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July 9, 2004

VIA EXPRESS MAIL

Commissioner for Patents
P.O. Box 1450
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CONTINUATION-IN-PART UTILITY PATENT APPLICATION TRANSMITTAL

Sir:

Transmitted herewith for filing is the continuation-in-part patent application of:

INVENTORS: Paniagua, et al.

FOR: Percutaneously implantable replacement heart valve device and method of making same.

Enclosed are:

1. 34 pages of specification, claims, abstract.
2. 12 pages of figures.
3. Petition for extension of time under 37 CFR 1.136(a) with respect to application serial no. 10/037,266, (to which the enclosed application is a continuation in part).
4. Postage paid return postcard.

Please charge the filing fee of $545.00 for this application (33 claims, including one excess independent claim), the petition fee of $210.00 for the petition for extension of time with respect to application serial no. 10/037,266 and any other required charges to Deposit Account No. 50-1792. A duplicate of this letter is enclosed for charging purposes.

The enclosed application is a continuation-in-part of U.S. Non-Provisional Patent Application Serial No. 10/037,266 filed on January 4, 2002. A Declaration and Power of Attorney, claim for small entity status and an Information Disclosure Statement were filed in connection with Application Serial No. 10/037,266, and are incorporated into the present application by this reference. The Applicants claim small entity status.

Please direct all communications regarding the foregoing to the undersigned.

Respectfully submitted,

GREENBERG TRAURIG, P.A.

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MRV/kfh

Enclosures

Express Mail Mailing Label No. ER940080602US

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Docket No. 51458.010100

CONTINUATION IN PART

NON-PROVISIONAL PATENT APPLICATION

SPECIFICATION

TO WHOM IT MAY CONCERN:

BE IT KNOWN THAT WE, David Paniagua, Eduardo Induni, Carlos Mejia, Francisco Lopez and R. David Fish, have invented a new and useful percutaneously implantable replacement heart valve device and method of making same, of which the following is the Specification.

CONTINUITY INFORMATION

This Application is a continuation in part of U.S. non-provisional patent application serial number 10/037,266 filed on January 4, 2002. The Applicants hereby claim the benefit under 35 U.S.C. §120 based on said application.

BACKGROUND OF THE INVENTION

[0001] 1. Field of the Invention

The present invention is in the field of heart valve replacement. More specifically, the present invention is directed to a percutaneously implantable replacement heart valve and method of making same.

[0002] 2. Description of Related Art

There have been numerous efforts in the field of heart valve replacement to improve both the durability and effectiveness of replacement heart valves as well as the ease of implantation. A brief description of heart valves and heart function follows to provide relevant background for the present invention.

[0003] There are four valves in the heart that serve to direct the flow of blood through the two sides of the heart in a forward direction. On the left (systemic) side of the heart are: 1) the mitral valve, located between the left atrium and the left ventricle, and 2) the aortic valve, located between the left ventricle and the aorta. These two valves direct oxygenated blood coming from the lungs through the left side of the heart into the aorta for distribution to the body. On the right (pulmonary) side of the heart are: 1) the tricuspid valve, located between the right atrium and the right ventricle, and 2) the pulmonary valve, located between the right ventricle and the pulmonary artery. These two valves direct de-oxygenated blood coming from the body through the right side of the heart into the pulmonary artery for distribution to the lungs, where it again becomes re-oxygenated to begin the circuit anew.

[0004] Heart valves are passive structures that simply open and close in response to differential pressures on either side of the particular valve. They consist of moveable

"leaflets" that are designed simply to open and close in response to differential pressures on either side of the valve's leaflets. The mitral valve has two leaflets and the tricuspid valve has three. The aortic and pulmonary valves are referred to as "semilunar valves" because of the unique appearance of their leaflets, which are more aptly termed "cusps" and are shaped somewhat like a half-moon. The aortic and pulmonary valves each have three cusps.

[0005] In general, the components of heart valves include the valve annulus, which will remain as a roughly circular open ring after the leaflets of a diseased or damaged valve have been removed; leaflets or cusps; papillary muscles which are attached at their bases to the interior surface of the left or right ventricular wall; and multiple chordae tendineae, which couple the valve leaflets or cusps to the papillary muscles. There is no one-to-one chordal connection between the leaflets and the papillary muscles; instead, numerous chordae are present, and chordae from each papillary muscle attach to both of the valve leaflets.

[0006] When the left ventricular wall relaxes so that the ventricular chamber enlarges and draws in blood, the leaflets of the mitral valve separate and the valve opens. Oxygenated blood flows in a downward direction through the valve, to fill the expanding ventricular cavity. Once the left ventricular cavity has filled, the left ventricle contracts, causing a rapid rise in the left ventricular cavitary pressure. This causes the mitral valve to close while the aortic valve opens, allowing the oxygenated blood to be ejected from the left ventricle into the aorta. The chordae tendineae of the mitral valve prevent the mitral leaflets from prolapsing back into the left atrium when the left ventricular chamber contracts.

[0007] The three leaflets, chordae tendineae, and papillary muscles of the tricuspid valve function in a similar manner, in response to the filling of the right ventricle and its subsequent contraction. The cusps of the aortic valve also respond passively to pressure differentials between the left ventricle and the aorta. When the left ventricle contracts, the aortic valve cusps open to allow the flow of oxygenated blood from the left ventricle into the aorta. When the left ventricle relaxes, the aortic valve cusps reapproximate to prevent the blood which has entered the aorta from leaking (regurgitating) back into the left ventricle. The pulmonary valve cusps respond passively in the same manner in response to relaxation and contraction of the right ventricle in moving de-oxygenated blood into the pulmonary artery and thence to the lungs for re-oxygenation. Neither of these semilunar valves has associated chordae tendineae or papillary muscles.

[0008] Problems that can develop with heart valves consist of stenosis, in which a valve does not open properly, and/or insufficiency, also called regurgitation, in which a valve does not close properly. In addition to stenosis and insufficiency of heart valves, heart valves may need to be surgically repaired or replaced due to certain types of bacterial or fungal infections in which the valve may continue to function normally, but nevertheless harbors an overgrowth of bacteria (vegetation) on the leaflets of the valve that may embolize and lodge downstream in a vital artery. If such vegetations are on the valves of the left side (i.e., the systemic circulation side) of the heart, embolization may occur, resulting in sudden loss of the blood supply to the affected body organ and immediate malfunction of that organ. The organ most commonly affected by such embolization is the brain, in which case the patient suffers a stroke. Thus, surgical

replacement of either the mitral or aortic valve (left-sided heart valves) may be necessary for this problem even though neither stenosis nor insufficiency of either valve is present. Likewise, bacterial or fungal vegetations on the tricuspid valve may embolize to the lungs resulting in a lung abscess and therefore, may require replacement of the tricuspid valve even though no tricuspid valve stenosis or insufficiency is present.

[0009] These problems are treated by surgical repair of valves, although often the valves are too diseased to repair and must be replaced. If a heart valve must be replaced, there are currently several options available, and the choice of a particular type of artificial valve depends on factors such as the location of the valve, the age and other specifics of the patient, and the surgeon's experiences and preferences. Currently in the United States over 100,000 defective heart valves are replaced annually, at an approximate cost of $30-50,000 per procedure, and thus it would be desirable if heart valves could be replaced using minimally invasive techniques and without having to repeat the procedure within a matter of years due to the lack of durability of the replacement heart valve. It would be especially advantageous if a defective heart valve could be removed via an endovascular procedure, that is, a procedure where the invasion into the body is through a blood vessel such as the femoral artery. The procedure is then carried out percutaneously and transluminally using the vascular system to convey appropriate devices to the position in the body wherein it is desired to carry out the desired procedure. An example of such a procedure would be angioplasty, wherein a catheter carrying a small balloon at its distal end is manipulated through the body's vessels to a point where there is a blockage in a vessel. The balloon

is expanded to create an opening in the blockage, and then the balloon is deflated and the catheter and balloon are removed from the vessel.

[0010] Endovascular procedures have substantial benefits both from the standpoint of health and safety as well as cost. Such procedures require minimal invasion of the human body, and there is consequently considerable reduction and in some instances even elimination, of the use of a general anesthesia and much shorter hospital stays.

[0011] Replacement heart valves can be categorized as either artificial mechanical valves, transplanted valves and tissue valves. Replacement heart valves are designed to optimize hemodynamic performance, thrombogenicity and durability. Another factor taken into consideration is the relative ease of surgical implantation.

[0012] Mechanical valves are typically constructed from nonbiological materials such as plastics, metals and other artificial materials which, while durable, are expensive and prone to blood clotting which increases the risk of an embolism. Anticoagulants taken to help against blood clotting can further complicate the patient's health due to increased risks for hemorrhages.

[0013] Transplanted valves are natural valves taken from cadavers. These valves are typically removed and frozen in liquid nitrogen, and are stored for later use. They are typically fixed in glutaraldehyde to eliminate antigenicity and are sutured in place, typically with a stent.

[0014] Artificial tissue valves are valves constructed from animal tissue, such as bovine or porcine tissue. Efforts have also been made at using tissue from the patient for which the valve will be constructed.

[0015] Most tissue valves are constructed by sewing the leaflets of pig aortic valves to a stent to hold the leaflets in proper position, or by constructing valve leaflets from the pericardial sac of cows or pigs and sewing them to a stent. The porcine or bovine tissue is chemically treated to alleviate any antigenicity. The pericardium is a membrane that surrounds the heart and isolates it from the rest of the chest wall structures. The pericardium is a thin and very slippery, which makes it difficult for suturing in a millimetricly precise way. The method of making the replacement heart valve of the present invention solves this problem through a process that includes drying and compressing the pericardium using photo-mechanical compression in such a way that makes it possible to handle and fold the material more easily.

[0016] For example, one prior replacement heart valve requires each sculpted leaflet to be trimmed in a way that forms an extended flap, which becomes a relatively narrow strand of tissue near its tip. The tip of each pericardial tissue strand is sutured directly to a papillary muscle, causing the strand to mimic a chordae tendineae. Each strand extends from the center of a leaflet in the valve, and each strand is sutured directly to either an anterior and posterior papillary muscle. This requires each leaflet to be positioned directly over a papillary muscle. This effectively rotates the leaflets of the valve about 90 degrees as compared to the leaflets of a native valve. The line of commissure between the leaflets, when they are pressed together during systole, will bisect (at a perpendicular angle) an imaginary line that crosses the peaks of the two papillary muscles, instead of lying roughly along that line as occurs in a native valve.

[0017] A different approach to creating artificial tissue valves is described in U.S. Patent Nos. 5,163,955 to Calvin, et al. and 5,571,174 and 5,653,749 to Love. Using a cutting

die, the pericardial tissue is cut into a carefully defined geometric shape, treated with glutaraldehyde, then clamped in a sandwich-fashion between two stent components. This creates a tri-leaflet valve that resembles an aortic or pulmonary valve, having semilunar-type cusps rather than atrioventricular-type leaflets.

[0018] U.S. Patent No. 3,671,979 to Moulopoulos describes an endovascularly inserted conical shaped umbrella-like valve positioned and held in place by an elongated mounting catheter at a supra-annular site to the aortic valve in a nearby arterial vessel. The conical end points toward the malfunctioning aortic valve and the umbrella's distal ends open up against the aorta wall with reverse blood flow, thereby preventing regurgitation.

[0019] U.S. Patent No. 4,056,854 to Boretos describes an endovascularly inserted, catheter mounted, supra-annular valve in which the circular frame abuts the wall of the artery and attached flaps of flexible membrane extend distally in the vasculature. The flaps lie against the artery wall during forward flow, and close inward towards the central catheter to prevent regurgitation during reverse blood flow. The Boretos valve was designed to be positioned against the artery wall during forward flow, as compared to the mid-center position of the Moulopoulos valve, to reduce the stagnation of blood flow and consequent thrombus and embolic formation expected from a valve at mid-center position.

[0020] The main advantage of tissue valves is that they do not cause blood clots to form as readily as do the mechanical valves, and therefore, they do not absolutely require systemic anticoagulation. The major disadvantage of tissue valves is that they lack the long-term durability of mechanical valves. Tissue valves have a significant failure rate,

usually within ten years following implantation. One cause of these failures is believed to be the chemical treatment of the animal tissue that prevents it from being antigenic to the patient. In addition, the presence of extensive suturing prevents the artificial tissue valve from being anatomically accurate in comparison to a normal heart valve, even in the aortic valve position.

[0021] A shortcoming of prior artificial tissue valves has been the inability to effectively simulate the exact anatomy of a native heart valve. Although transplanted human or porcine aortic valves have the gross appearance of native aortic valves, the fixation process (freezing with liquid nitrogen, and chemical treatment, respectively) alters the histologic characteristics of the valve tissue. Porcine and bovine pericardial valves not only require chemical preparation (usually involving fixation with glutaraldehyde), but the leaflets must be sutured to cloth-covered stents in order to hold the leaflets in position for proper opening and closing of the valve. Additionally, the leaflets of most such tissue valves are constructed by cutting or suturing the tissue material, resulting in leaflets that do not duplicate the form and function of a real valve and are more susceptible to failure.

SUMMARY OF THE INVENTION

[0022] The present invention is a replacement heart valve device and method of making same. The replacement heart valve device, in a preferred embodiment, comprises a stent made of stainless steel or self-expanding nitinol and a completely newly designed artificial biological tissue valve disposed within the inner space of the stent. The cusp or leaflet portion of the valve means is formed by folding of the pericardium material preferably used to create the valve without cutting of slits to form leaflets or suturing or

otherwise affixing of separate leaflet portions. Other forms of tissue and suitable synthetic materials can also be used for the valve, formed in a sheet of starting material. The folded design provides a number of advantages over prior designs, including improved resistance to tearing at suture lines. The cusps/leaflets open in response to blood flow in one direction and close in response to blood flow in the opposite direction. Preferably the tubular portion of the valve means contains the same number of cusps as the native valve being replaced, in substantially the same size and configuration. The outer surface of the valve means is attached to the stent member.

[0023] The replacement heart valve device is preferably implanted using a delivery system having a central part which consists of a flexible hollow tube catheter that allows a metallic guide wire to be advanced inside it. The stented valve is collapsed over the central tube and it is covered by a movable sheath. The sheath keeps the stented valve in the collapsed position. Once the cover sheath is moved backwards, the stented valve can be deployed. The endovascular stented-valve, in a preferred embodiment, is a glutaraldehyde fixed mammal pericardium or synthetic biocompatible material which has two or three cusps that open distally to permit unidirectional blood flow. The stent can either be self-expanding or the stent can be expandable through use of a balloon catheter.

[0024] The present invention also comprises a method of making a replacement heart valve device. In order to make the valve, the pericardium starting material is isolated and all the fat tissue and extra fibers are removed. The biological membrane material is cleaned by mechanical separation of unwanted layers using hydromechanical force means. Once the pericardium is completely clean, the material is dried in order to make

it easier to handle and fold. Preferably, this drying is done by exposing the biocompatible membrane material to photo-mechanical compression to remove all lipids from the pericardium or other biocompatible membrane material and to cause protein denaturalization, transforming the material into a stronger and more homogeneous surface. The valve is formed by taking a flat sheet of the material and folding in such a way that forms a three-leaflet or other number of leaflet valve. Then it is placed in a sequence of solutions, one of isopropyl alcohol of about 70-100%, one of ethanol of about 70-100%, one of glycerol and one of gluteraldehyde, preferably at a concentration of about 0.07-25% for approximately 36 hours. The material is dried in order to make it easier to handle and fold. Preferably this drying is done by exposing the biocompatible membrane material to light and then mechanically compressing the material to cause protein denaturation. This results in material that is stronger and more homogeneous. The valve is formed by taking a flat sheet of bovine pericardium and folding it in such a way that forms a three-leaflet valve. The valve can also be made in the same manner from fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts or synthetic non-biological, non-thrombogenic material. The folding of the pericardium material to create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of the valve leaflets. The cleaning, pressing and drying technique used to create the valve material makes the folding more practicable. The valve is rehydrated after being formed. The method of the present invention also greatly reduces the risk of tearing of the cusps or leaflets, since they are formed by folding a single uncut portion of material forming the valve rather than being attached by suturing.

[0025] Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The replacement heart valve device of the present invention can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation medication and treatment. The present invention can be practiced in applications with respect to each of the heart's valves.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] Fig. 1 depicts a side perspective view of the replacement heart valve device of the present invention in one embodiment with the valve in the closed position.

[0027] Fig. 2 depicts the folds which form the leaflets or cusps of the replacement heart valve of the present invention in one embodiment.

[0028] Figs. 3A and 3B depict a preferred procedure for folding the pericardium tissue starting material to create the replacement heart valve of the present invention.

[0029] Fig. 4 depicts a side perspective view of the replacement heart valve device of the present invention in one embodiment represented as if implanted within an artery.

[0030] Fig. 5 depicts a side view of one embodiment of the replacement heart valve device of the present invention mounted within a self-expanding stent, with the stent in the expanded position.

[0031] Fig. 6 depicts a side perspective view of one embodiment of the replacement heart valve device of the present invention mounted within a self-expanding stent in the collapsed position.

[0032] Fig. 7 depicts the suture points of one embodiment of the replacement heart valve device of the present invention.

[0033] Fig. 8 depicts the implantation/delivery system used with the present invention in a preferred embodiment.

[0034] Figs. 9A, 9B and 9C depicts a representation of a sheet of biocompatible valve material showing preferred folds.

DESCRIPTION OF A PREFERRED EMBODIMENT

[0034] The present invention comprises a percutaneously implantable replacement heart valve and a method for making same. The artificial heart valve device of the present invention is capable of exhibiting a variable diameter between a compressed or collapsed position and an expanded position. A preferred embodiment of the replacement heart valve device according to the present invention is set forth in FIG. 5. The replacement heart valve device comprises a stent member 100 and a flexible valve means 200. The stent member 100 is preferably self-expanding, although balloon-expandable stents can be used as well, and has a first polygonal shape in its compressed or collapsed configuration and a second, larger polygonal shape in its expanded configuration. Referring to FIG. 1, the valve means 200 comprises a generally tubular portion 210 and, preferably, a peripheral upstanding cusp or leaflet portion 220. The valve means 200 is disposed within the cylindrical stent member 100 with the tubular portion 210 transverse of and at some acute angle relative to the stent

walls. The diameter of the tubular portion 210 is substantially the same as the inside diameter of the stent member in its initial expanded configuration. The peripheral upstanding cusp or leaflet portion 220 is disposed on valve means 200 substantially parallel to the walls of the stent member similar to a cuff on a shirt. The cusp or leaflet portion 220 of the valve means 200 is generally tubular in shape and comprises three leaflets 221, 222 and 223 as shown, although it is understood that there could be from two to four leaflets. The tubular portion of the valve means 200 is attached to the stent member 100 by a plurality of sutures 300, as depicted in FIG. 7.

[0035] The leaflet portion 220 of the valve means 200 extends across or transverse of the cylindrical stent 100. The leaflets 221, 222 and 223 are the actual valve and allow for one-way flow of blood. The leaflet portion 220 as connected to the rest of the valve resembles the cuff of a shirt. FIG. 9 depicts the folds preferred for valve cusp and leaflet formation involving three leaflets. The configuration of the stent member 100 and the flexible, resilient material of construction allows the valve to collapse into a relatively small cylinder as seen in FIG. 6. The replacement heart valve will not stay in its collapsed configuration without being restrained. Once the restraint is removed, the self-expanding stent member 100 will cause the artificial heart valve to take its expanded configuration, as seen in FIG. 5.

Stent Member

[0036] The stent member 100 preferably comprises a self-expanding nickel-titanium alloy stent, also called "nitinol," in a sine wave-like configuration as shown in FIG. 5. An enlarged view of a preferred embodiment of the stent member for use in the replacement heart valve of the invention is depicted in FIG. 5. The stent member 100

includes a length of wire 110 formed in a closed zigzag configuration. The wire can be a single piece, stamped or extruded, or it could be formed by welding the free ends together. The straight sections of the stent member 100 are joined by bends. The stent is readily compressible to a small cylindrical shape as depicted in FIGS. 6 and 8, and resiliently self-expandable to the shape shown in FIG. 5.

[0037] The stent member 100 of the artificial heart valve device of the present invention may be made from various metal alloys, titanium, titanium alloy, nitinol, stainless steel, or other resilient, flexible non-toxic, non-thrombogenic, physiologically acceptable and biocompatible materials. The configuration may be the zigzag configuration shown or a sine wave configuration, mesh configuration or a similar configuration which will allow the stent to be readily collapsible and self-expandable. When a zigzag or sine wave configured stent member is used, the diameter of the wire from which the stent is made is preferably from about 0.010 to 0.035 inches and still, preferably from about 0.012 to 0.025 inches. The diameter of the stent member will be from about 1.5 to 3.5 cm, preferably from about 1.75 to 3.00 cm, and the length of the stent member will be from about 1.0 to 10 cm, preferably from about 1.1 to 5 cm.

[0038] The stent used in a preferred embodiment of the present invention is fabricated from a "shaped memory" alloy, nitinol, which is composed of nickel and titanium. Nitinol wire is first fashioned into the desired shape for the device and then the device is heat annealed. A meshwork of nitinol wire of approximately 0.008 inch gauge is formed into a tubular structure with a minimum central diameter of 20 min to make the stent. Away from its central portion, the tubular structure flares markedly at both ends in a trumpet-like configuration. The maximum diameter of the flared ends of the stent is

approximately 50 mm. The purpose of the stent is to maintain a semi-rigid patent channel through the diseased cardiac valve following its implantation.

[0039] When the components of the replacement heart valve device are exposed to cold temperatures, they become very flexible and supple, allowing them to be compressed down and pass easily through the delivery sheath. A cold temperature is maintained within the sheath during delivery to the deployment site by constantly infusing the sheath with an iced saline solution. Once the valve components are exposed to body temperature at the end of the sheath, they instantaneously reassume their predetermined shapes, thus allowing them to function as designed.

[0040] Preferably the stent member 100 carries a plurality of barbs extending outwardly from the outside surface of the stent member for fixing the heart valve device in a desired position. More preferably the barbs are disposed in two spaced-apart, circular configurations with the barbs in one circle extending in an upstream direction and the barbs in the other circle extending in a downstream direction. It is especially preferable that the barbs on the inflow side of the valve point in the direction of flow and the barbs on the outflow side point in the direction opposite to flow. It is preferred that the stent be formed of titanium alloy wire or other flexible, relatively rigid, physiologically acceptable material arranged in a closed zigzag configuration so that the stent member will readily collapse and expand as pressure is applied and released, respectively.

Valve Means

[0041] The valve means 200 is flexible, compressible, host-compatible, and non-thrombogenic. The valve means 200 can be made from various materials, for example, fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts. Synthetic

biocompatible materials such as polytetrafluoroethylene, polyester, polyurethane, nitinol or other alloy/metal foil sheet material and the like may be used. The preferred material for the valve means 200 is mammal pericardium tissue, particularly juvenile-age animal pericardium tissue. The valve means 200 is disposed within the cylindrical stent member 100 with the tubular portion 210 transverse of and at some acute angle relative to the stent walls. The diameter of the tubular portion 210 is substantially the same as the inside diameter of the stent member 100 in its initial expanded configuration. The peripheral upstanding cusp or leaflet portion 220 is disposed substantially parallel to the walls of the stent member 100 similar to a cuff on a shirt.

[0042] The cusp or leaflet portion 220 of the valve means 200 is formed by folding of the pericardium material used to create the valve. FIGS. 3A and 3B depict the way the sheet of heart valve starting material is folded. The starting material is preferably a flat dry sheet, which can be rectangular or other shaped. The cusps/leaflets 221, 222 and 223 open in response to blood flow in one direction and close in response to blood flow in the opposite direction. Preferably the cusp or leaflet portion 220 of the valve means 200 contains the same number of cusps as the native valve being replaced, in substantially the same size and configuration. FIGS. 9A-9C depict a preferred configuration for folds to create the leaflets/cusps. The leaflet forming portion is a single, continuous, uncut layer affixed to the interior of the cuff layer to form the leaflets/cusps, unlike prior efforts that have involved suturing of three separate leaflet/cusp portions onto the main valve body portion. The leaflets are formed from the free edge of the material after forming the cuff portion. Referring now to FIGS. 9-A, 9B, and 9C, with flat sheet on a table, a person facing the sheet would create a cuff at the

upper border of sheet by folding the horizontal top edge away/downwardly (fold no.1). The leaflet portion is formed by folding the sheet's lower half towards the folder/upwardly, as shown in FIG. 9A (fold no. 2). The sheet, now with the upper cuff and bottom inward fold, is folded inwardly at two preferably equidistant vertical points as shown in FIG. 9B to create the leaflet/cusp portion (folds nos. 3 and 4). The leaflets/cusps are formed by folding fold nos. 6, 7 and 8 after the two opposite vertical edges of sheet are joined to create a cylindrical valve shape, depicted in FIGS. 1 and 3B. The inner leaflet layer is preferably attached to the outer cuff layer by curved or straight continuous suturing. Although a preferred embodiment of the invention comprises a single piece of valve material folded to create the valve body and a leaflet-forming portion that has no cuts or sutures, the inventors have discovered that as long as the leaflet portion of the valve itself is formed from a single piece of biocompatible valve material, the other portions of the valve can be formed by suturing of one or more separate pieces of material without losing the novel and improved qualities of the present invention. This allows for the valve to be made even stronger, more durable and easier to make. This alternate embodiment comprises a leaflet forming layer made of a single piece of valve material attached to a separate piece forming the valve body having a folded cuff portion. The single piece leaflet forming layer is preferably cylindrical in shape and can be formed with or without folding. In this embodiment the single piece leaflet layer can itself be attached to the stent with or without a cylindrical cuff portion. Attachment is preferably by suturing, particularly continuous single or double sutures.

Method of Making Replacement Heart Valve Device

[0043] The present invention also comprises a method of making a replacement heart valve device. In order to make the valve, the biocompatible tissue material is isolated and all the fat tissue and extra fibers are removed. Cleaning is preferably accomplished by using a hydromechanical force-based cleaning device to separate tissue layers and hydration with distilled water to remove unwanted layers. Once the pericardium is completely clean, it is subjected to photo-mechanical compression, then the valve is formed and placed in sequential solutions of isopropyl alcohol of about 70-100%, ethanol of about 70-100% glycerol and gluteraldehyde preferably at a concentration of about 0.07-25% for about 36 hours, respectively. The material is preferably photomechanically compressed to remove lipids and produce protein coagulation to make the surface smoother and more compact and biocompatible, decreasing the molecular distance of collagen fibers. The exposure to light and mechanical compression cause protein denaturation making the material stronger and more homogeneous and biocompatible. Gas sterilization can also be used to sterilize the tissue membrane material. The valve is formed by taking a flat sheet of the material and folding it in such a way that forms a three-leaflet or desired number of leaflet valve as shown in FIGS. 3A and 3B and/or FIGS. 9A, 9B and 9C. The folding of the pericardium material to create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of the valve leaflets. It also greatly reduces the risk of tearing of the cusps or leaflets, since they are integral to the valve rather than being attached by suturing.

[0044] In a preferred embodiment, the single continuous piece of membrane is folded inward to form an inner leaflet layer within the outer cuff. The single leaflet layer is then

attached to the cuff layer to form valve cusps in one of three preferred ways: (i) by curved or straight continuous single or double sutures that affix and form the bases or recesses of the valve cusps; (ii) by lengthwise suture lines attaching the leaflet layer to the cuff layer with the bases or recesses of the valve cusps being thus formed of the folded edge of the membrane; (iii) by further folding of the membrane into lengthwise pleats secured by lengthwise suture attaching the leaflet layer to the cuff layer with the bases or recesses of the valve cusps being thus formed of the folded edge of the membrane, done for the purpose of giving greater strength and durability to the attachment points of the leaflet layer.

[0045] In order to make the pericardium material less slippery and easier to fold, the pericardium is dried, preferably with artificial light using a multi-watt lamp with the pericardium or other biocompatible membrane material placed in a flat aluminum surface to dry it homogeneously. A photomechanical drying machine can also be used. The final result is a homogeneous tissue that looks like plastic paper and makes it easy to manipulate to fold and suture the valve. Once the valve is formed, it is re-hydrated by placing it in a solution of water and 70% alcohol. In approximately 3 days the valve is fully rehydrated. The suturing of membrane layers to form the valve is done with single, double, or more continuous suture material. This form of suturing has great advantages for durability and avoidance of damage to the membrane and can be performed by sewing machines. The attachment points of the leaflet layer to the cuff layer may be reinforced by folding an additional layer of membrane over the attachment point before suturing, this layer being formed of a projected tab of the continuous piece of leaflet membrane. The free edge of the leaflet layer may be straight or curved, and this free

edge forming the free edges of the individual leaflets may be contoured in parabolic or curved shape.

Attachment of the Valve Means to the Stent Member

[0046] The valve means 200 is then attached to the inner channel of the stent member 100 by suturing the outer surface of the valve means' pericardium material to the stent member. FIG. 7 depicts preferred suture points of one embodiment of the present invention: 3-point fixation or 6-point fixation at each border of the stent. Other fixation schemes can be utilized, such as, by way of non-limiting example, fixation on both borders 18 points at each end following a single plane and 36 fixation points following to adjacent vertical planes. The use of only one plane of fixation points helps prevent systolic collapse of the proximal edge of the valve means. A fold on the border of the pericardium material prevents tearing. The attachment position of the valve is preferably closer to the proximal and wider part of the stent.

[0047] The sequence of steps can vary. The pericardium material can be fixed in glutaraldehyde before attachment to the stent or the valve can be formed and then fixed with gluteraldehyde after mounting it in the stent. One observation noted is that the material becomes whiter and apparently increases its elasticity. 1mm vascular clips keep the cusps coapted while fixing them in gluteraldehyde. The use of metallic clips to keep both cusps adjacent to each other after 24 hours of fixation in gluteraldehyde helps to educate the material and make the primary position of the valve cusps adjacent to each other. After the clips are removed, there are no lesions to the valve.

[0048] Different suture materials can be used, including, in a preferred embodiment, Prolene 1-0 to 8-0 and Mersilene 1-0 to 8-0 which is a braided suture.

Implantation of Replacement Heart Valve Device

[0049] The replacement heart valve device of the present invention is preferably used in surgical procedures involving the percutaneous and transluminal removal of the diseased or defective heart valve and the percutaneous and transluminal implantation of the new heart valve described above. The defective heart valve is removed by a suitable modality, such as, for example, laser, ultrasound, mechanical, or other suitable forms of delivery of energy, or phacoemulsion, including, but not limited to, laser lithotripsy, mechanical lithotripsy, electrohydraulic lithotripsy, and laser or mechanical ablation. To remove the native heart valve that is being replaced, a guidewire is inserted percutaneously and transluminally using standard vascular or angiography techniques. The distal end of the guidewire is manipulated to extend through and across the defective heart valve. Then a catheter is advanced distally through the femoral artery to a point proximal to the defective heart valve, between the origin of the coronary artery and the origin of the right subclavian artery. The position of the distal end of catheter can be monitored by observation of radiopaque markers. Collector member is preferably inflated and occludes the aorta at a point between the origin of the coronary artery and the right subclavian artery. Next, a balloon and cutting tool are advanced through the catheter so that the cutting tool and uninflated balloon are distal to the defective heart valve. Optionally an additional step, such as balloon dilatation or atherectomy, may be required to provide a passageway through the heart valve. A catheter is also placed into the coronary sinus via a transjugular puncture. This catheter is used for infusion of blood or cardioplegia solution during the portion of the procedure when the aorta is occluded. The absence of valves in the cardiac venous system allows retrograde flow so that there will be an effluence of fluid from the coronary arteries. This

flow of fluid is desired to prevent embolization of material into the coronary arteries during the procedure. Once the cutting tool is in place, the balloon is inflated and flexible shaft is rotated. Once the cutting tool has reached the appropriate rotation speed, the cutting tool is pulled proximally to remove the defective heart valve. The balloon and the cutting tool are spaced apart so that the inflated balloon will be stopped by the perimeter, unremoved portion of the defective heart valve, which will signal the physician that the valve has been removed, as well as protect the heart and aorta from damage from the valve removal device. Once it is determined that the defective heart valve has been removed, the cutting tool is slowed or stopped altogether and the balloon is deflated. The cutting tool and the deflated balloon are pulled proximally through catheter. Then, a catheter containing an artificial heart valve is inserted and the artificial heart valve is placed as described above.

[0050] The delivery and implantation system of the replacement artificial heart valve of the present invention percutaneously and transluminally includes a flexible catheter 400 which may be inserted into a vessel of the patient and moved within that vessel as depicted in FIG. 8. The distal end 410 of the catheter 400, which is hollow and carries the replacement heart valve device of the present invention in its collapsed configuration, is guided to a site where it is desired to implant the replacement heart valve. The catheter has a pusher member 420 disposed within the catheter lumen 430 and extending from the proximal end 440 of the catheter to the hollow section at the distal end 410 of the catheter. Once the distal end 410 of the catheter is positioned as desired, the pusher mechanism 420 is activated and the distal portion of the replacement heart valve device is pushed out of the catheter and the stent member 100

partially expands. In this position the stent member 100 is restrained so that it doesn't pop out and is held for controlled release, with the potential that the replacement heart valve device can be recovered if there is a problem with the positioning. The catheter 400 is then retracted slightly and the replacement heart valve device is completely pushed out of the catheter 400 and released from the catheter to allow the stent member 100 to fully expand. If the stent member 100 preferably includes two circles of barbs on its outer surface as previously described, the first push and retraction will set one circle of barbs in adjacent tissue and the second push and release of the replacement heart valve device will set the other circle of barbs in adjacent tissue and securely fix the replacement heart valve device in place when the device is released from the catheter.

[0051] Alternatively, or in combination with the above, the replacement heart valve device could be positioned over a metallic guidewire that is advanced through the catheter. The replacement heart valve device of the present invention is preferably implanted percutaneously through an aortic passageway to, or near to, the location from which the natural heart valve has been removed. Referring to FIG. 8, the implantation system comprises a flexible hollow tube catheter 410 with a metallic guide wire 450 disposed within it. The stented valve device is collapsed over the tube and is covered by a moveable sheath 460. The moveable sheath 460 maintains the stented valve device in the collapsed position. The implantation method comprises the following steps: inserting the replacement heart valve device in the lumen of a central blood vessel via entry through the brachial or femoral artery using a needle or exposing the artery surgically; placing a guide wire 450 through the entry vessel and advancing it to

the desired position; advancing dilators over the wire to increase the lumen of the entry site, thereby preparing the artery to receive the heart-valve; and advancing the heart-valve device to the desired place. The stented-valve device is released by pulling the cover sheath 460 of the delivery system allowing the self-expanding stent to achieve its full expansion. A baloon expandable stent can alternately be used to deliver the valve to its desired position. At this point, a pigtail catheter is advanced over the wire and an aortogram is performed to assess the competency of the valve.

[0052] Before creation of the valve means and implantation, the patient is studied to determine the architecture of the patient's heart. Useful techniques include fluoroscopy, transesophageal echocardiography, MRI, and angiography. The results of this study will enable the physician to determine the appropriate size for the replacement heart valve.

[0053] In one procedure for implantation of the replacement heart valve device of the present invention, the femoral artery of the patient is canulated using a Cook needle and a standard J wire is advanced into the artery either percutaneously or after surgical exposure of the artery. An 8 F introducer is advanced into the femoral artery over the wire. The J wire is then withdrawn and anticoagulation is started using heparin 60 U/Kg intravenously. Once vascular access is obtained an aortogram is performed for anatomical evaluation. A special wire (Lunderquist or Amplatz superstiff) is advanced into the aortic arch and dilators progressively larger are advanced over the wire, starting with 12 F all the way to 18 F. After this the valve introducer device containing the prosthetic valve device is then inserted and used to transport the replacement valve over a guidewire to the desired position. The stented-valve is released by pulling the cover sheath of the delivery system allowing the self-expanding stent to achieve its full

expansion. At this point, a pigtail catheter is advanced over the wire and repeat aortogram is performed to assess the competency of the valve.

[0054] When the device is used to treat severe leakage of the aortic valve, the native valve is left in place and the prosthetic stented valve is deployed below the subclavian artery. When the device is used to treat aortic stenosis, first the stenotic valve needs to be opened using either aortic valvuloplasty or cutting and if this procedure induces aortic insufficiency the stented valve is placed to prevent the regurgitation.

[0055] Intravascular ultrasound or an angioscope passed intravascularly via either the venous system through the intra-atrial septum across the mitral valve and into the left ventricle or retrograde via the femoral artery would provide the added benefit of allowing constant high definition imaging of the entire procedure and high flow irrigation.

[0056] Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The prosthetic valve device can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation. In addition, with the development of longer-life, flexible, non-thrombogenic synthetic valve alternatives to bioprosthesis, the prosthetic valve device will be indicated in all patients where the relative advantages of the life-span, the non-thrombogenic quality, and the ease of insertion of prosthetic valve

devices outweigh the disadvantages of mechanical valves. Anticoagulation may be beneficial in certain clinical situations for either short or long term use.

[0057] This method of percutaneous endovascular heart-valve replacement, in contrast to open heart surgical procedures, requires only local anesthesia, partial or no cardiac bypass, one to two days hospitalization, and should result in a reduced mortality rate as compared to open heart procedures.

[0058] While the present invention has been shown and described herein in what is considered to be a preferred embodiment thereof, illustrating the results and advantages over the prior art obtained through the present invention, the invention is not limited to the specific embodiments described above. Thus, the forms of the invention shown and described herein are to be taken as illustrative and other embodiments may be selected without departing from the spirit and scope of the present invention.

CLAIMS

Having thus described the invention, what is claimed is:

1. A percutaneously implantable replacement heart valve device comprising an expandable stent member and a flexible, compressible artificial valve made of biocompatible tissue material and disposed within the inner cavity of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve having cusps or leaflets formed by folding of a sheet of said biocompatible tissue material without affixing of separate cusps or leaflets or cutting slits into said material to form said cusps or leaflets.

2. The percutaneously implantable replacement heart valve device of claim 1, wherein said expandable stent member is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium and stainless steel.

3. The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible tissue material of said artificial valve comprises mammal pericardium tissue.

4. The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible tissue material of said artificial valve comprises porcine pericardium tissue.

5. The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible tissue material of said artificial valve is obtained from a juvenile animal pericardium.

6. The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible tissue material of said artificial valve comprises

autologous tissue obtained from the patient into whom said replacement heart valve device will be implanted.

7. The percutaneously implantable heart valve device of claim 1, wherein said biocompatible tissue material of said artificial valve comprises a synthetic biocompatible material.

8. The percutaneously implantable heart valve device of claim 7, wherein said synthetic biocompatible material is selected from the group consisting of polytetrafluoroethylene, polyester, metal, metal alloy including combinations thereof.

9. The percutaneously implantable heart valve device of claim 1, wherein said stent member is self-expanding when implanted.

10. The percutaneously implantable heart valve device of claim 1, wherein said stent member is balloon catheter expandable when implanted.

11. A method of making a percutaneously implantable replacement heart valve device comprising the following steps:

obtaining a sheet of biocompatible tissue material;

drying said biocompatible tissue material;

folding said dried biocompatible tissue material to create inner cusps or leaflets and an outer tubular cuff structure without affixing of separate cusps or leaflets or cutting slits into said material to form said cusps or leaflets;

affixing said folded biocompatible tissue material at one or more points on its outer surface to the inner cavity of a stent; and

soaking said biocompatible tissue material in one or more alcohol solutions and a solution of gluteraldehyde.

12. The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said soaking step comprises soaking said biocompatible tissue material in a solution of isopropyl alcohol, a solution of ethanol, a solution of glycerol and a solution of gluteraldehyde.

13. The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material comprises bovine pericardium tissue.

14. The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material comprises porcine pericardium tissue.

15. The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material is obtained from a juvenile animal pericardium.

16. The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material comprises autologous tissue obtained from the patient into whom said replacement heart valve device will be implanted.

17. The percutaneously implantable heart valve device of claim 11, wherein said biocompatible tissue material of said artificial valve comprises a synthetic biocompatible material.

18. The percutaneously implantable heart valve device of claim 17, wherein said synthetic biocompatible material is selected from the group consisting of polytetrafluoroethylene, polyester, metal, metal alloy including combinations thereof.

19. The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said stent is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium and stainless steel.

20. The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said stent is self-expanding when implanted.

21. The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said stent is balloon catheter expandable when implanted.

22. The method of making a percutaneously implantable replacement heart valve device of claim 11, further comprising the step of cleaning said biocompatible tissue material using hydromechanical force means.

23. The method of making a percutaneously implantable replacement heart valve of claim 11, further comprising the step of compressing said biocompatible tissue material.

24. The method of making a percutaneously implantable replacement heart valve of claim 11, further comprising the step of gas sterilization of said biocompatible tissue material.

25. The method of making a percutaneously implantable replacement heart valve of claim 11, wherein said drying step comprises photomechanical compression of said biocompatible tissue material.

26. The method of making a percutaneously implantable replacement heart valve of claim 11, wherein said folding step comprises folding of a first piece of said biocompatible tissue material to create an outer tubular cuff structure, folding of a

second separate piece of biocompatible tissue material to create inner cusps or leaflets without affixing of separate cusps or cutting slits into said second separate piece of biocompatible tissue material, and afixing said second separate piece to said first piece.

27. A percutaneously implantable replacement heart valve device comprising an expandable stent member and a flexible, compressible artificial valve made of biocompatible tissue material and disposed within the inner cavity of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising a leaflet or cusp portion formed by folding of a first sheet portion of said biocompatible tissue material without affixing of separate cusps or leaflets or cutting slits into said sheet to form said cusps or leaflets, and an outer tubular cuff structure formed by folding a second sheet portion of biocompatible tissue material, said first and second sheet portions being affixed together.

28. The device of claim 27, wherein said first sheet portion and said second sheet portions are affixed together by suturing.

29. The device of claim 28, wherein said suturing is in the form of double continuous sutures.

30. A percutaneously implantable replacement heart valve device comprising an outer cylindrical cuff portion and an inner uncut/unslit leaflet layer attached within said outer cuff portion.

31. The device of claim 30, wherein said leaflet layer is attached within said outer cuff portion by suturing.

32. The device of claim 31, wherein said suturing is in the form of double continuous sutures.

33. A percutaneously implantable replacement heart valve device comprising an expandable stent member and a flexible, compressible artificial valve made of biocompatible tissue material and disposed within the inner cavity of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising a leaflet or cusp portion formed by folding of a first sheet portion of said biocompatible tissue material without affixing of separate cusps or leaflets or cutting slits into said sheet to form said cusps or leaflets.

ABSTRACT

The present invention comprises a percutaneously implantable replacement heart valve device and a method of making same. The replacement heart valve device comprises a stent member made of stainless steel or self-expanding nitinol, a biological tissue artificial valve means disposed within the inner space of the stent member. An implantation and delivery system having a central part which consists of a flexible hollow tube catheter that allows a metallic wire guide to be advanced inside it. The endovascular stented-valve is created from a glutaraldehyde fixed biocompatible tissue material which has two or three cusps that open distally to permit unidirectional blood flow. The present invention also comprises a novel method of making a replacement heart valve by taking a fragment of biocompatible tissue material and treating, drying, folding and rehydrating it in such a way that forms a two- or three-leaflet/cusp valve with the leaflets/cusps formed by folding, thereby eliminating the extent of suturing required, providing improved durability and function.

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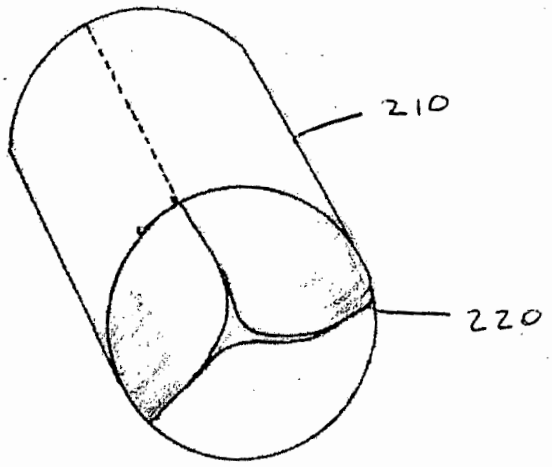


Fig. 1

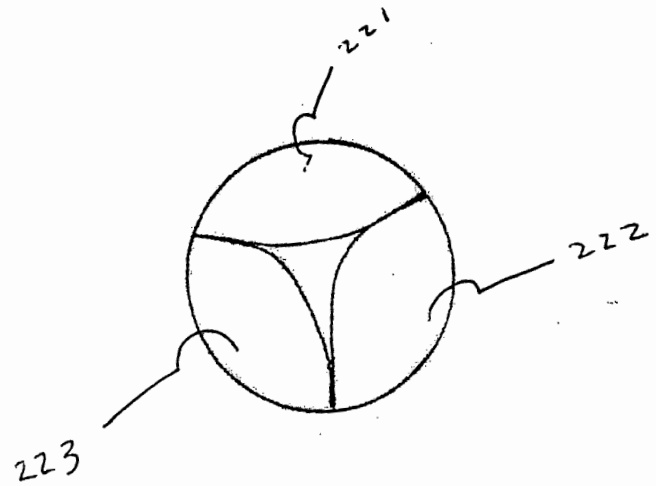


Fig. 2

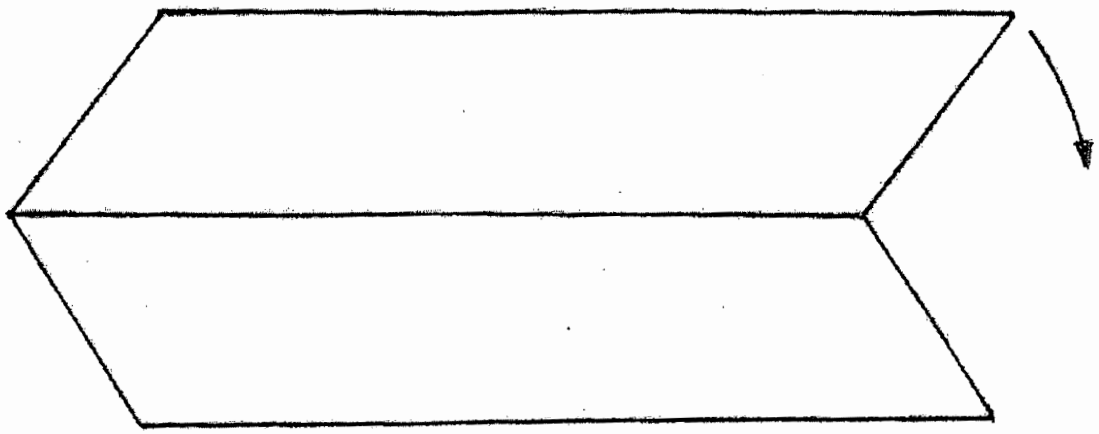


Fig. 3A

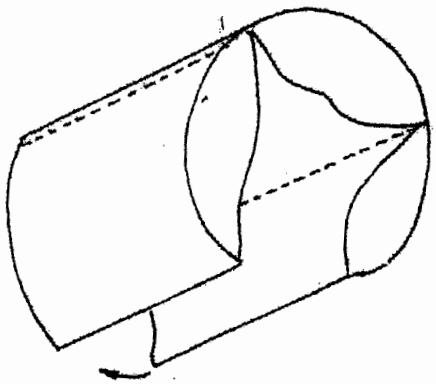


Fig. 3B

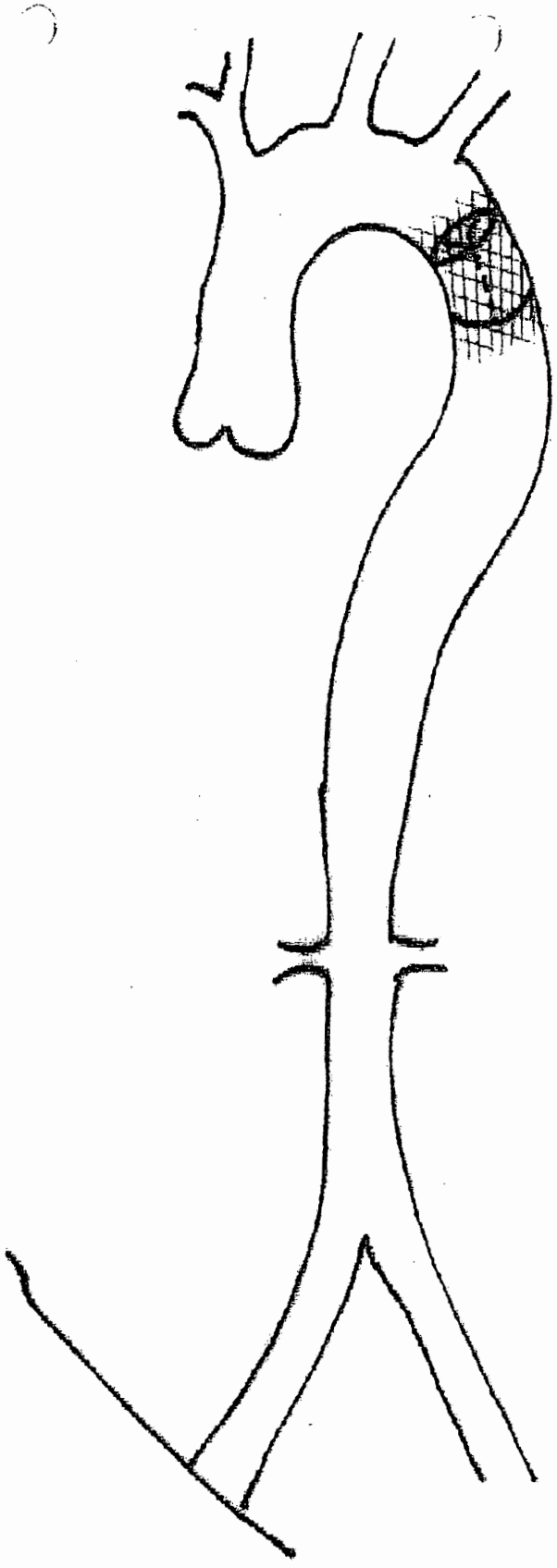


Fig. 4

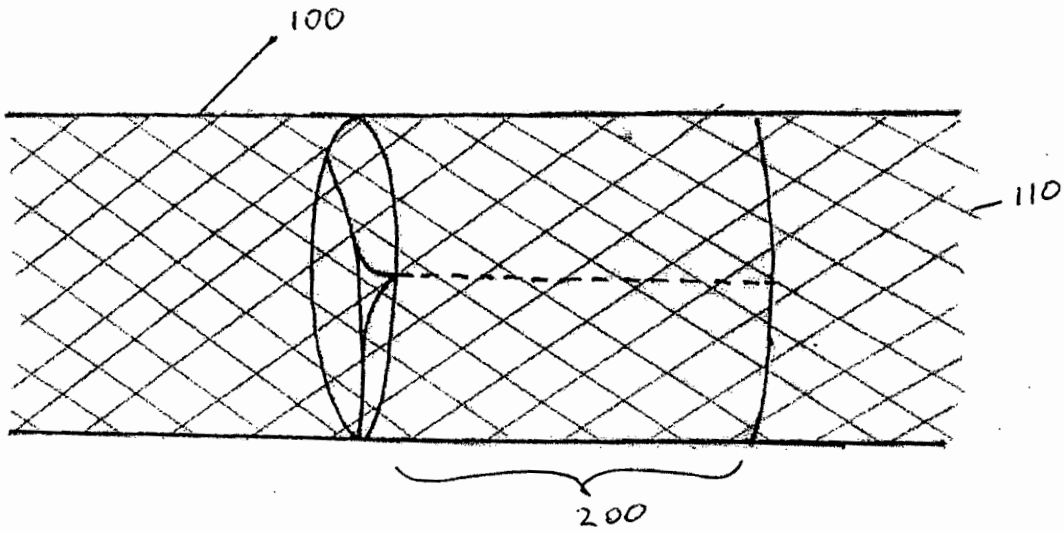


Fig. 5

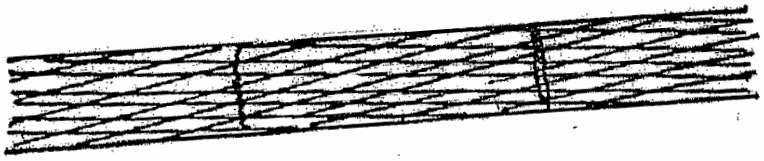


Fig. 6

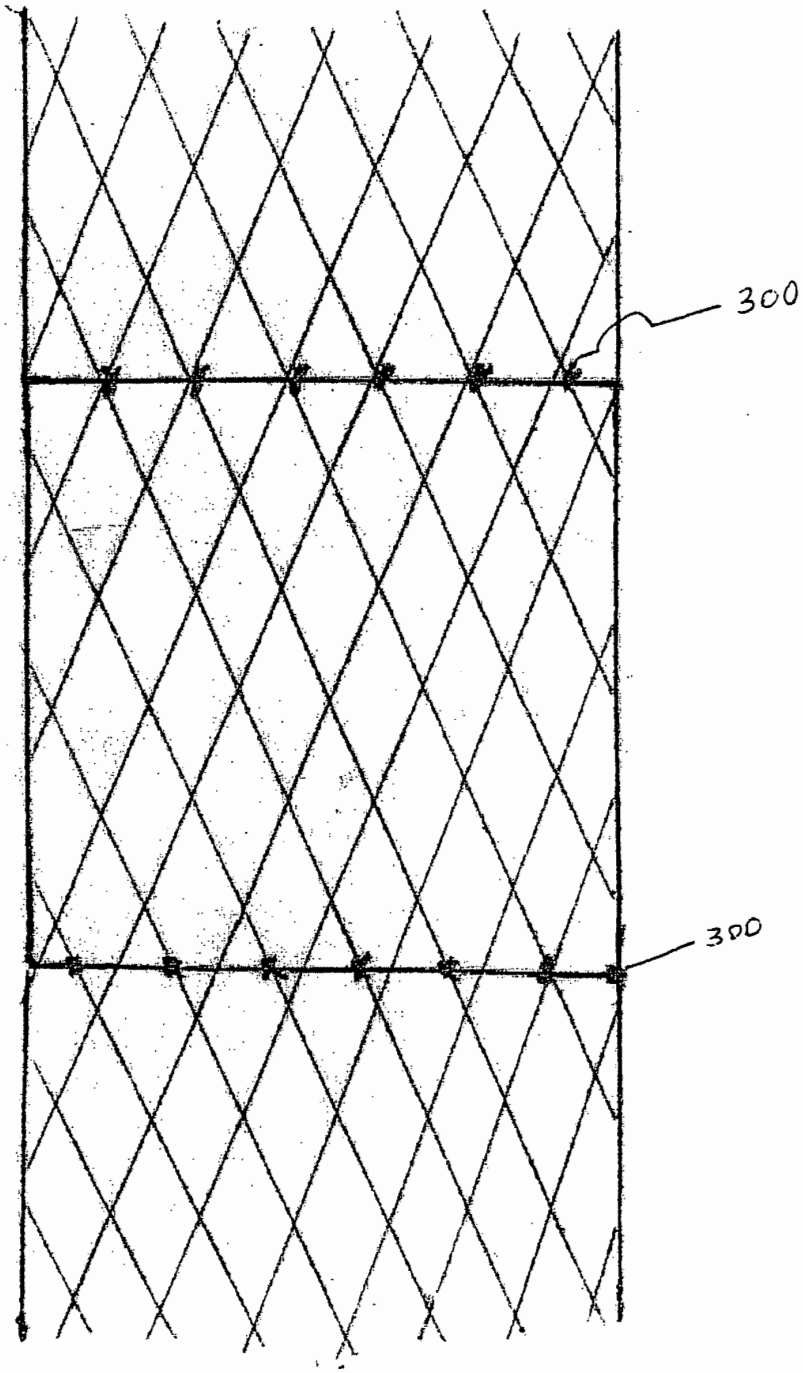


Fig. 7

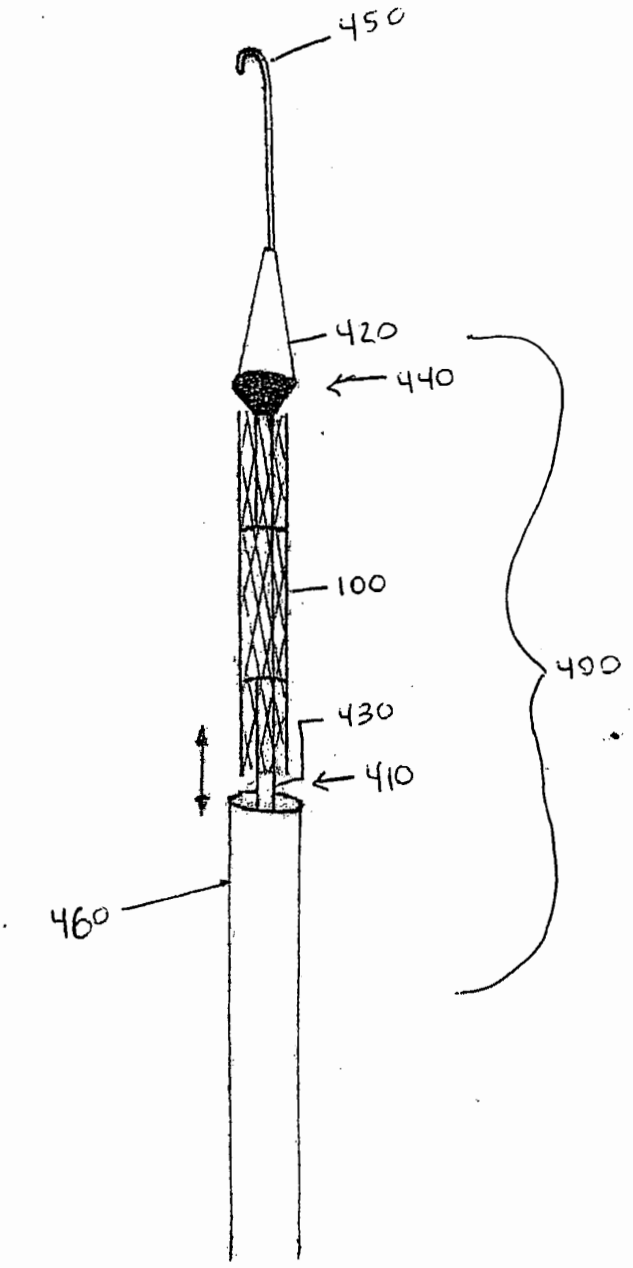
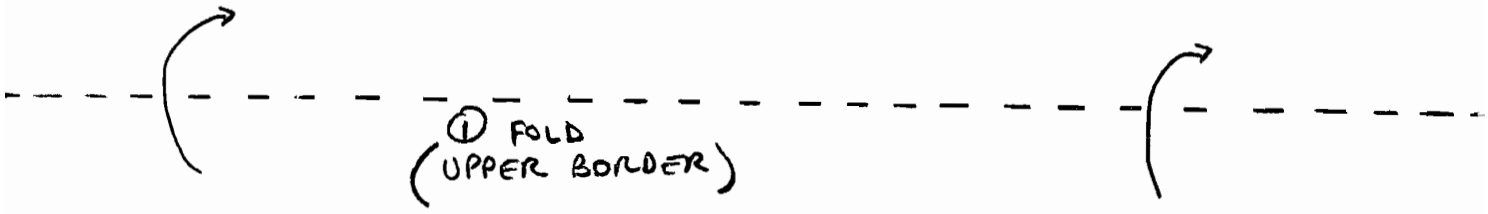


Fig. 8



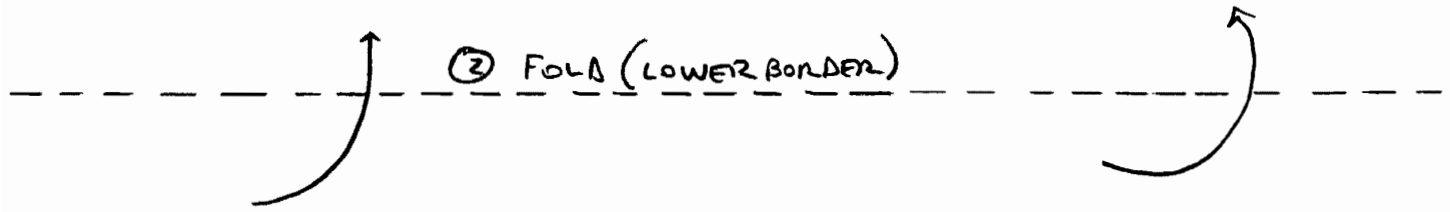


Fig. 9A

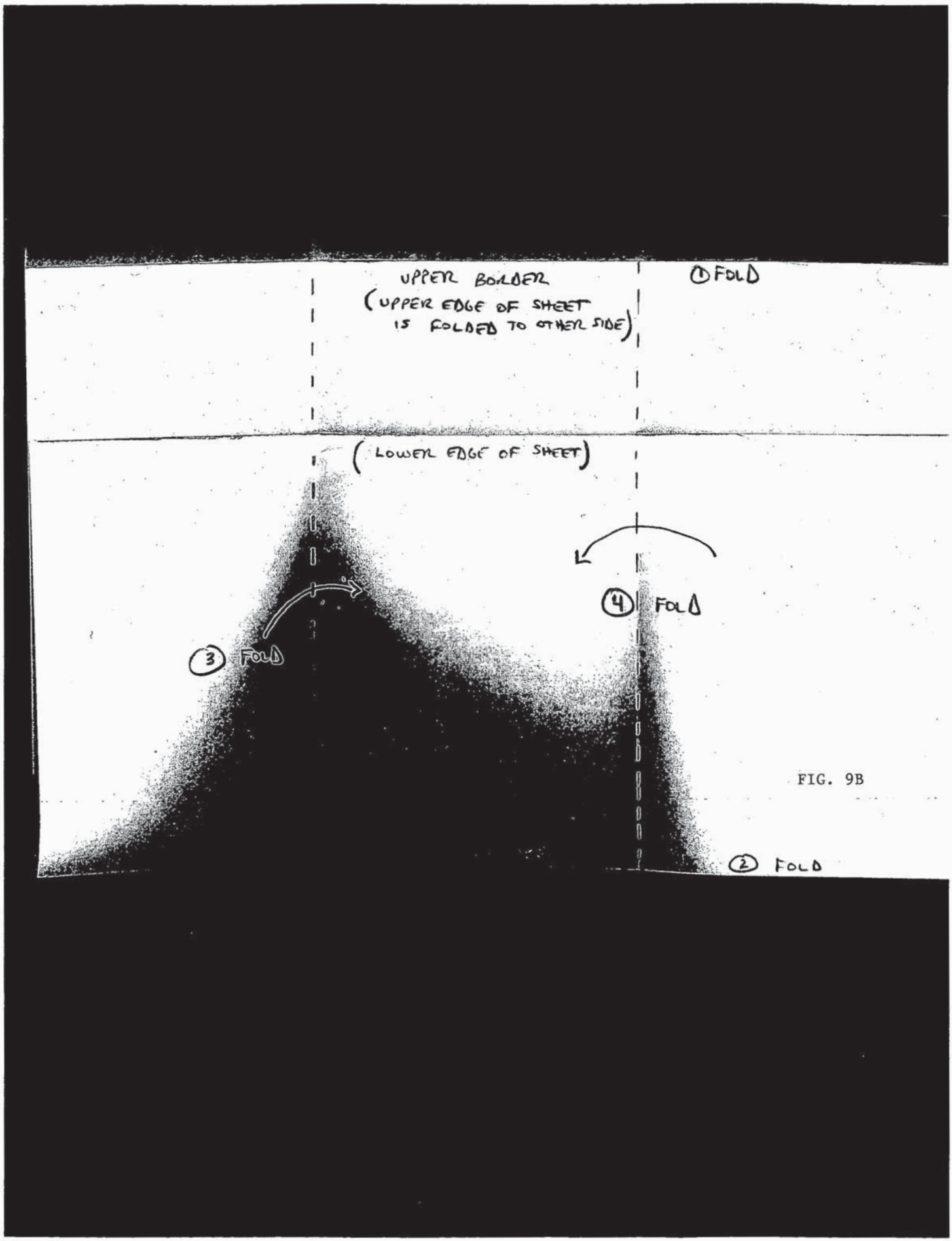

UPPER BORDER
(UPPER EDGE OF SHEET
IS FOLDED TO OTHER SIDE)
(1) FOLD
(LOWER EDGE OF SHEET)
(4) FOLD
(3) FOLD
(2) FOLD

FIG. 9B

Fold
(Upper Edge of Sheet is Folded to other side)
Upper Border
(Lower Edge of Sheet)
Fold to Leaflet/cusp shape
Fold to Leaflet/cusp shape
Fold to Leaflet/cusp shape
Fold
Lower Border
1
2
3
4
5
6
7
8

FIG. 9C

Attorney Docket No.: 51458.010100

UTILITY PATENT APPLICATION DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence post office and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter claimed and for which a patent is sought on the invention entitled percutaneously implantable replacement heart valve device and method of making same, the specification of which

☐ is attached hereto ☒ was filed on January 4, 2002 as Application Serial No. 10/037,266 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information that is known to me to be material to patentability in accordance with Title 37, Code of Federal Regulations, Section 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s):

			Priority Claimed	
Number	**Country**	**Day/Month/Year Filed**	**Yes**	**No**

I hereby claim the benefit under Title 35, United States Code, Section 119 of United States provisional application(s), and/or Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) that occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Prior U.S. Application(s):

Serial No.	**Filing Date**	**Status: Patented, Pending, Abandoned**

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I hereby appoint the following attorney(s) and/or agent(s):

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1221 Brickell Avenue
Miami, Florida 33131

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****

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Inventor's signature: Date: ____, 2003

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Citizenship: Costa Rica

Post office address: same as above

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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MARKED FOR COMPARISON
TO APPLIC. SER. NO
10/037,266

Docket No. 51458.010100

CONTINUATION IN PART

NON-PROVISIONAL PATENT APPLICATION

SPECIFICATION

TO WHOM IT MAY CONCERN:

BE IT KNOWN THAT WE, David Paniagua, Eduardo Induni, Carlos Mejia, Francisco Lopez and R. David Fish, have invented a new and useful percutaneously implantable replacement heart valve device and method of making same, of which the following is the Specification.

