets. This condition favors design geometries in which closing apposition of the leaflet surfaces is achieved with a minimum of traction force on the valve attachment points to the frame. To this end the inventive valve achieves this and other operational advantages by situating the operating tissue membrane to the exterior/abluminal surface of the valve frame rather than the interior/luminal space of the frame and by distributing the operating force loads of the valve along the curved edges forming the distal (downstream to flow direction) end of the frame. No other known percutaneously implantable or even surgical valve bioprosthesis utilizes this configuration with the tissue membrane mounted entirely upon the abluminal aspect of the device frame which carries the closed valve force loads along the distal formed edge of the frame corresponding to the lines of attachment of the leaflet membrane.

Accordingly, in at least one embodiment, an implantable prosthetic valve is provided that includes a frame and tissue membrane. Advantageously, the tissue membrane resides to the exterior of the frame along an axial length of the frame in the flow direction of the implantable prosthetic valve when implanted. That is, the membrane sheet resides entirely exterior or abluminal to the frame when the valve is in the fully open condition and at least at all attachment points when the valve is partly or completely closed. The attachment points may comprise a plurality of sutures that are used to attach the membrane sheet to the frame at a variety of locations, such as at one or more intersections of the frame.

The descriptions of the inventive valve are focused for the purpose of technical specification upon the replacement heart valve application, but will apply as well to the blood vessel valve device. By way of example, in addition to use of the valves described herein to replace heart valves, methods and devices described herein also provide for transcatheter implantation of a valve into the inferior vena cava (the principal conduit vein from the lower body inserting into the right heart) to act as an upstream substitute in part for the tricuspid valve. Such a valve device would be advantageously designed to be low in mass with large effective orifice. The inventive valve device is proposed as suitable to this purpose. Alternatively, the condition of right heart failure may be treated in part by interposing valves into the vein system farther upstream in the venous return flow, such as in the subclavian or principal iliac veins.

Accordingly, in at least one embodiment, an implantable prosthetic valve is provided for controlling, at least in part, a flow of blood, comprising:

a frame having an abluminal frame surface, a proximal end, and a distal end, wherein the proximal end is situated at an inlet end of the frame relative to the flow of blood when implanted, and wherein the distal end is situated at an outlet end of the frame relative to the flow of blood when implanted, the frame having a tubular flow path through its interior; and a tissue membrane attached to the frame, the tissue membrane having an interior surface and an exterior surface;

wherein the interior surface of the tissue membrane is situated exterior the abluminal frame surface of the frame between the proximal end and distal end of the frame, when the valve is in the fully open position, the interior surface of the tissue membrane intersecting the tubular flow path of the frame when the tissue membrane is located in a closed position.

A percutaneous, trans-catheter prosthetic valve for implantation in a patient is provided, comprising:

a frame including an abluminal surface extending between a proximal end of the frame and a distal end of the frame, wherein the frame is collapsible and expandable and adapted for trans-catheter delivery; and

a biocompatible tissue material mounted to the abluminal surface of the frame to form a plurality of valve leaflets, wherein an entire interior surface of the biocompatible tissue material between the proximal end of the frame and the distal end of the frame resides radially exterior to the abluminal surface of the frame:

(a) at all points of attachment; and

(b) when the plurality of valve leaflets are in an operationally fully open position.

In at least one embodiment the frame comprises a metal alloy substantially configured as tubular stent member. In at least one embodiment a proximal portion of the frame includes a ring. In at least one embodiment a proximal portion of the frame comprises a circumferential zig-zag of wire. In at least one embodiment a proximal portion of the frame includes a lattice. In at least one embodiment the lattice is circumferentially continuous. In at least one embodiment the lattice is circumferentially discontinuous. In at least one embodiment a distal end of the frame includes two or more areas of axial continuity with the proximal end, wherein the two or more areas of axial continuity comprise axially oriented projections. In at least one embodiment the frame further comprises a distally positioned stabilization framework comprising at least one of circumferential or radial continuity with the axially oriented projections. In at least one embodiment the frame includes two or more regions of circumferential discontinuity through which operating leaflets of the biocompatible tissue material move radially inward and outward in closing and opening operation, respectively. In at least one embodiment the biocompatible tissue material between the proximal end of the frame and the distal end of the frame resides substantially adjacent the abluminal surface of the frame. In at least one embodiment the biocompatible tissue material does not contact a luminal surface of the frame. In at least one embodiment an exterior surface of the biocompatible tissue material does not contact a luminal surface of the frame.

In accordance with at least one embodiment, the frame can be a closed cell lattice type construct of circumferentially corrugated/sinusoidal/zig-zag rings. In accordance with at least one embodiment, the frame can be a wire loop with axial loops forming a support for each commissure. In at least one embodiment, the frame includes a proximal portion, wherein at least some of the abluminal surface of the proximal portion includes a tissue sheet attached thereto.

In at least one embodiment, a prosthetic valve for implantation in a patient is provided, comprising:

a frame including an abluminal surface extending between a proximal edge of the frame and a distal edge of the frame, the distal edge undulating axially to define at least two areas of circumferential discontinuity in the frame, wherein the frame is collapsible and expandable and adapted for trans-catheter delivery; and

a single layer of a biocompatible membrane material mounted to the abluminal surface of the frame to form leaflet portions, wherein the leaflet portions are collocated with the at least two areas of circumferential discontinuity in the frame.

In at least one embodiment the leaflet portions are attached to the frame at least along curved frame members formed by the distal edge of the frame and corresponding to the radially outward boundaries of the leaflet cusps.

In at least one embodiment, no portion of the biocompatible membrane material is mounted to an interior surface of the frame. In at least one embodiment, the frame comprises a metal alloy substantially configured as tubular stent member. In at least one embodiment, a proximal portion of the frame includes a lattice to which the biocompatible membrane material is circumferentially mounted entirely upon the abluminal aspect of the tubular stent member. In at least one embodiment, at least some proximal portion of the frame does not include biocompatible membrane material mounted to its luminal or abluminal surfaces. In at least one embodiment, the biocompatible membrane material extends between the proximal edge and the distal edge of the frame. In at least one embodiment, a distal portion of the frame further includes a distally extending stabilizing framework comprising a plurality of axially oriented support members that each extend from a distally extending frame projection situated adjacent the at least two areas of circumferential discontinuity in the frame. In at least one embodiment, the prosthetic valve further comprises a plurality of radial support members interconnecting the axially oriented support members. In at least one embodiment, the prosthetic valve further comprises a wire guide, wherein the wire guide is coaxially aligned with an axis of the valve, and wherein the wire guide is configured to allow for a coaxial passage of a guide wire such that coaxial alignment of the distally extending stabilizing framework may be facilitated during valve deployment. In at least one embodiment, the wire guide comprises at least one of a ring and a tube.

A method of preparing a percutaneous, trans-catheter prosthetic valve is also provided, the method comprising mounting a single layer of a biocompatible tissue material to an abluminal surface of a trans-catheter deliverable frame such that an interior surface of the biocompatible tissue material between a proximal end of the trans-catheter deliverable frame and a distal end of the trans-catheter deliverable frame resides radially exterior to and substantially adjacent the abluminal surface of the trans-catheter deliverable frame. In at least one embodiment the method further comprises compressing and crimping the trans-catheter deliverable frame, with the biocompatible tissue material mounted thereto, upon a delivery catheter. In at least one embodiment the method further comprises implanting the trans-catheter deliverable frame with the biocompatible tissue material mounted thereto into a patient. In at least one embodiment the trans-catheter deliverable frame comprises a stent. In at least one embodiment the method further comprises mounting the trans-catheter deliverable frame and the biocompatible tissue material mounted thereto on a mandrel.

In accordance with at least one embodiment, a method of constructing a prosthetic valve is provided, the method, comprising attaching a biocompatible membrane material to a collapsible and expandable frame to form a trans-catheter deliverable prosthetic valve, wherein an entire interior surface of the biocompatible membrane material is located exterior of the abluminal surface of the collapsible and expandable frame when leaflet portions of the biocompatible membrane material are in the valve's operationally open position. In at least one embodiment, the method further comprises associating the biocompatible prosthetic valve with a catheter.

In at least one embodiment, a prosthetic trans-catheter deliverable valve is provided that does not include one or more biasing members within the inner flow channel of the valve. That is, with the exception of the membrane during closure of the valve (when the flow cycle is not antegrade from proximal to distal through the valve), the inner flow channel is devoid of flow channel obstructions.

In at least one embodiment, a prosthetic trans-catheter valve includes a flat membrane sheet interconnected to a frame. In at least one embodiment, a flat membrane sheet is interconnected to the abluminal surface of a frame using a plurality of sutures, wherein at least some of the sutures are applied in a buttonhole suture pattern.

Various components are referred to herein as "operably associated." As used herein, "operably associated" refers to components that are linked together in operable fashion, and encompasses embodiments in which components are linked directly, as well as embodiments in which additional components are placed between the two linked components.

As used herein, "at least one," "one or more," and "and/or" are open-ended expressions that are both conjunctive and disjunctive in operation. For example, each of the expressions "at least one of A, B and C," "at least one of A, B, or C," "one or more of A, B, and C," "one or more of A, B, or C" and "A, B, and/or C" means A alone, B alone, C alone, A and B together, A and C together, B and C together, or A, B and C together.

As used herein, "sometime" means at some indefinite or indeterminate point of time. So for example, as used herein, "sometime after" means following, whether immediately following or at some indefinite or indeterminate point of time following the prior act.

Various embodiments of the present inventions are set forth in the attached figures and in the Detailed Description as provided herein and as embodied by the claims. It should be understood, however, that this Summary does not contain all of the aspects and embodiments of the one or more present inventions, is not meant to be limiting or restrictive in any manner, and that the invention(s) as disclosed herein is/are understood by those of ordinary skill in the art to encompass obvious improvements and modifications thereto.

Additional advantages of the present invention will become readily apparent from the following discussion, particularly when taken together with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

To further clarify the above and other advantages of various embodiments and features of the one or more present inventions, a more particular description of the one or more present inventions is rendered by reference to specific embodiments thereof which are illustrated in the appended drawings. It should be appreciated that these drawings depict only typical embodiments of the one or more present inventions and are therefore not to be considered limiting in scope. The one or more present inventions are described and explained with additional specificity and detail through the use of the accompanying drawings in which:

Fig. 1A is a side perspective view of an embodiment of a percutaneously deliverable valve with the valve membrane illustrated in a closed position;

Fig. 1B is a side elevation view of the frame suited to balloon expansion shown in Fig. 1A;

Fig. 1C is a top plan view of the frame shown in Fig. 1B;

Fig. 1D is a side perspective view of the frame shown in Fig. 1B;

Fig. 1E is a bottom perspective view of the frame shown in Fig. 1B;

Fig. 1F is a side elevation view of the frame shown in Fig. 1B, wherein the cylindrical frame is depicted in an "unrolled" or flat projection to illustrate the geometry of the frame members;

Fig. 1G is a side elevation view of another embodiment of a frame suited to self-expansion, wherein the cylindrical frame is depicted in an "unrolled" or flat projection to illustrate the geometry of the frame members;

Fig. 1H is a side elevation view of the frame shown in Fig. 1G;

Fig. 1I is a top plan view of the frame shown in Fig. 1H;

Fig. 1J is a side perspective view of the frame shown in Fig. 1H;

Fig. 1K is a bottom perspective view of the frame shown in Fig. 1H;

Fig. 1L is a side perspective view of an embodiment of a membrane sheet and its attachment to a frame in accordance with at least one embodiment described herein;

Fig. 2 is a simplified distal end view of an embodiment of a frame illustrating relative locations of the distal ends of two distally positioned frame projections located approximately 180 degrees apart;

Fig. 3 is a simplified distal end view of an embodiment of a frame illustrating relative locations of the distal ends of four distally positioned frame projections located approximately 90 degrees apart;

Fig. 4 is a perspective view of an embodiment of a schematic of a frame having optional stabilization framework with circumferential supports;

Fig. 5 is a perspective view of an embodiment of a schematic of a frame having optional stabilization framework with radial supports;

Fig. 6 is a flow chart of a method of constructing an embodiment of a prosthetic heart valve as described herein;

Fig. 7 is flow chart of a method of deploying an embodiment of a prosthetic heart valve as described herein; and

Fig. 8 is a schematic of a heart showing an embodiment of a heart valve as described herein implanted within a heart.

The drawings are not necessarily to scale.

DETAILED DESCRIPTION

Embodiments of the one or more inventions described herein include one or more devices, assemblies and/or methods related to prosthetic heart valves and to prosthetic blood vessel valves. A prosthetic heart valve in accordance with at least one embodiment described herein can be surgically implanted, such as by percutaneous, trans-catheter delivery, to the implantation site within the patient. One or more embodiments of the prosthetic heart valves described herein have application for at least aortic and pulmonary valve positions, including for structural defects and diseased valves. Other embodiments have application to the vascular system and in particular to the vein system. When reduced in scale they have particular application to the branch veins of the body and the extremities. The descriptions for these devices are effectively provided in the descriptions and specifications provided for the inventive percutaneously implantable heart valve device.

In at least one embodiment, biocompatible material is mounted to a frame to form an implantable prosthetic heart valve, and then at a later time, the implantable prosthetic heart valve is implanted within a patient, such as by way of a percutaneous, trans-catheter delivery mechanism. The percutaneously implantable heart valve is suitable for implantation into a native (orthotopic or ectopic) valve seat of a patient. Once implanted, the prosthetic heart valve serves to regulate the flow of blood associated with the patient's heart by allowing forward blood flow and substantially preventing backflow or valvular regurgitation.

Referring now to Fig. 1A, and in accordance with at least one embodiment, an implantable prosthetic heart valve 100 is shown that includes a frame 104 and a single layer membrane sheet 108, such as a biocompatible tissue membrane sheet. All or substantially all of the membrane sheet 108 is located on the exterior or abluminal side of the frame 104 between the proximal end 112 and the distal end 116 of the frame 104 when the valve leaflets are in the operationally fully open position and in any case at all points of attachment. The implantable prosthetic heart valve 100 includes a proximal (upstream) portion/margin of membrane sheet 108 that is circumferentially attached to and residing entirely upon the abluminal surface of the frame 104. In at least one embodiment, the membrane sheet 108 is connected to the frame 104 by a plurality of sutures 120. In at least one embodiment, the plurality of sutures comprise curved lines of attachment, axially concave to the distal end 116 of the frame, along the frame members at the frame's distal edge interconnecting the distally extending frame projections 124a-c. It is to be understood that alternate ways of attaching the membrane sheet 108 to the frame 104 may be used, such as staples, an adhesive, an anchoring ring, one or more bands, clips or combinations of the foregoing.

By whatever technique of attachment, the lines of attachment by which the arcuate proximal basal margin of each leaflet is anchored to the arcuate distal edge of the frame act to distribute the force loads acting on the leaflets along these lines while in the operationally closed position. The securement of the leaflets in this manner is advantageous in a high-pressure application such as the aortic valve position. Moreover, these lines of attachment also act to seal the proximal basal margin of each cusp to the frame and are critical in the case of aortic valve implantation, because some portion of these arcuate cusp margins are likely to be disposed "above" (downstream) of the aortic valve annulus and without anatomic luminal contact to the outer aspect of the valve at this level. As such, those portions that are disposed in the "suprannular" position after implantation can be subject to high pressure blood being injected between the leaflet layer and the frame which can in turn lead to acute and chronic compromise of valve function. The specific form of leaflet attachment provided in the inventive valve addresses this problem that arises as a consequence of the abluminal/exterior position of the leaflet membrane in relation to the frame.

In at least one embodiment, the plurality of sutures 120 attaching the leaflet membrane to the distal arcuate portions of the distal edge of the frame comprise, for each arcuate segment 144, a continuous series of "buttonhole"-technique sutures 120 wherein the segments of suture interconnecting the knots are disposed to the outer/abluminal surface of the membrane. This suture configuration advantageously imposes a small biasing effect upon the leaflet towards the operationally closed position.

With regard to particular material types that may be used to form the membrane sheet, in at least one embodiment the membrane sheet 108 forming the cusp or leaflet portions includes a one-piece, single layer sheet of biocompatible membrane, such as fixed mammalian pericardium tissue or synthetic biocompatible material such as ePTFE. In at least one embodiment, the membrane sheet is made from a tissue preparation process that yields a leaflet material of suitable strength and durability for use in a prosthetic trans-catheter deliverable heart valve. The content of WO 2011/109450A2 published on September 9, 2011, is incorporated herein by reference. Although not preferred, one or more embodiments may alternatively comprise a plurality of sections of membrane sheet connected to form a contiguous sheet.

In at least one embodiment, the membrane sheet is a single layer of a substantially homogenous material. In at least one embodiment, the membrane sheet is an unlaminated single layer of material. In at least one embodiment, the membrane sheet is a single layer of material that does not include any reinforcement, such as reinforcing fibers. In at least one embodiment, the membrane sheet is a single layer of treated pericardium tissue. In at least one embodiment, the membrane sheet is a single layer of a synthetic film.

The frame 104 may include a balloon expandable material. Alternatively, the frame 104 may include one or more of a self expanding alloy such as nitinol, stainless steel, cobalt chromium, bioabsorbable metal, and non-elastic bioabsorbable plastic, such as polylactides, polyglycolides, their co-polymers, or polydioxanones. As further seen in Figs. 1A-1F, in at least one embodiment the geometry of the frame 104 at the distal end 116 may include three distally extending frame projections 124a, 124b and 124c. This configuration is described for exemplary purposes. Accordingly, alternate configurations may be used, including collapsible and expandable percutaneously deliverable frames that include two, four, five or any multiple number of distally extending frame projections, provided the configuration in combination with the abluminally situated single layer membrane sheet 108 accommodates inward closure of the membrane sheet 108 sufficiently to facilitate operational closure of the valve after being implanted. Thus, those skilled in the art will appreciate that configurations shown and described herein are for purposes of enablement, and therefore, alternate configurations from those shown are encompassed by the claims. Consistent with the foregoing, the distally extending frame projections 124a-c are spaced apart around the circumference of the frame 104 as appropriate to facilitate closure of the membrane sheet 108 when the flow cycle is not antegrade from proximal to distal through the valve.

Referring still to Figs. 1A-1F, in at least one embodiment, the frame 104 has three distally positioned inverted “v” members also referred to herein as distally extending frame projections 124a-c located at substantially equal angular distances apart from each other at the distal end 116 of the frame 104. Alternatively, each of these distally extending frame projections may take other forms such as a single projecting beam or an extending loop formed of a continuous loop of wire. Accordingly, in at least one embodiment, each inverted “v” member or distally extending frame projection 124a-c is about 120 degrees (at the point or apex of the inverted “v” members) away on either side from the other two inverted “v” members at the distal end 116 of the frame 104. In at least one embodiment, the inverted “v” members serve as attachment locations for the membrane sheet 108. In at least one embodiment, the “v” members are integral parts of a generally arcuate configuration of frame members spanning the distal frame edge between the distally extending frame projections 124a-c such that each arcuate span forms: 1) the radially outermost margin of a leaflet cusp; and 2) the line of attachment of each leaflet membrane to the distal edge of the frame. In at least one embodiment, the proximal end 112 of the frame 104 includes a continuous framework, although minor axially oriented recessions 136 in the framework are situated between the proximal-most portions 140 of the frame 104.

With further reference to Figs. 1B-1F, in at least one embodiment, the struts 126 forming the inverted “v” members are located between approximately 40 to 90 degrees apart, and more preferably, at between approximately 50 to 70 degrees apart. By way of example and not limitation, as shown in the example depicted in Fig. 1F, the struts 126 forming distally extending frame projection 124a are about 50 degrees apart. The angular values provided herein are given for purposes of enablement and for exemplary purposes, and are not intended to be limiting. Other values are possible, and such other values are within the scope of the one or more present inventions.

Referring again to Fig. 1A, cusp or leaflet portions 128a, 128b, and 128c reside between the spaced apart distally extending frame projections 124a-c. More particularly, circumferential discontinuities 132 in the frame 104 substantially correspond to the location of leaflet portions 128a-c in the membrane sheet 108. That is, since the membrane sheet 108 is situated exterior of the frame 104, including at the frame projections 124a-c, the absence of framework, internal struts or other types of support for a portion of the distally located membrane sheet 108 allows the abluminally positioned membrane sheet 108 to occupy an area within the flow path of the valve 100 when the flow cycle is not antegrade from proximal to distal through the valve. Therefore, when flow conditions are not antegrade, the leaflet portions 128a-c operate to close the valve 100 because of the absence of framework circumferentially between the distally extending frame projections 124a-c allows the leaflet portions 128a-c of the membrane sheet 108 to close radially inward.

Referring again to Fig. 1A, in the closed position, the leaflet portions 128a-c reside within the interior flow channel or lumen of the valve 100. Accordingly, the valve 100 includes a biocompatible membrane with a distal (downstream) portion/margin that is attached to the abluminal/exterior aspect of the frame 104 at at least two or more points (at or near the apices of the distally extending frame projections 124a-c) corresponding to two or more valve leaflet commissures, wherein the free edge of the membrane sheet 108 between the points of attachment constitutes the free edge of the valve leaflets or leaflet portions 128a-c that are free to move radially inward into a closed position contacting the other leaflet or leaflets, and radially outward into an open position.

In at least one embodiment, when the leaflets 128a-c are in their open position, the membrane sheet 108 at the distal end 116 resides entirely to the radial exterior of the frame 104 including at the distally extending frame projections 124a-c. Accordingly, when flow conditions are antegrade, the leaflets 128a-c extend radially outward from the lumen of valve 100.

In at least one embodiment, the membrane sheet 108, including the material constituting the operating leaflets portions 128a-c, is exterior/abluminal to the frame 104 and may be continuous from the leaflet portions 128a-c to the proximal end 112 of the frame 108. Alternatively, the membrane sheet 108 does not have to extend abluminally along the entire axial length of the frame 104 from the distal end 116 to the proximal end 112. More particularly, with limited proximal coverage, the membrane sheet 108 may only cover a portion of the abluminal surface of the frame 104 and reside at the distal end 116 and extend axially along the abluminal surface sufficiently to provide leaflet portions 128a-c such that there is enough membrane sheet 108 to cover the discontinuities in the frame 104 and thus function as leaflet portions 128a-c by moving radially inward and outward through the frame discontinuities

132. For such a configuration the membrane sheet 108 needs to extend proximally from the distal end 116 a sufficient proximal distance so as to provide a sufficient seal against leakage/regurgitation through the frame 104. Simply stated, the membrane sheet 108 needs to extend axially only a limited distance axially in the proximal direction, that being to slightly beyond the annular intersection or the valve seat formed between the abluminal surface of the membrane sheet 108 situated against the native tissue. Therefore, the proximal extent of the membrane tissue 108 beyond the intersection of the valve 100 against the native tissue may vary.

In at least one embodiment, the membrane sheet 108 may wrap around the proximal edge 136 of the frame 104 so as to make a continuous inner/luminal layer within the proximal end 112 of the frame 104. In contrast, leaving a portion of the proximal end 112 uncovered by the membrane sheet 108 permits the frame to provide additional structure. By way of example, the proximal end 112 can incorporate other structural elements including flared or hooked frame projections for effective securement of the implanted valve. Such configurations have applicability to providing advantageous structure for certain valve implantation sites, such as the mitral valve.

In at least one embodiment, the membrane sheet 108 may wrap around the proximal edge of the frame 104 so as to make a continuous inner/luminal layer within the proximal end 112 of the frame 104. That is, the valve 100 does not require the membrane sheet 108 to extend proximally to the proximal edge 136 of the frame 108, however, the membrane sheet 108 may extend proximally including to the proximal end 112, and indeed, the membrane sheet 108 may wrap around the proximal edge 136 to the luminal side of the frame 104.

With reference to Fig. 1F, a side elevation view of the cylindrical frame 104 is depicted in “unrolled” flat projection to illustrate the geometry of the frame members. The structural differences of the frame 104 at the proximal end 112 and distal end 116 are readily apparent, with the areas of circumferential discontinuities 132 observable between the distally extending frame projections 124a-c. Each circumferential discontinuity 132 includes a pair of generally arcuate side portions 144 that, in at least one embodiment, include a concave (in relation to the distal end of the frame) shape relative to the circumferential discontinuity 132. These arcuate spanning side portions 144 form: 1) lines of attachment of the leaflet membrane to the frame; and 2) the proximal/radially outermost margin of the leaflet cusp, along which are borne the forces exerted upon the closed leaflets. While the leaflets are attached to the arcuate side portions 144 as by suturing, the mobile leaflet portions and the cuff portion of the membrane are preferably continuous, formed of a single sheet of biocompatible membrane disposed around and upon the abluminal aspect of the frame. As noted above, to attach the single layer membrane sheet 108 to the arcuate side portions 144, sutures may be applied using a continuous series of “buttonhole”-technique sutures 120 wherein the segments of suture interconnecting the knots are disposed to the outer/abluminal surface of the membrane. This suture configuration advantageously imposes a small biasing effect upon the leaflet towards the operationally closed position.

Referring now to Figs. 1G-1K, an alternative embodiment comprising a frame 104′ suited to self-expansion is shown is shown. When comparing frame 104 to frame 104′, differences in the frame structure are apparent. However, both frames 104 and 104′ have circumferential discontinuities 132 that substantially correspond to the location of leaflet portions 128a-c in the membrane sheet 108. Again, since the membrane sheet 108 is situated exterior of the frame 104′, including at the frame projections 124a-c, the absence of framework, internal struts or other types of support for a portion of the distally located membrane sheet 108 allows the abluminally positioned membrane sheet 108 to occupy an area within the flow path of the valve 100 when the flow cycle is not antegrade from proximal to distal through the valve. Similar to frame 104, the location of the circumferential discontinuities 132 in frame 104′ allow the leaflet portions 128a-c operate to close the valve 100 because of the absence of framework circumferentially between the distally extending frame projections 124a-c in frame 104′ allows the leaflet portions 128a-c of the membrane sheet 108 to close radially inward. Also similar to frame 104, each circumferential discontinuity 132 includes a pair of generally arcuate side portions 144 that, in at least one embodiment, include a concave (in relation to the distal end of the frame) shape relative to the circumferential discontinuity 132. These arcuate spanning side portions 144 form: 1) lines of attachment of the leaflet membrane to the frame; and 2) the proximal/radially outermost margin of the leaflet cusp, along which are born the forces exerted upon the closed leaflets.

As noted above, although the embodiment shown in Fig. 1A illustrates a frame 104 including three distally extending frame projections 124a-c, an alternative number of distally extending frame projections may be used, thereby yielding an implantable prosthetic heart valve with fewer or greater than three cusps. By way of example, and with reference now to Fig. 2, for a frame having two distally extending frame projections 124 that are positioned at substantially diametrically opposite sides of the frame’s circumference, then two cusps would be provided. Similarly, and with reference now to Fig. 3, for a frame having four distally extending frame projections 124 that are positioned with substantially 90 degrees of separation from one another around the frame’s circumference, then four cusps would be provided.

Referring now to Fig. 1L, a frame 104 is shown relative to a single layer membrane sheet 108. The illustrated single layer membrane sheet 108 includes substantially straight edges.

However, in at least one embodiment, the distal free edge of each membrane leaflet portion has a non-linear shape. Preferentially when the leaflet free edge is not linear, it is cut in the shape of a parabola with central axis of curvature aligned to the center of the free edge of the leaflet. This effectively extends the coaptation margin and area of the leaflet free edge for a given leaflet radius, reduces the pressure on the contacting leaflet areas when the valve is closed and improves the effectiveness of orifice sealing in closure. Accordingly, free edge shapes for the leaflets are cut from the corresponding edge of the flat sheet membrane before wrapping and mounting of the membrane upon the frame.

Alternatively, in at least one embodiment, the circumference of the membrane exceeds the outer circumference of the frame. The membrane is then gathered in folds or pleats and attached at the proximal (inlet) end of the frame so as to reduce the effective circumference of the membrane at the proximal end of the frame to equal that of the frame at this level. While the proximal end of the encircling membrane sheet is then directly apposed to the abluminal aspect of the frame for secure attachment, the leaflet free edge of the membrane at the distal (outlet) end of the valve remains at the original larger circumference. This has the effect of increasing the length of each leaflet free edge and the area of each leaflet for a given radius of frame, and is useful to improve valve function, especially for large valve diameters. It will be understood that various curved and polygonal membrane shapes may be used to achieve various three dimensional leaflet shapes in a similar manner. Accordingly, in at least one embodiment, a prosthetic trans-catheter deliverable valve is provided that includes a membrane sheet formed into a tubular shape, wherein a circumference of the tubular shape is greater than a circumference of a radially adjacent portion of the frame. In at least one embodiment, a circumference of the tubular shape is between about 5 to 25% greater than a circumference of a radially adjacent portion of the frame. More preferably, a circumference of the tubular shape is between about 7 to 20% greater than a circumference of a radially adjacent portion of the frame. More preferably yet, a circumference of the tubular shape is between about 10 to 15% greater than a circumference of a radially adjacent portion of the frame. The difference in the circumference of the membrane sheet as compared to the radially adjacent portion of the frame provides leaflet portions that extend within the lumen along lines of apposition with improved sealing characteristics relative to a membrane sheet having a circumference that is substantially the same as the circumference of a radially adjacent portion of the frame.

Referring now to Fig. 4, and in accordance with a separate embodiment, the frame 104 may optionally include a distally extending stabilizing framework 400 that includes axially oriented support members 404 extending from the distally extending frame projections 124a-c. In at least one embodiment, a distally-positioned circumferential ring, or alternatively, a circumferentially segmented lattice 408 interconnects the axially oriented support members 404. The stabilization framework is located distally of the membrane sheet 108 that is attached to the frame 104.

Referring now to Fig. 5, and in accordance with yet a separate embodiment, an alternative to the stabilization framework of Fig. 4 is shown. More particularly, similar to the distally extending stabilizing framework 400, distally extending stabilizing framework 500 includes a plurality of axially oriented support members 404 that extend from the distally extending frame projections 124a-c; however, a plurality of radial support members 504 are used to interconnect the axially oriented support members 404, thereby providing additional stability to the distal end 116 of the frame 104. In addition, at the central point of intersection of the radial support members, a small ring or short tube coaxially aligned with the central axis of the valve and frame may be provided in order to allow for the coaxial passage of a guide wire such that coaxial alignment of the distal support framework may be facilitated during valve deployment.

With reference now to Fig. 6, and in accordance with at least one embodiment, a method 600 of constructing a prosthetic heart valve or a prosthetic vascular valve is provided. At 604, the method includes attaching a biocompatible membrane material to a frame to form a prosthetic heart valve, wherein an entire interior surface of the biocompatible membrane material is located exterior of the abluminal surface of the frame when leaflet portions of the biocompatible membrane material are in the operationally open position. As described above, a number of different ways of attaching the membrane sheet to the frame may be used, such as by suturing the membrane sheet to the exterior of the frame. At 608, the method includes associating the biocompatible prosthetic heart valve or prosthetic vascular valve with a catheter. The 604 step of associating may be preformed at a different location than the step 608 of attaching.

Referring now to Fig. 7, a flow chart illustrating the general procedure associated with implantation of the percutaneously deliverable heart valve 100 is provided. However, those skilled in the art will understand that with appropriate modification (e.g., changing the vascular entry location) the methodology also has application to a percutaneously deliverable blood vessel valve.

At 704, catheter access is gained to the patient's femoral artery and a guidewire is placed through the plane of the diseased valve that is targeted to receive the implant. Thereafter, the percutaneously deliverable heart valve 100 is removed from its packaging. If the valve was not mounted upon or otherwise associated with a delivery catheter at manufacture, then the valve is cleaned and rinsed and radially compressed upon the delivery catheter and constrained within a covering sheath coaxial to the delivery catheter. The prosthetic heart valve assembly, including its lumens, is preferably flushed and prepared in the usual fashion for standard balloons and catheters that do not contain a biocompatible tissue. At 708, the carrier catheter or balloon catheter is then coaxially mounted and advanced over the guidewire, such as under fluoroscopic vision initially to the level of the great vessel where it can be inspected under fluoroscopy. At 712, and after the nominal position and configuration is confirmed, the delivery system is advanced through the plane of the diseased valve under fluoroscopy, and the covering sheath is withdrawn, either at this point or during the advance prior to it, thus exposing the mounted implantable prosthetic heart valve 100 in place. At 716, in the case of a balloon expandable frame, the balloon is then inflated, deploying the percutaneously deliverable heart valve 100 in the plane of the valve. The deployed prosthetic heart valve 100 is shown in Fig. 8, wherein the percutaneously deliverable heart valve 100 serves to properly control the flow blood.

One or more of the embodiments of the percutaneously deliverable heart valve described herein may be implanted into the patient using a balloon-expandable frame or a self-expanding frame. Expandable frames are generally conveyed to the site of the target valve on balloon catheters. For insertion, the expandable frame is positioned in a compressed configuration along the delivery device, for example crimped onto the balloon of a balloon catheter that is part of the delivery device intended for coaxial mounting on a guidewire. After the expandable frame is positioned across the plane of the valve, the expandable frame is expanded by the delivery device. For a self-expanding frame, commonly a sheath is retracted, allowing expansion of the self-expanding frame.

In at least one embodiment, the frame comprises a metal alloy frame possessing a high strain design tolerance that is compressible to a relatively small diameter. By providing a device with a low profile, the implantable prosthetic heart valve allows standard retrograde arterial aortic delivery via femoral artery insertion, without surgical cutdown or general anesthesia.

The present invention may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

The one or more present inventions, in various embodiments, include components, methods, processes, systems and/or apparatus substantially as depicted and described herein, including various embodiments, subcombinations, and subsets thereof. Those of skill in the art will understand how to make and use the present invention after understanding the present disclosure.

The present invention, in various embodiments, includes providing devices and processes in the absence of items not depicted and/or described herein or in various embodiments hereof, including in the absence of such items as may have been used in previous devices or processes (e.g., for improving performance, achieving ease and/or reducing cost of implementation).

The foregoing discussion of the invention has been presented for purposes of illustration and description. The foregoing is not intended to limit the invention to the form or forms disclosed herein. In the foregoing Detailed Description for example, various features of the invention are grouped together in one or more embodiments for the purpose of streamlining the disclosure. This method of disclosure is not to be interpreted as reflecting an intention that the claimed invention requires more features than are expressly recited in each claim. Rather, as the following claims reflect, inventive aspects lie in less than all features of a single foregoing disclosed embodiment. Thus, the following claims are hereby incorporated into this Detailed Description, with each claim standing on its own as a separate preferred embodiment of the invention.

Moreover, though the description of the invention has included description of one or more embodiments and certain variations and modifications, other variations and modifications are within the scope of the invention (e.g., as may be within the skill and knowledge of those in the art, after understanding the present disclosure). It is intended to obtain rights which include alternative embodiments to the extent permitted, including alternate, interchangeable and/or equivalent structures, functions, ranges or acts to those claimed, whether or not such alternate, interchangeable and/or equivalent structures, functions, ranges or acts are disclosed herein, and without intending to publicly dedicate any patentable subject matter.

CLAIMS

What is claimed is:

1. A percutaneous, trans-catheter prosthetic valve for implantation in a patient, comprising:

a frame including an abluminal surface extending between a proximal end of the frame and a distal end of the frame, wherein the frame is collapsible and expandable and adapted for trans-catheter delivery; and

a biocompatible tissue material mounted to the abluminal surface of the frame to form a plurality of valve leaflets, wherein an entire interior surface of the biocompatible tissue material between the proximal end of the frame and the distal end of the frame resides radially exterior to the abluminal surface of the frame:

(a) at all points of attachment; and

(b) when the plurality of valve leaflets are in an operationally fully open position.

2. The percutaneous, trans-catheter prosthetic valve of Claim 1, wherein the frame comprises a metal alloy substantially configured as tubular stent member.

3. The percutaneous, trans-catheter prosthetic valve of Claim 2, wherein a proximal portion of the frame includes a ring.

4. The percutaneous, trans-catheter prosthetic valve of Claim 2, wherein a proximal portion of the frame comprises a circumferential zig-zag of wire.

5. The percutaneous, trans-catheter prosthetic valve of Claim 2, wherein a proximal portion of the frame includes a lattice.

6. The percutaneous, trans-catheter prosthetic valve of Claim 5, wherein the lattice is circumferentially continuous.

7. The percutaneous, trans-catheter prosthetic valve of Claim 5, wherein the lattice is circumferentially discontinuous.

8. The percutaneous, trans-catheter prosthetic valve of Claim 1, wherein a distal end of the frame includes two or more areas of axial continuity with the proximal end, and wherein the two or more areas of axial continuity comprise axially oriented projections.

9. The percutaneous, trans-catheter prosthetic valve of Claim 8, further comprising a distally positioned stabilization framework comprising at least one of circumferential or radial continuity with the axially oriented projections.

10. The percutaneous, trans-catheter prosthetic valve of Claim 8, wherein the frame includes two or more regions of circumferential discontinuity through which the plurality of valve leaflets of the biocompatible tissue material move radially inward and outward in closing and opening operation, respectively.

11. The percutaneous, trans-catheter prosthetic valve of Claim 1, wherein the biocompatible tissue material between the proximal end of the frame and the distal end of the frame resides substantially adjacent the abluminal surface of the frame.

12. The percutaneous, trans-catheter prosthetic valve of Claim 1, wherein the biocompatible tissue material does not contact a luminal surface of the frame.

13. The percutaneous, trans-catheter prosthetic valve of Claim 1, wherein an exterior surface of the biocompatible tissue material does not contact a luminal surface of the frame.

14. A prosthetic valve for implantation in a patient, comprising:

a frame including an abluminal surface extending between a proximal edge of the frame and a distal edge of the frame, the distal edge undulating axially to define at least two areas of circumferential discontinuity in the frame, wherein the frame is collapsible and expandable and adapted for trans-catheter delivery; and

a single layer of a biocompatible membrane material mounted to the abluminal surface of the frame to form leaflet portions, wherein the leaflet portions are collocated with the at least two areas of circumferential discontinuity in the frame.

15. The prosthetic valve of Claim 14, wherein no portion of the biocompatible membrane material is mounted to an interior surface of the frame.

16. The prosthetic valve of Claim 14, wherein the frame comprises a metal alloy substantially configured as tubular stent member.

17. The prosthetic valve of Claim 16, wherein a proximal portion of the frame includes a lattice to which the biocompatible membrane material is circumferentially mounted entirely upon the abluminal surface of the tubular stent member.

18. The prosthetic valve of Claim 17, wherein the lattice is circumferentially continuous.

19. The prosthetic valve of Claim 17, wherein the lattice is circumferentially discontinuous.

20. The prosthetic valve of Claim 14, wherein a proximal portion of the frame comprises a circumferential zig-zag of wire.

21. The prosthetic valve of Claim 14, wherein the biocompatible membrane material extends between the proximal edge and the distal edge of the frame.

22. The prosthetic valve of Claim 14, wherein at least some proximal portion of the frame does not include biocompatible membrane material mounted to its luminal or abluminal surfaces.

23. The prosthetic valve of Claim 14, wherein a distal portion of the frame further includes a distally extending stabilizing framework comprising a plurality of axially oriented

support members that each extend from a distally extending frame projection situated adjacent the at least two areas of circumferential discontinuity in the frame.

24. The prosthetic valve of Claim 23, further comprising a plurality of radial support members interconnecting the plurality of axially oriented support members.

25. The prosthetic valve of Claim 24, further comprising a wire guide, wherein the wire guide is coaxially aligned with an axis of the prosthetic valve, and wherein the wire guide is configured to allow for a coaxial passage of a guide wire such that coaxial alignment of the distally extending stabilizing framework may be facilitated during valve deployment.

26. The prosthetic valve of Claim 25, wherein the wire guide comprises at least one of a ring and a tube.

27. The prosthetic valve of Claim 14, wherein a circumference of the biocompatible membrane material is between about 5 to 25% greater than a circumference of a radially adjacent portion of the frame.

28. A method of preparing a percutaneous, trans-catheter prosthetic valve, comprising:

mounting a single layer of a biocompatible tissue material to an abluminal surface of a trans-catheter deliverable frame such that an interior surface of the biocompatible tissue material between a proximal end of the trans-catheter deliverable frame and a distal end of the trans-catheter deliverable frame resides radially exterior to and substantially adjacent the abluminal surface of the trans-catheter deliverable frame at all points of attachment and in entirety when a plurality of leaflets of the biocompatible tissue material are in a fully open position.

29. The method of preparing a percutaneous, trans-catheter prosthetic valve of Claim 28, further comprising compressing and crimping the trans-catheter deliverable frame, with the biocompatible tissue material mounted thereto, upon a delivery catheter.

30. The method of preparing a percutaneous, trans-catheter prosthetic valve of Claim 29, further comprising implanting the trans-catheter deliverable frame with the biocompatible tissue material mounted thereto into a patient.

31. The method of preparing a percutaneous, trans-catheter prosthetic valve of Claim 28, wherein the trans-catheter deliverable frame comprises a stent.

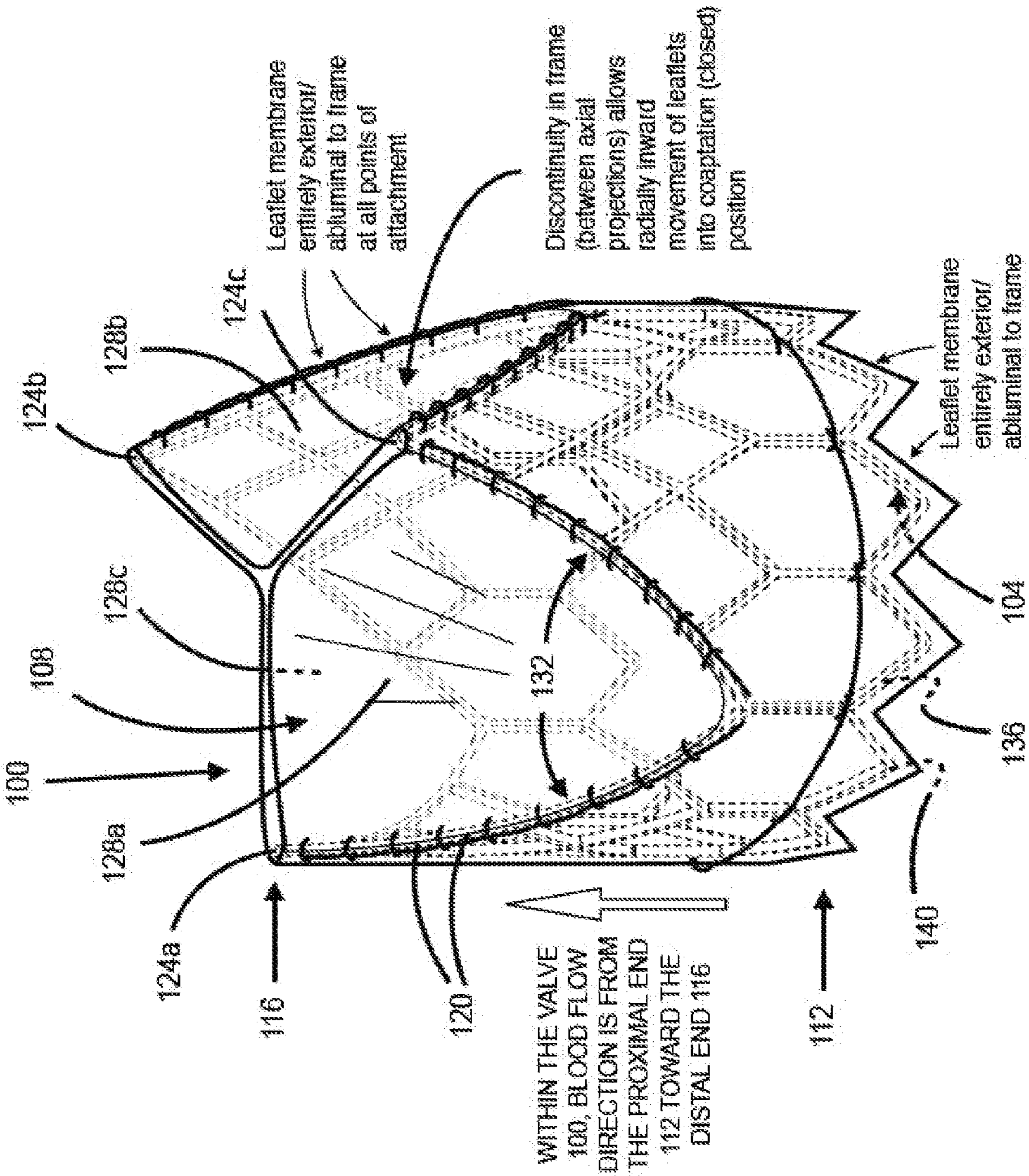
32. The method of preparing a percutaneous, trans-catheter prosthetic valve of Claim 28, further comprising mounting the trans-catheter deliverable frame and the biocompatible tissue material mounted thereto on a mandrel.

33. A method, comprising:

attaching a biocompatible membrane material to a collapsible and expandable frame to form a trans-catheter deliverable prosthetic valve, wherein an entire interior surface of the biocompatible membrane material is located exterior of an abluminal surface of the collapsible and expandable frame when leaflet portions of the biocompatible membrane material are in a fully open position.

34. The method of Claim 33, wherein the attaching includes suturing the biocompatible membrane material to a distal edge of the collapsible and expandable frame that undulates in an axial direction around the collapsible and expandable frame.

35. The method of Claim 33, further comprising associating the trans-catheter deliverable prosthetic valve with a catheter.