CONTINUITY INFORMATION

This Application is a continuation in part of U.S. non-provisional patent application serial number 10/037,266 filed on January 4, 2002. The Applicants hereby claim the benefit under 35 U.S.C. §120 based on said application.

BACKGROUND OF THE INVENTION

[0001] 1. Field of the Invention

The present invention is in the field of heart valve replacement. More specifically, the present invention is directed to a percutaneously implantable replacement heart valve and method of making same.

[0002] 2. Description of Related Art

There have been numerous efforts in the field of heart valve replacement to improve both the durability and effectiveness of replacement heart valves as well as the ease of implantation. A brief description of heart valves and heart function follows to provide relevant background for the present invention.

[0003] There are four valves in the heart that serve to direct the flow of blood through the two sides of the heart in a forward direction. On the left (systemic) side of the heart are: 1) the mitral valve, located between the left atrium and the left ventricle, and 2) the aortic valve, located between the left ventricle and the aorta. These two valves direct oxygenated blood coming from the lungs through the left side of the heart into the aorta for distribution to the body. On the right (pulmonary) side of the heart are: 1) the tricuspid valve, located between the right atrium and the right ventricle, and 2) the pulmonary valve, located between the right ventricle and the pulmonary artery. These two valves direct de-oxygenated blood coming from the body through the right side of the heart into the pulmonary artery for distribution to the lungs, where it again becomes re-oxygenated to begin the circuit anew.

[0004] Heart valves are passive structures that simply open and close in response to differential pressures on either side of the particular valve. They consist of moveable "leaflets" that are designed simply to open and close in response to differential pressures on either side of the valve's leaflets. The mitral valve has two leaflets and the tricuspid valve has three. The aortic and pulmonary valves are referred to as "semilunar valves" because of the unique appearance of their leaflets, which are more aptly termed "cusps" and are shaped somewhat like a half-moon. The aortic and pulmonary valves each have three cusps.

[0005] In general, the components of heart valves include the valve annulus, which will remain as a roughly circular open ring after the leaflets of a diseased or damaged valve have been removed; leaflets or cusps; papillary muscles which are attached at their bases to the interior surface of the left or right ventricular wall; and multiple chordae tendineae, which couple the valve leaflets or cusps to the papillary muscles. There is no one-to-one chordal connection between the leaflets and the papillary muscles; instead, numerous chordae are present, and chordae from each papillary muscle attach to both of the valve leaflets.

[0006] When the left ventricular wall relaxes so that the ventricular chamber enlarges and draws in blood, the leaflets of the mitral valve separate and the valve opens. Oxygenated blood flows in a downward direction through the valve, to fill the expanding ventricular cavity. Once the left ventricular cavity has filled, the left ventricle contracts, causing a rapid rise in the left ventricular cavitary pressure. This causes the mitral valve to close while the aortic valve opens, allowing the oxygenated blood to be ejected from the left ventricle into the aorta. The chordae tendineae of the mitral valve

prevent the mitral leaflets from prolapsing back into the left atrium when the left ventricular chamber contracts.

[0007] The three leaflets, chordae tendineae, and papillary muscles of the tricuspid valve function in a similar manner, in response to the filling of the right ventricle and its subsequent contraction. The cusps of the aortic valve also respond passively to pressure differentials between the left ventricle and the aorta. When the left ventricle contracts, the aortic valve cusps open to allow the flow of oxygenated blood from the left ventricle into the aorta. When the left ventricle relaxes, the aortic valve cusps reapproximate to prevent the blood which has entered the aorta from leaking (regurgitating) back into the left ventricle. The pulmonary valve cusps respond passively in the same manner in response to relaxation and contraction of the right ventricle in moving de-oxygenated blood into the pulmonary artery and thence to the lungs for re-oxygenation. Neither of these semilunar valves has associated chordae tendineae or papillary muscles.

[0008] Problems that can develop with heart valves consist of stenosis, in which a valve does not open properly, and/or insufficiency, also called regurgitation, in which a valve does not close properly. In addition to stenosis and insufficiency of heart valves, heart valves may need to be surgically repaired or replaced due to certain types of bacterial or fungal infections in which the valve may continue to function normally, but nevertheless harbors an overgrowth of bacteria (vegetation) on the leaflets of the valve that may embolize and lodge downstream in a vital artery. If such vegetations are on the valves of the left side (i.e., the systemic circulation side) of the heart, embolization may occur, resulting in sudden loss of the blood supply to the affected body organ and

immediate malfunction of that organ. The organ most commonly affected by such embolization is the brain, in which case the patient suffers a stroke. Thus, surgical replacement of either the mitral or aortic valve (left-sided heart valves) may be necessary for this problem even though neither stenosis nor insufficiency of either valve is present. Likewise, bacterial or fungal vegetations on the tricuspid valve may embolize to the lungs resulting in a lung abscess and therefore, may require replacement of the tricuspid valve even though no tricuspid valve stenosis or insufficiency is present.

[0009] These problems are treated by surgical repair of valves, although often the valves are too diseased to repair and must be replaced. If a heart valve must be replaced, there are currently several options available, and the choice of a particular type of artificial valve depends on factors such as the location of the valve, the age and other specifics of the patient, and the surgeon's experiences and preferences. Currently in the United States over 100,000 defective heart valves are replaced annually, at an approximate cost of $30-50,000 per procedure, and thus it would be desirable if heart valves could be replaced using minimally invasive techniques and without having to repeat the procedure within a matter of years due to the lack of durability of the replacement heart valve. It would be especially advantageous if a defective heart valve could be removed via an endovascular procedure, that is, a procedure where the invasion into the body is through a blood vessel such as the femoral artery. The procedure is then carried out percutaneously and transluminally using the vascular system to convey appropriate devices to the position in the body wherein it is desired to carry out the desired procedure. An example of such a

procedure would be angioplasty, wherein a catheter carrying a small balloon at its distal end is manipulated through the body's vessels to a point where there is a blockage in a vessel. The balloon is expanded to create an opening in the blockage, and then the balloon is deflated and the catheter and balloon are removed from the vessel.

[0010] Endovascular procedures have substantial benefits both from the standpoint of health and safety as well as cost. Such procedures require minimal invasion of the human body, and there is consequently considerable reduction and in some instances even elimination, of the use of a general anesthesia and much shorter hospital stays.

[0011] Replacement heart valves can be categorized as either artificial mechanical valves, transplanted valves and tissue valves. Replacement heart valves are designed to optimize hemodynamic performance, thrombogenicity and durability. Another factor taken into consideration is the relative ease of surgical implantation.

[0012] Mechanical valves are typically constructed from nonbiological materials such as plastics, metals and other artificial materials which, while durable, are expensive and prone to blood clotting which increases the risk of an embolism. Anticoagulants taken to help against blood clotting can further complicate the patient's health due to increased risks for hemorrhages.

[0013] Transplanted valves are natural valves taken from cadavers. These valves are typically removed and frozen in liquid nitrogen, and are stored for later use. They are typically fixed in glutaraldehyde to eliminate antigenicity and are sutured in place, typically with a stent.

[0014] Artificial tissue valves are valves constructed from animal tissue, such as bovine or porcine tissue. Efforts have also been made at using tissue from the patient for which the valve will be constructed.

[0015] Most tissue valves are constructed by sewing the leaflets of pig aortic valves to a stent to hold the leaflets in proper position, or by constructing valve leaflets from the pericardial ~~sack~~[1]sac[2] of cows or pigs and sewing them to a stent. The porcine or bovine tissue is chemically treated to alleviate any antigenicity. The pericardium is a membrane that surrounds the heart and isolates it from the rest of the chest wall structures. The pericardium is a thin and very slippery, which makes it difficult for suturing in a millimetricly precise way. The method of making the replacement heart valve of the present invention solves this problem through a process that includes drying and compressing [3]the pericardium using photo-mechanical compression [4]in such a way that makes it possible to handle and fold the material[5] more easily.

[0016] For example, one prior replacement heart valve requires each sculpted leaflet to be trimmed in a way that forms an extended flap, which becomes a relatively narrow strand of tissue near its tip. The tip of each pericardial tissue strand is sutured directly to a papillary muscle, causing the strand to mimic a chordae tendineae. Each strand extends from the center of a leaflet in the valve, and each strand is sutured directly to either an anterior and posterior papillary muscle. This requires each leaflet to be positioned directly over a papillary muscle. This effectively rotates the leaflets of the valve about 90 degrees as compared to the leaflets of a native valve. The line of commissure between the leaflets, when they are pressed together during systole, will

bisect (at a perpendicular angle) an imaginary line that crosses the peaks of the two papillary muscles, instead of lying roughly along that line as occurs in a native valve.

[0017] A different approach to creating artificial tissue valves is described in U.S. Patent Nos. 5,163,955 to Calvin, et al. and 5,571,174 and 5,653,749 to Love. Using a cutting die, the pericardial tissue is cut into a carefully defined geometric shape, treated with glutaraldehyde, then clamped in a sandwich-fashion between two stent components. This creates a tri-leaflet valve that resembles an aortic or pulmonary valve, having semilunar-type cusps rather than atrioventricular-type leaflets.

[0018] U.S. Patent No. 3,671,979 to Moulopoulos describes an endovascularly inserted conical shaped umbrella-like valve positioned and held in place by an elongated mounting catheter at a supra-annular site to the aortic valve in a nearby arterial vessel. The conical end points toward the malfunctioning aortic valve and the umbrella's distal ends open up against the aorta wall with reverse blood flow, thereby preventing regurgitation.

[0019] U.S. Patent No. 4,056,854 to Boretos describes an endovascularly inserted, catheter mounted, supra-annular valve in which the circular frame abuts the wall of the artery and attached flaps of flexible membrane extend distally in the vasculature. The flaps lie against the artery wall during forward flow, and close inward towards the central catheter to prevent regurgitation during reverse blood flow. The Boretos valve was designed to be positioned against the artery wall during forward flow, as compared to the mid-center position of the Moulopoulos valve, to reduce the stagnation of blood flow and consequent thrombus and embolic formation expected from a valve at mid-center position.

[0020] The main advantage of tissue valves is that they do not cause blood clots to form as readily as do the mechanical valves, and therefore, they do not absolutely require systemic anticoagulation. The major disadvantage of tissue valves is that they lack the long-term durability of mechanical valves. Tissue valves have a significant failure rate, usually within ten years following implantation. One cause of these failures is believed to be the chemical treatment of the animal tissue that prevents it from being antigenic to the patient. In addition, the presence of extensive suturing prevents the artificial tissue valve from being anatomically accurate in comparison to a normal heart valve, even in the aortic valve position.

[0021] A shortcoming of prior artificial tissue valves has been the inability to effectively simulate the exact anatomy of a native heart valve. Although transplanted human or porcine aortic valves have the gross appearance of native aortic valves, the fixation process (freezing with liquid nitrogen, and chemical treatment, respectively) alters the histologic characteristics of the valve tissue. Porcine and bovine pericardial valves not only require chemical preparation (usually involving fixation with glutaraldehyde), but the leaflets must be sutured to cloth-covered stents in order to hold the leaflets in position for proper opening and closing of the valve. Additionally, the leaflets of most such tissue valves are constructed by cutting or suturing the tissue material, resulting in leaflets that do not duplicate the form and function of a real valve and are more susceptible to failure.

SUMMARY OF THE INVENTION

[0022] The present invention is a replacement heart valve device and method of making same. The replacement heart valve device, in a preferred embodiment,

comprises a stent made of stainless steel or self-expanding nitinol and a completely newly designed artificial biological tissue valve disposed within the inner space of the stent. The cusp or leaflet portion of the valve means is formed by folding of the pericardium material preferably used to create the valve without cutting of slits to form leaflets or suturing or otherwise affixing of separate leaflet portions. Other forms of tissue and suitable synthetic materials can also be used for the valve, formed in a sheet of starting material. The folded design provides a number of advantages over prior designs, including improved resistance to tearing at suture lines. The cusps/leaflets open in response to blood flow in one direction and close in response to blood flow in the opposite direction. Preferably the tubular portion of the valve means contains the same number of cusps as the native valve being replaced, in substantially the same size and configuration. The outer surface of the valve means is attached to the stent member.

[0023] The replacement heart valve device is preferably implanted using a delivery system having a central part which consists of a flexible hollow tube catheter that allows a metallic guide wire to be advanced inside it. The stented valve is collapsed over the central tube and it is covered by a movable sheath. The sheath keeps the stented valve in the collapsed position. Once the cover sheath is moved backwards, the stented valve can be deployed. The endovascular stented-valve, in a preferred embodiment, is a glutaraldehyde fixed ~~bovine~~[6]mammal[7] pericardium or synthetic biocompatible material[8] which has two or three cusps that open distally to permit unidirectional blood flow. The stent can either be self-expanding or the stent can be expandable through use of a balloon catheter.

[0024] The present invention also comprises a method of making a replacement heart valve device. In order to make the valve, the pericardium starting material is isolated and all the fat tissue and extra fibers are removed. The biological membrane material is cleaned by mechanical separation of unwanted layers using hydromechanical force means. Once the pericardium is completely clean, the material is dried in order to make it easier to handle and fold. Preferably, this drying is done by exposing the biocompatible membrane material to photo-mechanical compression to remove all lipids from the pericardium or other biocompatible membrane material and to cause protein denaturalization, transforming the material into a stronger and more homogeneous surface. The valve is formed by taking a flat sheet of the material and folding in such a way that forms a three-leaflet or other number of leaflet valve. Then [9]it is placed in a ~~solution~~[10]sequence of solutions, one of isopropyl alcohol of about 70-100%, one of ethanol of about 70-100%, one of glycerol and one[11] of gluteraldehyde, preferably at a concentration of about 0.07-25[12]% for approximately 36 hours~~, then the pericardium is transferred to a solution of ethanol, preferably at a concentration of about 60% before making the valve~~[13]. The material is dried in order to make it easier to handle and fold. Preferably this drying is done by exposing the biocompatible membrane material to light and then mechanically compressing the material to cause protein denaturation. This results in material that is stronger and more homogeneous. The valve is formed by taking a flat sheet of bovine pericardium and folding it in such a way that forms a three-leaflet valve. The valve can also be made in the same manner from fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts or synthetic non-biological, non-thrombogenic material. The folding of the pericardium material to

create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of the valve leaflets. The cleaning, pressing and drying technique used to create the valve material makes the folding more practicable. The valve is rehydrated after being formed. The method of the present invention also greatly reduces the risk of tearing of the cusps or leaflets, since they are formed by folding a single uncut portion of material forming the valve rather than being attached by suturing.

[0025] Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The replacement heart valve device of the present invention can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation medication and treatment. The present invention can be practiced in applications with respect to each of the heart's valves.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] Fig. 1 depicts a side perspective view of the replacement heart valve device of the present invention in one embodiment with the valve in the closed position.

[0027] Fig. 2 depicts the folds which form the leaflets or cusps of the replacement heart valve of the present invention in one embodiment.

[0028] Figs. 3A and 3B depict a preferred procedure for folding the pericardium tissue starting material to create the replacement heart valve of the present invention.

[0029] Fig. 4 depicts a side perspective view of the replacement heart valve device of the present invention in one embodiment represented as if implanted within an artery.

[0030] Fig. 5 depicts a side view of one embodiment of the replacement heart valve device of the present invention mounted within a self-expanding stent, with the stent in the expanded position.

[0031] Fig. 6 depicts a side perspective view of one embodiment of the replacement heart valve device of the present invention mounted within a self-expanding stent in the collapsed position.

[0032] Fig. 7 depicts the suture points of one embodiment of the replacement heart valve device of the present invention.

[0033] Fig. 8 depicts the implantation/delivery system used with the present invention in a preferred embodiment.

[0034] Figs. 9A, 9B and 9C depicts a representation of a sheet of biocompatible valve material showing preferred folds.

DESCRIPTION OF A PREFERRED EMBODIMENT

[0034] The present invention comprises a percutaneously implantable replacement heart valve and a method for making same. The artificial heart valve

device of the present invention is capable of exhibiting a variable diameter between a compressed or collapsed position and an expanded position. A preferred embodiment of the replacement heart valve device according to the present invention is set forth in FIG. 5. The replacement heart valve device comprises a stent member 100 and a flexible valve means 200. The stent member 100 is preferably self-expanding, although balloon-expandable stents can be used as well, and has a first ~~cylindrical~~[14]polygonal[15] shape in its compressed or collapsed configuration and a second, larger ~~cylindrical~~[16]polygonal[17] shape in its expanded configuration. Referring to FIG. 1, the valve means 200 comprises a generally tubular portion 210 and, preferably, a peripheral upstanding cusp or leaflet portion 220. The valve means 200 is disposed within the cylindrical stent member 100 with the tubular portion 210 transverse of and at some acute angle relative to the stent walls. The diameter of the tubular portion 210 is substantially the same as the inside diameter of the stent member in its initial expanded configuration. The peripheral upstanding cusp or leaflet portion 220 is disposed on valve means 200 substantially parallel to the walls of the stent member similar to a cuff on a shirt. The cusp or leaflet portion 220 of the valve means 200 is generally tubular in shape and comprises three leaflets 221, 222 and 223 as shown, although it is understood that there could be from two to four leaflets. The tubular portion of the valve means 200 is attached to the stent member 100 by a plurality of sutures 300, as depicted in FIG. 7.

[0035] The leaflet portion 220 of the valve means 200 extends across or transverse of the cylindrical stent 100. The leaflets 221, 222 and 223 are the actual valve and allow for one-way flow of blood. The leaflet portion 220 as connected to the

rest of the valve resembles the cuff of a shirt. FIG. 9 depicts the folds preferred for valve cusp and leaflet formation involving three leaflets. The configuration of the stent member 100 and the flexible, resilient material of construction allows the valve to collapse into a relatively small cylinder as seen in FIG. 6. The replacement heart valve will not stay in its collapsed configuration without being restrained. Once the restraint is removed, the self-expanding stent member 100 will cause the artificial heart valve to take its expanded configuration, as seen in FIG. 5.

Stent Member

[0036] The stent member 100 preferably comprises a self-expanding nickel-titanium alloy stent, also called "nitinol," in a sine wave-like configuration as shown in FIG. 5. An enlarged view of a preferred embodiment of the stent member for use in the replacement heart valve of the invention is depicted in FIG. 5. The stent member 100 includes a length of wire 110 formed in a closed zigzag configuration. The wire can be a single piece, stamped or extruded, or it could be formed by welding the free ends together. The straight sections of the stent member 100 are joined by bends. The stent is readily compressible to a small cylindrical shape as depicted in FIGS. 6 and 8, and resiliently self-expandable to the shape shown in FIG. 5.

[0037] The stent member 100 of the artificial heart valve device of the present invention may be made from various metal alloys, titanium, titanium alloy, nitinol, stainless steel, or other resilient, flexible non-toxic, non-thrombogenic, physiologically acceptable and biocompatible materials. The configuration may be the zigzag configuration shown or a sine wave configuration, mesh configuration or a similar configuration which will allow the stent to be readily collapsible and self-expandable.

When a zigzag or sine wave configured stent member is used, the diameter of the wire from which the stent is made is preferably from about 0.010 to 0.035 inches and still, preferably from about 0.012 to 0.025 inches. The diameter of the stent member will be from about 1.5 to 3.5 cm, preferably from about 1.75 to 3.00 cm, and the length of the stent member will be from about 1.0 to 10 cm, preferably from about 1.1 to 5 cm.

[0038] The stent used in a preferred embodiment of the present invention is fabricated from a "shaped memory" alloy, nitinol, which is composed of nickel and titanium. Nitinol wire is first fashioned into the desired shape for the device and then the device is heat annealed. A meshwork of nitinol wire of approximately 0.008 inch gauge is formed into a tubular structure with a minimum central diameter of 20 min to make the stent. Away from its central portion, the tubular structure flares markedly at both ends in a trumpet-like configuration. The maximum diameter of the flared ends of the stent is approximately ~~30~~[18]50[19] mm. The purpose of the stent is to maintain a semi-rigid patent channel through the diseased cardiac valve following its implantation.

[0039] When the components of the replacement heart valve device are exposed to cold temperatures, they become very flexible and supple, allowing them to be compressed down and pass easily through the delivery sheath. A cold temperature is maintained within the sheath during delivery to the deployment site by constantly infusing the sheath with an iced saline solution. Once the valve components are exposed to body temperature at the end of the sheath, they instantaneously reassume their predetermined shapes, thus allowing them to function as designed.

[0040] Preferably the stent member 100 carries a plurality of barbs extending outwardly from the outside surface of the stent member for fixing the heart valve device

in a desired position. More preferably the barbs are disposed in two spaced-apart, circular configurations with the barbs in one circle extending in an upstream direction and the barbs in the other circle extending in a downstream direction. It is especially preferable that the barbs on the inflow side of the valve point in the direction of flow and the barbs on the outflow side point in the direction opposite to flow. It is preferred that the stent be formed of titanium alloy wire or other flexible, relatively rigid, physiologically acceptable material arranged in a closed zigzag configuration so that the stent member will readily collapse and expand as pressure is applied and released, respectively.

Valve Means

[0041] The valve means 200 is flexible, compressible, host-compatible, and non-thrombogenic. The valve means 200 can be made from various materials, for example, fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts. Synthetic biocompatible materials such as polytetrafluoroethylene, polyester, polyurethane, nitinol or other [20]alloy/metal foil sheet material and the like may be used. The preferred material for the valve means 200 is ~~bovine~~[21]mammal[22] pericardium tissue, particularly juvenile-age animal pericardium tissue. The valve means 200 is disposed within the cylindrical stent member 100 with the tubular portion 210 transverse of and at some acute angle relative to the stent walls. The diameter of the tubular portion 210 is substantially the same as the inside diameter of the stent member 100 in its initial expanded configuration. The peripheral upstanding cusp or leaflet portion 220 is disposed substantially parallel to the walls of the stent member 100 similar to a cuff on a shirt.

[0042] The cusp or leaflet portion 220 of the valve means 200 is formed by folding of the pericardium material used to create the valve. FIGS. 3A and 3B depict the way the sheet of heart valve starting material is folded. The starting material is preferably a flat dry sheet, which can be rectangular or other shaped. The cusps/leaflets 221, 222 and 223 open in response to blood flow in one direction and close in response to blood flow in the opposite direction. Preferably the cusp or leaflet portion 220 of the valve means 200 contains the same number of cusps as the native valve being replaced, in substantially the same size and configuration. FIGS. 9A-9C depict a preferred configuration for folds to create the leaflets/cusps. The leaflet forming portion is a single, continuous, uncut layer affixed to the interior of the cuff layer to form the leaflets/cusps, unlike prior efforts that have involved suturing of three separate leaflet/cusp portions onto the main valve body portion. The leaflets are formed from the free edge of the material after forming the cuff portion. Referring now to FIGS. 9-A, 9B, and 9C, with flat sheet on a table, a person facing the sheet would create a cuff at the upper border of sheet by folding the horizontal top edge away/downwardly (fold no.1). The leaflet portion is formed by folding the sheet's lower half towards the folder/upwardly, as shown in FIG. 9A (fold no. 2). The sheet, now with the upper cuff and bottom inward fold, is folded inwardly at two preferably equidistant vertical points as shown in FIG. 9B to create the leaflet/cusp portion (folds nos. 3 and 4). The leaflets/cusps are formed by folding fold nos. 6, 7 and 8 after the two opposite vertical edges of sheet are joined to create a cylindrical valve shape, depicted in FIGS. 1 and 3B. The inner leaflet layer is preferably attached to the outer cuff layer by curved or straight[23] continuous suturing. Although a preferred embodiment of the invention

comprises a single piece of valve material folded to create the valve body and a leaflet-forming portion that has no cuts or sutures, the inventors have discovered that as long as the leaflet portion of the valve itself is formed from a single piece of biocompatible valve material, the other portions of the valve can be formed by suturing of one or more separate pieces of material without losing the novel and improved qualities of the present invention. This allows for the valve to be made even stronger, more durable and easier to make. This alternate embodiment comprises a leaflet forming layer made of a single piece of valve material attached to a separate piece forming the valve body having a folded cuff portion. The single piece leaflet forming layer is preferably cylindrical in shape and can be formed with or without folding. In this embodiment the single piece leaflet layer can itself be attached to the stent with or without a cylindrical cuff portion. Attachment is preferably by suturing, particularly continuous single or double sutures.

Method of Making Replacement Heart Valve Device

[0043] The present invention also comprises a method of making a replacement heart valve device. In order to make the valve, the biocompatible tissue material is isolated and all the fat tissue and extra fibers are removed. Cleaning is preferably accomplished by using a hydromechanical force-based cleaning device to separate tissue layers and hydration with distilled water to remove unwanted layers. Once the pericardium is completely clean, it is subjected to photo-mechanical compression, then the valve is formed and [24]placed in ~~a~~[25]sequential[26] ~~solution~~[27]solutions[28] of isopropyl alcohol of about 70-100%, ethanol of about 70-100% glycerol and[29] gluteraldehyde~~,~~[30] preferably at a concentration of about 0.07-25[31]% for about 36 hours, ~~then the~~

~~pericardium is transferred to a solution of ethanol, preferably at a concentration of about 60% before making the valve~~[32]respectively[33]. The material is ~~then~~[34] preferably photomechanically compressed to remove lipids and produce protein coagulation to make the surface smoother and more compact and biocompatible[35], decreasing the molecular distance of collagen fibers. The exposure to light and mechanical compression cause protein denaturation making the material stronger and more homogeneous and biocompatible[36]. Gas sterilization can also be used to sterilize the tissue membrane material. The valve is formed by taking a flat sheet of the material and folding it in such a way that forms a three-leaflet or desired number of leaflet valve as shown in FIGS. 3A and 3B and/or FIGS. 9A, 9B and 9C. The folding of the pericardium material to create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of the valve leaflets. It also greatly reduces the risk of tearing of the cusps or leaflets, since they are integral to the valve rather than being attached by suturing.

[0044] In a preferred embodiment, the single continuous piece of membrane is folded inward to form an inner leaflet layer within the outer cuff. The single leaflet layer is then attached to the cuff layer to form valve cusps in one of three preferred ways: (i) by curved or straight continuous single or double sutures that affix and form the bases or recesses of the valve cusps; (ii) by lengthwise suture lines attaching the leaflet layer to the cuff layer with the bases or recesses of the valve cusps being thus formed of the folded edge of the membrane; (iii) by further folding of the membrane into lengthwise pleats secured by lengthwise suture attaching the leaflet layer to the cuff layer with the bases or recesses of the valve cusps being thus formed of the folded edge of the

membrane, done for the purpose of giving greater strength and durability to the attachment points of the leaflet layer.

[0045] In order to make the pericardium material less slippery and easier to fold, the pericardium is dried, preferably with artificial light using a ~~60~~[37]multi[38]-watt lamp with the pericardium or other biocompatible membrane[39] material placed in a flat aluminum surface to dry it homogeneously. A photomechanical drying machine can also be used. The final result is a homogeneous tissue that looks like plastic paper and makes it easy to manipulate to fold and suture the valve. Once the valve is formed, it is re-hydrated by placing it in a solution of water and 70% alcohol. In approximately 3 days the valve is fully rehydrated. The suturing of membrane layers to form the valve is done with single, double, or more continuous suture material. This form of suturing has great advantages for durability and avoidance of damage to the membrane and can be performed by sewing machines. The attachment points of the leaflet layer to the cuff layer may be reinforced by folding an additional layer of membrane over the attachment point before suturing, this layer being formed of a projected tab of the continuous piece of leaflet membrane. The free edge of the leaflet layer may be straight or curved, and this free edge forming the free edges of the individual leaflets may be contoured in parabolic or curved shape.

Attachment of the Valve Means to the Stent Member

[0046] The valve means 200 is then attached to the inner channel of the stent member 100 by suturing the outer surface of the valve means' pericardium material to the stent member. FIG. 7 depicts preferred suture points of one embodiment of the present invention: 3-point fixation or 6-point fixation at each border of the stent. Other

fixation schemes can be utilized, such as, by way of non-limiting example, fixation on both borders 18 points at each end following a single plane and 36 fixation points following to adjacent vertical planes. The use of only one plane of fixation points helps prevent systolic collapse of the proximal edge of the valve means. A fold on the border of the pericardium material prevents tearing. The attachment position of the valve is preferably closer to the proximal and wider part of the stent.

[0047] The sequence of steps can vary. The pericardium material can be fixed in glutaraldehyde before attachment to the stent or the valve can be formed and then fixed with gluteraldehyde after mounting it in the stent. One observation noted is that the material becomes whiter and apparently increases its elasticity. 1mm vascular clips keep the cusps coapted while fixing them in gluteraldehyde. The use of metallic clips to keep both cusps adjacent to each other after 24 hours of fixation in gluteraldehyde helps to educate the material and make the primary position of the valve cusps adjacent to each other. After the clips are removed, there are no lesions to the valve.

[0048] Different suture materials can be used, including, in a preferred embodiment, ~~prolene 6~~[40]Prolene 1-0 to 8[41]-0 and Mersilene ~~6~~[42]1-0 to 8[43]-0 which is a braided suture.

Implantation of Replacement Heart Valve Device

[0049] The replacement heart valve device of the present invention is preferably used in surgical procedures involving the percutaneous and transluminal removal of the diseased or defective heart valve and the percutaneous and transluminal implantation of the new heart valve described above. The defective heart valve is removed by a suitable modality, such as, for example, laser, ultrasound, mechanical, or other suitable

forms of delivery of energy, or phacoemulsion, including, but not limited to, laser lithotripsy, mechanical lithotripsy, electrohydraulic lithotripsy, and laser or mechanical ablation. To remove the native heart valve that is being replaced, a guidewire is inserted percutaneously and transluminally using standard vascular or angiography techniques. The distal end of the guidewire is manipulated to extend through and across the defective heart valve. Then a catheter is advanced distally through the femoral artery to a point proximal to the defective heart valve, between the origin of the coronary artery and the origin of the right subclavian artery. The position of the distal end of catheter can be monitored by observation of radiopaque markers. Collector member is preferably inflated and occludes the aorta at a point between the origin of the coronary artery and the right subclavian artery. Next, a balloon and cutting tool are advanced through the catheter so that the cutting tool and uninflated balloon are distal to the defective heart valve. Optionally an additional step, such as balloon dilatation or atherectomy, may be required to provide a passageway through the heart valve. A catheter is also placed into the coronary sinus via a transjugular puncture. This catheter is used for infusion of blood or cardioplegia solution during the portion of the procedure when the aorta is occluded. The absence of valves in the cardiac venous system allows retrograde flow so that there will be an effluence of fluid from the coronary arteries. This flow of fluid is desired to prevent embolization of material into the coronary arteries during the procedure. Once the cutting tool is in place, the balloon is inflated and flexible shaft is rotated. Once the cutting tool has reached the appropriate rotation speed, the cutting tool is pulled proximally to remove the defective heart valve. The balloon and the cutting tool are spaced apart so that the inflated balloon will be stopped

by the perimeter, unremoved portion of the defective heart valve, which will signal the physician that the valve has been removed, as well as protect the heart and aorta from damage from the valve removal device. Once it is determined that the defective heart valve has been removed, the cutting tool is slowed or stopped altogether and the balloon is deflated. The cutting tool and the deflated balloon are pulled proximally through catheter. Then, a catheter containing an artificial heart valve is inserted and the artificial heart valve is placed as described above.

[0050] The delivery and implantation system of the replacement artificial heart valve of the present invention percutaneously and transluminally includes a flexible catheter 400 which may be inserted into a vessel of the patient and moved within that vessel as depicted in FIG. 8. The distal end 410 of the catheter 400, which is hollow and carries the replacement heart valve device of the present invention in its collapsed configuration, is guided to a site where it is desired to implant the replacement heart valve. The catheter has a pusher member 420 disposed within the catheter lumen 430 and extending from the proximal end 440 of the catheter to the hollow section at the distal end 410 of the catheter. Once the distal end 410 of the catheter is positioned as desired, the pusher mechanism 420 is activated and the distal portion of the replacement heart valve device is pushed out of the catheter and the stent member 100 partially expands. In this position the stent member 100 is restrained so that it doesn't pop out and is held for controlled release, with the potential that the replacement heart valve device can be recovered if there is a problem with the positioning. The catheter 400 is then retracted slightly and the replacement heart valve device is completely pushed out of the catheter 400 and released from the catheter to allow the stent

member 100 to fully expand. If the stent member 100 preferably includes two circles of barbs on its outer surface as previously described, the first push and retraction will set one circle of barbs in adjacent tissue and the second push and release of the replacement heart valve device will set the other circle of barbs in adjacent tissue and securely fix the replacement heart valve device in place when the device is released from the catheter.

[0051] Alternatively, or in combination with the above, the replacement heart valve device could be positioned over a metallic guidewire that is advanced through the catheter. The replacement heart valve device of the present invention is preferably implanted percutaneously through an aortic passageway to, or near to, the location from which the natural heart valve has been removed. Referring to FIG. 8, the implantation system comprises a flexible hollow tube catheter 410 with a metallic guide wire 450 disposed within it. The stented valve device is collapsed over the tube and is covered by a moveable sheath 460. The moveable sheath 460 maintains the stented valve device in the collapsed position. The implantation method comprises the following steps: inserting the replacement heart valve device in the lumen of a central blood vessel via entry through the brachial or femoral artery using a needle or exposing the artery surgically; placing a guide wire 450 through the entry vessel and advancing it to the desired position; advancing dilators over the wire to increase the lumen of the entry site, thereby preparing the artery to receive the heart-valve; and advancing the heart-valve device to the desired place. The stented-valve device is released by pulling the cover sheath 460 of the delivery system allowing the self-expanding stent to achieve its full expansion. A baloon expandable stent can alternately be used to deliver

the valve to its desired position. [44]At this point, a pigtail catheter is advanced over the wire and an aortogram is performed to assess the competency of the valve.

[0052] Before creation of the valve means and implantation, the patient is studied to determine the architecture of the patient's heart. Useful techniques include fluoroscopy, transesophageal echocardiography, MRI, and angiography. The results of this study will enable the physician to determine the appropriate size for the replacement heart valve.

[0053] In one procedure for implantation of the replacement heart valve device of the present invention, the femoral artery of the patient is canulated using a Cook needle and a standard J wire is advanced into the artery either percutaneously or after surgical exposure of the artery. An 8 F introducer is advanced into the femoral artery over the wire. The J wire is then withdrawn and anticoagulation is started using heparin 60 U/Kg intravenously. Once vascular access is obtained an aortogram is performed for anatomical evaluation. A special wire (Lunderquist or Amplatz superstiff) is advanced into the aortic arch and dilators progressively larger are advanced over the wire, starting with 12 F all the way to 18 F. After this the valve introducer device containing the prosthetic valve device is then inserted and used to transport the replacement valve over a guidewire to the desired position. The stented-valve is released by pulling the cover sheath of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advanced over the wire and repeat aortogram is performed to assess the competency of the valve.

[0054] When the device is used to treat severe leakage of the aortic valve, the native valve is left in place and the prosthetic stented valve is deployed below the

subclavian artery. When the device is used to treat aortic stenosis, first the stenotic valve needs to be opened using either aortic valvuloplasty or cutting and if this procedure induces aortic insufficiency the stented valve is placed to prevent the regurgitation.

[0055] Intravascular ultrasound or an angioscope passed intravascularly via either the venous system through the intra-atrial septum across the mitral valve and into the left ventricle or retrograde via the femoral artery would provide the added benefit of allowing constant high definition imaging of the entire procedure and high flow irrigation.

[0056] Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The prosthetic valve device can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation. In addition, with the development of longer-life, flexible, non-thrombogenic synthetic valve alternatives to bioprosthesis, the prosthetic valve device will be indicated in all patients where the relative advantages of the life-span, the non-thrombogenic quality, and the ease of insertion of prosthetic valve devices outweigh the disadvantages of mechanical valves. Anticoagulation may be beneficial in certain clinical situations for either short or long term use.

[0057] This method of percutaneous endovascular heart-valve replacement, in contrast to open heart surgical procedures, requires only local anesthesia, partial or no cardiac bypass, one to two days hospitalization, and should result in a reduced mortality rate as compared to open heart procedures.

[0058] While the present invention has been shown and described herein in what is considered to be a preferred embodiment thereof, illustrating the results and advantages over the prior art obtained through the present invention, the invention is not limited to the specific embodiments described above. Thus, the forms of the invention shown and described herein are to be taken as illustrative and other embodiments may be selected without departing from the spirit and scope of the present invention.

CLAIMS

Having thus described the invention, what is claimed is:

1. A percutaneously implantable replacement heart valve device comprising an expandable stent member and a flexible, compressible artificial valve made of biocompatible tissue material and disposed within the inner cavity of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve having cusps or leaflets formed by folding of a sheet of said biocompatible tissue material without affixing of separate cusps or leaflets or cutting slits into said material to form said cusps or leaflets.

2. The percutaneously implantable replacement heart valve device of claim 1, wherein said expandable stent member is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium and stainless steel.

3. The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible tissue material of said artificial valve comprises ~~bovine~~[45] mammal[46] pericardium tissue.

4. The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible tissue material of said artificial valve comprises porcine pericardium tissue.

5. The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible tissue material of said artificial valve is obtained from a juvenile animal pericardium.

6. The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible tissue material of said artificial valve comprises autologous

tissue obtained from the patient into whom said replacement heart valve device will be implanted.

7. The percutaneously implantable heart valve device of claim 1, wherein said biocompatible tissue material of said artificial valve comprises a synthetic biocompatible material.

8. The percutaneously implantable heart valve device of claim 7, wherein said synthetic biocompatible material is selected from the group consisting of polytetrafluoroethylene, polyester, metal, metal alloy including combinations thereof.

9. The percutaneously implantable heart valve device of claim 1, wherein said stent member is self-expanding when implanted.

10. The percutaneously implantable heart valve device of claim 1, wherein said stent member is balloon catheter expandable when implanted.

11. A method of making a percutaneously implantable replacement heart valve device comprising the following steps:

obtaining a sheet of biocompatible tissue material;

~~soaking said biocompatible tissue material in a gluteraldehyde solution;~~[47]

~~transferring said biocompatible tissue material from said gluteraldehyde solution to an ethanol solution;~~[48]

drying said biocompatible tissue material;

folding said dried biocompatible tissue material to create inner cusps or leaflets and an outer tubular cuff structure without affixing of separate cusps or leaflets or cutting slits into said material to form said cusps or leaflets;

affixing said folded biocompatible tissue material at one or more points on its outer surface to the inner cavity of a stent~~.~~[49]; and[50]

soaking said biocompatible tissue material in one or more alcohol solutions and a solution of gluteraldehyde.[51]

12. The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said soaking step comprises soaking said biocompatible tissue material in a solution of isopropyl alcohol, a solution of ethanol, a solution of glycerol and a solution of gluteraldehyde.[52]

~~12.~~[53]13.[54] The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material comprises bovine pericardium tissue.

~~13.~~[55]14.[56] The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material comprises porcine pericardium tissue.

~~14~~[57]15.[58] The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material is obtained from a juvenile animal pericardium.

~~15.~~[59]16.[60] The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material comprises autologous tissue obtained from the patient into whom said replacement heart valve device will be implanted.

~~16.~~[61]17.[62] The percutaneously implantable heart valve device of claim 11, wherein said biocompatible tissue material of said artificial valve comprises a synthetic biocompatible material.

~~17.~~[63]18.[64] The percutaneously implantable heart valve device of claim ~~16,~~[65]17.[66] wherein said synthetic biocompatible material is selected from the group consisting of polytetrafluoroethylene, polyester, metal, metal alloy including combinations thereof.

~~18.~~[67]19.[68] The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said stent is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium and stainless steel.

~~19.~~[69]20.[70] The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said stent is self-expanding when implanted.

~~20.~~[71]21.[72] The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said stent is balloon catheter expandable when implanted.

~~21.~~[73]22.[74] The method of making a percutaneously implantable replacement heart valve device of claim 11, further comprising the step of cleaning said biocompatible tissue material using hydromechanical force means.

~~22.~~[75]23.[76] The method of making a percutaneously implantable replacement heart valve of claim 11, further comprising the step of compressing said biocompatible tissue material.

~~23.~~[77]24.[78] The method of making a percutaneously implantable replacement heart valve of claim 11, further comprising the step of gas sterilization of said biocompatible tissue material.

~~24.~~[79]25.[80] The method of making a percutaneously implantable replacement heart valve of claim 11, wherein said drying step comprises photomechanical compression of said biocompatible tissue material.

~~25.~~[81]26.[82] The method of making a percutaneously implantable replacement heart valve of claim 11, wherein said folding step comprises folding of a first piece of said biocompatible tissue material to create an outer tubular cuff structure, folding of a second separate piece of biocompatible tissue material to create inner cusps or leaflets without affixing of separate cusps or cutting slits into said second separate piece of biocompatible tissue material, and afixing said second separate piece to said first piece.

~~26.~~[83]27.[84] A percutaneously implantable replacement heart valve device comprising an expandable stent member and a flexible, compressible artificial valve made of biocompatible tissue material and disposed within the inner cavity of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising a leaflet or cusp portion formed by folding of a first sheet portion of said biocompatible tissue material without affixing of separate cusps or leaflets or cutting slits into said sheet to form said cusps or leaflets, and an outer tubular cuff structure formed by folding a second sheet portion of biocompatible tissue material, said first and second sheet portions being affixed together.

~~27.~~[85]28.[86] The device of claim ~~26,~~[87]27.[88] wherein said first sheet portion and said second sheet portions are affixed together by ~~suturing.~~[89]~~28. The device of claim 27, wherein said~~ [90]suturing ~~is in the form of double continuous sutures~~[91].

29. The device of claim 28, wherein said suturing is in the form of double continuous sutures.[92]

~~29.~~[93]30.[94] A percutaneously implantable replacement heart valve device comprising an outer cylindrical cuff portion and an inner uncut/unslit leaflet layer attached within said outer cuff portion.

~~30.~~[95]31.[96] The device of claim ~~29,~~[97]30.[98] wherein said leaflet layer is attached within said outer cuff portion by ~~suturing.~~[99]~~31. The device of claim 30, wherein said~~ [100]suturing ~~is in the form of double continuous sutures~~[101].

32. The device of claim 31, wherein said suturing is in the form of double continuous sutures.[102]

~~32.~~[103]33.[104] A percutaneously implantable replacement heart valve device comprising an expandable stent member and a flexible, compressible artificial valve made of biocompatible tissue material and disposed within the inner cavity of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising a leaflet or cusp portion formed by folding

of a first sheet portion of said biocompatible tissue material without affixing of separate cusps or leaflets or cutting slits into said sheet to form said cusps or leaflets.

ABSTRACT

The present invention comprises a percutaneously implantable replacement heart valve device and a method of making same. The replacement heart valve device comprises a stent member made of stainless steel or self-expanding nitinol, a biological tissue artificial valve means disposed within the inner space of the stent member. An implantation and delivery system having a central part which consists of a flexible hollow tube catheter that allows a metallic wire guide to be advanced inside it. The endovascular stented-valve is created from a glutaraldehyde fixed biocompatible tissue material which has two or three cusps that open distally to permit unidirectional blood flow. The present invention also comprises a novel method of making a replacement heart valve by taking a fragment of biocompatible tissue material and treating, drying, folding and rehydrating it in such a way that forms a two- or three-leaflet/cusp valve with the leaflets/cusps formed by folding, thereby eliminating the extent of suturing required, providing improved durability and function.

\\MIA-SRV01\1570069v01

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

07/14/2004 MBELETE1 00000027 501792 10887688

01 FC:2001 385.00 DA
02 FC:2201 86.00 DA
03 FC:2202 117.00 DA

PTO-1556
(5/87)

*U.S. Government Printing Office: 2002 — 489-267/59033

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2003

Application or Docket Number: 10887688

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	33	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	33 minus 20=	* 13
INDEPENDENT CLAIMS	5 minus 3 =	* 2
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	385.00	OR	BASIC FEE	770.00
XS 9=	117	OR	XS18=	
X43=	86	OR	X86=	
+145=		OR	+290=	
TOTAL	588	OR	TOTAL	

CLAIMS AS AMENDED - PART II

AMENDMENT A	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. 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."
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APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
10/887,688	07/10/2004	David Paniagua	51458.010100

CONFIRMATION NO. 4909

Manuel R. Valcarcel
GREENBERG TRAURIG, P.A.
1221 Brickell Avenue
Miami, FL 33131

FORMALITIES LETTER

OC000000013837228

Date Mailed: 09/17/2004

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given TWO MONTHS from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

The required item(s) identified below must be timely submitted to avoid abandonment:

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121 are required. The drawings submitted are not acceptable because:
    - The drawings must be made on paper that has a white background (see 37 CFR 1.84 (e)). For example, drawings on graph paper, lined paper, or paper that has a non-white background are not acceptable. See Figure(s) 9B-C.

Replies should be mailed to: Mail Stop Missing Parts
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A copy of this notice MUST be returned with the reply.

N. Mohammed

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10/887,688	07/10/2004	David Paniagua	51458.010100

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N. Mohammed

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PART 1 - ATTORNEY/APPLICANT COPY

Greenberg Traurig

Manuel R. Valcarcel, Esq.
305-579-0812

January 26, 2005

VIA EXPRESS MAIL

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313

Re: Notice to File Corrected Application Papers
Patent Application No. 10/887,688

Dear Sir:

Enclosed under cover of this transmittal letter are the following documents submitted in response to the Notice to File Corrected Application Papers having a mailing date of September 17, 2004 in connection with the above-referenced application:

1. Copy of Notice to File Corrected Application Papers.

2. Substitute drawings in compliance with 37 C.F.R.§1.84.

3. Petition for Extension of Time pursuant to 37 C.F.R. 12.136 (a). Please charge the petition fee to deposit account 50-1792.

Please confirm receipt of the enclosed documents by date-stamping and returning the enclosed postcard. Please direct all communications regarding the foregoing to the undersigned.

Respectfully submitted,

GREENBERG TRAURIG, P.A.

Manuel R. Valcarcel, Esq.
Reg. No. 41,360

MRV
Enclosures

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PTO/SB/22 (8-00)
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 51458-010100

In re Application of Paniagua, et al.	
Application Number 10/887,688	Filed July 10, 2004
Group Art Unit 3738	Examiner: not assigned

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows:
(check time period desired):

- ☐ One month (37 CFR 1.17(a)(1)) $ _____
- ☐ Two months (37 CFR 1.17(a)(2)) $_____
- ☒ Three months (37 CFR 1.17(a)(3)) $1020.00
- ☐ Four months (37 CFR 1.17(a)(4)) $_____
- ☐ Five months (37 CFR 1.17(a)(5)) $_____

☒ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: $510

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Commissioner has already been authorized to charge fees in this application to a Deposit Account.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50-1792.

I have enclosed a duplicate copy of this sheet.

I am the ☐ assignee of record of the entire interest.

☐ applicant.

☒ attorney or agent of record.

☐ attorney or agent under 37 CFR 1.34(a).
Registration number if acting under 37 CFR 1.34(a) _____.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

January 25, 2005
Date

Signature

Manuel Valcarcel, Esq.
Typed or printed name (Reg. 41,360)

EXPRESS MAIL MAILING LABEL NO. ER 940079391 US

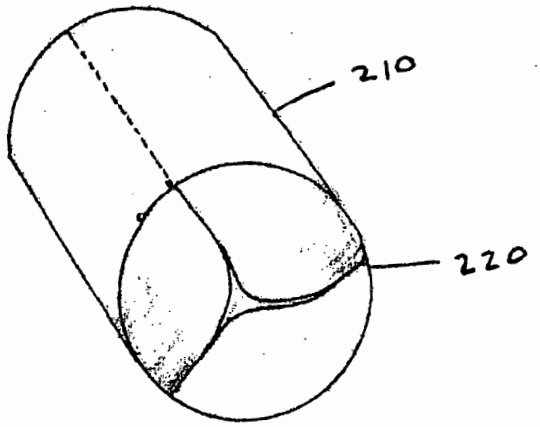


Fig. 1

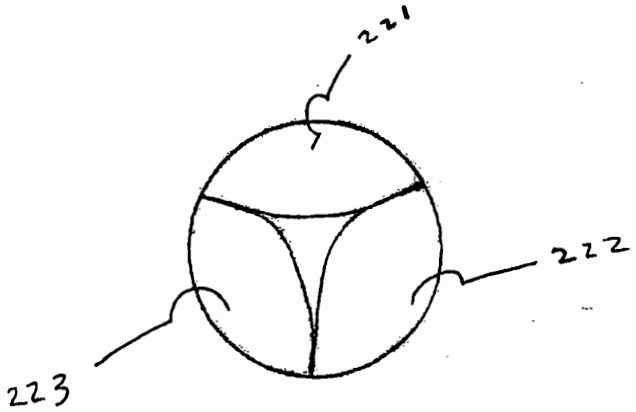


Fig. 2

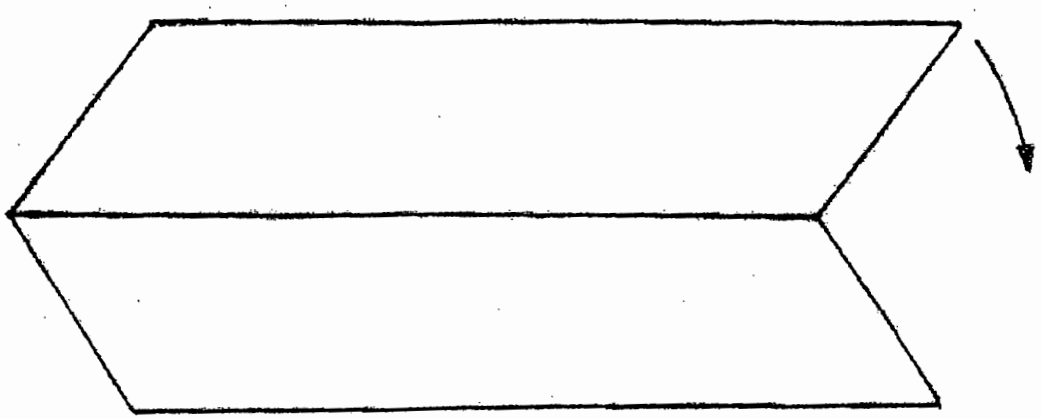


Fig. 3A

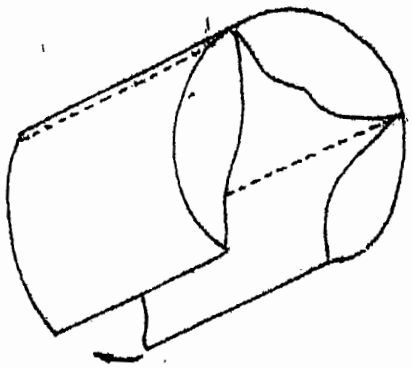


Fig. 3B

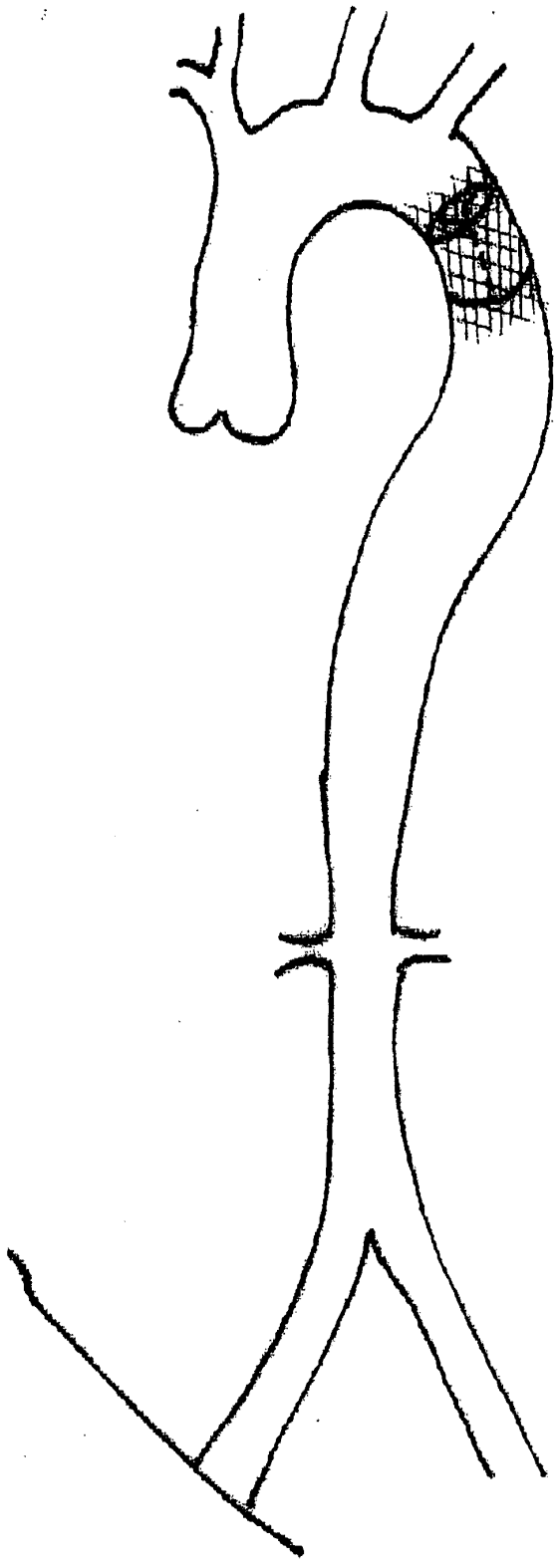


Fig. 4

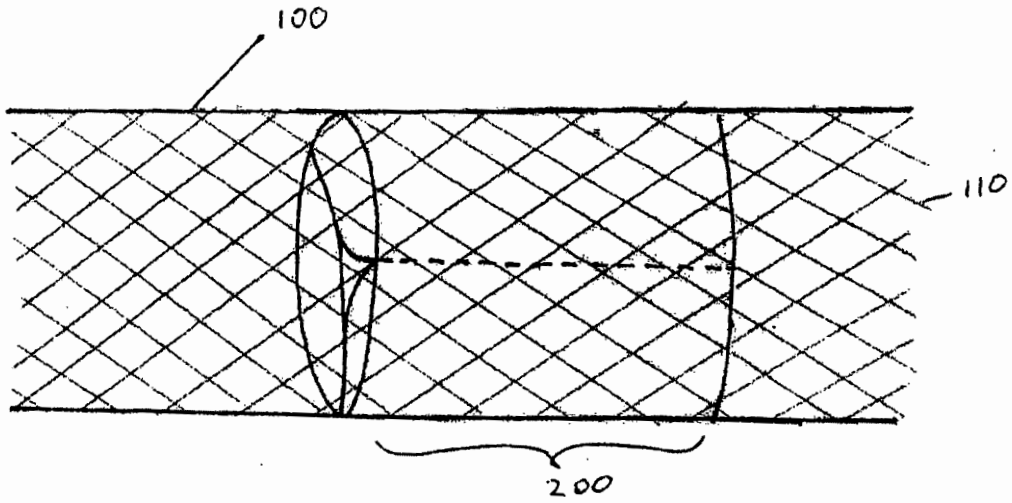


Fig. 5

Fig. 6

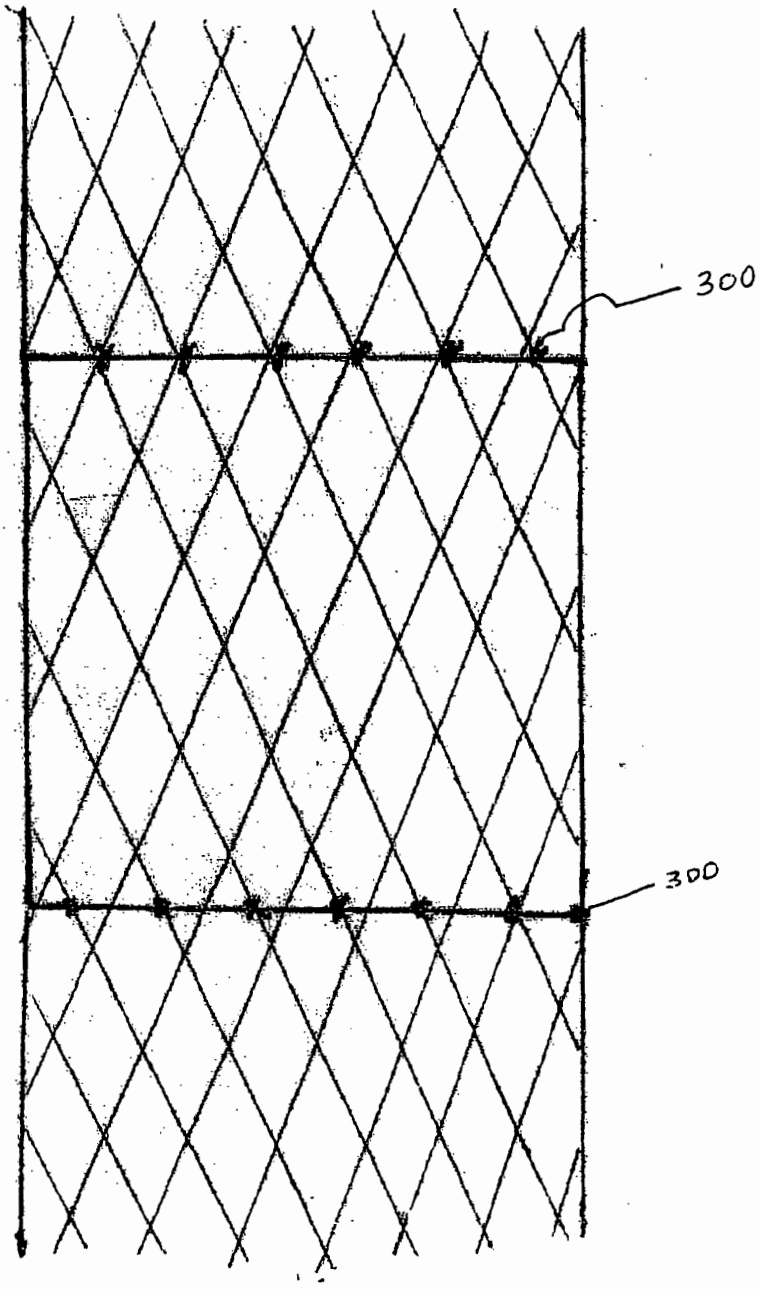


Fig. 7

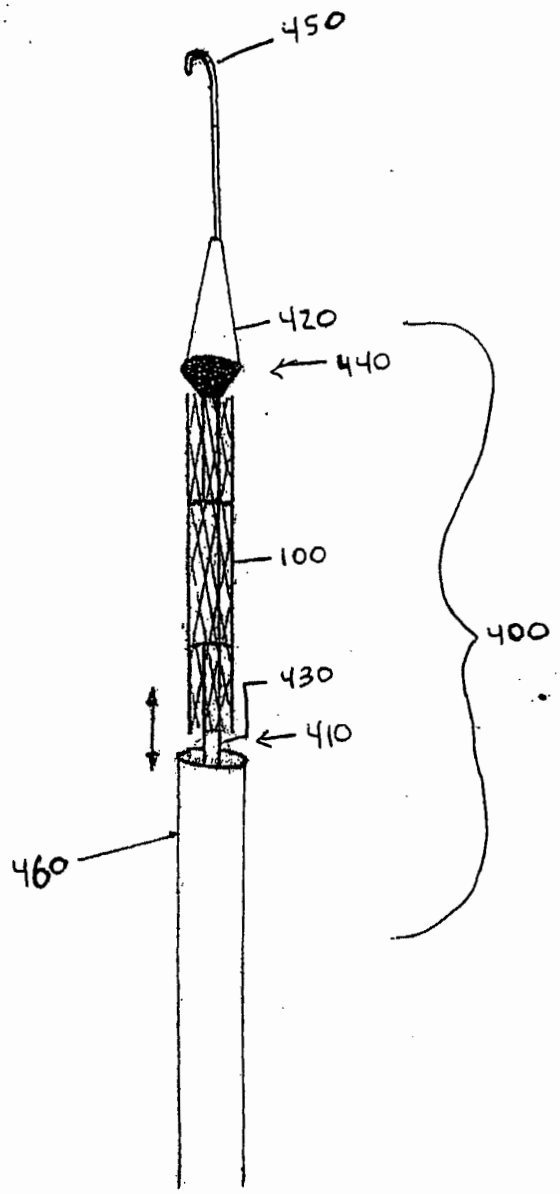
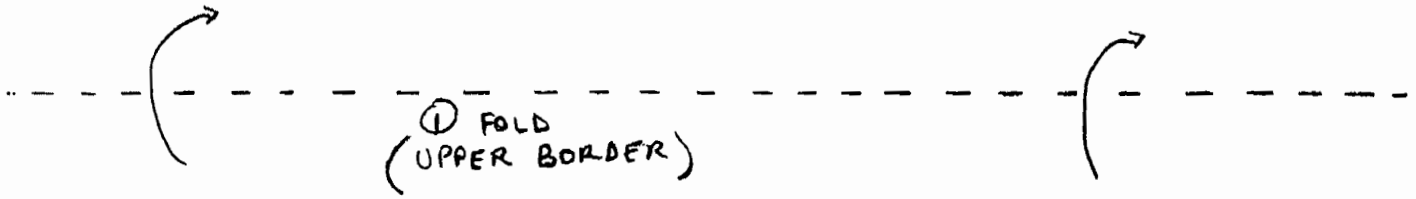


Fig. 8



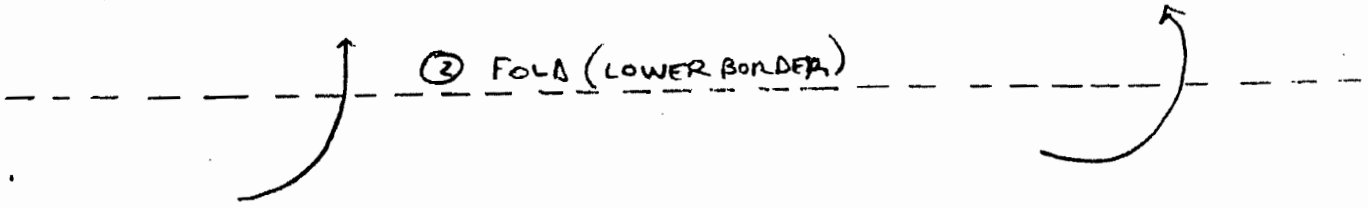
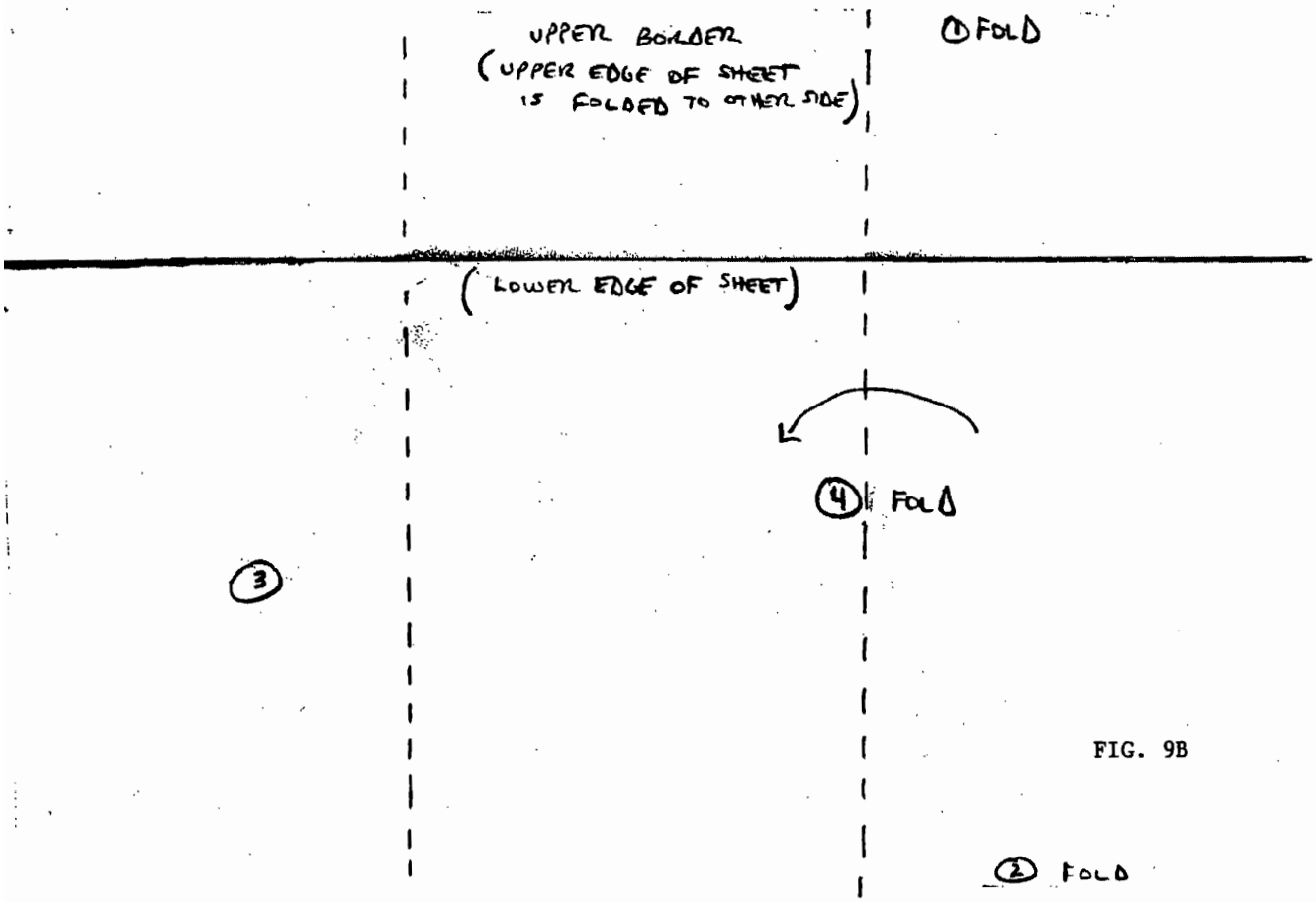


Fig. 9A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(UPPER EDGE OF SHEET IS FOLDED TO OTHER SIDE)
① FOLD
(LOWER EDGE OF SHEET)
④ FOLD
③
② FOLD

FIG. 9B

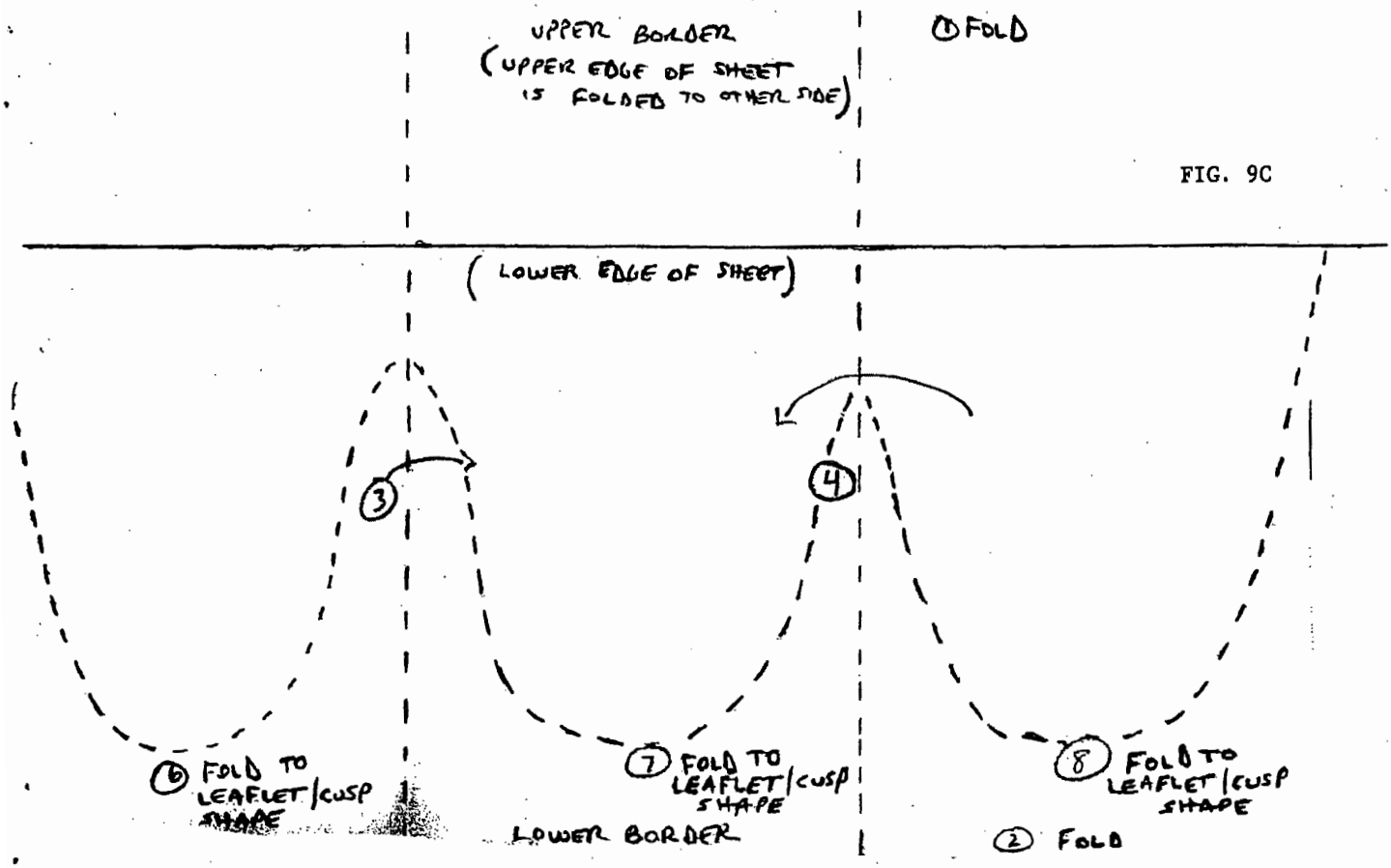
UPPER BORDER
(UPPER EDGE OF SHEET IS FOLDED TO OTHER SIDE)
① FOLD
(LOWER EDGE OF SHEET)
③
④
⑥ FOLD TO LEAFLET/CUSP SHAPE
⑦ FOLD TO LEAFLET/CUSP SHAPE
⑧ FOLD TO LEAFLET/CUSP SHAPE
LOWER BORDER
② FOLD

FIG. 9C

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NUMBER	PATENT NUMBER	GROUP ART UNIT	FILE WRAPPER LOCATION
10/887,688		3738	

Correspondence Address / Fee Address Change

The following fields have been set to Customer Number 54353 on 06/13/2005

- Correspondence Address
- Maintenance Fee Address

The address of record for Customer Number 54353 is:
MANUEL VALCACEL
c/o GREENBERG TRAURIG, P.A.
1221 BRICKELL AVENUE
MIAMI,FL 33131

PLUS Search Results for S/N 10887688, Searched Thu Mar 22 11:43:43 EDT 2007

The Patent Linguistics Utility System (PLUS) is a USPTO automated search system for U.S. Patents from 1971 to the present PLUS is a query-by-example search system which produces a list of patents that are most closely related linguistically to the application searched. This search was prepared by the staff of the Scientific and Technical Information Center, SIRA.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/887,688	07/10/2004	David Paniagua	51458.010100	4909

54353 7590 09/14/2007

MANUEL VALCACEL
c/o GREENBERG TRAURIG, P.A.
1221 BRICKELL AVENUE
MIAMI, FL 33131

EXAMINER	
MILLER, CHERYL L	
ART UNIT	**PAPER NUMBER**
3738	

MAIL DATE	DELIVERY MODE
09/14/2007	PAPER

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.

Office Action Summary	Application No.	Applicant(s)	
	10/887,688	PANIAGUA ET AL.	
	Examiner	Art Unit	
	Cheryl Miller	3738	

-- 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 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *10 July 2007*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ 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

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-33* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ 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).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

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).

a)☐ All b)☐ Some * c)☐ None of:

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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-10 and 27-33, drawn to a heart valve, classified in class 623, subclass 2.14.

II. Claims 11-26, drawn to a method of making a valve, classified in class 623, subclass 909.

The inventions are distinct, each from the other because of the following reasons:

Inventions II. and I. are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make another and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the product may be made by a different process, such as molding or cutting and attaching separate pieces by welding or adhesive or stitching. Further, the process of making may make a different product such as a teaching model or tool, the device need not be implanted.

Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions have acquired a separate status in the art in view of their different classification, restriction for examination purposes as indicated is proper.

Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the

inventions require a different field of search (see MPEP § 808.02), restriction for examination purposes as indicated is proper.

Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions have acquired a separate status in the art due to their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

A telephone call was made to Manuel Valcarcel (Registration No.41,360) on September 10, 2007 to request an oral election to the above restriction requirement, but did not result in an election being made.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C.103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

It is also requested by the examiner, if at all possible to send a sample of the device or even of a piece of paper, having the foldings made, in order provide the examiner a better understanding of exactly how the device is folded to form the final product.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cheryl Miller whose telephone number is (571) 272-4755. The examiner can normally be reached on Monday-Friday 7:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Corrine McDermott can be reached on (571) 272-4755. 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.

Cheryl Miller

BRUCE SNOW
PRIMARY EXAMINER

Greenberg Traurig

10-11-07

IFW

Manuel R. Valcarcel, Esq.
305-579-0812 Tel.
305-961-5812 Fax
mrv@gtlaw.com

October 10, 2007

VIA EXPRESS MAIL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Re: U.S. Patent Application No. 10/887,688
Invention: Percutaneously implantable replacement heart valve device and method of making same
Response to Office Action No. 1
Our Ref. No. 051458.010100

Dear Sir:

Enclosed under cover of this transmittal letter is a response to office action no. 1 in the above-referenced application.

Please charge and any required fees for the enclosed submission to Deposit Account No. 50-1792.

Please confirm receipt of the enclosed documents by date-stamping and returning the enclosed postage paid return postcard. Please direct all communications regarding the foregoing to the undersigned.

Respectfully submitted,

GREENBERG TRAURIG, P.A.

Manuel R. Valcarcel, Esq.
Reg. No. 41,360

EXPRESS MAIL MAILING LABEL NO. EB 580600101 US

MRV/mam
Enclosures

cc: David Paniagua, M.D.

MIA 179764891v1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of
Paniagua, et al.
Serial No. 10/887,688
Filed: July 10, 2004
Invention: Percutaneously Implantable Replacement Heart Valve Device and Method of Making Same.

Examiner: Cheryl Miller
Group Art Unit 3738

RESPONSE TO OFFICE ACTION No. 1

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

In response to Office Action No. 1 dated September 14, 2007 in the above-referenced application, the Applicants respectfully submit the following response:

ELECTION OF CLAIMS

Applicants hereby elect claims 1-10 and 27-33, directed to the device for examination in the present application and are filing a divisional application for claims 11-26, directed to the method of making the device.

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AMENDMENTS TO THE CLAIMS

The following listing will replace all prior versions of the claims in the application:

1. (original) A percutaneously implantable replacement heart valve device comprising an expandable stent member and a flexible, compressible artificial valve made of biocompatible tissue material and disposed within the inner cavity of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve having cusps or leaflets formed by folding of a sheet of said biocompatible tissue material without affixing of separate cusps or leaflets or cutting slits into said material to form said cusps or leaflets.

2. (original) The percutaneously implantable replacement heart valve device of claim 1, wherein said expandable stent member is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium and stainless steel.

3. (original) The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible tissue material of said artificial valve comprises mammal pericardium tissue.

4. (original) The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible tissue material of said artificial valve comprises porcine pericardium tissue.

5. (original) The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible tissue material of said artificial valve is obtained from a juvenile animal pericardium.

6. (original) The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible tissue material of said artificial valve comprises autologous tissue obtained from the patient into whom said replacement heart valve device will be implanted.

7. (original) The percutaneously implantable heart valve device of claim 1, wherein said biocompatible tissue material of said artificial valve comprises a synthetic biocompatible material.

8. (original) The percutaneously implantable heart valve device of claim 7, wherein said synthetic biocompatible material is selected from the group consisting of polytetrafluoroethylene, polyester, metal, metal alloy including combinations thereof.

9. (original) The percutaneously implantable heart valve device of claim 1, wherein said stent member is self-expanding when implanted.

10. (original) The percutaneously implantable heart valve device of claim 1, wherein said stent member is balloon catheter expandable when implanted.

11. (withdrawn) A method of making a percutaneously implantable replacement heart valve device comprising the following steps: obtaining a sheet of biocompatible tissue material; drying said biocompatible tissue material; folding said dried biocompatible tissue material to create inner cusps or leaflets and an outer tubular cuff structure without affixing of separate cusps or leaflets or cutting slits into said material to form said cusps or leaflets; affixing said folded biocompatible tissue material at one or more points on its outer surface to the inner cavity of a stent; and soaking said biocompatible tissue material in one or more alcohol solutions and a solution of gluteraldehyde.

12. (withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said soaking step comprises soaking said biocompatible tissue material in a solution of isopropyl alcohol, a solution of ethanol, a solution of glycerol and a solution of gluteraldehyde.

13. (withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material comprises bovine pericardium tissue.

14. (withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material comprises porcine pericardium tissue.

15. (withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material is obtained from a juvenile animal pericardium.

16. (withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material comprises autologous tissue obtained from the patient into whom said replacement heart valve device will be implanted.

17. (withdrawn) The percutaneously implantable heart valve device of claim 11, wherein said biocompatible tissue material of said artificial valve comprises a synthetic biocompatible material.

18. (withdrawn) The percutaneously implantable heart valve device of claim 17, wherein said synthetic biocompatible material is selected from the group consisting of polytetrafluoroethylene, polyester, metal, metal alloy including combinations thereof.

19. (withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said stent is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium and stainless steel.

20. (withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said stent is self-expanding when implanted.

21. (withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said stent is balloon catheter expandable when implanted.

22. (withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, further comprising the step of cleaning said biocompatible tissue material using hydromechanical force means.

23. (withdrawn) The method of making a percutaneously implantable replacement heart valve of claim 11, further comprising the step of compressing said biocompatible tissue material.

24. (withdrawn) The method of making a percutaneously implantable replacement heart valve of claim 11, further comprising the step of gas sterilization of said biocompatible tissue material.

25. (withdrawn) The method of making a percutaneously implantable replacement heart valve of claim 11, wherein said drying step comprises photomechanical compression of said biocompatible tissue material.

26. (withdrawn) The method of making a percutaneously implantable replacement heart valve of claim 11, wherein said folding step comprises folding of a first piece of said biocompatible tissue material to create an outer tubular cuff structure, folding of a second separate piece of biocompatible tissue material to create inner cusps or leaflets without affixing of separate cusps or cutting slits into said second separate piece of biocompatible tissue material, and affixing said second separate piece to said first piece.

27. (original) A percutaneously implantable replacement heart valve device comprising an expandable stent member and a flexible, compressible artificial valve made of biocompatible tissue material and disposed within the inner cavity of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising a leaflet or cusp portion formed by folding of a first sheet portion of said biocompatible tissue material without affixing of separate cusps or leaflets or cutting slits into said sheet to form said cusps or leaflets, and an outer tubular cuff structure formed by folding a second sheet portion of biocompatible tissue material, said first and second sheet portions being affixed together.

28. (original) The device of claim 27, wherein said first sheet portion and said second sheet portions are affixed together by suturing.

29. (original) The device of claim 28, wherein said suturing is in the form of double continuous sutures.

30. (original) A percutaneously implantable replacement heart valve device comprising an outer cylindrical cuff portion and an inner uncut/unslit leaflet layer attached within said outer cuff portion.

31. (original) The device of claim 30, wherein said leaflet layer is attached within said outer cuff portion by suturing.

32. (original) The device of claim 31, wherein said suturing is in the form of double continuous sutures.

33. (original) A percutaneously implantable replacement heart valve device comprising an expandable stent member and a flexible, compressible artificial valve made of biocompatible tissue material and disposed within the inner cavity of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising a leaflet or cusp portion formed by folding of a first sheet portion of said biocompatible tissue material without affixing of separate cusps or leaflets or cutting slits into said sheet to form said cusps or leaflets.

Remarks

Claims 1-10 and 27-33 remain in the application. The Applicants note the examiner's request for a sample of the device or other materials to assist the examiner in understanding the invention, and will provide such materials separately as soon as possible. Nonetheless, should the examiner have any comments, questions or suggestions, the examiner is respectfully requested to telephone the undersigned at the telephone number listed below.

Respectfully submitted,

Date: October 10, 2007

GREENBERG TRAURIG, P.A.
1221 Brickell Avenue
Miami, Florida 33131
Tel: (305) 579-0812
Fax: (305) 579-0717

Manuel R. Valcarcel, Esq.
Reg. No. 41,360

MIA 179765011v1

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PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 10/887,688	Filing Date 07/10/2004	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☒		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			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 $250 ($125 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			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	10/10/2007	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 17	Minus	** 33	= 0	X $25 =	0	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 2	Minus	***5	= 0	X $105 =	0	OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE	

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	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.

Legal Instrument Examiner:
Linda Wise

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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/887,688	07/10/2004	David Paniagua	51458.010100	4909

54353 7590 11/28/2007

MANUEL VALCACEL
c/o GREENBERG TRAURIG, P.A.
1221 BRICKELL AVENUE
MIAMI, FL 33131

EXAMINER	
MILLER, CHERYL L	
ART UNIT	**PAPER NUMBER**
3738	

MAIL DATE	DELIVERY MODE
11/28/2007	PAPER

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.

PTOL-90A (Rev. 04/07)

Office Action Summary	Application No.	Applicant(s)	
	10/887,688	PANIAGUA ET AL.	
	Examiner	Art Unit	
	Cheryl Miller	3738	

-- 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 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *10 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ 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

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *11-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 27-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ 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).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

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).

a)☐ All b)☐ Some * c)☐ None of:

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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Invention 1, claims 1-10 and 27-33 is acknowledged. Claims 11-26 are withdrawn from examination by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> 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 1-10, 27-29 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the inner cavity" in line 3. There is insufficient antecedent basis for this limitation in the claim. Claims 2-10 depend upon claim 1 and inherit all problems with the claim.

Claims 7 and 8 are rendered indefinite since the independent claim requires the valve to be made of biocompatible tissue and claims 7 and 8 are attempting to alter the claim to make the tissue synthetic. It is unclear how biocompatible tissue may be also synthetic.

Claim 27 recites the limitations "the inner cavity" and "said sheet" in lines 3 and 7 respectively. There is insufficient antecedent basis for these limitations in the claim. Claims 28-29 depend upon claim 27 and inherit all problems associated with the claim.

Claim 33 recites the limitations "the inner cavity" and "said sheet" in lines 3 and 7 respectively. There is insufficient antecedent basis for these limitations in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 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 –
>
> (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 1, 2, 7, 9, 10, and 27-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Spenser et al. (US 2003/0153974 A1). Spenser discloses an implantable heart valve (20; fig.1) comprising an expandable stent (22) and an inner flexible compressible valve (26) made of biocompatible tissue (P0099) disposed within the stent (22) and affixed to the stent (at 25; P0103) the valve having leaflets without slits (see fig.1; valve body disclosed as a conduit; P0108). Spenser discloses the stent to be made of the materials claimed (nitinol; P0100). Spenser discloses the valve to be formed of biological or synthetic materials (P0099). Spenser's valve is capable of self-expansion or balloon expansion (P0100, P0098). Spenser discloses an outer cuff portion (21). Spenser disclosed the cuff (21) and valve leaflets (26) sutured (46) to stent support rails (23; P0109; P0119; fig.9d, 9a, 2), thus they are attached to one another by sutures. Referring to the claim recitation, "formed by folding of a sheet of said biocompatible tissue material without affixing of separate cusps or leaflets or cutting slits into said material to form said cusps or leaflets", this is a product by process limitation is weight is given only to the end product, not the method of forming. See MPEP 2113.

Claims 1, 2, 7-10, 27, 30, and 33 are rejected under 35 U.S.C. 102(e) as being anticipated by Bailey et al. (US 6,652,578). Bailey discloses an implantable heart valve (fig.2, 8, 14) comprising an expandable stent (12) and an inner flexible compressible valve (26) made of biocompatible tissue (col.8, lines 47-49) disposed within the stent (12) and affixed to the stent (col.9, lines 55-59) the valve having leaflets without slits (see fig.2; valve body disclosed as a tubular graft extension, col.9, lines 7-26). Bailey discloses the stent (12) to be made of the materials claimed (nitinol; col.8, lines 13-18). Bailey discloses the valve to be formed of biological or synthetic materials (col.8, lines 46-49). Bailey's valve is capable of self-expansion or balloon expansion (col.8, lines 13-18). Bailey discloses an outer cuff portion (considered either 11a or 11b). Referring to the claim recitation, "formed by folding of a sheet of said biocompatible tissue material without affixing of separate cusps or leaflets or cutting slits into said material to form said cusps or leaflets", this is a product by process limitation is weight is given only to the end product, not the method of forming. See MPEP 2113.

Claim Rejections - 35 USC § 103

The following is a quotation of 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 3-6 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spenser et al. (US 2003/0153974 A1). Spenser discloses an implantable valve, the valve being formed of either a biological pericardium tissue or biocompatible synthetic polymer (P0099). Spenser does not however, disclose the specific type of pericardium or synthetic polymer (such as claimed,

mammal, porcine, or juvenile pericardium or PTFE or polyester biopolymers). It would have been obvious to one having ordinary skill in the art at the time the invention was made to have the specific pericardium sources claimed or biopolymers, since it has been held to be within the general skill of a worker in the art to select a known material (PTFE, polyester, mammal, porcine, juvenile pericardium) on the basis of its suitability for the intended use (valve replacement) as a matter of obvious design choice. *In re Leshin*, 125 USPQ 416.

Claims 3-6, 28-29 and 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bailey et al. (US 6,652,578 B2). Referring to claims 3-6, Bailey discloses an implantable valve, the valve being formed of either biological tissue or biocompatible synthetic polymer (col.8, lines 46-49). Bailey does not however, disclose a specific type of biological material (such as claimed, mammal, porcine, or juvenile pericardium or PTFE or polyester biopolymers). It would have been obvious to one having ordinary skill in the art at the time the invention was made to have the specific biological materials claimed, since it has been held to be within the general skill of a worker in the art to select a known material (mammal, porcine, juvenile pericardium) on the basis of its suitability for the intended use (valve replacement) as a matter of obvious design choice. *In re Leshin*, 125 USPQ 416.

Referring to claims 28-29 and 31-32, Bailey discloses attachment of the cuff (11a) to the valve (11b extension 26; col.9, lines 10-19), however is silent to mention how the members are coupled. It would have been obvious to one having ordinary skill in the art at the time the invention was made to use sutures, double sutures to attach the two membranes (cuff and valve) since suturing is a common means of attachment in the vascular art and would be applicable to Bailey's invention. See Fogarty et al, US 6,491,719 B1; col.10, lines 5-8 as evidence of common

means of attaching layers of material (31, 32) in the vascular art which include stitching, welding, adhering.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cheryl Miller whose telephone number is (571) 272-4755. The examiner can normally be reached on Monday-Friday 7:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Corrine McDermott can be reached on (571) 272-4755. 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.

/Cheryl Miller/

BRUCE SNOW
PRIMARY EXAMINER

Notice of References Cited	Application/Control No. 10/887,688	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-2003/0153974 A1	08-2003	Spenser et al.	623/2.11
*	B	US-6,652,578 B2	11-2003	Bailey et al.	623/1.24
*	C	US-2001/0010017 A1	07-2001	Letac et al.	623/2.11
*	D	US-6,491,719 B1	12-2002	Fogarty et al.	623/1.37
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	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.

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/887,688	PANIAGUA ET AL.	
	Examiner	Art Unit	
	Cheryl Miller	3738	

SEARCHED			
Class	Subclass	Date	Examiner
623	1.24, 1.26, 2.12-2.19, 900	11/25/2007	CM

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR

Greenberg Traurig

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02-29-08 IFW

February 27, 2008

VIA EXPRESS MAIL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Re: U.S. Patent Application No. 10/887,688
Invention: Percutaneously implantable replacement heart valve device and method of making same
Response to Office Action No. 2
Our Ref. No. 051458.010100

Dear Sir:

Enclosed under cover of this transmittal letter is a response to office action no. 2 in the above-referenced application.

Please charge and any required fees for the enclosed submission to Deposit Account No. 50-1792.

Please confirm receipt of the enclosed documents by date-stamping and returning the enclosed postage paid return postcard. Please direct all communications regarding the foregoing to the undersigned.

Respectfully submitted,

GREENBERG TRAURIG, P.A.

by /Valcarcel/

Manuel R. Valcarcel, Esq.
Reg. No. 41,360

EXPRESS MAIL MAILING LABEL NO. EH 041385288 US

MRV/mam
Enclosures

cc: David Paniagua, M.D.

MIA 179,967,083v1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of
Paniagua, et al.
Serial No. 10/887,688
Filed: July 10, 2004
Invention: Percutaneously Implantable Replacement Heart Valve Device and Method of Making Same

Examiner: Cheryl Miller
Group Art Unit 3738

RESPONSE TO OFFICE ACTION No. 2

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

In response to Office Action No. 2 dated November 28, 2007 in the above-referenced application, the Applicants respectfully submit this response. Claim amendments begin on page 2. Remarks begin on page 9. A Declaration under 37 C.F.R. § 1.131 is enclosed antedating both the Spenser, et al. reference (US 2003) 0153974A1) and the Bailey et al. reference (6,652,578B2).

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AMENDMENTS TO THE CLAIMS

The following listing will replace all prior versions of the claims in the application:

1. (currently amended) A percutaneously implantable replacement heart valve device comprising an expandable stent member having an inner space and a flexible, compressible artificial valve ~~made of biocompatible tissue material and~~ disposed within said inner space~~the inner cavity~~ of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve having a cusps or leaflets portion comprising a ~~formed by folding of a~~ folded unslit sheet of ~~said~~ biocompatible tissue material without ~~affixing of~~ separate cusps or leaflets affixed thereto ~~or cutting slits into said material to form said cusps or leaflets~~.

2. (original) The percutaneously implantable replacement heart valve device of claim 1, wherein said expandable stent member is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium and stainless steel.

3. (original) The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible tissue material of said artificial valve comprises mammal pericardium tissue.

4. (original) The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible tissue material of said artificial valve comprises porcine pericardium tissue.

5. (original) The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible tissue material of said artificial valve is obtained from a juvenile animal pericardium.

6. (original) The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible tissue material of said artificial valve comprises autologous tissue obtained from the patient into whom said replacement heart valve device will be implanted.

7. (original) The percutaneously implantable heart valve device of claim 1, wherein said biocompatible tissue material of said artificial valve comprises a synthetic biocompatible material.

8. (original) The percutaneously implantable heart valve device of claim 7, wherein said synthetic biocompatible material is selected from the group consisting of polytetrafluoroethylene, polyester, metal, metal alloy including combinations thereof.

9. (original) The percutaneously implantable heart valve device of claim 1, wherein said stent member is self-expanding when implanted.

10. (original) The percutaneously implantable heart valve device of claim 1, wherein said stent member is balloon catheter expandable when implanted.

11. (previously withdrawn) A method of making a percutaneously implantable replacement heart valve device comprising the following steps: obtaining a sheet of biocompatible tissue material; drying said biocompatible tissue material; folding said dried biocompatible tissue material to create inner cusps or leaflets and an outer tubular cuff structure without affixing of separate cusps or leaflets or cutting slits into said material to form said cusps or leaflets; affixing said folded biocompatible tissue material at one or more points on its outer surface to the inner cavity of a stent; and soaking said biocompatible tissue material in one or more alcohol solutions and a solution of gluteraldehyde.

12. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said soaking step comprises soaking said biocompatible tissue material in a solution of isopropyl alcohol, a solution of ethanol, a solution of glycerol and a solution of gluteraldehyde.

13. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material comprises bovine pericardium tissue.

14. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material comprises porcine pericardium tissue.

15. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material is obtained from a juvenile animal pericardium.

16. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material comprises autologous tissue obtained from the patient into whom said replacement heart valve device will be implanted.

17. (previously withdrawn) The percutaneously implantable heart valve device of claim 11, wherein said biocompatible tissue material of said artificial valve comprises a synthetic biocompatible material.

18. (previously withdrawn) The percutaneously implantable heart valve device of claim 17, wherein said synthetic biocompatible material is selected from the group consisting of polytetrafluoroethylene, polyester, metal, metal alloy including combinations thereof.

19. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said stent is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium and stainless steel.

20. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said stent is self-expanding when implanted.

21. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said stent is balloon catheter expandable when implanted.

22. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, further comprising the step of cleaning said biocompatible tissue material using hydromechanical force means.

23. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve of claim 11, further comprising the step of compressing said biocompatible tissue material.

24. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve of claim 11, further comprising the step of gas sterilization of said biocompatible tissue material.

25. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve of claim 11, wherein said drying step comprises photomechanical compression of said biocompatible tissue material.

26. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve of claim 11, wherein said folding step comprises folding of a first piece of said biocompatible tissue material to create an outer tubular cuff structure, folding of a second separate piece of biocompatible tissue material to create inner cusps or leaflets without affixing of separate cusps or cutting slits into said second separate piece of biocompatible tissue material, and affixing said second separate piece to said first piece.

27. (currently amended) A percutaneously implantable replacement heart valve device comprising an expandable stent member having an inner space and a flexible, compressible artificial valve made of biocompatible tissue material and disposed within said inner space~~the inner cavity~~ of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising a leaflet or cusp portion formed by folding of a first sheet portion of said biocompatible tissue material without affixing of separate cusps or leaflets or cutting slits into said first sheet portion to form said cusps or leaflets, and an outer tubular cuff structure formed by folding a second sheet portion of biocompatible tissue material, said first sheet portion and second sheet portions being affixed together.

28. (original) The device of claim 27, wherein said first sheet portion and said second sheet portions are affixed together by suturing.

29. (original) The device of claim 28, wherein said suturing is in the form of double continuous sutures.

30. (original) A percutaneously implantable replacement heart valve device comprising an outer cylindrical cuff portion and an inner uncut/unslit leaflet layer attached within said outer cuff portion.

31. (original) The device of claim 30, wherein said leaflet layer is attached within said outer cuff portion by suturing.

32. (original) The device of claim 31, wherein said suturing is in the form of double continuous sutures.

33. (currently amended) A percutaneously implantable replacement heart valve device comprising an expandable stent member having an inner space and a flexible, compressible artificial valve made of biocompatible tissue material and disposed within said inner space~~the inner cavity~~ of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising a leaflet or cusp portion formed by folding of a first sheet portion of said biocompatible tissue material without affixing of separate cusps or leaflets or cutting slits into said sheet to form said cusps or leaflets.

34. (new) A percutaneously implantable replacement heart valve device comprising an expandable stent member having an inner space and a flexible, compressible artificial valve having a generally tubular portion and a peripheral upstanding cusp or leaflet portion disposed within said inner space of said stent member and affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising a continuous uncut, unslit sheet of biocompatible tissue material having an upper border with an outward fold, a lower border with an inward fold, a first edge and a second edge, said first edge and second edge being disposed perpendicular to said upper border and said lower border, said first edge being

joined to said second edge to form said generally tubular portion having an inner space, with said inner fold being disposed within said inner space of said generally tubular portion.

35. (new) A percutaneously implantable replacement heart valve device comprising:

an expandable stent member having an inner space, and

a flexible, compressible artificial valve disposed within said inner space of said stent member, affixed at one or more points on said artificial valve's outer surface to said stent member, comprising a first single continuous uncut, unslit sheet of biocompatible tissue material having an upper border, a lower border opposite and parallel to said upper border, an inner fold disposed at said lower border, and two opposite edges perpendicular to said upper border and said lower border and joined to eachother, and a second sheet of biocompatible tissue material having an upper border with an outward fold and a lower border opposite and parallel to said upper border, and having two opposite edges perpendicular to said upper border and said lower border and joined to eachother, said upper border of said first sheet joined to said lower border of said second sheet.

36. (new) A percutaneously implantable replacement heart valve device comprising an expandable stent member having an inner space and a flexible, compressible artificial valve disposed within said inner space of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising a generally tubular portion and a cusp or leaflet portion, said generally tubular portion and said cusp or leaflet portion comprising a folded unslit sheet of biocompatible tissue material without separate cusps or leaflets affixed thereto.

Remarks

The Applicants have noted the examiner's Section 112, 102(e) and 103 rejections of the claims and respectfully request reconsideration and withdrawal of said rejections based on the claim amendments and remarks contained in this response as well as the Applicant's Declaration under 37 CFR §1.131 antedating U.S. Patent Application Publication No. US2003/0153974A1 by Spenser, et al. and U.S. Patent No. 6,652,578B2 to Bailey. Claims 1-10 and 27-33, as amended, remain in the application. New claims 34-36 have been added. Please charge the fee for addition of said claims and any other required fee to Deposit Account No. 50-1792.

Claims 1, 27 and 33 have been amended to include antecedent basis for the limitation "the inner cavity" (revised to "inner space" which is supported by paragraph 0024 of the specification as published, at line 6 of said paragraph). Such claims were also amended to provide antecedent basis for "sheet" to address the examiner's Section 112, second paragraph rejection. With regard to the examiner's indefiniteness rejection with respect to claims 7 and 8, the Applicants respectfully submit that synthetic tissue can be biocompatible and needs to be, to be useful. "Biocompatible" is generally understood to mean being biologically compatible by not producing a toxic, injurious, or immunological response in living tissue The Applicants respectfully request that the examiner withdraw the Section 112 rejections.

With respect to the examiner's Section 102(e) and 103(a) rejections, the Applicants respectfully submit the enclosed Declaration under 37 CFR §1.131 antedating U.S. Patent Application Publication No. US2003/0153974A1 by Spenser et al. as well as U.S. Patent No. 6,652,578B2 to Bailey. In addition, while the cited references are effectively overcome by antedating, the Applicants note their disagreement with the examiner's assertion that the product by process limitations in claims 1-33 should not be given weight because they impart structural

limitations, namely, folds, rather than slits or sutures connecting separate leaflet pieces, and thereby impart a number of advantages over prior devices, including reducing susceptibility to failure by improving resistance to tearing of leaflets, and providing a more closely resembling the form and function of a native heart valve. "The structure implied by the process steps should be considered when assessing the patentability of product by process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process would be expected to impart distinctive structural characteristics to the final product." MPEP Section 2113 (citing *In re Garnero*, 412 F.2d 276, 279 (CCPA 1979)). The Applicants therefore respectfully request withdrawal of the examiner's Section 102(e) and Section 103(a) rejections and allow the present case. Nonetheless, should the examiner have any comments, questions or suggestions, the examiner is respectfully requested to telephone the undersigned at the telephone number listed below.

Respectfully submitted,

Date: February 27, 2008

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MIA 179,917,332v1

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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

In re the application of:	)	
	)	
Paniagua, et al.	)	Group Art Unit 3738
Serial No. 10/887,688	)	
Filed: 7/10/2004	)	Examiner: Miller, Cheryl L.
	)	

For: Percutaneously Implantable Replacement Heart Valve Device and Method of Making Same

DECLARATION UNDER 37 CFR 1.131

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia

Sir:

State of (various)	)	
	)	S.S.
	)	
County of (various)	)	

The undersigned co-inventors each hereby declare as follows:

1. I am a co-inventor of the invention claimed in the patent application identified above.

2. I was directly and personally involved in the conception and reduction to practice of the invention throughout the period from prior to December 31, 1999 until the filing date of U.S. Patent Application Serial No. 10/037,266 on January 4, 2002, of which the present application is a continuation in part.

3. Prior to December 31, 1999, the percutaneously implantable replacement heart valve device and method of making same described and claimed in the above-referenced application had been conceived in the U.S. by co-inventors David Paniagua and Francisco-Lopez Jimenez who were at the time cardiology fellows at Mount Sinai Medical Center in Miami Beach, Florida. Attached as Exhibit A is a copy of an electronic diary that was kept with respect to development of the invention by co-inventor Paniagua, with entries dating back to prior to December 31, 1999 indicating that the Applicants had by then already conceived of the invention. The dates for certain of the entries are blacked out but predate December 31, 1999.

4. During the time period from prior to December 31, 1999 through January 4, 2002, which is the filing date of Patent Application Serial No. 10/037,266, to which the above-referenced application is a continuation in part and claims priority, efforts to reduce the invention

to practice in the U.S. were undertaken diligently. The first prototypes and the method of making same of the invention were created and tested. A protocol for in-vitro testing was written by Co-Inventor Paniagua in the early months of 2000. The in-vitro model consisted of a plastic hose tubing filled with a 30% solution of glycerol to resemble blood viscosity, a continuous pump, pressure recording instruments and pressure generating clamps. The study indicated excellent opening and closing profiles of the valve with no evidence of regurgitation even at pressures of 200 mmHg.

5. During the time period from prior to December 31, 1999 through January 4, 2002, we also worked with diligence toward reduction to practice of the invention by preparing a written description of the invention (see copy of a later draft dated April 22, 2001, attached hereto as Exhibit B).

6. During the time period from prior to December 31, 1999 through January 4, 2002, we also worked with diligence toward reduction to practice of the invention by conducting various tests and trials relating to preparation of the valve starting material, formation of the valve, optimal stent composition and configuration, attachment of the valve to the stent and attachment of the stented valve to an artery. See the attached entries from the electronic diary attached hereto as Exhibit A, which include entries relating to tests regarding preparation of the valve starting materials and formation of the valve in October, November and December 2000 and January, February, March, and June 2001. See also the attached entries from the electronic diary attached hereto as Exhibit A, which include entries pertaining to animal studies in June, September and November 2000 and April, 2001.

7. In August 2001, patent counsel was engaged to conduct a patent search directed to the invention and prepare and file a patent application for same. Enclosed as Exhibit C are copies of a search patent request letter dated August 29, 2001 which was sent to order a patent search for the invention, the invention being described in the letter. Said request letter was received by the patent search provider on August 30, 2001 as evidenced by the stamped confirmation of receipt attached to Exhibit C.

8. The patent search results were received on or about mid-September, 2001 and were reviewed by patent counsel, as well as by the undersigned, in the weeks that followed (bearing in mind that during such time period there were various office closures and disruptions due to the September 11, 2001 terrorist attacks and their immediate aftermath).

9. After the patent search results were reviewed and discussed with patent counsel, the patent application was prepared, reviewed, revised, figures for the application were prepared, and the application and figures were submitted on January 4, 2002, the Applicant's priority date. Attached as Exhibit D are copies of correspondence from patent counsel enclosing drafts of the patent application for the invention dated November 27, 2001 and December 28, 2001.

The undersigned co-inventors each hereby declare that all statements made herein of his own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

DAVID PANIAGUA

Signature: _____

Date: January 18, 2008

ACKNOWLEDGEMENT

COUNTY OF Brazoria)
) SS:
STATE OF Texas)

The foregoing Declaration was signed before me this 18th day of January, 2008 by David Paniagua. He is personally known to me or has produced drivers license as identification.

Notary: Janice D Kelley
Print Name: Janice D Kelley

[NOTARIAL SEAL]
Notary Public, 7/21/09

My commission expires:

JANICE D. KELLEY
MY COMMISSION EXPIRES
JULY 21, 2009

FRANCISCO LOPEZ-JIMENEZ

Signature: _____

Date: January 18, 2008

ACKNOWLEDGEMENT

COUNTY OF Olmsted)
) SS:
STATE OF Minnesota)

The foregoing Declaration was signed before me this 18th day of January, 2008 by Francisco Lopez-Jimenez. He is personally known to me or has produced _____ as identification.

Notary: Vicki Virginia Yount [NOTARIAL SEAL]
Print Name: Vicki Virginia Yount Notary Public, _____

VICKI VIRGINIA YOUNT
Notary Public-Minnesota
My Commission Expires Jan 31, 2010

My commission expires: January 31, 2010

CARLOS MEJIA

Signature: Carlos Mejia

Date: January 21st, 2008

ACKNOWLEDGEMENT

COUNTY OF Brazoria)
) SS:
STATE OF Texas)

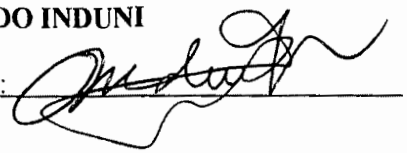
The foregoing Declaration was signed before me this 21st day of January, 2008 by Carlos Mejia. He is personally known to me or has produced Drivers License as identification.

Notary: Janice D Kelley [NOTARIAL SEAL]
Print Name: Janice D Kelley Notary Public, _____

My commission expires: 7/21/09

JANICE D. KELLEY
MY COMMISSION EXPIRES
JULY 21, 2009

EDUARDO INDUNI

Signature: 

Date: January 18, 2008

ACKNOWLEDGEMENT

COUNTY OF _____)
) SS:
STATE OF _____)

The foregoing Declaration was signed before me this ____ day of January, 2008 by Eduardo Induni. He is personally known to me or has produced _____ as identification.

Notary: _____ [NOTARIAL SEAL]
Print Name: _____ Notary Public, _____

My commission expires:

R. DAVID FISH

Signature: RDFish

Date: January 18, 2008

ACKNOWLEDGEMENT

COUNTY OF Brazoria)
) SS:
STATE OF Texas)

The foregoing Declaration was signed before me this 18th day of January, 2008 by R. David Fish. He is personally known to me or has produced drivers license as identification.

Notary: Janice D Kelley
Print Name: Janice D Kelley

[NOTARIAL SEAL]
Notary Public, 7/21/09

My commission expires:

MIA 179,917,544v1

JANICE D. KELLEY
MY COMMISSION EXPIRES
JULY 21, 2009

St Lizy Project: A new percutaneous device to decrease Valvular insufficiency

[redacted]

David Paniagua and **Francisco Lopez-Jimenez** (cardiology fellows at that time) discussed the need to develop a percutaneous valve. This discussion took place in the cardiology fellow's room at Mount Sinai Medical Center in Miami Beach Florida.

After this initial discussion a careful and extensive literature search was started. All articles in the field were reviewed as well as all information regarding patents filed.

[redacted]

The candidate stents that we thought of using in our project were: balloon expandable and self-expandable stents. The balloon expandable stents have been used in the past in two animal experiments reported in the literature. One of them was in Denmark and the other in New York. No other study has been reported after these two original reports. No one has implanted a percutaneous valve in a human being. We believe that the main limitation of the balloon expandable stents is its bulky design.

Among the self-expandable stents, we decided to start using in the first phase the Wallstent and we were planning to use the Smart stent in the second phase. These self-expandable stents has never been used for percutaneous implantation of a valve.

The **Wallstent** is a stainless steel self-expandable stent (Boston Scientific, Boston, MA) that has been used in human since 1987. The main advantage of this stent is its protruding metal wires suitable for fixation in the arterial wall. The main limitation is that the length of the stent changes significant from the collapsed state to the expanded state.

The **SMART** is a stent made of smart material, nitinol an alloy of [redacted]. It has the particularity that the stent changes form with temperature. The Smart stent expands when it is in contact with body temperature. The main advantages on the other hand that its length in the collapse and expanded state is quite similar.

The valves that we thought of placing in the stent: porcine pulmonary valve, porcine aortic valve, a new special valve made of bovine pericardium or a valve made of smart materials.

David Fish suggested the utility of using Smart materials in the development of the valve.

September to December 1999
Anatomical studies in animals
David Paniagua and his wife Elizabeth while in Houston, Texas studied more than 100 porcine aortic and pulmonary valves as well as the aortic arch. Carefull measurement of the valve length, cusp length, vertical diameters, attachment points, interaction with the other cusps, interaction with the Sino tubular junction, coronary ostium. Characteristics of the opening and closing, redundancy of the tissue, sinus of Valsalva measurements

[redacted]

On a trip to Vienna, Austria; Francisco Lopez-Jimenez and David Paniagua discussed all the research synthesis. The pros and cons of different options were discussed and finally a strategy to develop our new percutaneous valve took place.

Porcine pulmonary valve

The main advantage of this valve is the thickness of the arterial wall is significantly less than the aortic wall.

Limitations Still bulky

Porcine aortic valve

Limitations Still bulky and the ostium of both coronaries

Bovine pericardium

We designed a new model of valve with special features to be suitable to use in the stent.

<u>The bovine pericardium</u>

Design

The horizontal length of the stent is equal to diameter x π.
The vertical length suffer a lot of modifications in the last 18 months

The process of management of the pericardium

The pericardium is membrane that surrounds the heart and isolates it from the rest of the chest wall structures.

The pericardium is a thin and very slippery, what makes it difficult for suturing in a millimetric precise way that is required for the valve that we were planning to develop.

Carlos Mejia is a High-Fashion tailor with experience in tissue management, leather, wool, cotton, etc. developed a process to dry the pericardium in such a way that makes it possible to handle the way we needed.

Dry process

Since the pericardium is such a slippery material we started looking the way to make it easier to manipulate.

We try to dry it at room temperature, but se hacia muy duro y corrugado tieso

Then we try ironing and it shrinks to much and corrugate

We try with artificial light using a 60-watt lamp reflecting its light to the pericardium that was placed in a flat aluminium surface to dry it homogeneously

We also tried to photo drying machine.

When we dry it this way, the final result was an homogeneous tissue that looked like a plastic paper and makes it easy to manipulate to suture the valve.

Hydrating process

Once the valve was done we hydrated the valve back again by placing it in a solution of water and 70% alcohol. In approximately 3 days the valve hydrate back again.

Converting the pericardium into a valve

David Paniagua and **Eduardo Induni** (a cardiovascular surgeon) discussed the best way to suture a flat pericardium and converted into a complete valve.

Many designs were made in paper until we developed a working model in that resembles the human valve.

See diagrams

Types of sutures

Sutures planes

Francisco Lopez-Jimenez introduced the trapezoid modification
We tested the trapezoid modification but it did not work. It introduces too much redundant tissue.

Attachment of the valve to the stent
3-point fixation on border of the stent

6-point fixation at each border of the stent

Fixation on both borders 18 points at each end following a single plane
36 fixation points following to adjacent vertical planes.

Fixation without any fold in the border resulted in tears, so we made a fold that resolved the problem.

Attachment of the valve to the aorta
R. David Fish suggested the possibility of attaching the mother stent to the subclavian artery using a daughter stent deployed first in the subclavian artery and attached to the mother stent that will be deployed in the descending aorta.

Hooks to the arterial wall Like the Ancure

Double stents

Acute Doppler studies in vitro

Francisco Lopez-Jimenez and David Paniagua performed the first Doppler studies in an in-vitro model.

The model consisted of a plastic hose tubing filled with a 30% solution of glycerol to resemble the blood viscosity, a continuous pump, pressure recording instruments and pressure generating clamps.

In this acute in vitro study we document excellent opening and closing profile of the valve. There was no evidence of regurgitation even at pressures of 200 mmHg.

See video

October 5th to 11th 2000

We studied different ways to fix the pericardium.

1- Piece of pericardium-- dried with light in our standard procedure then placed in glutaraldehyde for 36 hours and hydrate back in alcohol 70%. It looses resistant and it breaks easily.

2- Natural pericardium that was in alcohol solution for 2 months at least and we fix it with gluteraldehyde for 36 hours and then place in the alcohol solution with excellent results in terms of tissue resistance. We were not able to break it.

3 We fix a piece of diaphragm after drying it with light and then gluteraldehyde and we obtained the same result than with the pericardium.. The tissue resistance significant decreased and we were able to tear the tissue.

4 We placed a previously done valve in the stent in the gluteraldehyde solution for 36 hours to fix it and later put it back in the alcohol solution

5 Pericardium dried with light then hydrate with alcohol until it is completely hydrated and then fix it with gluteraldehyde for 36 hours and then re hydrate it back again.

6 Pericardium fix with gluteraldehyde for 36 hours and then dry it with light.

Delivery device

Chronic studies in vitro

On Sep 17 2001, we created a chronic model to test the valve. The model consisted of a pump attached to an 18 mm tubing system that is also attached to a 3 liters container that is placed 180 cms above the pump.

The stented valve was placed at the bottom of a 180 cm water column to mimic the diastolic pressure.

Histological studies

Preservation of the pericardium several month in ETOH

Glutaraldehido

[redacted]

E-mails

[redacted]

Materials

Calf
The device Delivery system
Cook needle Wires
Pigtails Dilators 11 F, 14F, 16F, 18F, 20F
Contrast media
Balloons PTA of the aorta.

Heparin Plavix for the animal

Surgical equipment

Echo Doppler

OR equipment cri solution

Injector X ray tech
Person in charge of anesthesia, monitoring

Circulating person	Endotracheal tube	IV fluids
IV connections	angiocaths	4 liter of IV fluids

Ventilators Lamps

KYJELLY	
ET TUBE	KETAMINE
ANTIBIOTICS	EMERGENCY DRUGS
HEPARIN	PROPOFOL XYLAZINE
XYLOCAINE	INJECTION T SPRAY
BETADINE	ALCOHOL

STERILE TOWELS T DRAPES
STERILE SURGICAL TRAY
RECTAL TEMP PROBE
STERILE BOWL FOR SALINE
NS SALINE D5RL
COLLOID
SYRINGES-DIFFERENT SIZES
NEEDLES- DIFFERENT SIZES
HEATING PAD
IV CATLETERS, TOURNIGUETS
VASCULAR CLAMPS
SUCTION CATLETERS
SCISSORS
SECADORA PELO

[redacted]

Carlos Mejia and David Paniagua meet to discuss and design the next experiment.

We reviewed the previous information in video tapes, all films were discussed with emphasis in how we can decrease the size of the valve to try to identify the optimal Dimension of the valves.

We are going to try a valve 10mm deep and the circumference of the valve is going to be 71 mm for a 24mm diameter stent. The width of each pocket is going to be 22 mm

We did the valve in a rubber model with 10 mm deep and it was competent, for this reason we decided to try it in the pericardium.

The change in dimension of the valve with hydration after it is place in alcohol is unpredictable at the present time.

We are going to make two valves

1- Following our previous method of drying the valve with light and sewing to the stent when it its dried and then hydrating it with alcohol. Same design than previously, with folds.
2- A valve with pericardium fixed with gluteraldehyde. No folds in the upper part.

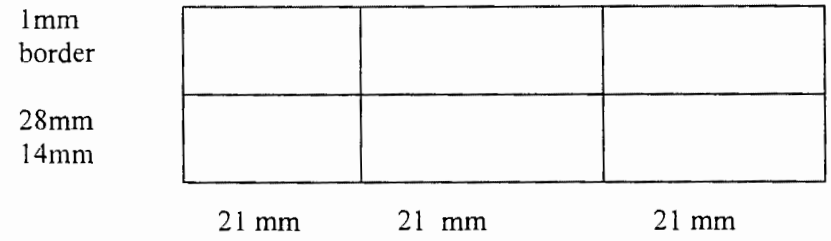
December 2 2000

Eduardo Induni, Carlos Mejia, David Paniagua review all the data collected so far in all the previous experiments and plan a strategy.
We found out that the material needs to be fix with gluteraldehyde before we implant the device. We study different concentrations of gluteraldehyde to fix the valve.

Finally we conclude that we the best is to fix the valve with 0.7% gluteraldehyde and keep it in this solution until the time to use it. At this moment we need to put the valve in normal saline before we implant it

January 2001

We designed a new valve with modification of its length. The pericardium was fixed with gluteraldehyde at 0.7% and later we did the valve and kept it in the same solution until the time to implant it.
During the creation of the valve constant hydration was maintain with frequent immersion of the pericardium in gluteraldehyde.



1 mm at each end to suture the valve.

February 2001

David Fish, Eduardo Induni and David Paniagua review the new stent-pericardium-valve and discussed the design improvement and decided to implant it in a new animal experiment.

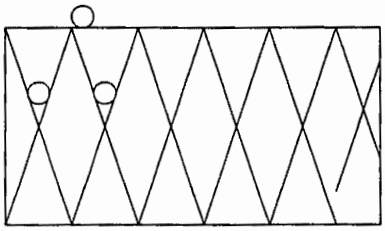
[redacted]

The valve required 7-0 prolene, 24-inch long 10 packs
3 to suture the valve and 7 to attach the valve to the stent.

The valve was attached to a 24 mm maximal diameter Wallstent.

We eliminate the folds at each end of the valve.

The valve was fixed in its **superior border** using two fixation planes with 18 fixation points at each plane.



○ Fixation points

18 fixation points at each plane

There are two rows of fixation point at the upper or proximal end of the stent and one row of fixation point at the lower or distal end of the stent.

Each fixation point was knotted 5 times in the upper plane and 7 knots in the lower plane.

The fixation of the **inferior border** of the valve to the stent was done with a single plane with 18 fixation points. Each fixation point was knotted 7 times using prolene 7-0.

The vertical fixation of the valve to the stent was done along the suture line of each cusp of the valve. We used 3 fixation points at each vertical suture line. Each fixation point was knotted 7 times.

The vertical fixation was mildly loose to allow easy collapsibility of the valve.

The approximate time to suture and attach the valve was 10 hours.

The stent-valve is maintained in 0.7% glutéraldehyde solution.

March 24, 2001

We plan to place the valve in a chronic in vitro model to evaluate its chronic function.

We will perform collapsibility test of the valve.

The delivery system that we plan to use is the AneuRx deployment device.

April 21, 2001

We did an animal experiment in Costa Rica, see description in animal studies.

June 9, 2001

Carlos Mejia and David Paniagua in Miami got together to discuss about the evolution of the valve.

We were discussing how to reduce the dimension to the optimal size of the valve and prevent valvular folds.

The last valve length was 65 mm after fixation, but if you pull it to its maximum length it grows 10 mm more up to 75 mm. Carlos decreased the length of the valve to 55 mm and 57 mm. We were concerned about the elastic recoil of the pericardium once implanted in the valve, because if it is not tense the pericardium makes folds, we want to achieve the optimal length that does not produce folds and that it is not so tight that causes so much elastic recoil that does not allow the stent to expand.

We had the idea of fixing the valve in the closing position using tiny metallic clips to keep the cusps close to each other.

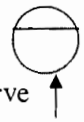
We tried the aortic valvuloplasty balloon to test if it can be used to expand the distal end of the stented valve in the case this extreme does not open.

We tried the consistency of different suture materials: Ticro 4-0, braided nylon and prolene. We discussed pros and cons of monofilament versus braided suture material.

June 12, 2001

At Carlos Mejia's' house we evaluated the design of the valve.

The new valve design includes the creation of a curve in each cusp of the valve



The other modification that we are doing in the handling process is to fix the pericardium in gluteraldehyde and transfer it to a solution of alcohol while making the valve and attaching it to the stent.

We changed the attachment position of the valve to be closer to the proximal and wider part of the Walstent, based on the previous experience during the animal study Alba.

We discussed the use of a pericardium piece fix in glutaraldehyde in a flat glass and the possibility of doing the valve with the natural pericardium and then fixing it with gluteraldehyde after mounting it in the stent.

One observation that we noted is that the material becomes whiter and apparently increases its elasticity

We obtained 1mm vascular clips to keep the cusps coapted while fixing them in gluteraldehyde.

June 13 2001

We evaluated the results of the use of metallic clips to keep both cusps adjacent to each other after 24 hours of fixation in gluteraldehyde. The results were very satisfactory to educate the material and make the primary position of the valve cusps adjacent to each other. After we removed the clips, there were no lesions to the valve. After doing this test, we use the metallic clips to keep both cusps together and immersed it in gluteraldehyde for 24 hours.

We evaluated different suture material that included praline 6-0 and Madrilène 6- 0 which is a braided suture.

We make more fixing fluid using gluteraldehyde 25% in a concentration of 3ml per 97 ml of fluid.

The pericardium of the first valve was in gluteraldehyde for 6 months approximately, then we put it in alcohol 60 during 2 to 3 days and after making the valve and placing in the transport fluid which consist of 60% alcohol.

June 16 2001

We were ready to perform another animal experiment in Costa Rica, but unfortunately all our equipment of dilator and the temporary delivery system was lost.

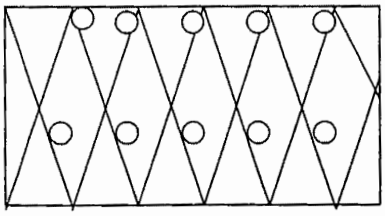
We developed a temporary delivery system that consisted of a central catheter big enough to let a 0.38 wire pass through its lumen, a cover sheath made of plastic material with a sliding device that allows to expose the stented valve.

Dr Eduardo Induni and David Paniagua discussed different ways to improve the collapsibility of the valve
The new observation was that the fixation points at the proximal part should be placed at the midpoint of the rhomboid structure to allow some mobility of the valve when we collapse it. This is true when using Walstent material not smart materials

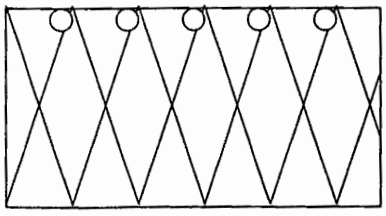
The other observation is that two planes of fixation point at the distal attachment of the valve to the stent causes a lot of tension to the valve when we are collapsing it.