100
108
128c
124b
128b
124c
Leaflet membrane entirely exterior/ abluminal to frame at all points of attachment
Discontinuity in frame (between axial projections) allows radially inward movement of leaflets into coaptation (closed) position
128a
124a
132
Leaflet membrane entirely exterior/ abluminal to frame
104
136
140
116
120
112
WITHIN THE VALVE 100, BLOOD FLOW DIRECTION IS FROM THE PROXIMAL END 112 TOWARD THE DISTAL END 116

Figure 1A

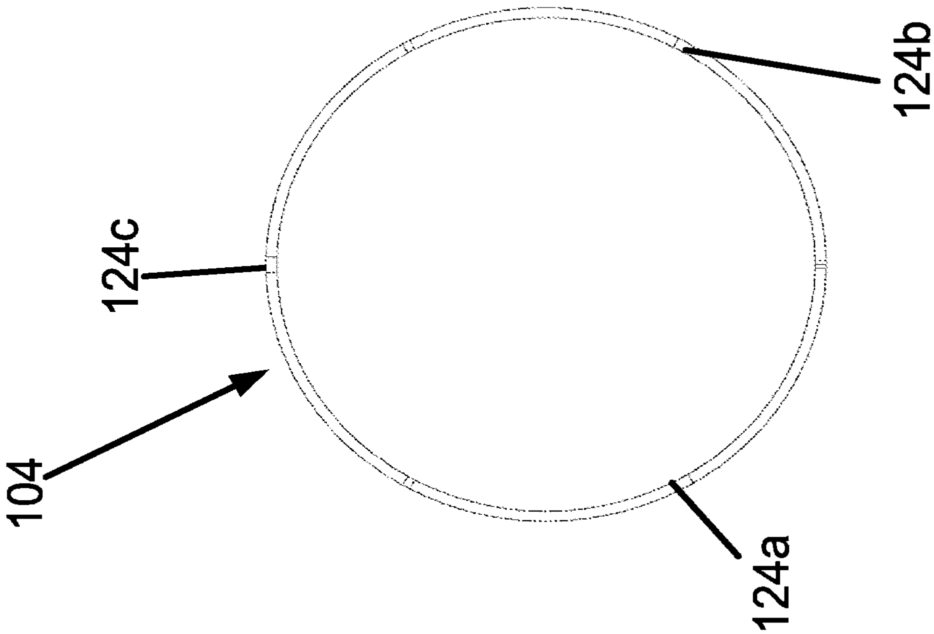


FIG. 1C

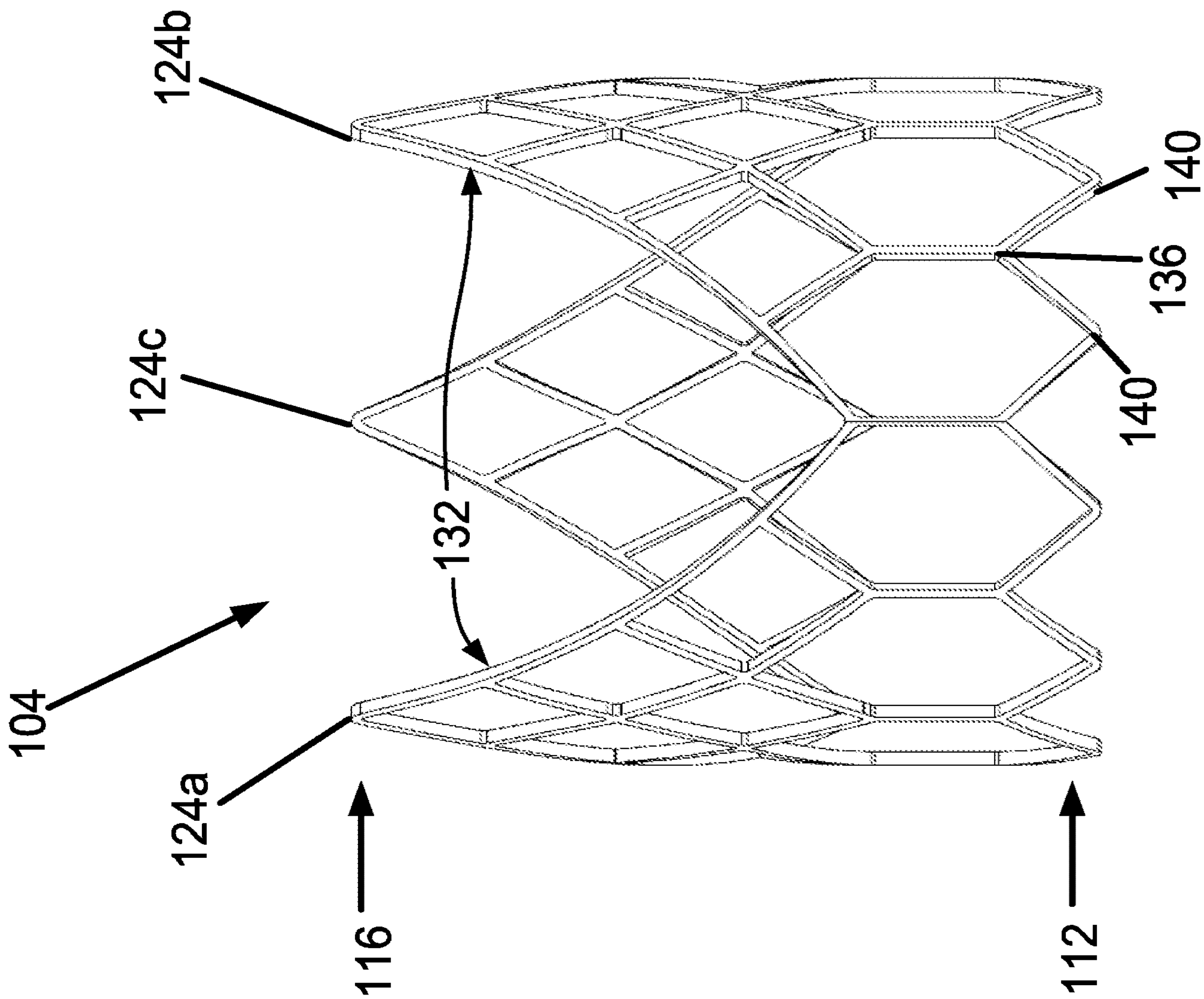
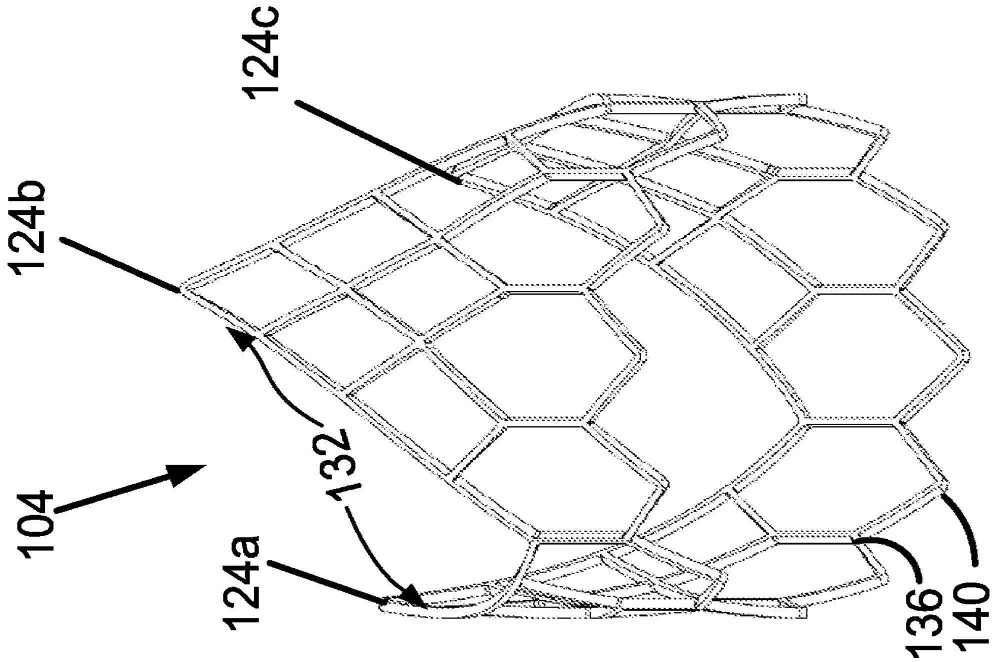


FIG. 1B

FIG. 1E


124c
124b
104
132
124a
136
140

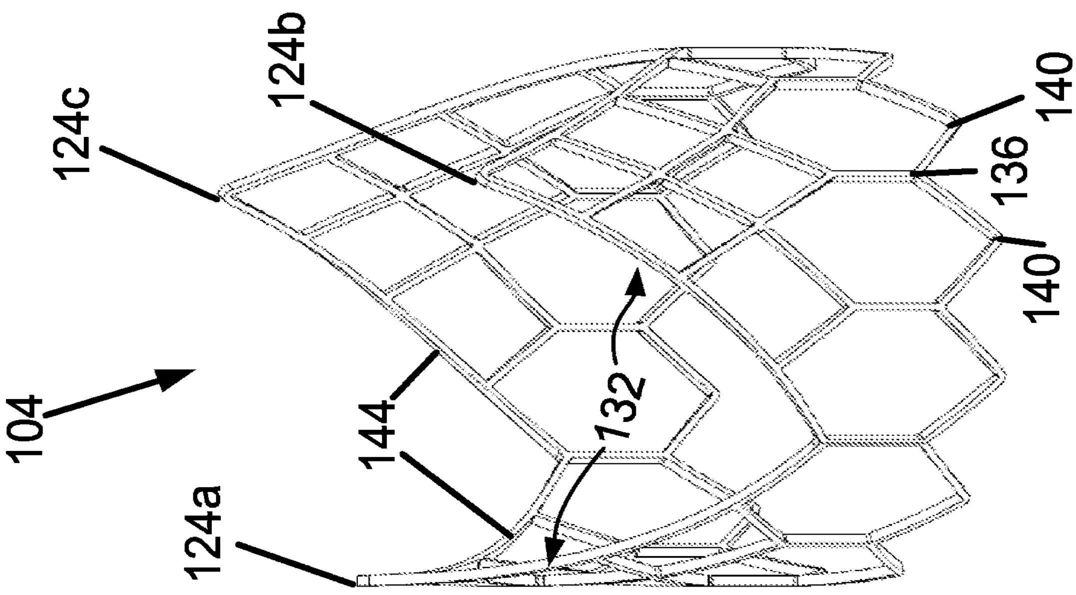

124c
124b
140
136
140
104
144
132
124a

FIG. 1D

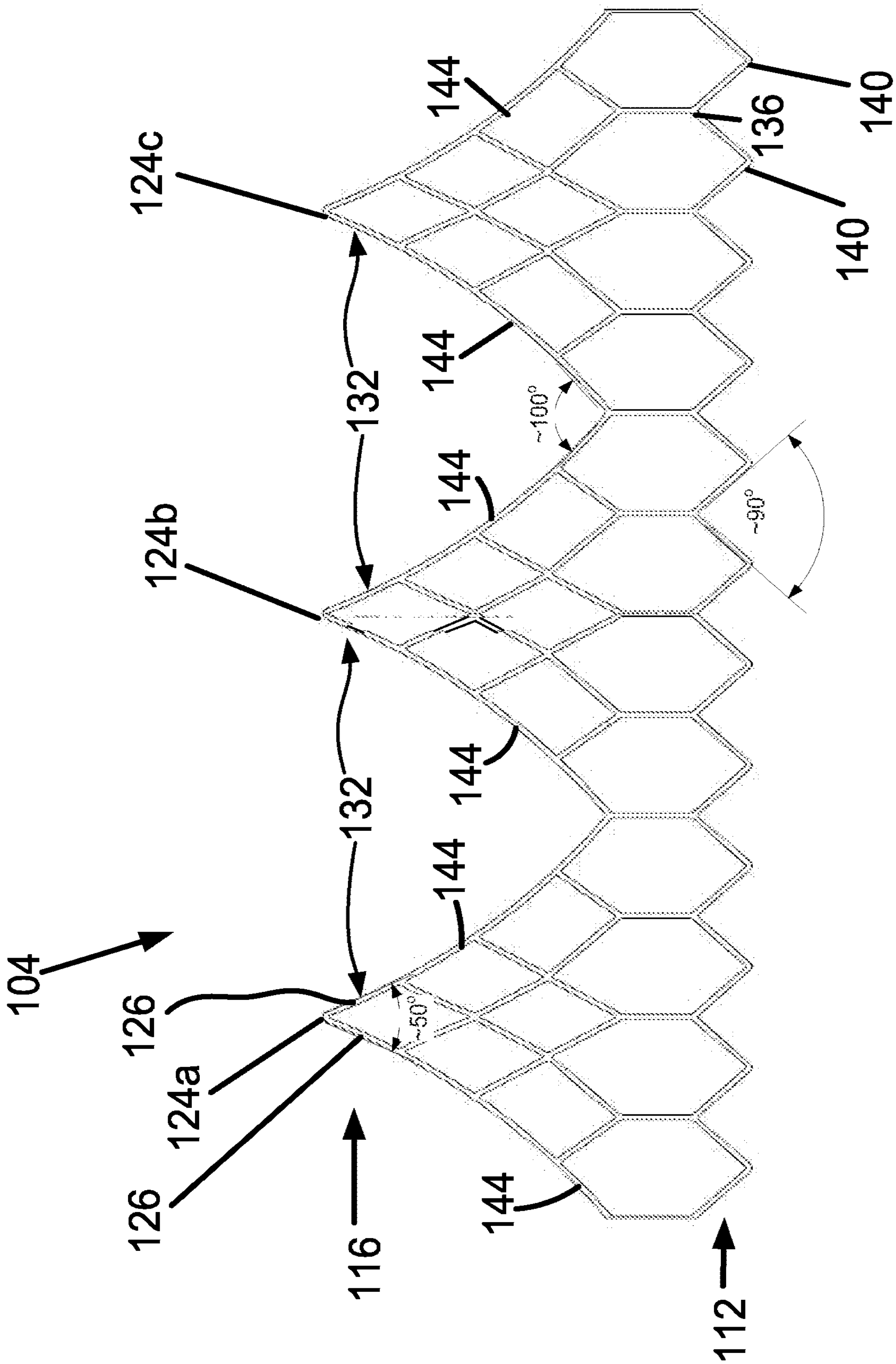

104
126
124a
126
116
112
132
132
144
144
144
144
144
144
124b
124c
136
140
140
~50°
~100°
~90°

FIG. 1F

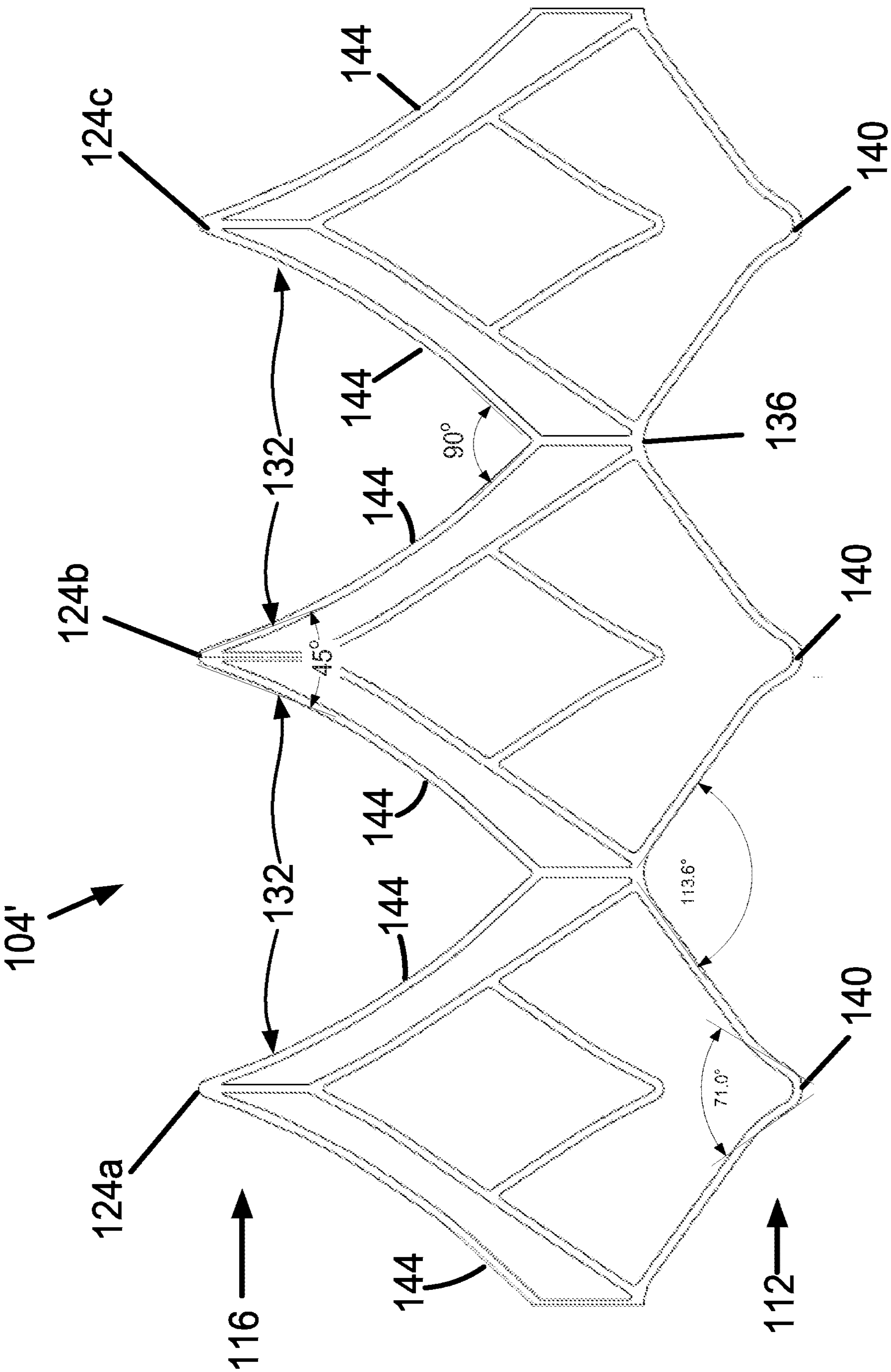

104'
116
112
124a
124b
124c
132
132
132
144
144
144
144
144
144
144
136
140
140
140
90°
45°
113.6°
71.0°

FIG. 1G

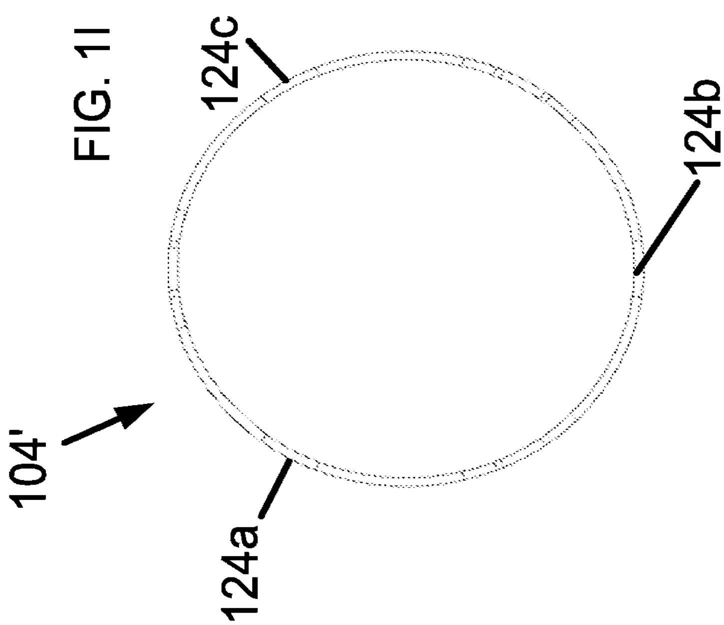

124c
124b
104'
124a

FIG. 1I

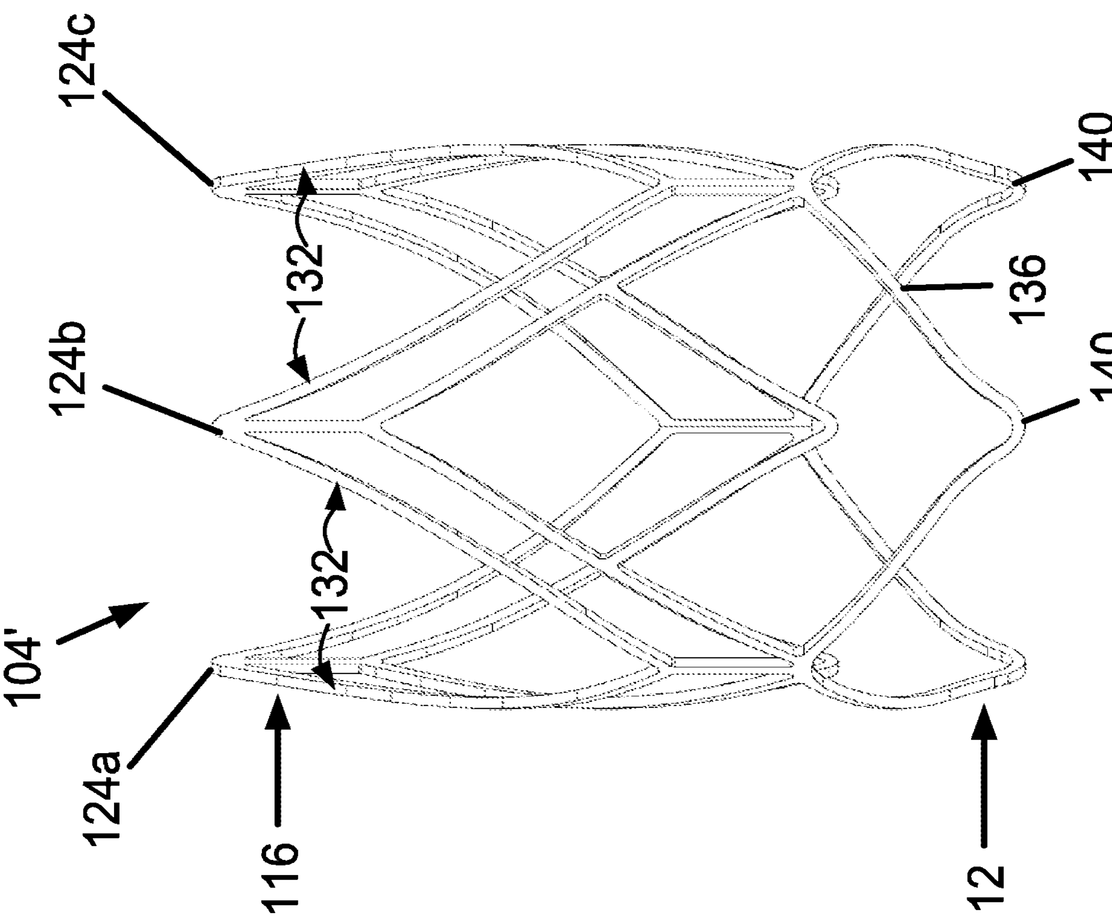

124c
124b
132
132
104'
124a
116
140
136
140
112

FIG. 1H

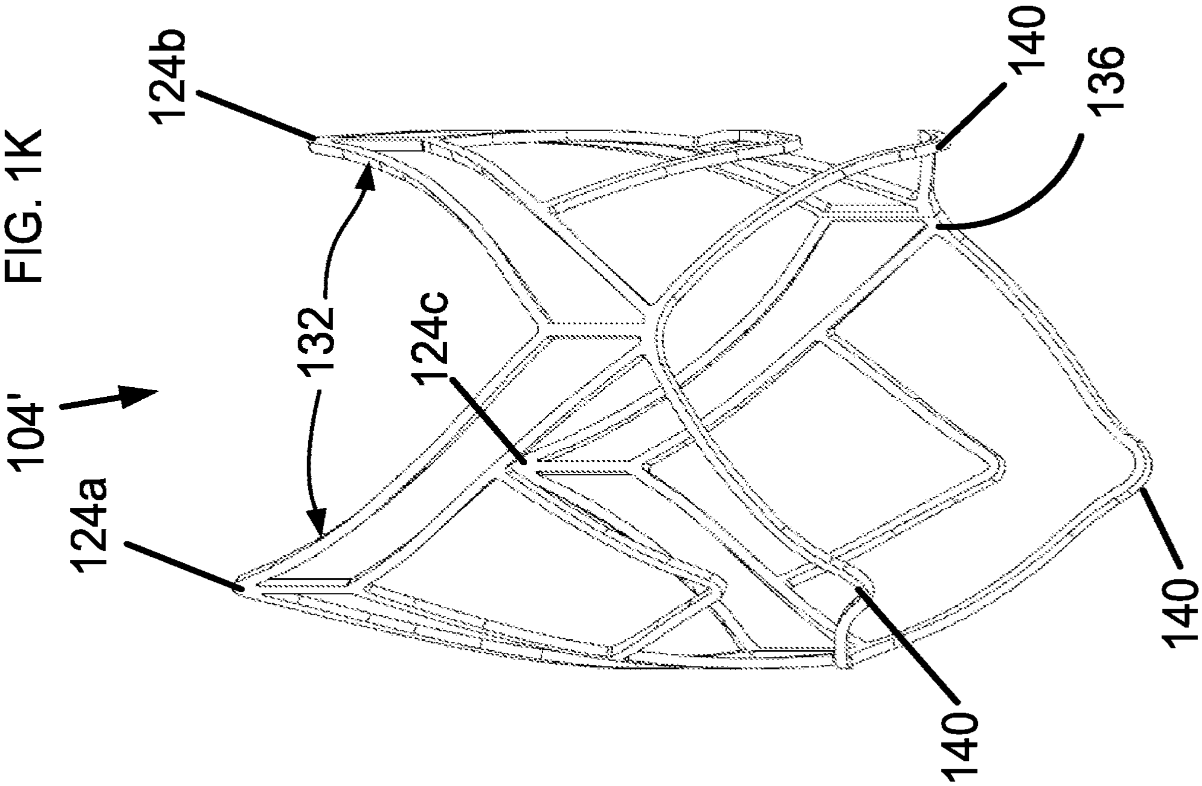

104'
132
124a
124b
124c
136
140
140
140
140

FIG. 1K

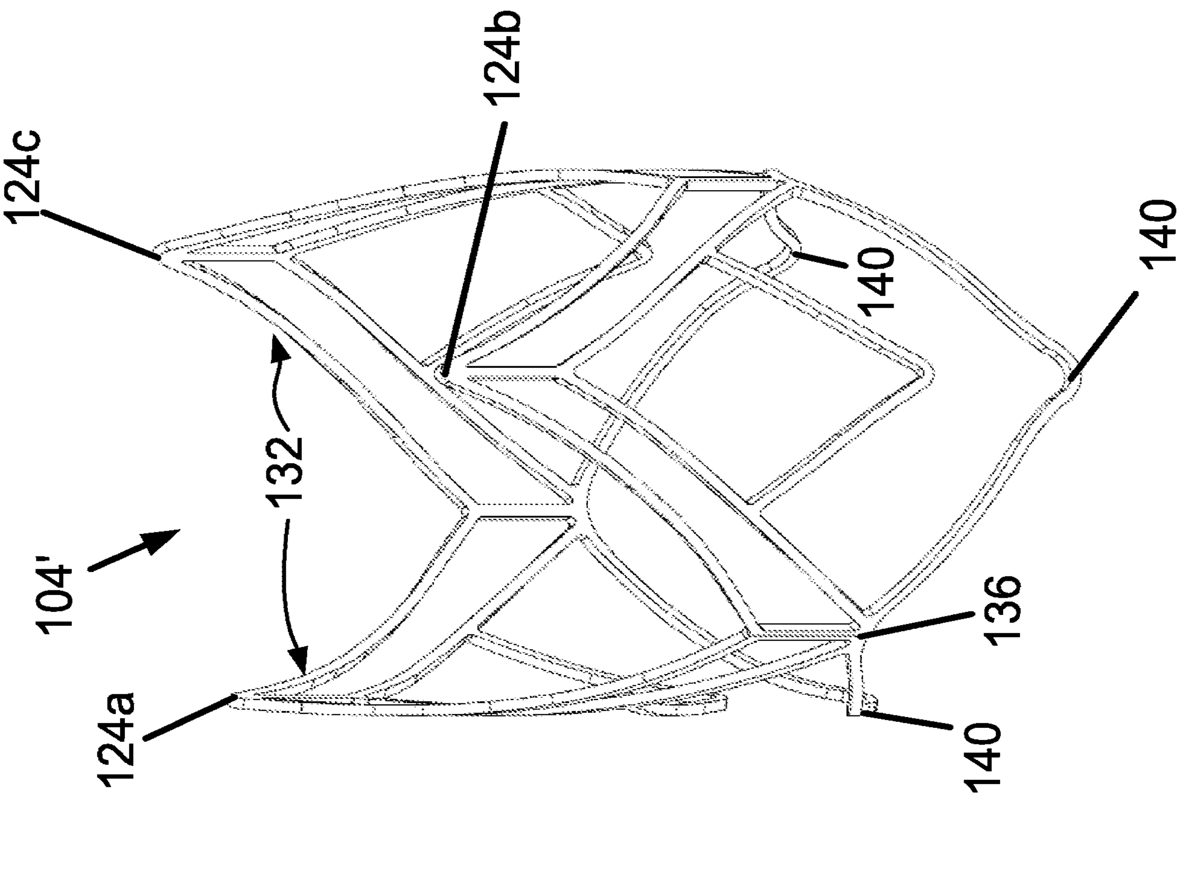

104'
124c
124b
132
124a
136
140
140
140

FIG. 1J

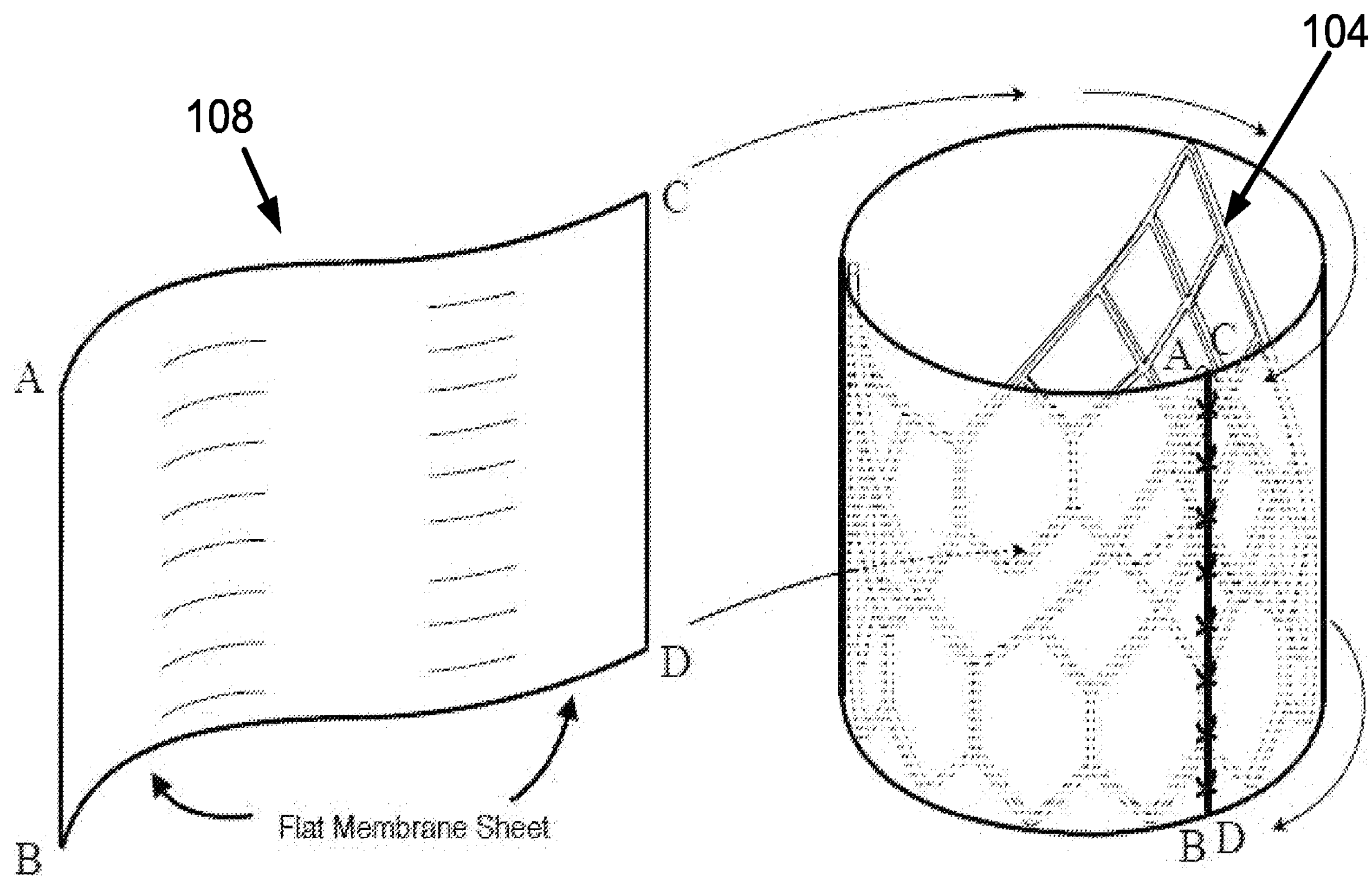


FIG. 1L

Flat membrane sheet is wrapped around outside/abluminal aspect of cylindrical frame and is secured in closed form by attaching membrane free edges A-B to C-D as by suturing. Membrane is subsequently attached to underlying frame.

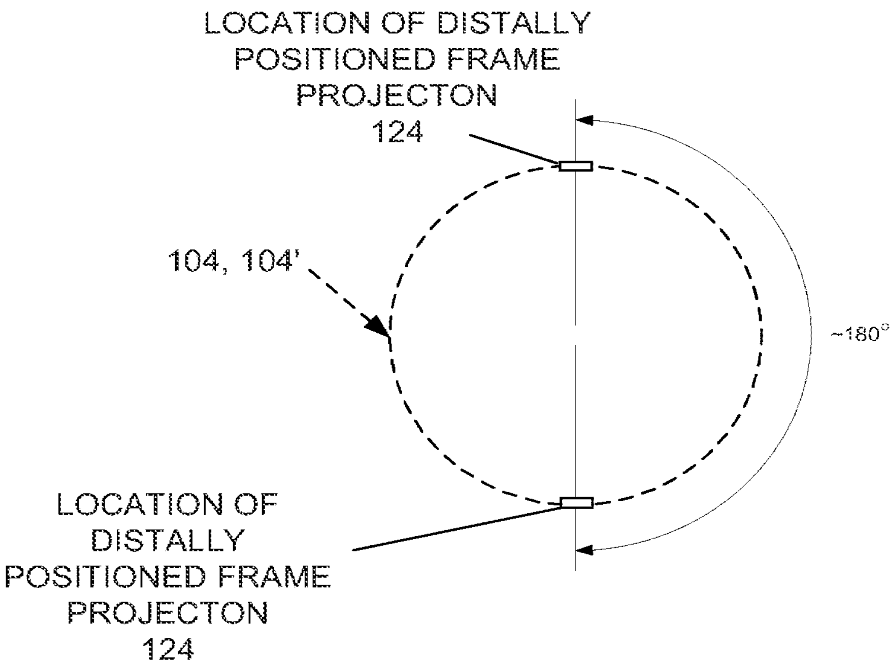

LOCATION OF DISTALLY POSITIONED FRAME PROJECTON 124
104, 104'
~180°
LOCATION OF DISTALLY POSITIONED FRAME PROJECTON 124

Fig. 2

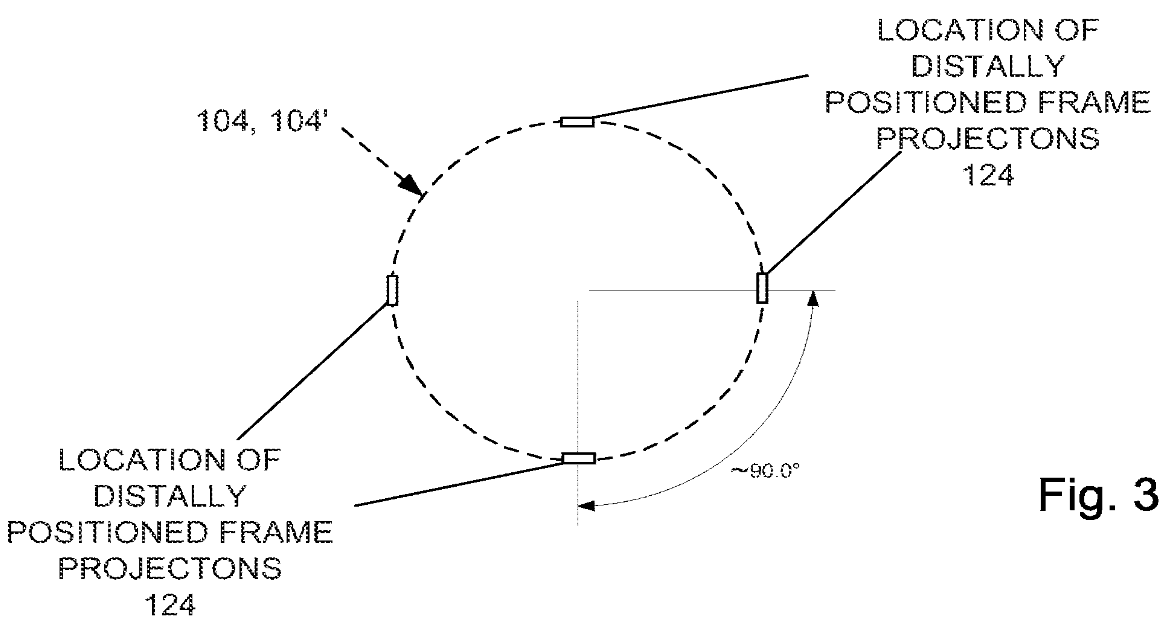

LOCATION OF DISTALLY POSITIONED FRAME PROJECTONS 124
104, 104'
~90.0°
LOCATION OF DISTALLY POSITIONED FRAME PROJECTONS 124

Fig. 3

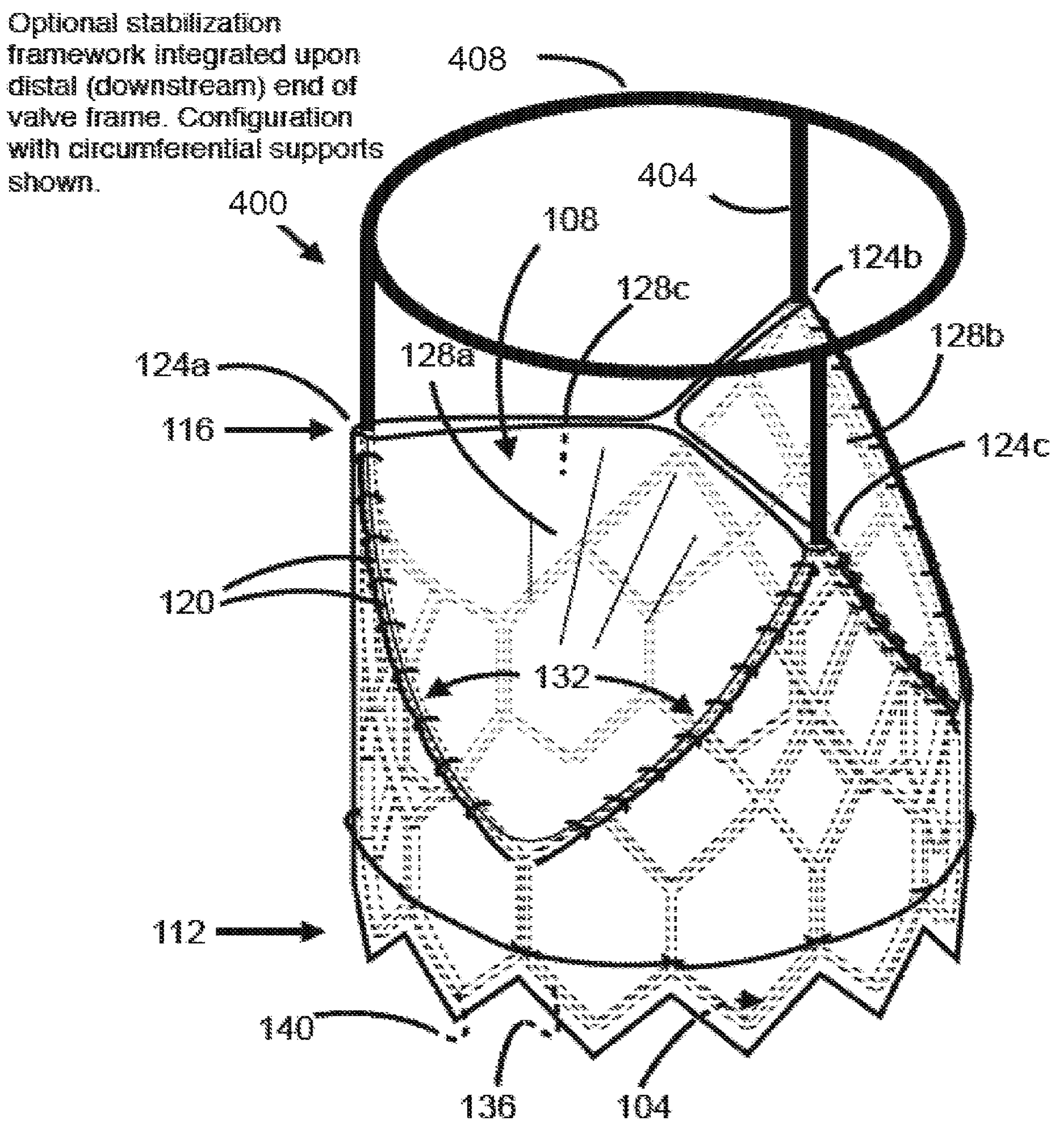

Optional stabilization framework integrated upon distal (downstream) end of valve frame. Configuration with circumferential supports shown.
408
404
400
108
124b
128c
128b
124a
128a
116
124c
120
132
112
140
136
104

Fig. 4

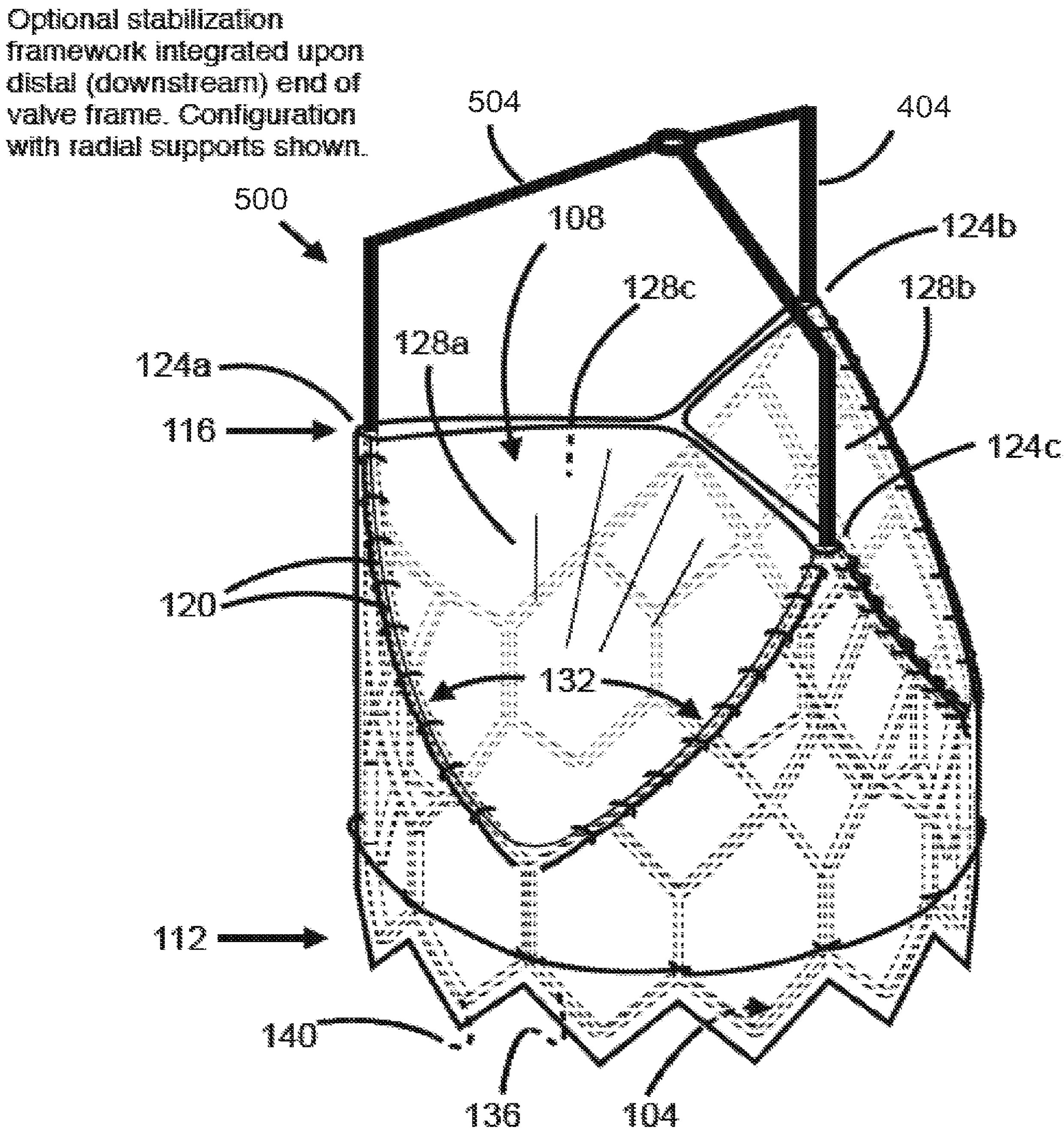

Optional stabilization framework integrated upon distal (downstream) end of valve frame. Configuration with radial supports shown.
504
404
500
108
124b
128c
128b
128a
124a
116
124c
120
132
112
140
136
104

Fig. 5

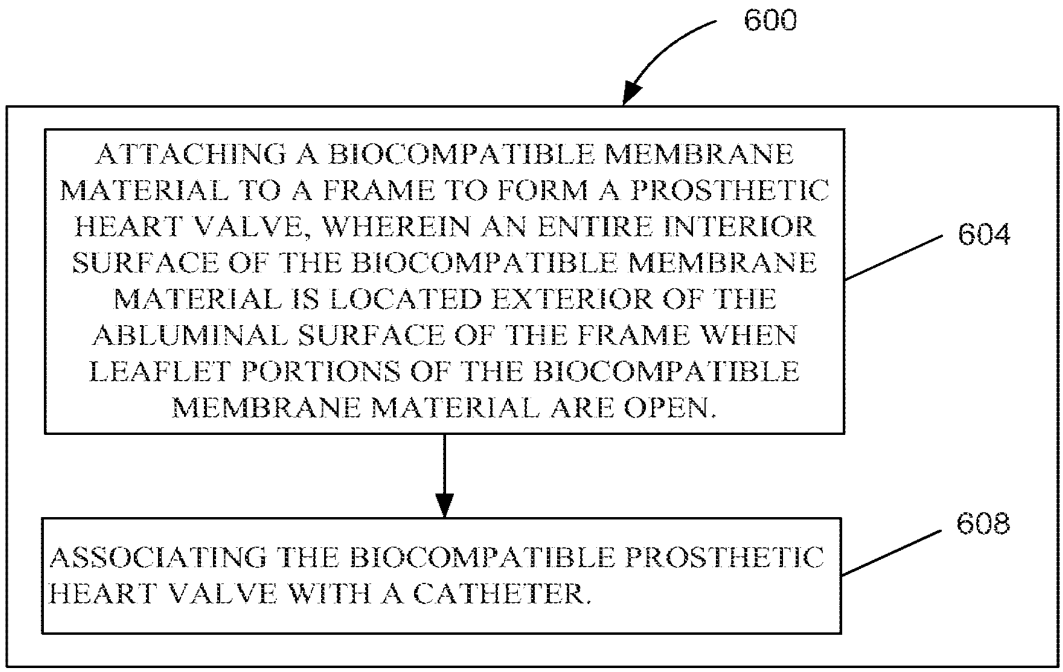

600
ATTACHING A BIOCOMPATIBLE MEMBRANE MATERIAL TO A FRAME TO FORM A PROSTHETIC HEART VALVE, WHEREIN AN ENTIRE INTERIOR SURFACE OF THE BIOCOMPATIBLE MEMBRANE MATERIAL IS LOCATED EXTERIOR OF THE ABLUMINAL SURFACE OF THE FRAME WHEN LEAFLET PORTIONS OF THE BIOCOMPATIBLE MEMBRANE MATERIAL ARE OPEN.
604
ASSOCIATING THE BIOCOMPATIBLE PROSTHETIC HEART VALVE WITH A CATHETER.
608

FIG. 6

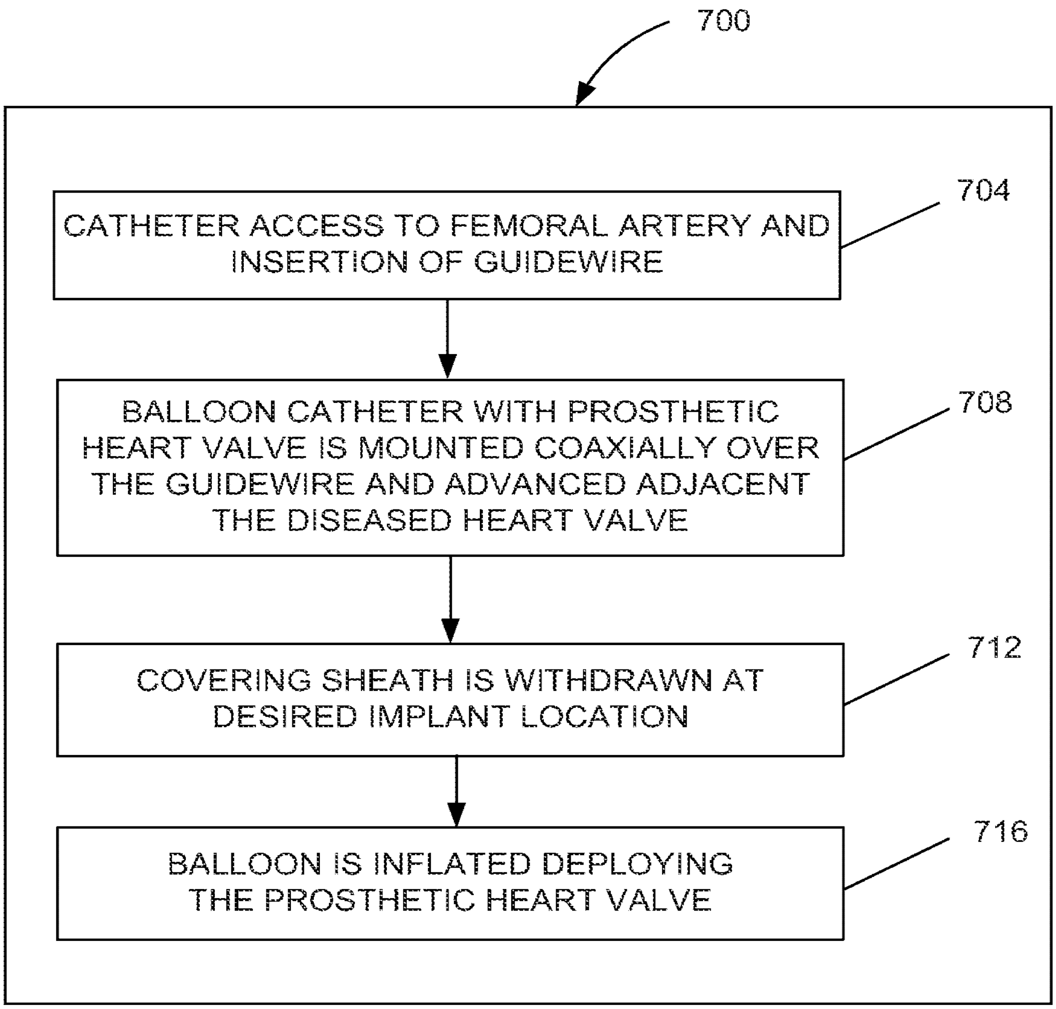

700
CATHETER ACCESS TO FEMORAL ARTERY AND INSERTION OF GUIDEWIRE
704
BALLOON CATHETER WITH PROSTHETIC HEART VALVE IS MOUNTED COAXIALLY OVER THE GUIDEWIRE AND ADVANCED ADJACENT THE DISEASED HEART VALVE
708
COVERING SHEATH IS WITHDRAWN AT DESIRED IMPLANT LOCATION
712
BALLOON IS INFLATED DEPLOYING THE PROSTHETIC HEART VALVE
716

FIG.7

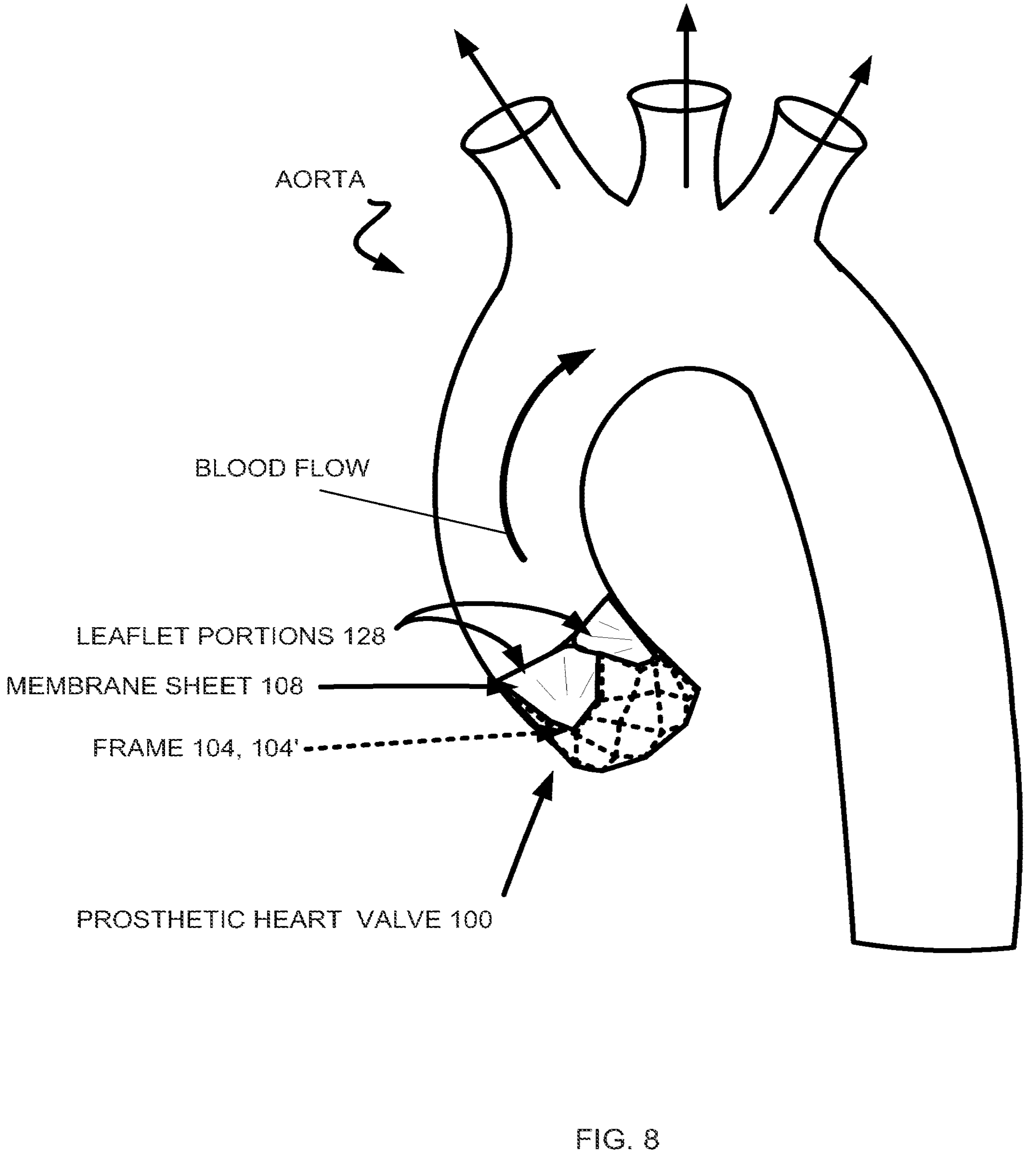

AORTA
BLOOD FLOW
LEAFLET PORTIONS 128
MEMBRANE SHEET 108
FRAME 104, 104'
PROSTHETIC HEART VALVE 100

FIG. 8

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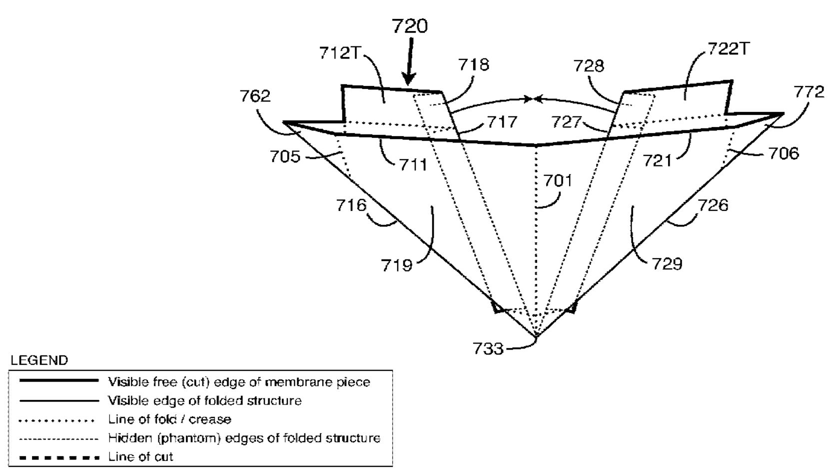
Figure 7D



(57) **Abstract**: A transcatheter, percutaneously implantable, prosthetic heart valve is provided that comprises a lattice frame and two or more integrated cusp and leaflet folded structures attached to the lattice frame. The two or more integrated cusp and leaflet folded structures each comprise a flat sheet of biocompatible membrane that is folded to include a substantially conical shape according to a flat folding pattern. The substantially conical shape is further formed by joining apposing sides of the substantially conical shape along a seam. The two or more integrated cusp and leaflet folded structures are each attached along their respective seams to the lattice frame in a direction substantially parallel to an axis of the lattice frame. Embodiments of valves described herein have application within the entire vascular system.