One plane of fixation points will probably be enough to prevent systolic collapsed of the proximal edge of the valve

Proximal fixation points / expanded



Proximal fixation points sliding down



when stent collapses

○ ○ ○ ○ ○

○ Fixation points

18 fixation points at each plane

June 29, 2001

We discussed again the fixation points of the valve to the stent in such a way that they allow mobility of the stent over the valve without exerting too much tension. We believe this will allow better profile to the valve.

We also discussed the different suture materials and call Eduardo Induni and we make the decision that a braided suture is better than a monofilament, for this reason we are going to use mersilene which is a polyester braided suture.

[redacted]

September 8

Carlos Mejia and David Paniagua designed the in vitro model to test chronically the valve and list all the required material

September 22

The valve is mounted in the chronic testing model

Description of the model

United States Patent

Paniagua, Induni, Mejia, Lopez, Fish, April 22, 2001

PERCUTANEOUS VALVE REPLACEMENT

Abstract

The invention relates to a new technique and a special type of device that allows percutaneous heart-valve replacement without the need for open-heart surgery.

The valve replacement system includes the following components:

(1) A system for removing a damaged heart valve
(2) a delivery system of the prosthetic valve device
(3) a prosthetic valve device
(4) an implantation technique

Inventors:

David Paniagua
Eduardo Induni
Carlos Mejia
Francisco Lopez
R. David Fish

Exhibit B

U.S. Patent Documents

4056854	Nov.1977	Boretos et al.	623/2.
4631052	Dec., 1986	Kensey	606/159.
4883458	Nov., 1989	Shiber	606/159.
4966604	Oct., 1990	Reiss	606/159.
4979939	Dec., 1990	Shiber	606/159.
5007896	Apr., 1991	Shiber	606/159.
5011488	Apr., 1991	Ginsburg	606/159.
5026366	Jun., 1991	Leckrone	606/7.
5032128	Jul., 1991	Alonso	623/2.
5047041	Sep., 1991	Samuels	606/159.
5080660	Jan., 1992	Buelna	606/49.
5152771	Oct., 1992	Sabbaghian	606/159.

Foreign Patent Documents

WO91/17720	Nov., 1991	WO.
WO91/17118	Oct., 1992	WO.

Claims

What is claimed is:

1- An endovasculat system for delivering a heart valve.
2- An artificially percutaneous heart valve
3- An implantation technique

1. An endovascular system for delivering a replacement heart valve through an aortic passageway to or near to the location from which the natural heart valve has been removed, comprising:

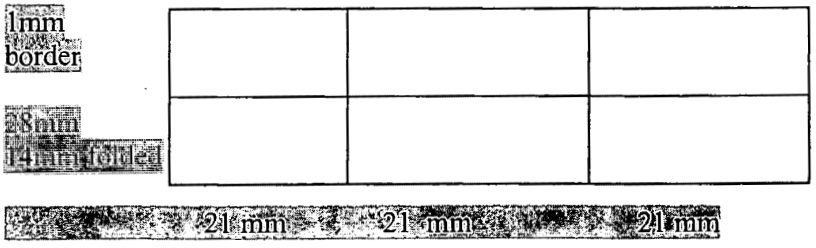
a- The delivery system has a central part which consist of a hollow tube that allows a metallic wire to be advanced inside it. The stented valve is collapsed over the central metallic tubing and it is covered by a movable sheath. The sheath keeps the stented valve in the collapsed position. Once the cover sheath is move backwards this will allow the stented valve to be deployed.

b- The stented valve consist of a stainless steel or nitinol self expanding stent in which a completely newly designed biological valve is attached.
One of the novelties of our invention is the use of self-expanding stents instead of balloon expandable stents.

c- The valve is made of bovine pericardium. Initially the pericardium is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean. It is fixed using a solution of gluteraldehyde at a concentration of 0.07% during 36 hours, then the pericardium is transfered to a solution of ethanol at 60% before making the valve.

d- The designed of the valve consist of a rectangular fragment of pericardium that is folded in such a way that forms a three leaflet valve.

The horizontal length of the pericardium piece is equal to the desired diameter x π.
The vertical length suffer a lot of modifications in the last 18 months



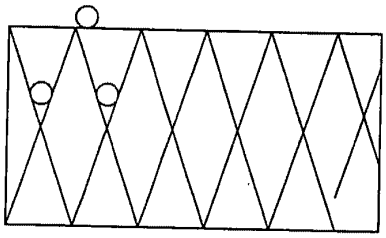
1 mm at each end to suture the valve.

The valve required 7-0 prolene, 24 inch long 10 packs
3 to suture the valve and 7 to attach the valve to the stent.

The valve was attached to a 24 mm maximal diameter Wallstent.

We eliminate the folds at each end of the valve.

The valve was fixed in its **superior border** using one or two fixation planes with multiple fixation points at each plane.



○ Fixation points

There are one or two rows of fixation points at the upper or proximal end of the stent and one row of fixation point at the lower or distal end of the stent.

Each fixation point was knotted 5 times in the upper plane and 7 knots in the lower plane.

The fixation of the **inferior border** of the valve to the stent was done with a single plane with 18 fixation points. Each fixation point was knotted 7 times using prolene 7-0.

The vertical fixation of the valve to the stent was done along the suture line of each cusp of the valve. We used 3 fixation points at each vertical suture line. Each fixation point was knotted 7 times.

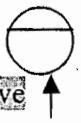
The vertical fixation was mildly loose to allow easy collapsibility of the valve.

The approximate time to suture and attach the valve was 10 hours.

The stent-valve is maintained in 0.7% gluteraldehyde solution.

We had the idea of fixing the valve in the closing position using tiny metallic clips to keep the cusps close to each other and help the material maintain closing memory.

The new valve design includes the creation of a curve in each cusp of the valve

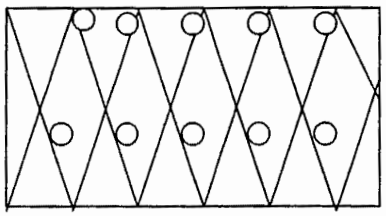


Curve

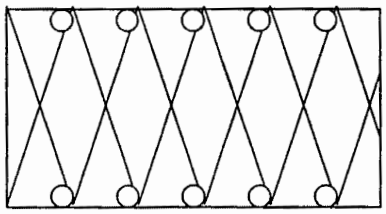
We also used straight suture lines of the cusp.
The other observation is that two planes of fixation point at the distal attachment of the the valve to the stent causes a lot of tension to the valve when we are collapsing it.

One plane of fixation points will probably be enough to prevent systolic collapsed of the proximal edge of the valve

Proximal fixation points / expanded



Proximal fixation points sliding down when stent collapses



○ Fixation points

18 fixation points at each plane

NEEDS DETAIL DESCRIPTION OF WHAT IS CLAIM

DESCRIPTION

FIELD OF THE INVENTION

This invention relates to devices and methods for percutaneous endovascular replacement of heart valves.

BACKGROUND

When a heart valve is malfunctioning in such a degree that interferes with normal cardiac function it may be necessary to replace it. Currently this requires a surgical procedure that involves open-heart surgery requiring general anesthesia, full cardiopulmonary bypass with complete cessation of cardiopulmonary activity. Usually after the surgical procedure seven to ten days of hospitalization and months of recuperation time are required. This valve replacement surgery is not free of complication and it is associated with a mortality rate in the best hands and circumstances of about five to six percent.

Endovascular procedures for valve replacement provide an alternative to open heart surgery and this is the goal of our new invention.

Previous endovascular treatments of disease heart-valves have focus in opening stenotic lesions in the mitral and aortic valve using specially designs balloons to dilate or split commissures in diseased aortic or mitral valves with commissural fusion and to crack calcific plaques in calcified stenotic aortic valves.

The success for the mitral valve has been rewarding but the aortic valve results have been discouraging This method provides only partial and temporary relief for a patient with a stenotic aortic valve and this method cannot be used to treat valves with leakage. Moreover, aortic valvuloplasty in a few cases may induce severe aortic leakage that is not compatible with life.

The method that we describe is to use a percutaneously endovascular valve replacement. supplantation. In this procedure, a delivery system is used to insert a biological or mechanical valve in the lumen of a central blood vessel via entry through the brachial or femoral artery. Vascular access is obtained using a needle or exposing the artery surgically and a guide wire is placed through the entry vessel and it is advanced to the desired placed under fluoroscopically guidance. Dilators are advanced over the wire to increase the lumen of the entry site preparing the artery to receive the delivery system of our heart-valve. The heart-valve is then advanced to the desired place and deployed under X-ray guidance.

This new technique of percutaneous endovascular heart-valve replacement, in contrast to open heart surgical procedures, would require only local anesthesia, partial or no cardiac bypass, one to two days hospitalization, and should have a reduced mortality rate as compared to open heart procedures.

The endovascular stented valve is a glutaraldehyde fixed bovine pericardium which has two of three cusps that open distally to permit unidirectional blood flow. Bioprosthetic valves are presently a mainstay in aortic valve replacement and they are preferable in patients who cannot tolerate long-term anticoagulant therapy or are otherwise potentially noncompliant with a long term medical regimen.

The endovascular valve can also be fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts or synthetic non-biological, non-thrombogenic material

RELEVANT LITERATURE

U.S. Pat. No. 3,671,979 to Moulopoulos, issued Jun. 27, 1972, describes a endovascularly inserted conical shaped umbrella-like valve positioned and held in place by an elongated mounting catheter at a supra-annular site to the aortic valve in a nearby arterial vessel. The conical end points toward the malfunctioning aortic valve and the umbrella's distal ends open up against the aorta wall with reverse blood flow, thereby preventing regurgitation.

U.S. Pat. No. 4,056,854 to Boretos, issued Nov. 8, 1977, describes a endovascularly inserted, catheter mounted, supra-annular valve in which the circular frame abuts the wall of the artery and attached flaps of flexible membrane extend distally in the vasculature. The flaps lie against the artery wall during forward flow, and close inward towards the central catheter to prevent regurgitation during reverse blood flow. The Boretos valve was designed to be positioned against the artery wall during forward flow, as compared to the mid-center position of the Moulopoulos valve, to reduce the stagnation of blood flow and consequent thrombus and embolic formation expected from a valve at mid-center position.

SUMMARY OF THE INVENTION

The invention relates to a new technique and a special type of device that allows percutaneous heart-valve replacement without the need for open-heart surgery.

The valve replacement system includes the following components:

1- A delivery system of the prosthetic valve device.
2- A prosthetic valve device.
3- An implantation technique

DESCRIPTION OF THE DRAWINGS

FIG. 1 Delivery system of the self-expanded stented valve.

FIG. 2 Initial deployment of the self-expanded stented valve.

FIG. 3 illustrates a bottom view of stented valve.

FIG. 4 illustrates a top view of the stented valve.

FIG. 5 illustrates a tissue laser wire used to cut the commisures of stenotic valve.

FIG. 6 illustrates a diagram of the relationships, dimensions and folds used to create the valve.

FIG. 7 illustrates a side view of a valve introducer.

FIG. 9 illustrates a side view of the attachment point of the valve to the stent.

FIG. 10 illustrates a top view showing the attachment points of the cusp of the valve.

FIG. 11 illustrates an aortic valve in the side position.

FIG. 12 illustrates an aortic valve from the top view.

FIG. 13 is a side cross-sectional view of the valve mounted in the self-expanded stent.

FIG. 14 illustrates a front view of the valve mounted in the stent in the open position.

FIG. 15A is a close-up side cross-sectional view of the mounting stent and FIG. 15B in the closed position.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

The present invention relates to the supplantation or replacement of a cardiac valve in a host through percutaneous endovascular means.

The valve replacement system includes
(1) a delivery device
(2) a prosthetic valve device
(3) an implantation technique.

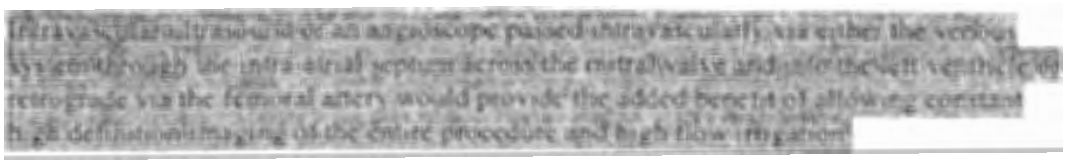
GENERAL DESCRIPTION OF THE PROCEDURE

The Femoral artery is canulated using a Cook needle and a standard J wire is advance into the artery either perutaneously or after surgical exposure of the artery. An 8 F introducer is advanced into the femoral artery over the wire. The J wire is then withdraw and anticoagulation is started using heparin 60 U/Kg intravenously. Once vascular access is obtained an aortogram is performed for anatomical evaluation.

A special wire (Lunderquist or Amplatz superstiff) is advanced into the aortic arch and dilators progressively larger are advance over the wire, starting with 12 F all the way to 18 F after this the valve introducer device containing the prosthetic valve device is then inserted and used to transport the replacement valve over a guidewire to the desired position.

The stented-valve is released by pulling the cover sheath of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advance over the wire and repeat aortogram is performed to assess the competency of the valve.

When the device is used to treat severe leakage of the aortic valve, the native valve is left in placed and the prostetic stented valve is deployed below the subclavian artery.
When the device is used to treat aortic stenosis, first the stenotic valve needs to be opened using either aortic valvuloplasty or the new laser wire cutters and if this procedure induces aortic insufficiency the stented valve is placed to prevent the regurgitation.



Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The prosthetic valve device can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation. In addition, with the development of longer-life, flexible, non thrombogenic synthetic valve alternatives to bioprosthesis', the prosthetic valve device will be indicated in all patients where the relative advantages of the life-span, the non-thrombogenic quality, and the ease of insertion of prosthetic valve devices outweigh the disadvantages of mechanical valves. Anticoagulation may be beneficial in certain clinical situations for either short or long term use.

All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

* * * * *

GREENBERG
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Manuel R. Valcarcel
305-579-0812
valcarcelm@gtlaw.com

ATTORNEY-CLIENT PRIVILEGED
CONFIDENTIAL INFORMATION

August 29, 2001

VIA FACSIMILE (703) 413-4150
AND FED EX

Mr. Mark Miller
Just Files
2001 Jefferson Davis Highway
Suite 506
Arlington, VA 22202

Re: Novelty Search for Percutaneous heart valve replacement device and method
Our Reference No. 51458.010100

Dear Mr. Miller:

Please conduct a novelty search for the above-identified invention which is described below.

A. Replacement Heart Valve Device. The replacement heart valve device comprises a stent made of stainless steel or self-expanding nitinol, a completely newly designed biological valve disposed within the inner space of the stent, and a delivery system having a central part which consists of a hollow tube that allows a metallic wire to be advanced inside it. The stented valve is collapsed over this central metallic tubing and it is covered by a movable sheath. The sheath keeps the stented valve in the collapsed position. Once the cover sheath is moved backwards, the stented valve can be deployed.

The endovascular stented-valve is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow. Bioprostetic valves are presently a mainstay in aortic valve replacement and they are preferable in patients who cannot tolerate long-term anticoagulant therapy or are otherwise potentially noncompliant with a long term medical regimen.

In making of the valve initially, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a

Exhibit C

solution of gluteraldehyde at a concentration of 0.07% during 36 hours, then the pericardium is transferred to a solution of ethanol at 60% before making the valve.

The valve is formed by taking a rectangular fragment of bovine pericardium and folding it in such a way that forms a three-leaflet valve.

The endovascular valve can also be fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts or synthetic non-biological, non-thrombogenic material.

B. Implantation Method.

The method for implanting said replacement heart valve device through an aortic passageway to, or near to, the location from which the natural heart valve has been removed comprises the following steps:

inserting the replacement heart valve device in the lumen of a central blood vessel via entry through the brachial or femoral artery using a needle or exposing the artery surgically; placing a guide wire through the entry vessel and advancing it to the desired position; advancing dilators over the wire to increase the lumen of the entry site, thereby preparing the artery to receive the heart-valve; and advancing the heart-valve to the desired place.

This new technique of percutaneous endovascular heart-valve replacement, in contrast to open heart surgical procedures, would require only local anesthesia, partial or no cardiac bypass, one to two days hospitalization, and should have a reduced mortality rate as compared to open heart procedures.

When the device is used to treat severe leakage of the aortic valve, the native valve is left in placed and the prosthetic stented valve is deployed below the subclavian artery. When the device is used to treat aortic stenosis, first the stenotic valve is opened using either aortic valvuloplasty or laser wire cutters and if this procedure induces aortic insufficiency the stented valve is placed to prevent the regurgitation.

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Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The prosthetic valve device can be used in any patient where

bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation.

Please do not hesitate to contact me at 305-579-0812 if you have any questions or need additional information to complete the search. Please let me know beforehand if the search will cost more than $400.00.

Sincerely,

GREENBERG TRAURIG, P.A.

Manuel R. Valcarcel, Esq.

MRV/ps

\\MIA-SRV01\VALCARCELM\1333881v01\8/29/01\51458.010100

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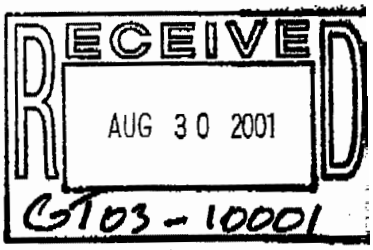

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ATTORNEY-CLIENT PRIVILEGED
CONFIDENTIAL INFORMATION

August 29, 2001

VIA FACSIMILE (703) 413-4150
AND FED EX

Mr. Mark Miller
Just Files
2001 Jefferson Davis Highway
Suite 506
Arlington, VA 22202

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Our Reference No. 51458.010100

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A. Replacement Heart Valve Device. The replacement heart valve device comprises a stent made of stainless steel or self-expanding nitinol, a completely newly designed biological valve disposed within the inner space of the stent, and a delivery system having a central part which consists of a hollow tube that allows a metallic wire to be advanced inside it. The stented valve is collapsed over this central metallic tubing and it is covered by a movable sheath. The sheath keeps the stented valve in the collapsed position. Once the cover sheath is moved backwards, the stented valve can be deployed.

The endovascular stented-valve is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow. Bioprostetic valves are presently a mainstay in aortic valve replacement and they are preferable in patients who cannot tolerate long-term anticoagulant therapy or are otherwise potentially noncompliant with a long term medical regimen.

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GREENBERG
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TRAURIG

Manuel R. Valcarcel
(305) 579-0812

November 27, 2001

ATTORNEY-CLIENT PRIVILEGED
CONFIDENTIAL COMMUNICATION

VIA HAND DELIVERY

David Paniagua, M.D.
1865 – 79th Street Causeway
Apartment 7-H
Miami Beach, Florida 33141

Re: Draft of patent application specification for percutaneously implantable heart valve replacement device and method of making same

Dear Dr. Paniagua:

Enclosed for your review and revision as appropriate is the draft of the nonprovisional patent application specification for your above-referenced invention. Please review the draft at your earliest convenience (please also review the draft with the other co-inventors) and provide your comments, revisions and additional text. Please note the descriptions of the figures in the draft and if you have drawings or clear digital photographs that provide the views described in the description of the drawings, please provide them. The photographs provided previously are not clear enough for use in the application. If you do not have such photographs, please let me know if you can provide an actual sample of the device so that a draftsman can prepare the figures.

Best regards,

GREENBERG TRAURIG, P.A.

Manuel R. Valcarcel, Esq.

MRV/ps
Enclosures

\\MIA-SRV01\VALCARCELM\1353475v01\11/27/01\51458.010100

Exhibit D

Docket No. 51458.010100

NON-PROVISIONAL PATENT APPLICATION

SPECIFICATION

TO WHOM IT MAY CONCERN:

BE IT KNOWN THAT WE, David Paniagua, Eduardo Induni, Carlos Mejia, Francisco Lopez and R. David Fish, each citizens of the United States of America, have invented a new and useful percutaneously implantable replacement heart valve and method of making same, of which the following is the Specification.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is in the field of heart valve replacement. More specifically, the present invention is directed to a percutaneously implantable replacement heart valve and method of making same.

2. Description of Related Art

There have been numerous efforts in the field of heart valve replacement to improve both the durability and effectiveness of replacement heart valves as well as the ease of implantation. A brief description of heart valves and heart function follows to provide relevant background for the present invention.

There are four valves in the heart that serve to direct the flow of blood through the two sides of the heart in a forward direction. On the left (systemic) side of the heart are: 1) the mitral valve, located between the left atrium and the left ventricle, and 2) the aortic valve, located between the left ventricle and the aorta. These two valves direct oxygenated blood coming from the lungs through the left side of the heart into the aorta for distribution to the body. On the right (pulmonary) side of the heart are: 1) the tricuspid valve, located between the right atrium and the right ventricle, and 2) the pulmonary valve, located between the right ventricle and the pulmonary artery. These two valves direct de-oxygenated blood coming from the body through the right side of the heart into the pulmonary artery for distribution to the lungs, where it again becomes re-oxygenated to begin the circuit anew.

Heart valves are passive structures that simply open and close in response to differential pressures on either side of the particular valve. They consist of moveable "leaflets" that are designed simply to open and close in response to differential pressures on either side of the valve's leaflets. The mitral valve has two leaflets and the tricuspid valve has three. The aortic and pulmonary valves are referred to as "semilunar valves" because of the unique appearance

of their leaflets, which are more aptly termed "cusps" and are shaped somewhat like a half-moon. The aortic and pulmonary valves each have three cusps.

In general, the components of heart valves include the valve annulus, which will remain as a roughly circular open ring after the leaflets of a diseased or damaged valve have been removed; leaflets or cusps; papillary muscles which are attached at their bases to the interior surface of the left or right ventricular wall; and multiple chordae tendineae, which couple the valve leaflets or cusps to the papillary muscles. There is no one-to-one chordal connection between the leaflets and the papillary muscles; instead, numerous chordae are present, and chordae from each papillary muscle attach to both of the valve leaflets.

When the left ventricular wall relaxes so that the ventricular chamber enlarges and draws in blood, the leaflets of the mitral valve separate and the valve opens. Oxygenated blood flows in a downward direction through the valve, to fill the expanding ventricular cavity. Once the left ventricular cavity has filled, the left ventricle contracts, causing a rapid rise in the left ventricular cavitary pressure. This causes the mitral valve to close while the aortic valve opens, allowing the oxygenated blood to be ejected from the left ventricle into the aorta. The chordae tendineae of the mitral valve prevent the mitral leaflets from prolapsing back into the left atrium when the left ventricular chamber contracts.

The three leaflets, chordae tendineae, and papillary muscles of the tricuspid valve function in a similar manner, in response to the filling of the right ventricle and its subsequent contraction. The cusps of the aortic valve also respond passively to pressure differentials between the left ventricle and the aorta. When the left ventricle contracts, the aortic valve cusps open to allow the flow of oxygenated blood from the left ventricle into the aorta. When the left ventricle relaxes, the aortic valve cusps reapproximate to prevent the blood which has entered the aorta from leaking (regurgitating) back into the left ventricle. The pulmonary valve cusps respond passively in the same manner in response to relaxation and contraction of the right ventricle in moving de-oxygenated blood into the pulmonary artery and thence to the lungs for

re-oxygenation. Neither of these semilunar valves has associated chordae tendineae or papillary muscles.

Problems that can develop with heart valves consist of stenosis, in which a valve does not open properly, and/or insufficiency, also called regurgitation, in which a valve does not close properly. In addition to stenosis and insufficiency of heart valves, heart valves may need to be surgically repaired or replaced due to certain types of bacterial or fungal infections in which the valve may continue to function normally, but nevertheless harbors an overgrowth of bacteria (vegetation) on the leaflets of the valve that may embolize and lodge downstream in a vital artery. If such vegetations are on the valves of the left side (i.e., the systemic circulation side) of the heart, embolization may occur, resulting in sudden loss of the blood supply to the affected body organ and immediate malfunction of that organ. The organ most commonly affected by such embolization is the brain, in which case the patient suffers a stroke. Thus, surgical replacement of either the mitral or aortic valve (left-sided heart valves) may be necessary for this problem even though neither stenosis nor insufficiency of either valve is present. Likewise, bacterial or fungal vegetations on the tricuspid valve may embolize to the lungs resulting in a lung abscess and therefore, may require replacement of the tricuspid valve even though no tricuspid valve stenosis or insufficiency is present.

These problems are treated by surgical repair of valves, although often the valves are too diseased to repair and must be replaced. If a heart valve must be replaced, there are currently several options available, and the choice of a particular type of artificial valve depends on factors such as the location of the valve, the age and other specifics of the patient, and the surgeon's experiences and preferences. Currently in the United States over 100,000 defective heart valves are replaced annually, at an approximate cost of $30-50,000 per procedure, and thus it would be desirable if heart valves could be replaced using minimally invasive techniques and without having to repeat the procedure within a matter of years due to the lack of durability of the replacement heart valve. It would be especially advantageous if a defective heart valve

could be removed via an endovascular procedure, that is, a procedure where the invasion into the body is through a blood vessel such as the femoral artery. The procedure is then carried out percutaneously and transluminally using the vascular system to convey appropriate devices to the position in the body wherein it is desired to carry out the desired procedure. An example of such a procedure would be angioplasty, wherein a catheter carrying a small balloon at its distal end is manipulated through the body's vessels to a point where there is a blockage in a vessel. The balloon is expanded to create an opening in the blockage, and then the balloon is deflated and the catheter and balloon are removed from the vessel.

Endovascular procedures have substantial benefits both from the standpoint of health and safety as well as cost. Such procedures require minimal invasion of the human body, and there is consequently considerable reduction and in some instances even elimination, of the use of a general anesthesia and much shorter hospital stays.

Replacement heart valves can be categorized as either artificial mechanical valves, transplanted valves and tissue valves. Replacement heart valves are designed to optimize hemodynamic performance, thrombogenicity and durability. Another factor taken into consideration is the relative ease of surgical implantation.

Mechanical valves are typically constructed from nonbiological materials such as plastics, metals and other artificial materials which, while durable, are expensive and prone to blood clotting which increases the risk of an embolism. Anticoagulants taken to help against blood clotting can further complicate the patient's health due to increased risks for hemorrhages.

Transplanted valves are natural valves taken from cadavers. These valves are typically removed and frozen in liquid nitrogen, and are stored for later use. They are typically fixed in glutaraldehyde to eliminate antigenicity and are sutured in place, typically with a stent.

Artificial tissue valves are valves constructed from animal tissue, such as bovine or porcine tissue. Efforts have also been made at using tissue from the patient for which the valve will be constructed.

Most tissue valves are constructed by sewing the leaflets of pig aortic valves to a stent to hold the leaflets in proper position, or by constructing valve leaflets from the pericardial sac of cows or pigs and sewing them to a stent. The porcine or bovine tissue is chemically treated to alleviate any antigenicity. The pericardium is a membrane that surrounds the heart and isolates it from the rest of the chest wall structures. The pericardium is a thin and very slippery, which makes it difficult for suturing in a millimetricly precise way. The method of making the replacement heart valve of the present invention solves this problem through a process to dry the pericardium in such a way that makes it possible to handle and fold more easily.

For example, one prior replacement heart valve requires each sculpted leaflet to be trimmed in a way that forms an extended flap, which becomes a relatively narrow strand of tissue near its tip. The tip of each pericardial tissue strand is sutured directly to a papillary muscle, causing the strand to mimic a chordae tendineae. Each strand extends from the center of a leaflet in the valve, and each strand is sutured directly to either an anterior and posterior papillary muscle. This requires each leaflet to be positioned directly over a papillary muscle. This effectively rotates the leaflets of the valve about 90 degrees as compared to the leaflets of a native valve. The line of commissure between the leaflets, when they are pressed together during systole, will bisect (at a perpendicular angle) an imaginary line that crosses the peaks of the two papillary muscles, instead of lying roughly along that line as occurs in a native valve.

A different approach to creating artificial tissue valves is described in U.S. Patent Nos. 5,163,955 to Calvin, et al. and 5,571,174 and 5,653,749 to Love. Using a cutting die, the pericardial tissue is cut into a carefully defined geometric shape, treated with glutaraldehyde, then clamped in a sandwich-fashion between two stent components. This creates a tri-leaflet

valve that resembles an aortic or pulmonary valve, having semilunar-type cusps rather than atrioventricular-type leaflets.

U.S. Patent No. 3,671,979 to Moulopoulos describes an endovascularly inserted conical shaped umbrella-like valve positioned and held in place by an elongated mounting catheter at a supra-annular site to the aortic valve in a nearby arterial vessel. The conical end points toward the malfunctioning aortic valve and the umbrella's distal ends open up against the aorta wall with reverse blood flow, thereby preventing regurgitation.

U.S. Patent No. 4,056,854 to Boretos describes an endovascularly inserted, catheter mounted, supra-annular valve in which the circular frame abuts the wall of the artery and attached flaps of flexible membrane extend distally in the vasculature. The flaps lie against the artery wall during forward flow, and close inward towards the central catheter to prevent regurgitation during reverse blood flow. The Boretos valve was designed to be positioned against the artery wall during forward flow, as compared to the mid-center position of the Moulopoulos valve, to reduce the stagnation of blood flow and consequent thrombus and embolic formation expected from a valve at mid-center position.

The main advantage of tissue valves is that they do not cause blood clots to form as readily as do the mechanical valves, and therefore, they do not absolutely require systemic anticoagulation. The major disadvantage of tissue valves is that they lack the long-term durability of mechanical valves. Tissue valves have a significant failure rate, usually within ten years following implantation. One cause of these failures is believed to be the chemical treatment of the animal tissue that prevents it from being antigenic to the patient. In addition, the presence of extensive suturing prevents the artificial tissue valve from being anatomically accurate in comparison to a normal heart valve, even in the aortic valve position.

A shortcoming of prior artificial tissue valves has been the inability to effectively simulate the exact anatomy of a native heart valve. Although transplanted human or porcine aortic valves have the gross appearance of native aortic valves, the fixation process (freezing with

liquid nitrogen, and chemical treatment, respectively) alters the histologic characteristics of the valve tissue. Porcine and bovine pericardial valves not only require chemical preparation (usually involving fixation with glutaraldehyde), but the leaflets must be sutured to cloth-covered stents in order to hold the leaflets in position for proper opening and closing of the valve. Additionally, the leaflets of most such tissue valves are constructed by cutting or suturing the tissue material, resulting in leaflets that do not duplicate the form and function of a real valve.

SUMMARY OF THE INVENTION

The present invention is a replacement heart valve device and method of making same. The replacement heart valve device, in a preferred embodiment, comprises a stent made of stainless steel or self-expanding nitinol and a completely newly designed artificial biological tissue valve disposed within the inner space of the stent. The cusp or leaflet portion of the valve means is formed by folding of the pericardium material used to create the valve. The cusps/leaflets open in response to blood flow in one direction and close in response to blood flow in the opposite direction. Preferably the tubular portion of the valve means contains the same number of cusps as the native valve being replaced, in substantially the same size and configuration. The outer surface of the valve means is attached to the stent member.

The replacement heart valve device is preferably implanted using a delivery system having a central part which consists of a flexible hollow tube catheter that allows a metallic guide wire to be advanced inside it. The stented valve is collapsed over the central tube and it is covered by a movable sheath. The sheath keeps the stented valve in the collapsed position. Once the cover sheath is moved backwards, the stented valve can be deployed. The endovascular stented-valve, in a preferred embodiment, is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow.

The present invention also comprises a method of making a replacement heart valve device. In order to make the valve, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a

solution of gluteraldehyde, preferably at a concentration of about 0.07% during 36 hours, then the pericardium is transferred to a solution of ethanol, preferably at a concentration of about 60% before making the valve. The material is dried in order to make it easier to handle and fold. The valve is formed by taking a rectangular fragment of bovine pericardium and folding it in such a way that forms a three-leaflet valve. The valve can also be made from fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts or synthetic non-biological, non-thrombogenic material. The folding of the pericardium material to create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of the valve leaflets. The valve is rehydrated after being formed. The method of the present invention also greatly reduces the risk of tearing of the cusps or leaflets, since they are integral to the valve rather than being attached by suturing.

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The replacement heart valve device of the present invention can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation medication and treatment. The present invention can be practiced in applications with respect to each of the heart's valves.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 depicts a side perspective view of the replacement heart valve of the present invention in one embodiment without the stent.

Fig. 2 depicts the folds which form the leaflets or cusps of the replacement heart valve of the present invention in one embodiment.

Fig. 3 depicts the procedure for folding the pericardium tissue starting material to create the replacement heart valve of the present invention.

Fig. 4 depicts a side perspective view of the replacement heart valve of the present invention in one embodiment mounted within a stent.

Fig. 5 depicts a cross-sectional view of one embodiment of the replacement heart valve of the present invention mounted within a self-expanding stent, with the stent in the expanded position.

Fig. 6 depicts a side perspective view of one embodiment of the replacement heart valve of the present invention mounted within a self-expanding stent in the collapsed position.

Fig. 7 depicts the suture points of one embodiment of the replacement heart valve of the present invention.

Fig. 8 depicts the implantation/delivery system used with the present invention in a preferred embodiment.

DESCRIPTION OF A PREFERRED EMBODIMENT

The present invention comprises a percutaneously implantable replacement heart valve and a method for making same. The artificial heart valve device of the present invention is capable of exhibiting a variable diameter between a compressed or collapsed position and an expanded position. A preferred embodiment of the replacement heart valve according to the present invention is set forth in FIGS. 1 and 2. The replacement heart valve comprises a stent member __ and a flexible valve means __. The stent member is self-expanding and has a first cylindrical shape in its compressed or collapsed configuration and a second, larger cylindrical shape in its expanded configuration. The valve means comprises a generally tubular center portion and, preferably, a peripheral upstanding cusp or leaflet portion. The valve means is

disposed within the cylindrical stent member with the tubular portion transverse of and at some acute angle relative to the stent walls. The diameter of the tubular portion is substantially the same as the inside diameter of the stent member in its initial expanded configuration. The peripheral upstanding cusp or leaflet portion is disposed substantially parallel to the walls of the stent member similar to a cuff on a shirt. The center portion __ of the valve means __ is generally tubular in shape and comprises three leaflets __ as shown, although it is understood that there could be from two to four leaflets. The tubular portion of the valve means is attached to the stent member __ by a plurality of sutures __.

The leaflet portion of the valve means __ extends across or transverse of the cylindrical stent. The leaflets __ are the actual valve and allow for one-way flow of blood. The leaflet portion as connected to the rest of the valve resembles the cuff of a shirt. The configuration of the stent member __ and the flexible, resilient material of construction allows the valve to collapse into a relatively small cylinder __ as seen in FIG. 6. The replacement heart valve will not stay in its collapsed configuration without being restrained. Once the restraint is removed, the self-expanding stent member __ will cause the artificial heart valve to take its expanded configuration, as seen in FIG. __.

Stent Member

The stent member __ comprises self-expanding nickel-titanium alloy, also called "nitinol," in a sine wave-like configuration as shown in FIG. 1. An enlarged view of a preferred embodiment of the stent member for use in the replacement heart valve of the invention is depicted in FIG. 5. The stent member __ includes a length of wire __ formed in a closed zigzag configuration. The wire can be a single piece, stamped or extruded, or it could be formed by welding the free ends together as at __. The straight sections __ of the stent are joined by bends __. The stent is readily compressible to a small cylindrical shape and resiliently self-expandable to the shape shown in FIG. 5.

The stent members of the artificial heart valves of the present invention may be made from various metal alloys, titanium, titanium alloy, nitinol, stainless steel, or other resilient, flexible non-toxic, non-thrombogenic, physiologically acceptable and biocompatible materials. The configuration may be the zigzag configuration shown or a sine wave configuration, mesh configuration or a similar configuration which will allow the stent to be readily collapsible and self-expandable. When a zigzag or sine wave configured stent member is used, the diameter of the wire from which the stent is made should be from about [0.010 to 0.035] inches, preferably from about [0.012 to 0.025] inches. The diameter of the stent member will be from about [1.5 to 3.5 cm], preferably from about [1.75 to 3.00 cm], and the length of the stent member will be from about [1.0 to 10 cm], preferably from about [1.1 to 5 cm.]

The stent used in a preferred embodiment of the present invention is fabricated from a "shaped memory" alloy, nitinol, which is composed of nickel and titanium. Nitinol wire is first fashioned into the desired shape for the device and then the device is heat annealed. A meshwork of nitinol wire of approximately 0.008 inch gauge is formed into a tubular structure with a minimum central diameter of 20 min to make the stent. Away from its central portion, the tubular structure flares markedly at both ends in a trumpet-like configuration. The maximum diameter of the flared ends of the stent is approximately 30 mm. The purpose of the stent is to maintain a semi-rigid patent channel through the diseased cardiac valve following its implantation.

When the components of the replacement heart valve device are exposed to cold temperatures, they become very flexible and supple, allowing them to be compressed down and pass easily through the delivery sheath. A cold temperature is maintained within the sheath during delivery to the deployment site by constantly infusing the sheath with an iced saline solution. Once the valve components are exposed to body temperature at the end of the sheath, they instantaneously reassume their predetermined shapes, thus allowing them to function as designed.

Preferably the stent member carries a plurality of barbs extending outwardly from the outside surface of the stent member for fixing the heart valve in a desired position. More preferably the barbs are disposed in two spaced-apart, circular configurations with the barbs in one circle extending in an upstream direction and the barbs in the other circle extending in a downstream direction. It is especially preferable that the barbs on the inflow side of the valve point in the direction of flow and the barbs on the outflow side point in the direction opposite to flow. It is preferred that the stent be formed of titanium alloy wire or other flexible, relatively rigid, physiologically acceptable material arranged in a closed zigzag configuration so that the stent member will readily collapse and expand as pressure is applied and released, respectively.

Valve Means

The valve means is flexible, compressible, host-compatible, and non-thrombogenic. The valve can be, for example, fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts. Synthetic biocompatible materials such as polytetrafluoroethylene, polyester and the like may be used. The preferred material for the valve means is bovine pericardium tissue. The valve means is disposed within the cylindrical stent member with the tubular portion transverse of and at some acute angle relative to the stent walls. The diameter of the tubular portion is substantially the same as the inside diameter of the stent member in its initial expanded configuration. The peripheral upstanding cusp or leaflet portion is disposed substantially parallel to the walls of the stent member similar to a cuff on a shirt.

The cusp or leaflet portion of the valve means is formed by folding of the pericardium material used to create the valve. The cusps/leaflets open in response to blood flow in one direction and close in response to blood flow in the opposite direction. Preferably the tubular portion of the valve means contains the same number of cusps as the native valve being replaced, in substantially the same size and configuration.

Method of Making Replacement Heart Valve Device

The present invention also comprises a method of making a replacement heart valve device. In order to make the valve, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a solution of gluteraldehyde, preferably at a concentration of about 0.07% during 36 hours, then the pericardium is transferred to a solution of ethanol, preferably at a concentration of about 60% before making the valve. The valve is formed by taking a rectangular fragment of bovine pericardium and folding it in such a way that forms a three-leaflet or desired number of leaflet valve. FIG. 2 depicts the folds which form the cusps or leaflets, and FIG. 3 depicts the folding procedure. The folding of the pericardium material to create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of the valve leaflets. It also greatly reduces the risk of tearing of the cusps or leaflets, since they are integral to the valve rather than being attached by suturing.

In order to make the pericardium material less slippery and easier to fold, the pericardium is dried, preferably with artificial light using a 60-watt lamp with the pericardium material placed in a flat aluminum surface to dry it homogeneously. A photo drying machine can also be used. The final result is a homogeneous tissue that looks like plastic paper and makes it easy to manipulate to fold and suture the valve. Once the valve is formed it is re-hydrated by placing it in a solution of water and 70% alcohol. In approximately 3 days the valve is fully rehydrated.

Attachment of the Valve Means to the Stent Member

The valve means is then attached to the inner channel of the stent member by suturing the outer surface of the valve means' pericardium material to the stent member. Fig. 7 depicts preferred suture points of one embodiment of the present invention: 3-point fixation or 6-point fixation at each border of the stent. Other fixation schemes can be utilized, such as, by way of

non-limiting example, fixation on both borders 18 points at each end following a single plane and 36 fixation points following to adjacent vertical planes. The use of only one plane of fixation points helps prevent systolic collapse of the proximal edge of the valve means. A fold on the border of the pericardium material prevents tearing. The attachment position of the valve is preferably closer to the proximal and wider part of the stent.

The sequence of steps can vary. The pericardium material can be fixed in glutaraldehyde before attachment to the stent or the valve can be formed and then fixed with gluteraldehyde after mounting it in the stent. One observation noted is that the material becomes whiter and apparently increases its elasticity. 1mm vascular clips keep the cusps coapted while fixing them in gluteraldehyde. The use of metallic clips to keep both cusps adjacent to each other after 24 hours of fixation in gluteraldehyde helps to educate the material and make the primary position of the valve cusps adjacent to each other. After the clips are removed, there are no lesions to the valve.

Different suture materials can be used, including, in a preferred embodiment, prolene 6-0 and Mersilene 6-0 which is a braided suture.

Implantation of Replacement Heart Valve Device

The replacement heart valve device of the present invention is preferably used in surgical procedures involving the percutaneous and transluminal removal of the diseased or defective heart valve and the percutaneous and transluminal implantation of the new heart valve described above. The defective heart valve is removed by a suitable modality, such as, for example, laser, ultrasound, mechanical, or other suitable forms of delivery of energy, or phacoemulsion, including, but not limited to, laser lithotripsy, mechanical lithotripsy, electrohydraulic lithotripsy, and laser or mechanical ablation. To remove the native heart valve that is being replaced, a guidewire is inserted percutaneously and transluminally using standard vascular or angiography techniques. The distal end of the guidewire is manipulated to extend

through and across the defective heart valve. Then a catheter is advanced distally through the femoral artery to a point proximal to the defective heart valve, between the origin of the coronary artery and the origin of the right subclavian artery. The position of the distal end of catheter can be monitored by observation of radiopaque markers. Collector member is preferably inflated and occludes the aorta at a point between the origin of the coronary artery and the right subclavian artery. Next, a balloon and cutting tool are advanced through the catheter so that the cutting tool and uninflated balloon are distal to the defective heart valve. Optionally an additional step, such as balloon dilatation or atherectomy, may be required to provide a passageway through the heart valve. A catheter is also placed into the coronary sinus via a transjugular puncture. This catheter is used for infusion of blood or cardioplegia solution during the portion of the procedure when the aorta is occluded. The absence of valves in the cardiac venous system allows retrograde flow so that there will be an effluence of fluid from the coronary arteries. This flow of fluid is desired to prevent embolization of material into the coronary arteries during the procedure. Once the cutting tool is in place, the balloon is inflated and flexible shaft is rotated. Once the cutting tool has reached the appropriate rotation speed, the cutting tool is pulled proximally to remove the defective heart valve. The balloon and the cutting tool are spaced apart so that the inflated balloon will be stopped by the perimeter, unremoved portion of the defective heart valve, which will signal the physician that the valve has been removed, as well as protect the heart and aorta from damage from the valve removal device. Once it is determined that the defective heart valve has been removed, the cutting tool is slowed or stopped altogether and the balloon is deflated. The cutting tool and the deflated balloon are pulled proximally through catheter. Then, a catheter containing an artificial heart valve is inserted and the artificial heart valve is placed as described above.

The delivery and implantation system of the replacement artificial heart valve of the present invention percutaneously and transluminally includes a flexible catheter which may be inserted into a vessel of the patient and moved within that vessel. The distal end of the catheter,

which is hollow and carries the replacement heart valve of the present invention in its collapsed configuration, is guided to a site where it is desired to implant the replacement heart valve. The catheter has a pusher member disposed within the catheter lumen and extending from the proximal end of the catheter to the hollow section at the distal end of the catheter. Once the distal end of the catheter is positioned as desired, the pusher mechanism is activated and the distal portion of the replacement heart valve is pushed out of the catheter and the stent member partially expands. In this position the stent member is restrained so that it doesn't pop out and is held for controlled release, with the potential that the replacement heart valve can be recovered if there is a problem with the positioning. The catheter is them retracted slightly and the replacement heart valve is completely pushed out of the catheter and released from the catheter to allow the stent member to fully expand. If the stent member includes two circles of barbs on its outer surface as previously described, the first push and retraction will set one circle of barbs in adjacent tissue and the second push and release of the replacement heart valve will set the other circle of barbs in adjacent tissue and securely fix the replacement heart valve in place when the valve is released from the catheter.

Alternatively, or in combination with the above, the replacement heart valve could be positioned over a metallic guidewire that is advanced through the catheter. The replacement heart valve device of the present invention is preferably implanted percutaneously through an aortic passageway to, or near to, the location from which the natural heart valve has been removed. Referring to Fig. 8, the implantation system comprises a flexible hollow tube catheter with a metallic guide wire disposed within it. The stented valve is collapsed over the tube and is covered by a moveable sheath. The moveable sheath maintains the stented valve in the collapsed position. comprises the following steps: inserting the replacement heart valve device in the lumen of a central blood vessel via entry through the brachial or femoral artery using a needle or exposing the artery surgically; placing a guide wire through the entry vessel and advancing it to the desired position; advancing dilators over the wire to increase the lumen of

the entry site, thereby preparing the artery to receive the heart-valve; and advancing the heart-valve to the desired place. The stented-valve is released by pulling the cover sheath of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advanced over the wire and an aortogram is performed to assess the competency of the valve.

Before creation of the valve means and implantation, the patient is studied to determine the architecture of the patient's heart. Useful techniques include fluoroscopy, transesophageal echocardiography, MRI, and angiography. The results of this study will enable the physician to determine the appropriate size for the replacement heart valve.

In one procedure for implantation of the replacement heart valve device of the present invention, the femoral artery of the patient is canulated using a Cook needle and a standard J wire is advanced into the artery either percutaneously or after surgical exposure of the artery. An 8 F introducer is advanced into the femoral artery over the wire. The J wire is then withdrawn and anticoagulation is started using heparin 60 U/Kg intravenously. Once vascular access is obtained an aortogram is performed for anatomical evaluation. A special wire (Lunderquist or Amplatz superstiff) is advanced into the aortic arch and dilators progressively larger are advanced over the wire, starting with 12 F all the way to 18 F. After this the valve introducer device containing the prosthetic valve device is then inserted and used to transport the replacement valve over a guidewire to the desired position. The stented-valve is released by pulling the cover sheath of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advanced over the wire and repeat aortogram is performed to assess the competency of the valve.

When the device is used to treat severe leakage of the aortic valve, the native valve is left in place and the prosthetic stented valve is deployed below the subclavian artery. When the device is used to treat aortic stenosis, first the stenotic valve needs to be opened using either

aortic valvuloplasty or cutting and if this procedure induces aortic insufficiency the stented valve is placed to prevent the regurgitation.

Intravascular ultrasound or an angioscope passed intravascularly via either the venous system through the intra-atrial septum across the mitral valve and into the left ventricle or retrograde via the femoral artery would provide the added benefit of allowing constant high definition imaging of the entire procedure and high flow irrigation.

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The prosthetic valve device can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation. In addition, with the development of longer-life, flexible, non-thrombogenic synthetic valve alternatives to bioprosthesis, the prosthetic valve device will be indicated in all patients where the relative advantages of the life-span, the non-thrombogenic quality, and the ease of insertion of prosthetic valve devices outweigh the disadvantages of mechanical valves. Anticoagulation may be beneficial in certain clinical situations for either short or long term use.

This method of percutaneous endovascular heart-valve replacement, in contrast to open heart surgical procedures, requires only local anesthesia, partial or no cardiac bypass, one to two days hospitalization, and should result in a reduced mortality rate as compared to open heart procedures.

While the present invention has been shown and described herein in what is considered to be a preferred embodiment thereof, illustrating the results and advantages over the prior art obtained through the present invention, the invention is not limited to the specific embodiments

described above. Thus, the forms of the invention shown and described herein are to be taken as illustrative and other embodiments may be selected without departing from the spirit and scope of the present invention.

CLAIMS

Having thus described the invention, what is claimed is:

1. A percutaneously implantable replacement heart valve device comprising a self-expanding stent member and an artificial valve means made of biocompatible tissue material and disposed within the inner cavity of said stent member affixed at one or more points to said stent member, said valve means having cusps or leaflets formed by folding of said biocompatible tissue material.

2. The percutaneously implantable replacement heart valve of claim 1, wherein said stent member is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium, stainless steel [add others].

3. The percutaneously implantable replacement heart valve of claim 1, wherein said biocompatible tissue material of said valve means comprises bovine pericardium tissue.

4. The percutaneously implantable replacement heart valve of claim 1, wherein said biocompatible tissue material of said valve means comprises porcine pericardium tissue.

5. The percutaneously implantable replacement heart valve of claim 1, wherein said biocompatible tissue material of said valve means comprises autologous tissue obtained from the patient into whom said replacement heart valve will be implanted.

6. A method of making a percutaneously implantable replacement heart valve comprising the following steps:

obtaining a substantially rectangular segment of biocompatible tissue material;

soaking said biocompatible tissue material in a gluteraldehyde solution;

transferring said biocompatible tissue material from said gluteraldehyde solution to an ethanol solution;

drying said biocompatible tissue material;

folding said dried biocompatible tissue material to create cusps or leaflets and a cuffed tubular valve structure;

affixing said folded biocompatible tissue material to the inner cavity of a stent.

ABSTRACT

The present invention comprises a percutaneously implantable replacement heart valve device and a method of making same. The replacement heart valve device comprises a stent member made of stainless steel or self-expanding nitinol, a biological tissue artificial valve means disposed within the inner space of the stent member. An implantation and delivery system having a central part which consists of a flexible hollow tube catheter that allows a metallic wire guide to be advanced inside it. The endovascular stented-valve is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow. The present invention also comprises a novel method of making a replacement heart valve by taking a rectangular fragment of bovine pericardium treating, drying, folding and rehydrating it in such a way that forms a two- or three-leaflet/cusp valve with the leaflets/cusps formed by folding, thereby eliminating the extent of suturing required, providing improved durability and function.

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December 28, 2001

ATTORNEY-CLIENT PRIVILEGED
CONFIDENTIAL COMMUNICATION

VIA HAND DELIVERY

David Paniagua, M.D.
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Miami Beach, Florida 33141

Re: Revised draft of patent application specification for percutaneously implantable heart valve replacement device and method of making same

Dear Dr. Paniagua:

Enclosed for your review and revision is a revised draft of the nonprovisional patent application specification for your above-referenced invention. Please review the draft at your earliest convenience (please also review the draft with the other co-inventors) and provide your comments, revisions and additional text.

Best regards,

GREENBERG TRAURIG, P.A.

Manuel R. Valcarcel, Esq.

MRV/mp

Enclosure

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Docket No. 51458.010100

NON-PROVISIONAL PATENT APPLICATION

SPECIFICATION

TO WHOM IT MAY CONCERN:

BE IT KNOWN THAT WE, David Paniagua, Eduardo Induni, Carlos Mejia, Francisco Lopez and R. David Fish, ~~each citizens of the United States of America,~~ have invented a new and useful percutaneously implantable replacement heart valve **device** and method of making same, of which the following is the Specification.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is in the field of heart valve replacement. More specifically, the present invention is directed to a percutaneously implantable replacement heart valve and method of making same.

2. Description of Related Art

There have been numerous efforts in the field of heart valve replacement to improve both the durability and effectiveness of replacement heart valves as well as the ease of implantation. A brief description of heart valves and heart function follows to provide relevant background for the present invention.

There are four valves in the heart that serve to direct the flow of blood through the two sides of the heart in a forward direction. On the left (systemic) side of the heart are: 1) the mitral valve, located between the left atrium and the left ventricle, and 2) the aortic valve, located between the left ventricle and the aorta. These two valves direct oxygenated blood coming from the lungs through the left side of the heart into the aorta for distribution to the body. On the right (pulmonary) side of the heart are: 1) the tricuspid valve, located between the right atrium and the right ventricle, and 2) the pulmonary valve, located between the right ventricle and the pulmonary artery. These two valves direct de-oxygenated blood coming from the body through the right side of the heart into the pulmonary artery for distribution to the lungs, where it again becomes re-oxygenated to begin the circuit anew.

Heart valves are passive structures that simply open and close in response to differential pressures on either side of the particular valve. They consist of moveable "leaflets" that are designed simply to open and close in response to differential pressures on either side of the valve's leaflets. The mitral valve has two leaflets and the tricuspid valve has three. The

aortic and pulmonary valves are referred to as "semilunar valves" because of the unique appearance of their leaflets, which are more aptly termed "cusps" and are shaped somewhat like a half-moon. The aortic and pulmonary valves each have three cusps.

In general, the components of heart valves include the valve annulus, which will remain as a roughly circular open ring after the leaflets of a diseased or damaged valve have been removed; leaflets or cusps; papillary muscles which are attached at their bases to the interior surface of the left or right ventricular wall; and multiple chordae tendineae, which couple the valve leaflets or cusps to the papillary muscles. There is no one-to-one chordal connection between the leaflets and the papillary muscles; instead, numerous chordae are present, and chordae from each papillary muscle attach to both of the valve leaflets.

When the left ventricular wall relaxes so that the ventricular chamber enlarges and draws in blood, the leaflets of the mitral valve separate and the valve opens. Oxygenated blood flows in a downward direction through the valve, to fill the expanding ventricular cavity. Once the left ventricular cavity has filled, the left ventricle contracts, causing a rapid rise in the left ventricular cavitary pressure. This causes the mitral valve to close while the aortic valve opens, allowing the oxygenated blood to be ejected from the left ventricle into the aorta. The chordae tendineae of the mitral valve prevent the mitral leaflets from prolapsing back into the left atrium when the left ventricular chamber contracts.

The three leaflets, chordae tendineae, and papillary muscles of the tricuspid valve function in a similar manner, in response to the filling of the right ventricle and its subsequent contraction. The cusps of the aortic valve also respond passively to pressure differentials between the left ventricle and the aorta. When the left ventricle contracts, the aortic valve cusps open to allow the flow of oxygenated blood from the left ventricle into the aorta. When the left ventricle relaxes, the aortic valve cusps reapproximate to prevent the blood which has entered the aorta from leaking (regurgitating) back into the left ventricle. The pulmonary valve cusps

respond passively in the same manner in response to relaxation and contraction of the right ventricle in moving de-oxygenated blood into the pulmonary artery and thence to the lungs for re-oxygenation. Neither of these semilunar valves has associated chordae tendineae or papillary muscles.

Problems that can develop with heart valves consist of stenosis, in which a valve does not open properly, and/or insufficiency, also called regurgitation, in which a valve does not close properly. In addition to stenosis and insufficiency of heart valves, heart valves may need to be surgically repaired or replaced due to certain types of bacterial or fungal infections in which the valve may continue to function normally, but nevertheless harbors an overgrowth of bacteria (vegetation) on the leaflets of the valve that may embolize and lodge downstream in a vital artery. If such vegetations are on the valves of the left side (i.e., the systemic circulation side) of the heart, embolization may occur, resulting in sudden loss of the blood supply to the affected body organ and immediate malfunction of that organ. The organ most commonly affected by such embolization is the brain, in which case the patient suffers a stroke. Thus, surgical replacement of either the mitral or aortic valve (left-sided heart valves) may be necessary for this problem even though neither stenosis nor insufficiency of either valve is present. Likewise, bacterial or fungal vegetations on the tricuspid valve may embolize to the lungs resulting in a lung abscess and therefore, may require replacement of the tricuspid valve even though no tricuspid valve stenosis or insufficiency is present.

These problems are treated by surgical repair of valves, although often the valves are too diseased to repair and must be replaced. If a heart valve must be replaced, there are currently several options available, and the choice of a particular type of artificial valve depends on factors such as the location of the valve, the age and other specifics of the patient, and the surgeon's experiences and preferences. Currently in the United States over 100,000 defective heart valves are replaced annually, at an approximate cost of $30-50,000 per procedure, and

thus it would be desirable if heart valves could be replaced using minimally invasive techniques and without having to repeat the procedure within a matter of years due to the lack of durability of the replacement heart valve. It would be especially advantageous if a defective heart valve could be removed via an endovascular procedure, that is, a procedure where the invasion into the body is through a blood vessel such as the femoral artery. The procedure is then carried out percutaneously and transluminally using the vascular system to convey appropriate devices to the position in the body wherein it is desired to carry out the desired procedure. An example of such a procedure would be angioplasty, wherein a catheter carrying a small balloon at its distal end is manipulated through the body's vessels to a point where there is a blockage in a vessel. The balloon is expanded to create an opening in the blockage, and then the balloon is deflated and the catheter and balloon are removed from the vessel.

Endovascular procedures have substantial benefits both from the standpoint of health and safety as well as cost. Such procedures require minimal invasion of the human body, and there is consequently considerable reduction and in some instances even elimination, of the use of a general anesthesia and much shorter hospital stays.

Replacement heart valves can be categorized as either artificial mechanical valves, transplanted valves and tissue valves. Replacement heart valves are designed to optimize hemodynamic performance, thrombogenicity and durability. Another factor taken into consideration is the relative ease of surgical implantation.

Mechanical valves are typically constructed from nonbiological materials such as plastics, metals and other artificial materials which, while durable, are expensive and prone to blood clotting which increases the risk of an embolism. Anticoagulants taken to help against blood clotting can further complicate the patient's health due to increased risks for hemorrhages.

Transplanted valves are natural valves taken from cadavers. These valves are typically removed and frozen in liquid nitrogen, and are stored for later use. They are typically fixed in glutaraldehyde to eliminate antigenicity and are sutured in place, typically with a stent.

Artificial tissue valves are valves constructed from animal tissue, such as bovine or porcine tissue. Efforts have also been made at using tissue from the patient for which the valve will be constructed.

Most tissue valves are constructed by sewing the leaflets of pig aortic valves to a stent to hold the leaflets in proper position, or by constructing valve leaflets from the pericardial sac of cows or pigs and sewing them to a stent. The porcine or bovine tissue is chemically treated to alleviate any antigenicity. The pericardium is a membrane that surrounds the heart and isolates it from the rest of the chest wall structures. The pericardium is a thin and very slippery, which makes it difficult for suturing in a millimetricly precise way. The method of making the replacement heart valve of the present invention solves this problem through a process to dry the pericardium in such a way that makes it possible to handle and fold more easily.

For example, one prior replacement heart valve requires each sculpted leaflet to be trimmed in a way that forms an extended flap, which becomes a relatively narrow strand of tissue near its tip. The tip of each pericardial tissue strand is sutured directly to a papillary muscle, causing the strand to mimic a chordae tendineae. Each strand extends from the center of a leaflet in the valve, and each strand is sutured directly to either an anterior and posterior papillary muscle. This requires each leaflet to be positioned directly over a papillary muscle. This effectively rotates the leaflets of the valve about 90 degrees as compared to the leaflets of a native valve. The line of commissure between the leaflets, when they are pressed together during systole, will bisect (at a perpendicular angle) an imaginary line that crosses the peaks of the two papillary muscles, instead of lying roughly along that line as occurs in a native valve.

A different approach to creating artificial tissue valves is described in U.S. Patent Nos. 5,163,955 to Calvin, et al. and 5,571,174 and 5,653,749 to Love. Using a cutting die, the pericardial tissue is cut into a carefully defined geometric shape, treated with glutaraldehyde, then clamped in a sandwich-fashion between two stent components. This creates a tri-leaflet valve that resembles an aortic or pulmonary valve, having semilunar-type cusps rather than atrioventricular-type leaflets.

U.S. Patent No. 3,671,979 to Moulopoulos describes an endovascularly inserted conical shaped umbrella-like valve positioned and held in place by an elongated mounting catheter at a supra-annular site to the aortic valve in a nearby arterial vessel. The conical end points toward the malfunctioning aortic valve and the umbrella's distal ends open up against the aorta wall with reverse blood flow, thereby preventing regurgitation.

U.S. Patent No. 4,056,854 to Boretos describes an endovascularly inserted, catheter mounted, supra-annular valve in which the circular frame abuts the wall of the artery and attached flaps of flexible membrane extend distally in the vasculature. The flaps lie against the artery wall during forward flow, and close inward towards the central catheter to prevent regurgitation during reverse blood flow. The Boretos valve was designed to be positioned against the artery wall during forward flow, as compared to the mid-center position of the Moulopoulos valve, to reduce the stagnation of blood flow and consequent thrombus and embolic formation expected from a valve at mid-center position.

The main advantage of tissue valves is that they do not cause blood clots to form as readily as do the mechanical valves, and therefore, they do not absolutely require systemic anticoagulation. The major disadvantage of tissue valves is that they lack the long-term durability of mechanical valves. Tissue valves have a significant failure rate, usually within ten years following implantation. One cause of these failures is believed to be the chemical treatment of the animal tissue that prevents it from being antigenic to the patient. In addition,

the presence of extensive suturing prevents the artificial tissue valve from being anatomically accurate in comparison to a normal heart valve, even in the aortic valve position.

A shortcoming of prior artificial tissue valves has been the inability to effectively simulate the exact anatomy of a native heart valve. Although transplanted human or porcine aortic valves have the gross appearance of native aortic valves, the fixation process (freezing with liquid nitrogen, and chemical treatment, respectively) alters the histologic characteristics of the valve tissue. Porcine and bovine pericardial valves not only require chemical preparation (usually involving fixation with glutaraldehyde), but the leaflets must be sutured to cloth-covered stents in order to hold the leaflets in position for proper opening and closing of the valve. Additionally, the leaflets of most such tissue valves are constructed by cutting or suturing the tissue material, resulting in leaflets that do not duplicate the form and function of a real valve.

SUMMARY OF THE INVENTION

The present invention is a replacement heart valve device and method of making same. The replacement heart valve device, in a preferred embodiment, comprises a stent made of stainless steel or self-expanding nitinol and a completely newly designed artificial biological tissue valve disposed within the inner space of the stent. The cusp or leaflet portion of the valve means is formed by folding of the pericardium material used to create the valve. **Other forms of tissue and suitable synthetic materials can also be used for the valve, formed in a sheet of starting material. The folded design provides a number of advantages over prior designs, including improved resistance to tearing at suture lines.** The cusps/leaflets open in response to blood flow in one direction and close in response to blood flow in the opposite direction. Preferably the tubular portion of the valve means contains the same number of cusps as the native valve being replaced, in substantially the same size and configuration. The outer surface of the valve means is attached to the stent member.