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PERCUTANEOUSLY DELIVERABLE HEART VALVE INCLUDING FOLDED MEMBRANE CUSPS WITH INTEGRAL LEAFLETS

FIELD

The present invention relates to the field of medical devices, and more particularly, to percutaneously deliverable heart valves.

BACKGROUND

The native heart valves, and in particular, the aortic valve, has a complex geometry that endows both ideal opening and closing geometries through an anatomic joining of a tubular inflow structure of the left ventricular outflow tract and an expansion of the valve sinuses above the hinging point of the valve leaflets defined by the aortic valve annular ring, part of the fibrous "skeleton" of the heart.

For the purposes of discussion and definition in the ensuing descriptions, the "upper", downstream outlet structure of the native aortic valve above its hinging point contains three valve "cusps" of a generally spherical contour with central mobile portions termed "leaflets" that are induced by fluid pressure gradients to meet centrally to close and to move radially outward to open in valve operation. The cusps are further continuous with downstream curved tissue walls meeting the tubular great vessel, the aorta, at the "sino-tubular junction". Each cusp and its upper, downstream extension above the level of leaflet closure ("coaptation") are a continuous structure of a generally spherical contour and together define the envelope of the "sinus of Valsalva. Typically, surgical prosthetic valves are implanted by excision of the diseased native valve leaflets at the level of the annular ring, and suturing of the prosthetic valve at this point, thus replacing only the opening geometry of the valve and leaving the outer structures of the cusps and the sinuses of Valsalva, the anatomy that confers proper closing geometry, generally intact.

Surgical valve prostheses are generally constructed as analogs to this central portion of the native valve geometry involved in the opening phase of the valve cycle. This approach to modeling the replacement valve prosthesis is enabled by the nature of the surgical technique: the replacement valve is sutured into the valve seat under direct vision. In contrast, a percutaneous stent-mounted heart valve ("PHV") is typically a construct in which the operating valve membrane leaflets are mounted and confined within the tubular envelope of a collapsible frame for effective transvascular delivery.

Further, in order to preclude valve regurgitation, the base of each leaflet must lie in exact apposition to the valve seat to form a seal, a condition that is difficult to satisfy without implantation under direct vision. Even then, since the diseased native valve would not be removed and its axial geometry is often distorted, it may not be possible to seat a PHV exactly under any circumstances. Thus, a cylindrical cuff layer, interior or exterior to the frame, is usually employed that acts as a seal and provides some latitude in the positioning and alignment of the PHV along the axis of flow, allowing for reliable and effective PHV implantation and minimizing the risk of significant valve regurgitation. Finally, the diseased native valve leaflets, when pushed outward by the deployed PHV frame, may themselves form a barrier separating the sinuses of Valsalva from the leaflets of the PHV, then disrupting the native closing geometry of the valve so that the sinuses are no longer continuous with the pressurized space above the PHV leaflets.

These issues illustrate some of the challenges to the formation of a PHV; that is, how to confine operating leaflets within a partially sealed tubular structure while preserving ideal opening and closing valve behavior without the benefit of the natural mechanism of the sinuses of Valsalva in a single valve and leaflet geometry, such as the separate and distinct upper and lower geometries of the native valve. As such, there is a need for additional devices, systems and/or methods that address one or more of the problems or shortcomings noted above.

SUMMARY

It is to be understood that the present invention includes a variety of different versions or embodiments, and this Summary is not meant to be limiting or all-inclusive. This Summary provides some general descriptions of some of the embodiments, but may also include some more specific descriptions of other embodiments.

Two goals of at least some embodiments of the present inventions are: (1) to maximize effective orifice area and minimize opening pressure gradients through geometry that mimics the natural form of inflow into the valve — the tubular outflow tract of the heart pumping chamber; and (2) to minimize the inward tension on the leaflet commissures in the closed position through geometry that mimics the natural effect of the sinuses of Valsalva - an effect that prevents downward displacement of the leaflet free edges under closing pressure, thus distributing force along the lines of leaflet apposition rather than focusing it at the points of leaflet attachment to the frame.

The first of these goals dictates that the inflow to the valve, similar to that of the natural aortic valve, encounters then outwardly displaces the most central portion of the leaflets first, with opening moving progressively outward along the surface of the leaflets. The second suggests that the cross-sectional profile of the valve sinus/cusp formed in its central portion by the free edge of the leaflets, like that of the natural aortic valve, should be approximately elliptical, and that the cross-sectional diameter of each cusp should progressively decrease below the plane of leaflet apposition, like that of the natural valve cusps. One or more embodiments of the one or more present inventions answer the configuration ideals with a robust balance of functional geometries for valve opening and closing.

The spherical geometry of the native aortic valve leaflets is difficult to replicate in a transcatheter valve. First, while this shape is functionally robust in vivo, even if reproduced in some form it is not suited to efficient radial compression typically required for collapse into a small diameter delivery catheter used in transcatheter valve delivery systems, and discontinuities would develop in the leaflet surface that would resolve into irregular folds with at least some circumferential component, thereby threatening the restitution of the geometry on reopening at deployment. Second, tissue bioprosthetic valve leaflets, if not actually constituted of the animal valve itself, are typically constructed of flat sheet tissue membrane from which rendering of cusps with leaflets of a spherical contour would be difficult if not impossible without the use of traction force on the material, or extensive cutting and suturing of the leaflet cusp portion — an impractical approach, and a threat to the material integrity of the thin tissue membrane.

At least one embodiment of the one or more present inventions answers these challenges by employing conical rather than spherical cusp geometry, thereby reproducing some benefits of the latter with near-elliptical leaflet cross-section that progressively decreases moving proximal to the plane of leaflet apposition while being readily conformed on outward radial compression in the valve opening phase into a substantially flat folded construct against the interior tubular walls of the containing frame. This favorable resolution of the conical geometry in opening phase expresses the opening efficiency of this valve design with a large effective orifice area and low transvalvular energy losses. In the closed position, the free edges of the separate leaflets of the conical cusps meet in apposition, each cone acting as an independent valve; pressure load-bearing is enhanced by the material continuity of the cone structure with the inner apposing wall and outer wall of each cone being part of a single continuous membrane structure. Further, the conical cusps are particularly suited for compression and containment within a collapsible frame for transcatheter delivery.

In at least one embodiment, a transcatheter, percutaneously implantable, bioprosthetic heart valve having a lattice frame comprising a substantially tubular alloy metal mesh, and two or more valve cusps with leaflets mounted to the lattice frame, is provided. Further, the cusps include a flat sheet of processed mammalian tissue membrane that is folded into a substantially conical shape according to a flat folding pattern, the substantially conical shape is further formed by joining opposing sides of the substantially conical shape along a seam that is oriented along a longitudinal axis of the substantially conical shape. In at least one embodiment, the two or more cusps are attached along their seams (which may or may not include the apexes of the cusps), such as, by way of example and not limitation, along the axial centerline of the outer circumference of the cone, to an interior portion of the lattice frame along an axial flow direction of the valve and are further attached along the distal, downstream, edge of the substantially conical shape along at least an outer half of the substantially conical shape's edge. When the membrane valve leaflet is attached to the frame, its principal line of securement along the axial centerline of the outer circumference of the cone is attached at a non-commissural seam or edge, effecting a coaxial (to the flow axis) line of attachment at an area of the structure that advantageously bears load, thereby relieving the commissural attachment of loads associated with the securement of the cusp structures to the frame. As such, the leaflet commissure attachments, thus located at points where the leaflet membrane is continuous and uncut, advantageously need only bear the centripetal loads associated with the radially inward movement and operation of the free edges of the leaflets.

In at least one embodiment, a transcatheter, percutaneously implantable, bioprosthetic heart valve is provided wherein two distal, downstream, vertices of the flattened cusp and leaflet structure are folded over in a radially outward direction and fixed to the frame such that the vertex folds of neighboring leaflets are adjacent and define an extent of leaflet apposition at the points corresponding to leaflet commissures.

In at least one embodiment, a transcatheter, percutaneously implantable, bioprosthetic heart valve is provided wherein a vertex forming a proximal, upstream, apex of the substantially conical shape is folded over in a radially outward direction and affixed to an inner portion of the frame.

In at least one embodiment, a transcatheter, percutaneously implantable, bioprosthetic heart valve is provided wherein the flat folding pattern is polygonal and includes extending portions that, when the leaflet is mounted, extend circumferentially outward from an axial line of attachment of the leaflet to the frame so as to form, when joined and attached to corresponding extending portions of neighboring leaflets, an integral, inner, luminal, circumferentially partial or complete sealing cuff.

In at least one embodiment, a transcatheter, percutaneously implantable, bioprosthetic heart valve is provided wherein a separate tubular sealing cuff of tissue membrane is attached to an outer, abluminal surface of the frame to form a sealing cuff. In at least one embodiment, the membrane sheet is a single layer of a substantially homogenous material. In at least one embodiment, the membrane sheet is an unlaminated single layer of material. In at least one embodiment, the membrane sheet is a single layer of material that does not include any reinforcement, such as reinforcing fibers. In at least one embodiment, the membrane sheet is a single layer of treated pericardium tissue. In at least one embodiment, the membrane sheet is a single layer of a synthetic film.

Therefore, in accordance with at least one embodiment, a transcatheter, percutaneously implantable, prosthetic heart valve is provided, comprising:

a lattice frame; and

two or more integrated cusp and leaflet folded structures attached to the lattice frame, the two or more integrated cusp and leaflet folded structures each comprising a flat sheet of biocompatible membrane that is folded to include a mobile leaflet layer and a cusp wall layer, wherein the cusp wall layer located radially outside of the mobile leaflet layer, and wherein the cusp wall layer is further formed by joining apposing sides of the cusp wall layer along a seam. In accordance with at least one embodiment, the two or more integrated cusp and leaflet folded structures are each attached along their respective seams to the lattice frame. In accordance with at least one embodiment, the seams are oriented in a direction substantially parallel to an axis of the lattice frame. In accordance with at least one embodiment, the flat sheet of biocompatible membrane forming at least one integrated cusp and leaflet folded structure of the two or more integrated cusp and leaflet folded structures comprises two or more pieces of biocompatible membrane material.

In accordance with at least one embodiment, a transcatheter, percutaneously implantable, prosthetic heart valve is provided, comprising:

a lattice frame; and

two or more integrated cusp and leaflet folded structures attached to the lattice frame, the two or more integrated cusp and leaflet folded structures each comprising a flat sheet of a biocompatible membrane that is folded to include a valve cusp according to a flat folding pattern, wherein the valve cusp is further formed by joining apposing sides of the valve cusp along a seam, and wherein the two or more integrated cusp and leaflet folded structures are each attached along their respective seams to the lattice frame in a direction substantially parallel to an axis of the lattice frame. In accordance with at least one embodiment, two distal, downstream, vertices of the integrated cusp and leaflet folded structure are folded over as vertex folds in a radially outward direction and fixed to the lattice frame such that the vertex folds of circumferentially adjacent leaflets are adjacent and define a degree of leaflet apposition at the points corresponding to leaflet commissures. In accordance with at least one embodiment, the two distal, downstream, vertices are fixed to the lattice frame by attachment not along an alignment with the vertex folds. In accordance with at least one embodiment, a vertex forming a proximal, upstream, tip of the substantially conical shape is folded over in a radially outward direction and attached to an inner portion of the lattice frame. In accordance with at least one embodiment, the flat folding pattern is polygonal and includes extending portions that, when the cusp is mounted, extend circumferentially outward from an axial line of attachment of the cusp to the frame so as to form, when joined and attached to corresponding extending portions of neighboring cusps, an integral, inner, luminal, circumferentially complete sealing cuff. In accordance with at least one embodiment, the flat folding pattern is polygonal and includes extending portions that, when the two or more cusps are mounted, extend circumferentially outward from an axial line of attachment of the cusp to the lattice frame so as to form a circumferentially incomplete sealing cuff portion associated with each cusp. In accordance with at least one embodiment, a separate tubular sealing cuff of biocompatible membrane is attached to an outer, abluminal surface of the lattice frame to form a sealing cuff. In accordance with at least one embodiment, the lattice frame is collapsible and expandable and comprises a metal alloy substantially configured as tubular stent member. In accordance with at least one embodiment, the biocompatible membrane comprises processed mammalian pericardium tissue. In accordance with at least one embodiment, the biocompatible membrane does not comprise a treated tissue. In accordance with at least one embodiment, the biocompatible membrane comprises a synthetic material. In accordance with at least one embodiment, the seams of the two or more integrated cusp and leaflet folded structures are each oriented along an axis of flow of the valve. In accordance with at least one embodiment, the two or more integrated cusp and leaflet folded structures are each further attached to a circumferential portion of the lattice frame along at least a portion of their distal downstream edges. In accordance with at least one embodiment, the two or more integrated cusp and leaflet folded structures are attached to the lattice frame at least at a non-commissural seam aligned with an axial flow direction of the valve.

In accordance with at least one embodiment, a transcatheter, percutaneously implantable, prosthetic heart valve is provided, comprising:

a lattice frame; and

two or more integrated cusp and leaflet structures attached to the lattice frame, the two or more integrated cusp and leaflet structures each comprising a flat sheet of biocompatible membrane that is folded to include a mobile leaflet layer and a cusp wall layer, wherein with the mobile leaflet layer in a closed position a transverse cross-sectional area of a cusp-sinus space decreases monotonically from a distal end to a proximal end of the mobile leaflet layer. In accordance with at least one embodiment, the cusp wall layer is located radially outside of the mobile leaflet layer. In accordance with at least one embodiment, the cusp wall layer is further formed by joining apposing sides of the cusp wall layer along a seam. In accordance with at least one embodiment, the mobile leaflet layer in the closed position a transverse cross-sectional length of the mobile leaflet layer decreases monotonically from a distal end to a proximal end of the mobile leaflet layer. In accordance with at least one embodiment, the mobile leaflet layer and the cusp wall layer of each integrated cusp and leaflet structure are a single continuous piece of biocompatible membrane.

At least one invention of the one or more present inventions is a novel integrated cusp and leaflet structure that has application for a variety uses, including implantable valves other than prosthetic heart valves. Accordingly, in at least one embodiment, and in subcombination, an integrated cusp and leaflet structure for attachment to a lattice frame to form a valve configured for implantation in a vascular system of a patient is provided, the integrated cusp and leaflet structure comprising:

a flat sheet of biocompatible membrane that is folded to include a mobile leaflet layer and a cusp wall layer, wherein the cusp wall layer is divided along a seam, and wherein the mobile leaflet layer is continuous and apposes the cusp wall layer when the integrated cusp and leaflet structure is pressed substantially flat. In accordance with at least one embodiment, the mobile leaflet layer and the cusp wall layer of the integrated cusp and leaflet structure are a single continuous piece of biocompatible membrane. In accordance with at least one embodiment, the biocompatible membrane comprises a synthetic material. In accordance with at least one embodiment, the integrated cusp and leaflet structure further comprises at least one commissure tab. In accordance with at least one embodiment, the at least one commissure tab is configured for engaging a slot within a member of the lattice frame.

One or more embodiments of the one or more present inventions are also directed to methods for forming the inventive valves described herein, as well as its component elements. Accordingly, a method of forming an integrated cusp and leaflet folded structure for use in an implantable valve having an axial flow direction is provided, comprising: folding a flat sheet of biocompatible membrane to form an integrated cusp and leaflet folded structure according to a flat folding pattern, wherein said folding includes making two diagonal folds in the flat sheet of biocompatible membrane, the two diagonal folds separating a mobile leaflet layer from a cusp wall layer of the integrated cusp and leaflet folded structure. In accordance with at least one embodiment, the two diagonal folds are angled at between about 10 to 80 degrees from the axial flow direction. In accordance with at least one embodiment, the method further comprises forming first and second cusp wall folds, wherein the cusp wall layer is further formed by joining apposing membrane portions adjacent the first and second cusp wall folds along a seam that is oriented substantially parallel with the axial flow direction.

In addition to the foregoing, in accordance with at least one embodiment, a method of forming a transcatheter, percutaneously implantable, prosthetic heart valve is provided, comprising: folding a plurality of integrated cusp and leaflet folded structures, each integrated cusp and leaflet folded structure of the plurality of integrated cusp and leaflet folded structures comprising a flat sheet of biocompatible membrane that is folded to form a cusp according to a flat folding pattern, wherein the cusp is further formed by joining apposing sides of the cusp along a seam; and attaching each integrated cusp and leaflet folded structure of the plurality of integrated cusp and leaflet folded structures to a lattice frame, wherein the two or more integrated cusp and leaflet folded structures are each attached along their respective seams to the lattice frame in a direction substantially parallel to an axis of the lattice frame.

Various components are referred to herein as "operably associated." As used herein, "operably associated" refers to components that are linked together in operable fashion, and encompasses embodiments in which components are linked directly, as well as embodiments in which additional components are placed between the two linked components.

As used herein, "at least one," "one or more," and "and/or" are open-ended expressions that are both conjunctive and disjunctive in operation. For example, each of the expressions "at least one of A, B and C," "at least one of A, B, or C," "one or more of A, B, and C," "one or more of A, B, or C" and "A, B, and/or C" means A alone, B alone, C alone, A and B together, A and C together, B and C together, or A, B and C together.

Various embodiments of the present inventions are set forth in the attached figures and in the Detailed Description as provided herein and as embodied by the claims. It should be understood, however, that this Summary does not contain all of the aspects and embodiments of the one or more present inventions, is not meant to be limiting or restrictive in any manner, and that the invention(s) as disclosed herein is/are understood by those of ordinary skill in the art to encompass obvious improvements and modifications thereto.

Additional advantages of the present invention will become readily apparent from the following discussion, particularly when taken together with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

To further clarify the above and other advantages and features of the one or more present inventions, a more particular description of the one or more present inventions is rendered by reference to specific embodiments thereof which are illustrated in the appended drawings. It should be appreciated that these drawings depict only typical embodiments of the one or more present inventions and are therefore not to be considered limiting of its scope. The one or more present inventions are described and explained with additional specificity and detail through the use of the accompanying drawings in which:

Fig. 1A is a plan view of a flat sheet membrane template for the formation of an integrated cusp and leaflet folded structure in accordance with at least one embodiment of the one or more present inventions;

Fig. 1B is an oblique axial top (distal) perspective view directed downward (proximal) and radially outward of a folded membrane sheet after execution of the template foldings illustrated in Fig. 1A, thereby yielding a completed integrated cusp and leaflet folded structure;

Fig. 1C is a side perspective view directed radially outward of the inner aspect of an initially folded version of the integrated cusp and leaflet template shown in Fig. 1A;

Fig. 1D is an oblique axial top (distal) perspective view directed downward (proximal) and radially outward of a further partially folded version of the integrated cusp and leaflet folded structure shown in Fig. 1C;

Fig. 1E is an another oblique axial top (distal) perspective view directed downward (proximal) and radially outward of a further partially folded version of the integrated cusp and leaflet folded structure shown in Fig. 1D;

Fig. 1F is a modified version of the integrated cusp and leaflet folded structure shown in Fig. 1E;

Fig. 1G is same structure and view shown in Fig. 1E, along with a top (distal) cross-section schematic view of the distal end of a three-leaflet valve in a closed operating position;

Fig. 2 is a plan view of another flat sheet membrane template for the formation of an integrated cusp and leaflet folded structure in accordance with at least one embodiment of the one or more present inventions;

Fig. 3 is a plan view of yet another flat sheet membrane template for the formation of an integrated cusp and leaflet folded structure in accordance with at least one embodiment of the one or more present inventions;

Fig. 4 is a plan view of still yet another flat sheet membrane template for the formation of an integrated cusp and leaflet folded structure in accordance with at least one embodiment of the one or more present inventions;

Fig. 5A is a plan view of another flat sheet membrane template for the formation of an integrated cusp and leaflet folded structure in accordance with at least one embodiment of the one or more present inventions;

Fig. 5B is an oblique axial top (distal) perspective view directed downward (proximal) and radially outward of a partially folded version of an integrated cusp and leaflet folded structure prepared in accordance with the template shown in Fig. 5A;

Fig. 5C is an oblique axial top (distal) perspective view directed downward (proximal) and radially outward of a further partially folded version of the integrated cusp and leaflet folded structure shown in Fig. 5B;

Fig. 5D is plan view of the inner (luminal) aspect of a completely folded version of the structure of Fig. 5C, thereby yielding a completed integrated cusp and leaflet folded structure prepared in accordance with the template shown in Fig. 5A (with the exception of unfolded commissure tabs);

Fig. 5E shows a detail perspective view of a folded commissure tab;

Fig. 5F shows a perspective view of the outer (abluminal) aspect of the device shown in Fig. 5D;

Fig. 6 is a plan view of yet another flat sheet membrane template for the formation of an integrated cusp and leaflet folded structure in accordance with at least one embodiment of the one or more present inventions;

Fig. 7A is a plan view of still yet another flat sheet membrane template for the formation of an integrated cusp and leaflet folded structure in accordance with at least one embodiment of the one or more present inventions;

Fig. 7B is an oblique axial top (distal) perspective view directed downward (proximal) and radially outward of a partially folded version of an integrated cusp and leaflet folded structure prepared in accordance with the template shown in Fig. 7A;

Fig. 7C is an oblique axial top (distal) perspective view directed downward (proximal) and radially outward of a further partially folded version of the integrated cusp and leaflet folded structure shown in Fig. 7B;

Fig. 7D is an oblique axial top (distal) perspective view directed downward (proximal) and radially outward of yet a further partially folded version of the integrated cusp and leaflet folded structure shown in Fig. 7C;

Fig. 7E shows a shallow oblique top perspective view of the outer (abluminal) aspect of the partially folded cusp and leaflet structure of Fig. 7D;

Fig. 7F is a plan view of the inner (luminal) aspect of a completely folded version of the structure of Fig. 7D yielding an integrated cusp and leaflet folded structure prepared in accordance with the template shown in Fig. 7A (excepting that the commissure tabs and apex are not yet folded outward);

Fig. 7G is a side perspective view of the outer (abluminal) aspect of the structure of Fig. 7F showing a completely folded version of an integrated cusp and leaflet folded structure prepared in accordance with the template shown in Fig. 7A (excepting that the commissure tabs and apex are not yet folded outward);

Fig. 7H is a plan view of the inner (luminal) aspect of a completely folded version of an integrated cusp and leaflet folded structure prepared in accordance with the template shown in Fig. 7A;

Fig. 7I is a plan view of the outer (abluminal) aspect of a completely folded version of an integrated cusp and leaflet folded structure prepared in accordance with the template shown in Fig. 7A;

Fig. 7J is an oblique top (distal) perspective view of a completely folded version of an integrated cusp and leaflet folded structure prepared in accordance with the template shown in Fig. 7A;

Fig. 7K is a top perspective view directed downward (proximal) into the cusp space of an integrated cusp and leaflet folded structure prepared in accordance with the template shown in Fig. 7A;

Fig. 8A is an oblique top (distal) perspective view of an embodiment of a lattice frame for mounting three of the single-piece folded integrated cusp and leaflet structures as described herein;

Fig. 8B is a side elevation view of the lattice frame shown in Fig. 8A;

Fig. 8C is a side elevation view of the lattice frame of Fig. 8A with a superimposed plan view of the radially outer aspect of the completely folded integrated cusp and leaflet structure of Fig. 7I;

Fig. 8D is an oblique axial (top/distal) perspective view of an assembled three-leaflet valve in accordance with at least one embodiment;

Figs. 9A and 9B are two different oblique axial (top/distal) perspective views of another embodiment of a lattice frame for mounting three of the single-piece folded integrated cusp and leaflet structures that include commissure tabs;

Fig. 9C is a side perspective view of the lattice frame shown in Figs. 9A and 9B with a superimposed plan view of the outer aspect of the completely folded integrated cusp and leaflet structure of Fig. 7I;

Fig. 9D is a side view of the lattice frame shown in Figs. 9A and 9B with superimposed views of the outer aspect of two circumferentially adjacent completely folded integrated cusp and leaflet structures; and

Fig. 9E is an oblique axial (top/distal) perspective view of an assembled three-leaflet valve comprising the lattice frame shown in Figs. 9A and 9B and three identical folded integrated cusp and leaflet structures.

The drawings are not necessarily to scale.

DETAILED DESCRIPTION

One or more embodiments of the one or more inventions described herein include an implantable prosthetic heart valve having a frame and two or more cusp and leaflet structures mounted to the frame. The frame preferably comprises a lattice of substantially tubular alloy metal mesh. The cusp and leaflet structures include a membrane operable to open and close, thereby providing a functioning valve when mounted within a frame. In at least one embodiment, the membrane preferably comprises a flat sheet of processed mammalian tissue membrane that is folded into a substantially conical shape according to a flat folding pattern.

In the ensuing descriptions and referenced figures it will be seen that, when applied to a dry sheet membrane, the folding initially results in a cusp shape of an inverted pyramid with a rhomboid base. On relaxation of the folds as occurs naturally with a flexible and pliable membrane, especially when the membrane is hydrated, the cusp shape becomes substantially conical in shape and will be described as such in the ensuing descriptions as it more closely represents the embodiment of the cusp in operation of the valve.

Formation of a valve construct as described herein provides a percutaneously deliverable heart valve with a relatively small diameter for transcatheter placement. That is, the substantially conical shape associated with the flat folding patterns used to form leaflets as described herein allow for construction of a valve that can be compressed prior to introduction to a catheter to an advantageously small diameter, thereby facilitating transcatheter percutaneous delivery of the valve within a patient. The substantially conical shape is further formed by joining two axially oriented sides of the substantially conical shape along a seam that is oriented along a longitudinal axis of the substantially conical shape. The two or more integrated cusp and leaflet structures are affixed to an interior portion of the lattice frame along an axial flow direction of the valve and are further affixed along the distal, downstream, edge of the substantially conical shape along at least an outer half of the substantially conical shape's edge.

One or more of the various embodiments described herein have a number of different features and characteristics as compared to other commercially available prosthetic heart valves. For example, at least one embodiment of a transcatheter, percutaneously implantable, prosthetic heart valve described below comprises a flat polygonal sheet membrane having more than four sides and which forms an integrated cusp and leaflet structure.

In addition, at least one embodiment of a transcatheter, percutaneously implantable, prosthetic heart valve described below comprises integrated cusp and leaflet structures that are attached to a lattice frame at the circumferential perimeter locations corresponding to the commissures. At such locations, the length of the seam that forms the common line of attachment of the cusp and integral leaflet to the frame is less than one-half to two-thirds of the axial length of the membrane portion of the valve.

In at least one embodiment of a transcatheter, percutaneously implantable, prosthetic heart valve, when the valve is in the open position, the mobile leaflet layer apposes or is geometrically free to appose its full outward surface completely to the immediately radially located outward structure, such as at least one of the cusp wall layer or interior surface of the lattice frame. In at least one embodiment, in the closed position the transverse cross-sectional length of the mobile leaflet layer and the cross-sectional area of the cusp/sinus space decreases monotonically from the distal end to proximal end of the membrane portion of the valve. (That is, generally the property of a cone as well as an inverted pyramid.)

In at least one embodiment, the mobile leaflet layer and the immediately outward structure for the full axial length of the leaflet (cusp wall layer, frame, or other) are a single continuous piece of material.

In at least one embodiment, at the base of each cusp (that is, at the most proximal extent of the leaflet), the circumferential extent of attachment of the membrane to the frame is less than the circumferential extent of attachment of the membrane to the frame at the distal end of the cusp. In addition, at the base of each cusp, the circumferential extent of transverse (that is, on a line or on the plane of a circumferential single-plane curve of folding that is generally perpendicular to the flow axis of the valve) folding of the membrane to the frame is less than the circumferential extent of transverse folding at the distal end of the cusp.

At least one embodiment, a prosthetic valve described herein comprises an integrated cusp and leaflet structure wherein the apposing sides of the cusp are joined at one or more axially oriented seams. In at least one embodiment, all folds and seams are located on line segments.

At least one embodiment of the one or more present inventions does not include frame elements, such as support members, spanning the interior of the valve luminal to support one or more portions of the membrane sheet. Moreover, at least one embodiment of the one or more present inventions does not include any hardware shaping form inward of or attached to any portion of the mobile leaflet portion of the membrane.

In addition, at least one embodiment of the one or more present inventions does not utilize attachment of the leaflet layer to the frame along the substantially complete circumferential distance separating the commissures at any point below (more proximal than) the commissure tabs.

At least one embodiment of the one or more present inventions does not include a transverse fold or reflection of the leaflet layer along the substantially complete circumferential distance separating the commissures at any point below (more proximal than) the commissure tabs.

Nomenclature

For all embodiments presented herein it is to be understood that a "membrane" includes suitable materials for forming the cusps and leaflets. Accordingly, with regard to particular material types that may be used to form the membrane sheet, in at least one embodiment the membrane sheet forming the cusp or leaflet portions includes a one-piece, single layer sheet of biocompatible membrane, such as fixed mammalian pericardium tissue or synthetic biocompatible material, such as ePTFE. In at least one embodiment, the membrane sheet is made from a tissue preparation process that yields a leaflet material of suitable strength and durability for use in a prosthetic transcatheter deliverable heart valve. The content of WO 2011/109450A2 published on September 9, 2011, is incorporated herein by reference. Although the membrane sheet is preferably a single piece of material, a membrane sheet formed of a plurality of pieces of material may be used, such as two to fifty or more pieces of material that are connected.

As used herein "proximal" means situated near or closer to the upstream or flow inlet end of the valve, and "distal" means situated near or closer to the downstream or flow outlet end of the valve. This convention is further applied in the description of the various folded structure elements (membrane sections, edge segments and fold lines) that are termed "proximal" or "distal" if the final position or orientation of said element within the completed folded structure satisfies the above definitions. Likewise, one of said elements is termed, "axial", "transverse" or "circumferential" to describe its position and orientation in the completed valve.

As used herein, a "cusp" means that structural portion of a valve related to a single leaflet that encompasses a space closed toward the lower (proximal) direction and open to the upper (distal) direction, formed by the joined and/or continuous structures of the mobile leaflet portion on the radially inner side and the cusp wall portion on the radially outer side. The "cusp" in the present invention is that structure described as having a substantially conical shape.

As used herein, the "mobile leaflet layer" or "leaflet" means that radially inward portion of the cusp that moves during operation of the valve. For example, when the valve is closing the mobile leaflet layer moves radially inward toward the central axis of the valve lumen. When the valve is opening, the mobile leaflet layer moves radially outward and away from the central axis of the valve lumen.

As used herein, the "cusp wall layer" means a portion of the cusp that resides radially outward of the mobile leaflet layer. In some embodiments, a portion of the cusp wall layer moves during operation of the valve. In other embodiments, the cusp wall layer remains substantially immobile during operation of the valve.

As used herein, the "cuff wall layer" means a portion of the folded membrane structure that resides radially outward of both the cusp wall layer and the mobile leaflet layer, and where present, is radially closest to the frame of the three layers comprising the mobile leaflet layer, the cusp wall layer, and the cuff wall layer. The cuff wall layer remains substantially immobile during operation of the valve.

A “frame” as used herein means a substantially tubular member that holds a plurality of cusps and/or leaflets. By way of example, the frame may be a wire lattice or a lattice cut from a single tubular piece of metal alloy, that is both collapsible and expandable.

A “valve” as used herein means a frame with a plurality of cusps and/or leaflets attached thereto. In the present invention each of said leaflets is an integral part of a folded membrane cusp structure. If a frame is used that is a metal lattice that is both collapsible and expandable, such a construct may be delivered through a catheter percutaneously to a target site within a patient, such as the aortic valve.

As used herein, “cone” or “conical” means resembling a cone or portion thereof at some point in the practical use of the structure.

As used herein “substantially conical” means resembling a cone or a portion thereof at some point in the practical use of the structure with the specific property that the transverse (that is, on a plane of section generally perpendicular to the axis of flow of the valve) cross-sectional perimeter or area of said structure in the operationally closed position decreases monotonically moving from the level of the leaflet apposition to the proximal end of the valve.

As used herein, “two or more leaflets,” “two or more valve leaflets,” “a plurality of leaflets” or a similar term means two, three, four, or more valve leaflets. Accordingly, “a valve with two or more leaflets” includes a valve with two leaflets, a valve with three leaflets, a valve with four leaflets, and a valve with more than four leaflets.

As used herein, a “folding” means the partition of a flat sheet section of material along a sharp line of folding or crease into subsections each lying on separate planes, but without interruption of material continuity.

As used herein, a “complete folding” means folding (as above) wherein the angular change of the planar axis at the line of folding is approximately 180 degrees, such that the subsections lie on approximately parallel planes and the subsections are in approximate overlying contact with each other at least at some point.

As used herein, a “cuff” means that portion of a valve structure that lies radially outward of the cusp wall portion that in some part circumferentially encompasses at least a portion of the cusp structure and acts to limit flow that may pass retrograde around the cusp.

As used herein, “commissure” means the site of union or junction between adjacent cusps and/or leaflets, and by extension, collectively those portions of the adjacent integrated cusp and leaflet structures that are coincident at the union or junction in the completed valve structure.

As used herein, an "integrated cusp and leaflet folded structure" means a membrane folded in accordance with one of the patterns described herein.

Folded Valve Integrated Cusp and Leaflet - Folding Pattern No. 1

Referring generally to Figs. 1A-7K, each cusp embodiment of an integrated cusp and leaflet structure described herein is a substantially flattened cone collapsed along an axis substantially perpendicular to its longitudinal axis. In one or more embodiments, the integrated cusp and leaflet structure, when being formed from a piece of membrane, is readily realized by folding a flat sheet of membrane from a closed polygon pattern. The pattern folding results in apposing seam lines aligned along their axial length. These are joined to close the cusp in the general shape of a cone with the joined seam forming the "spine" along which the cusp meets the inner aspect of the tubular frame. It can be seen that, when formed of a dry sheet membrane, the pattern results initially in a cusp shape that is an inverted pyramid with a rhomboid base that, with a flexible, pliable membrane, is congruent to a substantially conical shape. On relaxation of the folds in practical use a substantially conical cusp is realized wherein the inner mobile operating portions of the leaflet are continuous with the outer portion that forms the integral wall of the cusp sinus or pocket.

Referring now to Fig. 1A, a plan view of a rectangular flat sheet membrane template 100 is shown for the formation of a single-piece folded valve integrated cusp and leaflet. The plan view is shown with a view of that leaflet surface that faces radially inward once folded and mounted within a frame. Reference is also made to Fig. 1G, wherein a schematic of a valve in distal axial view is shown, and wherein three cusps with integral leaflets are shown within the frame that collectively form the valve. As described and illustrated in the present application, alternate polygons and other closed shapes may be employed with alternate folding patterns to generate alternate shapes and functional features of the valve cusp and leaflet, and complete valve.

Referring again to Fig. 1A, and in accordance with at least one embodiment of the one or more present inventions, dotted lines 101, 116, 117, 126 and 127 represent the position of folds or creases applied to a piece of membrane to form a leaflet structure 130. More particularly, folding at lines 116, 126 and 101 is initiated inward (with convexity of the surface disposed radially inward toward the central axis of the valve lumen) while folds 117 and 127 are folded initially outward (with convexity of surface disposed radially outward away from the central axis of the valve lumen). Since folding causes re-orientation of the various sections of the sheet template in relation to each other and to the valve geometry, final orientation of the fold lines within the structure on mounting and operation of the leaflets will not necessarily retain the same orientations as on initiation of the folds. The "inward" and "outward" conventions by this definition will be followed throughout the descriptions of the various folded geometries presented herein.

Referring again to Fig. 1A, a line of division by cutting is indicated at 102. Cutting at 102 results in opposing edges 115 and 125 that will be separated by folding. The other free edges of the structure are labeled as their position and orientation changes through the folding steps. Fold 101 defines the central axis of symmetry of the leaflet pattern, with the concave side of fold 101 facing radially outward toward the frame and away from the central axis of the valve lumen. Fold 101 assists in the maintenance of axial symmetry of the folded construct, but is not necessary to leaflet function and is not retained in the final operational form of the valve. (See Fig. 7A.)

Referring now to Fig. 1B, an oblique axial top (distal) perspective view of a substantially completed folded leaflet structure 130 is shown. (Three completed folded cusp and leaflet structures 130 are typically mounted to a frame to form an operating heart valve.)

The view of Fig. 1B is directed downward (proximally) and radially outward, with such view illustrating a substantially completed folded leaflet and cusp structure 130 that depicts the reoriented segments and sections of Fig. 1A after execution of the template foldings. Segments 111 and 121 form the left and right halves of the distal free edge of the mobile operating portion of the leaflet. Inward folding at 116 and 126 forms a second layer of membrane outward of the first, with segments 112 and 122 forming the distal free margin of the outer wall of the integrated cusp. In radially flatted form of the integrated cusp and leaflet structure (that is, approximating the open operating position of the leaflet), the segment 111 will appose to 112, and 121 will appose to 122.

The left cusp wall section 161 is bounded by folds 116 and 117 and edge segment 112. The right cusp wall section 171 is bounded by folds 126 and 127 and edge segment 122.

The left cuff wall section 118 is bounded by fold 117 and edge segments 113, 114 and 115. The right cuff wall section 128 is bounded by fold 127 and edge segments 123, 124 and 125. Inward folding at 117 and 127 cause these cuff wall sections 118 and 128 to position outward of the cusp wall sections 161 and 171, respectively. In radially flatted form of the completed folded structure (again, approximating the open operating position of the leaflet), the edge segment 113 will appose to 112, and edge segment 123 will appose to 122.

<u>Folded Valve Folding Sequence</u>

Referring now to Figs. 1C and 1D, oblique axial top (distal) perspective views of a partially completed folded leaflet and cusp are shown. The views provided by Figs. 1C and 1D are directed downward (proximally) and radially outward, with such views depicting the reoriented segments and sections of Fig. 1A after partial execution of the template foldings.

Fig. 1C shows a perspective view of the inner aspect of the template 100 after initiation of the foldings and cutting at 102 resulting in left and right cuff wall sections 118 and 128, respectively. The cut free edges 115 and 125 are separated along with the left and right cuff wall sections 118 and 128 by outward folding at 117 and 127, respectively. Completed folding at 117 and 127 results in the cuff wall sections 118 and 128, respectively. Distally situated (with respect to the blood flow direction) edge segments 113 and 123 of the cuff wall sections 118 and 128, as well as proximally situated edge segments 115 and 125 of the cuff wall sections 118 and 128, are positioned transverse, and in at least one embodiment, substantially perpendicular, to the central axis of the valve.

Fig. 1D shows the cusp and leaflet structure 120 with the folds 116, 126, 117 and 127 at an intermediate stage of completion. Triangular left and right mobile leaflet sections 119 and 129 respectively are bounded by folds 101 and 116 and free edge segment 111 on the left, and folds 101 and 126 and free edge segment 121 on the right. Folds 117 and 127 are then brought into apposition on the outward aspect of the integrated cusp and leaflet along a seam line 132 where the folds will be joined and attached to a frame to close the shape of the single-piece continuous conical integrated cusp and leaflet.

Referring now to Figs. 1E and 1F, oblique axial top (distal) perspective views of a substantially completed folded cusp and leaflet are shown. The views provided by Figs. 1E and 1F are directed downward (proximally) and radially outward, with such views depicting the reoriented segments and sections of Fig. 1A after execution of the template foldings.

Fig. 1E shows the cusp and leaflet folding substantially completed forming the structure 130 with the seam 132 formed by the apposition of folds 117 and 127, thus forming a generally conical cusp and sinus space 131. The triangular corners formed at the distal ends of folds 116 and 126 are apposed to and attached to the cuff wall sections 118 and 128, respectively. Between adjacent cusp and leaflet structures in a multi-leaflet valve, the folded corners form the junction joining the adjacent free edges (121 of leaflet A to 111 of leaflet B, for example) of the mobile leaflet portions. When further attached to the circumferential valve frame, these corners tether the free edges of the mobile leaflet portions to the circumferential inner boundary of the generally cylindrical valve frame, thus forming valve leaflet commissures at each similar join.

Referring now to Fig. 1F, a structure similar to that of Fig. 1E is depicted, but with the cuff wall sections 118B and 128B reduced in circumferential extent from that of leaflet structure 130 shown in Fig. 1E. More particularly, depending on the clinical application of the valve, a fully circumferential cuff wall may be unnecessary, and a valve with a limited cuff wall with less tissue membrane mass may offer functional advantages. Alternatively, an additional piece of membrane may be placed circumferentially around the outer abluminal surface of the valve frame to act as a sealing cuff to form a barrier against valvular regurgitation.

Referring again to Fig. 1E, the apex 133 (proximal tip) of the conical cusp and leaflet forms the lower (proximal) end of the seam 132. In at least one embodiment, the apex 133 is also attached to the circumferential boundary of the valve and valve frame.

Referring now to Fig. 1G, for ease of reference the structure of Fig. 1E is again shown in Fig. 1G at the top of the page, along with a top (distal) cross-section view of the distal end of a three-leaflet valve in the closed operating position. The three cusps with leaflets are shown residing within a lattice frame in order to indicate the configuration of elements between the folded integrated cusp and leaflet structure 130 and its disposition within a three-leaflet frame-mounted valve. Suture attachments are omitted for clarity.

For each folded integrated cusp and leaflet structure, the outer axial seam 132 is aligned with one or more frame members 141 in a manner to permit the attachment of the folds 117 to 127, and to the coincident frame member by the same attachment, for example, by a single knot or line of suture. Advantageously for this purpose, the frame may preferentially contain axially oriented members that align to the seam 132 for part or all of the full axial extent of the valve. Further, said axially oriented members may advantageously contain holes or notches for securing and tying suture.

In Fig. 1G at point A, an illustrated loop symbolizing a suture knot is shown to demonstrate that a single knot may advantageously pass through or engage the frame member and the six layers; that is, the mobile leaflet section, the cusp wall section, and the cuff wall section of each adjoining cusp and leaflet structure that are coincident at this site of the commissure.

Referring still to Fig. 1G, it can be seen that the folded integrated cusp and leaflet structure, when mounted within the lattice frame and placed in the closed operating position, manifests the following configurations: (1) the left leaflet free edge segment 111 is in each case apposed to the right leaflet free edge segment 121 of the adjacent leaflet; (2) the portions of the leaflets just proximal to the free edges, thus, are also apposed to form the contact seal that enables effective closing operation, thereby preventing valvular regurgitation; and (3) the distal edges 112 and 122 of the cusp wall sections are apposed to the distal edges of the cuff wall sections 113 and 123, respectively.

Folded Valve Pattern Variation No. 2

Referring now to Fig. 2, and in accordance with at least one embodiment, a plan view of a flat sheet membrane template 200 that is polygonal rather than rectangular is shown. Template 200 contains folds 201, 216, 226, 217 and 227 that correspond to folds 101, 116, 126, 117 and

127, respectively, and are disposed in like manner in folding execution, as are the segments enumerated. The folding pattern is designed to form a longer cone of the same diameter, which achieves a more distally disposed central point of valve leaflet coaptation, the mechanics of which are more tolerant of pressure loads. The pattern dimensions may be altered to suit the particular clinical application of the valve. The template examples disclosed herein are for enablement purposes and shall not be interpreted as limiting the scope of the claims. The example is shown for a cusp cone wall disposed at about a 60 degree angle to the horizontal (short axis) of the generally cylindrical valve geometry, whereas that angle for the rectangular pattern of Figs. 1A-1G was about 45 degrees.

Folded Valve Pattern Variation No. 3

Referring now to Fig. 3, and in accordance with at least one embodiment, a plan view of template 300 is shown for a flat sheet membrane that contains the pattern 200 of Fig. 2 with added sections that extend the distal contour of the structure when completed in folding. More particularly, the free edge of the mobile leaflet section is extended distally with a section having a polygonal or curved free edge in order to increase the contacting area of leaflet apposition in valve closing operation. Additionally, the distal contour of the cusp wall sections and cuff wall sections 318 and 328 are extended by "tab" sections 318T and 328T, respectively. These added "tab" extensions allow for increased area by which to mount the outer wall of the cusp and leaflet assembly to the frame and for elevating the cuff wall "above" (more distal to) the plane of leaflet apposition, thereby also increasing the effective volume of the cusp in closing operation. These "tab" extensions, being distally disposed after completion of folding and initial mounting within the lattice frame, or a distal portion of them may optionally be folded radially outward along 312-313 and 322-323, for example, to wrap around the distal edge of the frame such that the "tab" extension areas 318T and 328T lie on the outer, abluminal aspect of the frame where, when attached to the frame, they potentially increase the strength of the cusp attachment.

Referring still to Fig. 3, template 300 contains folds 301, 316, 326, 317 and 327 that correspond to folds 101, 116, 126, 117 and 127, respectively, and are disposed in like manner in folding execution, as are the edge segments similarly enumerated. In addition to the tab features discussed in the preceding paragraph, as with template 200, template 300 is designed to form a longer cone of the same diameter, which achieves a more distally disposed central point of valve leaflet coaptation. Again, the pattern dimensions may be altered to suit the particular clinical application of the valve. The example is shown for a cusp cone wall disposed at about a 60 degree angle to the horizontal (short axis) of the generally cylindrical valve geometry.

Folded Valve Pattern Variation No. 4

Referring now to Fig. 4, and in accordance with at least one embodiment, a plan view of pattern 400 is shown for a flat sheet membrane similar to pattern 300, except that the extension "tab" sections 412T and 422T are distal extensions of the cusp wall sections only. This limitation reduces the double layer of membrane extension at the distal end of the completely folded integrated cusp and leaflet structure to a single layer, thereby reducing the mass of membrane in the heart valve which might otherwise disadvantageously limit the efficiency of collapsing and compressing the valve for use in the percutaneous/transcatheter delivery application.

In addition, at the lower (proximal) apex 433 of the cusp cone pattern the lower (proximal) extent of the cuff wall sections 418 and 428 is limited so as to "expose" the apex of the cone in the pattern. This feature allows, on the completely folded integrated cusp and leaflet structure, the transverse, radially outward folding of the tip of the cone-shaped cusp at line 403 between points U and V. (See figures 7.) The folding of the apex reduces the overall axial length of the cusp and leaflet structure, allowing for increased cusp/sinus volume for a given valve diameter and frame length.

The template 400 contains folds 401, 416, 426, 417 and 427 that correspond to folds 101, 116, 126, 117 and 127, respectively, and are disposed in like manner in folding execution, as are the edge segments similarly enumerated. Similar to templates 200 and 300 described above, template 400 dimensions may be altered to suit the particular clinical application of the valve. The example is shown for a cusp cone wall disposed at about a 60 degree angle to the horizontal (short axis) of the generally cylindrical valve geometry.

<u>Folded Valve Pattern Variation No. 5</u>

Referring now to Figs. 5A-5F, yet another embodiment of a template pattern is illustrated. Referring specifically now to Fig. 5A, a plan view of template 500 is shown for a flat sheet membrane. The template 500 contains folds 501, 516, 526, 517 and 527 that correspond to folds 101, 116, 126, 117 and 127, respectively, and are disposed in like manner in folding execution, as are the edge segments similarly enumerated.

Template 500 illustrates a flat sheet membrane that is basically rectangular and is similar to the upper (distal) portion of template 100 of Figs. 1A-1G, except that (a) the distal extension areas 512T and 522T are added at the left and right margins of the template 500, and (b) the lower quadrants forming the cuff wall sections of the template 100 are truncated in template 500 to narrow cuff wall sections 518 and 528, the extent of which is defined by the length of cut 502. These limited interior cuff sections are still used for frame attachment along the central seam 532 of the cusp and leaflet cone, and the distal extension sections 512T and 522T are still used for attachment of the outer cusp wall to the distal edge of the frame.

Referring still to Figs. 5A-5F, corner folds 505 and 506 are now described. For template 500, after folds 516 and 526 are executed by complete folding, segments 512 and 522 are apposed and aligned to segments 511 and 521, respectively, and overlapping layers (mobile leaflet layer and cusp wall layer) form triangular corner sections at 562 and 572. Radially outward folding of these corner sections at 505 and 506 define the axial extent of the leaflet commissures such that joining the corner sections of adjacent leaflet structures along corner folds 505 and 506 causes the leaflet apposition to be at least the length of 505 in axial extent at the radial margin of the leaflet. (See Fig. 9E that illustrates an embodiment of a valve comprising a frame 920 with a plurality of integral cusp and leaflet structures 730 attached to the frame, wherein the structures 730 include corner sections 762 and 772 corresponding to the corner sections 562 and 572 of template 500.) Additionally, these double-layer triangular corner sections 562 and 572 are used for attachment of the commissures to the frame. The stent frame may optionally contain a slot at this point of attachment through which this triangular "tab" section may be inserted and attached on the abluminal surface of the frame. (Again, see Fig. 9E.)

With specific reference now to Fig. 5B, a perspective view of the inner aspect (that is, a view directed radially outward) of an initially folded structure 510 folded according to template 500 is shown. The central folding along 501 is initiated after cut 502 is executed as shown. Foldings along 501, 516, and 526 are depicted as initiated radially inward (out of the page) and foldings along 517 and 527 are depicted as initiated radially outward (into the page).