The replacement heart valve device is preferably implanted using a delivery system having a central part which consists of a flexible hollow tube catheter that allows a metallic guide wire to be advanced inside it. The stented valve is collapsed over the central tube and it is covered by a movable sheath. The sheath keeps the stented valve in the collapsed position. Once the cover sheath is moved backwards, the stented valve can be deployed. The endovascular stented-valve, in a preferred embodiment, is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow. **The stent can either be self-expanding or the stent can be expandable through use of a balloon catheter.**

The present invention also comprises a method of making a replacement heart valve device. In order to make the valve, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a solution of gluteraldehyde, preferably at a concentration of about 0.07% during 36 hours, then the pericardium is transferred to a solution of ethanol, preferably at a concentration of about 60% before making the valve. The material is dried in order to make it easier to handle and fold. The valve is formed by taking a rectangular fragment of bovine pericardium and folding it in such a way that forms a three-leaflet valve. The valve can also be made **in the same manner** from fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts or synthetic non-biological, non-thrombogenic material. The folding of the pericardium material to create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of the valve leaflets. The valve is rehydrated after being formed. The method of the present invention also greatly reduces the risk of tearing of the cusps or leaflets, since they are integral to the valve rather than being attached by suturing.

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as

used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The replacement heart valve device of the present invention can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation medication and treatment. The present invention can be practiced in applications with respect to each of the heart's valves.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 depicts a side perspective view of the replacement heart valve device of the present invention in one embodiment ~~without~~with the ~~stent~~valve in the closed position.

Fig. 2 depicts the folds which form the leaflets or cusps of the replacement heart valve of the present invention in one embodiment.

~~Fig.~~Figs. 3 ~~depicts~~A and 3B depict the procedure for folding the pericardium tissue starting material to create the replacement heart valve of the present invention.

Fig. 4 depicts a side perspective view of the replacement heart valve device of the present invention in one embodiment represented as if implanted within an artery.

Fig. 4~~5~~ depicts a side ~~perspective~~-view of one embodiment of the replacement heart valve device of the present invention ~~in one embodiment~~-mounted within a self-expanding stent, with the stent in the expanded position.

Fig. ~~5~~6 depicts a ~~cross-sectional~~side perspective view of one embodiment of the replacement heart valve device of the present invention mounted within a self-expanding stent~~,~~ ~~with the stent~~ in the ~~expanded~~collapsed position.

~~Fig. 6 depicts a side perspective view of one embodiment of the replacement heart valve of the present invention mounted within a self-expanding stent in the collapsed position.~~

~~Fig.~~Fig. 7 ~~depicts~~depicts the suture points of one embodiment of the replacement heart valve device of the present invention.

Fig. 8 depicts the implantation/delivery system used with the present invention in a preferred embodiment.

DESCRIPTION OF A PREFERRED EMBODIMENT

The present invention comprises a percutaneously implantable replacement heart valve and a method for making same. The artificial heart valve device of the present invention is capable of exhibiting a variable diameter between a compressed or collapsed position and an expanded position. A preferred embodiment of the replacement heart valve device according to the present invention is set forth in ~~FIGS~~FIG. ~~1 and 2.~~5. The replacement heart valve device comprises a stent member ~~—~~100 and a flexible valve means ~~—~~200. The stent member 100 is preferably self-expanding although balloon-expandable stents can be used as well, and has a first cylindrical shape in its compressed or collapsed configuration and a second, larger cylindrical shape in its expanded configuration. ~~The~~Referring to FIG. 1, the valve means 200 comprises a generally tubular ~~center~~ portion 210 and, preferably, a peripheral upstanding cusp or leaflet portion~~.~~ 220. The valve means 200 is disposed within the cylindrical stent member 100 with the tubular portion 210 transverse of and at some acute angle relative to the stent walls. The diameter of the tubular portion 210 is substantially the same as the inside diameter of the stent member in its initial expanded configuration. The peripheral upstanding cusp or leaflet portion 220 is disposed substantially parallel to the walls of the stent member similar to a cuff on a shirt. The ~~center~~cusp or leaflet portion ~~—~~220 of the valve means ~~—~~200

is generally tubular in shape and comprises three leaflets —221, 222 and 223 as shown, although it is understood that there could be from two to four leaflets. The tubular portion of the valve means 200 is attached to the stent member —100 by a plurality of sutures —300, as depicted in FIG. 7.

The leaflet portion 220 of the valve means —200 extends across or transverse of the cylindrical stent. 100. The leaflets —221, 222 and 223 are the actual valve and allow for one-way flow of blood. The leaflet portion 220 as connected to the rest of the valve resembles the cuff of a shirt. The configuration of the stent member —100 and the flexible, resilient material of construction allows the valve to collapse into a relatively small cylinder — as seen in FIG. 6. The replacement heart valve will not stay in its collapsed configuration without being restrained. Once the restraint is removed, the self-expanding stent member —100 will cause the artificial heart valve to take its expanded configuration, as seen in FIG. —5.

Stent Member

The stent member —100 preferably comprises a self-expanding nickel-titanium alloy stent, also called "nitinol," in a sine wave-like configuration as shown in FIG. ~~1.~~5. An enlarged view of a preferred embodiment of the stent member for use in the replacement heart valve of the invention is depicted in FIG. 5. The stent member —100 includes a length of wire —110 formed in a closed zigzag configuration. The wire can be a single piece, stamped or extruded, or it could be formed by welding the free ends together ~~as at~~ —. The straight sections — of the stent member 100 are joined by bends —. The stent is readily compressible to a small cylindrical shape as depicted in FIGS. 6 and 8, and resiliently self-expandable to the shape shown in FIG. 5.

The stent ~~members~~member 100 of the artificial heart ~~valves~~valve device of the present invention may be made from various metal alloys, titanium, titanium alloy, nitinol,

stainless steel, or other resilient, flexible non-toxic, non-thrombogenic, physiologically acceptable and biocompatible materials. The configuration may be the zigzag configuration shown or a sine wave configuration, mesh configuration or a similar configuration which will allow the stent to be readily collapsible and self-expandable. When a zigzag or sine wave configured stent member is used, the diameter of the wire from which the stent is made ~~should~~is ~~be~~preferably from about [0.010 to 0.035] inches and still, preferably from about [0.012 to 0.025] inches. The diameter of the stent member will be from about [1.5 to 3.5 cm], preferably from about [1.75 to 3.00 cm], and the length of the stent member will be from about [1.0 to 10 cm], preferably from about [1.1 to 5 cm.]

The stent used in a preferred embodiment of the present invention is fabricated from a "shaped memory" alloy, nitinol, which is composed of nickel and titanium. Nitinol wire is first fashioned into the desired shape for the device and then the device is heat annealed. A meshwork of nitinol wire of approximately 0.008 inch gauge is formed into a tubular structure with a minimum central diameter of 20 min to make the stent. Away from its central portion, the tubular structure flares markedly at both ends in a trumpet-like configuration. The maximum diameter of the flared ends of the stent is approximately 30 mm. The purpose of the stent is to maintain a semi-rigid patent channel through the diseased cardiac valve following its implantation.

When the components of the replacement heart valve device are exposed to cold temperatures, they become very flexible and supple, allowing them to be compressed down and pass easily through the delivery sheath. A cold temperature is maintained within the sheath during delivery to the deployment site by constantly infusing the sheath with an iced saline solution. Once the valve components are exposed to body temperature at the end of the sheath, they instantaneously reassume their predetermined shapes, thus allowing them to function as designed.

Preferably the stent member 100 carries a plurality of barbs extending outwardly from the outside surface of the stent member for fixing the heart valve device in a desired position. More preferably the barbs are disposed in two spaced-apart, circular configurations with the barbs in one circle extending in an upstream direction and the barbs in the other circle extending in a downstream direction. It is especially preferable that the barbs on the inflow side of the valve point in the direction of flow and the barbs on the outflow side point in the direction opposite to flow. It is preferred that the stent be formed of titanium alloy wire or other flexible, relatively rigid, physiologically acceptable material arranged in a closed zigzag configuration so that the stent member will readily collapse and expand as pressure is applied and released, respectively.

Valve Means

The valve means 200 is flexible, compressible, host-compatible, and non-thrombogenic. The valve means 200 can be made from various materials, for example, fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts. Synthetic biocompatible materials such as polytetrafluoroethylene, polyester and the like may be used. The preferred material for the valve means 200 is bovine pericardium tissue. The valve means 200 is disposed within the cylindrical stent member 100 with the tubular portion 210 transverse of and at some acute angle relative to the stent walls. The diameter of the tubular portion 210 is substantially the same as the inside diameter of the stent member 100 in its initial expanded configuration. The peripheral upstanding cusp or leaflet portion 220 is disposed substantially parallel to the walls of the stent member 100 similar to a cuff on a shirt.

The cusp or leaflet portion 220 of the valve means 200 is formed by folding of the pericardium material used to create the valve. FIGS. 3A and 3B depict the way the sheet of heart valve starting material is folded. The cusps/leaflets 221, 222 and 223 open in

response to blood flow in one direction and close in response to blood flow in the opposite direction. Preferably the ~~tubular~~cusp or leaflet portion 220 of the valve means 200 contains the same number of cusps as the native valve being replaced, in substantially the same size and configuration.

Method of Making Replacement Heart Valve Device

The present invention also comprises a method of making a replacement heart valve device. In order to make the valve, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a solution of gluteraldehyde, preferably at a concentration of about 0.07% during 36 hours, then the pericardium is transferred to a solution of ethanol, preferably at a concentration of about 60% before making the valve. The valve is formed by taking a rectangular fragment of bovine pericardium and folding it in such a way that forms a three-leaflet or desired number of leaflet valve. ~~FIG. 2 depicts the folds which form the cusps or leaflets, and FIG.~~ as shown in FIGS. 3A and 3 ~~depicts the folding procedure~~B. The folding of the pericardium material to create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of the valve leaflets. It also greatly reduces the risk of tearing of the cusps or leaflets, since they are integral to the valve rather than being attached by suturing.

In order to make the pericardium material less slippery and easier to fold, the pericardium is dried, preferably with artificial light using a 60-watt lamp with the pericardium material placed in a flat aluminum surface to dry it homogeneously. A photo drying machine can also be used. The final result is a homogeneous tissue that looks like plastic paper and makes it easy to manipulate to fold and suture the valve. Once the valve is formed it is re-hydrated by placing it in a solution of water and 70% alcohol. In approximately 3 days the valve is fully rehydrated.

Attachment of the Valve Means to the Stent Member

The valve means 200 is then attached to the inner channel of the stent member 100 by suturing the outer surface of the valve means' pericardium material to the stent member. ~~Fig~~FIG. 7 depicts preferred suture points of one embodiment of the present invention: 3-point fixation or 6-point fixation at each border of the stent. Other fixation schemes can be utilized, such as, by way of non-limiting example, fixation on both borders 18 points at each end following a single plane and 36 fixation points following to adjacent vertical planes. The use of only one plane of fixation points helps prevent systolic collapse of the proximal edge of the valve means. A fold on the border of the pericardium material prevents tearing. The attachment position of the valve is preferably closer to the proximal and wider part of the stent.

The sequence of steps can vary. The pericardium material can be fixed in glutaraldehyde before attachment to the stent or the valve can be formed and then fixed with gluteraldehyde after mounting it in the stent. One observation noted is that the material becomes whiter and apparently increases its elasticity. 1mm vascular clips keep the cusps coapted while fixing them in gluteraldehyde. The use of metallic clips to keep both cusps adjacent to each other after 24 hours of fixation in gluteraldehyde helps to educate the material and make the primary position of the valve cusps adjacent to each other. After the clips are removed, there are no lesions to the valve.

Different suture materials can be used, including, in a preferred embodiment, prolene 6-0 and Mersilene 6-0 which is a braided suture.

Implantation of Replacement Heart Valve Device

The replacement heart valve device of the present invention is preferably used in surgical procedures involving the percutaneous and transluminal removal of the diseased or defective heart valve and the percutaneous and transluminal implantation of the new heart

valve described above. The defective heart valve is removed by a suitable modality, such as, for example, laser, ultrasound, mechanical, or other suitable forms of delivery of energy, or phacoemulsion, including, but not limited to, laser lithotripsy, mechanical lithotripsy, electrohydraulic lithotripsy, and laser or mechanical ablation. To remove the native heart valve that is being replaced, a guidewire is inserted percutaneously and transluminally using standard vascular or angiography techniques. The distal end of the guidewire is manipulated to extend through and across the defective heart valve. Then a catheter is advanced distally through the femoral artery to a point proximal to the defective heart valve, between the origin of the coronary artery and the origin of the right subclavian artery. The position of the distal end of catheter can be monitored by observation of radiopaque markers. Collector member is preferably inflated and occludes the aorta at a point between the origin of the coronary artery and the right subclavian artery. Next, a balloon and cutting tool are advanced through the catheter so that the cutting tool and uninflated balloon are distal to the defective heart valve. Optionally an additional step, such as balloon dilatation or atherectomy, may be required to provide a passageway through the heart valve. A catheter is also placed into the coronary sinus via a transjugular puncture. This catheter is used for infusion of blood or cardioplegia solution during the portion of the procedure when the aorta is occluded. The absence of valves in the cardiac venous system allows retrograde flow so that there will be an effluence of fluid from the coronary arteries. This flow of fluid is desired to prevent embolization of material into the coronary arteries during the procedure. Once the cutting tool is in place, the balloon is inflated and flexible shaft is rotated. Once the cutting tool has reached the appropriate rotation speed, the cutting tool is pulled proximally to remove the defective heart valve. The balloon and the cutting tool are spaced apart so that the inflated balloon will be stopped by the perimeter, unremoved portion of the defective heart valve, which will signal the physician that the valve has been removed, as well as protect the heart and aorta from damage from the valve removal

device. Once it is determined that the defective heart valve has been removed, the cutting tool is slowed or stopped altogether and the balloon is deflated. The cutting tool and the deflated balloon are pulled proximally through catheter. Then, a catheter containing an artificial heart valve is inserted and the artificial heart valve is placed as described above.

The delivery and implantation system of the replacement artificial heart valve of the present invention percutaneously and transluminally includes a flexible catheter **400** which may be inserted into a vessel of the patient and moved within that vessel **as depicted in FIG. 8.** The distal end **410** of the catheter**, 400,** which is hollow and carries the replacement heart valve **device** of the present invention in its collapsed configuration, is guided to a site where it is desired to implant the replacement heart valve. The catheter has a pusher member **420** disposed within the catheter lumen **430** and extending from the proximal end **440** of the catheter to the hollow section at the distal end **410** of the catheter. Once the distal end **410** of the catheter is positioned as desired, the pusher mechanism **420** is activated and the distal portion of the replacement heart valve **device** is pushed out of the catheter and the stent member **100** partially expands. In this position the stent member **100** is restrained so that it doesn't pop out and is held for controlled release, with the potential that the replacement heart valve **device** can be recovered if there is a problem with the positioning. The catheter **400** is ~~them~~**then** retracted slightly and the replacement heart valve **device** is completely pushed out of the catheter **400** and released from the catheter to allow the stent member **100** to fully expand. If the stent member **100 preferably** includes two circles of barbs on its outer surface as previously described, the first push and retraction will set one circle of barbs in adjacent tissue and the second push and release of the replacement heart valve **device** will set the other circle of barbs in adjacent tissue and securely fix the replacement heart valve **device** in place when the ~~valve~~**device** is released from the catheter.

Alternatively, or in combination with the above, the replacement heart valve **device** could be positioned over a metallic guidewire that is advanced through the catheter. The replacement heart valve device of the present invention is preferably implanted percutaneously through an aortic passageway to, or near to, the location from which the natural heart valve has been removed. Referring to ~~Fig~~**FIG**. 8, the implantation system comprises a flexible hollow tube catheter **410** with a metallic guide wire **450** disposed within it. The stented valve **device** is collapsed over the tube and is covered by a moveable sheath **460**. The moveable sheath **460** maintains the stented valve **device** in the collapsed position. **The implantation method** comprises the following steps: inserting the replacement heart valve device in the lumen of a central blood vessel via entry through the brachial or femoral artery using a needle or exposing the artery surgically; placing a guide wire **450** through the entry vessel and advancing it to the desired position; advancing dilators over the wire to increase the lumen of the entry site, thereby preparing the artery to receive the heart-valve; and advancing the heart-valve **device** to the desired place. The stented-valve **device** is released by pulling the cover sheath **460** of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advanced over the wire and an aortogram is performed to assess the competency of the valve.

Before creation of the valve means and implantation, the patient is studied to determine the architecture of the patient's heart. Useful techniques include fluoroscopy, transesophageal echocardiography, MRI, and angiography. The results of this study will enable the physician to determine the appropriate size for the replacement heart valve.

In one procedure for implantation of the replacement heart valve device of the present invention, the femoral artery of the patient is canulated using a Cook needle and a standard J wire is advanced into the artery either percutaneously or after surgical exposure of the artery. An 8 F introducer is advanced into the femoral artery over the wire. The J wire is then

withdrawn and anticoagulation is started using heparin 60 U/Kg intravenously. Once vascular access is obtained an aortogram is performed for anatomical evaluation. A special wire (Lunderquist or Amplatz superstiff) is advanced into the aortic arch and dilators progressively larger are advanced over the wire, starting with 12 F all the way to 18 F. After this the valve introducer device containing the prosthetic valve device is then inserted and used to transport the replacement valve over a guidewire to the desired position. The stented-valve is released by pulling the cover sheath of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advanced over the wire and repeat aortogram is performed to assess the competency of the valve.

When the device is used to treat severe leakage of the aortic valve, the native valve is left in place and the prosthetic stented valve is deployed below the subclavian artery. When the device is used to treat aortic stenosis, first the stenotic valve needs to be opened using either aortic valvuloplasty or cutting and if this procedure induces aortic insufficiency the stented valve is placed to prevent the regurgitation.

Intravascular ultrasound or an angioscope passed intravascularly via either the venous system through the intra-atrial septum across the mitral valve and into the left ventricle or retrograde via the femoral artery would provide the added benefit of allowing constant high definition imaging of the entire procedure and high flow irrigation.

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The prosthetic valve device can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and

patients unable to tolerate open heart procedures or life-long anticoagulation. In addition, with the development of longer-life, flexible, non-thrombogenic synthetic valve alternatives to bioprosthesis, the prosthetic valve device will be indicated in all patients where the relative advantages of the life-span, the non-thrombogenic quality, and the ease of insertion of prosthetic valve devices outweigh the disadvantages of mechanical valves. Anticoagulation may be beneficial in certain clinical situations for either short or long term use.

This method of percutaneous endovascular heart-valve replacement, in contrast to open heart surgical procedures, requires only local anesthesia, partial or no cardiac bypass, one to two days hospitalization, and should result in a reduced mortality rate as compared to open heart procedures.

While the present invention has been shown and described herein in what is considered to be a preferred embodiment thereof, illustrating the results and advantages over the prior art obtained through the present invention, the invention is not limited to the specific embodiments described above. Thus, the forms of the invention shown and described herein are to be taken as illustrative and other embodiments may be selected without departing from the spirit and scope of the present invention.

CLAIMS

Having thus described the invention, what is claimed is:

1. A percutaneously implantable replacement heart valve device comprising a ~~self-expanding~~-stent member and an artificial valve means made of biocompatible tissue material and disposed within the inner cavity of said stent member affixed at one or more points to said stent member, said valve means having cusps or leaflets formed by folding of **a substantially rectangular sheet of** said biocompatible tissue material.

2. The percutaneously implantable replacement heart valve **device** of claim 1, wherein said stent member is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium, stainless steel **[add others]**.

3. The percutaneously implantable replacement heart valve **device** of claim 1, wherein said biocompatible tissue material of said valve means comprises bovine pericardium tissue.

4. The percutaneously implantable replacement heart valve **device** of claim 1, wherein said biocompatible tissue material of said valve means comprises porcine pericardium tissue.

5. The percutaneously implantable replacement heart valve **device** of claim 1, wherein said biocompatible tissue material of said valve means comprises autologous tissue obtained from the patient into whom said replacement heart valve **device** will be implanted.

6. The percutaneously implantable heart valve device of claim 1, wherein said stent member is self-expanding when implanted.

7. The percutaneously implantable heart valve device of claim 1, wherein said stent member is balloon catheter expandable when implanted.

~~6.~~8. A method of making a percutaneously implantable replacement heart valve_ device comprising the following steps:

obtaining a substantially rectangular ~~segment~~sheet of biocompatible tissue material;

soaking said biocompatible tissue material in a gluteraldehyde solution;

transferring said biocompatible tissue material from said gluteraldehyde solution to an ethanol solution;

drying said biocompatible tissue material;

folding said dried biocompatible tissue material to create cusps or leaflets and a cuffed tubular valve structure;

affixing said folded biocompatible tissue material to the inner cavity of a stent.

9. The method of making a percutaneously implantable replacement heart valve device claim 8, wherein said biocompatible tissue material comprises bovine pericardium tissue.

10. The method of making a percutaneously implantable replacement heart valve device claim 8, wherein said biocompatible tissue material comprises porcine pericardium tissue.

11. The method of making a percutaneously implantable replacement heart valve device claim 8, wherein said biocompatible tissue material comprises autologous tissue obtained from the patient into whom said replacement heart valve device will be implanted.

12. The method of making a percutaneously implantable replacement heart valve device of claim 8, wherein said stent is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium, stainless steel, [add others].

13. The method of making a percutaneously implantable replacement heart valve device of claim 8, wherein said stent is self-expanding when implanted.

14. The method of making a percutaneously implantable replacement heart valve device of claim 8, wherein said stent is balloon catheter expandable when implanted.

ABSTRACT

The present invention comprises a percutaneously implantable replacement heart valve device and a method of making same. The replacement heart valve device comprises a stent member made of stainless steel or self-expanding nitinol, a biological tissue artificial valve means disposed within the inner space of the stent member. An implantation and delivery system having a central part which consists of a flexible hollow tube catheter that allows a metallic wire guide to be advanced inside it. The endovascular stented-valve is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow. The present invention also comprises a novel method of making a replacement heart valve by taking a rectangular fragment of bovine pericardium treating, drying, folding and rehydrating it in such a way that forms a two- or three-leaflet/cusp valve with the leaflets/cusps formed by folding, thereby eliminating the extent of suturing required, providing improved durability and function.

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Document comparison done by DeltaView on Friday, December 28, 2001 12:48:46

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Document 2	pcdocs://MIAMI/1341939/2
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Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/887,688	07/10/2004	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☒		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			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 $250 ($125 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			TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
	02/28/2008	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	* 36	Minus	** 33	= 3	X $25 =	75	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 8	Minus	***5	= 3	X $105 =	315	OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE	390	OR	TOTAL ADD'L FEE	

		(Column 1)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	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.

Legal Instrument Examiner:
/JOY DOBBS/

Document code: WFEE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/887,688	07/10/2004	David Paniagua	51458.010100	4909

54353 7590 07/15/2008

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EXAMINER	
MILLER, CHERYL L	
ART UNIT	PAPER NUMBER
3738	

MAIL DATE	DELIVERY MODE
07/15/2008	PAPER

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.

Office Action Summary	Application No.	Applicant(s)	
	10/887,688	PANIAGUA ET AL.	
	Examiner	Art Unit	
	CHERYL MILLER	3738	

-- 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 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *28 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ 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

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *11-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 27-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ 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).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

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).

a)☐ All b)☐ Some * c)☐ None of:

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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

This application repeats a substantial portion of prior Application No. 10/037,266, filed January 4, 2002, and adds and claims additional disclosure not presented in the prior application. Since this application names an inventor or inventors named in the prior application, it may constitute a continuation-in-part of the prior application. Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78. Added subject new to the current application includes: the sheet material being *unslit* and *without affixing separate cusps* (claims 1, 33, and 36), the material to be made of *metals* (claim 8), a *second sheet* forming a *cuff* (claim 27), and the configuration and formation of multiple folds (claims 34, 35). All this subject matter has been given the priority date of July 10, 2004 as it was not found in the parent application.

Response to Amendment

The declaration filed on February 28, 2008 under 37 CFR 1.131 has been considered but is ineffective to overcome the Spenser (US 2003/0153974 A1) and Bailey (US 6,652,578 B2) references.

Although all inventors signatures are present in the declaration, the signature of Eduardo Induni was not singed before a notary public, thus the declaration is insufficient for this reason. See MPEP 715.04 [R-6], I, II.

The evidence submitted is additionally insufficient to establish a conception of the invention prior to the effective date of the Bailey reference. While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a

complete disclosure to another. Conception is more than a vague idea of how to solve a problem. The requisite means themselves and their interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897). Although the exhibits disclose general recitation of a "new valve" and details of the material used and how it is chemically treated, there is no evidence of the actual structure of the valve (location of the fold, how it is shaped or what it looks like). There is reference to diagrams or figures in Exhibit A, however no figures were found attached. It is not clear that applicants had support for the fold and location of the fold, non-slit and not separate attached leaflets that are claimed, at the time prior to December 31, 1999. The declaration is therefore insufficient to overcome the Bailey reference.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> 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 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7 and 8 are indefinite since the independent claims require the valve to be a *tissue* material (natural) and claims 7 and 8 are attempting to alter the claim to make the material synthetic (non tissue). It is unclear how the material may be tissue and also synthetic at the same time.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 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 –
>
> (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 1, 2, 7-10, 27, 30, and 33-36 are rejected under 35 U.S.C. 102(e) as being anticipated by Bailey et al. (US 6,652,578, cited previously). Bailey discloses an implantable heart valve (fig.2, 8, 14) comprising an expandable stent (12) and an inner flexible compressible valve (26) made of biocompatible tissue (col.8, lines 47-49) disposed within the stent (12) and affixed to the stent (col.9, lines 55-59) the valve having leaflets without slits (see fig.2; valve body disclosed as a tubular graft extension, col.9, lines 7-26). Bailey discloses the stent (12) to be made of the materials claimed (nitinol; col.8, lines 13-18). Bailey discloses the valve to be formed of biological or synthetic materials (col.8, lines 46-49). Bailey's valve is capable of self-expansion or balloon expansion (col.8, lines 13-18). Bailey discloses an outer cuff portion (considered 11a). Bailey discloses the sheet of tissue (11b) having an upper border (top of device in fig.4) with an outward fold (material 11b is folded outwardly at 11a) and a lower border (bottom of 11b in fig.4) having an inward fold (inward fold considered 26). See col.9, lines 27-32.

Claim Rejections - 35 USC § 103

The following is a quotation of 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 3-6, 28-29 and 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bailey et al. (US 6,652,578 B2, cited previously). Referring to claims 3-6, Bailey discloses an implantable valve, the valve being formed of either biological tissue or biocompatible synthetic polymer (col.8, lines 46-49). Bailey does not however, disclose a specific type of biological material (such as claimed, mammal, porcine, or juvenile pericardium or PTFE or polyester biopolymers). It would have been obvious to one having ordinary skill in the art at the time the invention was made to have the specific biological materials claimed, since it has been held to be within the general skill of a worker in the art to select a known material (mammal, porcine, juvenile pericardium) on the basis of its suitability for the intended use (valve replacement) as a matter of obvious design choice. *In re Leshin*, 125 USPQ 416.

Referring to claims 28-29 and 31-32, Bailey discloses attachment of the cuff (11a) to the valve (11b extension 26; col.9, lines 10-19), however is silent to mention how the members are coupled. It would have been obvious to one having ordinary skill in the art at the time the invention was made to use sutures, double sutures to attach the two membranes (cuff and valve) since suturing is a common means of attachment in the vascular art and would be applicable to Bailey's invention. See Fogarty et al, US 6,491,719 B1; col.10, lines 5-8 as evidence of common means of attaching layers of material (31, 32) in the vascular art which include stitching, welding, adhering.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

THIS ACTION IS MADE FINAL. 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 mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHERYL MILLER whose telephone number is (571)272-4755. The examiner can normally be reached on Monday-Friday 7:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Corrine McDermott can be reached on (571) 272-4755. 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.

/Cheryl Miller/
Examiner, Art Unit 3738

/Corrine M McDermott/
Supervisory Patent Examiner, Art Unit 3738

Notice of References Cited	Application/Control No. 10/887,688	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-5,855,601	01-1999	Bessler et al.	623/2.38
*	B	US-5,840,081	11-1998	Andersen et al.	623/1.11
*	C	US-6,425,916 B1	07-2002	Garrison et al.	623/2.11
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	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

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L2	76	garrison.in. and valve and frame	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 17:51
L3	10	garrison.in. and (623/1.24.ccls. or 623/1.26.ccls.)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 17:53
L4	31	(US-20060167543-$ or US-20060142846-$ or US-20050096736-$ or US-20040106976-$ or US-20040098098-$ or US-20040039436-$ or US-20030114913-$ or US-20030023300-$ or US-20020107565-$ or US-20010021872-$ or US-20010010017-$ or US-20050075725-$ or US-20030153974-$ or US-20030120330-$ or US-20010041928-$ or US-20080154356-$).did. or (US-7195641-$ or US-6979350-$ or US-6730118-$ or US-6652578-$ or US-6458153-$ or US-5957949-$ or US-5855601-$ or US-6491719-$ or US-6168614-$ or US-6027525-$ or US-5840081-$ or US-5713953-$ or US-5607465-$ or US-4655771-$ or US-4275469-$).did.	US-PGPUB; USPAT	OR	ON	2008/07/13 17:56
S1	367	623/1.24.ccls. or 623/1.26.ccls.	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/25 15:58
S2	1	"10/037,266"	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/25 16:12
S3	1	"10/887,688"	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/25 16:13
S4	123	S1 and @rlad<"20020104"	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/25 16:13
S5	119	S1 and @ad<"20020104"	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/25 16:14

S6	188	S4 S5	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/25 16:14
S7	17	(US-20060167543-$ or US-20060142846-$ or US-20050096736-$ or US-20040106976-$ or US-20040098098-$ or US-20040039436-$ or US-20030114913-$ or US-20030023300-$ or US-20020107565-$ or US-20010021872-$ or US-20010010017-$).did. or (US-7195641-$ or US-6979350-$ or US-6730118-$ or US-6652578-$ or US-6458153-$ or US-5957949-$).did.	US-PGPUB; USPAT	OR	ON	2007/11/25 16:49
S8	9	"09/975,750"	US-PGPUB; USPAT	OR	ON	2007/11/25 16:51
S9	1	623/900.ccls. and bessler.in.	US-PGPUB; USPAT	OR	ON	2007/11/25 16:52
S10	1	"5824063".pn.	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/26 08:14
S11	1	"5480424".pn.	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/26 08:17
S12	9	"09/975,750"	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/26 08:30
S13	24	((inner with (graft or liner)) with (stitched or suture$2) with (outer with (graft or liner))) and (623/1.$2.ccls. or 623/2.$2.ccls.)	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/26 08:32
S14	9	S13 and @rlad<"20020104"	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/26 08:32
S15	12	S13 and @ad<"20020104"	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/26 08:32
S16	14	S14 S15	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/26 08:32
S17	1	"6458153".pn.	US-PGPUB; USPAT; EPO; JPO	OR	ON	2008/07/11 19:49
S18	2	"6458153".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/11 19:50

S19	1448	623/1.24.ccls. or 623/1.26.ccls. or 623/2.1$.ccls.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 12:25
S20	906	S19 not 623/2.11.ccls.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 12:26
S21	278	S20 and @rlad<"20020104"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 12:26
S22	377	S20 and @ad<"20020104"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 12:26
S23	518	S21 S22	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 12:26
S24	194	S23 and @pd<"20010104"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 12:29
S25	93	jayaraman.in. and stent	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 15:42
S26	13	jayaraman.in. and stent and valve	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 15:42
S27	308	garrison.in. and valve	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 16:02
S28	27	garrison.in. and valve and stent	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 16:03

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Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/887,688	PANIAGUA ET AL.	
	Examiner	Art Unit	
	CHERYL MILLER	3738	

SEARCHED			
Class	Subclass	Date	Examiner
623	1.24, 1.26, 2.11-2.19	7/13/2008	CM

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
East text search	7/13/2008	CM

12-16-08

1st RCE

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PTO/SB/30 (11-08)
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Request for Continued Examination (RCE) Transmittal

Address to:
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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	10/887,688
Filing Date	July 10, 2004
First Named Inventor	Paniagua
Art Unit	3738
Examiner Name	Miller, Cheryl
Attorney Docket Number	051458.010100

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☑ Enclosed

      i. ☑ Amendment/Reply

      ii. ☑ Affidavit(s)/ Declaration(s)

      iii. ☐ Information Disclosure Statement (IDS)

      iv. ☐ Other _____

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. ☑ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 50-1792.

      i. ☑ RCE fee required under 37 CFR 1.17(e)

      ii. ☑ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☐ Other _____

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	Manuel Valcarcel	Date	November 26, 2008
Name (Print/Type)	Manuel Valcarcel, Esq.	Registration No.	41,360

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Signature			
Name (Print/Type)		Date	

This collection of information is required by 37 CFR 1.114. 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 1.11 and 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: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 051458.010100
In re Application of Paniagua, et al.	
Application Number 10/887,688	Filed July 10, 2004
Group Art Unit 3738	Examiner: Miller, Cheryl L.

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows: (check time period desired):

____	One month (37 CFR 1.17(a)(1))	$ ____
☒	Two months (37 CFR 1.17(a)(2))	$ 490.00
☐	Three months (37 CFR 1.17(a)(3))	$ ____
☐	Four months (37 CFR 1.17(a)(4))	$ ____
☐	Five months (37 CFR 1.17(a)(5))	$ ____

☒ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: $245.00

A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Commissioner has already been authorized to charge fees in this application to a Deposit Account.

☒ The Commissioner is hereby authorized to charge the fee and any additional fees which may be required, or credit any overpayment, to Deposit Account Number 50-1792.

I have enclosed a duplicate copy of this sheet.

I am the ☐ assignee of record of the entire interest.

☐ applicant.

☒ attorney or agent of record.

☐ attorney or agent under 37 CFR 1.34(a).
Registration number if acting under 37 CFR 1.34(a) _____.

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November 26, 2008
Date

Signature

Manuel Valcarcel, Esq.
Typed or printed name (Reg. 41,360)

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02 FC:2252 245.00 DA

Greenberg Traurig

Manuel R. Valcarcel, Esq.
305-579-0812 Tel.
305-961-5812 Fax
mrv@gtlaw.com

December 15, 2008

VIA EXPRESS MAIL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Re: U.S. Patent Application No. 10/887,688
Invention: Percutaneously implantable replacement heart valve device and method of making same
Request for Continued Examination, Petition for Extension of Time and Response to Office Action No. 3
Our Ref. No. 051458.010100

Dear Sir:

Enclosed under cover of this transmittal letter is a Request for Continued Examination together with a Petition for Extension of Time (two months) and response to office action no. 3 in the above-referenced application.

Please charge the RCE Fee ($405) and Extension Petition Fee ($245), the fee for one additional independent claim ($110.00), and any other required fees for the enclosed submission to Deposit Account No. 50-1792.

Please confirm receipt of the enclosed documents by date-stamping and returning the enclosed postage paid return postcard. Please direct all communications regarding the foregoing to the undersigned.

Respectfully submitted,

GREENBERG TRAURIG, P.A.

by /Valcarcel/
Manuel R. Valcarcel, Esq.
Reg. No. 41,360

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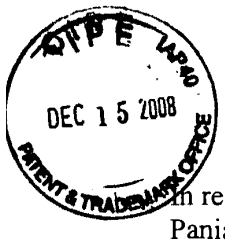
MRV/mam
Enclosures
cc: David Paniagua, M.D.
MIA 180,227,872v1



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of
Paniagua, et al.
Serial No. 10/887,688
Filed: July 10, 2004
Invention: Percutaneously Implantable Replacement Heart Valve Device and Method of Making Same

Examiner: Cheryl Miller
Group Art Unit 3738

RESPONSE TO OFFICE ACTION No. 3

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

In response to Office Action No. 3 dated July 15, 2008 in the above-referenced application, the Applicants respectfully submit this response. Claim amendments begin on page 2. Remarks begin on page 11. A new Declaration under 37 C.F.R. § 1.131 together with Exhibits A-H of evidence is enclosed antedating the Bailey et al. reference (6,652,578B2) cited as the basis for the claim rejections. The remarks also discuss differences between the Applicants' invention and the device taught by Bailey. Please charge the fee for new independent claim 37 to deposit account no. 50-1792.

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AMENDMENTS TO THE CLAIMS

The following listing will replace all prior versions of the claims in the application:

1. (currently amended) A percutaneously implantable replacement heart valve device comprising an expandable stent member having an inner space and a flexible, compressible artificial valve disposed within said inner space of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising ~~having a cusp or leaflet portion comprising~~ a ~~folded unslit~~ sheet of biocompatible ~~tissue~~ material having one or more folds defining one or more cusps or leaflets without slits cut into said material or separate cusps or leaflets ~~separate cusps or leaflets~~ affixed thereto.

2. (original) The percutaneously implantable replacement heart valve device of claim 1, wherein said expandable stent member is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium and stainless steel.

3. (currently amended) The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible ~~tissue~~ material of said artificial valve comprises mammal pericardium tissue.

4. (currently amended) The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible ~~tissue~~ material of said artificial valve comprises porcine pericardium tissue.

5. (currently amended) The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible ~~tissue~~ material of said artificial valve is obtained from a juvenile animal pericardium.

6. (currently amended) The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible ~~tissue~~ material of said artificial valve comprises autologous tissue obtained from the patient into whom said replacement heart valve device will be implanted.

7. (currently amended) The percutaneously implantable heart valve device of claim 1, wherein said biocompatible ~~tissue~~ material of said artificial valve comprises a synthetic biocompatible material.

8. (original) The percutaneously implantable heart valve device of claim 7, wherein said synthetic biocompatible material is selected from the group consisting of polytetrafluoroethylene, polyester, metal, metal alloy including combinations thereof.

9. (original) The percutaneously implantable heart valve device of claim 1, wherein said stent member is self-expanding when implanted.

10. (original) The percutaneously implantable heart valve device of claim 1, wherein said stent member is balloon catheter expandable when implanted.

11. (previously withdrawn) A method of making a percutaneously implantable replacement heart valve device comprising the following steps: obtaining a sheet of biocompatible tissue material; drying said biocompatible tissue material; folding said dried biocompatible tissue material to create inner cusps or leaflets and an outer tubular cuff structure without affixing of separate cusps or leaflets or cutting slits into said material to form said cusps or leaflets; affixing said folded biocompatible tissue material at one or more points on its outer surface to the inner cavity of a stent; and soaking said biocompatible tissue material in one or more alcohol solutions and a solution of gluteraldehyde.

12. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said soaking step comprises soaking said biocompatible tissue material in a solution of isopropyl alcohol, a solution of ethanol, a solution of glycerol and a solution of gluteraldehyde.

13. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material comprises bovine pericardium tissue.

14. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material comprises porcine pericardium tissue.

15. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material is obtained from a juvenile animal pericardium.

16. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material comprises autologous tissue obtained from the patient into whom said replacement heart valve device will be implanted.

17. (previously withdrawn) The percutaneously implantable heart valve device of claim 11, wherein said biocompatible tissue material of said artificial valve comprises a synthetic biocompatible material.

18. (previously withdrawn) The percutaneously implantable heart valve device of claim 17, wherein said synthetic biocompatible material is selected from the group consisting of polytetrafluoroethylene, polyester, metal, metal alloy including combinations thereof.

19. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said stent is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium and stainless steel.

20. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said stent is self-expanding when implanted.

21. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said stent is balloon catheter expandable when implanted.

22. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, further comprising the step of cleaning said biocompatible tissue material using hydromechanical force means.

23. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve of claim 11, further comprising the step of compressing said biocompatible tissue material.

24. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve of claim 11, further comprising the step of gas sterilization of said biocompatible tissue material.

25. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve of claim 11, wherein said drying step comprises photomechanical compression of said biocompatible tissue material.

26. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve of claim 11, wherein said folding step comprises folding of a first piece of said biocompatible tissue material to create an outer tubular cuff structure, folding of a second separate piece of biocompatible tissue material to create inner cusps or leaflets without affixing of separate cusps or cutting slits into said second separate piece of biocompatible tissue material, and affixing said second separate piece to said first piece.

27. (currently amended) A percutaneously implantable replacement heart valve device comprising an expandable stent member having an inner space and a flexible, compressible artificial valve made of biocompatible ~~tissue~~ material and disposed within said inner space of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising a leaflet or cusp portion formed by folding of a first sheet portion of said biocompatible tissue material without ~~affixing of separate cusps or leaflets or~~ cutting slits into said first sheet portion to form said cusps or leaflets, and an outer tubular cuff structure formed by folding a second sheet portion of biocompatible tissue material, said first sheet portion and second sheet portion being affixed together.

28. (original) The device of claim 27, wherein said first sheet portion and said second sheet portions are affixed together by suturing.

29. (original) The device of claim 28, wherein said suturing is in the form of double continuous sutures.

30. (currently amended) A percutaneously implantable replacement heart valve device comprising a sheet of flexible, compressible biocompatible material folded to form ~~an outer~~ tubular~~cylindrical~~ cuff portion having an inner tubular space and folded further to form an inner peripheral upstanding~~uncut/unslit~~ cusp or leaflet portion~~layer~~ disposed~~attached~~ within said inner tubular space of said tubular ~~outer~~ cuff portion, said cusps/leaflets opening in response to blood flow through said tubular inner space of said tubular cuff portion in one direction and closing in response to blood flow in the opposite direction.

31. (currently amended) The device of claim 30, wherein said leaflet portion~~layer~~ comprises a separate sheet of said compressible biocompatible material including one or more additional lengthwise pleats through which said leaflet portion is attached to said tubular cuff portion~~is attached within said outer cuff portion by suturing~~.

32. (currently amended) The device of claim 3~~1~~0, wherein said biocompatible material further includes a folded edge through which said material is attached to an expandable stent having an inner channel, said attachment being made to said inner channel of said expandable stent member ~~wherein said suturing is in the form of double continuous sutures~~ by suturing.

33. (currently amended) A percutaneously implantable replacement heart valve device comprising an expandable stent member having an inner space and a flexible, compressible artificial valve made of biocompatible ~~tissue~~ material and disposed within said inner space of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising a sheet of biocompatible material having a first inward fold disposed parallel to an edge of said sheet and one or more inward folds spaced along said sheet perpendicular to said first inward fold, the free edge of said first inward fold defining a

peripheral upstanding leaflet or cusp portion without cutting of slits to form said cusps or leaflets said sheet having two opposite ends perpendicular to said first inward fold, said opposite ends being joined to define a tubular portion within which said cusp or leaflet portion is disposed, said folded cusps or leaflets causing said valve to open in response to blood flow in one direction and close in response to blood flow in the opposite direction.

~~leaflet or cusp portion formed by folding of a first sheet portion of said biocompatible tissue material without affixing of separate cusps or leaflets or cutting slits into said sheet to form said cusps or leaflets.~~

34. (currently amended) A percutaneously implantable replacement heart valve device comprising an expandable stent member having an inner space and a flexible, compressible artificial valve having a generally tubular portion and a peripheral upstanding cusp or leaflet portion disposed within said inner space of said stent member and affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising a continuous uncut, unslit sheet of biocompatible tissue material having an upper border with an outward fold, a lower border with an inward fold, a first edge and a second edge, said first edge and second edge being disposed perpendicular to said upper border and said lower border, said first edge and said second edge being folded inwardly in relation to eachother and said inward folds of said first edge and said second edge being joined ~~to said second edge~~ to form said generally tubular portion having an inner space, with said inward~~ner~~ folds being disposed within said inner space of said generally tubular portion to form said peripheral upstanding cusp or leaflet portion.

35. (currently amended) A percutaneously implantable replacement heart valve device comprising:

an expandable stent member having an inner space, and

a flexible, compressible artificial valve disposed within said inner space of said stent member, affixed at one or more points on said artificial valve's outer surface to said stent member, comprising a first single continuous uncut, unslit sheet of biocompatible tissue material having an upper border, a lower border opposite and parallel to said upper border, an inner fold disposed at said lower border, and two opposite edges perpendicular to said upper border and said lower border and folded inwardly in relation to eachother with the edge of said inward folds of said two opposite edges ~~,~~ joined to eachother, and a second sheet of biocompatible tissue material having an upper border with an outward fold and a lower border opposite and parallel to said upper border, and having two opposite edges perpendicular to said upper border and said lower border and joined to eachother, said upper border of said first sheet joined to said lower border of said second sheet.

36. (currently amended) A percutaneously implantable replacement heart valve device comprising an expandable stent member having an inner space and a flexible, compressible artificial valve disposed within said inner space of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising a generally tubular portion and a cusp or leaflet portion, said generally tubular portion and said cusp or leaflet portion comprising a single folded unslit sheet of biocompatible tissue material ~~without separate cusps or leaflets affixed thereto~~.

37. (New) A percutaneously implantable replacement heart valve device comprising an expandable stent member having an inner space and a flexible, compressible artificial valve disposed within said inner space of said stent member affixed at one or more points on said

artificial valve's outer surface to said stent member, said artificial valve comprising a single sheet of biocompatible material having one or more folds defining one or more cusps or leaflets without slits cut into said material.

Remarks

Claims 1-10 and 27-36 remain in the application. A new claim 37 has been added, and claims 1, 3-7, 27 and 30-36 have been amended. The Applicants have noted the examiner's Section 112, 102(e) and 103 rejections of the claims and respectfully request reconsideration and withdrawal of said rejections based on the claim amendments and remarks contained in this response as well as the Applicants' new Declaration under 37 CFR §1.131 antedating U.S. Patent No. 6,652,578B2 to Bailey. Claims 1-10 and 27-36, as amended, remain in the application. The Applicants note the examiner's comments regarding priority at page 2 of the office action. The present application is a continuation in part application and the benefit of the filing date of the earlier application, which was application serial no. 10/037,266 filed on January 4, 2002, was requested on initial filing of the present application as noted in the first page of the application, as well as in the transmittal, and confirmation of present application's continuation in part status is indicated in the filing receipt.

Additionally, the Applicants respectfully note that the examiner's assertion that the subject matter consisting of the sheet material being unslit and without affixing separate cusps, and the configuration and formation of multiple folds is new to the current application and was not part of the parent application is incorrect. The parent application discusses the valve material being unslit and without affixing of cusps at the end of paragraphs [0027] and [0049] of the parent application ("the folding of the pericardium material to create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of valve leaflets. . . present invention also greatly reduces the risk of tearing of the cusps or leaflets, since they are integral to the valve rather than being attached by suturing.") Figures 3A and 3B of the

parent application also show the folding of the material, the material being unslit and without affixing of separate cusps or leaflets.

Regarding the prior Declaration under 37 C.F.R. 1.131 that was submitted, the undersigned respectfully submits that the prior Declaration was not insufficient for lack of notarization of one signature, because it was a Declaration including the required acknowledgment by the declarants that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. Section 1001) and may jeopardize the validity of the application or any patent issuing thereon, and set forth in the body of the declaration that all statements made of the declarants' own knowledge are true and that all statements made on information and belief are believed to be true. A Declaration in such form, unlike an Affidavit, does not require an oath or notarization. Notarization of a Declaration is beneficial in order to have a witness in the event that a witness to the signature is needed later, but is not required.

Claim 7 has been amended to eliminate the basis for examiner's Section 112 second paragraph rejection as to Claims 7 and 8. Said claims have been revised to refer to the biocompatible material instead of the biocompatible *tissue* material of said valve comprising a synthetic biocompatible material. The Applicants respectfully request that the examiner withdraw the Section 112 rejections.

With respect to the examiner's Section 102(e) and 103(a) rejections, the Applicants respectfully submit the enclosed new Declaration under 37 CFR §1.131 antedating U.S. Patent No. 6,652,578B2 to Bailey. Additional evidence has been provided showing that the inventors had conceived of and had begun taking steps to reduce to practice their invention as of a date prior to December 31, 1999, the priority date for Bailey. Such additional evidence includes a replica of a prototype of the folded valve of the present invention formed using a paper sheet as

well as a replica of a prototype of the folded stent mounted valve in addition to copies of sketches and other materials prior to December 31, 1999, as well as inventors' notes describing their conception and preliminary efforts to reduce to practice the folding of a sheet of valve material to form the valve and the leaflets rather than cutting slits into the material to create leaflets or affixing of separate leaflets. The Applicants respectfully submit that the enclosed new Declaration under 37 C.F.R. Section 1.131 is sufficient to antedate and Bailey.

In addition, while the cited reference is overcome by the enclosed Declaration, the Applicants note further that the Applicants' invention as claimed in the claims as amended, is not anticipated or rendered obvious by Bailey for the following reasons: Nowhere does Bailey teach a valve comprising a sheet of biocompatible material having one or more folds defining cusps or leaflets. In fact, the word "fold" is never even used in description of the invention disclosed in Bailey. The device disclosed in Bailey has a graft member 11 *consisting* of two parts, one which is affixed to the *inner surface* of the stent and the other affixed to the *outer surface* of the stent. It is not a folded sheet of material. The inner and outer graft members are coupled to each other through the stent. See Column 9, lines 12-19: "the graft member 11 consists of an outer or ablumenal graft member 11a and an inner or lumenal graft member 11b. The outer graft member 11a *encloses at least a portion of the ablumenal surface of the intermediate annular section of the stent body member, while the inner graft member 11b is coupled, on the lumenal surface of the intermediate annular section of the stent body member 12, to the outer graft member 11a through the interstices 14 of the stent body member.*" (emphasis added)).

The Applicants' valve, by contrast, is disposed entirely within the inner space of the stent. The valve material in the Applicants' invention is disposed entirely within the inner space of the stent-there is no encapsulation of the stent between inner and outer graft members as in

Bailey. By having the valve material the inner surface and outer surface of the stent, the device disclosed in Bailey is more complicated in design and manufacture, since the stent and the valve must be connected to eachother during creation of the valve portion (the valve material being partially inside and partially outside the stent and connected through the stent), whereas the Applicants' device allows for the valve to be created at one point in time and be coupled to the stent at a later point in time.

Additionally, Bailey includes as an essential element a stent that has "valve arms" or "regulator struts" that support the valve material and which control the opening and closing of the valve in Bailey, forcing separate valve flaps closed by applying a biasing force. (See Column 5, lines 61-63: "The stent body member is shaped to include the following stent sections: proximal and distal anchors, a [sic] intermediate annular section *and at least one valve arm or blood flow regulator struts*." (emphasis added)). Column 9, lines 7-10, referring to Figure 2 of Bailey, discloses a "valve body 26 and valve arms or flow regulator struts 24 coupled to the stent body member 12." The "*valve arms or regulator struts are coupled or formed integral with the stent body member* and are positioned adjacent the junction point between intermediate annular section and the proximal anchor flange 22 of the stent body member 12. The valve arms 24 are oriented radially inward toward the central longitudinal axis of stent body member 12 when in their zero strain state. The valve arms 24 are *attached or coupled* to *the valve flap portions 28 of the inner graft member leaflets* to bias the valve flap portions 28 to the closed position when under zero pressure differential across the stent valve 10." Bailey, Column 9 at lines 32-42 (emphasis added). Column 5, lines 58-60 in Bailey note that "the valve leaflets are preferably *formed* by sections of the graft material attached to the stent body member." The reference to "formed" does not teach or suggest "folding." Column 6 lines 20-39 of Bailey further state that

"[f]low regulation in the inventive stent valve prosthesis is provided by the combination of the prosthetic valve leaflets *and the valve arms and is biased closed in a manner to that described for a surgically implanted replacement heart valve by Boretos, U.S. Pat No. 4,222,126.* The valve regulator-struts are preferably configured to be positioned to radiate inward from the stent body member toward the central longitudinal axis of the prosthesis . . . *The struts of the stent are encapsulated by the outer graft membrane. The valve regulator struts are encapsulated by the inner leaflet membrane and serve to bias the valve to the closed position*. The regulator struts also prevent inversion or prolapse *of the otherwise unsupported leaflet membrane* during increased supra-valvular pressure." (emphasis added). If reference is made to Boretos U.S. Patent No. 4,222,126, it is made further clear that in Bailey the regulator struts support the valve material which is attached to the stent body member and is supported by the struts (see column 5 lines 55-60: "[the graft] is attached to the stent body member on at least portions of either or both of the lumenal and ablumenal surfaces of the stent body member by suturing to or encapsulating stent struts. The valve leaflets are preferably formed by sections of the graft material attached to the stent body member." As shown in Figure 4 in Bailey, the valve arms 24 force the valve leaflets 28 to collapse into the center of the lumen of the stent valve 10, thus biasing the valve to its closed position. The flow regulator struts in Bailey are thus connected to or are part of the stent itself at one end, and are encapsulated by the valve outer membrane and inner leaflet membrane and are responsible for providing support to the valve leaflets and opening and closing of the valve leaflets.

The Applicants' invention does not include such "valve arms" or "regulator struts" whether as part of the stent or as part of the valve. The Applicants' valve with folded cusps and leaflets provides more natural functioning, less susceptability to tearing and allow for effective

opening and closing of the valve without the regulator struts required in Bailey to support and bias the flaps. The folded design invented by the Applicants does not require struts that are part of the stent and are affixed to the valve by suturing or encapsulation in the valve material for valve leaflet material support or valve opening and closing. It is precisely such suturing or encapsulation that the Applicants' folded design is intended to eliminate, resulting in less susceptibility to suture failure and/or tearing of the valve material. In the Applicants' invention opening and closing of the valve is based on the natural blood flow pressure differential. The valve in Bailey does not function to control blood flow without the valve regulator struts. The Applicants have therefore eliminated at least one critical element of the Bailey valve while retaining valve functionality.

The Applicants further reiterate that the product by process limitations in the claims must be given weight because they impart structural limitations, namely, folds, rather than slits or sutures connecting separate leaflet pieces, and thereby impart a number of advantages over prior devices, including reducing susceptibility to failure by improving resistance to tearing of leaflets, and providing a more closely resembling the form and function of a native heart valve. "The structure implied by the process steps should be considered when assessing the patentability of product by process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process would be expected to impart distinctive structural characteristics to the final product." MPEP Section 2113 (citing *In re Garnero*, 412 F.2d 276, 279 (CCPA 1979)). Such is the case with the Applicants' invention. The Applicants therefore respectfully request withdrawal of the examiner's Section 102(e) and Section 103(a) rejections and allow the present case. Nonetheless,

should the examiner have any comments, questions or suggestions, the examiner is respectfully requested to telephone the undersigned at the telephone number listed below.

Respectfully submitted,

Date: December 15, 2008

GREENBERG TRAURIG, P.A.
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Reg. No. 41,360

MIA 180,225,752v2

EXPRESS MAIL MAILING LABEL NO. EM 248929807 US

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

In re the application of:	)	
	)	
Paniagua, et al.	)	Group Art Unit 3738
Serial No. 10/887,688	)	
Filed: 7/10/2004	)	Examiner: Miller, Cheryl L.
	)	

For: Percutaneously Implantable Replacement Heart Valve Device and Method of Making Same

DECLARATION UNDER 37 CFR 1.131

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia

Sir:

The undersigned co-inventors each hereby declare as follows:

1. I am a co-inventor of the invention claimed in the patent application identified above.

2. I was directly and personally involved in the conception and reduction to practice of the invention throughout the period from prior to December 31, 1999 until the filing date of U.S. Patent Application Serial No. 10/037,266 on January 4, 2002, of which the present application is a continuation in part.

3. Prior to December 31, 1999, the percutaneously implantable replacement heart valve device and method of making same described and claimed in the above-referenced application had been conceived by co-inventors David Paniagua and Francisco-Lopez Jimenez who were at the time cardiology fellows at Mount Sinai Medical Center in Miami Beach, Florida. Attached as Exhibit A is a copy of an electronic diary that was kept with respect to development of the invention by co-inventor Paniagua, with entries dating back to prior to December 31, 1999 indicating that the Applicants had by then already conceived of the invention. The dates for certain of the entries are blacked out but predate December 31, 1999.

4. Prior to December 31, 1999, co-inventors Eduardo Induni and David Paniagua conceived of the folded design of the valve means and the method of folding an unslit sheet of valve material to create a valve with cusps that are created by the folds without suturing separate leaflets or cutting of slits to create leaflets. Enclosed as Exhibit B is a replica of one of the co-inventors' initial paper models of the valve means created prior to December 31, 1999, showing a single piece folded design. Additionally, enclosed as Exhibit C is replica of one of the co-inventors' initial prototypes which was created prior to December 31, 1999, which includes the valve means with the folded design mounted in a stent. The original prototypes and related notes

from dating back prior to December 31, 1999 were lost when co-inventor Paniagua relocated from Miami to Houston and/or during Hurricane Ike. However, attached as Exhibit D are copies of sketches that were created prior to December 31, 1999 which show the co-inventors had already conceived of their folded sheet valve design, including valve cusps and leaflets formed by folding rather than by slitting material or affixing separate cusps or leaflets.

5. During the time period from prior to December 31, 1999 through January 4, 2002, the first prototypes and the method of making same of the invention were created and tested. As indicated in Exhibit A, during the time period from September 1999 through December 1999, anatomical studies were done with respect to porcine aortic and pulmonary valves as well as the aortic arch, including measurements of valve length, cusp length, vertical diameters, attachment points, interaction with other cusps, interaction with the Sino tubular junction and coronary ostium and observation of characteristics of the opening and closing, redundancy of tissue and sinus of Valsalva measurements and the initial prototypes were studied and tested. Durability and fatigue studies were conducted with regard to the valve material and folded design during the months prior to December 31, 1999. A protocol for in-vitro testing was written by Co-Inventor Paniagua in the early months of 2000. The in-vitro model consisted of a plastic hose tubing filled with a 30% solution of glycerol to resemble blood viscosity, a continuous pump, pressure recording instruments and pressure generating clamps. The study indicated excellent opening and closing profiles of the valve with no evidence of regurgitation even at pressures of 200 mmHg.

6. During the time period from prior to December 31, 1999 through January 4, 2002, which is the filing date of Patent Application Serial No. 10/037,266, to which the above-referenced application is a continuation in part and claims priority, we also worked with diligence toward reduction to practice of the invention by preparing a written description of the invention (see copy of a later draft dated April 22, 2001, attached hereto as Exhibit E).

7. During the time period from prior to December 31, 1999 through January 4, 2002, we also worked with diligence toward reduction to practice of the invention by conducting various tests and trials relating to preparation of the valve starting material, formation of the valve, optimal stent composition and configuration, attachment of the valve to the stent and attachment of the stented valve to an artery. See the attached entries from the electronic diary attached hereto as Exhibit A, which include entries relating to tests regarding preparation of the valve starting materials and formation of the valve in October, November and December 2000 and January, February, March, and June 2001. See also the attached entries from the electronic diary attached hereto as Exhibit A, which include entries pertaining to animal studies in June, September and November 2000 and April, 2001.

8. In August 2001, patent counsel was engaged to conduct a patent search directed to the invention and prepare and file a patent application for same. Enclosed as Exhibit F are copies of a search patent request letter dated August 29, 2001 which was sent to order a patent search for the invention, the invention being described in the letter. Said request letter was received by the patent search provider on August 30, 2001 as evidenced by the stamped confirmation of receipt attached to Exhibit G.

9. The patent search results were received on or about mid-September, 2001 and were reviewed by patent counsel, as well as by the undersigned, in the weeks that followed (bearing in mind that during such time period there were various office closures and disruptions due to the September 11, 2001 terrorist attacks and their immediate aftermath).

10. After the patent search results were reviewed and discussed with patent counsel, the patent application was prepared, reviewed, revised, figures for the application were prepared, and the application and figures were submitted on January 4, 2002. Attached as Exhibit H are copies of correspondence from patent counsel enclosing drafts of the patent application for the invention dated November 27, 2001 and December 28, 2001.

The undersigned co-inventors each hereby declare that all statements made herein of his own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

[THIS SPACE LEFT BLANK INTENTIONALLY]

DAVID PANIAGUA

Signature: _____

Date: October 11, 2008

ACKNOWLEDGEMENT

COUNTY OF Harris)
) SS:
STATE OF Texas)

The foregoing Declaration was signed before me this 11 day of October, 2008 by David Paniagua. He is personally known to me or has produced _____ as identification.

Notary: _____ [NOTARIAL SEAL]
Print Name: ROSIE HIDALGO Notary Public, _____

ROSIE HIDALGO
MY COMMISSION EXPIRES
AUGUST 18, 2009

My commission expires: 8/18/09

FRANCISCO LOPEZ-JIMENEZ

Signature: _____

Date: October 10, 2008

ACKNOWLEDGEMENT

COUNTY OF Olmsted)
) SS: 016 78 3147
STATE OF MN)

The foregoing Declaration was signed before me this 10th day of October, 2008 by Francisco Lopez-Jimenez. He is personally known to me or has produced _____ as identification.

Notary: Vicki Virginia Yount
Print Name: Vicki Virginia Yount

[NOTARIAL SEAL]

VICKI VIRGINIA YOUNT
Notary Public-Minnesota
My Commission Expires Jan 31, 2010

Notary Public, _____

My commission expires: January 31, 2010

R. DAVID FISH

Signature: _____

Date: October 13, 2008

ACKNOWLEDGEMENT

COUNTY OF Harris)
) SS:
STATE OF Texas)

The foregoing Declaration was signed before me this 13th day of October, 2008 by R. David Fish. He is personally known to me or has produced _____ as identification.

Notary: Mary R. Jones [NOTARIAL SEAL]
Print Name: Mary R. Jones Notary Public, 10-13-08

My commission expires: 8-27-10

MIA 180,228,061v1

MARY R. JONES
NOTARY PUBLIC
STATE OF TEXAS
MY COMM. EXP. 8-27-10

CARLOS MEJIA

Signature: Carlos Mejia A.

Date: October 10, 2008

ACKNOWLEDGEMENT

COUNTY OF HARRIS)
) SS:
STATE OF TEXAS)

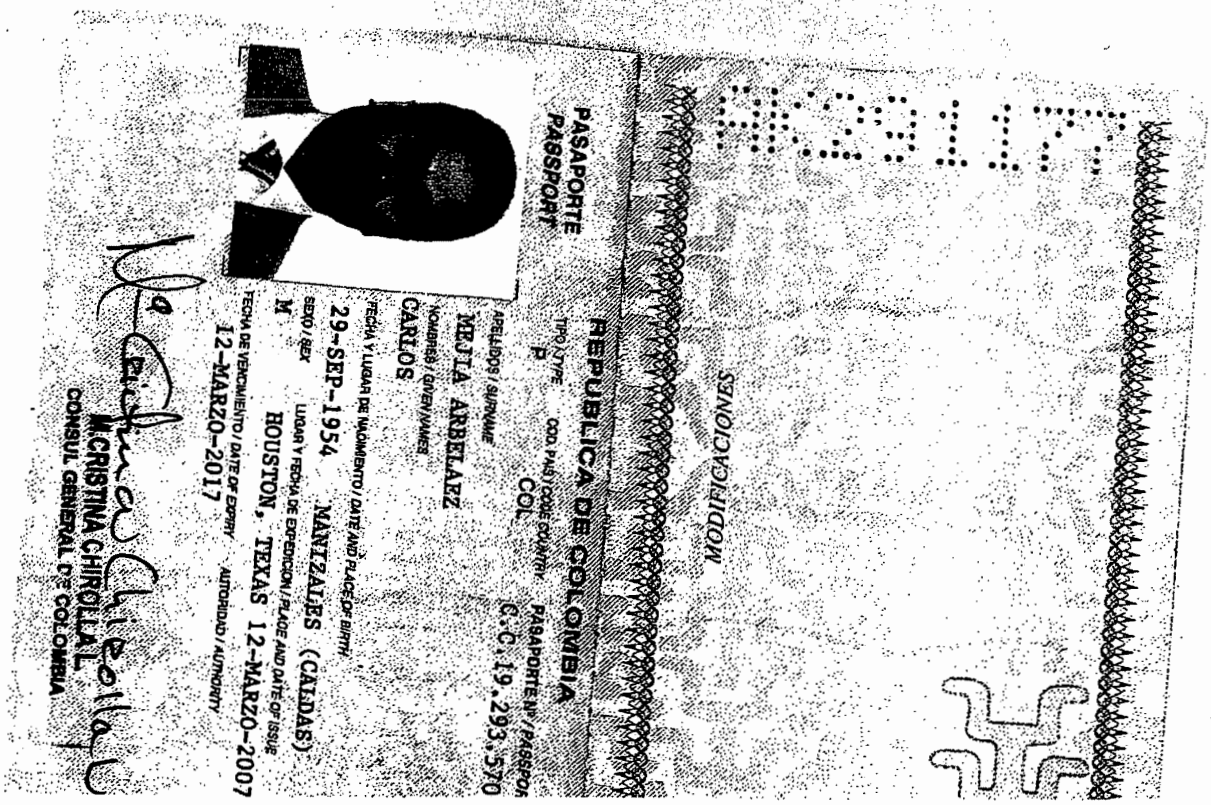
The foregoing Declaration was signed before me this 10th day of October, 2008 by Carlos Mejia. He is personally known to me or has produced COLOMBIAN PASSPORT as identification.

Notary: R Hidalgo
Print Name: ROSIE HIDALGO

[NOTARIAL SEAL] Notary Public,

ROSIE HIDALGO
MY COMMISSION EXPIRES
AUGUST 18, 2009

My commission expires: 8-18-09



EDUARDO INDUNI

Signature: _____

Date: October 10, 2008

ACKNOWLEDGEMENT

COUNTY OF HARRIS)
) SS:
STATE OF TEXAS)

The foregoing Declaration was signed before me this 11th day of October, 2008 by Eduardo Induni. He is personally known to me or has produced REPUBLICA OF COSTARICA as identification.

Notary: Hidalgo
Print Name: ROSIE HIDALGO

[NOTARIAL SEAL]
Notary Public, _____

ROSIE HIDALGO
MY COMMISSION EXPIRES
AUGUST 18, 2009

My commission expires: 8/18/09

EXHIBIT A

St Lizy Project: A new percutaneous device to decrease Valvular insufficiency

[redacted]

David Paniagua and **Francisco Lopez-Jimenez** (cardiology fellows at that time) discussed the need to develop a percutaneous valve. This discussion took place in the cardiology fellow's room at Mount Sinai Medical Center in Miami Beach Florida.

After this initial discussion a careful and extensive literature search was started. All articles in the field were reviewed as well as all information regarding patents filed.

[redacted]

The candidate stents that we thought of using in our project were: balloon expandable and self-expandable stents. The balloon expandable stents have been used in the past in two animal experiments reported in the literature. One of them was in Denmark and the other in New York. No other study has been reported after these two original reports. No one has implanted a percutaneous valve in a human being. We believe that the main limitation of the balloon expandable stents is its bulky design.

Among the self-expandable stents, we decided to start using in the first phase the Wallstent and we were planning to use the Smart stent in the second phase. These self-expandable stents has never been used for percutaneous implantation of a valve.

The **Wallstent** is a stainless steel self-expandable stent (Boston Scientific, Boston, MA) that has been used in human since 1987. The main advantage of this stent is its protruding metal wires suitable for fixation in the arterial wall. The main limitation is that the length of the stent changes significant from the collapsed state to the expanded state.

The SMART is a stent made of smart material nitinol an alloy of [redacted] that has the particularity that the stent changes form with temperature. The Smart stent expands when it is in contact with body temperature. The main advantages on the other hand that its length in the collapse and expanded state is quite similar.

The valves that we thought of placing in the stent: porcine pulmonary valve, porcine aortic valve, a new special valve made of bovine pericardium or a valve made of smart materials.

David Fish suggested the utility of using Smart materials in the development of the valve.

Exhibit A

September to December 1999
Anatomical studies in animals
David Paniagua and his wife Elizabeth while in Houston, Texas studied more than 100 porcine aortic and pulmonary valves as well as the aortic arch. Carefull measurement of the valve length, cusp length, vertical diameters, attachment points, interaction with the other cusps, interaction with the Sino tubular junction, coronary ostium. Characteristics of the opening and closing, redundancy of the tissue, sinus of Valsalva measurements

[redacted]

On a trip to Vienna, Austria; Francisco Lopez-Jimenez and David Paniagua discussed all the research synthesis. The pros and cons of different options were discussed and finally a strategy to develop our new percutaneous valve took place.

Porcine pulmonary valve

The main advantage of this valve is the thickness of the arterial wall is significantly less than the aortic wall.

Limitations Still bulky

Porcine aortic valve

Limitations Still bulky and the ostium of both coronaries

Bovine pericardium

We designed a new model of valve with special features to be suitable to use in the stent.

<u>The bovine pericardium</u>

Design

The horizontal length of the stent is equal to diameter x π.
The vertical length suffer a lot of modifications in the last 18 months

The process of management of the pericardium

The pericardium is membrane that surrounds the heart and isolates it from the rest of the chest wall structures.

The pericardium is a thin and very slippery, what makes it difficult for suturing in a millimetric precise way that is required for the valve that we were planning to develop.

Carlos Mejia [illegible] makes it possible to handle the way we needed.

Dry process

Since the pericardium is such a slippery material we started looking the way to make it easier to manipulate.

We try to dry it at room temperature but se hacia muy duro y corrugado feso

Then we try ironing and it shrinks to much and corrugate

We [illegible] pericardium with a plastic [illegible] surface to dry it homogeneously

We also tried to photo drying machine

When we dry it this way the final result was an homogeneous tissue that looked like a plastic paper and makes it easy to manipulate to suture the valve.

Hydrating process

Once the valve was done we hydrated the valve back again by placing it in a solution of water and 70% alcohol. In approximately 3 days the valve hydrate back again.

Converting the pericardium into a valve

David Paniagua and **Eduardo Induni** (a cardiovascular surgeon) discussed the best way to suture a flat pericardium and converted into a complete valve.

Many designs were made in paper until we developed a working model in that resembles the human valve.

See diagrams

Types of sutures

Sutures planes

Francisco Lopez-Jimenez introduced the trapezoid modification
We tested the trapezoid modification but it did not work. It introduces too much redundant tissue.

Attachment of the valve to the stent
3-point fixation on border of the stent

6-point fixation at each border of the stent

Fixation on both borders 18 points at each end following a single plane
36 fixation points following to adjacent vertical planes.

Fixation without any fold in the border resulted in tears, so we made a fold that resolved the problem.

Attachment of the valve to the aorta
R. David Fish suggested the possibility of attaching the mother stent to the subclavian artery using a daughter stent deployed first in the subclavian artery and attached to the mother stent that will be deployed in the descending aorta.

Hooks to the arterial wall Like the Ancure

Double stents

Acute Doppler studies in vitro

Francisco Lopez-Jimenez and David Paniagua performed the first Doppler studies in an in-vitro model.

The model consisted of a plastic hose tubing filled with a 30% solution of glycerol to resemble the blood viscosity, a continuous pump, pressure recording instruments and pressure generating clamps.

In this acute in vitro study we document excellent opening and closing profile of the valve. There was no evidence of regurgitation even at pressures of 200 mmHg.

See video

October 5th to 11th 2000

We studied different ways to fix the pericardium.

1- Piece of pericardium-- dried with light in our standard procedure then placed in glutaraldehyde for 36 hours and hydrate back in alcohol 70%. It looses resistant and it breaks easily.

2- Natural pericardium that was in alcohol solution for 2 months at least and we fix it with gluteraldehyde for 36 hours and then place in the alcohol solution with excellent results in terms of tissue resistance. We were not able to break it.

3 We fix a piece of diaphragm after drying it with light and then gluteraldehyde and we obtained the same result than with the pericardium.. The tissue resistance significant decreased and we were able to tear the tissue.

4 We placed a previously donic valve in the stent in the gluteraldehyde solution for 36 hours to fix it and later put it back in the alcohol solution

5 Pericardium dried with light. Pericardium was placed in saline solution to rehydrated and then fix with gluteraldehyde for 36 hours and then hydrate it back again

6 Pericardium fix with gluteraldehyde for 36 hours and then dry it with light

Delivery device

Chronic studies in vitro

On Sep 17 2001, we created a chronic model to test the valve. The model consisted of a pump attached to an 18 mm tubing system that is also attached to a 3 liters container that is placed 180 cms above the pump.

The stented valve was placed at the bottom of a 180 cm water column to mimic the diastolic pressure.

Histological studies

Preservation of the pericardium several month in ETOH

Glutaraldehido

[redacted]

E-mails

[redacted]

Materials

Calf
The device Delivery system
Cook needle Wires
Pigtails Dilators 11 F, 14F, 16F, 18F, 20F
Contrast media
Balloons PTA of the aorta.

Heparin Plavix for the animal

Surgical equipment

Echo Doppler

[redacted]

Injector X ray tech
Person in charge of anesthesia, monitoring

Circulating person	Endotracheal tube	IV fluids
IV connections	angiocaths	4 liter of IV fluids

Ventilators Lamps

KYJELLY
ET TUBE
ANTIBIOTICS
HEPARIN
XYLOCAINE
BETADINE
KETAMINE
EMERGENCY DRUGS
PROPOFOL XYLAZINE
INJECTION T SPRAY
ALCOHOL

STERILE TOWELS T DRAPES
STERILE SURGICAL TRAY
RECTAL TEMP PROBE
STERILE BOWL FOR SALINE
NS SALINE D5RL
COLLOID
SYRINGES-DIFFERENT SIZES
NEEDLES- DIFFERENT SIZES
HEATING PAD
IV CATLETERS, TOURNIGUETS
VASCULAR CLAMPS
SUCTION CATLETERS
SCISSORS
SECADORA PELO

[redacted]

Carlos Mejia and David Paniagua meet to discuss and design the next experiment.

We reviewed the previous information in video tapes, all films were discussed with emphasis in how we can decrease the size of the valve to try to identify the optimal Dimension of the valves.

We are going to try a valve 10mm deep and the circumference of the valve is going to be 71 mm for a 24mm diameter stent. The width of each pocket is going to be 22 mm

We did the valve in a rubber model with 10 mm deep and it was competent, for this reason we decided to try it in the pericardium.

The change in dimension of the valve with hydration after it is place in alcohol is unpredictable at the present time.

We are going to make two valves

1- Following our previous method of drying the valve with light and sewing to the stent when it its dried and then hydrating it with alcohol. Same design than previously, with folds.
2- A valve with pericardium fixed with gluteraldehyde. No folds in the upper part.

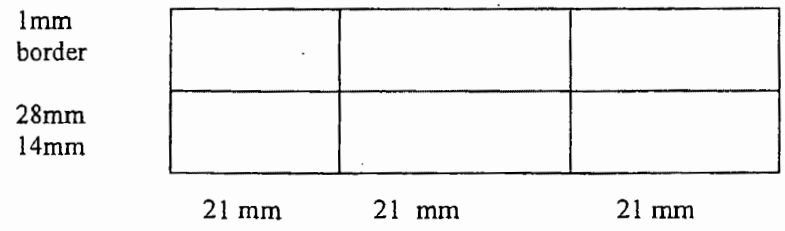
December 2 2000

Eduardo Induni, Carlos Mejia, David Paniagua review all the data collected so far in all the previous experiments and plan a strategy.
We found out that the material needs to be fix with gluteraldehyde before we implant the device. We study different concentrations of gluteraldehyde to fix the valve.

Finally we conclude that we the best is to fix the valve with 0.7% gluteraldehyde and keep it in this solution until the time to use it. At this moment we need to put the valve in normal saline before we implant it

January 2001

We designed a new valve with modification of its length. The pericardium was fixed with gluteraldehyde at 0.7% and later we did the valve and kept it in the same solution until the time to implant it.
During the creation of the valve constant hydration was maintain with frequent immersion of the pericardium in gluteraldehyde.



1 mm at each end to suture the valve.

February 2001

David Fish, Eduardo Induni and David Paniagua review the new stent-pericardium-valve and discussed the design improvement and decided to implant it in a new animal experiment.

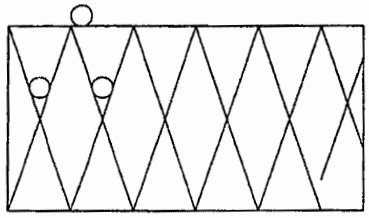
[redacted]

The valve required 7-0 prolene, 24-inch long 10 packs
3 to suture the valve and 7 to attach the valve to the stent.

The valve was attached to a 24 mm maximal diameter Wallstent.

We eliminate the folds at each end of the valve.

The valve was fixed in its **superior border** using two fixation planes with 18 fixation points at each plane.



○ Fixation points

18 fixation points at each plane

There are two rows of fixation point at the upper or proximal end of the stent and one row of fixation point at the lower or distal end of the stent.

Each fixation point was knotted 5 times in the upper plane and 7 knots in the lower plane.

The fixation of the **inferior border** of the valve to the stent was done with a single plane with 18 fixation points. Each fixation point was knotted 7 times using prolene 7-0.

The vertical fixation of the valve to the stent was done along the suture line of each cusp of the valve. We used 3 fixation points at each vertical suture line. Each fixation point was knotted 7 times.

The vertical fixation was mildly loose to allow easy collapsibility of the valve.

The approximate time to suture and attach the valve was 10 hours.

The stent-valve is maintained in 0.7% gluteraldehyde solution.

March 24, 2001

We plan to place the valve in a chronic in vitro model to evaluate its chronic function.

We will perform collapsibility test of the valve.

The delivery system that we plan to use is the AneuRx deployment device.

April 21, 2001

We did an animal experiment in Costa Rica, see description in animal studies.

June 9, 2001

Carlos Mejia and David Paniagua in Miami got together to discuss about the evolution of the valve.

We were discussing how to reduce the dimension to the optimal size of the valve and prevent valvular folds.

The last valve length was 65 mm after fixation, but if you pull it to its maximum length it grows 10 mm more up to 75 mm. Carlos decreased the length of the valve to 55 mm and 57 mm. We were concerned about the elastic recoil of the pericardium once implanted in the valve, because if it is not tense the pericardium makes folds, we want to achieve the optimal length that does not produce folds and that it is not so tight that causes so much elastic recoil that does not allow the stent to expand.

We had the idea of fixing the valve in the closing position using tiny metallic clips to keep the cusps close to each other.

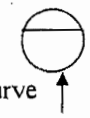
We tried the aortic valvuloplasty balloon to test if it can be used to expand the distal end of the stented valve in the case this extreme does not open.

We tried the consistency of different suture materials: Ticro 4-0, braided nylon and prolene. We discussed pros and cons of monofilament versus braided suture material.

June 12, 2001

At Carlos Mejia's' house we evaluated the design of the valve.

The new valve design includes the creation of a curve in each cusp of the valve



The other modification that we are doing in the handling process is to fix the pericardium in gluteraldehyde and transfer it to a solution of alcohol while making the valve and attaching it to the stent.

We changed the attachment position of the valve to be closer to the proximal and wider part of the Walstent, based on the previous experience during the animal study Alba.

We discussed the use of a pericardium piece fix in glutaraldehyde in a flat glass and the possibility of doing the valve with the natural pericardium and then fixing it with gluteraldehyde after mounting it in the stent.

One observation that we noted is that the material becomes whiter and apparently increases its elasticity

We obtained 1mm vascular clips to keep the cusps coapted while fixing them in gluteraldehyde.

June 13 2001

We evaluated the results of the use of metallic clips to keep both cusps adjacent to each other after 24 hours of fixation in gluteraldehyde. The results were very satisfactory to educate the material and make the primary position of the valve cusps adjacent to each other. After we removed the clips, there were no lesions to the valve. After doing this test, we use the metallic clips to keep both cusps together and immersed it in gluteraldehyde for 24 hours.

We evaluated different suture material that included praline 6-0 and Madrilène 6- 0 which is a braided suture.

We make more fixing fluid using gluteraldehyde 25% in a concentration of 3ml per 97 ml of fluid.

The pericardium of the first valve was in gluteraldehyde for 6 months approximately, then we put it in alcohol 60 during 2 to 3 days and after making the valve and placing in the transport fluid which consist of 60% alcohol.

June 16 2001

We were ready to perform another animal experiment in Costa Rica, but unfortunately all our equipment of dilator and the temporary delivery system was lost.

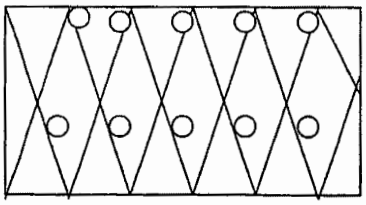
We developed a temporary delivery system that consisted of a central catheter big enough to let a 0.38 wire pass through its lumen, a cover sheath made of plastic material with a sliding device that allows to expose the stented valve.

Dr Eduardo Induni and David Paniagua discussed different ways to improve the collapsibility of the valve
The new observation was that the fixation points at the proximal part should be placed at the midpoint of the rhomboid structure to allow some mobility of the valve when we collapse it. This is true when using Walstent material not smart materials

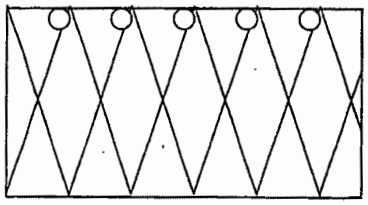
The other observation is that two planes of fixation point at the distal attachment of the valve to the stent causes a lot of tension to the valve when we are collapsing it.

One plane of fixation points will probably be enough to prevent systolic collapsed of the proximal edge of the valve

Proximal fixation points / expanded



Proximal fixation points sliding down



when stent collapses

- Fixation points

  18 fixation points at each plane

June 29, 2001

We discussed again the fixation points of the valve to the stent in such a way that they allow mobility of the stent over the valve without exerting too much tension. We believe this will allow better profile to the valve.

We also discussed the different suture materials and call Eduardo Induni and we make the decision that a braided suture is better than a monofilament, for this reason we are going to use mersilene which is a polyester braided suture.

[redacted]

September 8

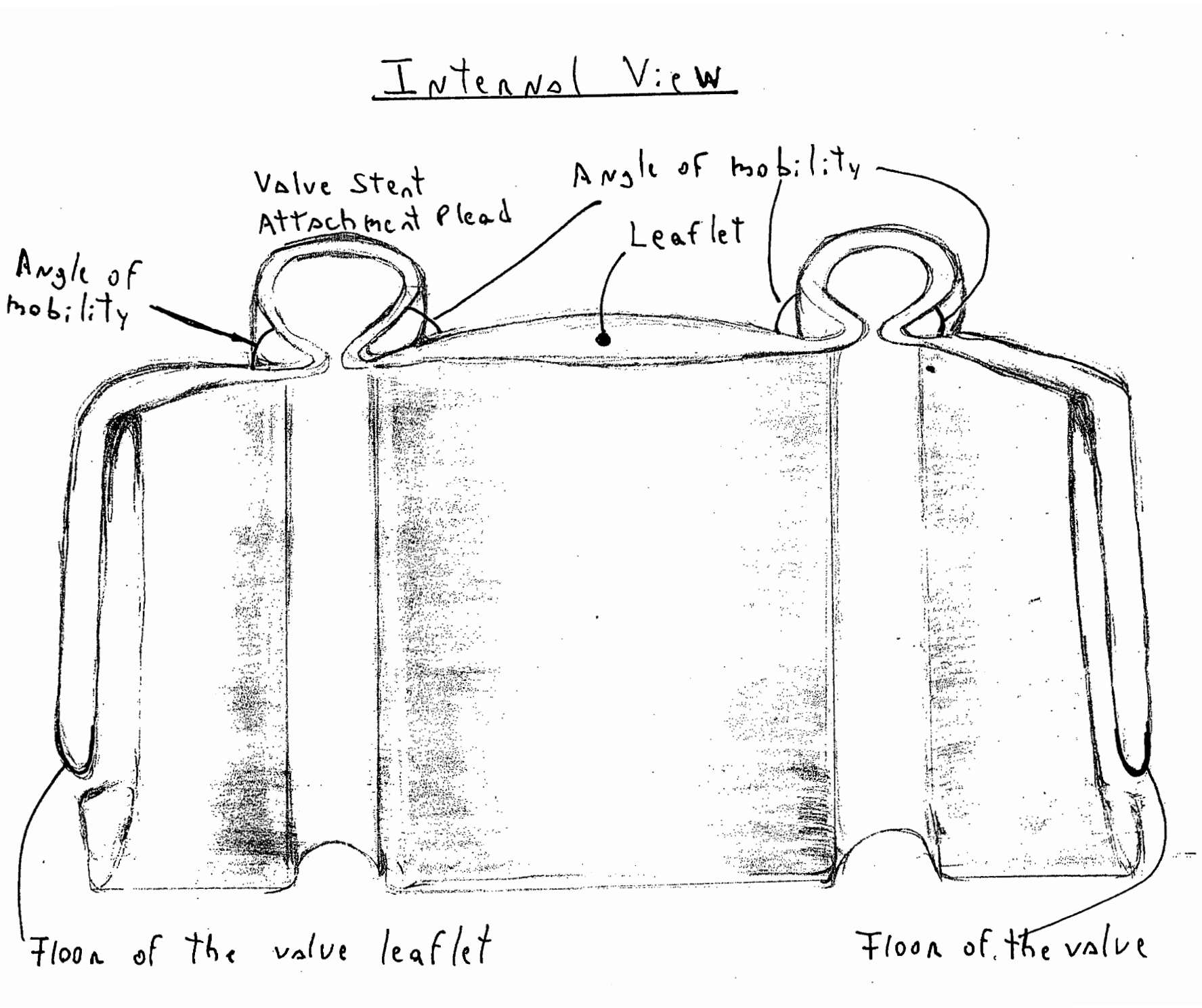
Carlos Mejia and David Paniagua designed the in vitro model to test chronically the valve and list all the required material

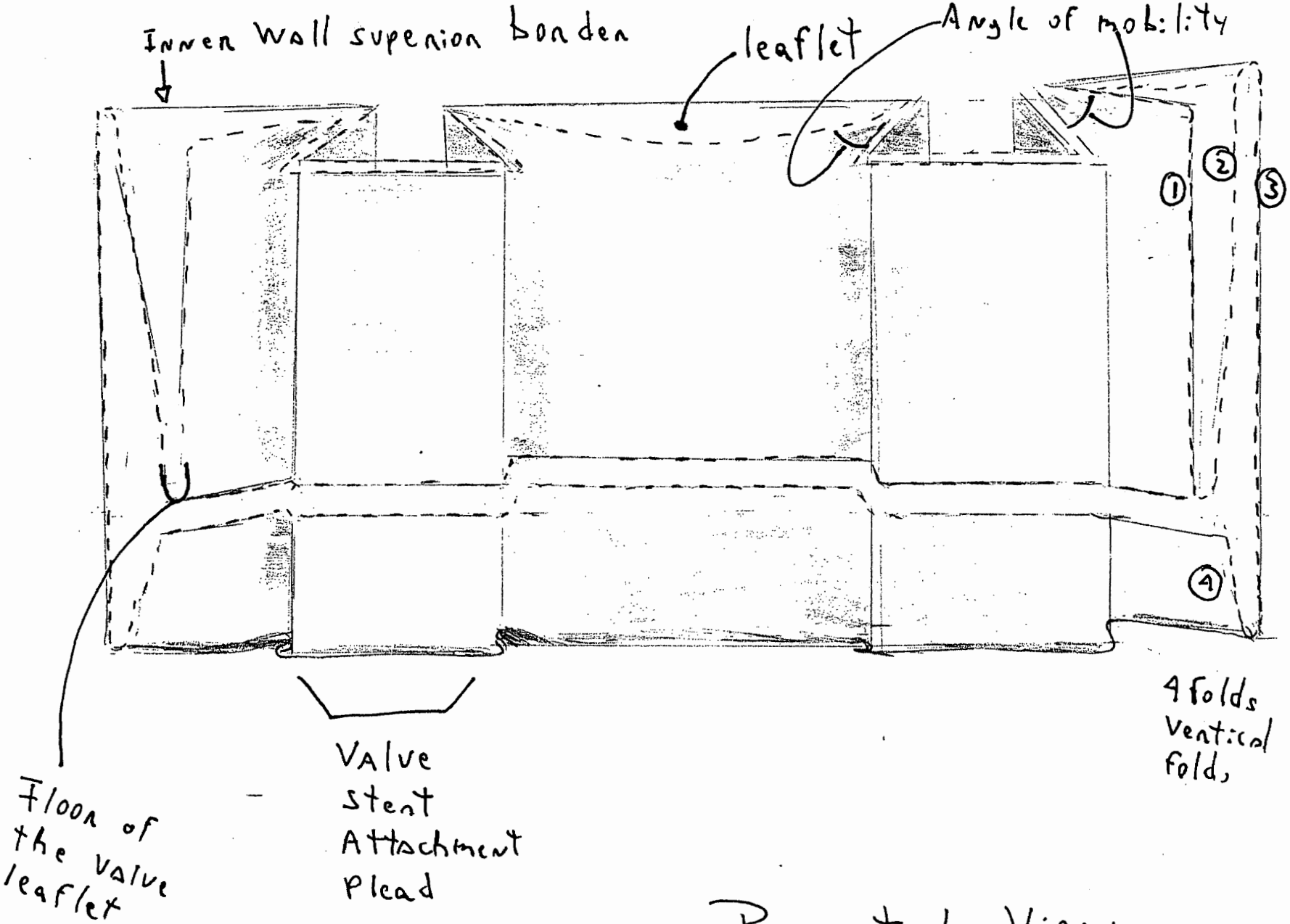
September 22

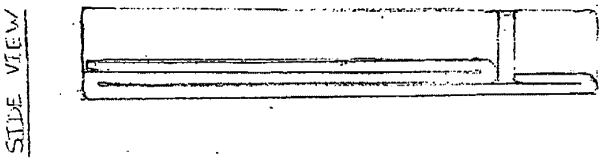
The valve is mounted in the chronic testing model

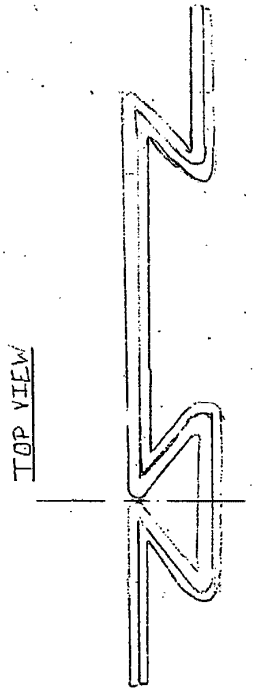
[redacted]

EXHIBIT D






SIDE VIEW


TOP VIEW

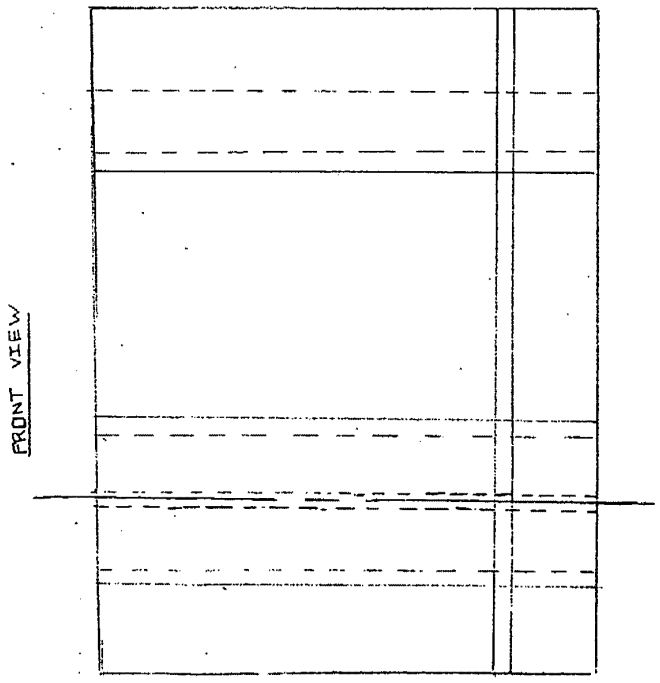

FRONT VIEW

EXHIBIT E

United States Patent

Paniagua, Induni, Mejia, Lopez, Fish, April 22, 2001

PERCUTANEOUS VALVE REPLACEMENT

Abstract

The invention relates to a new technique and a special type of device that allows percutaneous heart-valve replacement without the need for open-heart surgery.

The valve replacement system includes the following components:

(1) A system for removing a damaged heart valve
(2) a delivery system of the prosthetic valve device
(3) a prosthetic valve device
(4) an implantation technique

Inventors:

David Paniagua
Eduardo Induni
Carlos Mejia
Francisco Lopez
R. David Fish

U.S. Patent Documents

4056854	Nov.1977	Boretos et al.	623/2.
4631052	Dec., 1986	Kensey	606/159.
4883458	Nov., 1989	Shiber	606/159.
4966604	Oct., 1990	Reiss	606/159.
4979939	Dec., 1990	Shiber	606/159.
5007896	Apr., 1991	Shiber	606/159.
5011488	Apr., 1991	Ginsburg	606/159.
5026366	Jun., 1991	Leckrone	606/7.
5032128	Jul., 1991	Alonso	623/2.
5047041	Sep., 1991	Samuels	606/159.
5080660	Jan., 1992	Buelna	606/49.
5152771	Oct., 1992	Sabbaghian	606/159.

Foreign Patent Documents

WO91/17720	Nov., 1991	WO.
WO91/17118	Oct., 1992	WO.

Claims

What is claimed is:

1- An endovasculat system for delivering a heart valve.
2- An artificially percutaneous heart valve
3- An implantation technique

1. An endovascular system for delivering a replacement heart valve through an aortic passageway to or near to the location from which the natural heart valve has been removed, comprising:

[redacted]

[redacted]

The horizontal length of the pericardium piece is equal to the desired diameter x π.
The vertical length suffer a lot of modifications in the last 18 months

[redacted]			
[redacted]			

[redacted]

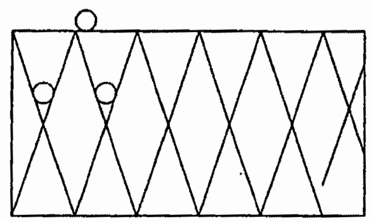
1 mm at each end to suture the valve.

[illegible] the valve to the stent.

The valve was attached to a 24 mm maximal diameter Wallstent.

We eliminate the folds at each end of the valve.

The valve was fixed in its **superior border** using one or two fixation planes with multiple fixation points at each plane.



○ Fixation points

There are one or two rows of fixation points at the upper or proximal end of the stent and one row of fixation point at the lower or distal end of the stent.

Each fixation point was knotted 5 times in the upper plane and 7 knots in the lower plane.

The fixation of the **inferior border** of the valve to the stent was done with a single plane [illegible] fixation points. Each fixation point was knotted [illegible]

The vertical fixation of the valve to the stent was done along the suture line of each cusp of the valve. We used 3 fixation points at each vertical suture line. Each fixation point was knotted 7 times.

The vertical fixation was mildly loose to allow easy collapsibility of the valve.

The approximate time to suture and attach the valve was 10 hours.

The stent-valve is maintained in 0.7% gluteraldehyde solution.

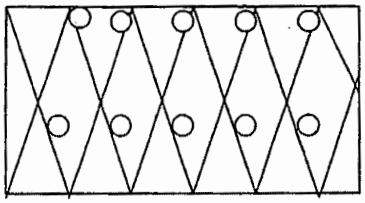
[redacted]

The new valve design includes the creation of a curve in each cusp of the valve

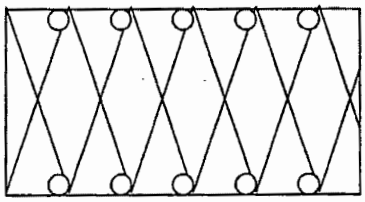
Curve

[redacted]

One plane of fixation points will probably be enough to prevent systolic collapsed of the proximal edge of the valve



Proximal fixation points expanded



Proximal position points shifted to distinct positions

Fixation points

18 fixation points at each plane

NEEDS DETAIL DESCRIPTION OF WHAT IS CLAIM

DESCRIPTION

FIELD OF THE INVENTION

This invention relates to devices and methods for percutaneous endovascular replacement of heart valves.

BACKGROUND

When a heart valve is malfunctioning in such a degree that interferes with normal cardiac function it may be necessary to replace it. Currently this requires a surgical procedure that involves open-heart surgery requiring general anesthesia, full cardiopulmonary bypass with complete cessation of cardiopulmonary activity. Usually after the surgical procedure seven to ten days of hospitalization and months of recuperation time are required. This valve replacement surgery is not free of complication and it is associated with a mortality rate in the best hands and circumstances of about five to six percent.

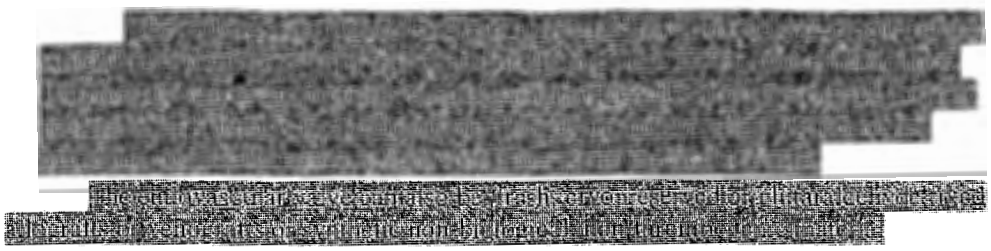
Endovascular procedures for valve replacement provide an alternative to open heart surgery and this is the goal of our new invention.

Previous endovascular treatments of disease heart-valves have focus in opening stenotic lesions in the mitral and aortic valve using specially designs balloons to dilate or split commissures in diseased aortic or mitral valves with commissural fusion and to crack calcific plaques in calcified stenotic aortic valves.

The success for the mitral valve has been rewarding but the aortic valve results have been discouraging This method provides only partial and temporary relief for a patient with a stenotic aortic valve and this method cannot be used to treat valves with leakage. Moreover, aortic valvuloplasty in a few cases may induce severe aortic leakage that is not compatible with life.

The method that we describe is to use a percutaneously endovascular valve replacement. supplantation. In this procedure, a delivery system is used to insert a biological or mechanical valve in the lumen of a central blood vessel via entry through the brachial or femoral artery. Vascular access is obtained using a needle or exposing the artery surgically and a guide wire is placed through the entry vessel and it is advanced to the desired placed under fluoroscopically guidance. Dilators are advanced over the wire to increase the lumen of the entry site preparing the artery to receive the delivery system of our heart-valve. The heart-valve is then advanced to the desired place and deployed under X-ray guidance.

This new technique of percutaneous endovascular heart-valve replacement, in contrast to open heart surgical procedures, would require only local anesthesia, partial or no cardiac bypass, one to two days hospitalization, and should have a reduced mortality rate as compared to open heart procedures.



RELEVANT LITERATURE

U.S. Pat. No. 3,671,979 to Moulopoulos, issued Jun. 27, 1972, describes a endovascularly inserted conical shaped umbrella-like valve positioned and held in place by an elongated mounting catheter at a supra-annular site to the aortic valve in a nearby arterial vessel. The conical end points toward the malfunctioning aortic valve and the umbrella's distal ends open up against the aorta wall with reverse blood flow, thereby preventing regurgitation.

U.S. Pat. No. 4,056,854 to Boretos, issued Nov. 8, 1977, describes a endovascularly inserted, catheter mounted, supra-annular valve in which the circular frame abuts the wall of the artery and attached flaps of flexible membrane extend distally in the vasculature. The flaps lie against the artery wall during forward flow, and close inward towards the central catheter to prevent regurgitation during reverse blood flow. The Boretos valve was designed to be positioned against the artery wall during forward flow, as compared to the mid-center position of the Moulopoulos valve, to reduce the stagnation of blood flow and consequent thrombus and embolic formation expected from a valve at mid-center position.

SUMMARY OF THE INVENTION

The invention relates to a new technique and a special type of device that allows percutaneous heart-valve replacement without the need for open-heart surgery.

The valve replacement system includes the following components:

1- A delivery system of the prosthetic valve device.
2- A prosthetic valve device.
3- An implantation technique

DESCRIPTION OF THE DRAWINGS

FIG. 1 Delivery system of the self-expanded stented valve.

FIG. 2 Initial deployment of the self-expanded stented valve.

FIG. 3 illustrates a bottom view of stented valve.

FIG. 4 illustrates a top view of the stented valve.

FIG. 5 illustrates a tissue laser wire used to cut the commisures of stenotic valve.

FIG. 6 illustrates a diagram of the relationships, dimensions and folds used to create the valve.

FIG. 7 illustrates a side view of a valve introducer.

FIG. 9 illustrates a side view of the attachment point of the valve to the stent.

FIG. 10 illustrates a top view showing the attachment points of the cusp of the valve.

FIG. 11 illustrates an aortic valve in the side position.

FIG. 12 illustrates an aortic valve from the top view.

FIG. 13 is a side cross-sectional view of the valve mounted in the self-expanded stent.

FIG. 14 illustrates a front view of the valve mounted in the stent in the open position.

FIG. 15A is a close-up side cross-sectional view of the mounting stent and FIG. 15B in the closed position.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

The present invention relates to the supplantation or replacement of a cardiac valve in a host through percutaneous endovascular means.

The valve replacement system includes
(1) a delivery device
(2) a prosthetic valve device
(3) an implantation technique.

GENERAL DESCRIPTION OF THE PROCEDURE

The Femoral artery is canulated using a Cook needle and a standard J wire is advance into the artery either perutaneously or after surgical exposure of the artery. An 8 F introducer is advanced into the femoral artery over the wire. The J wire is then withdraw and anticoagulation is started using heparin 60 U/Kg intravenously. Once vascular access is obtained an aortogram is performed for anatomical evaluation.

A special wire (Lunderquist or Amplatz superstiff) is advanced into the aortic arch and dilators progressively larger are advance over the wire, starting with 12 F all the way to 18 F after this the valve introducer device containing the prosthetic valve device is then inserted and used to transport the replacement valve over a guidewire to the desired position.

The stented-valve is released by pulling the cover sheath of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advance over the wire and repeat aortogram is performed to assess the competency of the valve.

When the device is used to treat severe leakage of the aortic valve, the native valve is left in placed and the prostetic stented valve is deployed below the subclavian artery.
When the device is used to treat aortic stenosis, first the stenotic valve needs to be opened using either aortic valvuloplasty or the new laser wire cutters and if this procedure induces aortic insufficiency the stented valve is placed to prevent the regurgitation.

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The prosthetic valve device can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation. In addition, with the development of longer-life, flexible, non thrombogenic synthetic valve alternatives to bioprosthesis', the prosthetic valve device will be indicated in all patients where the relative advantages of the life-span, the non-thrombogenic quality, and the ease of insertion of prosthetic valve devices outweigh the disadvantages of mechanical valves. Anticoagulation may be beneficial in certain clinical situations for either short or long term use.

All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

* * * * *

EXHIBIT F

GREENBERG
ATTORNEYS AT LAW
TRAURIG

Manuel R. Valcarcel
305-579-0812
valcarcelm@gtlaw.com

ATTORNEY-CLIENT PRIVILEGED
CONFIDENTIAL INFORMATION

August 29, 2001

VIA FACSIMILE (703) 413-4150
AND FED EX

Mr. Mark Miller
Just Files
2001 Jefferson Davis Highway
Suite 506
Arlington, VA 22202

Re: Novelty Search for Percutaneous heart valve replacement device and method
Our Reference No. 51458.010100

Dear Mr. Miller:

Please conduct a novelty search for the above-identified invention which is described below.

A. Replacement Heart Valve Device. The replacement heart valve device comprises a stent made of stainless steel or self-expanding nitinol, a completely newly designed biological valve disposed within the inner space of the stent, and a delivery system having a central part which consists of a hollow tube that allows a metallic wire to be advanced inside it. The stented valve is collapsed over this central metallic tubing and it is covered by a movable sheath. The sheath keeps the stented valve in the collapsed position. Once the cover sheath is moved backwards, the stented valve can be deployed.

The endovascular stented-valve is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow. Bioprostetic valves are presently a mainstay in aortic valve replacement and they are preferable in patients who cannot tolerate long-term anticoagulant therapy or are otherwise potentially noncompliant with a long term medical regimen.

In making of the valve initially, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a

solution of gluteraldehyde at a concentration of 0.07% during 36 hours, then the pericardium is transferred to a solution of ethanol at 60% before making the valve.

The valve is formed by taking a rectangular fragment of bovine pericardium and folding it in such a way that forms a three-leaflet valve.

The endovascular valve can also be fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts or synthetic non-biological, non-thrombogenic material.

B. Implantation Method.

The method for implanting said replacement heart valve device through an aortic passageway to, or near to, the location from which the natural heart valve has been removed comprises the following steps:

inserting the replacement heart valve device in the lumen of a central blood vessel via entry through the brachial or femoral artery using a needle or exposing the artery surgically; placing a guide wire through the entry vessel and advancing it to the desired position; advancing dilators over the wire to increase the lumen of the entry site, thereby preparing the artery to receive the heart-valve; and advancing the heart-valve to the desired place.

This new technique of percutaneous endovascular heart-valve replacement, in contrast to open heart surgical procedures, would require only local anesthesia, partial or no cardiac bypass, one to two days hospitalization, and should have a reduced mortality rate as compared to open heart procedures.

When the device is used to treat severe leakage of the aortic valve, the native valve is left in placed and the prosthetic stented valve is deployed below the subclavian artery. When the device is used to treat aortic stenosis, first the stenotic valve is opened using either aortic valvuloplasty or laser wire cutters and if this procedure induces aortic insufficiency the stented valve is placed to prevent the regurgitation.

The stented-valve is released by pulling the cover sheath of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advanced over he wire and an aortogram is performed to assess the competency of the valve.

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The prosthetic valve device can be used in any patient where

bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation.

Please do not hesitate to contact me at 305-579-0812 if you have any questions or need additional information to complete the search. Please let me know beforehand if the search will cost more than $400.00.

Sincerely,

GREENBERG TRAURIG, P.A.

Manuel R. Valcarcel, Esq.

MRV/ps

\\MIA-SRV01\VALCARCELM\1333881v01\8/29/01\51458.010100

EXHIBIT G

GREENBERG
ATTORNEYS AT LAW
TRAURIG

Manuel R. Valcarcel
305-579-0812
valcarcelm@gtlaw.com

ATTORNEY-CLIENT PRIVILEGED
CONFIDENTIAL INFORMATION

August 29, 2001

VIA FACSIMILE (703) 413-4150
AND FED EX

Mr. Mark Miller
Just Files
2001 Jefferson Davis Highway
Suite 506
Arlington, VA 22202

Re: Novelty Search for Percutaneous heart valve replacement device and method
Our Reference No. 51458.010100

Dear Mr. Miller:

Please conduct a novelty search for the above-identified invention which is described below.

A. Replacement Heart Valve Device. The replacement heart valve device comprises a stent made of stainless steel or self-expanding nitinol, a completely newly designed biological valve disposed within the inner space of the stent, and a delivery system having a central part which consists of a hollow tube that allows a metallic wire to be advanced inside it. The stented valve is collapsed over this central metallic tubing and it is covered by a movable sheath. The sheath keeps the stented valve in the collapsed position. Once the cover sheath is moved backwards, the stented valve can be deployed.

The endovascular stented-valve is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow. Bioprostetic valves are presently a mainstay in aortic valve replacement and they are preferable in patients who cannot tolerate long-term anticoagulant therapy or are otherwise potentially noncompliant with a long term medical regimen.

In making of the valve initially, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a

EXHIBIT H

GREENBERG
ATTORNEYS AT LAW
TRAURIG

Manuel R. Valcarcel
(305) 579-0812

November 27, 2001

ATTORNEY-CLIENT PRIVILEGED
CONFIDENTIAL COMMUNICATION

VIA HAND DELIVERY

David Paniagua, M.D.
1865 – 79th Street Causeway
Apartment 7-H
Miami Beach, Florida 33141

Re: Draft of patent application specification for percutaneously implantable heart valve replacement device and method of making same

Dear Dr. Paniagua:

Enclosed for your review and revision as appropriate is the draft of the nonprovisional patent application specification for your above-referenced invention. Please review the draft at your earliest convenience (please also review the draft with the other co-inventors) and provide your comments, revisions and additional text. Please note the descriptions of the figures in the draft and if you have drawings or clear digital photographs that provide the views described in the description of the drawings, please provide them. The photographs provided previously are not clear enough for use in the application. If you do not have such photographs, please let me know if you can provide an actual sample of the device so that a draftsman can prepare the figures.

Best regards,

GREENBERG TRAURIG, P.A.

Manuel R. Valcarcel, Esq.

MRV/ps
Enclosures

\\MIA-SRV01\VALCARCELM\1353475v01\11/27/01\51458.010100

Docket No. 51458.010100

NON-PROVISIONAL PATENT APPLICATION

SPECIFICATION

TO WHOM IT MAY CONCERN:

BE IT KNOWN THAT WE, David Paniagua, Eduardo Induni, Carlos Mejia, Francisco Lopez and R. David Fish, each citizens of the United States of America, have invented a new and useful percutaneously implantable replacement heart valve and method of making same, of which the following is the Specification.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is in the field of heart valve replacement. More specifically, the present invention is directed to a percutaneously implantable replacement heart valve and method of making same.

2. Description of Related Art

There have been numerous efforts in the field of heart valve replacement to improve both the durability and effectiveness of replacement heart valves as well as the ease of implantation. A brief description of heart valves and heart function follows to provide relevant background for the present invention.

There are four valves in the heart that serve to direct the flow of blood through the two sides of the heart in a forward direction. On the left (systemic) side of the heart are: 1) the mitral valve, located between the left atrium and the left ventricle, and 2) the aortic valve, located between the left ventricle and the aorta. These two valves direct oxygenated blood coming from the lungs through the left side of the heart into the aorta for distribution to the body. On the right (pulmonary) side of the heart are: 1) the tricuspid valve, located between the right atrium and the right ventricle, and 2) the pulmonary valve, located between the right ventricle and the pulmonary artery. These two valves direct de-oxygenated blood coming from the body through the right side of the heart into the pulmonary artery for distribution to the lungs, where it again becomes re-oxygenated to begin the circuit anew.

Heart valves are passive structures that simply open and close in response to differential pressures on either side of the particular valve. They consist of moveable "leaflets" that are designed simply to open and close in response to differential pressures on either side of the valve's leaflets. The mitral valve has two leaflets and the tricuspid valve has three. The aortic and pulmonary valves are referred to as "semilunar valves" because of the unique appearance

of their leaflets, which are more aptly termed "cusps" and are shaped somewhat like a half-moon. The aortic and pulmonary valves each have three cusps.

In general, the components of heart valves include the valve annulus, which will remain as a roughly circular open ring after the leaflets of a diseased or damaged valve have been removed; leaflets or cusps; papillary muscles which are attached at their bases to the interior surface of the left or right ventricular wall; and multiple chordae tendineae, which couple the valve leaflets or cusps to the papillary muscles. There is no one-to-one chordal connection between the leaflets and the papillary muscles; instead, numerous chordae are present, and chordae from each papillary muscle attach to both of the valve leaflets.

When the left ventricular wall relaxes so that the ventricular chamber enlarges and draws in blood, the leaflets of the mitral valve separate and the valve opens. Oxygenated blood flows in a downward direction through the valve, to fill the expanding ventricular cavity. Once the left ventricular cavity has filled, the left ventricle contracts, causing a rapid rise in the left ventricular cavitary pressure. This causes the mitral valve to close while the aortic valve opens, allowing the oxygenated blood to be ejected from the left ventricle into the aorta. The chordae tendineae of the mitral valve prevent the mitral leaflets from prolapsing back into the left atrium when the left ventricular chamber contracts.

The three leaflets, chordae tendineae, and papillary muscles of the tricuspid valve function in a similar manner, in response to the filling of the right ventricle and its subsequent contraction. The cusps of the aortic valve also respond passively to pressure differentials between the left ventricle and the aorta. When the left ventricle contracts, the aortic valve cusps open to allow the flow of oxygenated blood from the left ventricle into the aorta. When the left ventricle relaxes, the aortic valve cusps reapproximate to prevent the blood which has entered the aorta from leaking (regurgitating) back into the left ventricle. The pulmonary valve cusps respond passively in the same manner in response to relaxation and contraction of the right ventricle in moving de-oxygenated blood into the pulmonary artery and thence to the lungs for

re-oxygenation. Neither of these semilunar valves has associated chordae tendineae or papillary muscles.

Problems that can develop with heart valves consist of stenosis, in which a valve does not open properly, and/or insufficiency, also called regurgitation, in which a valve does not close properly. In addition to stenosis and insufficiency of heart valves, heart valves may need to be surgically repaired or replaced due to certain types of bacterial or fungal infections in which the valve may continue to function normally, but nevertheless harbors an overgrowth of bacteria (vegetation) on the leaflets of the valve that may embolize and lodge downstream in a vital artery. If such vegetations are on the valves of the left side (i.e., the systemic circulation side) of the heart, embolization may occur, resulting in sudden loss of the blood supply to the affected body organ and immediate malfunction of that organ. The organ most commonly affected by such embolization is the brain, in which case the patient suffers a stroke. Thus, surgical replacement of either the mitral or aortic valve (left-sided heart valves) may be necessary for this problem even though neither stenosis nor insufficiency of either valve is present. Likewise, bacterial or fungal vegetations on the tricuspid valve may embolize to the lungs resulting in a lung abscess and therefore, may require replacement of the tricuspid valve even though no tricuspid valve stenosis or insufficiency is present.

These problems are treated by surgical repair of valves, although often the valves are too diseased to repair and must be replaced. If a heart valve must be replaced, there are currently several options available, and the choice of a particular type of artificial valve depends on factors such as the location of the valve, the age and other specifics of the patient, and the surgeon's experiences and preferences. Currently in the United States over 100,000 defective heart valves are replaced annually, at an approximate cost of $30-50,000 per procedure, and thus it would be desirable if heart valves could be replaced using minimally invasive techniques and without having to repeat the procedure within a matter of years due to the lack of durability of the replacement heart valve. It would be especially advantageous if a defective heart valve

could be removed via an endovascular procedure, that is, a procedure where the invasion into the body is through a blood vessel such as the femoral artery. The procedure is then carried out percutaneously and transluminally using the vascular system to convey appropriate devices to the position in the body wherein it is desired to carry out the desired procedure. An example of such a procedure would be angioplasty, wherein a catheter carrying a small balloon at its distal end is manipulated through the body's vessels to a point where there is a blockage in a vessel. The balloon is expanded to create an opening in the blockage, and then the balloon is deflated and the catheter and balloon are removed from the vessel.

Endovascular procedures have substantial benefits both from the standpoint of health and safety as well as cost. Such procedures require minimal invasion of the human body, and there is consequently considerable reduction and in some instances even elimination, of the use of a general anesthesia and much shorter hospital stays.

Replacement heart valves can be categorized as either artificial mechanical valves, transplanted valves and tissue valves. Replacement heart valves are designed to optimize hemodynamic performance, thrombogenicity and durability. Another factor taken into consideration is the relative ease of surgical implantation.

Mechanical valves are typically constructed from nonbiological materials such as plastics, metals and other artificial materials which, while durable, are expensive and prone to blood clotting which increases the risk of an embolism. Anticoagulants taken to help against blood clotting can further complicate the patient's health due to increased risks for hemorrhages.

Transplanted valves are natural valves taken from cadavers. These valves are typically removed and frozen in liquid nitrogen, and are stored for later use. They are typically fixed in glutaraldehyde to eliminate antigenicity and are sutured in place, typically with a stent.

Artificial tissue valves are valves constructed from animal tissue, such as bovine or porcine tissue. Efforts have also been made at using tissue from the patient for which the valve will be constructed.

Most tissue valves are constructed by sewing the leaflets of pig aortic valves to a stent to hold the leaflets in proper position, or by constructing valve leaflets from the pericardial sac of cows or pigs and sewing them to a stent. The porcine or bovine tissue is chemically treated to alleviate any antigenicity. The pericardium is a membrane that surrounds the heart and isolates it from the rest of the chest wall structures. The pericardium is a thin and very slippery, which makes it difficult for suturing in a millimetricly precise way. The method of making the replacement heart valve of the present invention solves this problem through a process to dry the pericardium in such a way that makes it possible to handle and fold more easily.

For example, one prior replacement heart valve requires each sculpted leaflet to be trimmed in a way that forms an extended flap, which becomes a relatively narrow strand of tissue near its tip. The tip of each pericardial tissue strand is sutured directly to a papillary muscle, causing the strand to mimic a chordae tendineae. Each strand extends from the center of a leaflet in the valve, and each strand is sutured directly to either an anterior and posterior papillary muscle. This requires each leaflet to be positioned directly over a papillary muscle. This effectively rotates the leaflets of the valve about 90 degrees as compared to the leaflets of a native valve. The line of commissure between the leaflets, when they are pressed together during systole, will bisect (at a perpendicular angle) an imaginary line that crosses the peaks of the two papillary muscles, instead of lying roughly along that line as occurs in a native valve.

A different approach to creating artificial tissue valves is described in U.S. Patent Nos. 5,163,955 to Calvin, et al. and 5,571,174 and 5,653,749 to Love. Using a cutting die, the pericardial tissue is cut into a carefully defined geometric shape, treated with glutaraldehyde, then clamped in a sandwich-fashion between two stent components. This creates a tri-leaflet

valve that resembles an aortic or pulmonary valve, having semilunar-type cusps rather than atrioventricular-type leaflets.

U.S. Patent No. 3,671,979 to Moulopoulos describes an endovascularly inserted conical shaped umbrella-like valve positioned and held in place by an elongated mounting catheter at a supra-annular site to the aortic valve in a nearby arterial vessel. The conical end points toward the malfunctioning aortic valve and the umbrella's distal ends open up against the aorta wall with reverse blood flow, thereby preventing regurgitation.

U.S. Patent No. 4,056,854 to Boretos describes an endovascularly inserted, catheter mounted, supra-annular valve in which the circular frame abuts the wall of the artery and attached flaps of flexible membrane extend distally in the vasculature. The flaps lie against the artery wall during forward flow, and close inward towards the central catheter to prevent regurgitation during reverse blood flow. The Boretos valve was designed to be positioned against the artery wall during forward flow, as compared to the mid-center position of the Moulopoulos valve, to reduce the stagnation of blood flow and consequent thrombus and embolic formation expected from a valve at mid-center position.

The main advantage of tissue valves is that they do not cause blood clots to form as readily as do the mechanical valves, and therefore, they do not absolutely require systemic anticoagulation. The major disadvantage of tissue valves is that they lack the long-term durability of mechanical valves. Tissue valves have a significant failure rate, usually within ten years following implantation. One cause of these failures is believed to be the chemical treatment of the animal tissue that prevents it from being antigenic to the patient. In addition, the presence of extensive suturing prevents the artificial tissue valve from being anatomically accurate in comparison to a normal heart valve, even in the aortic valve position.

A shortcoming of prior artificial tissue valves has been the inability to effectively simulate the exact anatomy of a native heart valve. Although transplanted human or porcine aortic valves have the gross appearance of native aortic valves, the fixation process (freezing with

liquid nitrogen, and chemical treatment, respectively) alters the histologic characteristics of the valve tissue. Porcine and bovine pericardial valves not only require chemical preparation (usually involving fixation with glutaraldehyde), but the leaflets must be sutured to cloth-covered stents in order to hold the leaflets in position for proper opening and closing of the valve. Additionally, the leaflets of most such tissue valves are constructed by cutting or suturing the tissue material, resulting in leaflets that do not duplicate the form and function of a real valve.

SUMMARY OF THE INVENTION

The present invention is a replacement heart valve device and method of making same. The replacement heart valve device, in a preferred embodiment, comprises a stent made of stainless steel or self-expanding nitinol and a completely newly designed artificial biological tissue valve disposed within the inner space of the stent. The cusp or leaflet portion of the valve means is formed by folding of the pericardium material used to create the valve. The cusps/leaflets open in response to blood flow in one direction and close in response to blood flow in the opposite direction. Preferably the tubular portion of the valve means contains the same number of cusps as the native valve being replaced, in substantially the same size and configuration. The outer surface of the valve means is attached to the stent member.

The replacement heart valve device is preferably implanted using a delivery system having a central part which consists of a flexible hollow tube catheter that allows a metallic guide wire to be advanced inside it. The stented valve is collapsed over the central tube and it is covered by a movable sheath. The sheath keeps the stented valve in the collapsed position. Once the cover sheath is moved backwards, the stented valve can be deployed. The endovascular stented-valve, in a preferred embodiment, is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow.

The present invention also comprises a method of making a replacement heart valve device. In order to make the valve, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a

solution of gluteraldehyde, preferably at a concentration of about 0.07% during 36 hours, then the pericardium is transferred to a solution of ethanol, preferably at a concentration of about 60% before making the valve. The material is dried in order to make it easier to handle and fold. The valve is formed by taking a rectangular fragment of bovine pericardium and folding it in such a way that forms a three-leaflet valve. The valve can also be made from fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts or synthetic non-biological, non-thrombogenic material. The folding of the pericardium material to create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of the valve leaflets. The valve is rehydrated after being formed. The method of the present invention also greatly reduces the risk of tearing of the cusps or leaflets, since they are integral to the valve rather than being attached by suturing.

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The replacement heart valve device of the present invention can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation medication and treatment. The present invention can be practiced in applications with respect to each of the heart's valves.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 depicts a side perspective view of the replacement heart valve of the present invention in one embodiment without the stent.

Fig. 2 depicts the folds which form the leaflets or cusps of the replacement heart valve of the present invention in one embodiment.

Fig. 3 depicts the procedure for folding the pericardium tissue starting material to create the replacement heart valve of the present invention.

Fig. 4 depicts a side perspective view of the replacement heart valve of the present invention in one embodiment mounted within a stent.

Fig. 5 depicts a cross-sectional view of one embodiment of the replacement heart valve of the present invention mounted within a self-expanding stent, with the stent in the expanded position.

Fig. 6 depicts a side perspective view of one embodiment of the replacement heart valve of the present invention mounted within a self-expanding stent in the collapsed position.

Fig. 7 depicts the suture points of one embodiment of the replacement heart valve of the present invention.

Fig. 8 depicts the implantation/delivery system used with the present invention in a preferred embodiment.

DESCRIPTION OF A PREFERRED EMBODIMENT

The present invention comprises a percutaneously implantable replacement heart valve and a method for making same. The artificial heart valve device of the present invention is capable of exhibiting a variable diameter between a compressed or collapsed position and an expanded position. A preferred embodiment of the replacement heart valve according to the present invention is set forth in FIGS. 1 and 2. The replacement heart valve comprises a stent member __ and a flexible valve means __. The stent member is self-expanding and has a first cylindrical shape in its compressed or collapsed configuration and a second, larger cylindrical shape in its expanded configuration. The valve means comprises a generally tubular center portion and, preferably, a peripheral upstanding cusp or leaflet portion. The valve means is

disposed within the cylindrical stent member with the tubular portion transverse of and at some acute angle relative to the stent walls. The diameter of the tubular portion is substantially the same as the inside diameter of the stent member in its initial expanded configuration. The peripheral upstanding cusp or leaflet portion is disposed substantially parallel to the walls of the stent member similar to a cuff on a shirt. The center portion __ of the valve means __ is generally tubular in shape and comprises three leaflets __ as shown, although it is understood that there could be from two to four leaflets. The tubular portion of the valve means is attached to the stent member __ by a plurality of sutures __.

The leaflet portion of the valve means __ extends across or transverse of the cylindrical stent. The leaflets __ are the actual valve and allow for one-way flow of blood. The leaflet portion as connected to the rest of the valve resembles the cuff of a shirt. The configuration of the stent member __ and the flexible, resilient material of construction allows the valve to collapse into a relatively small cylinder __ as seen in FIG. 6. The replacement heart valve will not stay in its collapsed configuration without being restrained. Once the restraint is removed, the self-expanding stent member __ will cause the artificial heart valve to take its expanded configuration, as seen in FIG. __.

Stent Member

The stent member __ comprises self-expanding nickel-titanium alloy, also called "nitinol," in a sine wave-like configuration as shown in FIG. 1. An enlarged view of a preferred embodiment of the stent member for use in the replacement heart valve of the invention is depicted in FIG. 5. The stent member __ includes a length of wire __ formed in a closed zigzag configuration. The wire can be a single piece, stamped or extruded, or it could be formed by welding the free ends together as at __. The straight sections __ of the stent are joined by bends __. The stent is readily compressible to a small cylindrical shape and resiliently self-expandable to the shape shown in FIG. 5.

The stent members of the artificial heart valves of the present invention may be made from various metal alloys, titanium, titanium alloy, nitinol, stainless steel, or other resilient, flexible non-toxic, non-thrombogenic, physiologically acceptable and biocompatible materials. The configuration may be the zigzag configuration shown or a sine wave configuration, mesh configuration or a similar configuration which will allow the stent to be readily collapsible and self-expandable. When a zigzag or sine wave configured stent member is used, the diameter of the wire from which the stent is made should be from about [0.010 to 0.035] inches, preferably from about [0.012 to 0.025] inches. The diameter of the stent member will be from about [1.5 to 3.5 cm], preferably from about [1.75 to 3.00 cm], and the length of the stent member will be from about [1.0 to 10 cm], preferably from about [1.1 to 5 cm.]