Figure 5C shows a steeply oblique perspective view of the folded integrated cusp and leaflet 520 at an intermediate stage of completion of the foldings. The view is directed from the central axis outward and obliquely downward into the cusp space showing the formation of the outer wall of the structure, that is, the cusp wall layer of the subject cusp. Folding along 517 and 527 acts to position the extension sections 518 and 528 outward of the cusp wall sections 561 and 571, respectively. Completion of folding then will position folds 517 and 527 in an axially aligned orientation in apposition to each other along their length. Folding along 516 and 526 acts to position the cusp wall sections 561 and 571 outward of the mobile leaflet sections 519 and 529, respectively. Completion of folding, which radially collapses the folded flattened structure, positions the cusp wall sections 561 and 571 in apposition to the mobile leaflet sections 519 and 529, respectively. In the final folded configuration the structure embodies the integrated cusp and leaflet in the open operating position.

In addition, completed folding at 516 and 526 also forms triangular two-layer sections, 562 and 572, respectively, that are designated as "commissure tabs". These commissure tabs are bounded by the corner folds 505 and 506, folds 516 and 526, and the free edges 511 and 521 of the mobile leaflet sections 519 and 529, respectively. With further reference to Figs. 5D and 5E, these commissure tabs will be folded at 505 and 506 so as to position both layers of the tabs outward of the cusp wall sections 561 and 571, respectively, with the folds 505 and 506 oriented parallel to the central axis of the valve. With regard to a multi-leaflet valve, when the cusp and leaflet structure is mounted within the frame, this folded commissure tab is aligned along fold 505 in apposition to fold 506 of an adjacent complementary commissure tab of an adjacent integrated cusp and leaflet structure. Thus mounted, the commissure tabs join the mobile leaflet layers and the cusp wall layers of adjacent folded cusp and leaflet structures along a line coincident to both 505 and 506 that forms a common seam for attachment, such as by suturing of the commissure tabs to each other and to the frame forming the circumferential margin of the membrane portion of the folded cusp and leaflet structure.

Fig. 5D shows a plan view of the inner (luminal) aspect of the folded integrated cusp and leaflet structure 530 of template pattern 500. Structure 530 is depicted in a completed state of folding, excepting that the commissure tabs 562 and 572 are not yet folded outward along fold lines 505 and 506, respectively. The radially flattened form shown gives the general configuration and orientation of the membrane segments and sections for the open operating position of the valve cusp and leaflet.

Still referring to Fig. 5D, at the uppermost (distal) portion of the cusp wall layer, the extension tabs 512T and 522T are projected above (or distal to) the lines 512 and 522 (shown in figures 5A and 5B), respectively, that lie in apposition and alignment to the free edges 511 and 521, respectively, of the mobile leaflet layer. A portion or all of these tabs 512T and 522T may be optionally folded outward along 512 and 522, respectively, around the distal edge of the frame to lie upon the outer (abluminal) surface of the frame where they may be attached to both the frame and to the cusp wall sections (where the cusp wall sections are apposed to the inner surface of the frame) through the interstices of the frame. This optional configuration provides for increased strength of attachment for bearing downward (proximally directed) operational loads associated with the valve closing.

Completing the folding associated with template pattern 500 places folds 517 and 527 into axial alignment. Once in axial alignment, apposing folds 517 and 527 are joined along their axial length to form the seam 532 that closes the generally conical cusp structure with the extension sections 518 and 528 situated outward of the cusp wall sections 561 and 571, respectively. The cusp wall sections 561 and 571 are thus disposed outward of the mobile leaflet sections 519 and 529, respectively, with the cusp wall sections axially and circumferentially apposed to the inner surfaces of the generally cylindrical frame. Advantageously, for each valve cusp and leaflet to be mounted within, the frame may contain an element or elements that are axially oriented and span a significant portion of the axial length of the frame, so as to align with the seam 532 for attachment, such as by suturing to the frame.

Referring now to Fig. 5E, a partial detail perspective view is shown of the commissure tab 572 configuration of the completely folded integrated cusp and leaflet structure 530, indicating radially outward folding of the commissure tab 572 along fold line 506.

With reference now to Fig. 5F, a perspective view is shown of the outer (abluminal) aspect of the completely folded cusp and leaflet structure 530 (except that the triangular commissure tabs are not yet folded) of template 500 in substantially flattened form. This view is complementary to Fig. 5D that shows the inner aspect of the same structure 530. The central seam 532 is seen on the outer face of the cusp wall sections 561 and 571 and is depicted for purposes of illustration as partly separated with the extension sections 518 and 528 incompletely flattened and folds 517 and 527 in close, but not in the complete apposition and alignment that will form the final seam line 532 for attachment to the axially oriented frame members. The slight separation depicted between folds 517 and 527 exposes the centerpoint of the mobile leaflet free edge where the mobile leaflet free edge segments 511 and 521 meet as depicted behind the cusp wall sections 561 and 571, respectively, in this view.

Folded Valve Pattern Variation No. 6

In accordance with at least one embodiment, Fig. 6 shows a plan view of another template 600 that is similar to template 500 except that the cusp cone wall angle $\boldsymbol{a}$ exceeds the 45 degrees of the generally rectangular template 500, and that the mobile leaflet sections are extended by a polygonal or curved extension section 604 of the free edge.

The change in cusp cone wall angle $\boldsymbol{a}$ also results in changes in the angle relating the lower (proximal) margins of the template and fold lines 617 and 627 to the center line of the template in order that when folding is completely executed, the fold lines 617 and 627 and the seam between them will be parallel to the central axis of the assembled valve. Likewise, the further geometry of the cusp cone wall angle will result in fold lines (optional) 613 and 623 and the long axes of extension tabs 612T and 622T being parallel to the transverse axis of the assembled valve.

The template 600 contains folds 601, 616, 626, 617, 627, optional folds 612 and 622, corner folds 605 and 606, and cut line 602 that correspond to folds 501, 516, 526, 517, 527, optional folds 512 and 522, corner folds 505 and 506, and cut line 502, respectively, of template pattern 500 and are disposed in like manner in folding execution, as are the template sections and edge segments similarly enumerated.

Folded Valve Pattern Variation No. 7

Referring now to Figs. 7A-7F, still yet another embodiment of a template pattern is illustrated. Referring specifically now to Fig. 7A, a plan view of another template 700 is shown that is similar to template 600, but with a section of the lower (proximal) midline portion of the template cut away so as to expose the apex 733 of the triangular sections that, when folded, will form the apex of the cone-shaped cusp. Effectively, the midline portions of the extension sections 718 and 728 are removed in relation to template 600 to an extent determined by the desired length of the line segment U-V, which in turn determines the extent to which the apex of the cone-shaped cusp may be truncated by folding at U-V.

After the cusp and leaflet cone is formed by folding, the apex is folded radially outward at line U-V (703) to truncate the cone to reduce the overall length of the cusp and leaflet structure, allowing for increased cusp/sinus volume for a given valve diameter and frame length.

The template 700 contains folds 701, 716, 726, 717, 727, optional folds 712 and 722, and corner folds 705 and 706, that correspond to folds 601, 616, 626, 617, 627, optional folds 612 and 622, and corner folds 605 and 606, respectively, of template 600 and are disposed in like manner in folding execution, as are the template sections and edge segments similarly enumerated.

Fig. 7B shows a perspective view of the inner (luminal) aspect of the initially folded cusp and leaflet structure 710 of template 700 after initiation of the principal folds 716, 726, 717, 727 and 701. Inward folding along 701 assists in aligning the left and right sections of the structure, but is not necessary to the formation of the integrated cusp and leaflet folded structure or to the operation of the valve. The disposition of the folds that converge at the apex 733 of the cusp can be appreciated as later forming an overlapping two-layer triangular apex as the cusp wall sections 761 and 771 are folded outward along lines 716 and 726, respectively, so as to position the cusp wall sections 761 and 771 outward of, and in apposition to, the mobile leaflet sections 719 and 729, respectively.

Fig. 7C shows a steeply oblique perspective view of the folded integrated cusp and leaflet 720 at an intermediate stage of completion of the foldings. The view is directed from the central axis outward and obliquely downward into the cusp space showing the formation of the outer wall of the structure. Folding along 717 and 727 acts to position the extension sections 718 and 728 outward of the cusp wall sections 761 and 771, respectively. Completion of folding then will position folds 717 and 727 in an axially aligned orientation in apposition to each other along their length. Folding along 716 and 726 acts to position the cusp wall sections 761 and 771 outward of the mobile leaflet sections 719 and 729, respectively. Completion of folding, which radially collapses the folded flattened structure, positions the cusp wall sections 761 and 771 in apposition to the mobile leaflet sections 719 and 729, respectively. In the final folded configuration, the structure embodies the integrated cusp and leaflet in the open operating position.

With reference to Fig. 7D, completed folding at 716 and 726 also forms triangular two-layer sections, 762 and 772, respectively, that are designated as "commissure tabs." These commissure tabs are bounded by the corner folds 705 and 706, folds 716 and 726, and the free edges 711 and 721 of the mobile leaflet sections 719 and 729, respectively. With further reference to Figs. 7D and 7E, these commissure tabs will be folded at 705 and 706 so as to position both layers of the tabs outward of the cusp wall sections 761 and 771, respectively, with the folds 705 and 706 oriented parallel to the central axis of the valve. When the integrated cusp and leaflet structure is mounted within the frame, this folded commissure tab is aligned along fold 705 in apposition to fold 706 of an adjacent complementary commissure tab of an adjacent integrated cusp and leaflet structure of a multi-leaflet valve. Thus mounted, the commissure tabs join the mobile leaflet layers and the cusp wall layers of adjacent folded cusp and leaflet structures along a line coincident to both 705 and 706 that forms a common seam for attachment, such as by suturing of the commissure tabs to each other and to the frame forming the circumferential margin of the membrane portion of the folded cusp and leaflet strucutre.

Fig. 7D shows a perspective view of the inner (luminal) aspect of the partially folded integrated cusp and valve structure 720 of template 700. Integrated cusp and leaflet structure 720 is depicted in nearly completed state of folding, except that the commissure tabs 762 and 772, as well as the cusp apex 733 are not yet folded outward along fold lines 705, 706 and 703, respectively, and that the axial seam 732 is not yet formed by the apposition of the folds 717 and 727.

At the uppermost (distal) portion of the cusp wall layer, the extension tabs 712T and 722T are projected above (or distal to) the lines 712 and 722 (shown in Figs. 7A and 7B). All or a portion of these tabs 712T and 722T may be optionally folded outward along 712 and 722, respectively, around the distal edge of the frame to lie upon the outer (abluminal) surface of the frame where they may be attached to both the frame and to the cusp wall sections (apposed to the inner surface of the frame) through the interstices of the frame. This optional configuration provides for increased strength of attachment for bearing downward (proximally directed) operational loads associated with the valve closing.

Completing the folding associated with template pattern 700 places folds 717 and 727 into axial alignment. Once in axial alignment, apposing folds 717 and 727 are joined along their axial length to form the seam 732 that closes the generally conical cusp structure with the extension sections 718 and 728 situated outward of the cusp wall sections 761 and 771, respectively. The cusp wall sections 761 and 771 then are disposed outward of the mobile leaflet sections 719 and 729, respectively, with the cusp wall sections axially and circumferentially apposed to the inner surfaces of the generally cylindrical frame. Advantageously, for each integrated cusp and folded leaflet structure to be mounted within, the frame may contain an element or elements that are axially oriented and span a significant portion of the axial length of the frame, so as to align with the seam 732 for attachment as by suturing to the frame.

Fig. 7E shows a shallow oblique top perspective view of the outer (abluminal) aspect of the partially folded cusp and leaflet structure 720 of template 700 (except that the triangular commissure tabs 762 and 772 and apex 733 are not yet folded and that the axial seam 732 is not yet joined). This view is complementary to Fig. 7D that shows the inner aspect of the same structure 720. The central seam 732 will be formed on the outer face of the cusp wall sections 761 and 771 as folds 717 and 727 are brought together into apposition along the midline, with the extension sections 718 and 728 thus also aligned. The outward (abluminal) face of the mobile leaflet sections 719 and 729 are shown between the yet separated folds 717 and 727 before closure of the generally conical cusp along the outer seam 732.

Fig. 7F shows a plan view of the inner (luminal) aspect of the folded integrated cusp and leaflet structure 720 of template pattern 700. Structure 720 is depicted in a completed state of folding, excepting that the commissure tabs 762 and 772 are not yet folded outward along fold lines 705 and 706, respectively. In addition, the apex 733 is not folded outward. The radially flattened form shown gives the general configuration and orientation of the membrane line segments and areal sections for the open operating position of the valve cusp and leaflet.

At the uppermost (distal) portion of the cusp wall layer, the extension tabs 712T and 722T are projected above (distal to) the lines 712 and 722 (shown in Figs. 7A, 7B and 7G), respectively, below (proximal to) which the cusp wall sections 761 and 771 lie in radial apposition to the mobile leaflet sections 719 and 729, respectively, of the mobile leaflet layer. These tabs 712T and 722T may be optionally folded outward along 712 and 722, respectively, around the distal edge of the frame to lie upon the outer (abluminal) surface of the frame where they may be attached to both the frame and to the cusp wall sections (apposed to the inner surface of the frame) through the interstices of the frame. This optional configuration provides for increased strength of attachment for bearing downward (proximally directed) loads of valve closing.

Folding of the template positions folds 717 and 727 into axial alignment, joined along their axial length to form the seam that closes the generally conical cusp structure with the extension sections 718 and 728 reflected outward of the cusp wall sections 761 and 771, respectively. The cusp wall sections 761 and 771 then are disposed outward of the mobile leaflet sections 719 and 729, respectively, with the cusp wall sections 761 and 771 axially and circumferentially apposed to the inner surfaces of the generally cylindrical frame. Advantageously, for each valve cusp and leaflet folded structure to be mounted within, the frame may contain an element or elements that are axially oriented and span a significant portion of the axial length of the frame, so as to align with the seam 732 for attachment as by suturing to the frame.

Fig. 7G shows a perspective view of the outer (abluminal) aspect of the completely folded cusp and leaflet structure 720 (except that the triangular commissure tabs 762 and 772 and apex 733 are not yet folded) of template 700, in nearly flattened form. This view is complementary to Fig. 7F that shows the inner aspect of the same structure 720. The central seam 732 is seen on the outer face of the cusp wall sections 761 and 771 and is depicted for purposes of illustration as minimally separated with the extension sections 718 and 728 incompletely flattened and folds 717 and 727 in effectively complete apposition and alignment that forms the final seam line 732 for attachment to the axially oriented frame members. The slight separation depicted between folds 717 and 727 exposes the centerpoint between the mobile leaflet free edge segments 711 and 721 depicted behind the cusp wall sections 761 and 771, respectively, in this view.

Fig. 7H shows a plan view of the inner aspect of the completely folded integrated cusp and leaflet structure 730 of template 700. This view is substantially that of Fig. 7F except that the triangular commissure tabs 762 and 772 are folded radially outward of the cusp wall sections 761 and 771 along corner folds 705 and 706, respectively. Additionally, the apex (most proximal) portion of the cone-shaped cusp is folded radially outward along the fold line 703 (between points U and V) to the position radially outward of the joined extension sections 718 and 728 such that the apex point 733 then lies upon the seam line 732.

Fig. 7I shows a plan view of the radially outer aspect of the completely folded integrated cusp and leaflet structure 730 of template 700. The outwardly folded position of the triangular commissure tabs 762 and 772 can be seen so that they lie in apposition to the outer surface of the cusp wall sections 761 and 771, respectively. While they may attached in this position to the underlying cusp wall layer and to the frame, alternatively, the commissure tabs 762 and 772 may be positioned to point radially outward (out of the page in this view) to pass through a slot or space in the frame to be secured and attached to the outer (abluminal) surface of the frame.

Additionally, the apex (most proximal) portion of the cone-shaped cusp is folded radially outward along the fold line 703 (between points U and V) to the position radially outward of the joined extension sections 718 and 728 such that the apex point 733 then lies upon the seam line 732.

The apex portion of the cone-shaped cusp thus configured is to be attached in this position as by suturing and may be similarly attached into this position in the act of attaching or suturing this portion of the folded cusp and leaflet structure to the frame.

Fig. 7J shows an oblique top perspective view of the completely folded and formed cusp and leaflet structure 730 with the view directed radially outward and downward (proximal). The cusp and leaflet structure is shown with the free edge of the mobile leaflet layer in the inward central position corresponding to the substantially closed operating position of the valve leaflet.

The commissure tabs 762 and 772 are depicted in radially aligned positions directed outward as would be required for passing them through slots or spaces in a suitably designed frame.

Fig. 7K shows a top perspective view of the single-piece completely folded and formed cusp and leaflet structure 730 with the view directed downward (proximal) into the cusp space. The cusp and leaflet structure is shown with the free edge of the mobile leaflet layer sections 719 and 729 in the intermediate inward position corresponding to the partially closed operating position of the valve leaflet.

The membrane structure is depicted with the free edges in a relaxed state corresponding to the typical behavior of tissue membranes when hydrated as when implanted in the body.

The commissure tabs 762 and 772 are depicted in radially aligned positions directed outward as would be required for passing them through slots or spaces in a suitably designed frame.

<u>Metal Lattice Frame</u>

Fig. 8A is an oblique top perspective view of a metal lattice frame 910 for mounting three of the single-piece folded integrated cusp and leaflet structures of the ensuing description in order to form a three-leaflet valve. The frame comprises a plurality of strut members 911 and three axially oriented mounting bars 912 each with holes and/or slots for passing suture and/or portions of the folded membrane structure. Each mounting bar 912 is to align with and attach to the axial outer seam of one single-piece completely folded and formed cusp and leaflet structure 730. The diameter D of the open frame, e.g., 19 – 35 mm naturally defines the deployed and operating diameter of the valve assembly after implantation in the body. The strut members 911 are of specific length and orientation to permit radial collapse and compression of the frame to a small diameter, e.g., 3-7 mm. The mounting bars 912 are near to equally spaced around the circumferential course of the frame and the length L of the arc from the center of the mounting bar 912 to the center of the closest mounting bar 912 is approximately equal to (pi x D)/3. Thus defined, L also defines the transverse circumferential distance between folds 705 and 706 , approximating the circumferential extent of the portions of the joined cusp wall sections 761 and

771 extending between 705 and 706 of the folded cusp and leaflet structure of appropriate size when mounted within the frame 910.

Fig. 8B shows a side perspective view of the frame 910 with the view centered on the axial mounting bar 912. The axial bars are shown with holes and/or slots for passing suture and/or portions of the folded membrane structure to enable secure mounting of the folded cusp and leaflet structure within the frame.

Fig. 8C shows a side view of the frame of Fig. 8B with a superimposed plan view of the radially outer aspect of the completely folded integrated cusp and leaflet structure as depicted in Fig. 7I. The cusp wall seam 732 is aligned upon the inner surface of the mounting bar of the frame and attached by sutures in this example. (Example suture locations are shown in Figs. 8C, 9C and 9D shown with an "x"; however, it is to be understood that the locations shown are exemplary and not limiting.) As those skilled in the art will appreciate, means other than sutures for attaching folded integrated cusp and leaflet structure to the frame can be used.

The commissure tabs 762 and 772 are folded flat against the outer surface of the cusp wall layer along corner folds 705 and 706 for mounting entirely within the frame 910. Each fold 705 then forms an axially oriented seam along its length with the complementary fold 706 of the adjacent folded cusp and leaflet structure 730. (Adjacent complementary commissure tabs omitted for clarity.) Said seam is closed and attached by suture, for example, while also attaching to the radially overlying strut member 911 of the frame 910, and thereby affixes the distal margins of the cusp wall sections 761 and 771 and the mobile leaflet sections (obverse of this view) to the frame 910. The other suture points depicted attach only the cusp wall layer 761+771 to the overlying frame strut members 911. At no point within the interior operating volume of the valve is the mobile leaflet layer 719+729 penetrated by suture. This uninterrupted continuity of the operating leaflet material afforded by the folded design of the integrated cusp and leaflet structure endows the valve and its leaflets with strength, durability and resistance to stress damage at suture holes.

Fig. 8D shows an oblique axial (top/distal) perspective view of the assembled three-leaflet valve comprising the frame 910 and three identical folded integrated cusp and leaflet structures 730A, 730B and 730C attached within the frame with the view centered on an axial mounting bar 912A. The suture attachments are omitted for clarity. The cusp and leaflet structure 730A nearest in view is seen within the frame 910, with the outer aspect of the seam 732A, cuff wall extension sections 718A and 728A, and cusp wall sections 761A and 771A viewed through the interspaces of the frame 910. The seam 732A is aligned to the overlying axial mounting bar 912A to which it is attached along its length. The inner (luminal) aspect of the seams 732B and 732C and the cusp wall sections 761B, 771B, 761C and 771C of the other two folded cusp and leaflet structures 730B and 730C, respectively are seen on the far side of the view. The adjoined folded edges of the membrane portions of the commissure tabs 772B and 762C are shown in the far view in position opposite to the axial mounting bar 912A in the near view. The radially outward surface of the mobile leaflet sections 719A and 729A of the folded cusp and leaflet structure 730A is shown in the near view. The distal free edges of all three mobile leaflets are shown in the centrally apposed (coapted) position corresponding to the closed operating position of the valve. Fig. 8D also shows in that aspect interior to the cusps, folds 726B of cusp and leaflet structure 730B and 716C of cusp and leaflet structure 730C as they form the lower (proximal) boundary of the valve cusps.

Slotted Lattice Frame

Fig. 9A shows an oblique axial (top/distal) perspective view of a frame 920 of a design to receive the commissure tabs 762 and 772 through slots 924 in slotted members 923 in order that the tabs are secured and attached to the outer (abluminal) aspect of the frame. This approach to mounting and attaching the commissure tabs enables the loading forces on the leaflet commissures during valve operation to be advantageously distributed upon the frame slotted members 923 along their length rather than upon suture that directly tethers the leaflets, thus greatly reducing the risk of tearing of the material at points of suture penetration. The frame further comprises axial mounting bars 922 for mounting the central seams 732 joining the cusp wall sections 761 and 771 along folds 717 and 727. The frame further comprises a plurality of strut members 921 that otherwise form the metal lattice of the frame.

Each mounting bar 922 is to align with and attach to the axial outer seam of one single-piece completely folded and formed cusp and leaflet structure 730. The inner diameter D of the open frame, e.g., 19 – 35 mm naturally defines the deployed and operating diameter of the valve assembly after implantation in the body. The strut members 921 are of specific length and orientation to permit radial collapse and compression of the frame to a small diameter, e.g., 3-7 mm. The mounting bars 922 are near to equally spaced around the inner circumferential course of the frame. The length L of the arc along the inner circumference of the frame from the center of the mounting bar 922 to the center of the closest mounting bar 922 is approximately equal to (pi x D)/3. Thus defined, L also defines the transverse circumferential distance between folds 705 and 706 , approximating the circumferential extent of the portions of the joined cusp wall sections 761 and 771 extending between 705 and 706 of the folded cusp and leaflet structure of appropriate size when mounted within the frame 920.

The axial mounting bars 922 optionally contain holes and/or slots to facilitate suture attachment of the folded integrated cusp and leaflet structures 730. The frame is depicted in Figs. 9A-9E as having axial mounting bars 922 each with a hole near the proximal end to facilitate suture attachment of the apical (most proximal) portion of the folded cusp and leaflet structure.

Fig. 9B shows the metal lattice frame of Fig. 9A in the same perspective, but with the view centered on the slotted frame member 923.

Fig. 9C shows a side perspective view of the frame 920 centered on the axial mounting bar 922 with a superimposed plan view of the outer aspect of the completely folded integrated cusp and leaflet structure 730 (of Fig. 7I) as mounted within the frame 920 to demonstrate the relationships between the two. An example suture pattern for attachment is shown. The cusp wall seam 732 is aligned upon the inner surface of the mounting bar 922 of the frame 920 and attached by sutures in this example.

The commissure tabs 762 and 772 are to be understood as having been passed through the frame slots 924 from within the central space of the frame to the outer (abluminal) side and folded along 705 and 706, respectively onto the outer surface of the cusp and leaflet structure where they are attached along their common length both to the frame members 923 and, through the interspaces of the frame 920, to the radially underlying outer aspect of the cusp wall sections 761 and 771, respectively. The adjacent cusp and leaflet structures of the three-leaflet valve are not shown for clarity. The joining of adjacent commissure tabs at the slotted members 923 is demonstrated in Fig. 9D.

At the apical (most proximal) extent of the completely folded integrated cusp and leaflet structure 730, the apical portion folded radially outward along fold 703 is attached to the lower (most proximal) end of the axial mounting bar 922. When present, a hole near the end of the axial mounting bar 922 facilitates suture attachment at this point.

Fig. 9D shows a side perspective view of the frame 920 centered on the slotted frame member 923AB with a superimposed perspective view of the outer aspect of two circumferentially adjacent completely folded integrated cusp and leaflet structures 730A and 730B (of Fig. 7I) to demonstrate their relationships as mounted within the frame 920. An example suture pattern for attachment is shown. Suture attachment of the commissure folds 705 and 706 at the level of the slot is notably absent. Rather, attachment of the bodies of the commissure tabs 762A and 772B to the outer aspect of the frame at points removed from the free edges and folds of the material avoids suture penetration along the lines of traction in the slot and enhances the resistance of the structure to tearing at such suture attachments. The cusp wall seams 732A and 732B are aligned upon the inner surface of the mounting bars 922A and 922B, respectively of the frame 920 and attached by sutures in this example.

The commissure tabs 762A and 772B are to be understood as having been passed through the frame slot 924 from within the central space of the frame to the outer (abluminal) side and folded along 705A and 706B, respectively onto the outer surface of the cusp and leaflet structure where they are attached along their common length both to the frame member 923AB and, through the interspaces of the frame 920, to the radially underlying outer aspect of the cusp wall sections 761A and 771B, respectively.

Fig. 9E shows an oblique axial (top/distal) perspective view of the assembled three-leaflet valve comprising the frame 920 and three identical folded integrated cusp and leaflet structures 730A, 730B and 730C attached principally within the central space of the frame, but with the commissure tabs passed in complementary adjacent left-right pairs, 762A-772B, 762B-772C and 762C-772A, through the slots 924AB, 924BC and 924CA, of slotted frame members 923AB, 923BC, and 923CA, respectively. The view is centered on slotted member 923AB. The suture attachments are omitted for clarity.

The cusp and leaflet structure 730C farthest in view is seen within the frame 920, with the inner aspect of the seam 732C and cusp wall sections 761C and 771C in the far view. The cuff wall extension sections 718C and 728C are depicted as folded onto the outer aspect of the cusp wall sections 761C and 771C, respectively, but within the central space of the frame 920 and apposed to the inner surface of the frame. The inner (luminal) aspect of the seam 732C is shown aligned to the outwardly overlying axial mounting bar 922C to which it is attached along its length. The outer (abluminal) aspect of the top (most distal) portions of the seams 732A and 732B and the cusp wall sections 761A and 771B, of the other two folded cusp and leaflet structures 730A and 730B are also shown through the interspaces of the frame on either side of the near view.

The commissure tabs 762A and 772B, aligned and apposed along folds 705A and 706B, respectively are shown centered in the near view in position opposite to the axial mounting bar 922C and cusp wall seam 732C in the far view. The key mounting configuration of the valve commissures to the slotted frame members is here demonstrated. The triangular commissure tabs are formed as a result of the folding of the membrane template along folds 716 and 726, and are comprised of overlapping layers of the cusp wall section and the mobile leaflet section. Thus, with passage of the commissure tabs from within the interior space of the frame through the frame slots, both the cusp wall layer and the mobile leaflet layer are carried together to the outer aspect of the frame where they are attached. In addition, the interior aspect of the commissure folds 706A of cusp and leaflet structure 730A and 705B of cusp and leaflet structure 730B are shown where they mark the segment at which the commissure tabs 772A and 762B are passed through the frame slots 924CA and 924BC of slotted members 923CA and 923BC, respectively, and are tethered thereto.

The radially outward surface of the mobile leaflet sections 719A, 729A of the folded cusp and leaflet structure 730A and sections 719B, 729B of the folded cusp and leaflet structure 730B are shown on the left and right sides, respectively of the near view. (These labels omitted for clarity.)

The distal free edges of all three mobile leaflets are shown in the centrally apposed (coapted) position corresponding to the closed operating position of the valve. Fig. 9E also shows in that aspect interior to the cusps, a portion of folds 726A of cusp and leaflet structure 730A and 716B of cusp and leaflet structure 730B as they form the lower (proximal) boundary of the valve cusps.

The template examples disclosed herein are provided for enablement purposes and shall not be interpreted as limiting the scope of the claims. For example, angular values shown and/or described herein are not to be interpreted as limiting the scope of a claim unless included in a given claim.

As those skilled in the art will appreciate, circumference length varies with the diameter circumscribed therein. Accordingly, refinements in the valve manufacturing process may address adjusting the length of the leaflet free edge to be slightly less than the edge length of the cusp wall, i.e., less than the circumferential arc length between the commissures. This adjustment depends upon the dimensions of a given valve in production, as well as the dimensions of the given valve's component elements.

In still other embodiments of the one or more present inventions, the percutaneously deliverable heart valve may include various other configurations by using different variations of the polygon pattern, so as to include, for example, an inner sealing cuff for the valve that is continuous and integral with the leaflet structure itself. In yet other embodiments, the percutaneously deliverable heart valve may include different configurations by adjusting the pattern and folding technique, such as the angle of the cone and its surface area, or the extent of apposition between the leaflets may also be specified.

The present invention may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

The one or more present inventions, in various embodiments, include components, methods, processes, systems and/or apparatus substantially as depicted and described herein, including various embodiments, subcombinations, and subsets thereof. Those of skill in the art will understand how to make and use the present invention after understanding the present disclosure.

The present invention, in various embodiments, includes providing devices and processes in the absence of items not depicted and/or described herein or in various embodiments hereof, including in the absence of such items as may have been used in previous devices or processes (e.g., for improving performance, achieving ease and/or reducing cost of implementation).

The foregoing discussion of the invention has been presented for purposes of illustration and description. The foregoing is not intended to limit the invention to the form or forms disclosed herein. In the foregoing Detailed Description for example, various features of the invention are grouped together in one or more embodiments for the purpose of streamlining the disclosure. This method of disclosure is not to be interpreted as reflecting an intention that the claimed invention requires more features than are expressly recited in each claim. Rather, as the following claims reflect, inventive aspects lie in less than all features of a single foregoing disclosed embodiment. Thus, the following claims are hereby incorporated into this Detailed Description, with each claim standing on its own as a separate preferred embodiment of the invention.

Moreover, though the description of the invention has included description of one or more embodiments and certain variations and modifications, other variations and modifications are within the scope of the invention (e.g., as may be within the skill and knowledge of those in the art, after understanding the present disclosure). It is intended to obtain rights which include alternative embodiments to the extent permitted, including alternate, interchangeable and/or equivalent structures, functions, ranges or steps to those claimed, whether or not such alternate, interchangeable and/or equivalent structures, functions, ranges or steps are disclosed herein, and without intending to publicly dedicate any patentable subject matter.

CLAIMS

What is claimed is:

1. A transcatheter, percutaneously implantable, prosthetic heart valve, comprising:

a lattice frame; and

two or more integrated cusp and leaflet folded structures attached to the lattice frame, the two or more integrated cusp and leaflet folded structures each comprising a flat sheet of biocompatible membrane that is folded to include a mobile leaflet layer and a cusp wall layer, wherein the cusp wall layer located radially outside of the mobile leaflet layer, and wherein the cusp wall layer is further formed by joining apposing sides of the cusp wall layer along a seam.

2. The transcatheter, percutaneously implantable, prosthetic heart valve of Claim 1, wherein the two or more integrated cusp and leaflet folded structures are each attached along their respective seams to the lattice frame.

3. The transcatheter, percutaneously implantable, prosthetic heart valve of Claim 2, wherein the seams are oriented in a direction substantially parallel to an axis of the lattice frame.

4. The transcatheter, percutaneously implantable, prosthetic heart valve of Claim 1, wherein the flat sheet of biocompatible membrane forming at least one integrated cusp and leaflet folded structure of the two or more integrated cusp and leaflet folded structures comprises two or more pieces of biocompatible membrane material.

5. A transcatheter, percutaneously implantable, prosthetic heart valve, comprising:

a lattice frame; and

two or more integrated cusp and leaflet folded structures attached to the lattice frame, the two or more integrated cusp and leaflet folded structures each comprising a flat sheet of a biocompatible membrane that is folded to include a valve cusp according to a flat folding pattern, wherein the valve cusp is further formed by joining apposing sides of the valve cusp along a seam, and wherein the two or more integrated cusp and leaflet folded structures are each attached along their respective cusp seams to the lattice frame in a direction substantially parallel to an axis of the lattice frame.

6. The transcatheter, percutaneously implantable, prosthetic heart valve of Claim 5, wherein two distal, downstream, vertices of each of the two or more integrated cusp and leaflet folded structures are folded over as vertex folds in a radially outward direction and fixed to the lattice frame such that the vertex folds of circumferentially adjacent leaflets are adjacent and define a degree of leaflet apposition at points corresponding to leaflet commissures.

7. The transcatheter, percutaneously implantable, prosthetic heart valve of Claim 6, wherein the two distal, downstream, vertices are fixed to the lattice frame by attachment not along an alignment with the vertex folds.

8. The transcatheter, percutaneously implantable, prosthetic heart valve of Claim 5, wherein a vertex forming a proximal, upstream, tip of the valve cusp is folded over in a radially outward direction and attached to an inner portion of the lattice frame.

9. The transcatheter, percutaneously implantable, prosthetic heart valve of Claim 5, wherein the flat folding pattern is polygonal and includes extending portions that, when the cusp is mounted, extend circumferentially outward from an axial line of attachment of the cusp to the lattice frame so as to form, when joined and attached to corresponding extending portions of neighboring cusps, an integral, inner, luminal, circumferentially complete sealing cuff.

10. The transcatheter, percutaneously implantable, prosthetic heart valve of Claim 5, wherein the flat folding pattern is polygonal and includes extending portions that, when the two or more integrated cusp and leaflet folded structures are mounted, extend circumferentially outward from an axial line of attachment of the cusp to the lattice frame so as to form a circumferentially incomplete sealing cuff portion associated with each cusp.

11. The transcatheter, percutaneously implantable, prosthetic heart valve of Claim 5, wherein a separate tubular cuff of biocompatible membrane is attached to an outer, abluminal surface of the lattice frame to form a sealing cuff.

12. The transcatheter, percutaneously implantable, prosthetic heart valve of Claim 5, wherein the lattice frame is collapsible and expandable and comprises a metal alloy substantially configured as tubular stent member.

13. The transcatheter, percutaneously implantable, prosthetic heart valve of Claim 5, wherein the biocompatible membrane comprises processed mammalian pericardium tissue.

14. The transcatheter, percutaneously implantable, prosthetic heart valve of Claim 5, wherein the biocompatible membrane does not comprise a treated tissue.

15. The transcatheter, percutaneously implantable, prosthetic heart valve of Claim 5, wherein the biocompatible membrane comprises a synthetic material.

16. The transcatheter, percutaneously implantable, prosthetic heart valve of Claim 5, wherein the cusp seams of the two or more integrated cusp and leaflet folded structures are each oriented along an axis of flow of the valve.

17. The transcatheter, percutaneously implantable, prosthetic heart valve of Claim 5, wherein the two or more integrated cusp and leaflet folded structures are each further attached to a circumferential portion of the lattice frame along at least a portion of their distal downstream edges.

18. The transcatheter, percutaneously implantable, prosthetic heart valve of Claim 5, wherein the two or more integrated cusp and leaflet folded structures are attached to the lattice frame at least at a non-commissural seam aligned with an axial flow direction of the valve.

19. A transcatheter, percutaneously implantable, prosthetic heart valve, comprising:

a lattice frame; and

two or more integrated cusp and leaflet structures attached to the lattice frame, the two or more integrated cusp and leaflet structures each comprising a flat sheet of biocompatible membrane that is folded to include a mobile leaflet layer and a cusp wall layer, wherein with the mobile leaflet layer in a position corresponding to a closed operating configuration of the valve a transverse cross-sectional area of a cusp-sinus space decreases monotonically from a distal end to a proximal end of the mobile leaflet layer.

20. The transcatheter, percutaneously implantable, prosthetic heart valve of Claim 19, wherein the cusp wall layer is located radially outside of the mobile leaflet layer.

21. The transcatheter, percutaneously implantable, prosthetic heart valve of Claim 19, wherein the cusp wall layer is further formed by joining apposing sides of the cusp wall layer along a seam.

22. The transcatheter, percutaneously implantable, prosthetic heart valve of Claim 19, wherein with the mobile leaflet layer in a position corresponding to a closed operating configuration of the valve a transverse cross-sectional length of the mobile leaflet layer decreases monotonically from a distal end to a proximal end of the mobile leaflet layer.

23. The transcatheter, percutaneously implantable, prosthetic heart valve of Claim 19, wherein the mobile leaflet layer and the cusp wall layer of each integrated cusp and leaflet structure are a single continuous piece of biocompatible membrane.

24. In subcombination, an integrated cusp and leaflet structure for attachment to a lattice frame to form a valve configured for implantation in a vascular system of a patient, the integrated cusp and leaflet structure comprising:

a flat sheet of a biocompatible membrane that is folded to include a mobile leaflet layer and a cusp wall layer, wherein the cusp wall layer is divided along a seam, and wherein the mobile leaflet layer is continuous and apposes the cusp wall layer when the integrated cusp and leaflet structure is pressed substantially flat.

25. The subcombination of Claim 24, wherein the mobile leaflet layer and the cusp wall layer of the integrated cusp and leaflet structure are a single continuous piece of biocompatible membrane.

26. The subcombination of Claim 24, wherein the biocompatible membrane comprises processed mammalian pericardium tissue.

27. The subcombination of Claim 24, wherein the biocompatible membrane does not comprise a treated tissue.

28. The subcombination of Claim 24, wherein the biocompatible membrane

comprises a synthetic material.

29. The subcombination of Claim 24, wherein the integrated cusp and leaflet structure further comprises at least one commissure tab.

30. The subcombination of Claim 29, wherein the at least one commissure tab is configured for engaging a slot within a member of the lattice frame.

31. A method of forming an integrated cusp and leaflet folded structure for use in an implantable valve having an axial flow direction, comprising:

folding a flat sheet of biocompatible membrane to form an integrated cusp and leaflet folded structure according to a flat folding pattern, wherein said folding includes making two diagonal folds in the flat sheet of biocompatible membrane, the two diagonal folds separating a mobile leaflet layer from a cusp wall layer of the integrated cusp and leaflet folded structure.

32. The method of forming the integrated cusp and leaflet folded structure of Claim 31, wherein said two diagonal folds are angled at between 10 to 80 degrees from the axial flow direction.

33. The method of forming an integrated cusp and leaflet folded structure of Claim 31, further comprising forming first and second cusp wall folds, wherein the cusp wall layer is further formed by joining apposing membrane portions adjacent the first and second cusp wall folds along a seam that is oriented substantially parallel with the axial flow direction.

34. A method of forming a transcatheter, percutaneously implantable, prosthetic heart valve, comprising:

folding a plurality of integrated cusp and leaflet folded structures, each integrated cusp and leaflet folded structure of the plurality of integrated cusp and leaflet folded structures comprising a flat sheet of biocompatible membrane that is folded to form a cusp according to a flat folding pattern, wherein the cusp is further formed by joining apposing sides of the cusp along a seam; and

attaching each integrated cusp and leaflet folded structure of the plurality of integrated cusp and leaflet folded structures to a lattice frame, wherein the two or more integrated cusp and leaflet folded structures are each attached along their respective seams to the lattice frame in a direction substantially parallel to an axis of the lattice frame.

Figure 1A

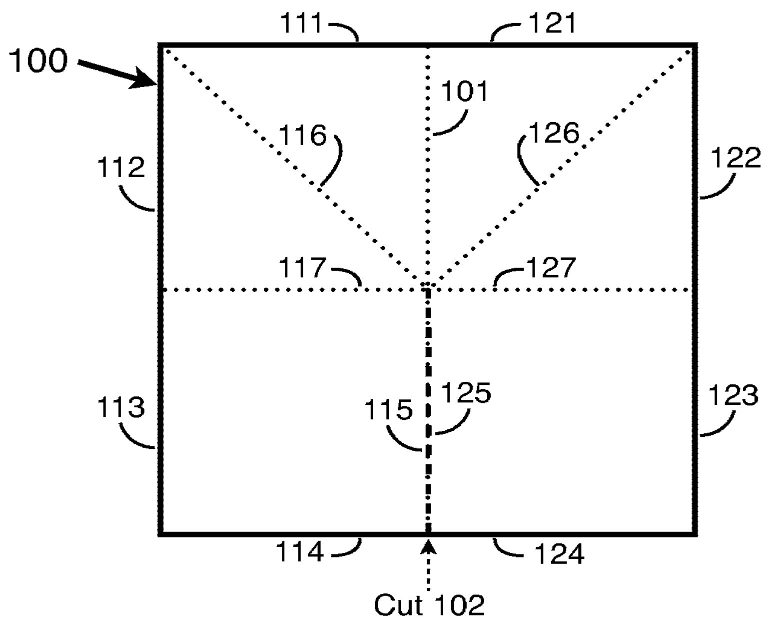
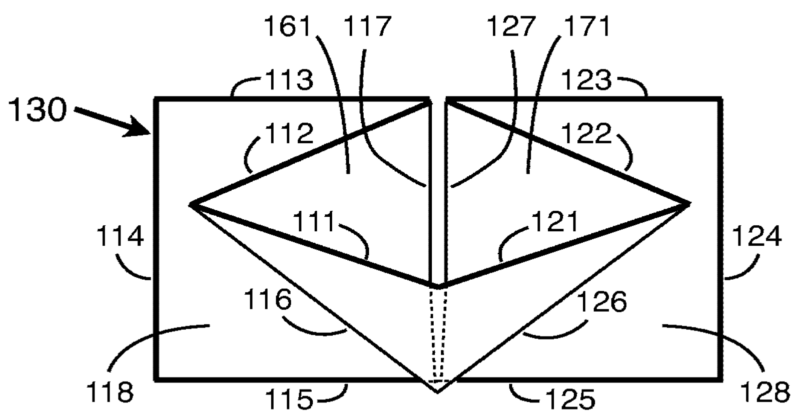


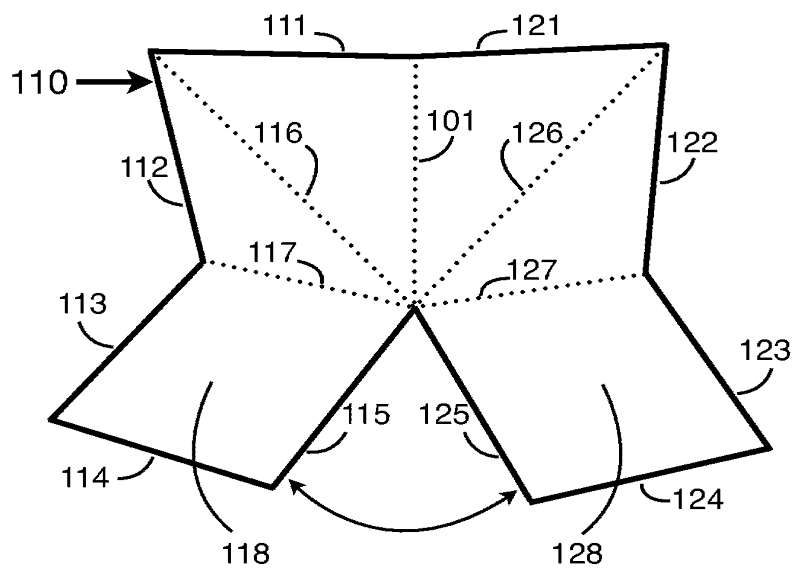
Figure 1B



LEGEND

(thick solid line)	Visible free (cut) edge of membrane piece
(thin solid line)	Visible edge of folded structure
(dotted line)	Line of fold / crease
(fine dashed line)	Hidden (phantom) edges of folded structure
(thick dashed line)	Line of cut

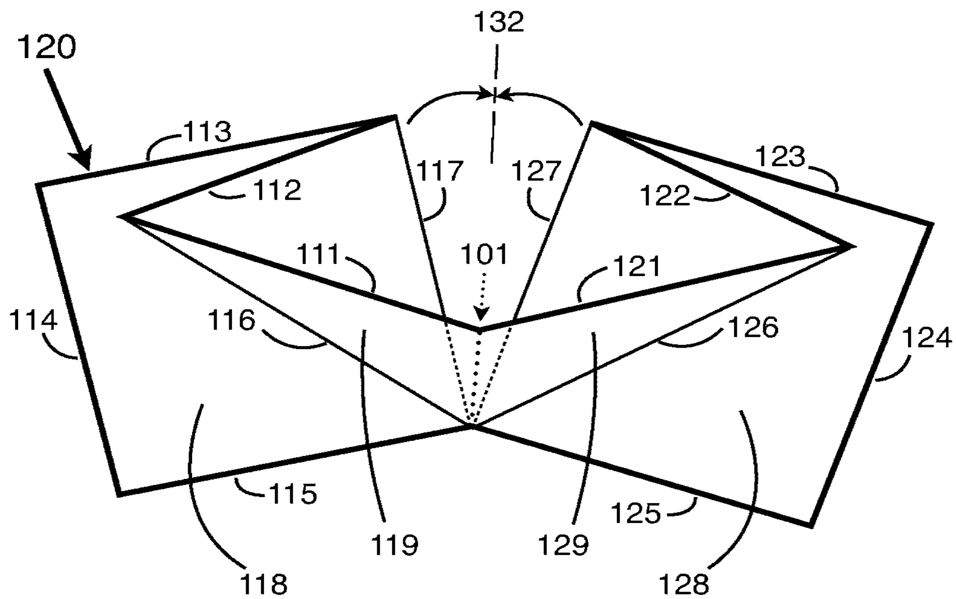
Figure 1C



LEGEND

▬▬▬	Visible free (cut) edge of membrane piece
———	Visible edge of folded structure
···········	Line of fold / crease
------------	Hidden (phantom) edges of folded structure
■ ■ ■ ■ ■	Line of cut

Figure 1D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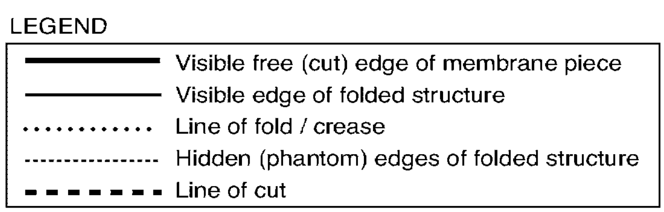

LEGEND
Visible free (cut) edge of membrane piece
Visible edge of folded structure
Line of fold / crease
Hidden (phantom) edges of folded structure
Line of cut

Figure 1E

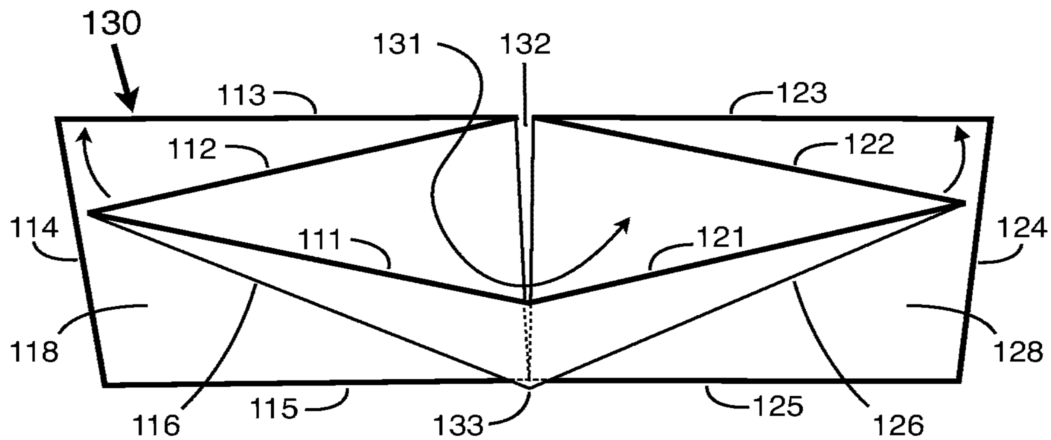
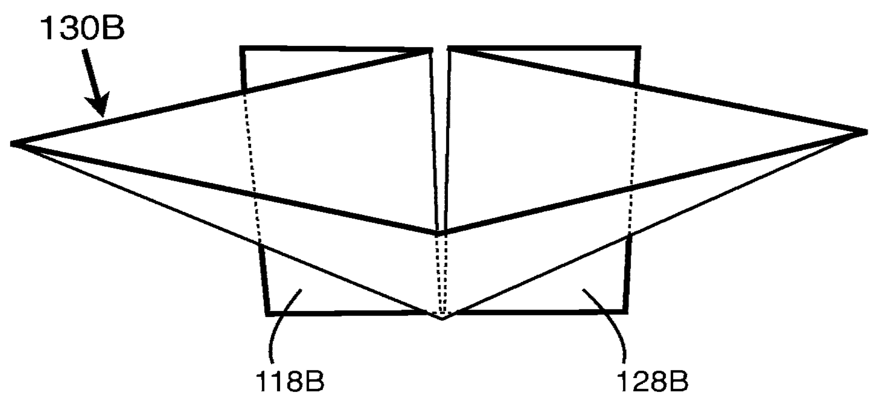


Figure 1F



LEGEND

(thick solid line)	Visible free (cut) edge of membrane piece
(solid line)	Visible edge of folded structure
(dotted line)	Line of fold / crease
(fine dotted line)	Hidden (phantom) edges of folded structure
(dashed line)	Line of cut

Figure 1G

Suture attachments omitted for clarity.