The stent used in a preferred embodiment of the present invention is fabricated from a "shaped memory" alloy, nitinol, which is composed of nickel and titanium. Nitinol wire is first fashioned into the desired shape for the device and then the device is heat annealed. A meshwork of nitinol wire of approximately 0.008 inch gauge is formed into a tubular structure with a minimum central diameter of 20 min to make the stent. Away from its central portion, the tubular structure flares markedly at both ends in a trumpet-like configuration. The maximum diameter of the flared ends of the stent is approximately 30 mm. The purpose of the stent is to maintain a semi-rigid patent channel through the diseased cardiac valve following its implantation.

When the components of the replacement heart valve device are exposed to cold temperatures, they become very flexible and supple, allowing them to be compressed down and pass easily through the delivery sheath. A cold temperature is maintained within the sheath during delivery to the deployment site by constantly infusing the sheath with an iced saline solution. Once the valve components are exposed to body temperature at the end of the sheath, they instantaneously reassume their predetermined shapes, thus allowing them to function as designed.

Preferably the stent member carries a plurality of barbs extending outwardly from the outside surface of the stent member for fixing the heart valve in a desired position. More preferably the barbs are disposed in two spaced-apart, circular configurations with the barbs in one circle extending in an upstream direction and the barbs in the other circle extending in a downstream direction. It is especially preferable that the barbs on the inflow side of the valve point in the direction of flow and the barbs on the outflow side point in the direction opposite to flow. It is preferred that the stent be formed of titanium alloy wire or other flexible, relatively rigid, physiologically acceptable material arranged in a closed zigzag configuration so that the stent member will readily collapse and expand as pressure is applied and released, respectively.

Valve Means

The valve means is flexible, compressible, host-compatible, and non-thrombogenic. The valve can be, for example, fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts. Synthetic biocompatible materials such as polytetrafluoroethylene, polyester and the like may be used. The preferred material for the valve means is bovine pericardium tissue. The valve means is disposed within the cylindrical stent member with the tubular portion transverse of and at some acute angle relative to the stent walls. The diameter of the tubular portion is substantially the same as the inside diameter of the stent member in its initial expanded configuration. The peripheral upstanding cusp or leaflet portion is disposed substantially parallel to the walls of the stent member similar to a cuff on a shirt.

The cusp or leaflet portion of the valve means is formed by folding of the pericardium material used to create the valve. The cusps/leaflets open in response to blood flow in one direction and close in response to blood flow in the opposite direction. Preferably the tubular portion of the valve means contains the same number of cusps as the native valve being replaced, in substantially the same size and configuration.

Method of Making Replacement Heart Valve Device

The present invention also comprises a method of making a replacement heart valve device. In order to make the valve, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a solution of gluteraldehyde, preferably at a concentration of about 0.07% during 36 hours, then the pericardium is transferred to a solution of ethanol, preferably at a concentration of about 60% before making the valve. The valve is formed by taking a rectangular fragment of bovine pericardium and folding it in such a way that forms a three-leaflet or desired number of leaflet valve. FIG. 2 depicts the folds which form the cusps or leaflets, and FIG. 3 depicts the folding procedure. The folding of the pericardium material to create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of the valve leaflets. It also greatly reduces the risk of tearing of the cusps or leaflets, since they are integral to the valve rather than being attached by suturing.

In order to make the pericardium material less slippery and easier to fold, the pericardium is dried, preferably with artificial light using a 60-watt lamp with the pericardium material placed in a flat aluminum surface to dry it homogeneously. A photo drying machine can also be used. The final result is a homogeneous tissue that looks like plastic paper and makes it easy to manipulate to fold and suture the valve. Once the valve is formed it is re-hydrated by placing it in a solution of water and 70% alcohol. In approximately 3 days the valve is fully rehydrated.

Attachment of the Valve Means to the Stent Member

The valve means is then attached to the inner channel of the stent member by suturing the outer surface of the valve means' pericardium material to the stent member. Fig. 7 depicts preferred suture points of one embodiment of the present invention: 3-point fixation or 6-point fixation at each border of the stent. Other fixation schemes can be utilized, such as, by way of

non-limiting example, fixation on both borders 18 points at each end following a single plane and 36 fixation points following to adjacent vertical planes. The use of only one plane of fixation points helps prevent systolic collapse of the proximal edge of the valve means. A fold on the border of the pericardium material prevents tearing. The attachment position of the valve is preferably closer to the proximal and wider part of the stent.

The sequence of steps can vary. The pericardium material can be fixed in glutaraldehyde before attachment to the stent or the valve can be formed and then fixed with gluteraldehyde after mounting it in the stent. One observation noted is that the material becomes whiter and apparently increases its elasticity. 1mm vascular clips keep the cusps coapted while fixing them in gluteraldehyde. The use of metallic clips to keep both cusps adjacent to each other after 24 hours of fixation in gluteraldehyde helps to educate the material and make the primary position of the valve cusps adjacent to each other. After the clips are removed, there are no lesions to the valve.

Different suture materials can be used, including, in a preferred embodiment, prolene 6-0 and Mersilene 6-0 which is a braided suture.

Implantation of Replacement Heart Valve Device

The replacement heart valve device of the present invention is preferably used in surgical procedures involving the percutaneous and transluminal removal of the diseased or defective heart valve and the percutaneous and transluminal implantation of the new heart valve described above. The defective heart valve is removed by a suitable modality, such as, for example, laser, ultrasound, mechanical, or other suitable forms of delivery of energy, or phacoemulsion, including, but not limited to, laser lithotripsy, mechanical lithotripsy, electrohydraulic lithotripsy, and laser or mechanical ablation. To remove the native heart valve that is being replaced, a guidewire is inserted percutaneously and transluminally using standard vascular or angiography techniques. The distal end of the guidewire is manipulated to extend

through and across the defective heart valve. Then a catheter is advanced distally through the femoral artery to a point proximal to the defective heart valve, between the origin of the coronary artery and the origin of the right subclavian artery. The position of the distal end of catheter can be monitored by observation of radiopaque markers. Collector member is preferably inflated and occludes the aorta at a point between the origin of the coronary artery and the right subclavian artery. Next, a balloon and cutting tool are advanced through the catheter so that the cutting tool and uninflated balloon are distal to the defective heart valve. Optionally an additional step, such as balloon dilatation or atherectomy, may be required to provide a passageway through the heart valve. A catheter is also placed into the coronary sinus via a transjugular puncture. This catheter is used for infusion of blood or cardioplegia solution during the portion of the procedure when the aorta is occluded. The absence of valves in the cardiac venous system allows retrograde flow so that there will be an effluence of fluid from the coronary arteries. This flow of fluid is desired to prevent embolization of material into the coronary arteries during the procedure. Once the cutting tool is in place, the balloon is inflated and flexible shaft is rotated. Once the cutting tool has reached the appropriate rotation speed, the cutting tool is pulled proximally to remove the defective heart valve. The balloon and the cutting tool are spaced apart so that the inflated balloon will be stopped by the perimeter, unremoved portion of the defective heart valve, which will signal the physician that the valve has been removed, as well as protect the heart and aorta from damage from the valve removal device. Once it is determined that the defective heart valve has been removed, the cutting tool is slowed or stopped altogether and the balloon is deflated. The cutting tool and the deflated balloon are pulled proximally through catheter. Then, a catheter containing an artificial heart valve is inserted and the artificial heart valve is placed as described above.

The delivery and implantation system of the replacement artificial heart valve of the present invention percutaneously and transluminally includes a flexible catheter which may be inserted into a vessel of the patient and moved within that vessel. The distal end of the catheter,

which is hollow and carries the replacement heart valve of the present invention in its collapsed configuration, is guided to a site where it is desired to implant the replacement heart valve. The catheter has a pusher member disposed within the catheter lumen and extending from the proximal end of the catheter to the hollow section at the distal end of the catheter. Once the distal end of the catheter is positioned as desired, the pusher mechanism is activated and the distal portion of the replacement heart valve is pushed out of the catheter and the stent member partially expands. In this position the stent member is restrained so that it doesn't pop out and is held for controlled release, with the potential that the replacement heart valve can be recovered if there is a problem with the positioning. The catheter is them retracted slightly and the replacement heart valve is completely pushed out of the catheter and released from the catheter to allow the stent member to fully expand. If the stent member includes two circles of barbs on its outer surface as previously described, the first push and retraction will set one circle of barbs in adjacent tissue and the second push and release of the replacement heart valve will set the other circle of barbs in adjacent tissue and securely fix the replacement heart valve in place when the valve is released from the catheter.

Alternatively, or in combination with the above, the replacement heart valve could be positioned over a metallic guidewire that is advanced through the catheter. The replacement heart valve device of the present invention is preferably implanted percutaneously through an aortic passageway to, or near to, the location from which the natural heart valve has been removed. Referring to Fig. 8, the implantation system comprises a flexible hollow tube catheter with a metallic guide wire disposed within it. The stented valve is collapsed over the tube and is covered by a moveable sheath. The moveable sheath maintains the stented valve in the collapsed position. comprises the following steps: inserting the replacement heart valve device in the lumen of a central blood vessel via entry through the brachial or femoral artery using a needle or exposing the artery surgically; placing a guide wire through the entry vessel and advancing it to the desired position; advancing dilators over the wire to increase the lumen of

the entry site, thereby preparing the artery to receive the heart-valve; and advancing the heart-valve to the desired place. The stented-valve is released by pulling the cover sheath of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advanced over the wire and an aortogram is performed to assess the competency of the valve.

Before creation of the valve means and implantation, the patient is studied to determine the architecture of the patient's heart. Useful techniques include fluoroscopy, transesophageal echocardiography, MRI, and angiography. The results of this study will enable the physician to determine the appropriate size for the replacement heart valve.

In one procedure for implantation of the replacement heart valve device of the present invention, the femoral artery of the patient is canulated using a Cook needle and a standard J wire is advanced into the artery either percutaneously or after surgical exposure of the artery. An 8 F introducer is advanced into the femoral artery over the wire. The J wire is then withdrawn and anticoagulation is started using heparin 60 U/Kg intravenously. Once vascular access is obtained an aortogram is performed for anatomical evaluation. A special wire (Lunderquist or Amplatz superstiff) is advanced into the aortic arch and dilators progressively larger are advanced over the wire, starting with 12 F all the way to 18 F. After this the valve introducer device containing the prosthetic valve device is then inserted and used to transport the replacement valve over a guidewire to the desired position. The stented-valve is released by pulling the cover sheath of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advanced over the wire and repeat aortogram is performed to assess the competency of the valve.

When the device is used to treat severe leakage of the aortic valve, the native valve is left in place and the prosthetic stented valve is deployed below the subclavian artery. When the device is used to treat aortic stenosis, first the stenotic valve needs to be opened using either

aortic valvuloplasty or cutting and if this procedure induces aortic insufficiency the stented valve is placed to prevent the regurgitation.

Intravascular ultrasound or an angioscope passed intravascularly via either the venous system through the intra-atrial septum across the mitral valve and into the left ventricle or retrograde via the femoral artery would provide the added benefit of allowing constant high definition imaging of the entire procedure and high flow irrigation.

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The prosthetic valve device can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation. In addition, with the development of longer-life, flexible, non-thrombogenic synthetic valve alternatives to bioprosthesis, the prosthetic valve device will be indicated in all patients where the relative advantages of the life-span, the non-thrombogenic quality, and the ease of insertion of prosthetic valve devices outweigh the disadvantages of mechanical valves. Anticoagulation may be beneficial in certain clinical situations for either short or long term use.

This method of percutaneous endovascular heart-valve replacement, in contrast to open heart surgical procedures, requires only local anesthesia, partial or no cardiac bypass, one to two days hospitalization, and should result in a reduced mortality rate as compared to open heart procedures.

While the present invention has been shown and described herein in what is considered to be a preferred embodiment thereof, illustrating the results and advantages over the prior art obtained through the present invention, the invention is not limited to the specific embodiments

described above. Thus, the forms of the invention shown and described herein are to be taken as illustrative and other embodiments may be selected without departing from the spirit and scope of the present invention.

CLAIMS

Having thus described the invention, what is claimed is:

1. A percutaneously implantable replacement heart valve device comprising a self-expanding stent member and an artificial valve means made of biocompatible tissue material and disposed within the inner cavity of said stent member affixed at one or more points to said stent member, said valve means having cusps or leaflets formed by folding of said biocompatible tissue material.

2. The percutaneously implantable replacement heart valve of claim 1, wherein said stent member is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium, stainless steel [add others].

3. The percutaneously implantable replacement heart valve of claim 1, wherein said biocompatible tissue material of said valve means comprises bovine pericardium tissue.

4. The percutaneously implantable replacement heart valve of claim 1, wherein said biocompatible tissue material of said valve means comprises porcine pericardium tissue.

5. The percutaneously implantable replacement heart valve of claim 1, wherein said biocompatible tissue material of said valve means comprises autologous tissue obtained from the patient into whom said replacement heart valve will be implanted.

6. A method of making a percutaneously implantable replacement heart valve comprising the following steps:

obtaining a substantially rectangular segment of biocompatible tissue material;

soaking said biocompatible tissue material in a gluteraldehyde solution;

transferring said biocompatible tissue material from said gluteraldehyde solution to an ethanol solution;

drying said biocompatible tissue material;

folding said dried biocompatible tissue material to create cusps or leaflets and a cuffed tubular valve structure;

affixing said folded biocompatible tissue material to the inner cavity of a stent.

ABSTRACT

The present invention comprises a percutaneously implantable replacement heart valve device and a method of making same. The replacement heart valve device comprises a stent member made of stainless steel or self-expanding nitinol, a biological tissue artificial valve means disposed within the inner space of the stent member. An implantation and delivery system having a central part which consists of a flexible hollow tube catheter that allows a metallic wire guide to be advanced inside it. The endovascular stented-valve is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow. The present invention also comprises a novel method of making a replacement heart valve by taking a rectangular fragment of bovine pericardium treating, drying, folding and rehydrating it in such a way that forms a two- or three-leaflet/cusp valve with the leaflets/cusps formed by folding, thereby eliminating the extent of suturing required, providing improved durability and function.

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December 28, 2001

ATTORNEY-CLIENT PRIVILEGED
CONFIDENTIAL COMMUNICATION

VIA HAND DELIVERY

David Paniagua, M.D.
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Miami Beach, Florida 33141

Re: Revised draft of patent application specification for percutaneously implantable heart valve replacement device and method of making same

Dear Dr. Paniagua:

Enclosed for your review and revision is a revised draft of the nonprovisional patent application specification for your above-referenced invention. Please review the draft at your earliest convenience (please also review the draft with the other co-inventors) and provide your comments, revisions and additional text.

Best regards,

GREENBERG TRAURIG, P.A.

Manuel R. Valcarcel, Esq.

MRV/mp

Enclosure

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Docket No. 51458.010100

NON-PROVISIONAL PATENT APPLICATION

SPECIFICATION

TO WHOM IT MAY CONCERN:

BE IT KNOWN THAT WE, David Paniagua, Eduardo Induni, Carlos Mejia, Francisco Lopez and R. David Fish, ~~each citizens of the United States of America,~~ have invented a new and useful percutaneously implantable replacement heart valve **device** and method of making same, of which the following is the Specification.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is in the field of heart valve replacement. More specifically, the present invention is directed to a percutaneously implantable replacement heart valve and method of making same.

2. Description of Related Art

There have been numerous efforts in the field of heart valve replacement to improve both the durability and effectiveness of replacement heart valves as well as the ease of implantation. A brief description of heart valves and heart function follows to provide relevant background for the present invention.

There are four valves in the heart that serve to direct the flow of blood through the two sides of the heart in a forward direction. On the left (systemic) side of the heart are: 1) the mitral valve, located between the left atrium and the left ventricle, and 2) the aortic valve, located between the left ventricle and the aorta. These two valves direct oxygenated blood coming from the lungs through the left side of the heart into the aorta for distribution to the body. On the right (pulmonary) side of the heart are: 1) the tricuspid valve, located between the right atrium and the right ventricle, and 2) the pulmonary valve, located between the right ventricle and the pulmonary artery. These two valves direct de-oxygenated blood coming from the body through the right side of the heart into the pulmonary artery for distribution to the lungs, where it again becomes re-oxygenated to begin the circuit anew.

Heart valves are passive structures that simply open and close in response to differential pressures on either side of the particular valve. They consist of moveable "leaflets" that are designed simply to open and close in response to differential pressures on either side of the valve's leaflets. The mitral valve has two leaflets and the tricuspid valve has three. The

aortic and pulmonary valves are referred to as "semilunar valves" because of the unique appearance of their leaflets, which are more aptly termed "cusps" and are shaped somewhat like a half-moon. The aortic and pulmonary valves each have three cusps.

In general, the components of heart valves include the valve annulus, which will remain as a roughly circular open ring after the leaflets of a diseased or damaged valve have been removed; leaflets or cusps; papillary muscles which are attached at their bases to the interior surface of the left or right ventricular wall; and multiple chordae tendineae, which couple the valve leaflets or cusps to the papillary muscles. There is no one-to-one chordal connection between the leaflets and the papillary muscles; instead, numerous chordae are present, and chordae from each papillary muscle attach to both of the valve leaflets.

When the left ventricular wall relaxes so that the ventricular chamber enlarges and draws in blood, the leaflets of the mitral valve separate and the valve opens. Oxygenated blood flows in a downward direction through the valve, to fill the expanding ventricular cavity. Once the left ventricular cavity has filled, the left ventricle contracts, causing a rapid rise in the left ventricular cavitary pressure. This causes the mitral valve to close while the aortic valve opens, allowing the oxygenated blood to be ejected from the left ventricle into the aorta. The chordae tendineae of the mitral valve prevent the mitral leaflets from prolapsing back into the left atrium when the left ventricular chamber contracts.

The three leaflets, chordae tendineae, and papillary muscles of the tricuspid valve function in a similar manner, in response to the filling of the right ventricle and its subsequent contraction. The cusps of the aortic valve also respond passively to pressure differentials between the left ventricle and the aorta. When the left ventricle contracts, the aortic valve cusps open to allow the flow of oxygenated blood from the left ventricle into the aorta. When the left ventricle relaxes, the aortic valve cusps reapproximate to prevent the blood which has entered the aorta from leaking (regurgitating) back into the left ventricle. The pulmonary valve cusps

respond passively in the same manner in response to relaxation and contraction of the right ventricle in moving de-oxygenated blood into the pulmonary artery and thence to the lungs for re-oxygenation. Neither of these semilunar valves has associated chordae tendineae or papillary muscles.

Problems that can develop with heart valves consist of stenosis, in which a valve does not open properly, and/or insufficiency, also called regurgitation, in which a valve does not close properly. In addition to stenosis and insufficiency of heart valves, heart valves may need to be surgically repaired or replaced due to certain types of bacterial or fungal infections in which the valve may continue to function normally, but nevertheless harbors an overgrowth of bacteria (vegetation) on the leaflets of the valve that may embolize and lodge downstream in a vital artery. If such vegetations are on the valves of the left side (i.e., the systemic circulation side) of the heart, embolization may occur, resulting in sudden loss of the blood supply to the affected body organ and immediate malfunction of that organ. The organ most commonly affected by such embolization is the brain, in which case the patient suffers a stroke. Thus, surgical replacement of either the mitral or aortic valve (left-sided heart valves) may be necessary for this problem even though neither stenosis nor insufficiency of either valve is present. Likewise, bacterial or fungal vegetations on the tricuspid valve may embolize to the lungs resulting in a lung abscess and therefore, may require replacement of the tricuspid valve even though no tricuspid valve stenosis or insufficiency is present.

These problems are treated by surgical repair of valves, although often the valves are too diseased to repair and must be replaced. If a heart valve must be replaced, there are currently several options available, and the choice of a particular type of artificial valve depends on factors such as the location of the valve, the age and other specifics of the patient, and the surgeon's experiences and preferences. Currently in the United States over 100,000 defective heart valves are replaced annually, at an approximate cost of $30-50,000 per procedure, and

thus it would be desirable if heart valves could be replaced using minimally invasive techniques and without having to repeat the procedure within a matter of years due to the lack of durability of the replacement heart valve. It would be especially advantageous if a defective heart valve could be removed via an endovascular procedure, that is, a procedure where the invasion into the body is through a blood vessel such as the femoral artery. The procedure is then carried out percutaneously and transluminally using the vascular system to convey appropriate devices to the position in the body wherein it is desired to carry out the desired procedure. An example of such a procedure would be angioplasty, wherein a catheter carrying a small balloon at its distal end is manipulated through the body's vessels to a point where there is a blockage in a vessel. The balloon is expanded to create an opening in the blockage, and then the balloon is deflated and the catheter and balloon are removed from the vessel.

Endovascular procedures have substantial benefits both from the standpoint of health and safety as well as cost. Such procedures require minimal invasion of the human body, and there is consequently considerable reduction and in some instances even elimination, of the use of a general anesthesia and much shorter hospital stays.

Replacement heart valves can be categorized as either artificial mechanical valves, transplanted valves and tissue valves. Replacement heart valves are designed to optimize hemodynamic performance, thrombogenicity and durability. Another factor taken into consideration is the relative ease of surgical implantation.

Mechanical valves are typically constructed from nonbiological materials such as plastics, metals and other artificial materials which, while durable, are expensive and prone to blood clotting which increases the risk of an embolism. Anticoagulants taken to help against blood clotting can further complicate the patient's health due to increased risks for hemorrhages.

Transplanted valves are natural valves taken from cadavers. These valves are typically removed and frozen in liquid nitrogen, and are stored for later use. They are typically fixed in glutaraldehyde to eliminate antigenicity and are sutured in place, typically with a stent.

Artificial tissue valves are valves constructed from animal tissue, such as bovine or porcine tissue. Efforts have also been made at using tissue from the patient for which the valve will be constructed.

Most tissue valves are constructed by sewing the leaflets of pig aortic valves to a stent to hold the leaflets in proper position, or by constructing valve leaflets from the pericardial sac of cows or pigs and sewing them to a stent. The porcine or bovine tissue is chemically treated to alleviate any antigenicity. The pericardium is a membrane that surrounds the heart and isolates it from the rest of the chest wall structures. The pericardium is a thin and very slippery, which makes it difficult for suturing in a millimetricly precise way. The method of making the replacement heart valve of the present invention solves this problem through a process to dry the pericardium in such a way that makes it possible to handle and fold more easily.

For example, one prior replacement heart valve requires each sculpted leaflet to be trimmed in a way that forms an extended flap, which becomes a relatively narrow strand of tissue near its tip. The tip of each pericardial tissue strand is sutured directly to a papillary muscle, causing the strand to mimic a chordae tendineae. Each strand extends from the center of a leaflet in the valve, and each strand is sutured directly to either an anterior and posterior papillary muscle. This requires each leaflet to be positioned directly over a papillary muscle. This effectively rotates the leaflets of the valve about 90 degrees as compared to the leaflets of a native valve. The line of commissure between the leaflets, when they are pressed together during systole, will bisect (at a perpendicular angle) an imaginary line that crosses the peaks of the two papillary muscles, instead of lying roughly along that line as occurs in a native valve.

A different approach to creating artificial tissue valves is described in U.S. Patent Nos. 5,163,955 to Calvin, et al. and 5,571,174 and 5,653,749 to Love. Using a cutting die, the pericardial tissue is cut into a carefully defined geometric shape, treated with glutaraldehyde, then clamped in a sandwich-fashion between two stent components. This creates a tri-leaflet valve that resembles an aortic or pulmonary valve, having semilunar-type cusps rather than atrioventricular-type leaflets.

U.S. Patent No. 3,671,979 to Moulopoulos describes an endovascularly inserted conical shaped umbrella-like valve positioned and held in place by an elongated mounting catheter at a supra-annular site to the aortic valve in a nearby arterial vessel. The conical end points toward the malfunctioning aortic valve and the umbrella's distal ends open up against the aorta wall with reverse blood flow, thereby preventing regurgitation.

U.S. Patent No. 4,056,854 to Boretos describes an endovascularly inserted, catheter mounted, supra-annular valve in which the circular frame abuts the wall of the artery and attached flaps of flexible membrane extend distally in the vasculature. The flaps lie against the artery wall during forward flow, and close inward towards the central catheter to prevent regurgitation during reverse blood flow. The Boretos valve was designed to be positioned against the artery wall during forward flow, as compared to the mid-center position of the Moulopoulos valve, to reduce the stagnation of blood flow and consequent thrombus and embolic formation expected from a valve at mid-center position.

The main advantage of tissue valves is that they do not cause blood clots to form as readily as do the mechanical valves, and therefore, they do not absolutely require systemic anticoagulation. The major disadvantage of tissue valves is that they lack the long-term durability of mechanical valves. Tissue valves have a significant failure rate, usually within ten years following implantation. One cause of these failures is believed to be the chemical treatment of the animal tissue that prevents it from being antigenic to the patient. In addition,

the presence of extensive suturing prevents the artificial tissue valve from being anatomically accurate in comparison to a normal heart valve, even in the aortic valve position.

A shortcoming of prior artificial tissue valves has been the inability to effectively simulate the exact anatomy of a native heart valve. Although transplanted human or porcine aortic valves have the gross appearance of native aortic valves, the fixation process (freezing with liquid nitrogen, and chemical treatment, respectively) alters the histologic characteristics of the valve tissue. Porcine and bovine pericardial valves not only require chemical preparation (usually involving fixation with glutaraldehyde), but the leaflets must be sutured to cloth-covered stents in order to hold the leaflets in position for proper opening and closing of the valve. Additionally, the leaflets of most such tissue valves are constructed by cutting or suturing the tissue material, resulting in leaflets that do not duplicate the form and function of a real valve.

SUMMARY OF THE INVENTION

The present invention is a replacement heart valve device and method of making same. The replacement heart valve device, in a preferred embodiment, comprises a stent made of stainless steel or self-expanding nitinol and a completely newly designed artificial biological tissue valve disposed within the inner space of the stent. The cusp or leaflet portion of the valve means is formed by folding of the pericardium material used to create the valve. **Other forms of tissue and suitable synthetic materials can also be used for the valve, formed in a sheet of starting material. The folded design provides a number of advantages over prior designs, including improved resistance to tearing at suture lines.** The cusps/leaflets open in response to blood flow in one direction and close in response to blood flow in the opposite direction. Preferably the tubular portion of the valve means contains the same number of cusps as the native valve being replaced, in substantially the same size and configuration. The outer surface of the valve means is attached to the stent member.

The replacement heart valve device is preferably implanted using a delivery system having a central part which consists of a flexible hollow tube catheter that allows a metallic guide wire to be advanced inside it. The stented valve is collapsed over the central tube and it is covered by a movable sheath. The sheath keeps the stented valve in the collapsed position. Once the cover sheath is moved backwards, the stented valve can be deployed. The endovascular stented-valve, in a preferred embodiment, is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow. **The stent can either be self-expanding or the stent can be expandable through use of a balloon catheter.**

The present invention also comprises a method of making a replacement heart valve device. In order to make the valve, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a solution of gluteraldehyde, preferably at a concentration of about 0.07% during 36 hours, then the pericardium is transferred to a solution of ethanol, preferably at a concentration of about 60% before making the valve. The material is dried in order to make it easier to handle and fold. The valve is formed by taking a rectangular fragment of bovine pericardium and folding it in such a way that forms a three-leaflet valve. The valve can also be made **in the same manner** from fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts or synthetic non-biological, non-thrombogenic material. The folding of the pericardium material to create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of the valve leaflets. The valve is rehydrated after being formed. The method of the present invention also greatly reduces the risk of tearing of the cusps or leaflets, since they are integral to the valve rather than being attached by suturing.

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as

used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The replacement heart valve device of the present invention can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation medication and treatment. The present invention can be practiced in applications with respect to each of the heart's valves.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 depicts a side perspective view of the replacement heart valve device of the present invention in one embodiment ~~without~~with the ~~stent~~valve in the closed position.

Fig. 2 depicts the folds which form the leaflets or cusps of the replacement heart valve of the present invention in one embodiment.

~~Fig.~~Figs. 3 ~~depicts~~A and 3B depict the procedure for folding the pericardium tissue starting material to create the replacement heart valve of the present invention.

Fig. 4 depicts a side perspective view of the replacement heart valve device of the present invention in one embodiment represented as if implanted within an artery.

Fig. 45 depicts a side ~~perspective~~ view of one embodiment of the replacement heart valve device of the present invention ~~in one embodiment~~ mounted within a self-expanding stent, with the stent in the expanded position.

Fig. ~~5~~6 depicts a ~~cross-sectional~~side perspective view of one embodiment of the replacement heart valve device of the present invention mounted within a self-expanding stent, ~~with the stent~~ in the ~~expanded~~collapsed position.

~~Fig. 6 depicts a side perspective view of one embodiment of the replacement heart valve of the present invention mounted within a self-expanding stent in the collapsed position.~~

~~Fig.~~Fig. 7 ~~depicts~~depicts the suture points of one embodiment of the replacement heart valve device of the present invention.

Fig. 8 depicts the implantation/delivery system used with the present invention in a preferred embodiment.

DESCRIPTION OF A PREFERRED EMBODIMENT

The present invention comprises a percutaneously implantable replacement heart valve and a method for making same. The artificial heart valve device of the present invention is capable of exhibiting a variable diameter between a compressed or collapsed position and an expanded position. A preferred embodiment of the replacement heart valve device according to the present invention is set forth in ~~FIGS~~FIG. ~~1 and 2.5.~~ The replacement heart valve device comprises a stent member ~~—~~100 and a flexible valve means ~~—~~200. The stent member 100 is preferably self-expanding although balloon-expandable stents can be used as well, and has a first cylindrical shape in its compressed or collapsed configuration and a second, larger cylindrical shape in its expanded configuration. ~~The~~Referring to FIG. 1, the valve means 200 comprises a generally tubular ~~center~~ portion 210 and, preferably, a peripheral upstanding cusp or leaflet portion~~.~~ 220. The valve means 200 is disposed within the cylindrical stent member 100 with the tubular portion 210 transverse of and at some acute angle relative to the stent walls. The diameter of the tubular portion 210 is substantially the same as the inside diameter of the stent member in its initial expanded configuration. The peripheral upstanding cusp or leaflet portion 220 is disposed substantially parallel to the walls of the stent member similar to a cuff on a shirt. The ~~center~~cusp or leaflet portion ~~—~~220 of the valve means ~~—~~200

is generally tubular in shape and comprises three leaflets —221, 222 and 223 as shown, although it is understood that there could be from two to four leaflets. The tubular portion of the valve means 200 is attached to the stent member —100 by a plurality of sutures —300, as depicted in FIG. 7.

The leaflet portion 220 of the valve means —200 extends across or transverse of the cylindrical stent, 100. The leaflets —221, 222 and 223 are the actual valve and allow for one-way flow of blood. The leaflet portion 220 as connected to the rest of the valve resembles the cuff of a shirt. The configuration of the stent member —100 and the flexible, resilient material of construction allows the valve to collapse into a relatively small cylinder —as seen in FIG. 6. The replacement heart valve will not stay in its collapsed configuration without being restrained. Once the restraint is removed, the self-expanding stent member —100 will cause the artificial heart valve to take its expanded configuration, as seen in FIG. —5.

Stent Member

The stent member —100 preferably comprises a self-expanding nickel-titanium alloy stent, also called "nitinol," in a sine wave-like configuration as shown in FIG. ~~1.~~5. An enlarged view of a preferred embodiment of the stent member for use in the replacement heart valve of the invention is depicted in FIG. 5. The stent member —100 includes a length of wire —110 formed in a closed zigzag configuration. The wire can be a single piece, stamped or extruded, or it could be formed by welding the free ends together ~~as at~~—. The straight sections —of the stent member 100 are joined by bends—. The stent is readily compressible to a small cylindrical shape as depicted in FIGS. 6 and 8, and resiliently self-expandable to the shape shown in FIG. 5.

The stent ~~members~~member 100 of the artificial heart ~~valves~~valve device of the present invention may be made from various metal alloys, titanium, titanium alloy, nitinol,

stainless steel, or other resilient, flexible non-toxic, non-thrombogenic, physiologically acceptable and biocompatible materials. The configuration may be the zigzag configuration shown or a sine wave configuration, mesh configuration or a similar configuration which will allow the stent to be readily collapsible and self-expandable. When a zigzag or sine wave configured stent member is used, the diameter of the wire from which the stent is made ~~should~~is ~~be~~preferably from about [0.010 to 0.035] inches and still, preferably from about [0.012 to 0.025] inches. The diameter of the stent member will be from about [1.5 to 3.5 cm], preferably from about [1.75 to 3.00 cm], and the length of the stent member will be from about [1.0 to 10 cm], preferably from about [1.1 to 5 cm.]

The stent used in a preferred embodiment of the present invention is fabricated from a "shaped memory" alloy, nitinol, which is composed of nickel and titanium. Nitinol wire is first fashioned into the desired shape for the device and then the device is heat annealed. A meshwork of nitinol wire of approximately 0.008 inch gauge is formed into a tubular structure with a minimum central diameter of 20 min to make the stent. Away from its central portion, the tubular structure flares markedly at both ends in a trumpet-like configuration. The maximum diameter of the flared ends of the stent is approximately 30 mm. The purpose of the stent is to maintain a semi-rigid patent channel through the diseased cardiac valve following its implantation.

When the components of the replacement heart valve device are exposed to cold temperatures, they become very flexible and supple, allowing them to be compressed down and pass easily through the delivery sheath. A cold temperature is maintained within the sheath during delivery to the deployment site by constantly infusing the sheath with an iced saline solution. Once the valve components are exposed to body temperature at the end of the sheath, they instantaneously reassume their predetermined shapes, thus allowing them to function as designed.

Preferably the stent member 100 carries a plurality of barbs extending outwardly from the outside surface of the stent member for fixing the heart valve device in a desired position. More preferably the barbs are disposed in two spaced-apart, circular configurations with the barbs in one circle extending in an upstream direction and the barbs in the other circle extending in a downstream direction. It is especially preferable that the barbs on the inflow side of the valve point in the direction of flow and the barbs on the outflow side point in the direction opposite to flow. It is preferred that the stent be formed of titanium alloy wire or other flexible, relatively rigid, physiologically acceptable material arranged in a closed zigzag configuration so that the stent member will readily collapse and expand as pressure is applied and released, respectively.

Valve Means

The valve means 200 is flexible, compressible, host-compatible, and non-thrombogenic. The valve means 200 can be made from various materials, for example, fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts. Synthetic biocompatible materials such as polytetrafluoroethylene, polyester and the like may be used. The preferred material for the valve means 200 is bovine pericardium tissue. The valve means 200 is disposed within the cylindrical stent member 100 with the tubular portion 210 transverse of and at some acute angle relative to the stent walls. The diameter of the tubular portion 210 is substantially the same as the inside diameter of the stent member 100 in its initial expanded configuration. The peripheral upstanding cusp or leaflet portion 220 is disposed substantially parallel to the walls of the stent member 100 similar to a cuff on a shirt.

The cusp or leaflet portion 220 of the valve means 200 is formed by folding of the pericardium material used to create the valve. FIGS. 3A and 3B depict the way the sheet of heart valve starting material is folded. The cusps/leaflets 221, 222 and 223 open in

response to blood flow in one direction and close in response to blood flow in the opposite direction. Preferably the ~~tubular~~cusp or leaflet portion 220 of the valve means 200 contains the same number of cusps as the native valve being replaced, in substantially the same size and configuration.

Method of Making Replacement Heart Valve Device

The present invention also comprises a method of making a replacement heart valve device. In order to make the valve, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a solution of gluteraldehyde, preferably at a concentration of about 0.07% during 36 hours, then the pericardium is transferred to a solution of ethanol, preferably at a concentration of about 60% before making the valve. The valve is formed by taking a rectangular fragment of bovine pericardium and folding it in such a way that forms a three-leaflet or desired number of leaflet valve. ~~FIG. 2 depicts the folds which form the cusps or leaflets, and FIG.~~ as shown in FIGS. 3A and 3 ~~depicts the folding procedure~~B. The folding of the pericardium material to create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of the valve leaflets. It also greatly reduces the risk of tearing of the cusps or leaflets, since they are integral to the valve rather than being attached by suturing.

In order to make the pericardium material less slippery and easier to fold, the pericardium is dried, preferably with artificial light using a 60-watt lamp with the pericardium material placed in a flat aluminum surface to dry it homogeneously. A photo drying machine can also be used. The final result is a homogeneous tissue that looks like plastic paper and makes it easy to manipulate to fold and suture the valve. Once the valve is formed it is re-hydrated by placing it in a solution of water and 70% alcohol. In approximately 3 days the valve is fully rehydrated.

Attachment of the Valve Means to the Stent Member

The valve means 200 is then attached to the inner channel of the stent member 100 by suturing the outer surface of the valve means' pericardium material to the stent member. ~~Fig~~FIG. 7 depicts preferred suture points of one embodiment of the present invention: 3-point fixation or 6-point fixation at each border of the stent. Other fixation schemes can be utilized, such as, by way of non-limiting example, fixation on both borders 18 points at each end following a single plane and 36 fixation points following to adjacent vertical planes. The use of only one plane of fixation points helps prevent systolic collapse of the proximal edge of the valve means. A fold on the border of the pericardium material prevents tearing. The attachment position of the valve is preferably closer to the proximal and wider part of the stent.

The sequence of steps can vary. The pericardium material can be fixed in glutaraldehyde before attachment to the stent or the valve can be formed and then fixed with gluteraldehyde after mounting it in the stent. One observation noted is that the material becomes whiter and apparently increases its elasticity. 1mm vascular clips keep the cusps coapted while fixing them in gluteraldehyde. The use of metallic clips to keep both cusps adjacent to each other after 24 hours of fixation in gluteraldehyde helps to educate the material and make the primary position of the valve cusps adjacent to each other. After the clips are removed, there are no lesions to the valve.

Different suture materials can be used, including, in a preferred embodiment, prolene 6-0 and Mersilene 6-0 which is a braided suture.

Implantation of Replacement Heart Valve Device

The replacement heart valve device of the present invention is preferably used in surgical procedures involving the percutaneous and transluminal removal of the diseased or defective heart valve and the percutaneous and transluminal implantation of the new heart

valve described above. The defective heart valve is removed by a suitable modality, such as, for example, laser, ultrasound, mechanical, or other suitable forms of delivery of energy, or phacoemulsion, including, but not limited to, laser lithotripsy, mechanical lithotripsy, electrohydraulic lithotripsy, and laser or mechanical ablation. To remove the native heart valve that is being replaced, a guidewire is inserted percutaneously and transluminally using standard vascular or angiography techniques. The distal end of the guidewire is manipulated to extend through and across the defective heart valve. Then a catheter is advanced distally through the femoral artery to a point proximal to the defective heart valve, between the origin of the coronary artery and the origin of the right subclavian artery. The position of the distal end of catheter can be monitored by observation of radiopaque markers. Collector member is preferably inflated and occludes the aorta at a point between the origin of the coronary artery and the right subclavian artery. Next, a balloon and cutting tool are advanced through the catheter so that the cutting tool and uninflated balloon are distal to the defective heart valve. Optionally an additional step, such as balloon dilatation or atherectomy, may be required to provide a passageway through the heart valve. A catheter is also placed into the coronary sinus via a transjugular puncture. This catheter is used for infusion of blood or cardioplegia solution during the portion of the procedure when the aorta is occluded. The absence of valves in the cardiac venous system allows retrograde flow so that there will be an effluence of fluid from the coronary arteries. This flow of fluid is desired to prevent embolization of material into the coronary arteries during the procedure. Once the cutting tool is in place, the balloon is inflated and flexible shaft is rotated. Once the cutting tool has reached the appropriate rotation speed, the cutting tool is pulled proximally to remove the defective heart valve. The balloon and the cutting tool are spaced apart so that the inflated balloon will be stopped by the perimeter, unremoved portion of the defective heart valve, which will signal the physician that the valve has been removed, as well as protect the heart and aorta from damage from the valve removal

device. Once it is determined that the defective heart valve has been removed, the cutting tool is slowed or stopped altogether and the balloon is deflated. The cutting tool and the deflated balloon are pulled proximally through catheter. Then, a catheter containing an artificial heart valve is inserted and the artificial heart valve is placed as described above.

The delivery and implantation system of the replacement artificial heart valve of the present invention percutaneously and transluminally includes a flexible catheter 400 which may be inserted into a vessel of the patient and moved within that vessel as depicted in FIG. 8. The distal end 410 of the catheter, 400, which is hollow and carries the replacement heart valve device of the present invention in its collapsed configuration, is guided to a site where it is desired to implant the replacement heart valve. The catheter has a pusher member 420 disposed within the catheter lumen 430 and extending from the proximal end 440 of the catheter to the hollow section at the distal end 410 of the catheter. Once the distal end 410 of the catheter is positioned as desired, the pusher mechanism 420 is activated and the distal portion of the replacement heart valve device is pushed out of the catheter and the stent member 100 partially expands. In this position the stent member 100 is restrained so that it doesn't pop out and is held for controlled release, with the potential that the replacement heart valve device can be recovered if there is a problem with the positioning. The catheter 400 is ~~them~~then retracted slightly and the replacement heart valve device is completely pushed out of the catheter 400 and released from the catheter to allow the stent member 100 to fully expand. If the stent member 100 preferably includes two circles of barbs on its outer surface as previously described, the first push and retraction will set one circle of barbs in adjacent tissue and the second push and release of the replacement heart valve device will set the other circle of barbs in adjacent tissue and securely fix the replacement heart valve device in place when the ~~valve~~device is released from the catheter.

Alternatively, or in combination with the above, the replacement heart valve **device** could be positioned over a metallic guidewire that is advanced through the catheter. The replacement heart valve device of the present invention is preferably implanted percutaneously through an aortic passageway to, or near to, the location from which the natural heart valve has been removed. Referring to ~~Fig~~**FIG**. 8, the implantation system comprises a flexible hollow tube catheter **410** with a metallic guide wire **450** disposed within it. The stented valve **device** is collapsed over the tube and is covered by a moveable sheath **460**. The moveable sheath **460** maintains the stented valve **device** in the collapsed position. **The implantation method** comprises the following steps: inserting the replacement heart valve device in the lumen of a central blood vessel via entry through the brachial or femoral artery using a needle or exposing the artery surgically; placing a guide wire **450** through the entry vessel and advancing it to the desired position; advancing dilators over the wire to increase the lumen of the entry site, thereby preparing the artery to receive the heart-valve; and advancing the heart-valve **device** to the desired place. The stented-valve **device** is released by pulling the cover sheath **460** of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advanced over the wire and an aortogram is performed to assess the competency of the valve.

Before creation of the valve means and implantation, the patient is studied to determine the architecture of the patient's heart. Useful techniques include fluoroscopy, transesophageal echocardiography, MRI, and angiography. The results of this study will enable the physician to determine the appropriate size for the replacement heart valve.

In one procedure for implantation of the replacement heart valve device of the present invention, the femoral artery of the patient is canulated using a Cook needle and a standard J wire is advanced into the artery either percutaneously or after surgical exposure of the artery. An 8 F introducer is advanced into the femoral artery over the wire. The J wire is then

withdrawn and anticoagulation is started using heparin 60 U/Kg intravenously. Once vascular access is obtained an aortogram is performed for anatomical evaluation. A special wire (Lunderquist or Amplatz superstiff) is advanced into the aortic arch and dilators progressively larger are advanced over the wire, starting with 12 F all the way to 18 F. After this the valve introducer device containing the prosthetic valve device is then inserted and used to transport the replacement valve over a guidewire to the desired position. The stented-valve is released by pulling the cover sheath of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advanced over the wire and repeat aortogram is performed to assess the competency of the valve.

When the device is used to treat severe leakage of the aortic valve, the native valve is left in place and the prosthetic stented valve is deployed below the subclavian artery. When the device is used to treat aortic stenosis, first the stenotic valve needs to be opened using either aortic valvuloplasty or cutting and if this procedure induces aortic insufficiency the stented valve is placed to prevent the regurgitation.

Intravascular ultrasound or an angioscope passed intravascularly via either the venous system through the intra-atrial septum across the mitral valve and into the left ventricle or retrograde via the femoral artery would provide the added benefit of allowing constant high definition imaging of the entire procedure and high flow irrigation.

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The prosthetic valve device can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and

patients unable to tolerate open heart procedures or life-long anticoagulation. In addition, with the development of longer-life, flexible, non-thrombogenic synthetic valve alternatives to bioprosthesis, the prosthetic valve device will be indicated in all patients where the relative advantages of the life-span, the non-thrombogenic quality, and the ease of insertion of prosthetic valve devices outweigh the disadvantages of mechanical valves. Anticoagulation may be beneficial in certain clinical situations for either short or long term use.

This method of percutaneous endovascular heart-valve replacement, in contrast to open heart surgical procedures, requires only local anesthesia, partial or no cardiac bypass, one to two days hospitalization, and should result in a reduced mortality rate as compared to open heart procedures.

While the present invention has been shown and described herein in what is considered to be a preferred embodiment thereof, illustrating the results and advantages over the prior art obtained through the present invention, the invention is not limited to the specific embodiments described above. Thus, the forms of the invention shown and described herein are to be taken as illustrative and other embodiments may be selected without departing from the spirit and scope of the present invention.

CLAIMS

Having thus described the invention, what is claimed is:

1. A percutaneously implantable replacement heart valve device comprising a ~~self-expanding~~-stent member and an artificial valve means made of biocompatible tissue material and disposed within the inner cavity of said stent member affixed at one or more points to said stent member, said valve means having cusps or leaflets formed by folding of **a substantially rectangular sheet of** said biocompatible tissue material.

2. The percutaneously implantable replacement heart valve **device** of claim 1, wherein said stent member is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium, stainless steel **[add others]**.

3. The percutaneously implantable replacement heart valve **device** of claim 1, wherein said biocompatible tissue material of said valve means comprises bovine pericardium tissue.

4. The percutaneously implantable replacement heart valve **device** of claim 1, wherein said biocompatible tissue material of said valve means comprises porcine pericardium tissue.

5. The percutaneously implantable replacement heart valve **device** of claim 1, wherein said biocompatible tissue material of said valve means comprises autologous tissue obtained from the patient into whom said replacement heart valve **device** will be implanted.

6. The percutaneously implantable heart valve device of claim 1, wherein said stent member is self-expanding when implanted.

7. The percutaneously implantable heart valve device of claim 1, wherein said stent member is balloon catheter expandable when implanted.

~~6.~~8. A method of making a percutaneously implantable replacement heart valve device comprising the following steps:

obtaining a substantially rectangular ~~segment~~sheet of biocompatible tissue material;

soaking said biocompatible tissue material in a gluteraldehyde solution;

transferring said biocompatible tissue material from said gluteraldehyde solution to an ethanol solution;

drying said biocompatible tissue material;

folding said dried biocompatible tissue material to create cusps or leaflets and a cuffed tubular valve structure;

affixing said folded biocompatible tissue material to the inner cavity of a stent.

9. The method of making a percutaneously implantable replacement heart valve device claim 8, wherein said biocompatible tissue material comprises bovine pericardium tissue.

10. The method of making a percutaneously implantable replacement heart valve device claim 8, wherein said biocompatible tissue material comprises porcine pericardium tissue.

11. The method of making a percutaneously implantable replacement heart valve device claim 8, wherein said biocompatible tissue material comprises autologous tissue obtained from the patient into whom said replacement heart valve device will be implanted.

12. The method of making a percutaneously implantable replacement heart valve device of claim 8, wherein said stent is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium, stainless steel, [add others].

13. The method of making a percutaneously implantable replacement heart valve device of claim 8, wherein said stent is self-expanding when implanted.

14. The method of making a percutaneously implantable replacement heart valve device of claim 8, wherein said stent is balloon catheter expandable when implanted.

ABSTRACT

The present invention comprises a percutaneously implantable replacement heart valve device and a method of making same. The replacement heart valve device comprises a stent member made of stainless steel or self-expanding nitinol, a biological tissue artificial valve means disposed within the inner space of the stent member. An implantation and delivery system having a central part which consists of a flexible hollow tube catheter that allows a metallic wire guide to be advanced inside it. The endovascular stented-valve is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow. The present invention also comprises a novel method of making a replacement heart valve by taking a rectangular fragment of bovine pericardium treating, drying, folding and rehydrating it in such a way that forms a two- or three-leaflet/cusp valve with the leaflets/cusps formed by folding, thereby eliminating the extent of suturing required, providing improved durability and function.

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2 Other, description: **EXHIBITS**
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March 8, 2004

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 10/887,688	Filing Date 07/10/2004	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☒		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			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 $250 ($125 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			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	12/15/2008	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 37	Minus	** 36	= 1	X $26 =	26	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 9	Minus	***8	= 1	X $110 =	110	OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE	136	OR	TOTAL ADD'L FEE	

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	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.

Legal Instrument Examiner:
/DAWN BREWER/

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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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/887,688	07/10/2004	David Paniagua	51458.010100	4909

54353 7590 03/16/2009

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EXAMINER	
MILLER, CHERYL L	
ART UNIT	PAPER NUMBER
3738	

MAIL DATE	DELIVERY MODE
03/16/2009	PAPER

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.

Office Action Summary	Application No.	Applicant(s)	
	10/887,688	PANIAGUA ET AL.	
	Examiner	Art Unit	
	CHERYL MILLER	3738	

-- 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 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *15 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ 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

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *11-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 27-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ 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).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

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).

a)☐ All b)☐ Some * c)☐ None of:

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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 15, 2008 has been entered.

Response to Arguments

Applicant's arguments with respect to claims 1-10 and 27-36 have been considered but are moot in view of the new ground(s) of rejection.

The Bailey et al. (US 6,652,578 B2) rejection has been maintained for some of the claims and the examiner has responded to applicants arguments. The applicant has argued that Bailey does not disclose a *sheet having one or more folds* defining cusps or leaflets. The examiner disagrees. Bailey discloses graft (sheet) *everted* (folded) into leaflets (28). See figure 10 which clearly shows leaflets (28) as a continuum of sheet (graft 11b) that is folded at 27, (see col.9, lines 19-27 which discussed everting the graft material). Bailey's additional cuff fold is when 11a is a continuum of 11b (col.9, lines 27-32) and sheet (graft 11a) is folded inward to form sheet (graft 11b).

The applicant has also argued that Bailey does not disclose the valve body entirely within the inner space of the stent. The examiner disagrees. When the valve body is considered 11b+26, it is entirely within the stent. When the valve body is considered 11a+11b+26, at least

11b+26 is within the valve body (as the *entirety* of the valve is not required by the claims to reside within the inner space).

The applicant has also argued that Bailey does not anticipate the claims as Bailey's device requires valve struts on the leaflets. The examiner disagrees as the applicant's claims do not preclude the use of additional elements such as struts. Although the struts help regulate the flow by helping the leaflets open and close by their bias, the leaflets themselves also help regulate the flow (as flow would not be regulated without the leaflets, if the struts were used alone).

The applicant further argues that patentable weight must be given to the process in a product by process claim. The examiner disagrees. Patentable weight is given only to the end product structure.

It is noted that although Bailey 578' has not been applied herein, the parent patent (Bailey et al. US 6,458,153 B1) has as it is believed to be applicable as a 102(b), see Priority section below. The same response to arguments for the 578' patent corresponds to the 153' patent.

Declaration

The declaration filed on December 15, 2008 under 37 CFR 1.131 has been considered but is ineffective to overcome the Bailey (US 6,652,578 B2) reference.

The evidence submitted is insufficient to establish a conception of the invention prior to the effective date of the Bailey reference. While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a complete disclosure

to another. Conception is more than a vague idea of how to solve a problem. The requisite means themselves and their interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897). Portions of the declaration that are declared to have occurred prior to December 31, 1999 do not provide sufficient support for a valve being *unslit or uncut* and also *an inner and an outer fold*.

Priority

Claims 1-10 and 27-37 have been given the priority date of July 10, 2004.

Regarding claims 1-10, 27-29, and 33-37, the language "unslit", "without slits", and "uncut" are not present in parent application 10/037,266. Although the parent application does not disclose cutting or slitting the valve body, it does not disclose the valve body to be unslit or uncut either. From the figures of the valve in the parent application (fig.1, 2, and 3b for example that best show the leaflets), it is unclear whether or not the leaflets have slits or cuts, as the leaflets appear to have an arcuate shape. Also, the negative limitation of "uncut", "unslit" and "without slits" precludes the use of cutting or slitting, which was not necessarily precluded in the parent application. As such, the limitation "unslit" and "without slits" are given the priority date of July 10, 2004.

The language of claims 5, 6, and 8 is not contained in the parent application (10/037,266) and is given the priority date of July 10, 2004.

Claims 27-32, and 34-35 require an upper border fold and lower border fold, which is not present in the parent application (10/037,266) and is given the priority date of July 10, 2004.

Claims 31 and 35 require two separate sheets attached to one another, not present in parent application (10/037,266) and receive the priority date of July 10, 2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 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.

Claim 35 is rejected under 35 U.S.C. 112, 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(s), at the time the application was filed, had possession of the claimed invention. The specification and drawings do not seem to provide support for two separate sheets of material, each having a fold, wherein the "upper border of said first sheet joined to said lower border of said second sheet". Although an embodiment of having two separate sheets is disclosed (not shown), the location of the attachment (where joined) is not disclosed. Thus applicant does not have support for the "upper border of said first sheet joined to said lower border of said second sheet".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 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 1, 2, 7-10, 27-28, 30-34, and 36-37 are rejected under **35 U.S.C. 102(b)** as being anticipated by Bailey et al. (US 6,458,153 B1; assuming all claims receive a priority date of July 10, 2004). Bailey discloses an implantable heart valve (figs.1-5 for example) comprising an expandable stent (12) and an inner flexible compressible valve (11b+26) made of biocompatible material (col.8, lines 37-40) disposed within the stent (12) and affixed to the stent (see figs) the valve having leaflets without slits (see fig.2; valve body disclosed as a tubular graft 11b extension, col.9, lines 11-20). Bailey discloses the stent (12) to be made of the materials claimed (nitinol; col.8, lines 4-8). Bailey discloses the valve to be formed of biological or synthetic materials (col.8, lines 37-40). Bailey's valve is capable of self-expansion or balloon expansion (col.8, lines 4-8). Bailey discloses an outer cuff portion (considered 11a; which may be integral to 11b and 26; see col.9, lines 20-24). Bailey discloses the sheet of tissue (11b) having an upper border (top of device in fig.4) with an outward fold (material 11b is folded outwardly at 11a; col.9, lines 20-24) and a lower border (bottom of 11b in fig.4) having an inward fold (inward fold/eversion located at 27 forms cusps/leaflets 28). See col.9, lines 11-20. Folds of sheet may be considered 27, 29 or where 11a folds into 11b (see col.9, lines 20-24, this embodiment not shown). Bailey discloses first sheet coupled to second sheet (by seams 29; col.9, lines 48-52).

In the alternative to the above rejection, claims 1, 2, 7-10, 27-28, 30-34, and 36-37 are rejected under **35 U.S.C. 102(e)** as being anticipated by Bailey et al. (US 6,458,153 B1;in the case that the claims receive the priority date of the parent application January 4, 2002). Bailey discloses an implantable heart valve (figs.1-5 for example) comprising an expandable stent (12) and an inner flexible compressible valve (11b+26) made of biocompatible material (col.8, lines

37-40) disposed within the stent (12) and affixed to the stent (see figs) the valve having leaflets without slits (see fig.2; valve body disclosed as a tubular graft 11b extension, col.9, lines 11-20). Bailey discloses the stent (12) to be made of the materials claimed (nitinol; col.8, lines 4-8). Bailey discloses the valve to be formed of biological or synthetic materials (col.8, lines 37-40). Bailey's valve is capable of self-expansion or balloon expansion (col.8, lines 4-8). Bailey discloses an outer cuff portion (considered 11a; which may be integral to 11b and 26; see col.9, lines 20-24). Bailey discloses the sheet of tissue (11b) having an upper border (top of device in fig.4) with an outward fold (material 11b is folded outwardly at 11a; col.9, lines 20-24) and a lower border (bottom of 11b in fig.4) having an inward fold (inward fold/eversion located at 27 forms cusps/leaflets 28). See col.9, lines 11-20. Folds of sheet may be considered 27, 29 or where 11a folds into 11b (see col.9, lines 20-24, this embodiment not shown). Bailey discloses first sheet coupled to second sheet (by seams 29; col.9, lines 48-52).

Claims 1, 2, 7, 9-10, 27, 30, 36, and 37 are rejected under **35 U.S.C. 102(b)** as being anticipated by Garrison et al. (US 6,425,916 B1, cited previously). See figures 32-38 and respective portions of the specification. Garrison discloses a valve device comprising an expandable stent member (111+26d+8d) having an inner space and a flexible compressible valve (6d) disposed in the inner space and affixed to the stent member (see fig.37, 38 for example), the valve (6d) comprising a sheet of biocompatible material (col.10, lines 55-57; col.5, lines 45-60) having at least one fold (folds shown at commissures of valve seen in fig.34, 38; and along the circumference of valve when inverted seen in fig.35) forming the leaflets and no slits (see figs). Garrison discloses the stent to be made of the materials claimed that are self-expandable or

balloon expandable materials (col.5, lines 4-7; col.10, lines 38-50, 59-61). Garrison discloses a first sheet (upper valve 6d having leaflets) folded (at commissures) and a second sheet (cuff attached to 26d and 111) folded (when inverted in figs.35-37), the sheet portions are attached/affixed (integral and connected).

In the alternative to the above rejection, claims 1, 2, 7, 9-10, 27, 30, 36, and 37 are rejected under **35 U.S.C. 102(e)** as being anticipated by Garrison et al. (US 6,425,916 B1, cited previously). See figures 32-38 and respective portions of the specification. Garrison discloses a valve device comprising an expandable stent member (111+26d+8d) having an inner space and a flexible compressible valve (6d) disposed in the inner space and affixed to the stent member (see fig.37, 38 for example), the valve (6d) comprising a sheet of biocompatible material (col.10, lines 55-57; col.5, lines 45-60) having at least one fold (folds shown at commissures of valve seen in fig.34, 38; and along the circumference of valve when inverted seen in fig.35) forming the leaflets and no slits (see figs). Garrison discloses the stent to be made of the materials claimed that are self-expandable or balloon expandable materials (col.5, lines 4-7; col.10, lines 38-50, 59-61). Garrison discloses a first sheet (upper valve 6d having leaflets) folded (at commissures) and a second sheet (cuff attached to 26d and 111) folded (when inverted in figs.35-37), the sheet portions are attached/affixed (integral and connected).

Claims 30 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Bessler et al. (US 5,855,601, cited previously). Bessler discloses a valve device (see figs.1-5) comprising a sheet of biocompatible material (col.4, lines 9-11) folded to form a tubular cuff portion (25; folded to form a cylinder, see figs also shows a folded top edge, see dotted lines in fig.4) and

folded further to form and upstanding cusp or leaflet portion (35) disposed in the inner space of cuff portion (25; see figs.1-5), the cups/leaflets opening and closing in response to blood flow (col.5, lines 37-38).

Claim Rejections - 35 USC § 103

The following is a quotation of 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 3-6 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bailey et al. (US 6,458,153 B1). Referring to claims 3-6, Bailey discloses an implantable valve, the valve being formed of either biological tissue or biocompatible synthetic polymer (col.8, lines 37-40). Bailey does not however, disclose a specific type of biological material (such as claimed, mammal, porcine, or juvenile pericardium or PTFE or polyester biopolymers). It would have been obvious to one having ordinary skill in the art at the time the invention was made to have the specific biological materials claimed, since it has been held to be within the general skill of a worker in the art to select a known material (mammal, porcine, juvenile pericardium) on the basis of its suitability for the intended use (valve replacement) as a matter of obvious design choice. *In re Leshin*, 125 USPQ 416.

Referring to claim 29, Bailey discloses attachment of the cuff first sheet (11a) to the valve second sheet (11b+26; col.9, lines 47-52 by longitudinal seams), however is silent to mention how the members are coupled (what types of seam). It would have been obvious to one having ordinary skill in the art at the time the invention was made to use sutures, double sutures

to attach the two membranes (cuff and valve) since suturing is a common means of attachment in the vascular art and would be applicable to Bailey's invention. See Fogarty et al, US 6,491,719 B1, cited previously; col.10, lines 5-8 as evidence of common means of attaching layers of material (31, 32) in the vascular art which include stitching, welding, adhering.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHERYL MILLER whose telephone number is (571)272-4755. The examiner can normally be reached on Monday-Friday 7:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Corrine McDermott can be reached at 571-272-4754. 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.

/Cheryl Miller/
Examiner, Art Unit 3738

/Corrine M McDermott/
Supervisory Patent Examiner, Art Unit 3738

Notice of References Cited	Application/Control No. 10/887,688	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-6,458,153 B1	10-2002	Bailey et al.	623/1.24
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	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.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10887688	PANIAGUA ET AL.
	Examiner	Art Unit
	CHERYL MILLER	3738

SEARCHED			
Class	Subclass	Date	Examiner
623	1.24, 1.26, 2.1-2.19	3/12/2009	cm

SEARCH NOTES		
Search Notes	Date	Examiner

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/887,688	07/10/2004	David Paniagua	51458.010100	4909

54353 7590 06/12/2009

MANUEL VALCACEL
c/o GREENBERG TRAURIG, P.A.
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MIAMI, FL 33131

EXAMINER	
MILLER, CHERYL L	
ART UNIT	PAPER NUMBER
3738	

MAIL DATE	DELIVERY MODE
06/12/2009	PAPER

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.

Interview Summary	Application No.	Applicant(s)	
	10/887,688	PANIAGUA ET AL.	
	Examiner	Art Unit	
	CHERYL MILLER	3738	

All participants (applicant, applicant's representative, PTO personnel):

(1) *CHERYL MILLER (Examiner)*. (3)_____.

(2) *Manuel Valcarcel (Reg No.41,360)*. (4)_____.

Date of Interview: *09 June 2009*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____.

Claim(s) discussed: _____.

Identification of prior art discussed: *Bailey (US 6,458,153), Garrison (US 6,425,916), and Bessler (US 5,855,601)*.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Attorney for applicant argued that support for unslit or uncut is provided in the parent application. When applicant responds, they intend to include references to the parent application which will be evaluated in more detail at that time. Applicant further noted that a prototype was submitted as exhibit b and c, which is not in the electronic file and the examiner will have to search for the location of the prototype. The applicant argued that Bailey shows an external graft. Language such as "including" following the preamble, and the sheet of biocompatible material or valve, "disposed entirely within the inner space of the stent" was discussed which potentially could overcome the Bailey rejections. Language such as "without suturing" the leaflets was discussed with regards to the Garrison reference. Applicant plans to file an official response which will be considered in more detail at that point in time. The applicant may also want to consider claiming the location of the folds, or the inner and outer cuff or entire sheet positioned interior of the stent* .