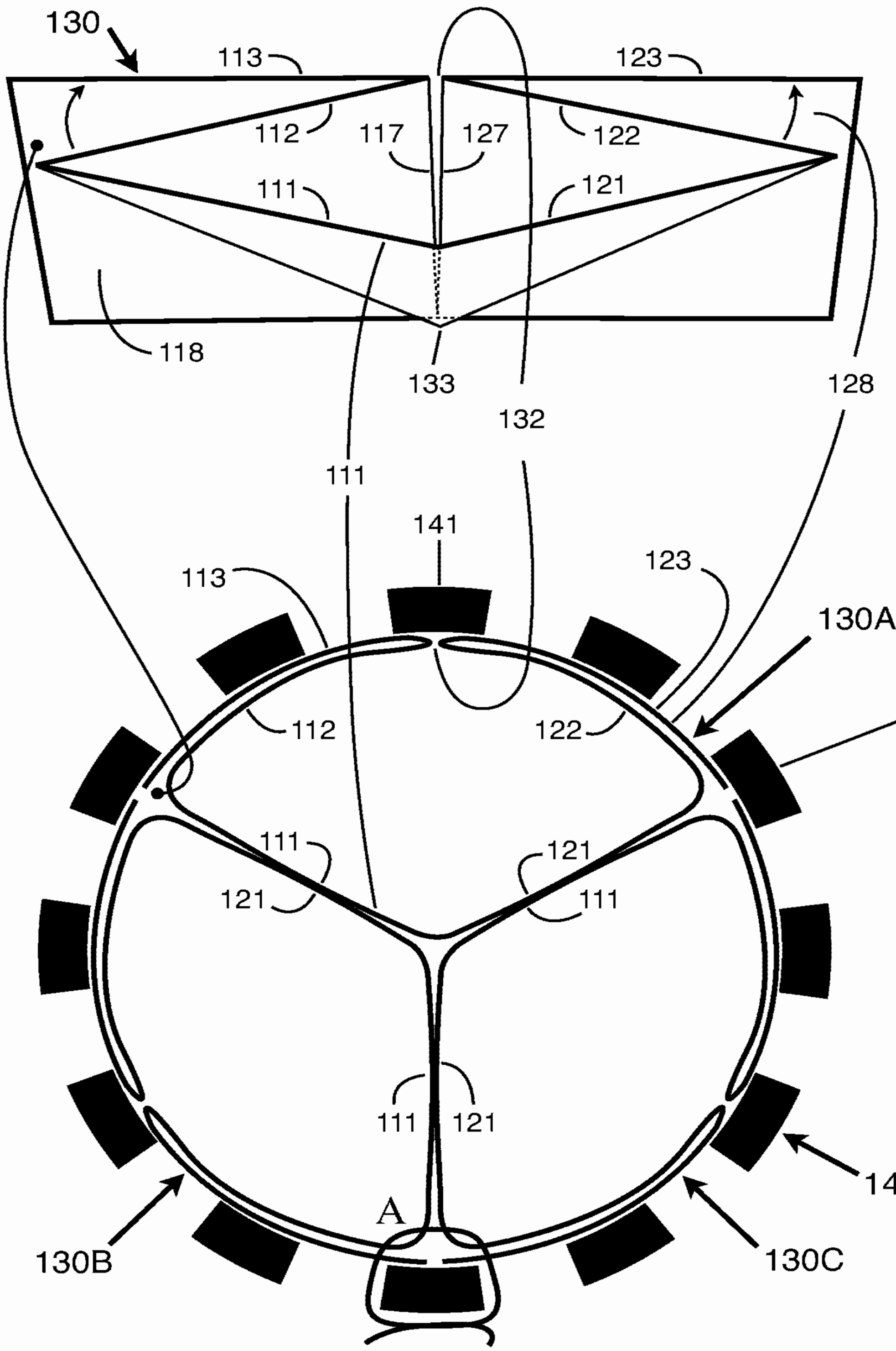
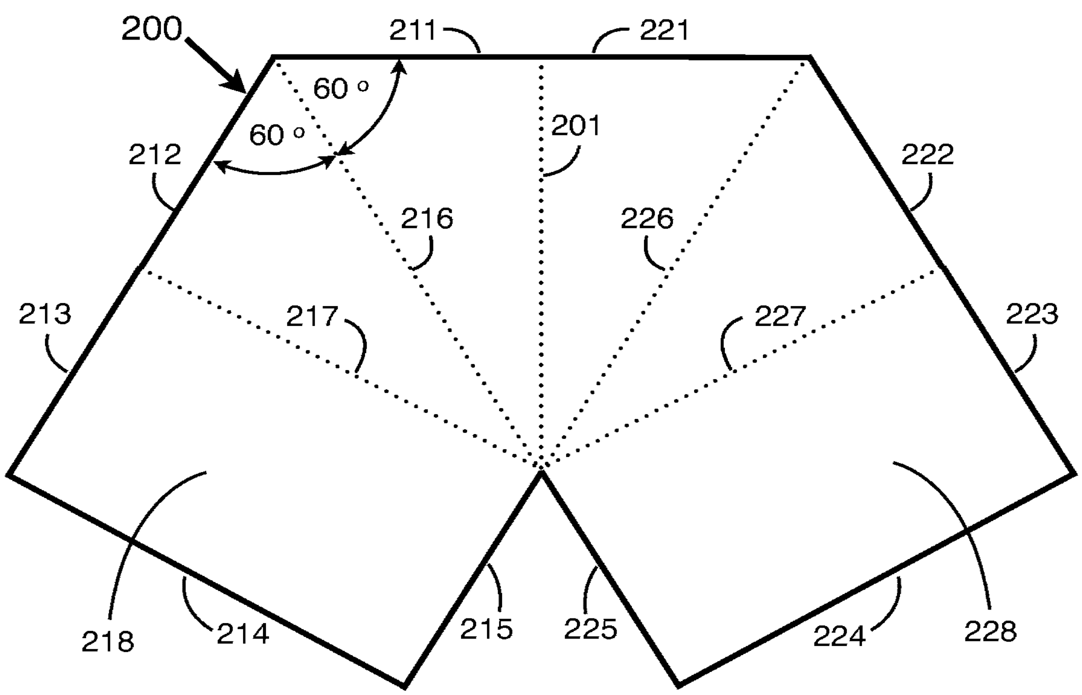


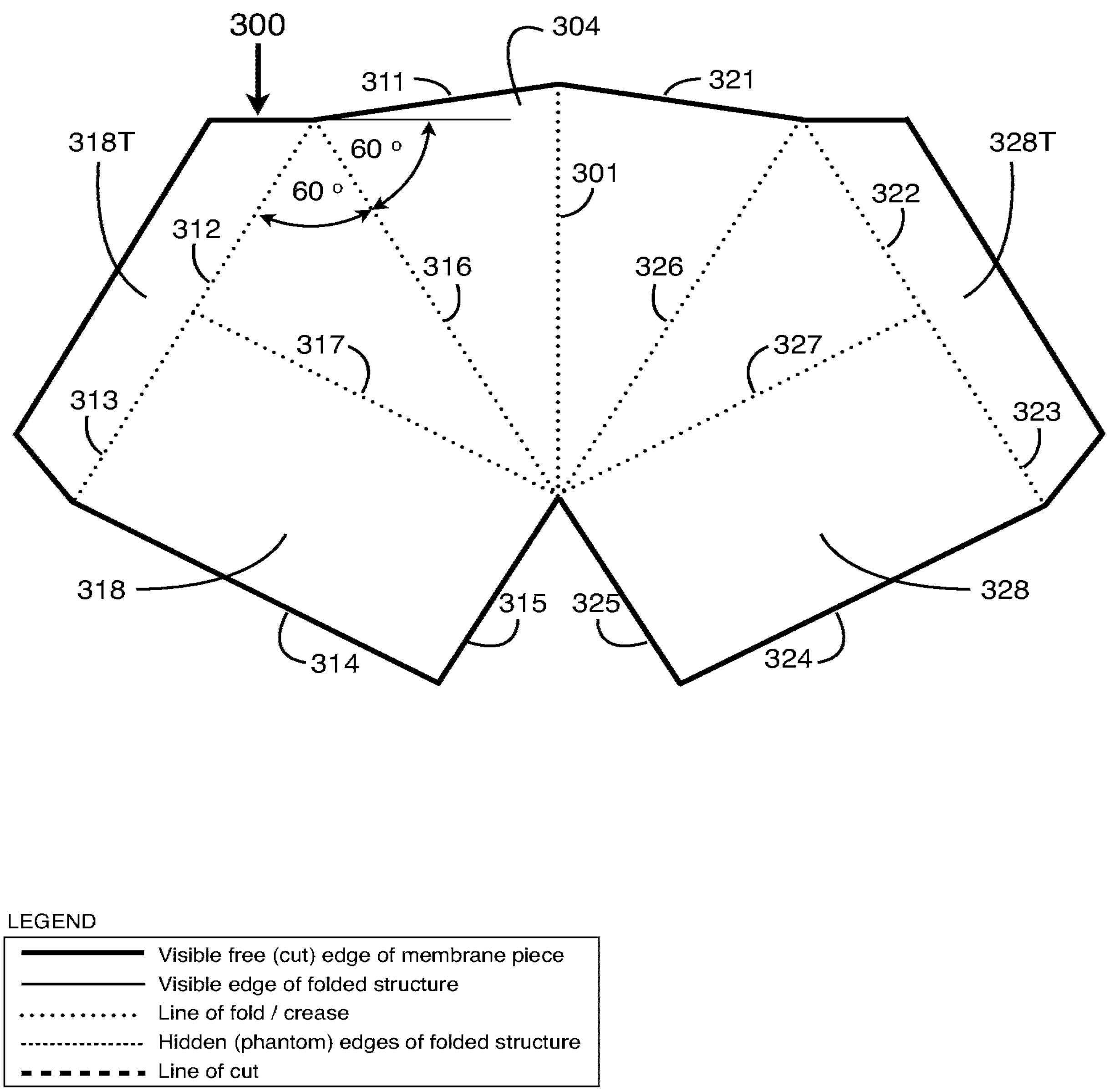
Figure 2



LEGEND

(thick solid line)	Visible free (cut) edge of membrane piece
(solid line)	Visible edge of folded structure
....	Line of fold / crease
----------------	Hidden (phantom) edges of folded structure
■ ■ ■ ■ ■ ■	Line of cut

Figure 3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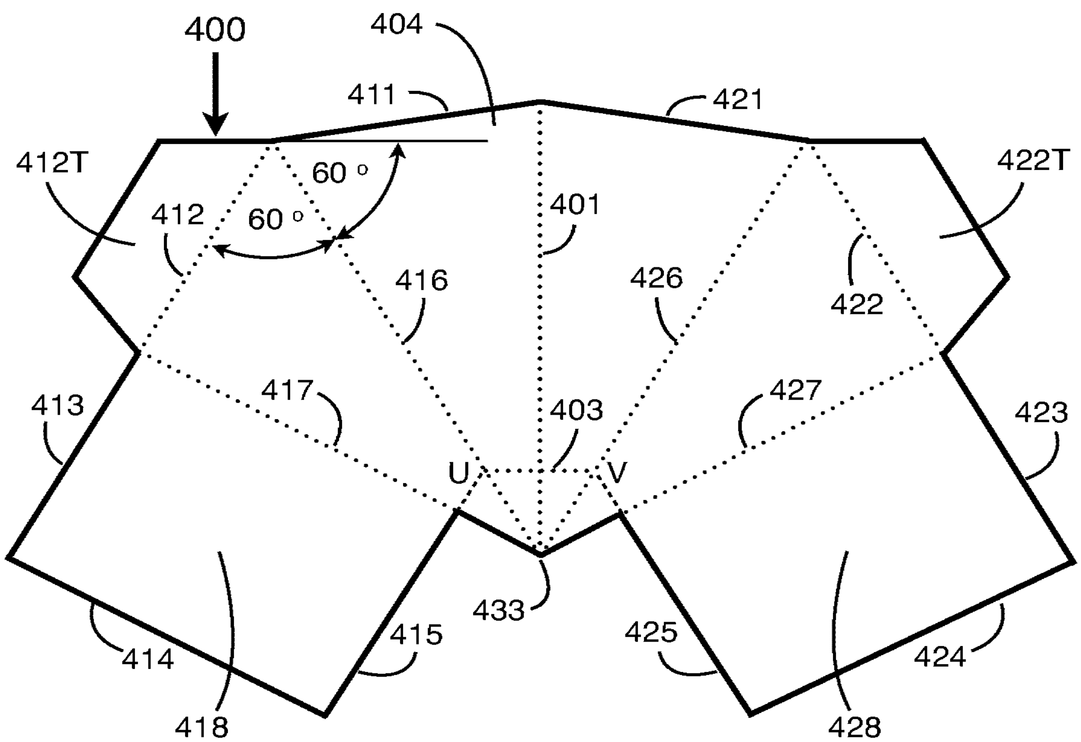
LEGEND
Visible free (cut) edge of membrane piece
Visible edge of folded structure
Line of fold / crease
Hidden (phantom) edges of folded structure
Line of cut

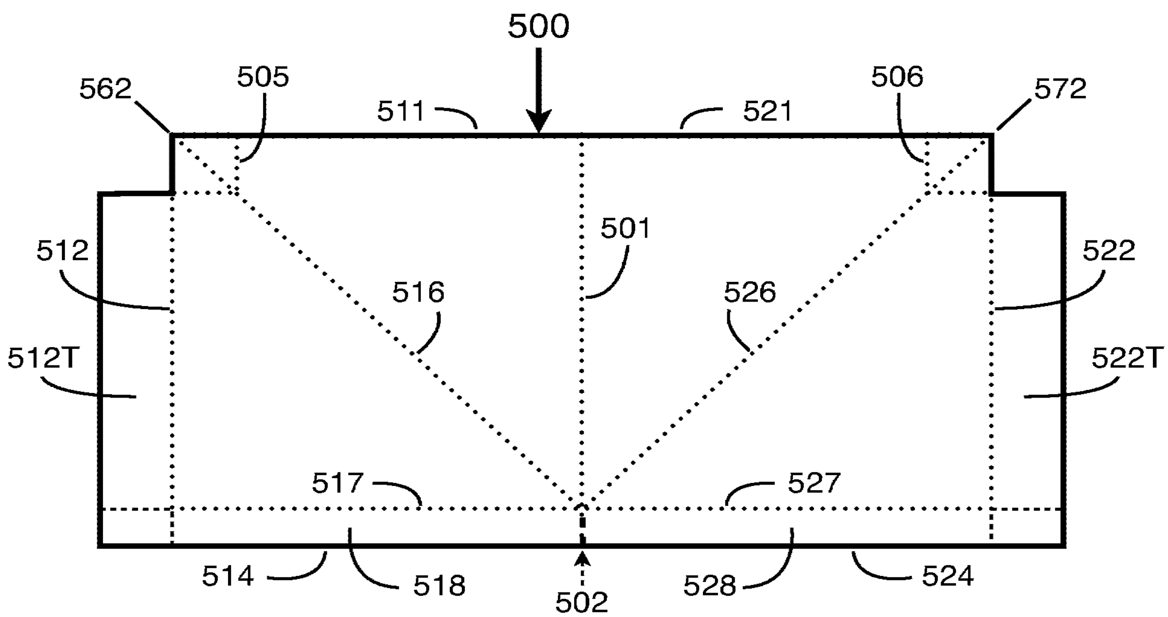
Figure 4



LEGEND

▬▬▬	Visible free (cut) edge of membrane piece
———	Visible edge of folded structure
···········	Line of fold / crease
----------------	Hidden (phantom) edges of folded structure
■ ■ ■ ■ ■ ■ ■	Line of cut

Figure 5A



LEGEND

▬▬▬	Visible free (cut) edge of membrane piece
———	Visible edge of folded structure
···········	Line of fold / crease
-------------	Hidden (phantom) edges of folded structure
■ ■ ■ ■ ■	Line of cut

Figure 5B

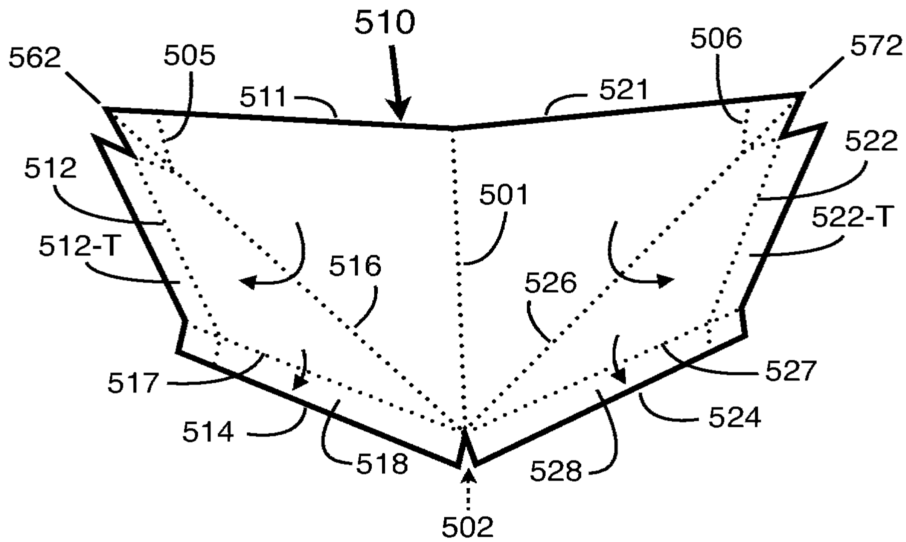
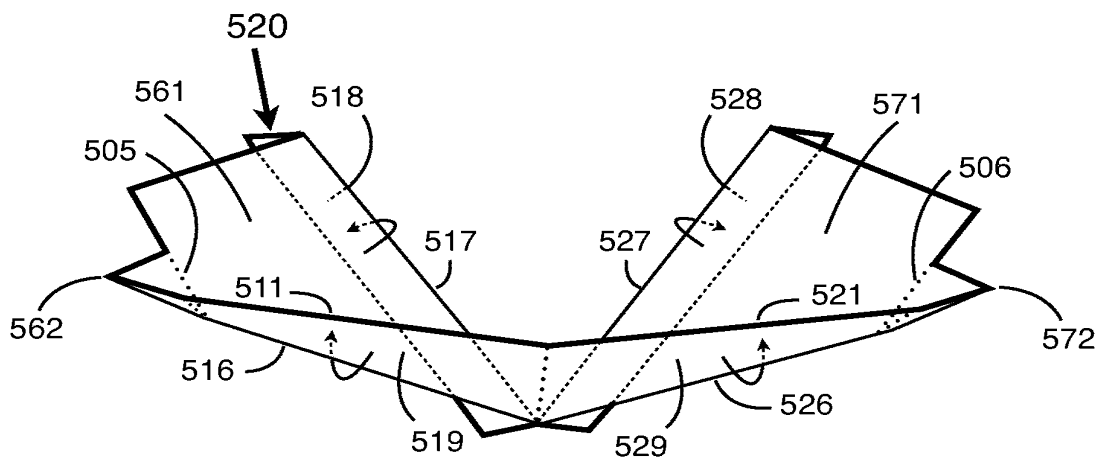


Figure 5C



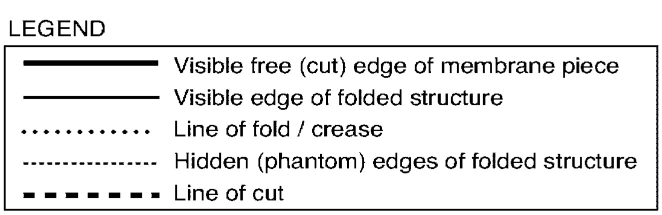
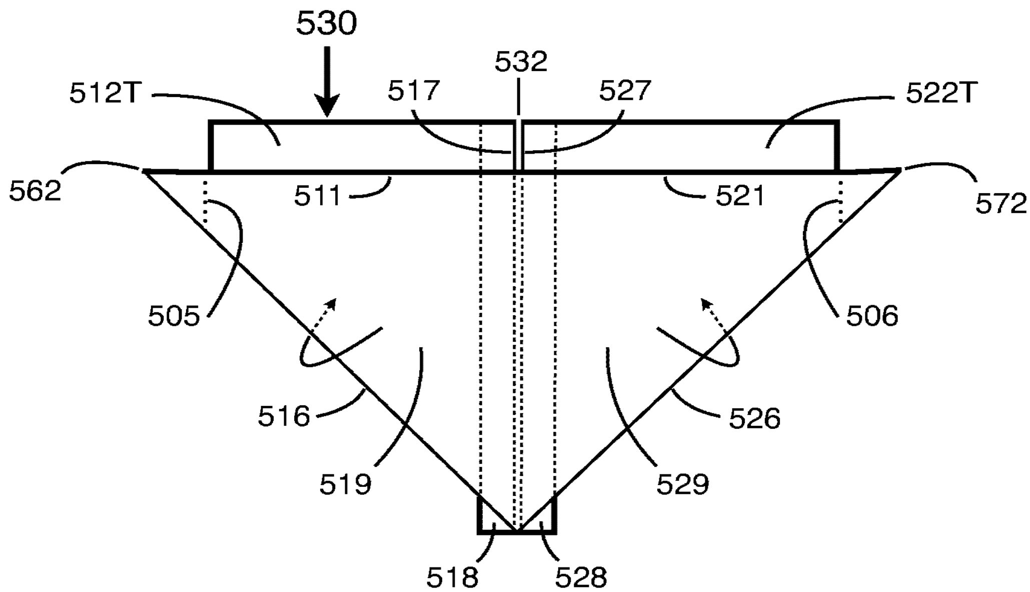


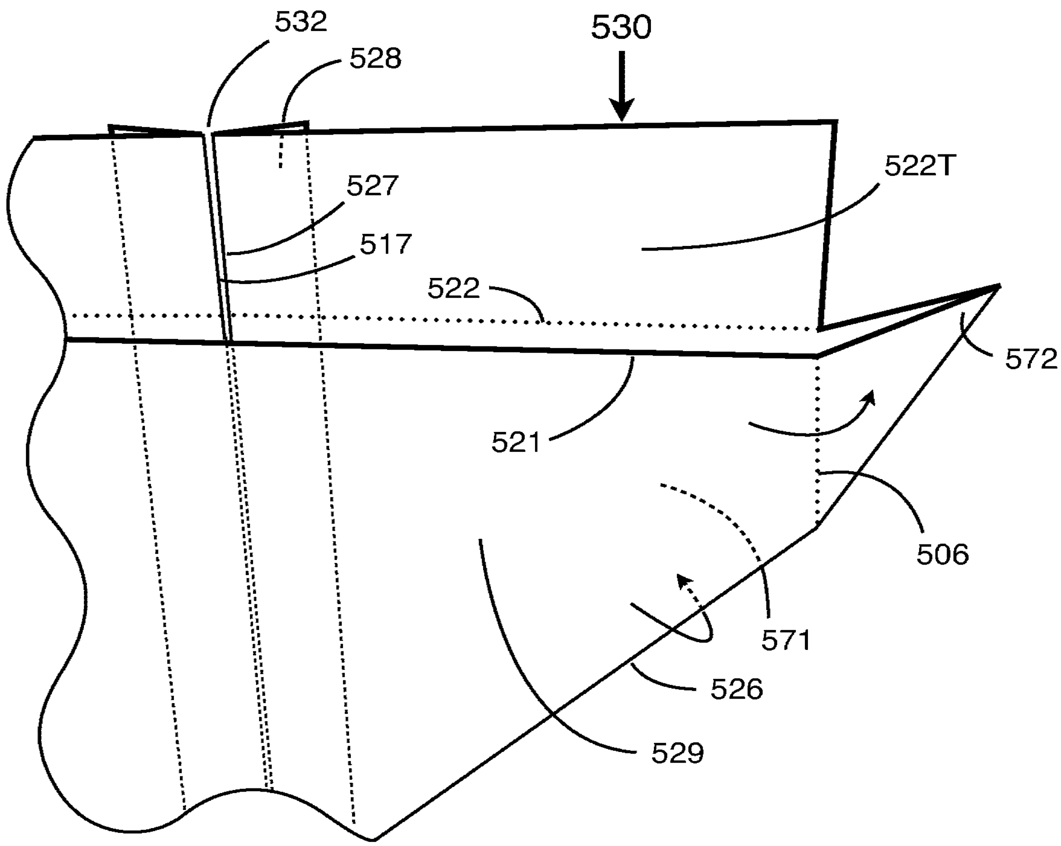
Figure 5D



LEGEND

▬▬▬	Visible free (cut) edge of membrane piece
———	Visible edge of folded structure
···········	Line of fold / crease
----------------	Hidden (phantom) edges of folded structure
▬ ▬ ▬ ▬	Line of cut

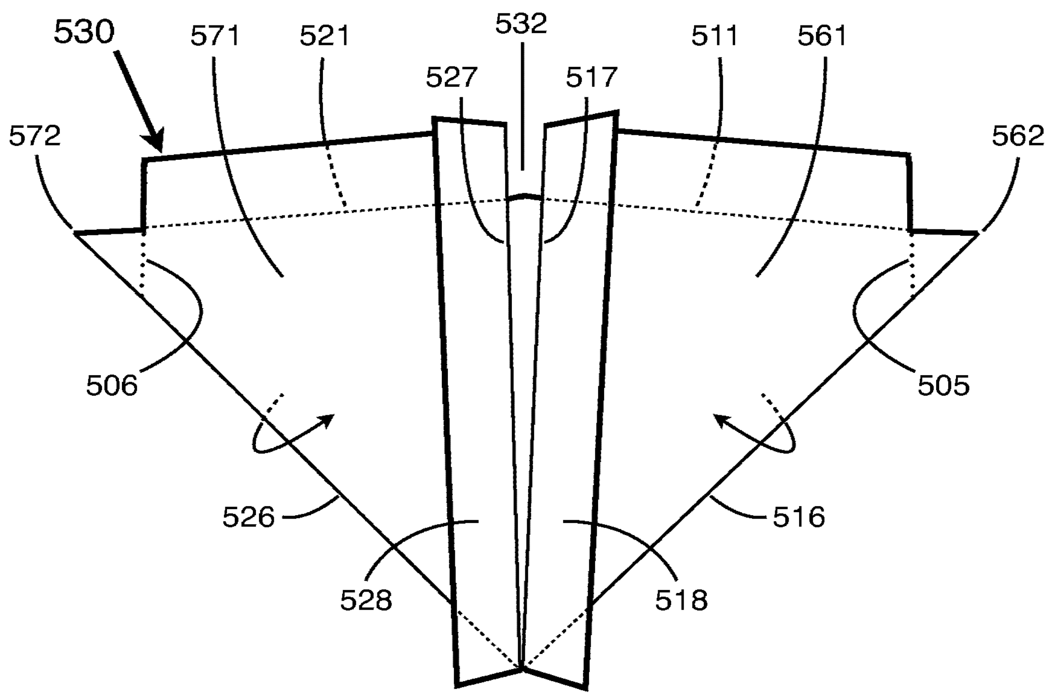
Figure 5E



LEGEND

━━━━	Visible free (cut) edge of membrane piece
────	Visible edge of folded structure
···········	Line of fold / crease
-------------	Hidden (phantom) edges of folded structure
▬ ▬ ▬ ▬	Line of cut

Figure 5F



LEGEND

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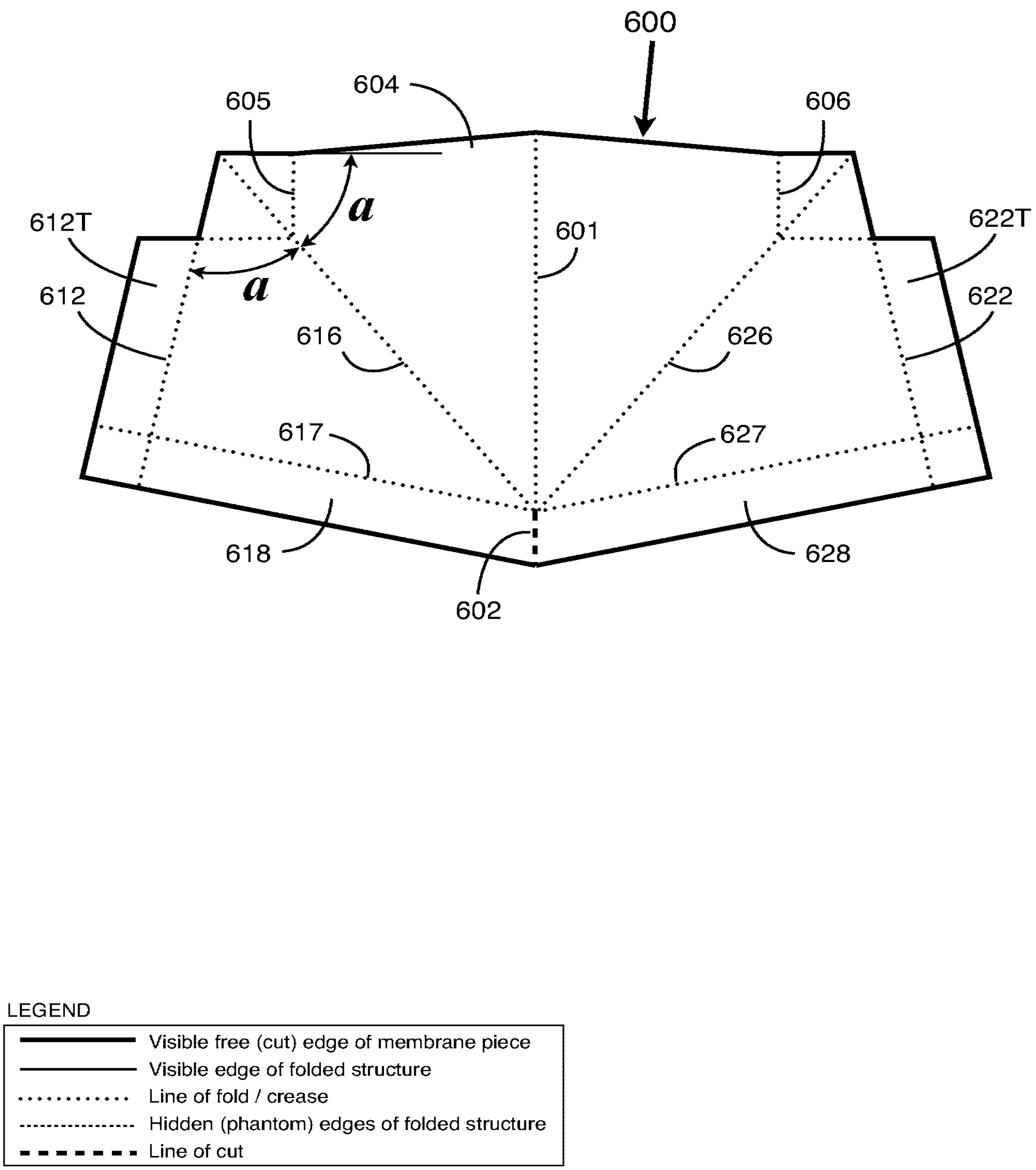
———	Visible edge of folded structure
···········	Line of fold / crease
-----------	Hidden (phantom) edges of folded structure
■ ■ ■ ■	Line of cut

Figure 6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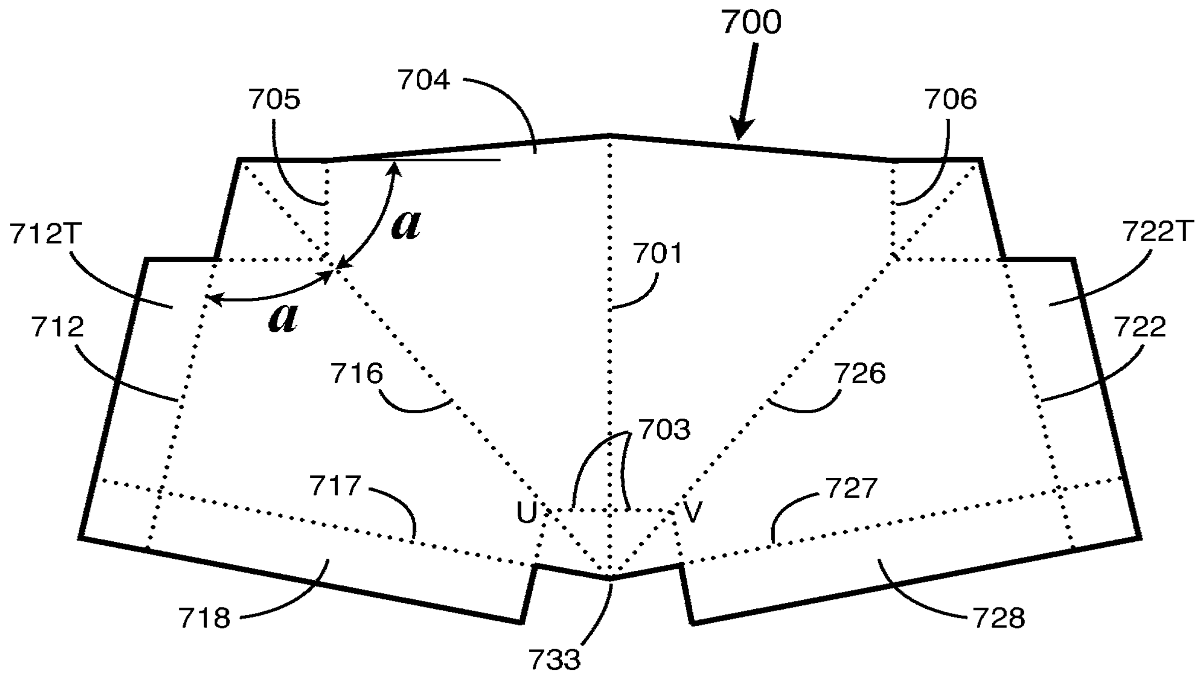
LEGEND
Visible free (cut) edge of membrane piece
Visible edge of folded structure
Line of fold / crease
Hidden (phantom) edges of folded structure
Line of cut

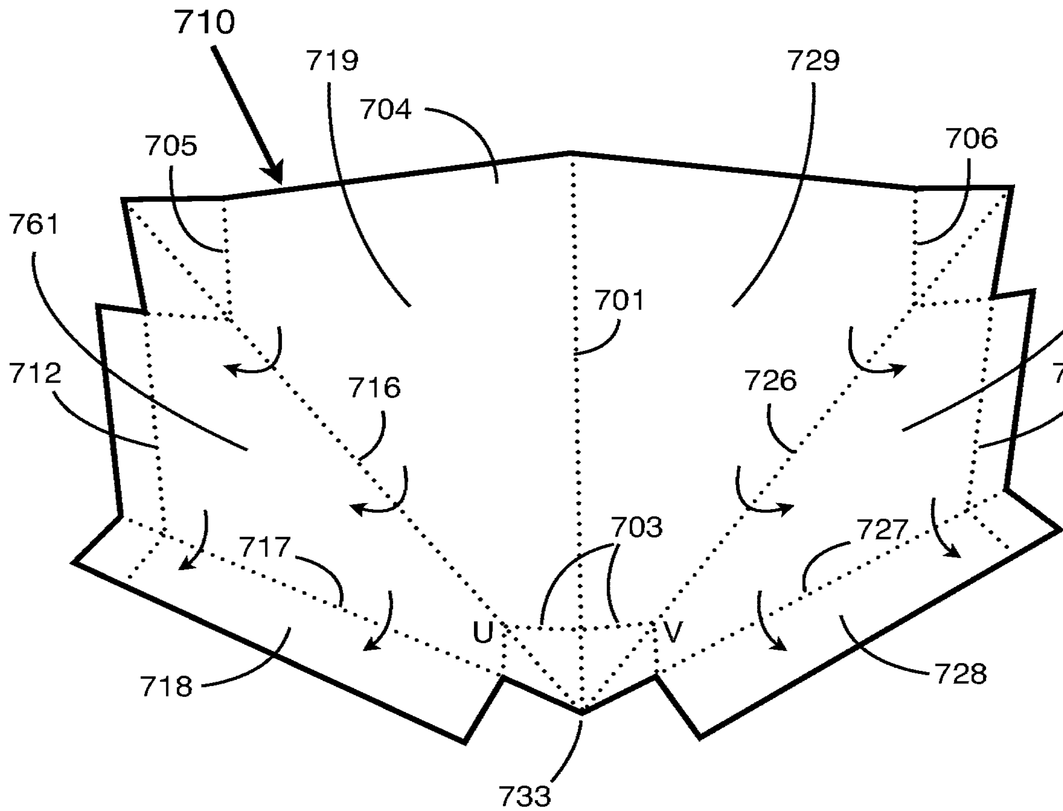
Figure 7A



LEGEND

▬▬▬	Visible free (cut) edge of membrane piece
───	Visible edge of folded structure
·········	Line of fold / crease
------------	Hidden (phantom) edges of folded structure
▬ ▬ ▬ ▬	Line of cut

Figure 7B



LEGEND

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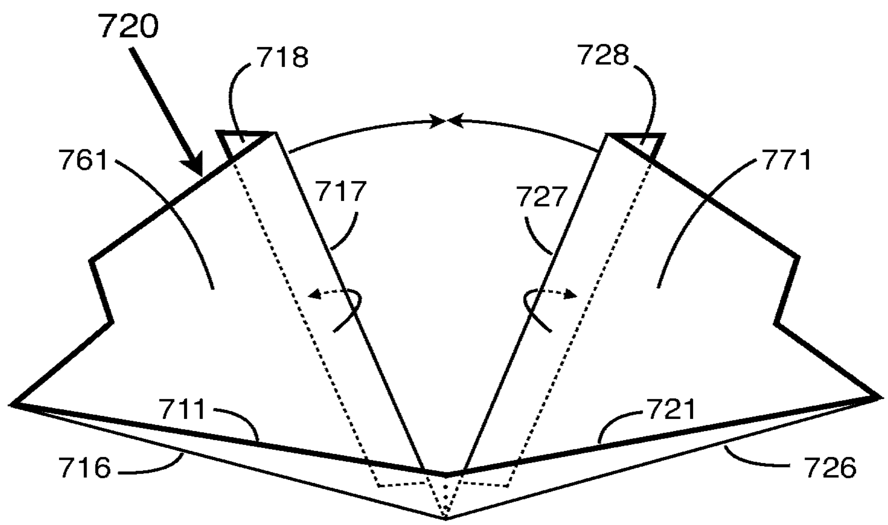
———	Visible edge of folded structure
··········	Line of fold / crease
----------	Hidden (phantom) edges of folded structure
■ ■ ■ ■	Line of cut

Figure 7C



LEGEND

▬▬▬	Visible free (cut) edge of membrane piece
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-----------------	Hidden (phantom) edges of folded structure
■ ■ ■ ■ ■ ■	Line of cut

Figure 7D

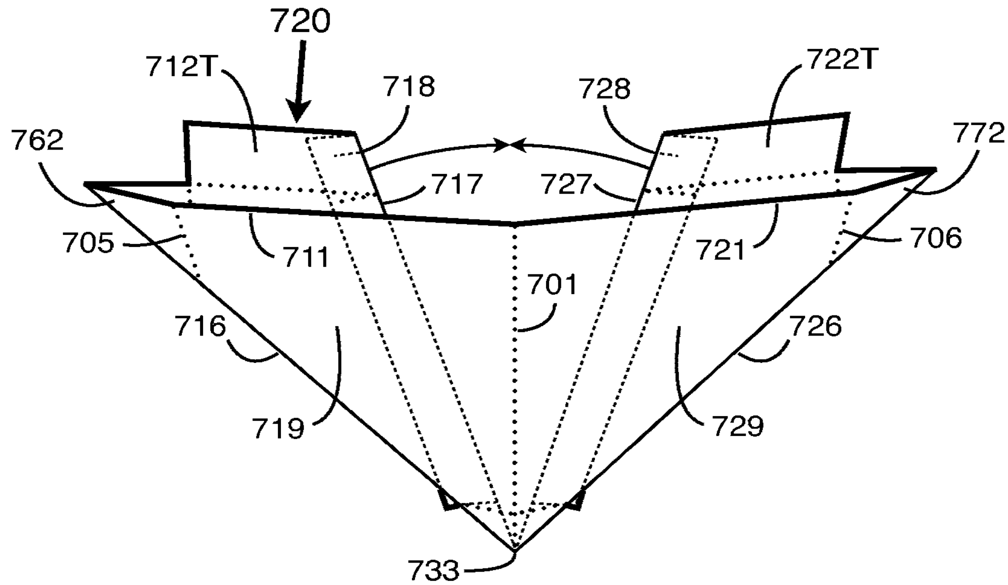
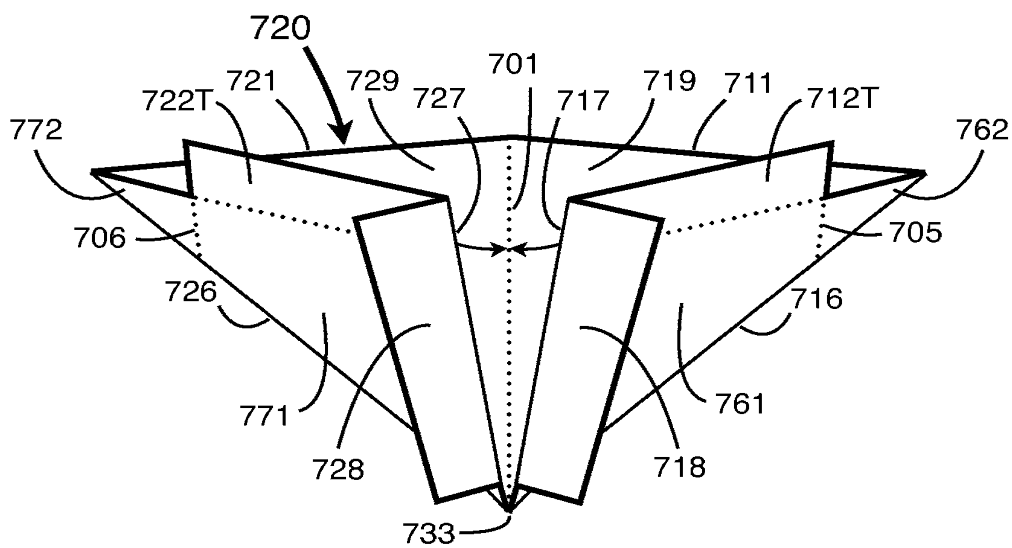


Figure 7E



LEGEND

(thick solid line)	Visible free (cut) edge of membrane piece
(solid line)	Visible edge of folded structure
(dotted line)	Line of fold / crease
(fine dashed line)	Hidden (phantom) edges of folded structure
(heavy dashed line)	Line of cut

Figure 7F

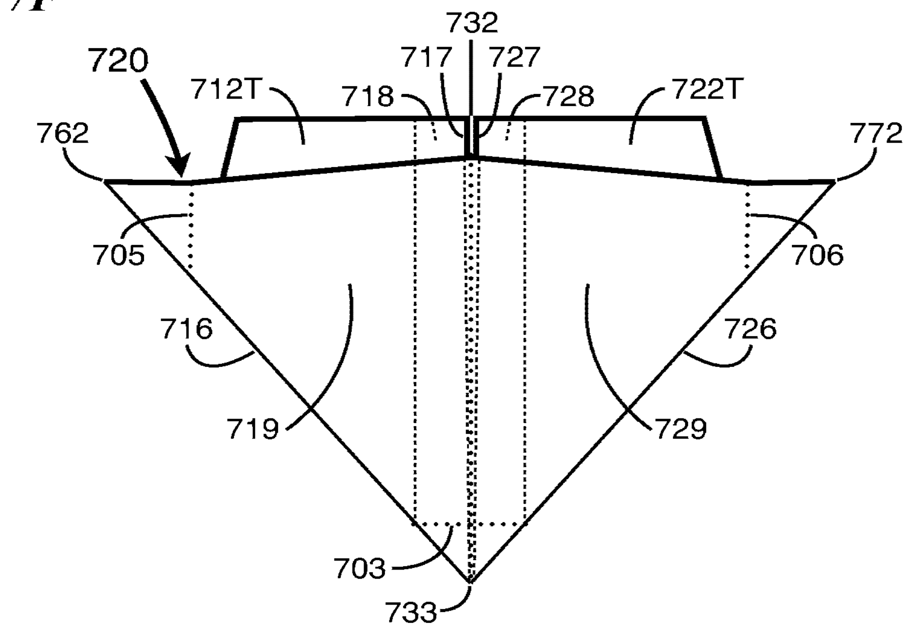


Figure 7G

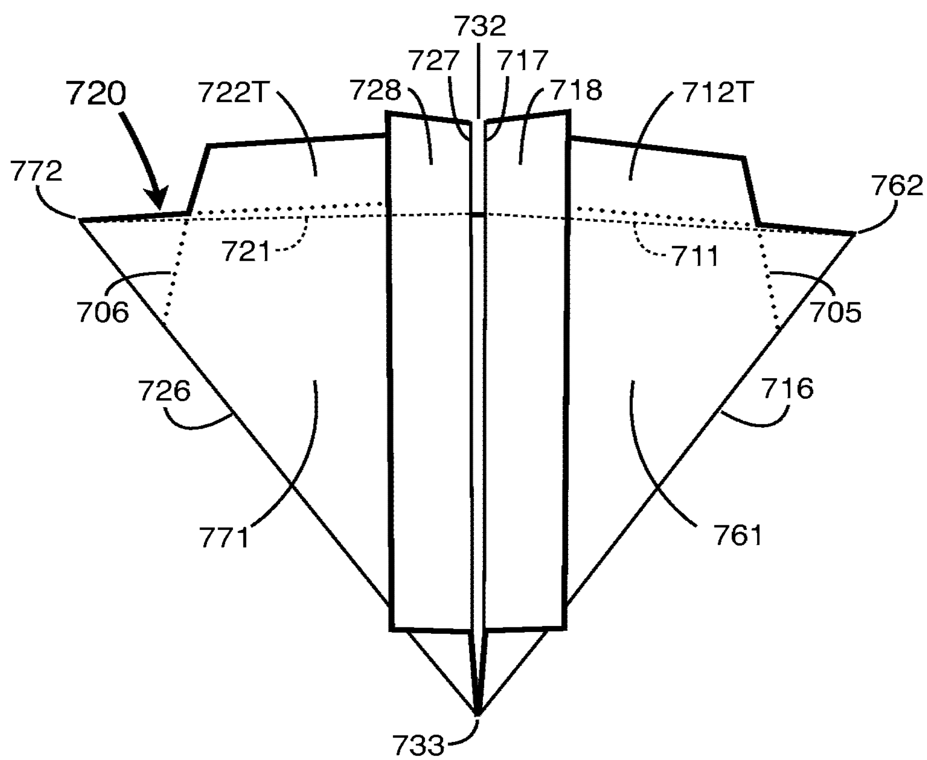


Figure 7H

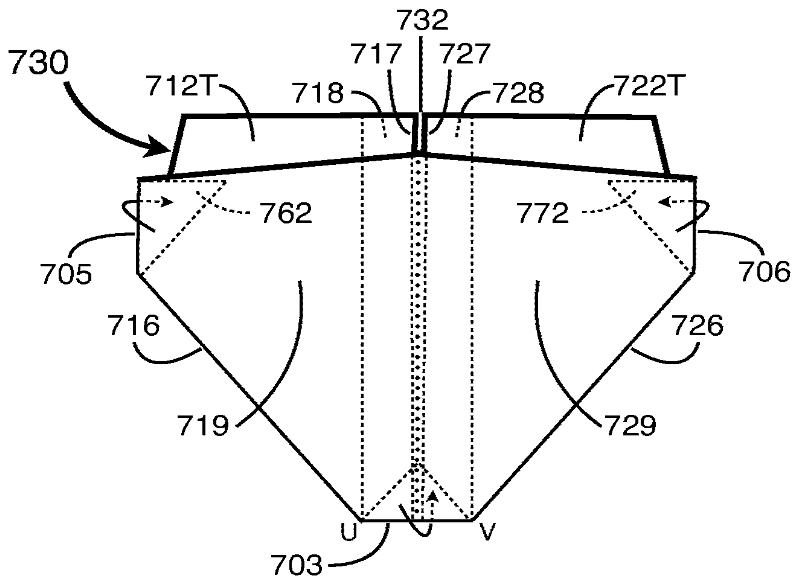


Figure 7I

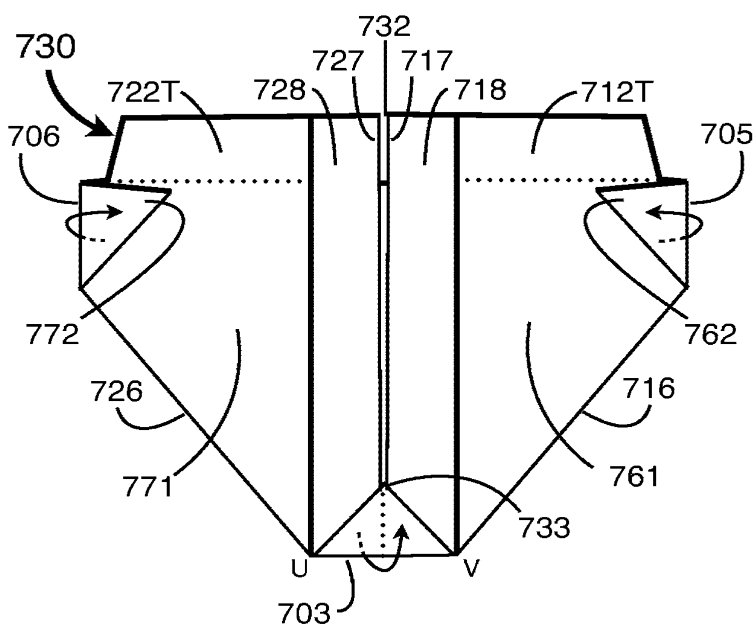
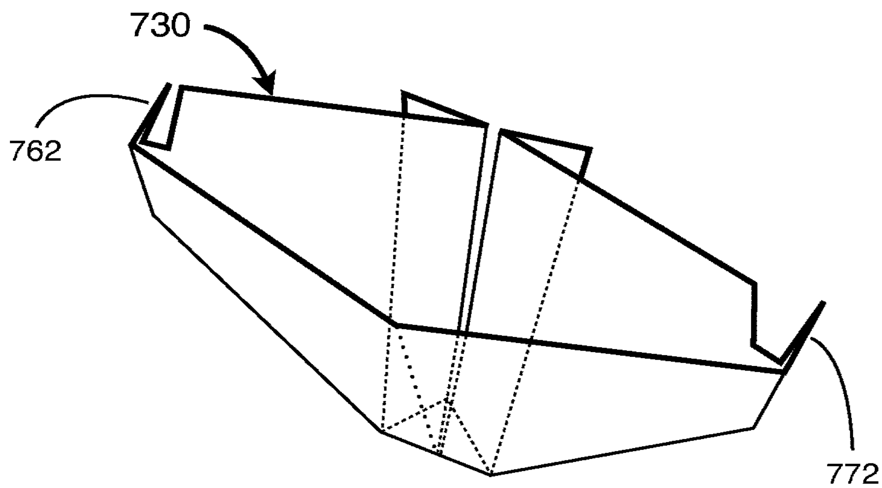


Figure 7J



LEGEND

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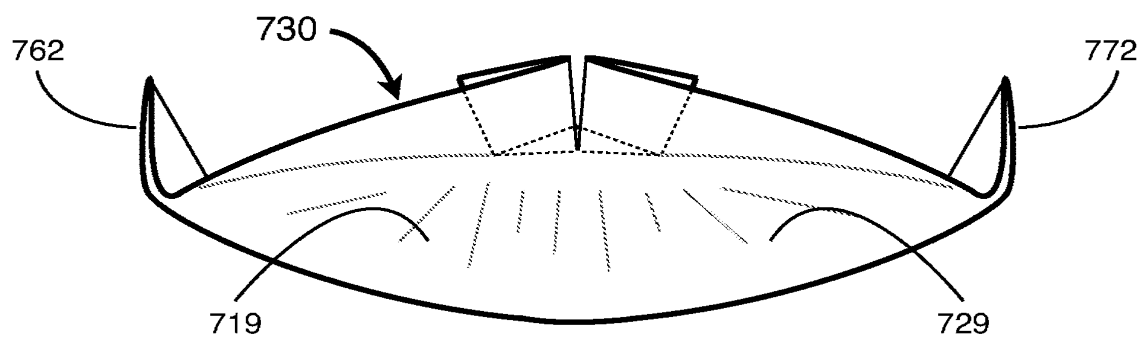
■ ■ ■ ■ ■ ■	Line of cut