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

/Cheryl Miller/ Examiner, Art Unit 3738	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

———

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

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PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	10/887,688
Filing Date	07/10/2004
First Named Inventor	Paniagua
Art Unit	3738
Examiner Name	Miller, Cheryl
Attorney Docket Number	051458.010100

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		US- 3,671,979	06-27-1972	Moulopoulos	
		US- 4,056,854	11-08-1977	Boretos et al.	
		US- 4,218,782	08-26-1980	Rygg	
		US- 4,222,126	09-16-1980	Boretos et al.	
		US- 4,759,758	07-26-1988	Gabbay	
		US- 5,163,955	11-17-1992	Love et al.	
		US- 5,509,930	04-23-1996	Love	
		US- 5,571,174	11-05-1996	Love et al.	
		US- 5,653,749	08-05-1997	Love et al.	
		US- 6,126,686	10-03-2000	Badylak et al.	
		US- 6,494,909 B2	08-08-2002	Greenhalgh	
		US- 6,626,938 B1	09-30-2003	Butaric et al.	
		US- 6,773,456 B1	08-10-2004	Gordon et al.	
		US- 7,331,993 B2	10-27-2005	White	
		US-			
		US-			
		US-			
		US-			
		US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
		WO 03/092554 A1	11-13-2003	White/The Gen. Hosp. Corp		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. 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 2 hours 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, 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

PTO/SB/08b (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	10/887,688
Filing Date	07/10/2004
First Named Inventor	Paniagua
Art Unit	3738
Examiner Name	Miller, Cheryl
Attorney Docket Number	051458.010100

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		CRIBIER, ALAIN, ET AL., Percut.Transcatheter Implant. of an Aortic Valve Prosthesis for Calcific Aortic Stensosis: First Human Case Descr., Circulation 2002, 3006-08, AHA, US.	
		PANIAGUA, DAVID, ET AL., Percutaneous Heart Valve In the Chronic In Vitro Testing Model, Circulation, 2002, pp.e51-52, Vol. 106, American Heart Association, US.	
		PANIAGUA, DAVID ET AL., First Human Case of Retrograde Transcatheter Implantation of an Aortic Valve Prosthesis, Texas Heart Institute Journal, 2005, pp.91-96, Vol. 32, US.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
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60/377,721 3 May 2002 (03.05.2002) US

(71) Applicant *(for all designated States except US)*: **THE GENERAL HOSPITAL CORPORATION** [—/US]; 55 Fruit Street, Boston, MA 02114 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **WHITE, Jennifer, K.** [US/US]; 102 Naples Road, Brookline, MA 02446 (US).

(74) Agent: **BERNSTEIN, Jason, A.**; Powell, Goldstein, Frazer & Murphy LLP, 16th Floor, 191 Peachtree Street, Atlanta, GA 30303-1736 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INVOLUTED ENDOVASCULAR VALVE AND METHOD OF CONSTRUCTION

(57) Abstract: A prosthetic tri-leaflet valve formed by involuting a portion of a tubular structure inside itself. The valve can be made by a method comprising providing a tubular segment in which three equidistant longitudinal incisions are made in one end of the tube creating three flaps which are involuted, *i.e.*, folded, in toward the inside of the tube and the edges of the flaps secured to the inner wall of the tube to form leaflets. The tube can be formed of a single sheet of synthetic, organic or biological material and can be solid, woven, braided or the like. A braided configuration permits the valve to be annularly compressed and delivered to the site using a minimally invasive delivery mechanism, then expanded at the implantation site.

WO 03/092554 A1

INVOLUTED ENDOVASCULAR VALVE AND METHOD OF CONSTRUCTION

FIELD OF THE INVENTION

The present invention relates to a prosthetic valve with an involuted structure. The present invention also relates to methods and apparatus for constructing an involution valve.

BACKGROUND OF THE INVENTION

Since the implant of the first cardiac valvular prosthesis in the anatomic position in 1960, more than 50 different cardiac valves have been introduced over the last forty years. Unfortunately, after years of development of mechanical and tissue valves there remain significant problems associated with both types of valves.

Mechanical vs. Tissue valves

Mechanical valves are durable in patients but require long-term anti-coagulation therapy. Tissue valves offer freedom from anticoagulation therapy and the problems of bleeding, but tend to degenerate rapidly, particularly in younger patients. The most commonly implanted tissue valves are constructed from chemically-treated animal tissues (i.e., glutaraldehyde-fixed pericardial or porcine valves). The preservation, sterilization, and fixation processes currently used in tissue valve preparation are believed to contribute to the lack of longevity of tissue valves.

Ross procedure

One alternative approach for aortic valve replacement has been to transpose the patient's own pulmonary valve into the aortic position in the same individual, as described by Ross in the late 1960's. Although a technically demanding procedure, the Ross procedure frees the patient from anti-coagulation therapy and has substantial longevity compared to other types of tissue valves. A disadvantage of using the pulmonary valve to replace the aortic valve in the same patient is that the pulmonary valve must also be replaced. Most commonly, the replacement tissue for the excised pulmonary valve is a valve (aortic or pulmonic) derived from a cadaver ("homograft"). Problems arise from lack of donor availability and size mismatches between the donor homograft and the living recipient. Unfortunately, replacing the pulmonary valve with a homograft is associated with immunologically-mediated stenosis in some patients which limits their longevity.

Monocusp Procedure

Alternatively, a single flap of tissue from the pulmonary trunk has been used to create a pulmonary "mono-cusp" valve in pediatric patients undergoing the Ross procedure. Long-term function of the monocusp valve has yet to be documented. Historically, it is known that a single leaflet valve design has a less efficient closure than a tri-leaflet valve. The suboptimal function of a monocusp valve may adversely impact long-term results. It is a drawback that the mono-cusp procedure is restricted to replace a valve at the location where

the tissue flap is created. The monocusp procedure does not provide a source for replacement of valves other than the pulmonary valve.

Trileaflet Valve Derived from Pulmonary Artery Tissue

Another previously described method to replace the aortic valve entails surgical reconstruction of a tube of tissue from the pulmonary artery of the same individual. In this procedure, a tube of tissue was harvested from the pulmonary trunk and reconfigured into a trileaflet valve. In order to create a valve, the base of the pulmonary tissue tube was sutured to the aortic annulus and to the aortic wall at three points. This procedure was attempted in three pediatric patients and abandoned due to immediate and severe aortic insufficiency in two patients. The failure of this valve replacement procedure resulted, in part, from the extreme technical challenge for the surgeon. In this procedure, the surgeon must simultaneously construct and implant the valve while attempting to surgically compensate for any size discrepancies between the donor tissue and the recipient valve site.

As described previously, promising attempts to create a tissue valve by reconfiguring an individual's own living tissues have been problematic. It would be advantageous to have a method to more efficiently, effectively, and reliably construct a functional and durable tissue valve. It would be desirable for the valve to be a non-immunogenic structure capable of cellular regeneration and repair.

U.S. Patent No. 5,713,950, issued to Cox discloses a valve constructed from a tubular structure. This invention is a nesting of tubes dependent on multiple suture lines or points to join the tubes to create a valvular structure. It is a drawback that these sutures are positioned in areas of high stress during the function of the valve through the cardiac cycle. Although this valve is a simple design, it would be inefficient and difficult to use this method to reconfigure the patient's own tissues into a valvular structure.

U.S. Patent No. 6,494,909, issued to Greenhalgh, discloses a device and means for a braided valve and minimally invasive deployment. The invention does not describe the area of attachment of the leaflets to the walls of the tubular

structure to create a functional three-dimensional tri-leaflet valve. This invention does not describe a means for creating an autologous or living tissue valve. It is a further disadvantage that this invention describes that it is placed in a catheter for deployment. This is distinguished from other braided structures which are deployed by an internal mechanism with the potential for more maneuverable and narrower insertion profiles (such as that disclosed in Patent Cooperation Treaty application (designating the U.S.) No. PCT/US02/40349, filed December 16, 2002, entitled "DYNAMIC CANNULA," and commonly assigned to the assignee of the present invention, the disclosure of which application is incorporated herein by reference in its entirety).

SUMMARY OF THE INVENTION

In one exemplary embodiment, the present invention provides for constructing a prosthetic valve by a technique referred to interchangeably as the "involuted cylinder" or "involution" method. The involution valve may be constructed of synthetic, semi-synthetic, organic or biological material or mixtures or combinations thereof. The valve is efficient to construct, may be derived from the patient's own tissues, and is particularly suitable for replacement of aortic or pulmonic valves.

In one exemplary embodiment, the present invention provides a valve constructed of a tubular structure involuted inside itself. The three-dimensional shape of the "involution valve" may be provided by folding, braiding, weaving, knitting, or combinations of these operations on the material. The material may be biological, synthetic, semi-synthetic, organic, or a combination of these materials. The patient's own tissue (e.g., pericardium, pulmonary artery, or aortic tissue) can be reconfigured into a functional valve using this method. Some examples of material sources include, but are not limited to, tissue derived from the same individual (e.g., pericardium, aortic, or pulmonary artery tissue) or a different individual of the same species (e.g., cadaver tissue) or a different species (e.g., decellularized porcine small intestinal submucosa).

The valve may be a scaffold, matrix, or other structure that undergoes a maturation process of living autologous cell deposition thereon. For the purposes of the present disclosure, the term scaffold will be referred to in an exemplary, but nonexclusive, manner. An example of a potentially suitable scaffold substance is decellularized porcine small intestinal submucosa. The scaffold could provide signaling to cells to organize as an autologous valve, provide a support structure for cell organization, or function as a non-immunogenic valve regardless of cell population. The scaffold can be a permanent, semi-permanent, or temporary structure capable of resorption or remodeling. In this manner, the valve would, when implanted and the patient adapted, have a lack of exposed immunogenic material.

The present invention provides a method of forming a valve or valve scaffold, comprising, in one exemplary embodiment: (1) providing a tube of material, (2) involuting the tube inside itself, (3) selectively attaching portions of the inside tube to the outer tube of material, (4) implanting the valve in a patient.

Accordingly, it is a feature of the present invention to provide a valve that has minimal immunogenic structure.

It is another feature of the present invention to provide a valve that is capable of cellular regeneration and repair and that is functional and durable.

Other features and advantages of the present invention will become apparent upon reading the following detailed description of embodiments of the invention, when taken in conjunction with the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The various features and advantages of the invention will be apparent from the attached drawings, in which like reference characters designate the same or similar parts throughout the figures, and in which:

Fig. 1 shows a cutaway view showing an exemplary embodiment of an involution valve of the present invention implanted in the aortic valve position on the left (systemic) side of the heart;

Fig. 2 is a cutaway view showing the involution valve implanted as a pulmonic valve replacement on the right (pulmonic) side of the heart;

Fig. 3 shows material in a braided configuration;

Fig. 4 shows material in knitted configuration;

Fig. 5 shows material in a woven configuration;

Fig. 6 shows material in a triaxial weave;

Fig. 7 shows a perspective view of multi-directional layering of materials;

Fig. 8 shows material in a full Leno weave;

Fig. 9 shows a perspective view showing a cylinder formed from a sheet;

Fig. 10 shows a perspective view of a collapsible braided cylinder;

Fig. 11 shows a perspective view of a cylinder with three equidistant incisions to create flaps or "leaflets";

Fig. 12 shows a perspective view of involution of the flaps inside the cylinder to create leaflets;

Fig. 13 shows a perspective view of an exemplary embodiment of an involution valve showing attachment of the leaflets to the inner side of the outermost tube with "U" sutures;

Fig. 14 shows a perspective view of the involution valve depicting scalloping of the outermost wall to allow for subcoronary implantation and preservation of the Sinuses of Valsalva;

Fig. 15 shows a perspective view of an exemplary embodiment of an involution valve constructed by involuting the tube inside itself without incisions to create flaps;

Fig. 16 shows a perspective view of a braided cylinder involuted inside itself to form an inner tube with a reduced diameter that acts as a one-way valve that opens under pressure;

Fig. 17 shows a perspective view of an involution valve constructed with a cuff of material at either end;

Fig. 18 shows material in a looped or tufted configuration;

Fig. 19 shows a finite element analysis of the involution valve depicting an area of high stress at the attachment area of the inner and outer walls of the valve, with a gray scale such that high stress areas are shown in black and low stress are shown in white;

Fig. 20 shows a perspective view of the involution valve showing the attachment of the inner and outer tube by weaving them together in an interleaflet triangular pattern;

Fig. 21 shows a perspective view of the involution valve showing sinuses enlarged by providing excess material between the annulus and the sinotubular junction with the creation of interleaflet triangle by selectively weaving the inner tube to the outer tube between sinuses;

Fig. 22 shows a top view of the involution valve depicting excess leaflet material in the radial and circumferential directions.

Fig. 23 shows a perspective view of the involution valve depicting excess leaflet material in the longitudinal plane;

Fig. 24 shows a perspective view of the involution valve depicting the integration of a rigid or semi-rigid stent into the structure;

Fig. 25 shows a perspective view of the involution valve depicting the outer with cut away sections for coronary artery reimplantation intended for use with "inclusion" or "mini-root" valve implantation techniques; and,

Fig. 26 shows a perspective view of the involution valve as collapsible braid depicting the ability of the structure to assume a reversible narrow endovascular insertion profile.

DESCRIPTION OF THE INVENTION

The present invention generally provides a prosthetic valve formed by involuting a tubular structure inside itself. The present invention also provides methods of forming an involution valve.

Primary Structure: Synthetic, Organic, and Biological Materials

In one exemplary embodiment of the present invention an involution valve is formed of synthetic or processed organic material. The material can be any of a number of different biologically inert materials. The following materials are set forth by way of illustration only and are not intended to be exclusive.

Synthetic materials

Polyglycolic acids (PGA) can be used as non-woven mesh, having high porosity, good cell attachment, good growth and extracellular matrix formation, rapid bioabsorption, and biocompatibility. Examples of materials include, but are not limited to, polyhydroxyalkanotes (PHA or PHO); poly-4-hydroxybutyrates (P4HB) (PHA and P4HB have the properties of elasticity, mechanical strength, thermoplasticity, and have demonstrated increase in cell attachment during seeding with increased collagen development); PGA and P4HB hybrid in the form of thin PGA coated with P4HB to reduce stiffness but provide mechanical strength; absorbable and nonabsorbable suture materials, polylactic acid (PLLA); polycaprolactone; fibrin-gels (moldable); hydrogels (polyethylene glycol-based hydrophilic substances); dacrons; metals, or nitinols (particularly biodegradable nitinols); mixtures and/or combinations thereof and the like.

Organic materials

The valve may also be constructed of polymer-based substances; examples include, but are not limited to, polypropylene, polyester, silk, nylon, plastics,

rubbers, silicones, papers or other suitable cellulose based product, polytetrafluoroethylenes (PTFE's), polyurethanes, mixtures and/or combinations thereof and the like.

Biological materials

Pericardial tissue, arteries, veins, portions of the gastrointestinal tract, combinations of the forgoing and the like can be used. The material can be a chemically-treated tissue such as glutaraldehyde-fixed pericardium or other suitable tissue.

Tissue can be harvested, isolated (for example, a segment of tubular blood vessels such as the autologous pulmonary artery trunk, left or right pulmonary artery, and aorta), created (cell cultures) or tissue engineered (for example, cells populating a scaffold). The living material can continuously bathed in, for example, cell culture medium or Hank's solution so as to retain viability. Tissue sources include autologous (self) tissues, xenograft (e.g., decellularized animal tissues) or allografts (e.g., cadaver tissue). More specific examples of these include decellularized porcine small intestine submucosa ("SIS") and segments of a decellularized aorta, or vena cava tissue from cadaver donors. An example of a decellularization process is incubation of in trypsin/EDTA for 48 hrs to extract endothelial cells and myofibroblasts.

In one exemplary embodiment, the scaffold is decellularized porcine small intestinal submucosa which is reconfigured into a valvular structure, implanted into the individual, and allowed to mature by populating with autologous cells. Population of the scaffold with autologous cells can occur outside (e.g., in pulsatile cell culture "bioreactor") or inside the body (e.g., following implantation). Exposing the cell-populated scaffold to mechanical stresses has been shown to physically signal the cells to produce extracellular matrix material. The mechanical stresses may influence the mass, directionality, strength, and types of biomolecules (e.g., collagen) and cells integrating with the scaffold.

The materials described previously, as well as others, may be used to create a functional three-dimensional valve or scaffold using a method of the present

invention. The valve is then implanted into the body, and depending upon the material and the configuration, allowed to mature by healing, endothelialization, autologous cell seeding, and extracellular matrix deposition.

Secondary structure: Homogeneous, Non-homogenous, and Porosity, and Layering.

Homogeneous

The texture or surface structure of the valve material is significant and may be homogeneous or non-homogeneous. Human heart valves and the entire human endovascular system is lined with a smooth homogeneous layer of endothelial cells which serve a multitude of functions, including the prevention of thrombus formation. The material for the present invention may be living tissue such as blood vessels from the patient. In this case, the valve's surface is lined, in part, with a homogeneous layer of endothelial cells.

Other parts of the involution valve, such as an adventitial layer, which are exposed to the endovascular space, may pose a risk to form thrombus. In time following implantation, the non-endothelialized surfaces have the potential to be populated with a homogeneous layer of endothelial cells In most instances, it is preferable for the valve to be substantially completely lined with a smooth homogenous layer of endothelial cells on all surfaces that contact blood. Temporary systemic anticoagulation therapy in this patient during the endothelization period may reduce or eliminate the risk of thrombus formation. Alternatively, chemicals, drugs, growth factors and other agents that promote endothelization and retard thrombus formation may be bound to the valve material to provide local therapy.

In another case, the starting material for valve construction is pericardial tissue which has a smooth side (faces the heart's surface) and a rougher side of collagen and other constituents. Despite the homogenous nature of each side of these materials (e.g., human blood vessels or pericardium), the involution valve may be preferentially constructed such that the smooth side is the diastolic surface and the rough side faces the systolic side of the blood flow

during the cardiac cycle. It appears to be advantageous to have the valve involuted such that the most homogeneous, smooth, endothelialized surface is facing the diastolic side of the circulation.. This follows from the previous observations of others that tissue valve material undergoes degenerative changes and tends to form thrombus on the diastolic side versus the systolic side of the leaflets. The anatomical orientation in the circulation of the present invention as an aortic valve replacement is depicted in Fig. 1 and is described further in Example 1. A pulmonic valve substitution with the involution valve is shown in Fig. 2 and described in more detail in Example 2. The involution valve may also be suited in other anatomical positions such as for replacement of a mitral or tricuspid valve. The present invention may also serve as a treatment for aortic insufficiency with implantation of the involution valve in the descending aorta.

Non-homogeneous

The material of the involution valve may also be non-homogeneous. For example, the material can be provided as a laminate, mesh, knit, woven or nonwoven material, braids, strands, combinations thereof and the like. Meshes, braids (Fig. 3) knits (Fig. 4), and weaves (Fig. 5) can be formed from interlocking, interlacing, or interweaving connecting fibers of scaffold materials. (e.g., strands of arteries, veins, or other autologous tissues woven, knitted, or braided into a sheet or cylinder);

These materials and fabrication methods may be exploited for their physical characteristics. For example, rib knit may be useful given its property of elasticity in its width direction. Jersey knit is known to have good wrinkle recovery and excellent drape. Double knits are known to be strong since production of the material is carried out on a circular-knitting machine with two sets of perpendicular needles. The physical characteristics of these materials and fabrication techniques may be exploited in light of the anatomy of the native human valve to construct a valve replacement with desirable elasticity, wrinkles, and strength properties.

Consider that the histology of the human native semilunar valves is referred to as highly anisotropic (i.e. not the same in all directions). It follows that the biomechanics of the "cusps" or "leaflets" are not the same in each direction. The leaflets are known to have gross wrinkles or "corrugations" of collagen fibers which expand perpendicular to the cuspal free margin (i.e. radial direction) and imparts a high compliance on the leaflet in this direction. The less compliant "crimp" or "pleat" in the collagen in circumferential direction is a predominate load bearing element, restricting leaflet during filling and cusp distention Strength is provided by groups of collagen cords radiate from the commissures (attachment points of leaflets to wall). These structural features enable the cusps to be pliable when the cusps are unloaded and the heart is contracted (systole), but inextensible when a load is applied during cardiac filling (diasole).

It may be advantageous to impart the physical properties of the human native valve to the present invention. For instance, one could purposefully choose a rib knit or jersey knit configuration of the material along the radial or circumferential direction of the valve construct in order to impart elasticity or draping characteristics to the leaflets. Imparting compliance to the valve leaflet has the potential to dissipate the force imposed by the cardiac cycle on the valve. This may increase strength and durability to the valve following implantation.

In prior studies of others, tissue engineered valve scaffolds have selectively populated with extracellular matrix material when stresses, such as imposed by the cardiac cycle, were mimicked *in vitro*. As exemplified, the selective use of the materials and fabrication techniques may be used to control the compliance and strength of the valve of the present invention. Controlling the physical properties of the materials and fabrication methods in this manner has the potential to more accurately signal the extracellular matrix materials and the cells that produce them to populate according to conditions that more precisely model the native system.

Strands or fibers of material may be elastic or nonelastic. The fiber diameter can vary in the same or in different fibers composing the material. One study

using polyglycolic acid as a scaffold material in valve construction, advocated a fiber diameter of 12 – 15 μm. In certain cases, fiber diameter can be custom-extruded. The fiber may be rectangular, round, or twisted around itself in a clockwise or counterclockwise position. Each fiber could be a bundle of smaller diameter fibers.

Pores

Porosity of the scaffold material may be significant. The pores or spaces in the material may purposefully be sized to retard thrombus formation and promote endothelization and adhesion of circulating autologous cells. The scaffold materials themselves may be rough or smooth and the pores between them can form smooth shapes or shapes with sharp angles. Variables include pore shape, pore size, open or closed qualities, interpore connectivity, and pore wall morphology. Pores can be the spaces in a weave, braids, or knits. Pores can be introduced into the material by a variety of different techniques, including, but not limited to, cell opening agents and mechanical aperturing. The pores or spaces in the material may purposefully be sized to retard thrombus formation and promote endothelization and adhesion of circulating autologous cells.

In another instance, materials used to construct the valve could change their homogeneous properties and pore size. For example, if one constructed a weave of strands of decellularized porcine small intestinal submucosa material, the hydrophilic nature of the material is such that it may form smaller pores and a more homogeneous structure after hydration or implantation in the body.

In certain substances, complex pore geometry (e.g., honeycomb shaped pores) can be created by dispersing paraffin spheres in the dissolved scaffold material (e.g., PLLA and PGA). The paraffin is subsequently dissolved to create pores in the scaffold material. Another technique is to use salt-leaching/sugar crystals/glass crystals to yield a porous matrix. The size of the pores can homogeneous (PGA) or heterogeneous (PLA). The scaffold pore sizes can range from approximately 100–500 microns, more preferably in the 100 to 240 micron range. Other investigators using PLA and PGA scaffolding have noted

a decrease in compressive modulus for smaller pore sizes (100–200 microns) as compared to large pore sizes (250–350 or 420-500 microns).

The pores in the material or the orientation of spaces between the materials can be purposefully used to impart strength or elasticity to the valve. For example, a triaxial weave is a process of weaving three strands of material at 60 degree angles to one another (Fig. 6). The resulting material has limited or no stretch or distortion in any direction. If equal size and number of strands are used in all three directions, the final material approaches equal strength and stiffness in all directions.

Layering

The valve materials can be single or multi-layered. The layers can be orientated such that the directionality of the materials is parallel, perpendicular, or angled. For example, the material may be "biased", "radial", or a combination ("biased/belted") such as that used in automobile tire construction. In a bias construction the material is laid alternating at bias angles of 25 to 40 degrees to the surface layer direction. In a radial design a layer is 90 degrees to the surface material direction. Between these layers can be a series of alternating layers at low angles of 10 to 30 degrees to the surface direction. A combination of these may also be used. The directionality within each layer and orientation of the layers in respect to one another may be used to selectively impose strength and elasticity to the valve (Fig. 7).

It is known from prior anatomical studies that the human semilunar valve leaflet consists of three histologically distinct layers; the ventricularis, the spongiosa, and the fibrosa. The ventricularis faces the inflow surface and consists of mostly collagen "corrugations" with radially aligned elastic fibers. The spongiosa is composed of loosely arranged collagen and glycoaminoglycans. The fibrosa opposes the outflow surface is mainly circumferentially arranged, "crimped," densely packed collagen fibers, mostly parallel to the free edge of the leaflet. With this in mind, the present invention could be constructed of layering material purposefully arranged. For example, the top layer (the future inflow surface of valve leaflet) may be compliant in

the radial direction and the most bottom layer could have a directionality perpendicular to the top layer, imparting less compliance in the circumferential direction. A middle layer could be sandwiched in between which has an multi-directional, oblique, or loosely arranged material.

Investigators have expressed concern that the use of layering, and in particular, lamination of porcine small intestinal submucosa, may delaminate inappropriately following implantation. One way to overcome this would be to weave, knit, or braid the material to prevent delamination. A specific example is the use of a Leno weave in which the strands are arranged in pairs with one twisted around the other between other strands (Fig. 8). This weave imparts firmness and strength to the material and prevents slippage and displacement of the strands. Alternatively, in certain instances, layering could be avoided by weaving, knitting, or braiding from a single layered strand.

Tertiary structure: Tubes, Sheets, and Sleeves

The scaffold can be formed according to the following exemplary method. A quantity of material is provided as a tube or as a sheet. If it is provided as a sheet, two opposing sides are joined together to form a tube by any of a number of techniques known to those skilled in the art and appropriate to the material being used, such as, but not limited to, weaving, interlacing, braiding, knitting, punching, tufting, laminating, suturing, stapling, gluing, welding, fusing, combinations thereof and the like (Fig. 9). The sheet can be knitted, woven, or braided from strands of material. A tubular or cylindrical structure can be created by sleeving techniques using braiding, knitting, weaving or combination of these methods. The structure can be a proper cylinder (the term cylinder and tube being used interchangeably in the present disclosure) or a slightly conical segment. The thickness of the scaffold cylinder can range from about 0.3 mm to 1.0 mm, although it may be thinner or thicker.

One advantage of a tubular braid configuration is the possibility of creating a tubular valve that is collapsible (Fig. 10). Braided tubes can be constructed which reduce diameter significantly when a longitudinal force is exerted on the tube. In one instance the diameter of the tubular valve can be reduced in

diameter, introduced into the endovascular space in minimally invasive manner, and deployed into a larger diameter structure at the valve replacement site (see Implantation section herein).

Quaternary Structure: Involution, Attachment, Interleaflet Triangles, Sinuses, Leaflet Modifications, and Stents.

Involution

Creating leaflets by involution allows the material at the site of the infolding (i.e., the base of the valve) to retain its compliant nature. This may improve valve durability by facilitating the transfer of stresses and strains on the leaflets to the wall of the implant site (e.g., aortic root). Since the valve is created prior to insertion, it can be tested prior to use and the valve function is not wholly dependent on surgical implantation techniques.

In one geometry of the involution valve shown in Fig. 11, the height "h" of the cylinder 12 is approximately equal to the diameter "d" of the valve implantation site (annulus diameter). Approximately half of the cylinder wall height form the leaflets which span half the diameter of the annulus. The remaining half of the cylinder wall forms the height of the commissures. The height of the commissures is based on the anatomical relationship of annulus to sinotubular junction distance verses annulus diameter in same patient, i.e., height of commissures is approximately half the annulus diameter. The material has a thickness "t".

In one exemplary embodiment, three longitudinal incisions about 120 degrees apart are made in the cylinder to create three flaps of tissue. Preferably, though not mandatorily, the length "L" of the incision is approximately one half the height of the tissue cylinder height "h" less about twice the tissue thickness "t"; i.e., L=½h-2t. The length "L" of the incision should preferably be less than half the height "h" of the cylinder in order to eliminate a potential hole in the base of the valve caused by the incisions.

As shown in Fig. 12 the cylinder is involuted into itself such that the innermost wall (in this case, the three flaps) become the "leaflets" of the valve

and the outermost wall becomes the site of attachment to the implantation site. The leaflets are secured to the inner side of the outermost wall (Fig. 13). If the valve construct is intended to be implanted in the aortic valve position, the outermost wall of the valve construct may be scalloped to allow for subcoronary implantation (Fig. 14).

In particular, with tubes of tissue such pulmonary artery, the longitudinal incisions in the cylinder release the constraints on the material and allow the flaps to be easily involuted and secured to the inner wall of the cylinder. Although, the incisions are not necessary, they allow each flap to be secured to the wall independently and may help the leaflets move distinctly from one another during the cardiac cycle. In addition, the perpendicular attachment of each leaflet edge to the wall may facilitate proper tissue repair and growth at each commissure. The presence of incisions at the commissure sites may promote healing and collagen deposition at the commissures.

In another embodiment, no incisions are made and the tubular structure is simply involuted inside itself and selectively attached to the outermost wall (Fig. 15).

In another embodiment, a braided tube is involuted inside itself and the inner tube forms a passively closed inner tube structure or one-way valve in part, due to the forces created by the involution of the braided tube (Fig. 16).

In another embodiment, the involution valve may be formed by a double cylinder structure in which the innermost tube is folded inside the outermost tube (Fig. 17). In the previous discussion of the present invention, the outermost tube is folded inside itself. In this configuration, there can exist an additional cuff of tissue or scaffold at one or both ends of the valve construct. An additional cuff at the base of the valve would ease the surgical implantation of the valve by decreasing the risk of distorting the leaflets during suture placement since the leaflet are a distant from the sewing area at the cuff. The additional cuff(s) may be particularly useful for implantation of a pulmonic valve replacement and reconstruction of the right ventricular outflow tract.

Attachment

One exemplary method of attachment of the inner wall (with or without flaps) to the outer wall is by using three or more "U" sutures (Fig. 13, referred to previously). Other techniques of attaching the inner to the outer wall of the valve include, but are not limited to, interlacing, interlocking, stapling, clipping, splicing, suturing, screwing, knitting, braiding, weaving, punching, tufting (see Fig. 18), stapling, gluing, welding, fusing, laminating and combinations thereof and the like.

Historically, tissue valves with leaflets secured by sutures failed due to the stress imposed at the sites of attachment. In the design of the present invention, the tissue has retained or imparted with healing capabilities that would theoretically offer reinforcement by enabling tissue growth and reinforcement at the suture sites.

A mathematical stress analysis of the involution valve constructed of human blood vessel, indicated that an area of high stress would occur in a discrete area at each commissure (attachment area of the inner leaflets to the outermost wall) (see Fig. 19). In a dynamic model of the theoretical involution valve structure during the cardiac cycle, this area of high stress was noted to move its position along the wall during various phases of the cycle. In order to provide strength and dissipate this small area of high stress, an involution valve can be created with an area of attachment between the leaflets and outer wall as opposed to a line or point of attachment.. As a more specific example, an involution valve can be constructed by weaving, knitting, or braiding the involution and attachment areas of the inner leaflets and outermost wall of the valve.

Interleaflet Triangles

Native human semilunar valves have structures referred to as interleaflet triangles. These structures represent a triangular region between leaflets created by the angled attachment of the each leaflet to the wall. In the present invention, an analogous structure can be imposed in the involution valve by creating a triangular area of attachment of the leaflets to wall of the valve

construct. This can be created by interlocking or interlacing the material with weaving, braiding or knitting techniques (Fig. 20).

In the native human semilunar valves the annulus (imaginary coronal circle representing the base of the valve) moves in opposition to the sinotubular junction (imaginary circle at the level of the leaflets most superior attachment to the wall or sinus) during the cardiac cycle. During diastole, the annulus increases diameter as the sinotubular junction decreases diameter. During systole, the reverse is true, namely, the annulus reduces diameter and the sinotubular junction increases diameter. This motion may be important for valve longevity and the sharing of stress between the leaflet and wall during the cycle. Inserting interleaflet triangles into the involution valve construct may help restore the opposing movement of the annulus with respect to the sinotubular junction. The alteration to the base of the valve construct to construct interleaflet triangles may permit independent movement of leaflets in relationship to one another.

In certain instances, the present invention is created from a tissue cylinder, in this case the interleaflet triangle can be re-approximated with a linear angle of sutures to relieve the point stress at the leaflet commissures. Angling of the base of each leaflet more closely approximates the normal anatomy and helps disperse the stress on the leaflet to a tapered row of sutures rather than a single point of attachment at each commissure.

Sinuses

In a human's native semilunar valve apparatus there exists a space between each leaflet and the vessel wall referred to as the Sinus of Valsalva. This space is known to increase the efficiency of valve function by providing an eddy current of circulating blood which functions, in part, to maintain the separation of the leaflet from the wall during the opening of the valve.

In the present invention, the outermost wall of the involuted cylinder valve construct can be purposefully enlarged at the base of the valve to recreate a potential space between the leaflet free edge and the outer wall. One exemplary method of creating the enlargement is to construct the valve such

that the outermost wall is a larger diameter than the innermost wall cylinder. If the starting material is a tube, one way to achieve this is to use a conical shape of the material such that the smaller diameter of the cone will be involuted into the larger diameter of the cone.

In more complicated methods of forming an involution valve, such as weaving, the sinuses can be integrated into the final geometry by creating selective pockets or outpouchings in the outer wall (see Fig. 21). Various techniques of weaving, knitting, and braiding can form pouches, pockets, pleats, corrugations, crimps and sinuses. Alternatively, portions of the outermost wall of the valve construct can be removed by incisions or scalloping to preserve a potential space (the native Sinus of Valsalva) to exist between the leaflet and the native aortic wall (Fig. 21).

Leaflet Modifications

As described previously, the native human semilunar valve leaflet ventricularis layer has gross corrugations of collagen and elastin in the radial direction which impart significant compliance in this orientation. In the circumferential direction, the fibrosa layer has a crimping of collagen that provides a counterforce to overextension of the leaflet during the period of more extreme loading-bearing (diastole). In order to more closely model the physical properties of the native human valve, the involution valve of the present invention may be constructed with excess material in the leaflet in the radial direction or circumferential directions. (Fig. 22). The techniques of fabricating the involution valve using knitting, weaving, or braiding of material are particularly useful, since excess material to create a "baggy" leaflet can be imparted during the sleeving process. Alternatively, excess material or pouches could be pleated during valve construction, particularly if the involution required folding of material. Using similar techniques, the leaflets of the involution valve can have excess material in the longitudinal direction (Fig. 23).

Modifications of the leaflets' shape by sculpturing the free edge may maximize leaflet coaptation (i.e., the adaptation or adjustment of parts to each

other). Such alternative shape of leaflets include scalloping or rounding off the edges (concave). Other potential leaflet shapes are convex or bi-convex with formation of a central nodule by purposefully imparting a node shape at the midpoint. In certain cases, these shapes may better mimic native valve anatomy and help valve function.

Stents

A sheet of woven, knitted, or braided material may be used in combination with a rigid or semi-rigid frame ("stent") to create a valve. The stent can function to hold the valve in the involuted position, which aids the surgeon in implantation. In another embodiment, a sheet of woven porcine (or other suitable source) decellularized small intestinal submucosa is suspended in a stent (Fig. 24).

Implantation

If the involuted cylinder valve formed by any of the aforementioned methods and materials is orientated such that following implantation, the most viable and anti-thrombogenic surface opposes the diastolic side (Fig. 1). The reason for this is that the highest mechanical stresses on the leaflets and greatest degenerative changes in tissues valves have been noted on the diastolic surface (i.e., the inflow surface). In the involution valve construct (if derived from a blood vessel), the endothelium is orientated towards the diastolic side since it since it may receive nutrients directly from the lumenal blood flow and most likely retains cellular repair capabilities.

As shown in Fig. 14 a design is provided for subcoronary implantation where the outer wall of the tissue cylinder is reduced between the three suture points to permit implantation below the coronary arteries when implanted into the aortic position.

As shown in Fig. 25 the outer wall of tissue cylinder can remain intact and cut out for coronary artery re-implantation, inclusion or mini-root implantation.

One advantage of a tubular braid configuration is the possibility of creating a tubular valve that is collapsible (Fig. 26). Braided tubes can be constructed which reduce diameter significantly when a longitudinal force is exerted on the tube. For example in one exemplary embodiment, the tubular valve is reduced in diameter by exerting a longitudinal force by a trocar on the inside of the tube, introduced into the endovascular space in minimally invasive manner, and is deployed as a larger diameter structure at the valve replacement site by removing the trocar.

Apparatus and methods for forming, inserting and using expandable and collapsible structures, e.g., cannulae, which may serve as an analogous technology useful for creating a scaffold capable of having a reduced diameter during implantation and expanding thereafter are disclosed in copending Patent Cooperation Treaty (designating the U.S.) application No. PCT/US02/40349, filed December 16, 2002, entitled "DYNAMIC CANNULA".

Alternative scaffolding techniques

A mold of scaffold can be created by a tricuspid "ventricular" and "aortic" stamp (e.g., a silicone-coated aluminum mold). Thermoplastic scaffolding material is inserted between the two stamps to create the complex shape of the aortic root and valve.

Some scaffold materials (such as, but not limited to, P4HB) with thermoplastic properties can be welded instead of sutured at the commissures.

Computer-aided molecular deposition of scaffold material potentially be used in lithography to create the three-dimensional valve. The same process could generate a flat sheet, cylinder, or cylinder with three equidistant incisions (see the involuted cylinder method) which then undergo secondary folding to create a valve.

Special Processes

The present invention also contemplates the construction of a scaffold generally having the configuration made of a synthetic material, which is then used as a support on which to seed and grow cells. The basic concept of seeding is to transplant autologous cells onto a biocompatible and biodegradable scaffold that has been pre-formed in the three dimensional structure of a heart valve. The cells are attached to the scaffold while keeping tissues *in vitro* with physical signals to guide development of tissues. As the cells form extracellular matrix, the biodegradable polymer scaffold starts to degrade. The scaffold and the attached cells are implanted into the body where cells continue to produce matrix materials, providing increasing mechanical strength while the scaffold finishes its degradation (usually in about 6-8 weeks).

Possible culture additives include, but are not limited to, cytokines, growth factors, microencapsulated growth factors, heparin products, cell markers to track cells post-implantation, transfection vectors (e.g., green fluorescent protein), anti-microbial anti-fungal agents, mixtures thereof and the like.

Possible cells which can be used to seed the scaffold include, but are not limited to, fibroblasts, endothelial cells, myofibroblasts, smooth muscle cells, fetal-type smooth muscle cells, mixtures thereof and the like.

Cell sources include, but are not limited to, peripheral blood, human umbilical cord, blood, arteries (e.g., carotid), human foreskin, bone marrow, adipose tissue, mixtures thereof and the like.

Advantages

The involution valve can be constructed from a wide range of materials. The use of scaffolding materials (e.g., porcine small intestinal mucosa) offer the advantage of a potentially autologous living valve capable of growth and repair following maturation of the implant in the circulation.

The involution valve can being constructed as a braid, a knit, or a weave of material. The ability to fabricate the valve using these techniques enables the potential to create a valve with physical properties analogous to the native human leaflet. These techniques increase the potential strength and durability of the valve the reinforcement provided by interlacing the material at the attachment areas of the leaflet to the wall. It is advantageous that the involution valve can be constructed as a continuous structure using these techniques.

In contrast to previous attempts to reconstruct autologous arteries into valvular structures, the method described in this present invention enables a tri-leaflet valve to be constructed independent from its site of implantation. The valve may be transplanted to any desirable anatomical implant site. This reduces the technical challenge and allows the potential for pre-operative or intra-operative dynamic function testing prior to implantation. In certain instances, it is advantageous that the involution valve can assume a narrow profile and be deployed into the endovascular space by a minimally invasive means.

The involution valve can also be constructed from the patient's own tissues in an economical manner, offering an alternative treatment for valvular disease. If the valve retains its growth potential, it may be particularly useful for pulmonic valve substitution in the Ross procedure or in pediatric patients with congenital abnormalities of the pulmonary valve such as tetralogy of Fallot with absent valve syndrome.

The invention may also have applicability to non-medical application. The advantage of this design and method is the potential to create a valve with the following properties; large effective orifice area, a low pressure gradient, efficient closure velocity, and low regurgitation volume. The valve is suitable in rigid or non-rigid systems and wet or dry environments. The valve leaflets can potentially form a seal around an inner rod or piston. The valve can be constructed from a wide range of materials. The valve is potentially efficient and economical to construct and insert into the stream of flow. The invention will be further described in connection with the following examples, which are

set forth for purposes of illustration only. Parts and percentages appearing in such examples are by weight unless otherwise stipulated.

EXAMPLES

Example 1

A tri-leaflet tissue valve can be constructed from the main pulmonary artery by the involution method and implanted into the aortic position in sheep (see experiment 1). This valve may also be suitable as a replacement for other valves (e.g., pulmonary valve).

Objective

An involuted cylinder valve constructed from pulmonary artery tissue and implanted in the aortic position in sheep.

Materials and Methods

From previously sacrificed donor swine (n=4, 50 kg +/- 10 kg), the main pulmonary artery and its main left and right branches were harvested. The main pulmonary artery trunk was trimmed to create a tissue cylinder of height equal to the diameter of the recipient aortic annulus. $A = h \approx d$, where A = recipient aortic annulus diameter (mm), h = tissue cylinder height (mm), and d = tissue cylinder diameter (mm). Excess fat was trimmed from the specimen and adventitial layer was carefully peeled off as a single sheet of tissue and discarded. The tissue cylinder was incised with three longitudinal incisions 120 degrees apart. $L = \frac{1}{2}h - 2t$, where L = incision length (mm), and t = wall thickness (mm) (see Fig. 1).

In two specimens, the edges of all three flaps of tissues were rounded-off along their free-edge, creating concave-shaped leaflets. In all constructs the flaps were involuted into the tissue cylinder and sutured to the cylinder wall at three equidistant points using "U" sutures (see Figs. 2 and 3.). The outer wall of the valve construct was reduced between the three points to allow space for implantation of the valve inferior to the coronary arteries (see Fig. 4). In all cases, the valve was prepared in less than 20 minutes. Prior to implantation,

the valve was inspected for competency by passive suspension of a column of saline.

A median sternotomy was performed and cardiopulmonary bypass was instituted in recipient sheep. Cold high potassium crystalloid cardioplegia was given by direct ostial cannulation. The ascending aorta was transversely transected 1 cm above the right coronary artery and native leaflets excised. The preformed valve construct was secured into the subcoronary position by interrupted 3-0 Tevdek™ sutures on the lower edge and a running 4-0 prolene along the superior aspect. The aortotomy was closed and the animal weaned from cardiopulmonary bypass. In animals that recovered cardiac function, echocardiography was performed to assess valve function.

Results

The two animals that received valve constructs without rounded-off leaflet free-edges displayed mild aortic regurgitation on two-dimensional echocardiography with continuous-wave Doppler using a hand-held epicardial probe. In the same group, the short-axis view exhibited coaptation of all three leaflets during valve closure. Symmetrical leaflet movement and good mobility was observed throughout the cardiac cycle in four-chamber apical view. A mean flow velocity of 2.49 m/sec was obtained in one animal with a 14 mm aortic annulus diameter. The two animals with rounded-off leaflet free edges had severe aortic insufficiency due to prolapse of two or all three leaflets and could not be weaned from bypass.

Conclusion

In this experiment, a segment of the main pulmonary artery was reconfigured into an aortic valve using a technique referred to as the "involuted cylinder" method and implanted into the subcoronary position in four sheep. In two constructs the leaflets were modified, creating concave leaflet free-edges. The modification was designed to eliminate deadspace at the base of the leaflets and reduce the risk of thrombosis formation. However, in these modified constructs the central region of the leaflets was not supported adequately which resulted in leaflet prolapse under diastolic load. The constructs without

rounded leaflets assumed a more cup-like configuration and exhibited no prolapse, most likely due to the suspension of the leaflets at all points along the free-edge. It may also be significant that the longitudinal axis of the pulmonary artery wall becomes the radial axis of the valve leaflet. Increased extensibility of the leaflet in the radial direction may act to lessen the central orifice by providing more coaptation area.

Example 2

A scaffold is constructed of decellularized porcine small intestinal submucosa. The involution method described above is used to form a functional three-dimensional valve. The valve is implanted into the individual and allowed to mature under *in vivo* conditions.

Objective

A Pulmonic Valve Replacement in Sheep Using an Involution Valve Constructed of Porcine Small Intestinal Submucosa

Materials and Methods

A sheet of 4-ply porcine small intestinal submucosa "SIS" (Cook, Inc.) of dimensions 68.2 mm long x 20 mm wide was prepared. Two equidistant 8mm long incisions were created extending from the free edge of the length to centerline of the material. The flat sheet was folded in half along the length with the smoother surface on the inside. A cylinder was formed by suturing the two free ends together with a running 7-0 prolene. The leaflets were secured in a perpendicular manner to the inner wall of the cylinder by "U" sutures. Two additional sheets of SIS were sutured to either end of the valve, creating two cylindrical cuffs of tissues at either end of the valve construct.

A median sternotomy was performed and cardiopulmonary bypass was instituted in a recipient sheep. Cold high potassium crystalloid cardioplegia was given by ascending aortic cannulation. The pulmonary artery was clamped and transected one millimeter above the pulmonary valve. The native pulmonary valve was excised. The preformed valve construct was secured at

the superior aspect to the distal pulmonary trunk using 5-0 prolene. The cuff at the base of the valve was sutured to the proximal remnant of the pulmonary trunk. Protomine™ was given and the animal was weaned from cardiopulmonary bypass. The animal recovered cardiac function and echocardiography was performed to assess valve function.

Results

The animal was successfully weaned from bypass. The pulmonary valve replacement displayed no pulmonic regurgitation on two-dimensional echocardiography with continuous-wave Doppler using a hand-held epicardial probe. The short-axis view exhibited coaptation of all three leaflets during valve closure. Symmetrical leaflet movement and good mobility was observed throughout the cardiac cycle in four-chamber apical view.

Conclusion

An involution valve constructed from decellularized porcine small intestinal submucosa functioned as a trileaflet pulmonary artery replacement in an acute sheep model. Chronic studies are necessary to determine the ability of the scaffold material to endothelialize and populate with autologous cells following endovascular implantation. Further investigation as to the function of the valve following implantation will help determine its usefulness in patients.

Example 3

A sheet of the patient's pericardium is harvested and formed into a valve construct using the involution method as described hereinabove at the surgical backtable. The valve construct is tested, then reimplanted into the same patient as a living autologous valve replacement.

Example 4

Formation of Scaffold

An unwoven polyglycolic acid ("PGA") mesh sheet 24 mm x 75 mm and 1.5 mm thick is prepared and rolled into a cylinder. Three equidistant longitudinal 10 mm incisions are used to create three flaps which are involuted inside the cylinder and secured 120 degrees apart to form commissures. Scallop-shaped segments of the outermost wall of the cylinder are removed between the commissures to form the scaffold.

Example 5

Seeding

The scaffold of Example 4 created of a material that will support cellular growth, e.g., celluloid. Peripheral blood is harvested, samples are spun in column and cells are recovered (e.g., circulating endothelial cells) which are then serial plated on fibronectin culture plates and allowed to expand (e.g., static growth for 1 week). Cells are then seeded onto a celluloid construct in a rotating, pulsatile, or continuous flow bioreactor for a period of time (e.g., 4 weeks), then the valve is implanted in the patient to continue to mature, differentiate, and evolve *in vivo*.

Example 6

A valve is created by any of the examples or methods discussed hereinabove and temporarily implanted in the body (endovascular or other site) to allow maturation. For instance, the valve can be deployed using a minimally invasive apparatus into the descending aorta, exposed to the blood stream and mechanical stresses of the cardiac cycle for a period of weeks, and then removed from the body and reimplanted as a permanent valve replacement.

Example 7

A valve is created by any of the examples or methods discussed hereinabove and implanted in the endovascular space using a minimally invasive means.

It will be understood that the terms "a" and "an" as used herein are not intended to mean only "one," but may also mean a number greater than "one." All patents, applications and publications referred to herein are hereby incorporated by reference in their entirety. While the invention has been described in connection with certain embodiments, it is not intended to limit the scope of the invention to the particular forms set forth, but, on the contrary, it is intended to cover such alternatives, modifications, and equivalents as may be included within the true spirit and scope of the invention as defined by the appended claims.

CLAIMS

CLAIMED IS:

1. A method of forming a prosthetic valve, comprising:

   a. providing a tube of material having an inner wall, an outer wall, a diameter "d", a height "h" and a wall thickness "t";

   b. cutting three longitudinal incisions from one end in said material about 120 degrees apart to form three flaps, each said flap having a first edge, a second edge generally parallel to said first edge, and a bottom edge;

   c. involuting each said flap within said tube; and,

   d. attaching each said first edge and second edge of each involuted flap to said inner wall of said tube.

2. The method of Claim 1, wherein said three longitudinal incisions have a length "L", such that L=½h-2t, where "h" is the cylinder height and "t" is the thickness of said tube.

3. The method of Claim 1, wherein said height "h" is approximately equal to the diameter of the recipient aortic annulus diameter "A".

4. The method of Claim 1, wherein the edges of each flap are cut to be rounded off along their free edge to create concave shaped leaflets.

5. The method of Claim 1, wherein scallop shaped segments of said tube wall are removed between commissures.

6. The method of Claim 1, wherein said attaching is achieved by suturing.

7. The method of Claim 1, wherein said tube is comprises a generally rectangular sheet of material that has two opposing sides joined together.

8. A method of constructing a support for development of an autologous valve, comprising:

9. An autologous valve formed by a process, comprising:

a. providing a tube of material having an inner wall, an outer wall, a diameter "a", a height "b" and a wall thickness "t";

b. cutting three longitudinal incisions from one end in said material about 120 degrees apart to form three flaps, each said flap having a first edge, a second edge generally parallel to said first edge, and a bottom edge;

c. involuting each said flap within said tube; and,

d. attaching each said first edge and second edge of each involuted flap to said inner wall of said tube.

10. A method of converting a tube into a valve, comprising:

a. providing a tube of material having an inner wall, an outer wall, a diameter "a", a height "b" and a wall thickness "t";

b. cutting three longitudinal incisions from one end in said material about 120 degrees apart to form three flaps, each said flap having a first edge, a second edge generally parallel to said first edge, and a bottom edge;

c. involuting each said flap within said tube; and,

d. attaching each said first edge and second edge of each involuted flap to said inner wall of said tube.

11. A endovascular valve, comprising:

a. a flexible tube having a first end and a second end, an inner wall and an outer wall;

b. a plurality of leaflets formed from a portion of said first end by making a plurality of longitudinal incisions in said downstream end to form a plurality of flaps, each flap having a first edge and second edge, involuting said flaps toward said inner wall and securing said first edge and second edge of each flap to said inner wall of said tube

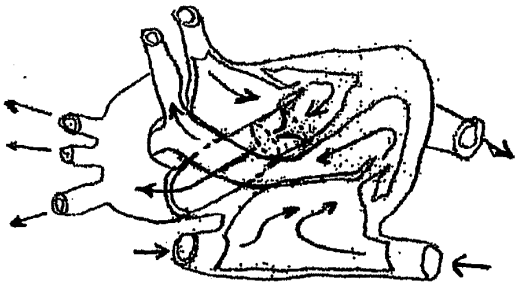


FIG. 1

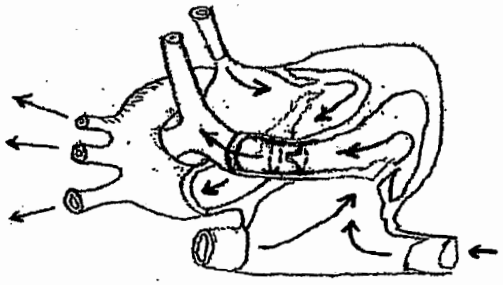


FIG. 2

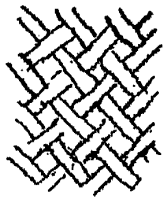


FIG. 3

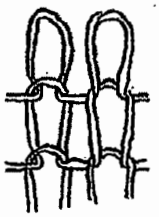


FIG. 4

FIG. 5

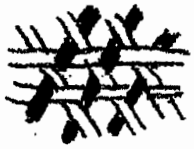


FIG. 6

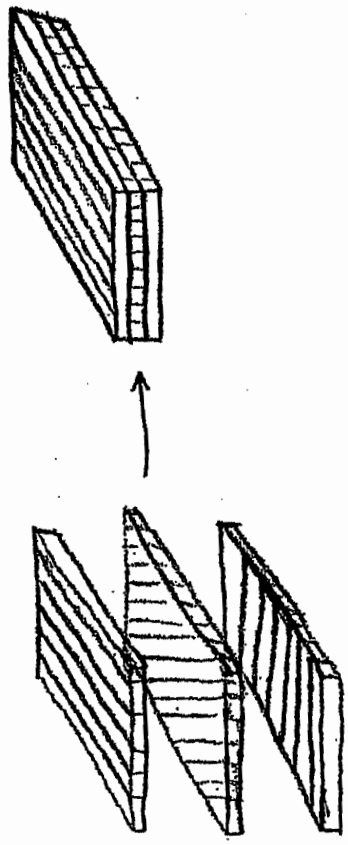


FIG. 7

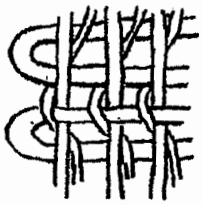


FIG. 8

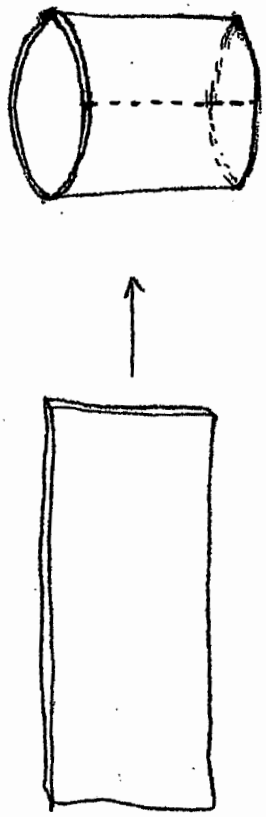


FIG. 9

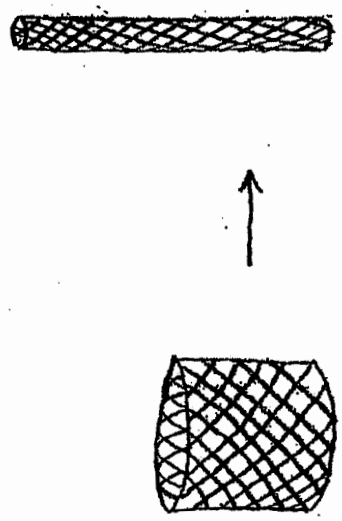


FIG. 10

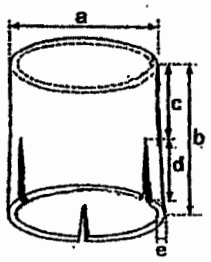


FIG. 11

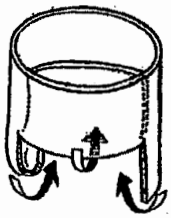


FIG. 12

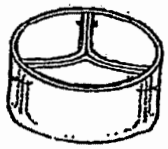


FIG. 13

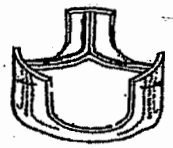


FIG. 14

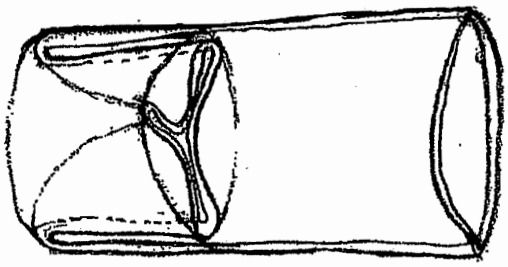


FIG. 15

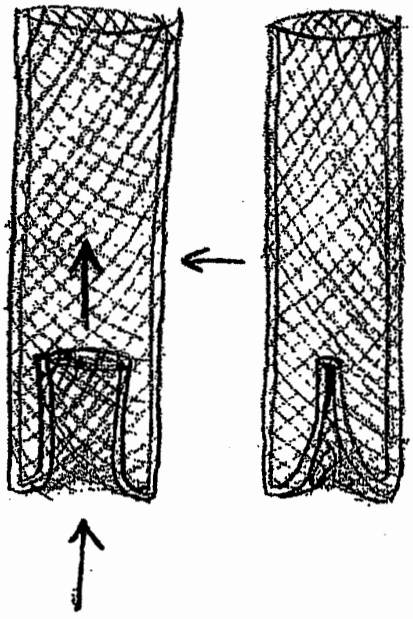


FIG. 16

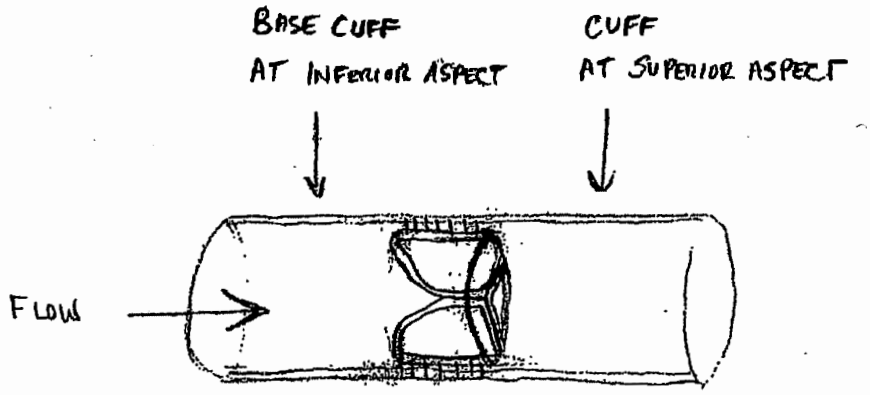


FIG. 17

FIG. 18

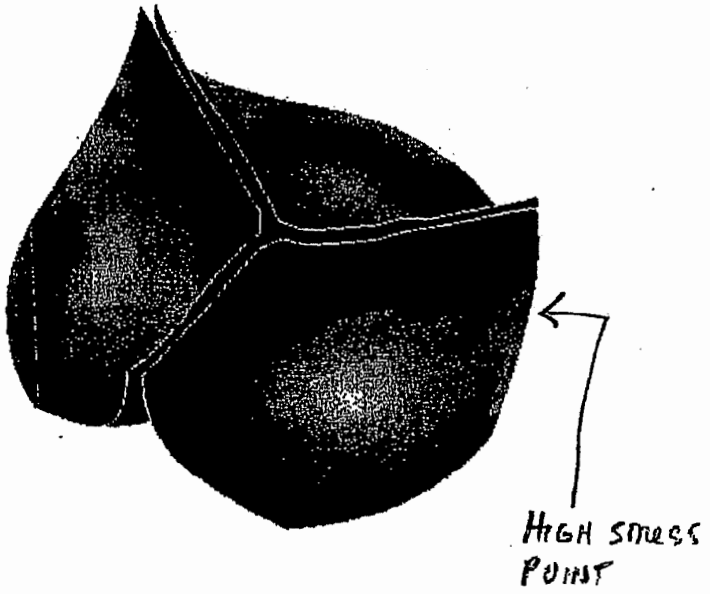


FIG. 19

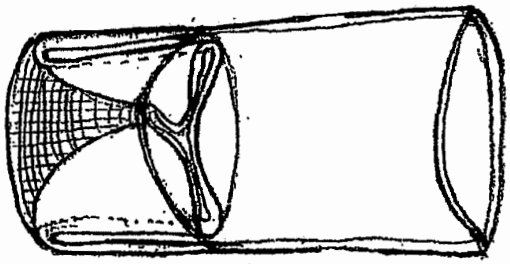


FIG. 20

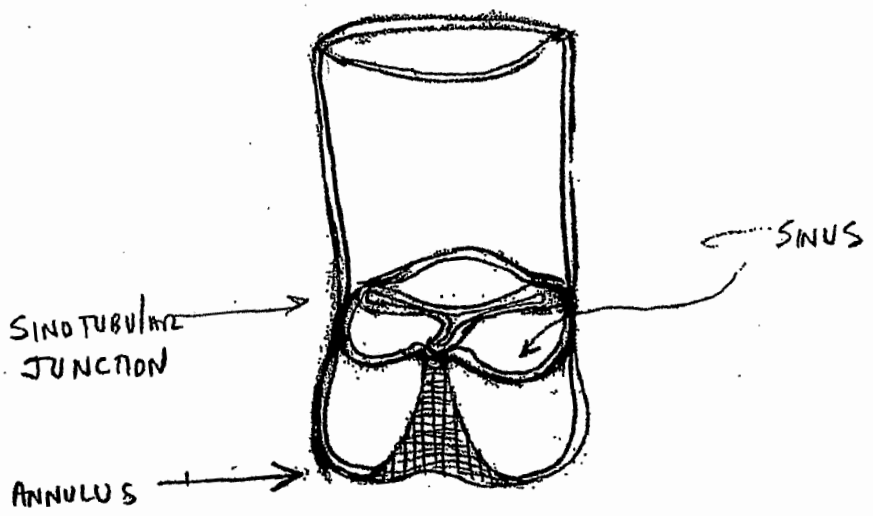


FIG. 21

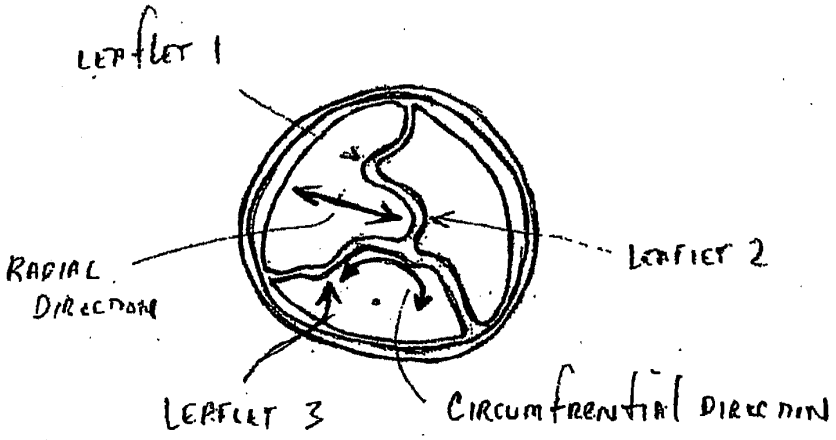