Figure 7K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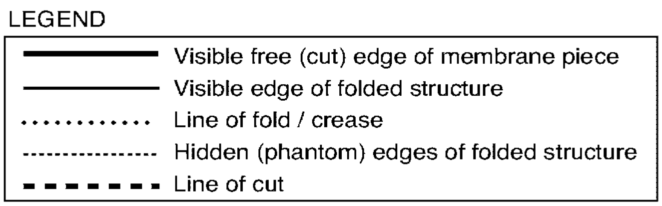
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Visible edge of folded structure
Line of fold / crease
Hidden (phantom) edges of folded structure
Line of cut

Figure 8A

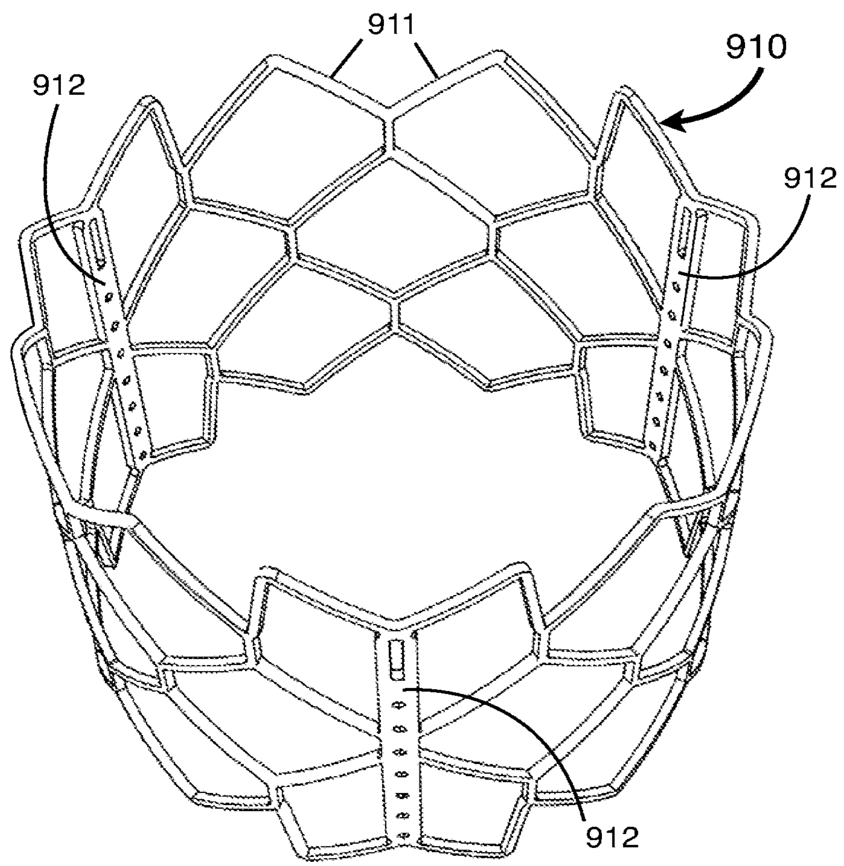

Figure 8B

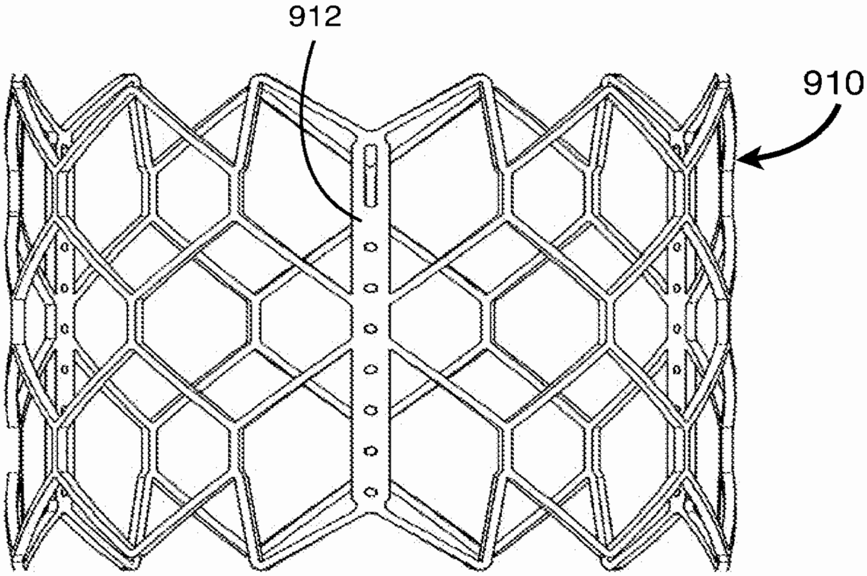

Figure 8C

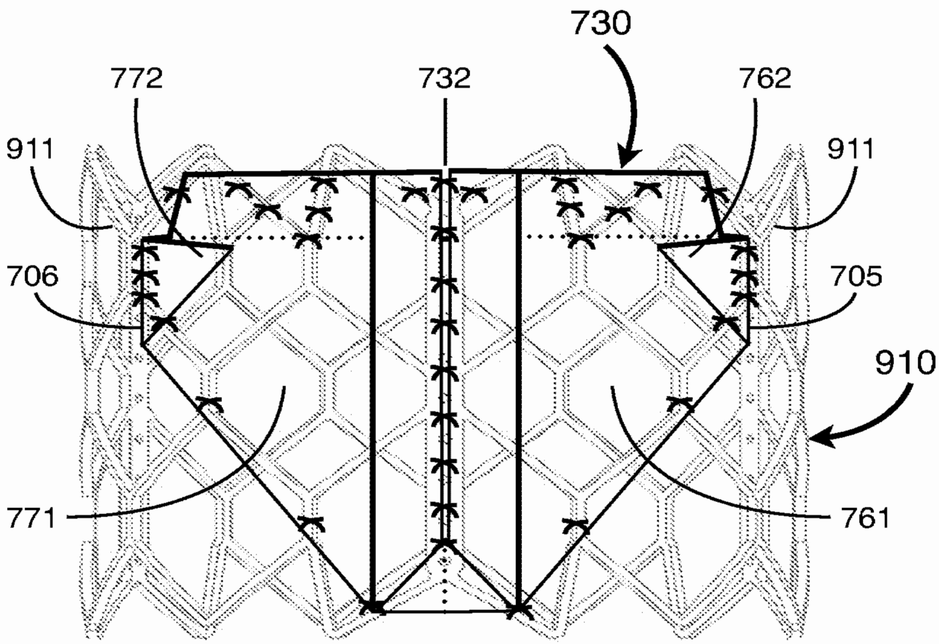

Figure 8D

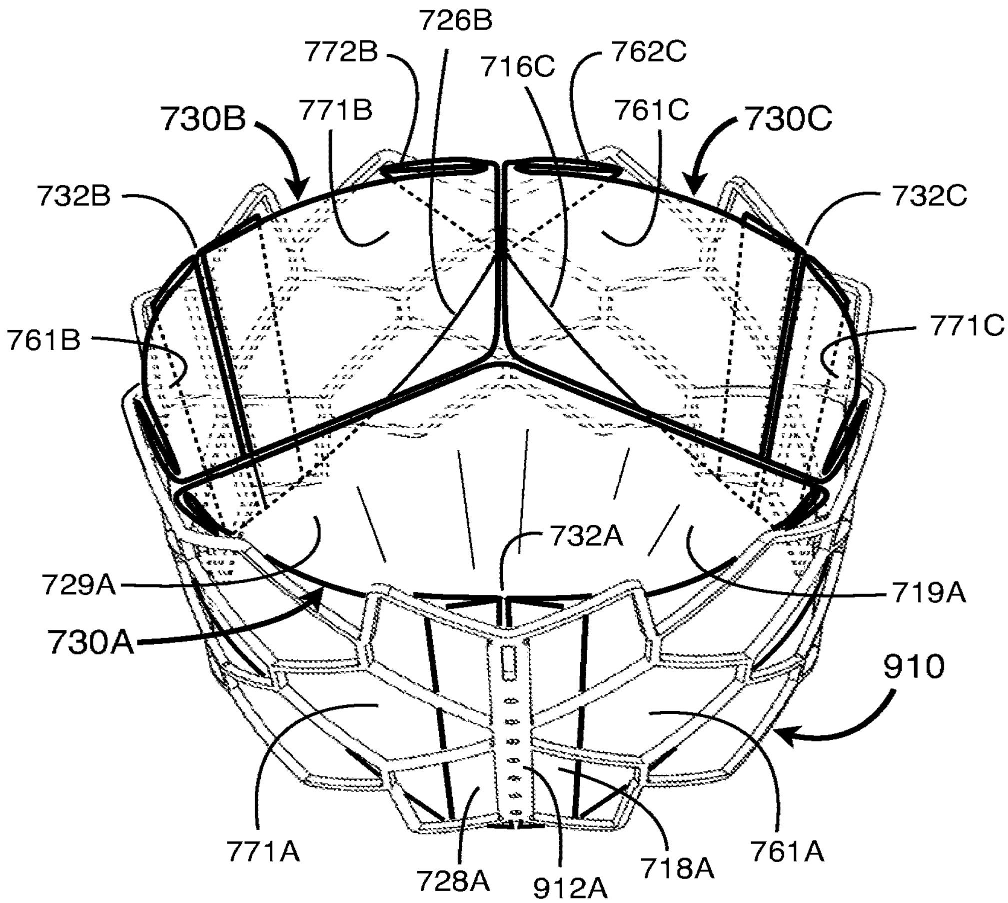

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Figure 9A

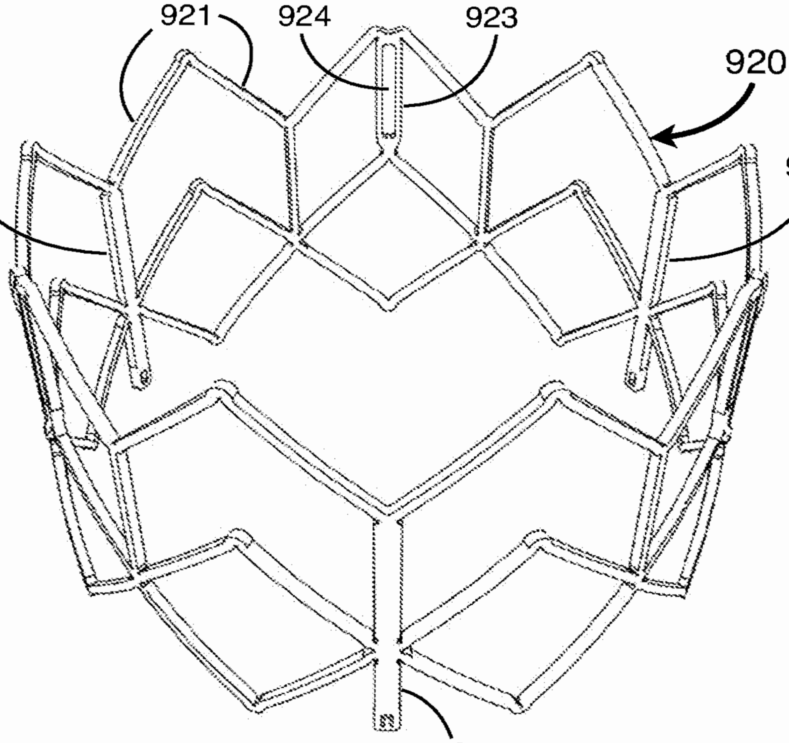


Figure 9B

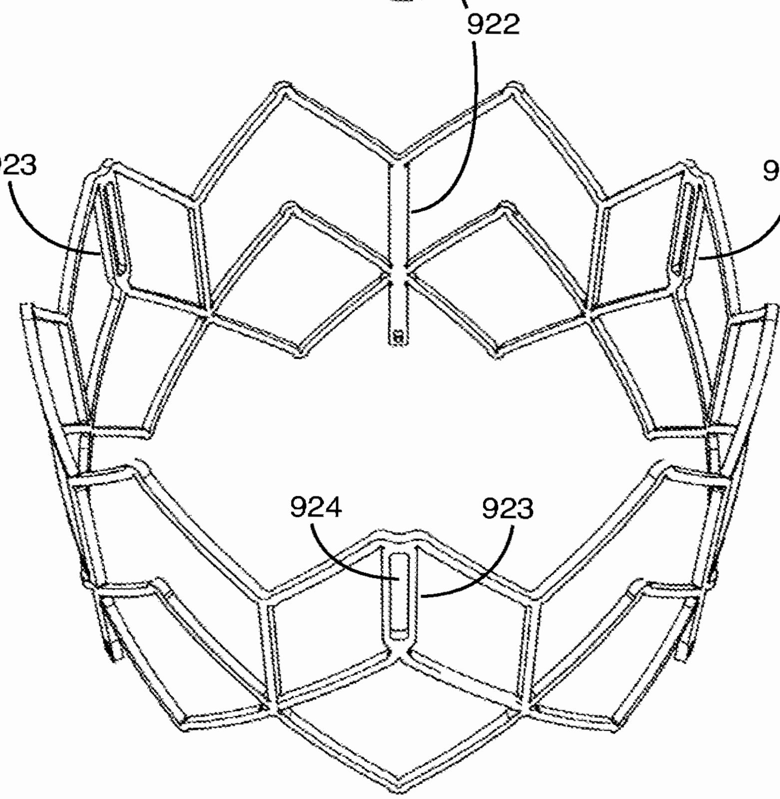


Figure 9C

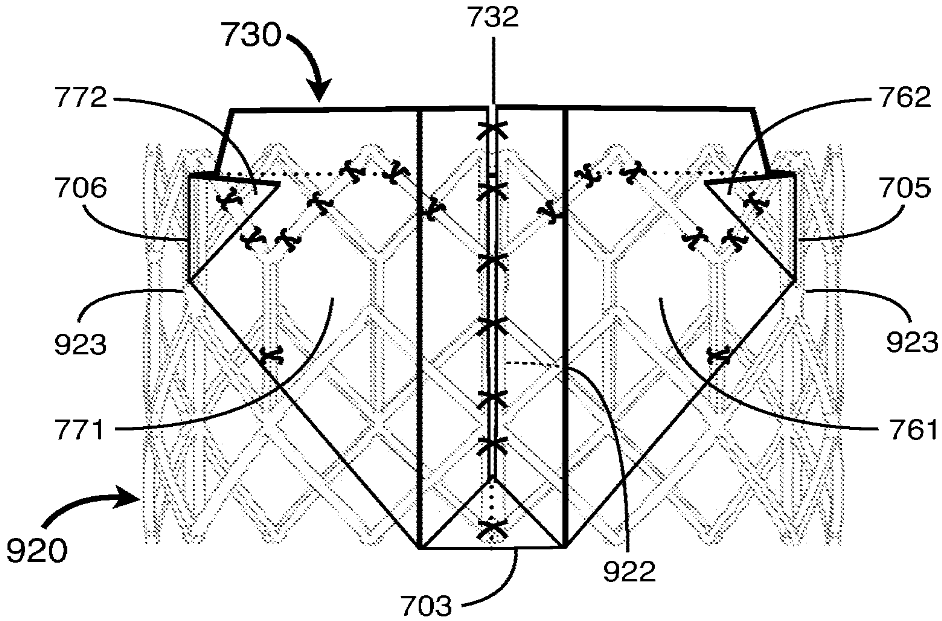


Figure 9D

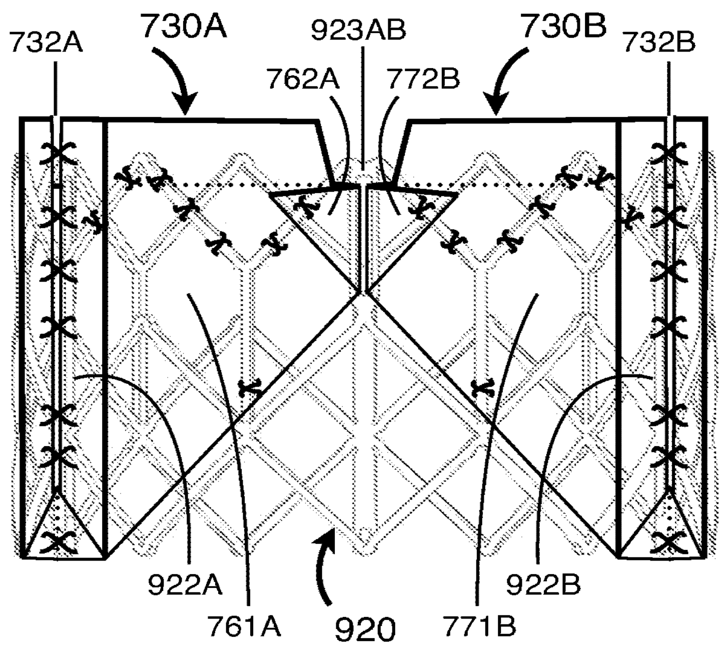
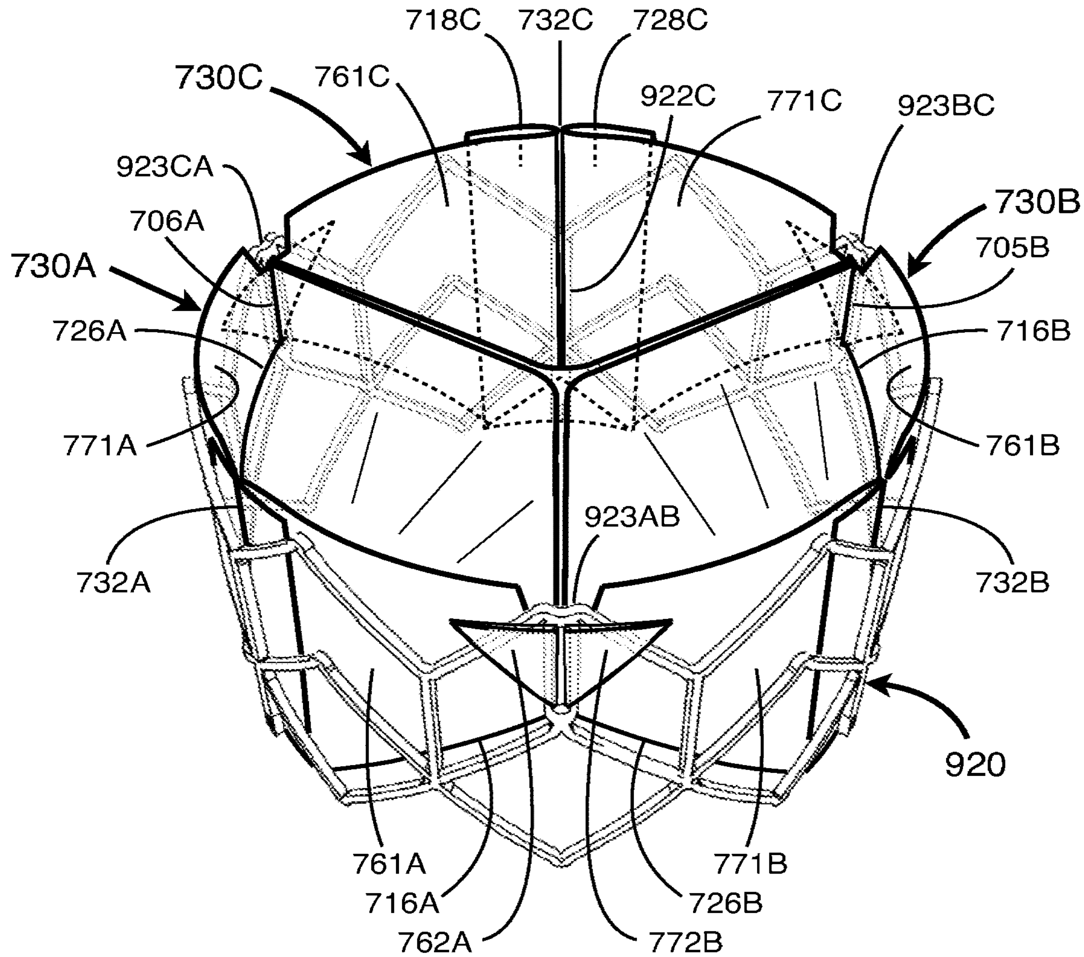


Figure 9E



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EFS ID:	19119590
Application Number:	14253656
International Application Number:	
Confirmation Number:	2795
Title of Invention:	METHOD OF CONTROLLED RELEASE OF A PERCUTANEOUS REPLACEMENT HEART VALVE
First Named Inventor/Applicant Name:	David PANIAGUA
Customer Number:	29880
Filer:	Mark Lauren Yaskanin/Carol Donahue
Filer Authorized By:	Mark Lauren Yaskanin
Attorney Docket Number:	109978.10113
Receipt Date:	23-MAY-2014
Filing Date:	15-APR-2014
Time Stamp:	18:09:10
Application Type:	Utility under 35 USC 111(a)

Payment information:

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	Application Number	14253656
	Filing Date	2014-04-15
	First Named Inventor	David PANIAGUA
	Art Unit	3738
	Examiner Name	Not assigned yet
	Attorney Docket Number	109978.10113

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	2	20010049558		2001-12-06	Liddicoat et al.	
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	14	20020151970		2002-10-17	Garrison et al.	
	15	20030078659		2003-04-24	Yang	
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	17	20030130727		2003-07-10	Drasler et al.	
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OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/ Mark L. Yaskanin /	Date (YYYY-MM-DD)	2014-05-23
Name/Print	Mark L. Yaskanin	Registration Number	45246

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14253656
	Filing Date	2014-04-15
	First Named Inventor	David PANIAGUA
	Art Unit	3738
	Examiner Name	Cheryl L. MILLER
	Attorney Docket Number	109978.10113

U.S.PATENTS

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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U.S.PATENT APPLICATION PUBLICATIONS

Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20020032481		2002-03-14	Gabbay	

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FOREIGN PATENT DOCUMENTS

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

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NON-PATENT LITERATURE DOCUMENTS

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	14253656
	Filing Date	2014-04-15
	First Named Inventor	David PANIAGUA
	Art Unit	3738
	Examiner Name	Cheryl L. MILLER
	Attorney Docket Number	109978.10113

	1	Office Action issued June 9, 2014, in U.S. Application No. 14/253,650 (109978.10104)	☐

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14253656
	Filing Date	2014-04-15
	First Named Inventor	David PANIAGUA
	Art Unit	3738
	Examiner Name	Cheryl L. MILLER
	Attorney Docket Number	109978.10113

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/ Mark L. Yaskanin /	Date (YYYY-MM-DD)	2014-06-17
Name/Print	Mark L. Yaskanin	Registration Number	45246

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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	19325550
Application Number:	14253656
International Application Number:	
Confirmation Number:	2795
Title of Invention:	METHOD OF CONTROLLED RELEASE OF A PERCUTANEOUS REPLACEMENT HEART VALVE
First Named Inventor/Applicant Name:	David PANIAGUA
Customer Number:	29880
Filer:	Mark Lauren Yaskanin/Carol Donahue
Filer Authorized By:	Mark Lauren Yaskanin
Attorney Docket Number:	109978.10113
Receipt Date:	17-JUN-2014
Filing Date:	15-APR-2014
Time Stamp:	12:53:31
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	Colibri_10113_Supp_IDS.pdf	555547 0e736baca66ac20b0a781362751020d92e3a546c	no	4

Warnings:

Information:

2	Non Patent Literature	10104_US_14-253650_Office_Action_2014-06-09.PDF	321329 e8440a26ba7de47d56ec1425b05252a020c00f9c	no	8

Warnings:

Information:

Total Files Size (in bytes):	876876

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHOD OF CONTROLLED RELEASE OF A PERCUTANEOUS REPLACEMENT HEART VALVE

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 14/253,656

filed on 2014-04-15.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: R. David FISH　　Date (Optional) : ____________

Signature: [signature]

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
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LEGAL NAME OF INVENTOR

Inventor: David PANIAGUA Date (Optional) :

Signature:

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

Electronic Acknowledgement Receipt

EFS ID:	19431990
Application Number:	14253656
International Application Number:	
Confirmation Number:	2795
Title of Invention:	METHOD OF CONTROLLED RELEASE OF A PERCUTANEOUS REPLACEMENT HEART VALVE
First Named Inventor/Applicant Name:	David PANIAGUA
Customer Number:	29880
Filer:	Mark Lauren Yaskanin/Carol Donahue
Filer Authorized By:	Mark Lauren Yaskanin
Attorney Docket Number:	109978.10113
Receipt Date:	27-JUN-2014
Filing Date:	15-APR-2014
Time Stamp:	11:13:14
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Oath or Declaration filed	Colibri_10113_Fish_Declaration.PDF	333178 a889edb681bd23ad8f3c74488b473678cd051df3	no	1

Warnings:

Information:

2	Oath or Declaration filed	Colibri_10113_Paniagua_Declaration.PDF	346665 7611af3716ab3892aa904c9e77b6388c23aa3834	no	1
Warnings:					
Information:					
			Total Files Size (in bytes):	679843	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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New International Application Filed with the USPTO as a Receiving Office
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/253,656	04/15/2014	David PANIAGUA	109978.10113	2795

29880 7590 07/08/2014
FOX ROTHSCHILD LLP
PRINCETON PIKE CORPORATE CENTER
997 LENOX DRIVE
BLDG. #3
LAWRENCEVILLE, NJ 08648

EXAMINER	
MILLER, CHERYL L	
ART UNIT	**PAPER NUMBER**
3738	

NOTIFICATION DATE	DELIVERY MODE
07/08/2014	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipdocket@foxrothschild.com

PTOL-90A (Rev. 04/07)

Office Action Summary	Application No. 14/253,656	Applicant(s) PANIAGUA ET AL.	
	Examiner CHERYL MILLER	Art Unit 3738	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _3_ MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _4/15/2014_.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) _34-53_ is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) _34-53_ is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _5/23/2014, 5/23/2014, 5/23/2014, 6/17/2014_.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-43 and 49-53 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification does not appear to provide support for the following combination of claimed steps in claims 39 and 49: retracting the moveable sheath to expose a portion of the valve device AND recovering the portion of the valve within the moveable sheath. The specification discloses two alternate methods of deployment: 1) pushing the pusher member/hollow tube catheter out of the moveable sheath to *partially* deploy the valve, with the option of recovery (P0052); and 2) pulling/retracting the moveable sheath, allowing *full* expansion of the valve (P0053). Thus, in the second method where the moveable sheath is retracted to expand the valve, the sheath is retracted fully and *no recovering is disclosed*. Recovery is only disclosed with respect to the first method, where the pusher member is pushed out partially. Applicant's amendment appears to be combining different embodiments not supported by the original disclosure. Claims 40-43 and 50-53 depend upon the above claims and inherit all issues associated therewith.

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34-53 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Each of claims 34, 39, 44, and 49 recite in line 11, "advancing the delivery and implantation system over the guide wire". This is unclear, as a guide wire has *not been positively claimed*. Instead, line 11 of the claims recite, "lumen for receiving a guide wire", thus a guide wire is not claimed to be present, *only a lumen capable of holding* a guide wire has been claimed. Thus, in line 17 of the claims, it is unclear if a guide wire is or is not present and required by the claimed method. It is also noted, if the guide wire is *part of* the delivery and implantation system, then it would be unclear how the delivery and implantation system be placed *over* the guide wire (cannot be part of the system, and yet at the same time, positioned relative the system; these are contradictory statements). Claims 35-38, 40-43, 45-48, and 50-53 depend upon the above claims and inherit all issues associated therewith.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 39-43 and 49-53 are rejected under pre-AIA 35 U.S.C. 102b as being anticipated by Leonhardt et al. (US 5,957,949). Leonhardt discloses a method of controlled release of a valve replacement comprising: providing a replacement heart valve device (20; fig.4) comprising a collapsible and expandable stent member (26) and a valve (22) attached thereto, the valve (22) having two to four leaflets (porcine valve; col.6, lines 23-34; fig.4); and providing a delivery and implantation system (fig.5; 9a-9d) including a pusher member/flexible hollow tube catheter (110) and a moveable sheath (106), the pusher/catheter (110) includes a lumen (124) for receiving a guide wire (col.10, lines 9-10), the moveable sheath (106) includes a lumen (108) for receiving the pusher/catheter (110; see fig.5), wherein the valve device (20) is collapsed onto the pusher/catheter (110; catheter 110 is within valve prior to and during deployment, col.7, lines 13-

17) to reside in a collapsed configuration on the pusher/catheter (110) and is restrained in the collapsed configuration by the moveable sheath (106; col.7, lines 10-12); advancing the delivery and implantation system over a guide wire within the patient (col.10, lines 6-11); partially deploying the valve device (20) by retracting the moveable sheath (106) to expose a portion of the valve device (seen in transition from fig.9a to fig.9b; col.10, lines 53-55); and recovering the portion of the valve device within the moveable sheath (slightly advanced to optimize placement, col.10, lines 58-61; repositioning, advance sheath 106, col.11, lines 37-58). Leonhardt discloses the advancing done transluminally (col.9, line 63-col.10, line 43). Leonhardt discloses the stent member (26) to be self-expanding (see fig.9b) and comprise nitinol (col.4, lines 26-28, 60-66; col.5, lines 46-48). Leonhardt discloses the stent member (26) to be a tubular structure with central portion and flares at ends in a trumpet-like configuration (seen in fig.2, 9d).

Claims 34-37 and 44-47 are rejected under pre-AIA 35 U.S.C. 102(e) as anticipated by or, in the alternative, under pre-AIA 35 U.S.C. 103(a) as obvious over Garrison et al. (US 6,425,916 B1). Garrison discloses a method of controlled release of a valve replacement (see figs.19-21) comprising: providing a replacement heart valve device (6a; fig.10) comprising a collapsible and expandable stent member (26) and a valve (38) attached thereto, the valve having two to four leaflets (39; col.8, line 51); and providing a delivery and implantation system (fig.21) including a pusher member/flexible hollow tube catheter (78B) and a moveable sheath (4B), the pusher/catheter (78) includes a lumen (86) for receiving a guide wire (72), the moveable sheath (4B) includes a lumen (seen in fig.21) for receiving the pusher/catheter (78B; see fig.21), wherein the valve device (6A) is collapsed onto the pusher/catheter (78B; see fig.21) to reside in a collapsed configuration on the pusher/catheter and is restrained in the collapsed configuration by the moveable sheath (4B; see fig.21); advancing the delivery and implantation system over a guide wire (72) within the patient (fig.16; col.9, lines 29-40); partially deploying the valve device (6A) by pushing out the pusher/catheter (78B) from the sheath (4B) to expose a portion of the valve device (seen in fig.19; advancing rod 78, col.9, lines 15-16, advance distal end, col.9, lines 45-48); and recovering the portion of the valve device (6A) within the moveable sheath (4B; catheter 4B moved as necessary, col.9, lines 48-51). Garrison discloses moving the moveable sheath (4B) as necessary to correctly position the replacement valve (6A) within the patient, thus is appears clear that the sheath may be moved proximally or distally, including recovering the valve device (6A) to reposition if necessary. However, in the case that recovery is not inherent within this disclosure, it would have been obvious to one having ordinary skill in the art at the time the invention was made to move the moveable sheath (4B) to recover the valve (6A) at this point of partial expansion, since Garrison has disclosed repositioning, and this would make sense to aid in the repositioning.

Garrison discloses the advancing done transluminally (see fig.19). Garrison discloses the stent member (26) to be self-expanding (fig.19) and comprise nitinol (col.8, lines 13-21).

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

In the alternative to the above rejection, under an alternate interpretation, claims 34-38 and 44-48 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Garrison et al. (US 6,425,916 B1) in view of Leonhardt et al. (US 5,957,949). Referring to claims 34 and 44, Garrison discloses a method of controlled release of a valve replacement comprising: providing a replacement heart valve device (6A+8B, coupled together as one assembly, see col.2, lines 16-17, 24-26; col.4, lines 51-54) comprising a collapsible and expandable stent member (8B) and a valve (6A) attached thereto (see fig.20; coupled, col.2, lines 16-17, 24-26; col.4, lines 51-54), the valve (6A) having two to four leaflets (39); and providing a delivery and implantation system (see fig.21) including a pusher member/flexible hollow tube catheter (78B) and a moveable sheath (4B), the pusher/catheter (78B) includes a lumen (86) for receiving a guide wire (72), the moveable sheath (4B) includes a lumen (see fig.21) for receiving the pusher/catheter (78B), wherein the valve device (6A+8B; in coupled embodiment, col.2, lines 16-17, 24-26; col.4, lines 51-54) is collapsed onto the pusher/catheter (78B) to reside in a collapsed configuration on the pusher/catheter and is restrained in the collapsed configuration by the moveable sheath (4B; see fig.21, with the alternate embodiment disclosed of having 6A and 8B coupled together as one unit); advancing the delivery and implantation system over a guide wire (72) within the patient (fig.16; col.9, lines 28-40); and partially deploying the valve device by pushing out the pusher/catheter (78B) from the sheath (4B) to expose a portion of the valve device (6A+8B combo; col.9, lines 40-48). Garrison discloses the method substantially as claimed, including partial deployment, however does not disclose recovering the portion of the valve device within the moveable sheath. Leonhardt teaches in the same field of method of implanting replacement heart valves that are self-expanding, the step of checking the position of the replacement valve after partial deployment, and recovering so the valve replacement is within the sheath, if repositioning or removal is necessary (col.11, lines 36-58). It would have been obvious to one having ordinary skill in the art at the time the invention was made to combine Garrison's method with Leonhardt's teaching of an additional step of recovery such that Garrison's valve replacement may be repositioned or removed if the positioning is not accurate.

Referring to claims 35-38 and 45-48: Garrison (as modified by Leonhardt) discloses the advancing done transluminally (fig.16). Garrison (as modified by Leonhardt) discloses the stent member (8B) to be self-expanding and comprise nitinol (col.5, lines 4-7). Garrison (as modified by Leonhardt) discloses the stent member (8B) to be a tubular structure with central portion and flares at ends in a trumpet-like configuration (see fig.8, 9; col.5, lines 10-14).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Cheryl Miller whose telephone number is 571-272-4755. The examiner can normally be reached on M- F (8am-5:30pm).

If attempts to reach the examiner by telephone are unsuccessful, please contact the examiner’s supervisor, Thomas Sweet at 571-272-4761. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/C. M./
Examiner, Art Unit 3738
/THOMAS J SWEET/

Supervisory Patent Examiner, Art Unit 3738

Notice of References Cited	Application/Control No. 14/253,656	Applicant(s)/Patent Under Reexamination PANIAGUA ET AL.	
	Examiner CHERYL MILLER	Art Unit 3738	Page 1 of 1

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*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,425,916 B1	07-2002	Garrison et al.	623/2.11
*	B	US-5,957,949	09-1999	Leonhardt et al.	623/1.24
	C	US-			
	D	US-			
	E	US-			
	F	US-			
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	14253656
	Filing Date	2014-04-15
	First Named Inventor	David PANIAGUA
	Art Unit	3738
	Examiner Name	Cheryl L. MILLER
	Attorney Docket Number	109978.10113

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14253656 - GAU: 3738

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	First Named Inventor	David PANIAGUA
	Art Unit	3738
	Examiner Name	Cheryl L. MILLER
	Attorney Docket Number	109978.10113

	1	Office Action issued June 9, 2014, in U.S. Application No. 14/253,650 (109978.10104)	☐

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	First Named Inventor	David PANIAGUA	
	Art Unit		3738
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Art Unit	3738
Examiner Name	Not assigned yet
Attorney Docket Number	109978.10113

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	38	Supplemental Declaration Under 37 CFR 1.131 by inventors filed in U.S. Application 10/887,688, filed February 28, 2008 (54813-10100)	☐
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	Art Unit	3738	
	Examiner Name	Not assigned yet	
	Attorney Docket Number	109978.10113	

	45	Office Action issued in U.S. Application 10/037,266, dated May 8, 2003	☐
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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
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L3	35	1 and @ad<"20020104"	US-PGPUB; USPAT; USOCR	OR	ON	2014/06/30 10:08
L4	88	2 3	US-PGPUB; USPAT; USOCR	OR	ON	2014/06/30 10:08
S1	3	"10/037,266"	USPAT	OR	OFF	2014/02/24 19:08
S2	9	"10/037,266"	US-PGPUB; USPAT	OR	OFF	2014/02/24 19:08
S3	1916	623/1.24.ccls. or 623/1.26.ccls. or 623/2.12.ccls. or 623/2.13.ccls. or 623/2.14.ccls. or 623/2.15.ccls. or 623/2.16.ccls. or 623/2.17.ccls. or 623/2.18.ccls. or 623/2.19.ccls. or 623/900.ccls.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/02/24 19:53
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S5	430	S3 and @ad<"20020104"	US-PGPUB; USPAT; USOCR	OR	OFF	2014/02/24 19:53
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S8	757	S3 and @ad<"20040710"	US-PGPUB; USPAT; USOCR	OR	OFF	2014/02/24 19:54
S9	195	S8 not S6	US-	OR	OFF	2014/02/24

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S11	11	S6 and (flare or flared or tapered or taper) and bailey.in.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/02/24 19:56
S12	306	S6 and ((valve or leaflet) with (tube or tubular))	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/24 20:01
S13	3	"7018406".pn. or "8579966".pn. or "6830584".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/24 20:04
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S20	1	"6346089".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/25 14:01
S21	1	"12/609,521"	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/25 14:10
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S37	65	S35 S36	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/27 12:02
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S53	1159	S51 S52	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:34
S54	578	S53 and ((tube or tubular) with (valve or leaflets))	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:34
S55	102	S53 and ((tube or tubular) adj (valve or leaflets))	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:34
S56	1	S53 and ((rectangle or rectangular or square) adj (valve or leaflets))	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:34
S57	5	S53 and ((rectangle or rectangular or square) adj (valve or leaflets or flaps))	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:35

S58	89	S53 and ((tube or tubular) adj (valve))	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:36
S59	2393	A61F2/24.cpc. or A61f2/2412.cpc. or A61F2/2475.cpc.	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:37
S60	1222	S59 not S50	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:37
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S62	477	S60 and @ad<"20040710"	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:37
S63	759	S61 S62	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:37
S64	294	S63 and ((tubular or tube or rectangle or rectangular or sqaure) with (leaflets or flaps or valve))	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:38
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S66	178	S53 and ((tube or tubular) with (valve or leaflets)) and (crease or fold$3) and (flar$3 or taper$3)	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 17:13
S67	150	S66 not S55	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 17:14
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6/30/2014 10:17:06 AM
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14253656
	Filing Date	2014-04-15
	First Named Inventor	David PANIAGUA
	Art Unit	3738
	Examiner Name	Not assigned yet
	Attorney Docket Number	109978.10113

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	RE40404		2008-06-24	Schmitt et al.	
	2	RE42395		2011-05-24	Wright et al.	
	3	3014024		1961-12-19	Lieberman et al.	
	4	3029819		1962-04-17	Edward	
	5	3105492		1963-10-01	Jeckel	
	6	3320972		1967-05-23	High et al.	
	7	3409914		1968-11-12	Jones	
	8	3548417		1970-12-22	Kischer et al.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CM/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	
Application Number	14253656
Filing Date	2014-04-15
First Named Inventor	David PANIAGUA
Art Unit	3738
Examiner Name	Not assigned yet
Attorney Docket Number	109978.10113

	9	3562820		1971-02-16	Braun	
	10	3588920		1971-06-29	Wesolowski	
	11	3671979		1972-06-27	Moulopoulos	
	12	3709175		1973-01-09	Edwards et al.	
	13	3878565		1975-04-22	Sauvage	
	14	3966401		1976-06-29	Hancock et al.	
	15	3945052		1976-03-23	Liebig	
	16	3983581		1976-10-05	Angell et al.	
	17	3986828		1976-10-19	Hoffman, Jr. et al.	
	18	4011947		1977-03-15	Sawyer	
	19	4035849		1977-07-19	Angell et al.	

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	20	4055861		1977-11-01	Carpentier et al.	
	21	4056854		1977-11-08	Boretos et al.	
	22	4060081		1977-11-29	Yannas et al.	
	23	4082507		1978-04-04	Sawyer	
	24	4084268		1978-04-18	Ionescu et al.	
	25	4106129		1978-08-15	Carpentier et al.	
	26	4164045		1979-08-14	Bokros et al.	
	27	4172295		1979-10-30	Batten	
	28	4218782		1980-08-26	Rygg	
	29	4222126		1970-09-16	Boretos et al.	
	30	4233493		1980-11-11	Nath et al.	

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	31	4265694		1981-05-05	Boretos et al.	
	32	4291420		1981-09-29	Reul	
	33	4340977		1982-07-27	Bownlee et al.	
	34	4350492		1982-09-21	Wright et al.	
	35	4364127		1982-12-21	Pierce et al.	
	36	4388735		1983-06-21	Ionescu et al.	
	37	4423525		1984-01-03	Vallana et al.	
	38	4441216		1984-04-10	Ionescu et al.	
	39	4456589		1984-06-26	Holman et al.	
	40	4473423		1984-09-25	Kolff	
	41	4477930		1984-10-23	Totten et al.	

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	42	4490859		1985-01-01	Black et al.	
	43	4517687		1985-05-21	Liebig et al.	
	44	4545082		1985-10-08	Hood	
	45	4597762		1986-07-01	Walter et al.	
	46	4600533		1986-07-15	Chu	
	47	4631052		1986-12-23	Kensey	
	48	4657133		1987-04-14	Komatsu et al.	
	49	4666442		1987-05-19	Arru et al.	
	50	4728328		1998-03-01	Hughes et al.	
	51	4743231		1988-05-10	Kay et al.	
	52	4759758		1988-07-26	Gabbay	

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	53	4759759		1988-07-26	Walker et al.	
	54	4798611		1989-01-17	Freeman, Jr.	
	55	4801299		1989-01-31	Brendel et al.	
	56	4870966		1989-10-03	Dellon et al.	
	57	4883458		1989-11-28	Shiber	
	58	4892539		1990-01-09	Koch	
	59	4966604		1990-10-30	Reiss	
	60	4976733		1990-12-11	Giradot	
	61	4979939		1990-12-25	Shiber	
	62	5006104		1991-04-09	Smith et al.	
	63	5007896		1991-04-16	Shiber	

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	64	5011488		1991-04-30	Ginsburg	
	65	5026366		1991-06-25	Leckrone	
	66	5032128		1991-07-16	Alonso	
	67	5047041		1991-09-10	Samuels	
	68	5047050		1991-09-10	Arpesani	
	69	5061277		1991-10-29	Carpentier et al.	
	70	5080660		1992-01-14	Buelna	
	71	5052771		1991-10-01	Williams et al.	
	72	5139515		1992-08-18	Robicsek	
	73	5163955		1992-11-17	Love et al.	
	74	5171273		1992-12-15	Silver et al.	

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	75	5226889		1993-07-13	Sheiban	
	76	5261878		1993-11-16	Galindo	
	77	5282847		1994-02-01	Trescony et al.	
	78	5326370		1994-07-05	Love et al.	
	79	5326371		1994-07-05	Love et al.	
	80	5332402		1994-07-26	Teitelbaum	
	81	5336616		1994-08-09	Livesey et al.	
	82	5360443		1994-11-01	Barone et al.	
	83	5374539		1994-12-20	Nimni et al.	
	84	5376110		1994-12-27	Tu et al.	
	85	5383927		1995-01-24	De Goiceochea et al.	

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	86	5411552		1995-05-02	Andersen et al.	
	87	5413601		1995-05-09	Keshelava	
	88	5449384		1995-09-12	Johnson	
	89	5476506		1995-12-19	Lunn	
	90	5480424		1996-01-02	Cox	
	91	5489297		1996-02-06	Duran	
	92	5500015		1996-03-19	Deac	
	93	5509930		1996-04-23	Love	
	94	5522879		1995-06-04	Scopelianos	
	95	5522881		1996-06-04	Lentz	
	96	5545215		1996-08-13	Duran	

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	97	5549664		1996-08-27	Hirata et al.	
	98	5549666		1996-08-27	Hata et al.	
	99	5571170		1996-11-05	Palmaz et al.	
	100	5571173		1996-11-05	Parodi	
	101	5571174		1996-11-05	Love et al.	
	102	5578071		1996-11-26	Parodi	
	103	5578072		1996-11-26	Barone et al.	
	104	5582168		1996-12-10	Samuels et al.	
	105	5591229		1997-01-07	Parodi	
	106	5634928		1997-06-03	Fischell et al.	
	107	5653749		1997-08-05	Love et al.	

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	108	5713953		1998-02-03	Vallana et al.	
	109	5728152		1998-03-17	Mirsch, II et al.	
	110	5733299		1998-03-21	Sheiban et al.	
	111	5741333		1998-04-21	Frid	
	112	5746775		1998-05-05	Levy et al.	
	113	5769780		1998-06-23	Hata et al.	
	114	5782914		1998-07-21	Schankereli	
	115	5787887		1998-08-04	Klingenbeck-Regn	
	116	5840081		1998-11-24	Anderson et al.	
	117	5855601		1999-01-05	Bessler et al.	
	118	5861028		1999-01-19	Angell	

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	119	5862806		1999-01-26	Cheung	
	120	5895420		1999-04-20	Mirsch, II et al.	
	121	5931969		1999-08-03	Carpentier et al.	
	122	5957949		1999-09-28	Leonhardt et al.	
	123	5961539		1999-10-05	Northup et al.	
	124	5961549		1999-10-05	Nguyen et al.	
	125	5972030		1999-10-26	Garrison et al.	
	126	5976179		1999-11-02	Inoue	
	127	6004328		1999-12-21	Solar	
	128	6004330		1999-12-21	Middleman et al.	
	129	6010531		2000-01-04	Donlon et al.	

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	130	6029671		2000-02-29	Stevens et al.	
	131	6045576		2000-04-04	Starr et al.	
	132	6053938		2000-04-25	Goldmann et al.	
	133	6091984		2000-07-18	Perelman et al.	
	134	6102944		2000-08-15	Huynh et al.	
	135	6117169		2000-09-12	Moe	
	136	6124523		2000-09-26	Banas et al.	
	137	6125852		2000-10-03	Stevens et al.	
	138	6126686		2000-10-03	Badylak et al.	
	139	6129756		2000-10-10	Kugler	
	140	6162245		2000-12-19	Jayaraman	

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	141	6168614		2001-01-02	Andersen et al.	
	142	6168619		2001-01-02	Dinh et al.	
	143	6171335		2001-01-09	Wheatley et al.	
	144	6174327		2001-01-16	Mertens et al.	
	145	6186999		2001-02-13	Chen	
	146	6197143		2001-03-06	Bodnar	
	147	6214055		2001-04-10	Simionescu et al.	
	148	6221091		2001-04-24	Khosravi	
	149	6231602		2001-05-15	Carpentier et al.	
	150	6245102		2001-06-12	Jayaraman	
	151	6254629		2001-07-03	Inoue	

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	152	6254630		2001-07-03	Inoue	
	153	6254636		2001-07-03	Peredo	
	154	6264691		2001-07-24	Gabbay	
	155	6269819		2001-08-07	Oz et al.	
	156	6270526		2001-08-07	Cox	
	157	6277397		2001-08-21	Shimizu	
	158	6277555		2001-08-21	Duran et al.	
	159	6287335		2001-09-11	Drasler et al.	
	160	6293970		2001-09-25	Wolfinbarger, Jr. et al.	
	161	6312462		2001-11-06	McDermott et al.	
	162	6312474		2001-11-06	Francis et al.	

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	163	6334873		2002-01-01	Lane et al.	
	164	6342069		2002-01-29	Deac et al.	
	165	6350282		2002-02-26	Eberhardt	
	166	6352554		2002-03-05	De Paulis	
	167	6352708		2002-03-05	Duran et al.	
	168	6358275		2002-03-19	McIlroy et al.	
	169	6358284		2002-03-19	Fearnot et al.	
	170	6371980		2002-04-16	Rudakov et al.	
	171	6376244		2002-04-23	Atala et al.	
	172	6378221		2002-04-30	Ekholm, Jr. et al.	
	173	6383171		2002-05-07	Gifford et al.	

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	174	6391333		2002-05-21	Li et al.	
	175	6409755		2002-06-25	Vrba	
	176	6418339		2002-07-09	Essenpreis et al.	
	177	6425916		2002-07-30	Garrison et al.	
	178	6432712		2002-08-13	Wolfinbarger, Jr. et al.	
	179	6440167		2002-08-27	Shimizu	
	180	6458153		2002-10-01	Bailey et al.	
	181	6461382		2002-10-08	Cao	
	182	6468313		2002-10-22	Claeson et al.	
	183	6471723		2002-10-29	Ashworth et al.	
	184	6482227		2002-11-19	Solovay	

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	185	6482228		2002-11-19	Norred	
	186	6482240		2002-11-19	Echmayer et al.	
	187	6491719		2002-12-10	Fogarty et al.	
	188	6494909		2002-12-17	Greenhalgh	
	189	6503272		2003-01-07	Duerig et al.	
	190	6534004		2003-03-18	Chen et al.	
	191	6540782		2003-04-01	Snyders	
	192	6558418		2003-05-06	Carpentier et al.	
	193	6569200		2003-05-27	Wolfinbarger Jr. et al.	
	194	6565960		2003-05-20	Koob et al.	
	195	6582458		2003-06-24	White et al.	

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	196	6582462		2003-06-24	Andersen et al.	
	197	6582464		2003-06-24	Gabbay	
	198	6599524		2003-07-29	Li et al.	
	199	6624890		2003-09-23	Backman et al.	
	200	6626938		2003-09-30	Butaric et al.	
	201	6652577		2003-11-25	Gianotti	
	202	6652578		2003-11-25	Bailey et al.	
	203	6553681		2003-04-29	Ekholm, Jr. et al.	
	204	6610088		2003-08-26	Gabbay	
	205	6666886		2003-12-23	Tranquillo et al.	
	206	6682559		2001-01-27	Myers et al.	

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	207	6685739		2004-02-03	Dimatteo et al.	
	208	6696074		2004-02-24	Dia et al.	
	209	6719788		2004-04-13	Cox	
	210	6719789		2004-04-13	Cox	
	211	6702826		2004-03-09	Liddicoat et al.	
	212	6736823		2004-05-18	Darios et al.	
	213	6764510		2004-07-20	Vidlund et al.	
	214	6773456		2004-08-10	Gordon et al.	
	215	6773457		2004-08-10	Ivancev	
	216	6790229		2004-09-14	Berreklouw	
	217	6792979		2004-09-21	Konya et al.	

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	218	6802319		2004-10-12	Stevens et al.	
	219	6802806		2004-10-12	McCarthy et al.	
	220	6821297		2004-11-23	Snyders	
	221	6821530		2004-11-23	Koob et al.	
	222	6830584		2004-12-14	Seguin	
	223	6893460		2005-05-17	Spenser et al.	
	224	6908481		2005-06-21	Cribier	
	225	6913608		2005-07-02	Liddicoat et al.	
	226	6916338		2005-07-12	Speziali	
	227	6942694		2005-09-13	Liddicoat et al.	
	228	6951571		2005-10-04	Srivastava	

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	229	6961123		2005-11-01	Wang et al.	
	230	6977231		2005-12-20	Matsuda	
	231	6986735		2006-01-17	Abraham et al.	
	232	7004925		2006-02-28	Navia et al.	
	233	7008763		2006-03-07	Cheung	
	234	7011688		2006-03-14	Gryska et al.	
	235	7018404		2006-03-28	Holmberg et al.	
	236	7018406		2006-03-28	Seguin et al.	
	237	7022348		2006-04-04	Ketharananthan	
	238	7025780		2006-04-11	Gabbay	
	239	7037333		2006-05-02	Myers et al.	

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	240	7039446		2006-05-02	Ruchti et al.	
	241	7041132		2006-05-09	Quijano et al	
	242	7053051		2006-05-30	Hendriks et al	
	243	7060092		2006-06-13	Kuribayashi et al.	
	244	7070616		2006-07-04	Majercak et al.	
	245	7077862		2006-07-18	Vidlund et al.	
	246	7084082		2006-08-01	Shimizu	
	247	7138226		2006-11-21	Vincek et al.	
	248	7153324		2006-12-26	Case et al.	
	249	7160322		2007-01-09	Gabbay	
	250	7164145		2007-01-16	Shakespeare	

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	251	7166570		2007-01-23	Hunter et al.	
	252	7189259		2007-03-13	Simionescu et al.	
	253	7213601		2007-05-08	Stevens et al.	
	254	7214242		2007-05-08	Abraham et al.	
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First Named Inventor	David PANIAGUA
Art Unit	3738
Examiner Name	Not assigned yet
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	1	Cross-reference is made to U.S. Application No. 14/253,650 filed on April 15, 2014, and its associated Preliminary Amendment (109978.10104)	☐
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Filing Date	2014-04-15
First Named Inventor	David PANIAGUA
Art Unit	3738
Examiner Name	Not assigned yet
Attorney Docket Number	109978.10113

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Class	Subclass	Date	Examiner
623	1.24, 1.26, 2-12-2.19, 900	6/29/2014	cm

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4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re the Application of:	) Group Art Unit: 3738
David PANIAGUA et al.	) Confirmation No. 2795
Application No.: 14/253,656	) Examiner: Cheryl L. MILLER
Filed: April 15, 2014	) AMENDMENT AND RESPONSE
Atty. File No.: 109978.10113	) **Filed Electronically**
Entitled: METHOD OF CONTROLLED RELEASE OF A PERCUTANEOUS REPLACEMENT HEART VALVE	)

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Typed or printed name of person signing this certificate: Carol Donahue
Signature: / Carol Donahue /

Dear Sir:

In response to the July 8, 2014 Office Action (the "Office Action"), please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 10 of this paper.

Fees for 21 total claims (that is, one additional claim beyond 20 total claims) are provided. (The Applicants previously paid for 4 independent claims.) Such claim totals are within the limits of 30 total claims including 4 independent claims that are allowed for prioritized patent applications. Other than claim fees, Applicants believe that no additional fees are due for this submission. However, please credit any over payment or debit any under payment to Deposit Account No. 50-1943.

AMENDMENTS TO THE CLAIMS

The listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims:

1.-33. (Cancelled)

34. (Currently Amended) A method of controlled release of a percutaneous replacement heart valve at a location of a native heart valve in a patient ~~where a bioprosthetic heart valve is indicated~~, the method comprising:

~~providing~~ obtaining a replacement heart valve device and a delivery and implantation system:

the replacement heart valve device including:

a stent member that is collapsible, expandable and configured for percutaneous delivery; and

a valve residing entirely within an inner channel of the stent member and attached to a proximal portion of the stent member, the valve including two to four individual leaflets made of fixed pericardial tissue;

the delivery and implantation system including:

a pusher member and a moveable sheath, wherein the pusher member includes a guide wire lumen ~~for receiving a guide wire~~, and wherein the moveable sheath includes a lumen configured for receiving the pusher member~~, and wherein the replacement heart valve device is collapsed onto the pusher member to reside in a collapsed configuration on the pusher~~

~~member and is restrained in a collapsed configuration by the moveable sheath~~;

after the obtaining step, loading the replacement heart valve device into the lumen of the moveable sheath such that the replacement heart valve device is collapsed onto the pusher member to reside in a collapsed configuration on the pusher member and is restrained in the collapsed configuration by the moveable sheath;

after the ~~providing~~ loading step, advancing the delivery and implantation system transluminally over [[the]] a guide wire within the patient to position the replacement heart valve device for deployment within the patient at the location of the native heart valve;

after the advancing step, partially deploying a distal portion of the replacement heart valve device within the patient by pushing out the pusher member from the moveable sheath to expose [[a]] the distal portion of the replacement heart valve device; [[and]]

after the partially deploying step, restraining the replacement heart valve device so that it does not pop out and is held for controlled release, with a potential that the replacement heart valve device can be recovered if there is a problem with positioning; and

after the ~~partially deploying~~ restraining step, recovering the distal portion of the replacement heart valve device within the moveable sheath that was exposed in order to address a problem with the position of the replacement heart valve device within the patient.

35. (Cancelled)

36. (Previously Presented) The method of Claim 34, wherein the stent member is self-expanding.

37. (Previously Presented) The method of Claim 36, wherein the stent member comprises nitinol.

38. (Previously Presented) The method of Claim 34, wherein the stent member includes a tubular structure away from its central portion that flares at both ends in a trumpet-like configuration.

39.-53. (Cancelled)

54. (New) The method of Claim 34, wherein after the obtaining step and before the loading step, exposing the replacement heart valve device to cold temperatures to cause the stent member of the replacement heart valve device to become flexible and supple.

55. (New) A method of controlled release of a percutaneous replacement heart valve at a location of a native heart valve in a patient, the method comprising:

advancing a delivery and implantation system transluminally over a guide wire within the patient to position a replacement heart valve device for deployment within the patient at the location of the native heart valve, the replacement heart valve device including a stent member that is collapsible, expandable and configured for percutaneous delivery, the replacement heart valve device further including a valve residing entirely within an inner channel of the stent member and attached to a proximal portion of the stent member, the valve including two to four individual leaflets made of fixed pericardial tissue, the delivery and implantation system including a pusher member and a moveable sheath, wherein the pusher member includes a lumen for receiving the guide wire, wherein the moveable sheath includes a lumen configured for receiving the pusher member, and wherein the replacement heart valve device is collapsed onto the pusher member to reside in a collapsed configuration on the pusher member and is restrained in the collapsed configuration by the moveable sheath;

after the advancing step, partially deploying a distal portion of the replacement heart valve device within the patient by partially exposing the distal portion of the replacement heart valve device from the moveable sheath;

after the partially deploying step, restraining the replacement heart valve device so that it does not pop out and is held for controlled release, with a potential that the replacement heart valve device can be recovered if there is a problem with positioning; and

after the restraining step, recovering the distal portion of the replacement heart valve device within the moveable sheath that was exposed in order to address a problem with the position of the replacement heart valve device within the patient.

56. (New) The method of Claim 55, wherein the stent member is self-expanding.

57. (New) The method of Claim 56, wherein the stent member comprises nitinol.

58. (New) The method of Claim 55, wherein the stent member includes a tubular structure away from its central portion that flares at both ends in a trumpet-like configuration.

59. (New) The method of Claim 55, wherein prior to the advancing step, loading the replacement heart valve device into the lumen of the moveable sheath such that the replacement heart valve device is collapsed onto the pusher member to reside in the collapsed configuration on the pusher member and is restrained in the collapsed configuration by the moveable sheath.

60. (New) The method of Claim 59, wherein prior to the loading step, exposing the replacement heart valve device to cold temperatures to cause the stent member of the replacement heart valve device to become flexible and supple.

61. (New) A method of controlled release of a percutaneous replacement heart valve at a location of a native heart valve in a patient, the method comprising:

advancing a delivery and implantation system transluminally over a guide wire within the patient to position a replacement heart valve device for deployment within the patient at the location of the native heart valve, the replacement heart valve device including a stent member that is collapsible, expandable and configured for percutaneous delivery, the replacement heart valve device further including a valve residing entirely within an inner channel of the stent member, the valve including two to four individual leaflets made of fixed pericardial tissue, the delivery and implantation system including a pusher member and a moveable sheath, wherein the pusher member includes a lumen for receiving the guide wire, wherein the moveable sheath includes a lumen configured for receiving the pusher member, and wherein the replacement heart valve device is collapsed onto the pusher member to reside in a collapsed configuration on the pusher member and is restrained in the collapsed configuration by the moveable sheath;

after the advancing step, partially deploying a distal portion of the replacement heart valve device within the patient by partially exposing the distal portion of the replacement heart valve device from the moveable sheath;

after the partially deploying step, restraining the replacement heart valve device so that it does not pop out and is held for controlled release, with a potential that the replacement heart valve device can be recovered if there is a problem with positioning; and

after the restraining step, recovering the distal portion of the replacement heart valve device within the moveable sheath that was exposed in order to address a problem with the position of the replacement heart valve device within the patient.

62. (New) The method of Claim 61, wherein the stent member is self-expanding.

63. (New) The method of Claim 62, wherein the stent member comprises nitinol.

64. (New) The method of Claim 61, wherein the stent member includes a tubular structure away from its central portion that flares at both ends in a trumpet-like configuration.

65. (New) The method of Claim 61, wherein prior to the advancing step, loading the replacement heart valve device into the lumen of the moveable sheath such that the replacement heart valve device is collapsed onto the pusher member to reside in the collapsed configuration on the pusher member and is restrained in the collapsed configuration by the moveable sheath.

66. (New) The method of Claim 65, wherein prior to the loading step, exposing the replacement heart valve device to cold temperatures to cause the stent member of the replacement heart valve device to become flexible and supple.

67. (New) The method of Claim 61, wherein the valve is attached to a proximal portion of the stent member.

68. (New) A method of controlled release of a percutaneous replacement heart valve at a location of a native heart valve in a patient, the method comprising:

exposing a replacement heart valve device to cold temperatures to cause a stent member of the replacement heart valve device to become flexible and supple, wherein the stent member comprises nitinol and is both collapsible and self-expanding, and wherein the stent member is configured for percutaneous delivery, the replacement heart valve device further including a valve residing entirely within an inner channel of the stent member and attached to a proximal portion of the stent member, the valve including two to four individual leaflets made of fixed pericardial tissue;

after the exposing step, loading the replacement heart valve device onto a pusher member and into a lumen of a moveable sheath of a delivery and implantation system such that the replacement heart valve device is restrained in a collapsed configuration by the moveable sheath, and wherein the pusher member includes a guide wire lumen;

after the loading step, advancing the delivery and implantation system transluminally over a guide wire within the patient to position the replacement heart valve device for deployment within the patient at the location of the native heart valve;

after the advancing step, partially deploying a distal portion of the replacement heart valve device within the patient by partially exposing the distal portion of the replacement heart valve device from the moveable sheath;

after the partially deploying step, restraining the replacement heart valve device so that it does not pop out and is held for controlled release, with a potential that the replacement heart valve device can be recovered if there is a problem with positioning; and

after the restraining step, recovering the distal portion of the replacement heart valve device within the moveable sheath that was exposed in order to address a problem with the position of the replacement heart valve device within the patient.

69. (New) The method of Claim 68, wherein the stent member includes a tubular structure away from its central portion that flares at both ends in a trumpet-like configuration.

70. (New) The method of Claim 69, wherein the valve attached to the proximal portion of the stent member is attached to a wider part of the stent member.

REMARKS/ARGUMENTS

The present Amendment and Response comprises Applicants' reply to the Examiner's July 8, 2014 Office Action. Claims 1-33 were previously cancelled and Claims 35 and 39-53 are cancelled herewith. Claim 34 is currently amended. New Claims 54-70 have been added, with new independent Claims 55 and 61 similar, but different than, amended independent Claim 34. Accordingly, Claims 34, 36-38 and 54-70 are now pending in view of the above amendments. Support for Claims 54-70 can be found in prior Claims 34-38, along with other portions of the specification and drawings as mentioned herein. (For example, support for amendments to Claim 34 are described herein, and therefore, similar limitations within new independent Claims 55, 61 and 68 also find corresponding support within the specification where indicated.) Applicants believe that all claim amendments made herein are consistent with U.S. Pat. App. Pub. No. 2003/0130729 (filed January 4, 2002) from which the present application claims priority.

Applicants believe that no new matter has been added with regard to the claim amendments provided herein. Applicants do not donate or disclaim any claims or subject matter with the claim amendments made herein, and the Applicants expressly reserve the right to prosecute the original claims, previously pending claims, or any unclaimed subject matter in one or more future filed continuing applications.

Reconsideration of the application is respectfully requested in view of the above amendments to the claims and the following remarks. Please note that the following remarks are not intended to be an exhaustive enumeration of the distinctions between any cited reference and the claimed invention. Rather, the distinctions identified and discussed below are presented solely by way of example to illustrate some of the differences between the claimed invention and the cited references. In addition, the Applicants request that the Examiner carefully review any references discussed below to ensure that Applicants' understanding and discussion of the references, if any, is consistent with the Examiner's understanding. Also, Applicants' arguments related to each cited reference are not an admission that the cited references are, in fact, prior art.

I. Rejection Under 35 U.S.C. § 112 (pre-AIA), First Paragraph

The Examiner rejected Claims 39-43 and 49-53 under 35 U.S.C. § 112 (pre-AIA), First Paragraph, on the grounds that the claims failed to comply with the written description requirement. As noted above, the Applicants have cancelled Claims 39-43 and 49-53, accordingly, the 35 U.S.C. § 112 (pre-AIA), First Paragraph, rejection of such claims is moot. Nonetheless, the Applicants note that support for such claims can be found in Paragraphs [0057] and [0058], as well as other portions of the specification of U.S. Pat. App. Pub. No. 2003/0130729 (filed January 4, 2002) from which the present application claims priority. Accordingly, Applicants believe appropriate support is provided in the specification filed on January 4, 2002. As mentioned elsewhere herein, the Applicants reserve the right to pursue cancelled Claims 39-43 and 49-53 in one or more future filed divisional or continuation patent applications.

II. Rejection Under 35 U.S.C. § 112 (pre-AIA), Second Paragraph

The Examiner rejected Claims 34-53 under 35 U.S.C. § 112 (pre-AIA), Second Paragraph, as being indefinite and failing to particularly point out and distinctly claim the subject matter of the invention. Applicants have amended independent Claim 34 to address the Examiner's rejection. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn from the independent claims as well as dependent Claims 36-38, which depend therefrom. Finally, Applicants note that new Claims 54-70 are believed to have been written to address the prior indefiniteness issues.

III. Prior Art Rejections

A. Rejection Under pre-AIA 35 U.S.C. § 102(e)

The Examiner rejected Claims 39-43 and 49-53 under pre AIA 35 U.S.C. § 102(e) as being anticipated by United States Patent No. 5,957,949 to Leonhardt et al. ("Leonhardt") and rejected Claims 34-37 and 44-47 under pre AIA 35 U.S.C. § 102(e) as being anticipated by United States Patent No. 6,425,916 to Garrison et al. ("Garrison"). The Applicants have addressed Garrison in the present reply, however, if necessary, the Applicants reserve the right to "swear behind" Garrison if the Applicants choose to do so at a later time.

The Applicants have cancelled Claims 39-53. Accordingly, the 35 U.S.C. § 102(e) rejections of Claims 39-53 are now moot. Here, Applicants note that the cancellation of Claims 39-53 is done to expedite allowance of the remaining pending claims, and the Applicants take this action to cancel the foregoing claims without acquiescing to the rejections. The Applicants reserve the right to pursue cancelled Claims 39-53 in one or more future-filed divisional or continuation patent applications.

With regard to independent Claim 34, the Applicants have amended Claim 34 to further recite that the valve includes "two to four individual leaflets <u>made of fixed pericardial tissue</u>." Support for this amended claim wording can be found at least in Paragraphs [0048]-[0053] of U.S. Pat. App. Pub. No. 2003/0130729 (filed January 4, 2002), from which the present application claims priority. New independent Claims 55, 61 and 68 also recite the foregoing limitation.

It is well recognized that claims are anticipated if, and only if, each and every element, as set forth in the claim is found in a single prior art reference. Vertegaal Bros. v. Union Oil Co. of Calif., 814 F.2d 628, 631 (Fed. Cir. 1987). Furthermore, "[t]he identical invention must be shown in as a complete detail as is contained in the . . . claim." Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236 (Fed. Cir. 1989). See MPEP § 2131. To constitute anticipation, all material elements of the claim must be found in one prior art source. In re Marshall, 198 U.S.P.Q. 344 (C.C.P.A. 1978). Additionally, the elements of the reference must be arranged as required by the claim. In re Bond, 15 U.S.P.Q. 2d 1566 (Fed. Cir. 1999).

Turning now to Garrison, while Garrison mentions synthetic materials (Garrison, col. 5, ll. 50-60), the only written description of a "tissue" material of Garrison is found at col. 5, ll. 42-48, wherein Garrison states:

> The posts 32 support a valve portion 38 which performs the functions of the patient's malfunctioning native valve. Referring to FIGS. 10 and 11, the valve portion 38 is preferably a stentless tissue valve such as a tri-leaflet 39 stentless porcine valve. The valve portion 38 has a base 41 which is secured to the support structure 26 with sutures (not shown).

Thus, review of Garrison reveals that Garrison uses "a trileaflet 39 stentless porcine valve." That is, Garrison does not disclose *"two to four individual leaflets made of fixed pericardial tissue,"* as claimed in amended Claim 34. Accordingly, Garrison fails to anticipate the amended wording of Claim 34. In addition, even though not asserted by the Examiner under 35 U.S.C. § 102 against Claim 34, with regard to Leonhardt, the Examiner indicated that Leonhardt discloses a "porcine valve." See Office Action, page 4.

For anticipation, every element and limitation of the claimed invention must be found in a single prior art reference, arranged as in the claim. See Karsten Mfg. Corp. v. Cleveland Golf Co., 242 F.3d 1376, 1383 (Fed. Cir. 2001). Based on the foregoing, Garrison (and Leonhardt) do not anticipate Claim 34 as amended. Accordingly, Garrison does not disclose the claim limitations as recited in amended Claim 34 presented herein, and for this reason alone, the Examiner is respectfully requested to withdraw the 35 U.S.C. § 102(e) rejection of Claim 34, as well as its dependent Claims 36-38, and allow such claims along with new dependent Claim 54.

In addition to the foregoing, the Applicants have amended Claim 34 to recite "a valve residing entirely within an inner channel of the stent member and attached to a proximal portion of the stent member." Support for this amended claim wording can be found at least in Paragraph [0052] and Figure 7 of U.S. Pat. App. Pub. No. 2003/0130729 (filed January 4, 2002), from which the present application claims priority. (New independent Claim 55 also recites the foregoing limitation. New independent Claim 61 does not include the limitation that the valve is attached to a proximal portion of the stent member, although this limitation is recited in new Claim 67 that depend from Claim 61. New independent Claim 68 recites "a valve residing entirely within an inner channel of the stent member and attached to a proximal portion of the stent member." Support for this claim wording to Claim 68 can also be found in Paragraph [0052] of U.S. Pat. App. Pub. No. 2003/0130729 (filed January 4, 2002), from which the present application claims priority.) Such limitations, in combination with "two to four individual leaflets made of fixed pericardial tissue," are not disclosed in Garrison.

Garrison does not attach commissures to the frame as is evidenced by the inverted valve structure shown in Figures 35 and 38.

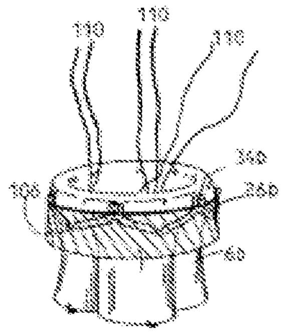

FIG. 35

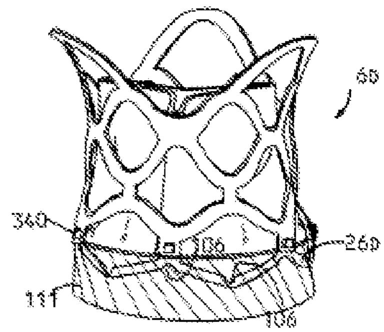

FIG. 38

With regard to Garrison, the valve 6D is attached to a circumferential ring 111 around the support structure 26D. (Garrison, col. 10, ll. 51-62.) This is at the distal end of the construct. Moreover, Garrison states that "[t]he valve 6D is coupled to a valve displacer 8D prior to introduction into the patient." (Garrison, col. 10, ll. 40-42.) Thus, when connected together for insertion, the valve is *inverted* as shown in Figure 35 of Garrison (provided above). This is the only method that Garrison discloses and describes when the components are together *before* implantation. Accordingly, Garrison cannot disclose that the "the replacement heart valve device is collapsed onto the pusher member to reside in a collapsed configuration on the pusher member and is restrained in a collapsed configuration by the moveable sheath," with the "valve residing entirely within an inner channel of the stent member and attached to a proximal portion of the stent member," as claimed in amended Claim 34, if the proximal end of the valve 6D is never attached to any structure other than the sutures 110 that are removed after inverting the valve 6D. "The catheter 4D is then removed and the sutures 110 are pulled to invert the valve 6D as shown in FIG. 33. An end of each suture 110 is then pulled to remove the sutures 110." (Garrison, col. 11, ll. 29-32.)

With regard to Figures 10 and 11, Garrison states "[r]eferring to FIGS. 10 and 11, the valve portion 38 is preferably a stentless tissue valve such as a tri-leaflet 39 stentless porcine valve. **The valve portion 38 has a base 41 which is secured to the support structure 26 with sutures (not shown)**." (Garrison, col. 5, ll. 44-48.) (Emphasis added.) Thus, Garrison discloses again that the base 41 of the valve portion 38 is attached to the support structure 26, but does not disclose the "valve residing entirely within an inner channel of the stent member and attached to a proximal portion of the stent member," as recited in amended Claim 34.

Accordingly, Garrison does not disclose a "replacement heart valve device including: a stent member that is collapsible, expandable and configured for percutaneous delivery; and a valve residing entirely within an inner channel of the stent member and attached to a proximal portion of the stent member, the valve including two to four individual leaflets made of fixed pericardial tissue," as recited in amended Claim 34.

Again, for anticipation, every element and limitation of the claimed invention must be found in a single prior art reference. Garrison fails to disclose the limitations as recited in Claim 34, and accordingly, the Examiner is respectfully requested to withdraw the 35 U.S.C. § 102(e) rejection of Claim 34, as well as its dependent Claims 36-38, and allow such claims along with new dependent Claim 54.

With further regard to the limitations of Claim 34, at line 7 on page 6 of the Office Action, the Examiner states "Garrison discloses moving the moveable sheath (4B) as necessary to correctly position the replacement valve (6A) within the patient, thus is appears clear that the sheath may be moved proximally or distally, **including recovering the valve device (6A) to reposition if necessary**." (Emphasis added.) However, in complete contrast to this statement, on page 7 of the Office Action, and starting at 4 lines up from the bottom of the page, the

Examiner admits that "**Garrison . . . does not disclose recovering the portion of the valve device within the moveable sheath**." (Emphasis added.) Moreover, when making the rejection on page 6 of the Office Action, the Examiner has referred multiple times to Figure 21 of Garrison. This is the embodiment of Garrison wherein the support structure 26 (with valve portion 38) is deployed separately from the valve displacer 8. The deployment configuration is shown in Figure 21 of Garrison, which is provided below:

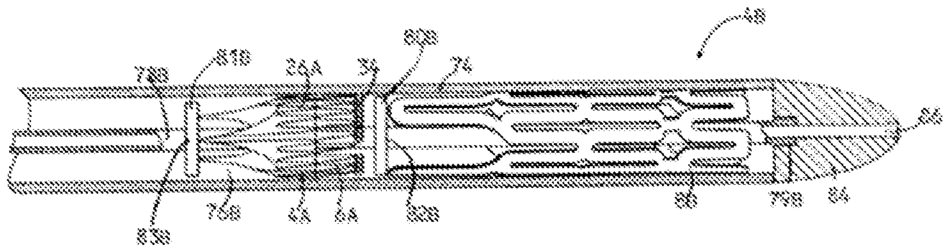

FIG. 21

For this method of deployment, Garrison requires that the valve displacer 8 be deployed at the location of the native valve. In the specification, Garrison states "[t]he valve displacer 8 is expanded within the native valve to hold the native cardiac leaflets 6 open." (Garrison, col. 4, ll. 45-46.) Garrison further states that "[t]he native leaflets are trapped in the recess 24 when the valve displacer 8 is deployed." (Garrison, col. 5, ll. 1-3.) Accordingly, Garrison teaches that the valve displacer 8 is to be deployed when the valve 6 is to be implanted at the location of the native heart valve. From Figure 21, it can be seen that Garrison shows the valve displacer 8B does not include the support structure 26A and valve portion 38 attached to the support structure 26A. This is because Garrison first deploys the valve displacer 8, and then subsequently deploys the valve 6A formed of the support structure 26 and valve portion 38. Accordingly, the valve displacer 8 resides in a distal position within the delivery catheter 4B so that it may be deployed in advance of deploying the valve 6A. Figure 24 of Garrison, provided below, illustrates this step:

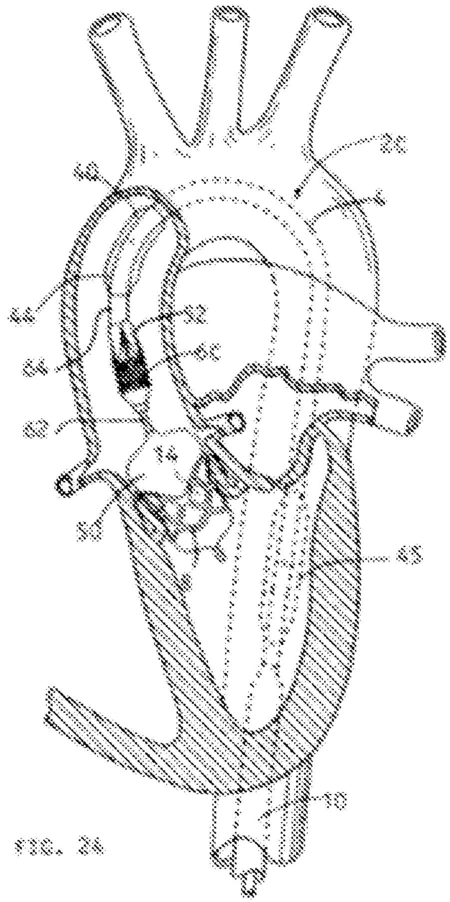

FIG. 24

Thus, after deployment of the valve displacer 8, but immediately before deploying the valve 6, the patient has received a valve displacer 8, but has not received a valve 6. After the valve displacer has been deployed, then the valve 6 with support structure 26 and attached valve portion 38 must be deployed because the patient does not have a working valve. Garrison states that "[t]he support structure 26 has a protrusion 34, preferably three, extending outwardly to form an interrupted lip around an end 35 of the support structure 26. The protrusions 34 engage the openings 14 in the valve displacer 8 as shown in FIG. 9 to secure the cardiac valve 6 to the valve displacer 8." (Garrison, col. 5, ll. 30-34.) Based on the foregoing, the Garrison valve 6 can only be deployed in one location at the native heart valve and this must occur after the valve displacer 8 is deployed, and that one location requires that the protrusions 34 engage the openings 14 in the valve displacer 8, which has already been deployed. Thus, there is no opportunity for the Garrison valve 6 to be repositioned as asserted by the Examiner because the valve 6 must be positioned to engage valve displacer 8, and the valve displacer must first be deployed to "hold the native cardiac leaflets 6 open," with the "native leaflets [] trapped in the recess 24 when the valve displacer 8 is deployed."

With regard to the step of "partially deploying a distal portion the replacement heart valve device within the patient by pushing out the pusher member from the moveable sheath to expose the distal portion of the replacement heart valve device," as recited in Claim 34, Garrison describes a "partially deployed" valve only in reference to engaging the support structure 26 to the valve displacer 8, and this is done inside the patient's body. In the Brief Description of the Drawings, Garrison states "FIG. 25 shows the valve **partially deployed** within the valve displacer." (Emphasis added.) Garrison then further states:

> The system 2C is introduced into the patient in any manner described above and FIG. 23 shows the delivery catheter 4 passing through the femoral artery. The valve displacer 8 is deployed in the manner described above wherein the valve displacer 8 is introduced into the valve leaflets and expanded with the balloon 50 to hold the native leaflets open as shown in FIG. 24. The delivery catheter 4 may then be advanced so that the cardiac valve 6C is expanded in the valve displacer 8 with the barbs 100 passing into the openings 14 to secure the cardiac valve 6C to the valve displacer 8 as shown in FIGS. 25 and 26 The barbs 100 may be long enough to pierce and anchor in the native valve leaflets or may be designed to merely pass into and engage the sides of the openings 14.

(Garrison, col. 10, ll. 10-23.) Thus, Garrison's use of the words "partially deployed" is for the *engagement process* of the support structure 26 engaging the valve displacer 8. For Garrison, the act of partial deployment is not for confirming that the valve is in the correct position relative to the native valve, the partial deployment is for engagement of the protrusions 34 of the support structure 26 to the openings 14 of the valve displacer 8 and the position of the valve relative to the native valve is not referenced. The Applicants note that support for the amendment "partially deploying a *distal* portion of the replacement heart valve device…" can be found in Paragraph [0057] of U.S. Pat. App. Pub. No. 2003/0130729 (filed January 4, 2002), from which the present application claims priority.

In addition, regarding the final step of Claim 34 herein that recites "recovering the distal portion of the replacement heart valve device within the moveable sheath that was exposed in order to address a problem with the position of the replacement heart valve device within the patient," there is no recovery of the valve 6 available with Garrison because once the valve displacer 8 is deployed, the valve 6 including the support structure 26 and the valve portion 38 contained therein must be deployed to engage the valve displacer 8. The Brief Description of the Drawings for Garrison states the following:

> FIG. 16 shows another system for implanting a cardiac valve.
> FIG. 17 shows the system of FIG. 16 with a distal portion of the valve displacer extending from the catheter.
> FIG. 18 shows the valve displacer fully deployed to hold the native leaflets open.
> FIG. 19 **shows the valve partially expanded with the catheter manipulated so that the valve engages the valve displacer**.
> FIG. 20 shows the valve fully deployed and the catheter removed.

(Garrison, col. 3, ll. 23-34.) (Emphasis added.)

Based on the foregoing, Applicants assert that Garrison does not anticipate Applicants' amended Claim 34 because Garrison fails to disclose the partially deployed and recovering steps as recited in the amended Claim 34. Accordingly, the Examiner is respectfully requested to withdraw the 35 U.S.C. § 102(e) rejection of Claim 34, as well as its dependent Claims 36-38 and new dependent Claim 54.

In addition to the foregoing, and with regard now to further steps as claimed in amended independent Claim 34, the Applicants have amended Claim 34 to recite an additional step with support provided in Paragraph [0043] of U.S. Pat. App. Pub. No. 2003/0130729 (filed January 4, 2002), from which the present application claims priority. More particularly, Claim 34 further recites:

> after the obtaining step, loading the replacement heart valve device into the lumen of the moveable sheath such that the replacement heart valve device is collapsed onto the pusher member to reside in a collapsed configuration on the pusher member and is restrained in the collapsed configuration by the moveable sheath.

With regard to the foregoing added loading step, there is no disclosure within Garrison that a replacement heart valve device with a valve including two to four individual leaflets made of fixed pericardial tissue that is attached to a stent member is loaded into a moveable sheath. Accordingly, the Examiner is respectfully requested to withdraw the 35 U.S.C. § 102(e) rejection of Claim 34, as well as its dependent Claims 36-38, and allow such claims along with new dependent Claim 54.

Regarding yet a further step as now recited in amended independent Claim 34, the Applicants have further amended Claim 34 to recite an additional step with support provided in Paragraph [0057] of U.S. Pat. App. Pub. No. 2003/0130729 (filed January 4, 2002), from which the present application claims priority. More particularly, Claim 34 further recites:

> after the partially deploying step, restraining the replacement heart valve device so that it does not pop out and is held for controlled release, with a potential that the replacement heart valve device can be recovered if there is a problem with positioning.

With regard to the foregoing added step, there is simply no disclosure within Garrison that, after partially deploying the replacement heart valve, the replacement heart valve is restrained so that it does not pop out and is held for controlled release, with the potential of recovering the replacement heart valve because of a problem associated with positioning, and then thereafter, recovering the replacement heart valve. Here, the Applicants again note that the foregoing wording further distinguishes over Garrison because the Garrison valve 6 cannot be recovered during deployment because, as explained above, Garrison uses both a valve displacer 8 and a valve 6 that must be coupled to the valve displacer 8. More particularly, the valve displacer 8 is required to be positioned at the location of the "native valve leaflets" of the patient. (Garrison, col. 7, ll. 52-53.) Accordingly, for Garrison, the valve displacer 8 is required to be deployed, and thereafter, the surgeon is committed to deploying the valve 6, and the valve 6 must be deployed such that the protrusions 34 of support structure 26 engage the openings 14 of the valve displacer 8. (Garrison, col. 8, ll. 5-6.)

For anticipation, every element and limitation of the claimed invention must be found in a single prior art reference. Garrison fails to disclose the limitations as recited in amended Claim 34, and accordingly, the Examiner is respectfully requested to withdraw the 35 U.S.C. § 102(e) rejection of Claim 34, as well as its dependent Claims 36-38, and allow such claims along with new dependent Claim 54.

B. Rejection Under pre-AIA 35 U.S.C. § 103(a)

The Examiner rejected Claims 34-38 and 44-48 under pre-AIA 35 U.S.C. § 103(a) as being unpatentable over Garrison in view of Leonhardt. As noted above, Claims 44-48 have been cancelled without prejudice, and the Applicants reserve the right to pursue such claims in or more continuation or divisional patent applications.

The U.S. Supreme Court, in KSR Int'l. Co. v. Teleflex Inc., 82 USPQ 2d 1385, 1391 (2007), reiterated the standard for determining obviousness under 35 U.S.C. § 103 as being the factual inquiries set forth in Graham v. John Deere Co. of Kansas City, 383 U.S. 1 (1966). In Graham, the Court stated that obviousness is determined by first determining the scope and content of the prior art, then ascertaining the differences between the invention, as claimed, and the prior art, and then resolving the level of ordinary skill in the prior art. Against this background, the obviousness or non-obviousness of the claimed subject matter is determined. Secondary considerations may also be utilized in this analysis to give light to the circumstances surrounding the origin of the subject matter sought to be patented. KSR Int'l Co., 82 USPQ 2d at 1391. When making any obviousness rejection, the Examiner must first acquire a thorough understanding of the claimed invention by reading the specification and claims to understand what the Applicant is claiming as his or her invention. MPEP § 904.

To establish a prima facie case of obviousness under 35 U.S.C. §103(a), the Examiner must clearly articulate the reason(s) why the claimed invention would have been obvious (i.e., the analysis supporting the rejection must be made explicit). See MPEP § 2142. "Rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." See MPEP § 2142 and In re Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006); see also KSR Int'l Co., 82 USPQ 2d at 1396. To support a § 103(a) rejection, the Examiner must demonstrate that a person of ordinary skill in the art would have had reason to attempt to make the claimed device, or carry out the claimed process, and would have had a reasonable expectation of success in doing so. See Noelle v. Lederman, 355 F.3d 1343, 1351–52 (Fed. Cir.

2004); Brown & Williamson Tobacco Co. v. Philip Morris, Inc., 229 F.3d 1120, 1121 (Fed. Cir. 2000); see also KSR Int'l Co., 82 USPQ2d at 1391.

On page 7 of the Office Action, the Examiner has intermixed and merged the two deployment methods of Garrison. More particularly, the Garrison reference discloses, in a broad sense, two procedures for deploying the Garrison valve. The first procedure Garrison discloses (also referred to hereafter as "Garrison Procedure #1") requires deployment of a valve displacer 8 to secure the native valve of the patient, wherein *after* the valve displacer 8 is deployed, then a valve is deployed, wherein the valve 6 includes support structure 26 and valve portion 38 attached thereto. When deploying the valve 6, the support structure 26 is engaged with the valve displacer 8 in the patient. (Alternatively, the valve 6, with support structure 26 and attached valve portion 38, are implanted at a location separated from both the valve displacer 8 and separated from the location of the native valve, as seen in Figures 27 and 28 of Garrison.) The second procedure Garrison discloses (also referred to hereafter as "Garrison Procedure #2") requires attaching the valve displacer 8 to the support structure 26 with the valve portion 38 attached thereto in an inverted position. This is done outside of the patient's body, and thereafter the combination is implanted in the patient through an incision in the patient's chest (Garrison, col. 11, ll. 11-12), with sutures 110 used pull the inverted position of the valve 6.

In the rejection, the Examiner is merging the two methodologies of Garrison. For example, the Examiner states that Garrison discloses "providing a replacement heart valve device … 6A+8B, coupled together as one assembly." (Office Action, pg. 7, ll. 4-5.) This corresponds to Garrison Procedure #2. See Figure 37 of Garrison provided below.

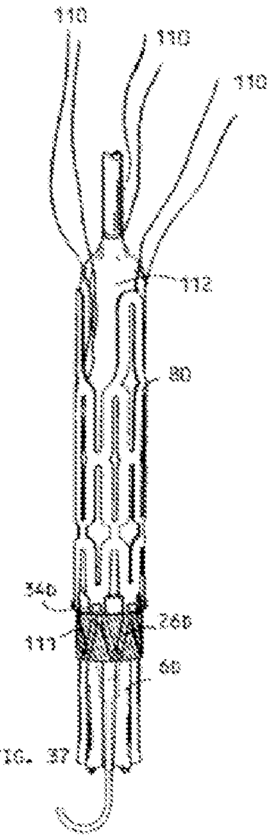

FIG. 37

The Examiner then states that Garrison provides "a delivery and implantation system (see fig. 21) including a pusher member/flexible hollow tube catheter (78B) and a moveable sheath (4B), the pusher/catheter (78B) includes a lumen (86) for receiving a guide wire (72), the moveable sheath (4B) includes a lumen (see fig. 21) for receiving the pusher/catheter (78B)." This corresponds to Garrison Procedure #1. See Figure 21 of Garrison below.

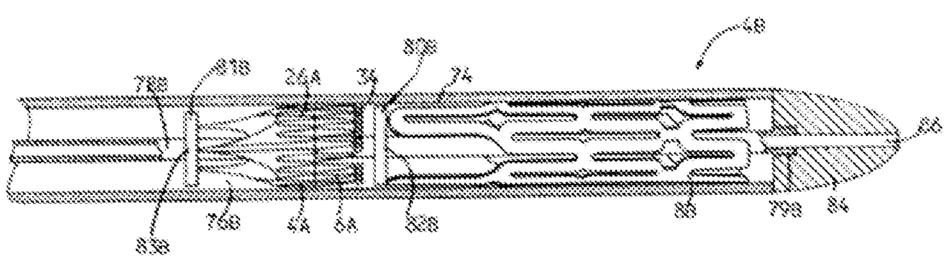

FIG. 21

As can be seen, Garrison Procedure #1 requires that the valve 6 *IS NOT* coupled to the valve displacer 8, while Garrison Procedure #2 requires that the valve 6 *IS* coupled to the valve displacer 8. Respectfully, as discussed in the paragraphs that follow, the Applicants assert that the two deployment methodologies of Garrison are not suitable for being merged.

First, Garrison does not disclose or teach how the two procedures can be interchangeable. Thus, there is no basis for the Examiner to merge the methodologies of Garrison, when Garrison did not merge the methodologies. Indeed, since Garrison teaches the methodologies separate, the Applicants assert that Garrison teaches away from merging the methodologies.

Second, the principle of operation of deployment of Garrison Procedure #1 is not compatible with Garrison Procedure #2 because in Garrison Procedure #1, the valve displacer 8 is separate and not yet connected to the valve 6. In Garrison Procedure #1, the connection between the valve displacer 8 and the valve 6 only occurs in the body of the patient. With Garrison Procedure #2, the connection occurs outside of the patient's body. These are completely opposite configurations. "**If the proposed modification** or combination of the prior art **would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious.**" MPEP § 2143.02; citing In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). (Emphasis added.)

Third, in Garrison Procedure #2, Garrison discloses that the valve portion 38 is inverted and must be pulled into the space occupied by the valve displacer 8. In contrast, the valve 6 formed of support structure 26 (plainly visible in Figure 21 of Garrison above) does not include an inverted valve portion 38. Figure 10 below of Garrison shows the support structure 26 with valve portion 38 attached. As can be seen in Figure 10 of Garrison, the valve portion 38 is not inverted.

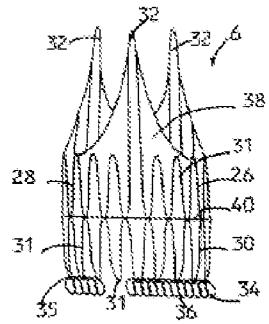

FIG. 10

Fourth, as mentioned above, Garrison Procedure #1 uses a support structure 26 to which the valve portion 38 is attached. Garrison Procedure #2 does not indicate that a support structure 26 is present. Accordingly, the presence and absence of the support structure 26 between Garrison Procedure #1 and Garrison Procedure #2, respectively, are completely opposite.

Fifth, Garrison Procedure #2 is conducted through an incision in the patient's chest. (Garrison, col. 11, ll. 11-12). There is no disclosure in Garrison indicating that the procedure identified for being conducted through an incision in the patient's chest can be merged into a procedure conducted as a transluminal percutaneous procedure, such as the Garrison Procedure #1.

Sixth, with regard to Garrison Procedure #2, as can be seen in Figure 37 of Garrison (provided above), the valve displacer 8D is located over a balloon and the valve 6D is not located over a pusher member as recited in Claim 34 of the present application, which recites, in part, that "the replacement heart valve device is collapsed onto the pusher member to reside in a collapsed configuration on the pusher member." Thus, Garrison Procedure #2 does not disclose the claim limitations as recited in amended Claim 34.

Seventh, Claim 34 recites that the "pusher member … **is restrained in the collapsed configuration by the moveable sheath**." Here, the Applicants assert that Garrison does not use a moveable sheath to restrain the collapsed configuration of the combination of valve displacer

8D and valve 6D in Garrison Procedure #2. Instead, the Examiner is using the moveable sheath from the deployment method Garrison Procedure #1 where the valve displacer 8D and valve 6D are separated. (Office Action, page 7.)

Accordingly, based on the foregoing, the principle of operation of Garrison Procedure #1 is incompatible with Garrison Procedure #2 and they cannot be merged together as asserted by the Examiner. On this basis alone, the Applicants respectfully request the Examiner to withdraw the 35 U.S.C. § 103(a) rejection of Claim 34, as well as its dependent Claims 36-38, and allow such claims along with new dependent Claim 54.

In addition to the foregoing, the Examiner proposes to modify the teachings of Garrison with Leonhardt to arrive at the claim limitation concerning recovering the replacement heart valve within the sheath. However, as discussed above, there is no recovery of the valve 6 available with Garrison because once the valve displacer 8 is deployed, the valve 6, including the support structure 26 and the valve portion 38 contained therein, must be deployed to engage the valve displacer 8. (Alternatively, if the native heart valve is removed, as mentioned by Garrison at column 4, lines 49-52, then the heart valve 6 must be placed to provide a working heart valve for the patient. However, Applicants have amended Claim 34 to now recite "advancing the delivery and implantation system transluminally over a guide wire within the patient to position the replacement heart valve device for deployment within the patient **at the location of the native heart valve**.")

In addition, use of Leonhardt to modify Garrison Procedure #1, which is the only transluminal percutaneous deployment methodology presented by Garrison, fails to yield the limitations as recited in Claim 34 (and new independent Claims 55, 61 and 68), because, among other things, Garrison fails to disclose any way of allowing recovery of the valve displacer 8, which must be deployed before deploying the valve 6. To allow recovery of the valve displacer 8 would also change the principle of operation of Garrison Procedure #1, because the valve displacer 8 is used to hold the valve 6. As Garrison states, "[t]he protrusions 34 engage the openings 14 in the valve displacer 8 as shown in FIG. 9 to secure the cardiac valve 6 to the valve displacer 8." (Garrison, col. 5, ll. 32-34.) (In addition, Applicants note that Garrison Procedure #2, is not a transluminal percutaneous deployment methodology. As mentioned above, Garrison Procedure #2 is conducted through an incision in the patient's chest. (Garrison, col. 11, ll. 11-12.))

Based on the foregoing, the Applicants assert that Garrison alone or Garrison in combination with Leonhardt fail to render amended Claim 34 unpatentable. Accordingly, the Examiner is respectfully requested to withdraw the 35 U.S.C. § 103(a) rejection of Claim 34 and its dependent Claims.

With regard to dependent Claims 36-38, the valve displacer 8 of Garrison is <u>not</u> a stent member, nor is the valve portion 38 attached to the valve displacer (when used, the valve is attached to support structure 26). Accordingly, Garrison or Garrison in view of Leonhardt fail to render the stent member as claimed in the present application as obvious (including in combination with other limitations of Claim 34), wherein the stent member is self-expanding; wherein the stent member comprises nitinol; and wherein the stent member includes a tubular structure away from its central portion that flares at both ends in a trumpet-like configuration. Moreover, if an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is nonobvious. <u>In re Fine</u>, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). <u>See</u> MPEP §2143.03. Accordingly, the Examiner is requested to withdraw the rejection of dependent Claims 36-38, and allow such claims along with new dependent Claim 54.

The Applicants have also added new dependent Claims 54, 59, 60, 65 and 66, wherein support for these claims is found in Paragraphs [0043] and [0057] of U.S. Pat. App. Pub. No. 2003/0130729 (filed January 4, 2002), from which the present application claims priority. The limitations in the foregoing dependent claims are also recited, at least in part, in new independent Claim 68. New dependent Claims 69 and 70 that depend from new independent Claim 68 find support in Paragraphs [0042] and [0052] of U.S. Pat. App. Pub. No. 2003/0130729 (filed January 4, 2002), from which the present application claims priority.

CONCLUSION

In view of the foregoing, Applicants believe the claims as amended are in allowable form. In the event that the Examiner finds a remaining impediment to a prompt allowance of this application that may be clarified through a telephone interview, or which may be overcome by an Examiner's Amendment, the Examiner is requested to contact the undersigned attorney at (303) 446-3852.

Applicants concurrently submit the small entity fee for one additional total claim bringing the total number of claims for this application to 21. Applicants believe no additional fees are due. However, lease credit any over payment or debit any under payment to Deposit Account No. 50-1943.

Respectfully submitted,

FOX ROTHSCHILD LLP

/ Mark L. Yaskanin /

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Dated: 21 August 2014

Electronic Patent Application Fee Transmittal

Application Number:	14253656
Filing Date:	15-Apr-2014
Title of Invention:	METHOD OF CONTROLLED RELEASE OF A PERCUTANEOUS REPLACEMENT HEART VALVE
First Named Inventor/Applicant Name:	David PANIAGUA
Filer:	Mark Lauren Yaskanin/Carol Donahue
Attorney Docket Number:	109978.10113

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in excess of 20	2202	1	40	40
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**40**

Electronic Acknowledgement Receipt

EFS ID:	19926352
Application Number:	14253656
International Application Number:	
Confirmation Number:	2795
Title of Invention:	METHOD OF CONTROLLED RELEASE OF A PERCUTANEOUS REPLACEMENT HEART VALVE
First Named Inventor/Applicant Name:	David PANIAGUA
Customer Number:	29880
Filer:	Mark Lauren Yaskanin/Carol Donahue
Filer Authorized By:	Mark Lauren Yaskanin
Attorney Docket Number:	109978.10113
Receipt Date:	21-AUG-2014
Filing Date:	15-APR-2014
Time Stamp:	13:58:03
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$40
RAM confirmation Number	183
Deposit Account	501943
Authorized User	YASKANIN, MARK L.

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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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Warnings:					
Information:					
2	Non Patent Literature	10117_US_14-284063_Office_Action_2014-08-15.PDF	405746 767cb51c75a56970fcae19c2c2d9362f0c07ac12	no	10
Warnings:					
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4		Colibri_10113_OA_Response.PDF	300441 5cd7f2e191bc977c2992dedcfb1a7a5cb8836cb3	yes	30

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	9
Applicant Arguments/Remarks Made in an Amendment	10	30

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	30383 a7eeae96766d5b40a2ddae1b63030e232a59611c	no	2
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ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	NUMBER FILED (Column 1)	NUMBER EXTRA (Column 2)	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	08/21/2014	CLAIMS REMAINING AFTER AMENDMENT (Column 1)		HIGHEST NUMBER PREVIOUSLY PAID FOR (Column 2)	PRESENT EXTRA (Column 3)	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 21	Minus	** 20	= 1	x $40 =	40
	Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	x $210 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**40**

AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT (Column 1)		HIGHEST NUMBER PREVIOUSLY PAID FOR (Column 2)	PRESENT EXTRA (Column 3)	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/RENEE M. COLLINS/

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/253,656	04/15/2014	David PANIAGUA	109978.10113

CONFIRMATION NO. 2795

PUBLICATION NOTICE

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29880
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LAWRENCEVILLE, NJ 08648

Title:METHOD OF CONTROLLED RELEASE OF A PERCUTANEOUS REPLACEMENT HEART VALVE

Publication No.US-2014-0243955-A1
Publication Date:08/28/2014

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	Application Number	14253656
	Filing Date	2014-04-15
	First Named Inventor	David PANIAGUA
	Art Unit	3738
	Examiner Name	Cheryl L. MILLER
	Attorney Docket Number	109978.10113

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	1	6676698		2004-01-13	McGuckin, Jr.	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14253656
	Filing Date	2014-04-15
	First Named Inventor	David PANIAGUA
	Art Unit	3738
	Examiner Name	Cheryl L. MILLER
	Attorney Docket Number	109978.10113

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T5
	1	Office Action issued September 11, 2014, in U.S. Application No. 14/268,190 (File: 109978.10115)	☐
	2	Office Action issued September 3, 2014, in U.S. Application No. 14/284,049 (File: 109978.10116)	☐
	3	Office Action issued September 12, 2014, in U.S. Application No. 14/268,184 (File: 109978.10114)	☐

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Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☒ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/ Mark L. Yaskanin /	Date (YYYY-MM-DD)	2014-09-12
Name/Print	Mark L. Yaskanin	Registration Number	45246

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	20123225
Application Number:	14253656
International Application Number:	
Confirmation Number:	2795
Title of Invention:	METHOD OF CONTROLLED RELEASE OF A PERCUTANEOUS REPLACEMENT HEART VALVE
First Named Inventor/Applicant Name:	David PANIAGUA
Customer Number:	29880
Filer:	Mark Lauren Yaskanin/Carol Donahue
Filer Authorized By:	Mark Lauren Yaskanin
Attorney Docket Number:	109978.10113
Receipt Date:	12-SEP-2014
Filing Date:	15-APR-2014
Time Stamp:	13:45:46
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	Colibri_10113_Supp_IDS_2014-09-12.PDF	656818 ef0eaae4e186279d9fe8548b91a243afcb848abd	no	4

Warnings:

Information:

2	Non Patent Literature	10114_US_14-264184_Office_Action_2014-09-12.PDF	459730 b11ce91ce36a866c33d03b2a7d3360d4ff025cfc	no	12
Warnings:					
Information:					
3	Non Patent Literature	10115_US_14-268190_Office_Action_2014-09-11.PDF	789645 6113f5cb5892a4df0d3c7c1a6375cda9a03c1a5d	no	19
Warnings:					
Information:					
4	Non Patent Literature	10116_US_14-284049_Office_Action_2014-09-03.PDF	416178 b343786491136eddbbad5222e392024a2a80ebde	no	11
Warnings:					
Information:					
		Total Files Size (in bytes):	2322371		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/253,656	04/15/2014	David PANIAGUA	109978.10113	2795

29880 7590 09/25/2014
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EXAMINER	
MILLER, CHERYL L	

ART UNIT	PAPER NUMBER
3738	

NOTIFICATION DATE	DELIVERY MODE
09/25/2014	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipdocket@foxrothschild.com

PTOL-90A (Rev. 04/07)

Office Action Summary	Application No. 14/253,656	Applicant(s) PANIAGUA ET AL.	
	Examiner CHERYL MILLER	Art Unit 3738	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/21/2014*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *34,36-38 and 54-70* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☒ Claim(s) *34 and 36-38* is/are allowed.

7)☒ Claim(s) *54-66 and 68-70* is/are rejected.

8)☒ Claim(s) *67* is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *8/21/2014, 9/12/2014*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Response to Arguments

Applicant's arguments with respect to claims 34-53 have been considered but are moot because the arguments do not apply to any of the references being used in the current rejection. Leonhardt (US 5,957,949) has been used herein, however on newly presented claims, detailed below. The Garrison (US 6,425,916 B1) rejection has been overcome, because upon further review by the examiner, Garrison's disclosure of manipulating the catheter after partial deployment to properly position the valve device (6; col.8, lines 53-61; col.9, lines 48-51), the manipulation and movement of 4a and 4b appears to be referring to manipulation and movement of *the entire catheter system as a whole* (outer sheath, inner pusher, and valve as one unit), and *not solely the outer sheath moving relative the valve*.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 54, 60, 66, and 68-70 rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention.

Each of claims 54, 60, 66, and 68 require the "stent member to become flexible and supple" when exposed to cold temperatures. Support was not found in the original specification for this limitation, thus this is being considered new matter. Claims 69-70 depend upon claim 68 and inherit all issues associated with the claim. Instead, the specification appears to disclose "When the components of the replacement heart valve device are exposed to cold temperatures, they become very flexible and supple", page 13 of priority application. Thus, the components (stent and valve) become supple and flexible, not the stent member alone. Thus, it is unclear if the stent become supple and flexible AND the valve becomes supple and flexible; or if for example, the stent becomes flexible and the valve becomes supple (that is components as a group become flexible and supple; and the stent alone not necessarily both flexible and supple). It is suggested to change the claim to require the replacement heart valve device (as a whole) to become supple and flexible.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 61-65 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Leonhardt et al. (US 5,957,949, cited previously) in view Spenser et al. (US 6,893,460 B2). Referring to claim 61, discloses a method of controlled release of a percutaneous replacement heart valve at a location of a native heart valve in a patient (fig.9a-9d), the method comprising: advancing a delivery and implantation system (seen in fig.5) transluminally over a guidewire (col.10, lines 6-11) within the patient to position the heart valve device for deployment within the patient at the location of the native heart valve, the heart valve device (20; fig.4) including a stent member (26) that is collapsible, expandable, and configured for percutaneous delivery, the heart valve device further including a valve (22) residing entirely within an inner channel of the stent member (see fig.4) and including two to four individual leaflets of fixed tissue (col.1, lines 32-48; col.3, lines 61-63; col.5, lines 7-10; col.6, lines 23-33; col.10, lines 64), the delivery and implantation system including a pusher member (110) and a moveable sheath (106), the pusher member (110) having a lumen (124) for receiving the guidewire and the moveable sheath (106) having a lumen (108) for receiving the pusher member (110; see fig.6), and wherein the heart valve device (20) is collapsed onto the pusher member (110) to reside in a collapsed configuration on the pusher member (sits in a collapsed configuration in front of 112, but in space between 110 and 106 seen in fig.6) and is restrained in the collapsed configuration by the moveable sheath (106); after the advancing step, partially deploying a distal portion of the heart valve device within the patient by partially exposing the distal portion of the heart valve device from the moveable sheath (fig.9b; col.10, lines 53-58); after partial deploying step, restraining the heart valve device so that it does not pop out and is held for controlled release (fig.9b, proximal end is restrained), with a potential that the heart valve device can be recovered if there is a problem with positioning; and after the restraining step, recovering the distal portion of the heart valve device within the moveable sheath that was exposed in order to address a problem with the position of the heart valve device within the patient (recover and reposition after partial deployment; col.11, lines 36-58).

Leonhardt discloses the method substantially as claimed (see above), however does not disclose the valve (22) to be pericardial tissue specifically, but discloses the valve may be synthetic or fixed biological tissue (col.1, lines 32-48; col.3, lines 61-63; col.5, lines 7-10; col.6, lines 23-33; col.10, lines 64). Spenser teaches in the same field of replacement heart valve devices, use of pericardial tissue as a known type of biological tissue that may be used for a valve attached to a stent (col.2, lines 47-56; col.8, lines 14-21). It would have been obvious to one having ordinary skill in the art at the time the invention was made to combine Leonhardt's method of controlled release of a replacement heart valve with a fixed biological or synthetic valve, with Spenser's teaching of an alternate valve material, pericardium, as such is shown as an obvious alternate material used in the art.

Referring to claims 62-65, Leonhardt discloses the stent member (26) to be self-expanding nitinol (col.5, lines 45-47; col.4, lines 26-28) and having a tubular shape flared at ends in a trumpet-like configuration (fig.2, 9d; col.5, lines 47-51). Leonhardt discloses prior to advancing, loading the heart valve device (20) into the lumen of the sheath (106) such that the valve device is collapsed onto the pusher (110) and restrained by the sheath (106; col.6, lines 58-60; col.7, lines 10-18).

Claims 55-59 and 67 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Leonhardt et al. (US 5,957,949, cited previously) in view of McGuckin, Jr. et al. (US 6,676,698 B2, cited in IDS) and Spenser et al. (US 6,893,,460 B2). Referring to claims 55 and 67, Leonhardt discloses a method of controlled release of a percutaneous replacement heart valve at a location of a native heart valve in a patient (fig.9a-9d), the method comprising: advancing a delivery and implantation system (seen in fig.5) transluminally over a guidewire (col.10, lines 6-11) within the patient to position the heart valve device for deployment within the patient at the location of the native heart valve, the heart valve device (20; fig.4) including a stent member (26) that is collapsible, expandable, and configured for percutaneous delivery, the heart valve device further including a valve (22) residing entirely within an inner channel of the stent member (see fig.4) and including two to four individual leaflets of fixed tissue (col.1, lines 32-48; col.3, lines 61-63; col.5, lines 7-10; col.6, lines 23-33; col.10, lines 64), the delivery and implantation system including a pusher member (110) and a moveable sheath (106), the pusher member (110) having a lumen (124) for receiving the guidewire and the moveable sheath (106) having a lumen (108) for receiving the pusher member (110; see fig.6), and wherein the heart valve device (20) is collapsed onto the pusher member (110) to reside in a collapsed configuration on the pusher member (sits in a collapsed configuration in front of 112, but in space between 110 and 106 seen in fig.6) and is restrained in the collapsed configuration by the moveable sheath (106); after the advancing step, partially deploying a distal portion of the heart valve device within the patient by partially exposing the distal portion of the heart valve device from the moveable sheath (fig.9b; col.10, lines 53-58); after partial deploying step, restraining the heart valve device so that it does not pop out and is held for controlled release (fig.9b, proximal end is restrained), with a potential that the heart valve device can be recovered if there is a problem with positioning; and after the restraining step, recovering the distal portion of the heart valve device within the moveable sheath that was exposed in order to address a problem with the position of the heart valve device within the patient (recover and reposition after partial deployment; col.11, lines 36-58).

Leonhardt discloses the method substantially as claimed (see above), however does not disclose 1) the valve to be pericardial tissue specifically and 2) the valve attached to the proximal portion of the stent member. Spenser teaches in the same field of replacement heart valve devices, use of pericardial tissue as a known type of biological tissue that may be used for a valve attached to a stent (col.2, lines 47-56; col.8, lines 14-21). McGuckin teaches in the same field of replacement stented valves percutaneously delivered, the placement of a valve may be at different locations, centered, or more distally or proximally located as obvious alternatives to one another (see figs.38-40; col.15, lines 55-60; col.16, lines 42-52; col.17, lines 8-11). It would have been obvious to one having ordinary skill in the art at the time the invention was made to combine Leonhardt's method of controlled release of a replacement heart valve with a fixed biological or synthetic valve positioned intermediate ends of stent member, with Spenser's teaching of an alternate valve material, pericardium, as such is shown as an obvious alternate material used in the art and with McGuckin's teaching of proximal attachment of valve to stent, as proximal, distal and intermediate attachment as shown to be obvious alternates of one another.

Referring to claims 56-59, Leonhardt discloses the stent member (26) to be self-expanding nitinol (col.5, lines 45-47; col.4, lines 26-28) and having a tubular shape flared at ends in a trumpet-like configuration (fig.2, 9d; col.5, lines 47-51). Leonhardt discloses prior to advancing, loading the heart valve device (20) into the lumen of the sheath (106) such that the valve device is collapsed onto the pusher (110) and restrained by the sheath (106; col.6, lines 58-60; col.7, lines 10-18).

Claim 68 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Bessler et al. (US 5,855,601) in view of Teitelbaum (US 5,332,402). Bessler discloses a method of controlled release of a percutaneous replacement heart valve at a location of a native heart valve in a patient (title, abstract), the method comprising: a replacement heart valve device (30; fig.4 for example) comprising a stent member (32) comprising nitinol (col.6, lines 3-7) that is collapsible (fig.5) and self-expanding and configured for percutaneous delivery (col.5, lines 43-50; col.2, lines 25-30), the heart valve device (30; fig.4) further including a valve (leaflets 36) residing entirely within an inner channel of the stent member (see fig.4; leaflets 36 are entirely within channel of stent 32; noting that "valve" is considered leaflets only, not cuff 37) and attached to a proximal portion of the stent member (bottom portion of stent, seen in fig.4), the valve (leaflets 36) including two to four individual leaflets (see fig.4; col.5, lines 23-24) made of fixed pericardial tissue (col.4, lines 9-11); loading the heart valve device (30; fig.4) onto a pusher member (103; see fig.14; valve 30 is loaded onto pusher by connection of sutures and holes 106 attachment) and into a lumen of a moveable sheath (102) of a delivery and implantation system (fig.14, 15) such that the heart valve device (30) is restrained in a collapsed configuration by the moveable sheath (seen in fig.12), and wherein the pusher member (103) includes a guidewire lumen (hollow lumen seen in fig.12, 14); after the loading step (fig.12), advancing the delivery and implantation system transluminally over a guidewire (94; col.5, lines 13-14) within the patient to position the heart valve device for deployment within the patient at the location of the native heart valve (col.4, lines 56-60); after the advancing step, partially deploying a distal portion of the heart valve device within the patient by partially exposing the distal portion of the heart valve device from the moveable sheath (seen in fig.14; col.4, lines 63-66); after partial deploying step, restraining the heart valve device so that it does not pop out and is held for controlled release (col.4, lines 66-col.5, line 3), with a potential that the heart valve device can be recovered if there is a problem with positioning (col.5 lines 1-3); and after the restraining step, recovering the distal portion of the heart valve device within the moveable sheath that was exposed in order to address a problem with the position of the heart valve device within the patient (controlled release, recovered; col.5, lines 1-3; fig.4, would be recovered back into sheath).

Bessler discloses the method substantially as claimed (see above), using a self-expanding stent member (32) that is made of shape memory nitinol (col.5, lines 42-51; col.6, lines 3-7), however does not disclose prior to loading, exposing the heart valve device with stent member, to cold temperatures. Teitelbaum teaches in the same field of replacement heart valve devices, a self-expanding nitinol stent member of the valve exposed to cold temperatures prior to loading in order to make the nitinol stent flexible and supple so that it may easily be compressed down to a small size for loading and delivery (col.2, lines 6-20; col.1, lines 24-50; col.3, lines 50-54; col.7, lines 1-17). It would have been obvious to one having ordinary skill in the art at the time the invention was made to combine Bessler's method using a self-expanding shape memory nitinol stent member loading into a delivery sheath, with Bessler's teaching of cooling the stent member prior to loading, in order to provide Bessler’s stent with an easier capability of loading into the sheath, due to the increased flexibility and suppleness from cooling.

Allowable Subject Matter

Claims 34 and 36-38 are allowed.

Claims 67 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 54, 60, 66, 69, and 70 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Vesely (US 6,530,952 B2) discloses recovery of an expandable heart valve device (20; fig.7a) within a moveable sheath (50) and on a pusher (31) after partial deployment (and after final deployment), however it does not appear that Vesely is recovery of the valve with the same sheath that is used to deliver the valve (since recovery occurs at a later date).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Cheryl Miller whose telephone number is 571-272-4755. The examiner can normally be reached on M- F (8am-5:30pm).

If attempts to reach the examiner by telephone are unsuccessful, please contact the examiner's supervisor, Thomas Sweet at 571-272-4761. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/C. M./
Examiner, Art Unit 3738

/THOMAS J SWEET/

Supervisory Patent Examiner, Art Unit 3738

Notice of References Cited	Application/Control No. 14/253,656	Applicant(s)/Patent Under Reexamination PANIAGUA ET AL.	
	Examiner CHERYL MILLER	Art Unit 3738	Page 1 of 1

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*	C	US-6,893,460 B2	05-2005	Spenser et al.	623/2.14
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	F	US-			
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	K	US-			
	L	US-			
	M	US-			

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NON-PATENT DOCUMENTS

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	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14253656	PANIAGUA ET AL.
	Examiner	**Art Unit**
	CHERYL MILLER	3738

CPC- SEARCHED

Symbol	Date	Examiner
A61F2/2436	6/29/2014	cm

CPC COMBINATION SETS - SEARCHED

Symbol	Date	Examiner

US CLASSIFICATION SEARCHED

Class	Subclass	Date	Examiner
623	1.24, 1.26, 2-12-2.19, 900	6/29/2014	cm
update		9/21/2014	cm

SEARCH NOTES

Search Notes	Date	Examiner
East text search	6/29/2014	cm
East text search	9/21/2014	cm

INTERFERENCE SEARCH

US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/C.M./ Examiner.Art Unit 3738	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	14253656
	Filing Date	2014-04-15
	First Named Inventor	David PANIAGUA
	Art Unit	3738
	Examiner Name	Cheryl L. MILLER
	Attorney Docket Number	109978.10113

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Examiner Initial*	Cite No	Patent Number	Kind Code1	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	6676698		2004-01-13	McGuckin, Jr.	
	2	6733525		2004-05-11	Yang et al.	

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Receipt date: 09/12/2014	Application Number	14253656	14253656 - GAU: 3738
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2014-04-15	
	First Named Inventor	David PANIAGUA	
	Art Unit	3738	
	Examiner Name	Cheryl L. MILLER	
	Attorney Docket Number	109978.10113	

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Office Action issued September 11, 2014, in U.S. Application No. 14/268,190 (File: 109978.10115)	☐
	2	Office Action issued September 3, 2014, in U.S. Application No. 14/284,049 (File: 109978.10116)	☐
	3	Office Action issued September 12, 2014, in U.S. Application No. 14/268,184 (File: 109978.10114)	☐

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	Application Number	14253656
	Filing Date	2014-04-15
	First Named Inventor	David PANIAGUA
	Art Unit	3738
	Examiner Name	Cheryl L. MILLER
	Attorney Docket Number	109978.10113

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	1	20030027332		2003-02-06	Lafrance et al.	
	2	20070061008		2007-03-15	Salahieh et al.	
	3	20100043197		2010-02-25	Abbate et al.	

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Receipt date: 08/21/2014

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
Application Number	14253656	14253656 - GAU: 3738
Filing Date	2014-04-15	
First Named Inventor	David PANIAGUA	
Art Unit	3738	
Examiner Name	Cheryl L. MILLER	
Attorney Docket Number	109978.10113	

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	1	Office Action issued August 15, 2014, in U.S. Application No. 14/284,063 (File: 109978.10117)	☐
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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
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S48	10	S47 and (ends with (bare or uncovered))	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/27 16:43
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S54	578	S53 and ((tube or tubular) with (valve or leaflets))	US-PGPUB; USPAT;	OR	ON	2014/03/19 16:34

			USOCR			
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S68	27	"11/066,126"	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 17:36
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			USPAT; USOCR			
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S71	1	"7101396".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 18:26
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S83	104	S80 and (reposition$4 or recover$4) and partially	US-PGPUB; USPAT; USOCR	OR	ON	2014/06/29 23:37
S84	7	S80 and (reposition$4 or recover$4 or retract$4) and (partially adj (deployed or expanding or expanded))	US-PGPUB; USPAT; USOCR	OR	ON	2014/06/29 23:47

S85	727	A61F2/2436.cpc.	US-PGPUB; USPAT; USOCR	OR	ON	2014/06/30 10:08
S86	71	S85 and @rlad<"20020104"	US-PGPUB; USPAT; USOCR	OR	ON	2014/06/30 10:08
S87	35	S85 and @ad<"20020104"	US-PGPUB; USPAT; USOCR	OR	ON	2014/06/30 10:08
S88	88	S86 S87	US-PGPUB; USPAT; USOCR	OR	ON	2014/06/30 10:08

9/21/2014 2:02:07 PM
C:\Users\cmiller2\Documents\EAST\Workspaces\14253656.wsp

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re the Application of:	) Group Art Unit: 3738
David PANIAGUA et al.	) Confirmation No. 2795
Application No.: 14/253,656	) Examiner: Cheryl L. MILLER
Filed: April 15, 2014	) AMENDMENT AND RESPONSE
Atty. File No.: 109978.10113	) **Filed Electronically**
Entitled: METHOD OF CONTROLLED RELEASE OF A PERCUTANEOUS REPLACEMENT HEART VALVE	)

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being electronically transmitted to the U.S. Patent & Trademark Office by the EFS-Web system on 25 September 2014.
Typed or printed name of person signing this certificate:
_Carol Donahue__
Signature: __/ Carol Donahue /_

Dear Sir:

In response to the September 25, 2014 Final Office Action (the "Office Action"), please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

Applicants believe no fees are due for this submission. However, please credit any over payment or debit any under payment to Deposit Account No. 50-1943.

AMENDMENTS TO THE CLAIMS

The listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims:

1.-33. (Cancelled)

34. (Previously Presented) A method of controlled release of a percutaneous replacement heart valve at a location of a native heart valve in a patient, the method comprising:

obtaining a replacement heart valve device and a delivery and implantation system:

the replacement heart valve device including:

a stent member that is collapsible, expandable and configured for percutaneous delivery; and

a valve residing entirely within an inner channel of the stent member and attached to a proximal portion of the stent member, the valve including two to four individual leaflets made of fixed pericardial tissue;

the delivery and implantation system including:

a pusher member and a moveable sheath, wherein the pusher member includes a guide wire lumen, and wherein the moveable sheath includes a lumen configured for receiving the pusher member;

after the obtaining step, loading the replacement heart valve device into the lumen of the moveable sheath such that the replacement heart valve device is collapsed onto the pusher member to reside in a collapsed configuration on the pusher member and is restrained in the collapsed configuration by the moveable sheath;

after the loading step, advancing the delivery and implantation system transluminally over a guide wire within the patient to position the replacement heart valve device for deployment within the patient at the location of the native heart valve;

after the advancing step, partially deploying a distal portion of the replacement heart valve device within the patient by pushing out the pusher member from the moveable sheath to expose the distal portion of the replacement heart valve device;

after the partially deploying step, restraining the replacement heart valve device so that it does not pop out and is held for controlled release, with a potential that the replacement heart valve device can be recovered if there is a problem with positioning; and

after the restraining step, recovering the distal portion of the replacement heart valve device within the moveable sheath that was exposed in order to address a problem with the position of the replacement heart valve device within the patient.

35. (Cancelled)

36. (Previously Presented) The method of Claim 34, wherein the stent member is self-expanding.

37. (Previously Presented) The method of Claim 36, wherein the stent member comprises nitinol.

38. (Previously Presented) The method of Claim 34, wherein the stent member includes a tubular structure away from its central portion that flares at both ends in a trumpet-like configuration.

39.-70. (Cancelled)

REMARKS/ARGUMENTS

The present Amendment and Response comprises Applicants' reply to the Examiner's September 25, 2014 Final Office Action. Applicants sincerely appreciate the Examiner's acknowledgement of the allowable subject matter. Applicants provide this reply to place the current application in a condition for allowance. Accordingly, Claims 39-70 are cancelled and any rejections pertaining to such claims are now moot.

Applicants believe that no new matter has been added with regard to the claim amendments provided herein. Applicants do not donate or disclaim any claims or subject matter with the claim amendments made herein, and the Applicants expressly reserve the right to prosecute the original claims, previously pending claims, other allowed subject matter and/or any unclaimed subject matter in one or more future filed continuing applications.

Reconsideration of the application is respectfully requested in view of the above amendments to the claims.

I. Notice of Allowance/ Advisory Action Requested

Applicants have filed this response within two months of the September 25, 2014 notification date of the Final Office Action. Accordingly, Applicants respectfully request the Examiner to issue a Notice of Allowance or an Advisory Action.

II. Allowed Subject Matter

Applicants express their appreciation to the Examiner for indicating that Claims 34 and 36-38 are allowable. A Notice of Allowance on such claims is respectfully requested. Other allowed subject matter may be pursued in one or more later filed continuing patent applications.

III. Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected Claims 54, 60, 66 and 68-70 under 35 U.S.C. § 112, first paragraph. Applicants have cancelled Claims 54, 60, 66 and 68-70, and the rejection of these claims is now moot.

IV. Prior Art Rejections Under 35 U.S.C. § 103(a)

The Examiner rejected a number of claims as unpatentable over prior art. Applicants have cancelled such claims in an effort to expedite allowance of Claims 34 and 36-38. Although now moot, Applicants do not acquiesce to the Examiner's prior art rejections.

CONCLUSION

In view of the foregoing, Applicants believe the pending claims are in allowable form. In the event that the Examiner finds a remaining impediment to a prompt allowance of this application that may be clarified through a telephone interview, or which may be overcome by an Examiner's Amendment, the Examiner is requested to contact the undersigned attorney at (303) 446-3852.

Applicants believe no fees are due for this submission. However, please credit any over payment or debit any under payment to Deposit Account No. 50-1943.

Respectfully submitted,

FOX ROTHSCHILD LLP

/ Mark L. Yaskanin /

Mark L. Yaskanin, Esq.
Registration No. 45,246
Customer No. 29880
Phone: (303) 446-3852
Facsimile: (303) 292-1300

Dated: 25 September 2014

Electronic Acknowledgement Receipt

EFS ID:	20246509
Application Number:	14253656
International Application Number:	
Confirmation Number:	2795
Title of Invention:	METHOD OF CONTROLLED RELEASE OF A PERCUTANEOUS REPLACEMENT HEART VALVE
First Named Inventor/Applicant Name:	David PANIAGUA
Customer Number:	29880
Filer:	Mark Lauren Yaskanin/Carol Donahue
Filer Authorized By:	Mark Lauren Yaskanin
Attorney Docket Number:	109978.10113
Receipt Date:	25-SEP-2014
Filing Date:	15-APR-2014
Time Stamp:	16:05:15
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Colibri_10113_FinalOA_Reply_2014-09-25.PDF	135985 1065d150bce0c411e6c8c3e9b2acc3213487f2ed	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Response After Final Action	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	6

Warnings:

Information:

Total Files Size (in bytes):	135985

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/253,656	Filing Date 04/15/2014	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	NUMBER FILED (Column 1)	NUMBER EXTRA (Column 2)	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 09/25/2014	CLAIMS REMAINING AFTER AMENDMENT (Column 1)		HIGHEST NUMBER PREVIOUSLY PAID FOR (Column 2)	PRESENT EXTRA (Column 3)	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 4	Minus	** 21	= 0	x $40 =	0
Independent (37 CFR 1.16(h))	* 1	Minus	***4	= 0	x $210 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT	CLAIMS REMAINING AFTER AMENDMENT (Column 1)		HIGHEST NUMBER PREVIOUSLY PAID FOR (Column 2)	PRESENT EXTRA (Column 3)	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/CHERYL CLARK/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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NOTICE OF ALLOWANCE AND FEE(S) DUE

29880 7590 10/07/2014

FOX ROTHSCHILD LLP
PRINCETON PIKE CORPORATE CENTER
997 LENOX DRIVE
BLDG. #3
LAWRENCEVILLE, NJ 08648

EXAMINER	
MILLER, CHERYL L	
ART UNIT	PAPER NUMBER
3738	

DATE MAILED: 10/07/2014

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/253,656	04/15/2014	David PANIAGUA	109978.10113	2795

TITLE OF INVENTION: METHOD OF CONTROLLED RELEASE OF A PERCUTANEOUS REPLACEMENT HEART VALVE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	01/07/2015

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

29880 7590 10/07/2014
FOX ROTHSCHILD LLP
PRINCETON PIKE CORPORATE CENTER
997 LENOX DRIVE
BLDG. #3
LAWRENCEVILLE, NJ 08648

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/253,656	04/15/2014	David PANIAGUA	109978.10113	2795

TITLE OF INVENTION: METHOD OF CONTROLLED RELEASE OF A PERCUTANEOUS REPLACEMENT HEART VALVE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	01/07/2015

EXAMINER	ART UNIT	CLASS-SUBCLASS
MILLER, CHERYL L	3738	623-002110

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 ____________________
2 ____________________
3 ____________________

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies ____________________

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number ____________ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29

  NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27

  NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status.

  NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature ____________________ Date ____________________

Typed or printed name ____________________ Registration No. ____________________

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/253,656	04/15/2014	David PANIAGUA	109978.10113	2795

29880 7590 10/07/2014

FOX ROTHSCHILD LLP
PRINCETON PIKE CORPORATE CENTER
997 LENOX DRIVE
BLDG. #3
LAWRENCEVILLE, NJ 08648

EXAMINER	
MILLER, CHERYL L	
ART UNIT	PAPER NUMBER
3738	

DATE MAILED: 10/07/2014

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)

(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 14/253,656	Applicant(s) PANIAGUA ET AL.	
	Examiner CHERYL MILLER	Art Unit 3738	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--
All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the after final amendment filed 9/25/2014*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on______.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *34 and 36-38*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:
   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. ______ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)
1. ☒ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 5/23/2014
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/C. M./ Examiner, Art Unit 3738	/THOMAS J SWEET/ Supervisory Patent Examiner, Art Unit 3738

AFTER FINAL AMENDMENT

The after final amendment filed September 25, 2014 has been entered. In addition to the after final amendment, an examiners amendment has been made, see below.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

The application has been amended as follows:

In claim 38, line 2, "its" has been changed to --a--.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Seguin (US 6,830,584 B1) discloses a method of percutaneously implanting a cardiac valve; Boretos et al. (US 4,056,854) discloses a method of implanting a heart valve with a recovery option; Ouriel et al. (US 6,682,537 B2) discloses a method of delivering a stent graft that may be recovered, the stent graft may have a valve (fig.39); Lenker et al. (US 5,683,451) and (US 6,350,278 B1) discloses a method of percutaneously delivering a stent graft, with recovery; Yang et al. (US 7,556,646 B2) discloses a method of delivering a heart valve by controlled expansion and recovery; Lambrecht et al. (US 6,896,690 B1) discloses a method of delivering a heart valve that may be repositioned after expansion; Hachtman et al. (US

5,645,559) discloses a method of delivering an expandable stent and recovery after partial deployment; Thompson et al. (US 5,876,448) discloses a method of delivering a stent graft with recovery after partial deployment; Braunschweiler et al. (US 5,484,444) discloses a method of delivering an expandable stent with recovery after partial deployment; and Andersen et al. (US 6,168,614 B1) discloses a method of percutaneously delivering a heart valve.

It is also noted that ***Information Disclosure Statement*** attached hereto (filed 5/23/2014) is a duplicate of that was already considered in full by the examiner, however attached hereto, to update in annotation certain NPL documents that were absent a publication date. The IDS has been considered.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Cheryl Miller whose telephone number is 571-272-4755. The examiner can normally be reached on M- F (8am-5:30pm).

If attempts to reach the examiner by telephone are unsuccessful, please contact the examiner's supervisor, Thomas Sweet at 571-272-4761. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/C. M./

Examiner, Art Unit 3738

/THOMAS J SWEET/

Supervisory Patent Examiner, Art Unit 3738

Notice of References Cited	Application/Control No. 14/253,656	Applicant(s)/Patent Under Reexamination PANIAGUA ET AL.	
	Examiner CHERYL MILLER	Art Unit 3738	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,830,584 B1	12-2004	Seguin, Jacques	623/2.11
*	B	US-4,056,854	11-1977	Boretos et al.	623/2.18
*	C	US-6,682,537 B2	01-2004	Ouriel et al.	606/108
*	D	US-5,683,451	11-1997	Lenker et al.	623/1.11
*	E	US-6,350,278 B1	02-2002	Lenker et al.	623/1.12
*	F	US-7,556,646 B2	07-2009	Yang et al.	623/2.11
*	G	US-6,896,690 B1	05-2005	Lambrecht et al.	606/200
*	H	US-5,645,559	07-1997	Hachtman et al.	623/1.2
*	I	US-5,876,448	03-1999	Thompson et al.	623/1.13
*	J	US-5,484,444	01-1996	Braunschweiler et al.	623/1.11
*	K	US-6,168,614 B1	01-2001	Andersen et al.	623/1.26
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	3	"10/037,266"	USPAT	OR	OFF	2014/02/24 19:08
S2	9	"10/037,266"	US-PGPUB; USPAT	OR	OFF	2014/02/24 19:08
S3	1916	623/1.24.ccls. or 623/1.26.ccls. or 623/2.12.ccls. or 623/2.13.ccls. or 623/2.14.ccls. or 623/2.15.ccls. or 623/2.16.ccls. or 623/2.17.ccls. or 623/2.18.ccls. or 623/2.19.ccls. or 623/900.ccls.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/02/24 19:53
S4	405	S3 and @rlad<"20020104"	US-PGPUB; USPAT; USOCR	OR	OFF	2014/02/24 19:53
S5	430	S3 and @ad<"20020104"	US-PGPUB; USPAT; USOCR	OR	OFF	2014/02/24 19:53
S6	669	S4 S5	US-PGPUB; USPAT; USOCR	OR	OFF	2014/02/24 19:53
S7	620	S3 and @rlad<"20040710"	US-PGPUB; USPAT; USOCR	OR	OFF	2014/02/24 19:54
S8	757	S3 and @ad<"20040710"	US-PGPUB; USPAT; USOCR	OR	OFF	2014/02/24 19:54
S9	195	S8 not S6	US-PGPUB; USPAT; USOCR	OR	OFF	2014/02/24 19:54
S10	228	S6 and (flare or flared or tapered or taper)	US-PGPUB; USPAT; USOCR	OR	OFF	2014/02/24 19:56
S11	11	S6 and (flare or flared or tapered or taper) and bailey.in.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/02/24 19:56
S12	306	S6 and ((valve or leaflet) with (tube or tubular))	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/24 20:01
S13	3	"7018406".pn. or "8579966".pn. or	US-	OR	ON	2014/02/24

		"6830584".pn.	PGPUB; USPAT; USOCR			20:04
S14	1	"6893460".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/24 20:10
S15	13	"6458153".pn. or "6893460".pn. or "6908481".pn. or "20080312735".pn. or "20030149477".pn. or "20030069635".pn. or "6425916".pn. or "6669724".pn. or "6245102".pn. or "6221091".pn. or "6027525".pn. or "5509930".pn. or "4491986".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/24 21:23
S16	14	"6458153".pn. or "6893460".pn. or "6908481".pn. or "20080312735".pn. or "20030149477".pn. or "20030069635".pn. or "6425916".pn. or "6669724".pn. or "6245102".pn. or "6221091".pn. or "6027525".pn. or "5509930".pn. or "4491986".pn. or "6254564".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/24 21:23
S17	1	"5762631".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/25 11:11
S18	6	"10/304,085"	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/25 13:12
S19	1	"5669924".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/25 13:30
S20	1	"6346089".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/25 14:01
S21	1	"12/609,521"	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/25 14:10
S22	1	"6918927".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/25 14:10
S23	1	"6217607".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/25 14:26
S24	7	"7018406".pn. or "7628803".pn. or "6730118".pn. or "20050137682".pn. or "20050055079".pn. or "20030199971".pn. or "7331993".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/26 14:30
S25	2	"10/412,377"	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/26 14:35
S26	149	("20020095994" | "20020123789" | "20020128708" | "20020151970" |	US-PGPUB;	OR	ON	2014/02/27 11:59

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S29	75	S27 S28	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/27 11:59
S30	74	("20010010017" | "20010023372" | "20010049558" | "20020005073" | "20020028243" | "20020029783" | "20020037940" | "20020042621" | "20020091441" | "20020095167" | "3014024" | "3029819" | "3105492" | "3320972" | "3409914" | "3548417" | "3562820" | "3588920" | "3671979" | "3709175" | "3878565" | "3945052" | "3966401" | "3983581" | "3986828" | "4035849" | "4055861" | "4056854" | "4060081" | "4082507" | "4084268" | "4106129" | "4164045" | "4172295" | "4218782" | "4222126" | "4233493" | "4265694" | "4291420" | "4340977" | "4350492" | "4364127" | "4388735" | "4423525" | "4441216" | "4456589" | "4473423" | "4477930" | "4490859" | "4517687" | "4545082" | "4597762" | "4600533" | "4631052" | "4666442" | "4728328" | "4759758" | "4759759" | "4798611" | "4801299" | "4870966" | "4883458" | "4892539" | "4966604" | "4976733" | "4979939").PN.	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/27 12:00
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S33	58	S31 S32	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/27 12:01
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S41	157	S39 S40	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/27 12:03
S42	1	"13/376,723"	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/27 12:23
S43	1	"6117159".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/27 12:31
S44	300	623/1.3.ccls. or 623/1.31.ccls.	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/27 16:43
S45	97	S44 and @rlad<"20020104"	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/27 16:43
S46	91	S44 and @ad<"20020104"	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/27 16:43
S47	143	S45 S46	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/27 16:43

S48	10	S47 and (ends with (bare or uncovered))	US-PGPUB; USPAT; USOCR	OR	ON	2014/02/27 16:43
S49	2224	623/1.24.ccls. or 623/1.26.ccls. or 623/2.12.ccls. or 623/2.13.ccls. or 623/2.14.ccls. or 623/2.15.ccls. or 623/2.16.ccls. or 623/2.17.ccls. or 623/2.18.ccls. or 623/2.19.ccls. or 623/900.ccls. or 623/2.1.ccls.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/03/19 16:33
S50	2224	623/1.24.ccls. or 623/1.26.ccls. or 623/2.12.ccls. or 623/2.13.ccls. or 623/2.14.ccls. or 623/2.15.ccls. or 623/2.16.ccls. or 623/2.17.ccls. or 623/2.18.ccls. or 623/2.19.ccls. or 623/900.ccls. or 623/2.1.ccls.	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:33
S51	716	S50 and @rlad<"20040710"	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:33
S52	837	S50 and @ad<"20040710"	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:34
S53	1159	S51 S52	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:34
S54	578	S53 and ((tube or tubular) with (valve or leaflets))	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:34
S55	102	S53 and ((tube or tubular) adj (valve or leaflets))	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:34
S56	1	S53 and ((rectangle or rectangular or square) adj (valve or leaflets))	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:34
S57	5	S53 and ((rectangle or rectangular or square) adj (valve or leaflets or flaps))	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:35
S58	89	S53 and ((tube or tubular) adj (valve))	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:36
S59	2393	A61F2/24.cpc. or A61f2/2412.cpc. or A61F2/2475.cpc.	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:37
S60	1222	S59 not S50	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:37
S61	573	S60 and @rlad<"20040710"	US-PGPUB; USPAT;	OR	ON	2014/03/19 16:37

			USOCR			
S62	477	S60 and @ad<"20040710"	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:37
S63	759	S61 S62	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:37
S64	294	S63 and ((tubular or tube or rectangle or rectangular or sqaure) with (leaflets or flaps or valve))	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 16:38
S65	1	"7276078".pn.	US-PGPUB; USPAT	OR	ON	2014/03/19 17:09
S66	178	S53 and ((tube or tubular) with (valve or leaflets)) and (crease or fold$3) and (flar$3 or taper$3)	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 17:13
S67	150	S66 not S55	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 17:14
S68	27	"11/066,126"	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 17:36
S69	1	"7101396".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2014/03/19 18:14
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S73	1	"6458153".pn.	USPAT	OR	OFF	2014/03/21 12:18
S74	3	"20030036791".pn. or "20030040792".pn. or "6363938".pn.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/03/21 13:06
S75	3	"20070179592".pn. or "6645242".pn. or "20040167606".pn.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/03/21 13:33
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S80	676	S78 S79	US-PGPUB; USPAT; USOCR	OR	ON	2014/06/29 23:34
S81	165	S80 and (reposition$4 or recover$4)	US-PGPUB; USPAT; USOCR	OR	ON	2014/06/29 23:34
S82	1	"6676698".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2014/06/29 23:35
S83	104	S80 and (reposition$4 or recover$4) and partially	US-PGPUB; USPAT; USOCR	OR	ON	2014/06/29 23:37
S84	7	S80 and (reposition$4 or recover$4 or retract$4) and (partially adj (deployed or expanding or expanded))	US-PGPUB; USPAT; USOCR	OR	ON	2014/06/29 23:47
S85	727	A61F2/2436.cpc.	US-PGPUB; USPAT; USOCR	OR	ON	2014/06/30 10:08
S86	71	S85 and @rlad<"20020104"	US-PGPUB; USPAT; USOCR	OR	ON	2014/06/30 10:08
S87	35	S85 and @ad<"20020104"	US-PGPUB; USPAT; USOCR	OR	ON	2014/06/30 10:08
S88	88	S86 S87	US-PGPUB; USPAT; USOCR	OR	ON	2014/06/30 10:08
S89	2073	623/1.24.ccls. or 623/1.26.ccls. or 623/2.12.ccls. or 623/2.13.ccls. or 623/2.14.ccls. or 623/2.15.ccls. or 623/2.16.ccls. or 623/2.17.ccls. or 623/2.18.ccls. or 623/2.19.ccls. or 623/900.ccls.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/09/21 13:46
S90	2073	S89	US-PGPUB; USPAT; USOCR	OR	OFF	2014/09/21 13:46
S91	416	S90 and @rlad<"20020104"	US-PGPUB; USPAT;	OR	OFF	2014/09/21 13:47

			USOCR			
S92	430	S90 and @ad<"20020104"	US-PGPUB; USPAT; USOCR	OR	OFF	2014/09/21 13:47
S93	680	S91 S92	US-PGPUB; USPAT; USOCR	OR	OFF	2014/09/21 13:47
S94	151	S93 and (recover$4 or retreiv$4 or retriev$4 or recaptur$4 or recollasp$4 or recompress$4)	US-PGPUB; USPAT; USOCR	OR	OFF	2014/09/21 13:48
S95	181	S93 and (recover$4 or retreiv$4 or retriev$4 or recaptur$4 or recollasp$4 or recompress$4 or reposition$4)	US-PGPUB; USPAT; USOCR	OR	OFF	2014/09/21 13:48
S96	3	"6740111".pn. or "6168614".pn. or "6299637".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/28 19:11
S97	209	A61F2002/9534.cpc.	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/28 19:51
S98	42	S97 and @rlad<"20020104"	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/28 19:51
S99	49	S97 and @ad<"20020104"	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/28 19:51
S100	63	S98 S99	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/28 19:51
S101	270	A61F2/2439.cpc.	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/28 20:18
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S103	6	S101 and @ad<"20020104"	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/28 20:18
S104	31	S102 S103	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/28 20:18
S105	1811	A61F2/2427.cpc. or A61F2/2433.cpc. or A61F2/2436.cpc.	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/28 20:19
S106	452	S105 and @rlad<"20020104"	US-	OR	ON	2014/09/28

			PGPUB; USPAT; USOCR			20:19
S107	298	S105 and @ad<"20020104"	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/28 20:19
S108	566	S106 S107	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/28 20:19
S109	208	S108 and (recaptur$4 or reposition$4 or recollaps$4 or recompress$4 or retriev$4 or retreiv$4)	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/28 20:20
S110	1622	A61F2002/9534.cpc. or A61F2002/9511.cpc. or A61F2002/966.cpc. or A61F2002/9665.cpc.	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/28 20:21
S111	389	S110 and @rlad<"20020104"	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/28 20:22
S112	306	S110 and @ad<"20020104"	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/28 20:22
S113	519	S111 S112	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/28 20:22
S114	80	S113 and (valve or leaflet) and (reposition$4 or recaptur$4 or retreiv$4 or retriev$4 or recompress$4 or recollaps$4)	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/28 20:22
S115	1	"6666883".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/28 20:39
S116	1	"5484444".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/28 20:47
S117	1	"6371979".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/29 10:04
S118	1	"5683451".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/29 18:42
S119	1	"6682537".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/29 18:44
S120	3	"20030027332".pn. or "20070061008".pn. or "20100043197".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2014/09/29 19:15

9/ 29/ 2014 9:23:45 PM
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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14253656	PANIAGUA ET AL.
	Examiner	**Art Unit**
	CHERYL MILLER	3738

CPC

Symbol					Type	Version
A61F		2	/	2427	F	2013-01-01
A61F		2	/	2412	I	2013-01-01
A61F		2	/	2415	I	2013-01-01
A61F		2	/	2418	I	2013-01-01
A61F		2	/	2436	I	2013-01-01
A61F		2	/	24	I	2013-01-01
A61F		2	/	2475	I	2013-01-01
A61B		8	/	12	I	2013-01-01
A61F		2	/	2433	I	2013-01-01
A61F		2002	/	9534	A	2013-01-01
A61F		2	/	2439	A	2013-01-01
Y10S		623	/	917	A	2013-01-01
A61F		2250	/	0039	A	2013-01-01
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CPC Combination Sets

Symbol					Type	Set	Ranking	Version
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			/					

/C.M./ Examiner.Art Unit 3738 (Assistant Examiner)	09/29/2014 (Date)	**Total Claims Allowed:** 4	
/THOMAS J SWEET/ Supervisory Patent Examiner.Art Unit 3738 (Primary Examiner)	09/30/2014 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 8

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14253656	PANIAGUA ET AL.
	Examiner	**Art Unit**
	CHERYL MILLER	3738

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**
623	2.11

INTERNATIONAL CLASSIFICATION					
CLAIMED					**NON-CLAIMED**
A	6	1	F	2 / 24 (2006.0)	

CROSS REFERENCE(S)

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
623	2.14				

/C.M./ Examiner.Art Unit 3738 (Assistant Examiner)	09/29/2014 (Date)	**Total Claims Allowed:** 4
/THOMAS J SWEET/ Supervisory Patent Examiner.Art Unit 3738 (Primary Examiner)	09/30/2014 (Date)	O.G. Print Claim(s): 1 / O.G. Print Figure: 8

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	14253656	PANIAGUA ET AL.
	Examiner	**Art Unit**
	CHERYL MILLER	3738

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		17		33		49		65						
	2		18	1	34		50		66						
	3		19		35		51		67						
	4		20	2	36		52		68						
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	16		32		48		64								

/C.M./ Examiner.Art Unit 3738 (Assistant Examiner)	09/29/2014 (Date)	**Total Claims Allowed:** 4	
/THOMAS J SWEET/ Supervisory Patent Examiner.Art Unit 3738 (Primary Examiner)	09/30/2014 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 8

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	14253656
	Filing Date	2014-04-15
	First Named Inventor	David PANIAGUA
	Art Unit	3738
	Examiner Name	Not assigned yet
	Attorney Docket Number	109978.10113

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Receipt date: 05/23/2014

14253656 - GAU: 3738

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	14253656
	Filing Date	2014-04-15
	First Named Inventor	David PANIAGUA
	Art Unit	3738
	Examiner Name	Not assigned yet
	Attorney Docket Number	109978.10113

	28	2011/109433	WO		2011-03-11	Paniagua et al.		☐
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	30	2012/006124	WO		2012-01-12	Fish		☐
	31	2012/040643	WO		2012-03-29	Fish et al.		☐
	32	2012/082952	WO		2012-06-21	Fish et al.		☐

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	1	Affidavit of Dr. Paolo Angelini, M.D., signed August 25, 2009	☐
	2	Affidavit of Dr. Gervasio A. Lamas, M.D., signed September 3, 2009	☐
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Filing Date	2014-04-15
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Examiner Name	Not assigned yet
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	First Named Inventor	David PANIAGUA
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Receipt date: 05/23/2014	Application Number	14253656 14253656 - GAU: 3738
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)	Filing Date	2014-04-15
	First Named Inventor	David PANIAGUA
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	First Named Inventor	David PANIAGUA
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	14253656	
	Filing Date	2014-04-15	
	First Named Inventor	David PANIAGUA	
	Art Unit	3738	
	Examiner Name	Not assigned yet	
	Attorney Docket Number	109978.10113	

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Search Notes	Application/Control No. 14253656	Applicant(s)/Patent Under Reexamination PANIAGUA ET AL.
	Examiner CHERYL MILLER	Art Unit 3738

CPC- SEARCHED

Symbol	Date	Examiner
A61F2/2436	6/29/2014	cm
A61F2002/9534, A61F2/2439, A61F2/2436, A61F2/2433, A61F2/2427	9/28/2014	cm

CPC COMBINATION SETS - SEARCHED

Symbol	Date	Examiner

US CLASSIFICATION SEARCHED

Class	Subclass	Date	Examiner
623	1.24, 1.26, 2-12-2.19, 900	6/29/2014	cm
update		9/21/2014	cm

SEARCH NOTES

Search Notes	Date	Examiner
East text search	6/29/2014	cm
East text search	9/21/2014	cm
East text search	9/28/2014	cm

INTERFERENCE SEARCH

US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
623	2.11-2.19	9/29/2014	cm

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CONFIRMATION NO. 2795

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/253,656	04/15/2014 RULE	623	3738	109978.10113

APPLICANTS
Colibri Heart Valve LLC, Broomfield, CO, Assignee (with 37 CFR 1.172 Interest);

INVENTORS
David PANIAGUA, Houston, TX;
R. David FISH, Houston, TX;

** **CONTINUING DATA** *************************
This application is a CON of 13/675,665 11/13/2012
which is a CON of 10/887,688 07/10/2004 PAT 8308797
which is a CIP of 10/037,266 01/04/2002 ABN

** **FOREIGN APPLICATIONS** *************************

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Foreign Priority claimed ❑ Yes ☑ No 35 USC 119(a-d) conditions met ❑ Yes ☑ No Verified and Acknowledged /CHERYL L MILLER/ Examiner's Signature	❑ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
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UNITED STATES

TITLE

METHOD OF CONTROLLED RELEASE OF A PERCUTANEOUS REPLACEMENT HEART VALVE

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In Re the Application of:	) Group Art Unit: 3738
David PANIAGUA et al.	) Confirmation No. 2795
Application No.: 14/253,656	) Examiner: Cheryl L. MILLER
Filed: April 15, 2014	) AMENDMENT AND RESPONSE
Atty. File No.: 109978.10113	) **Filed Electronically**
Entitled: METHOD OF CONTROLLED RELEASE OF A PERCUTANEOUS REPLACEMENT HEART VALVE	)

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In response to the September 25, 2014 Final Office Action (the "Office Action"), please amend the above-identified application as follows:

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Remarks/Arguments begin on page 5 of this paper.

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Carol Donahue	(Depositor's name)
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14 October 2014	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/253,656	04/15/2014	David PANIAGUA	109978.10113	2795

TITLE OF INVENTION: METHOD OF CONTROLLED RELEASE OF A PERCUTANEOUS REPLACEMENT HEART VALVE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	01/07/2015

EXAMINER	ART UNIT	CLASS-SUBCLASS
MILLER, CHERYL L	3738	623-002110

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
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(B) RESIDENCE: (CITY and STATE OR COUNTRY): Broomfield Colorado

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Authorized Signature / Mark L. Yaskanin / Date 14 October 2014

Typed or printed name Mark L. Yaskanin Registration No. 45 246

Electronic Patent Application Fee Transmittal

Application Number:	14253656
Filing Date:	15-Apr-2014
Title of Invention:	METHOD OF CONTROLLED RELEASE OF A PERCUTANEOUS REPLACEMENT HEART VALVE
First Named Inventor/Applicant Name:	David PANIAGUA
Filer:	Mark Lauren Yaskanin/Carol Donahue
Attorney Docket Number:	109978.10113

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Utility under 35 USC 111(a) Filing Fees

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Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**480**

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EFS ID:	20411714
Application Number:	14253656
International Application Number:	
Confirmation Number:	2795
Title of Invention:	METHOD OF CONTROLLED RELEASE OF A PERCUTANEOUS REPLACEMENT HEART VALVE
First Named Inventor/Applicant Name:	David PANIAGUA
Customer Number:	29880
Filer:	Mark Lauren Yaskanin/Carol Donahue
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Attorney Docket Number:	109978.10113
Receipt Date:	14-OCT-2014
Filing Date:	15-APR-2014
Time Stamp:	16:17:15
Application Type:	Utility under 35 USC 111(a)

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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/253,656	12/02/2014	8900294	109978.10113	2795

29880 7590 11/12/2014
FOX ROTHSCHILD LLP
PRINCETON PIKE CORPORATE CENTER
997 LENOX DRIVE
BLDG. #3
LAWRENCEVILLE, NJ 08648

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

David PANIAGUA, Houston, TX;
Colibri Heart Valve LLC, Broomfield, CO, Assignee (with 37 CFR 1.172 Interest);
R. David FISH, Houston, TX;

AO 120 (Rev. 08/10)

TO: **Mail Stop 8** **Director of the U.S. Patent and Trademark Office** **P.O. Box 1450** **Alexandria, VA 22313-1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Central District of California, Southern Division on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	12/5/2019	Central District of California, Southern Division

PLAINTIFF	DEFENDANT
Colibri Heart Valve LLC	Medtronic CoreValve LLC; and Medtronic plc

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 9,125,739	9/9/2015	Colibri Heart Valve LLC
2 8,900,294	12/2/2014	Colibri Heart Valve LLC
3		
4		
5		

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	**DATE OF PATENT OR TRADEMARK**	**HOLDER OF PATENT OR TRADEMARK**
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

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DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy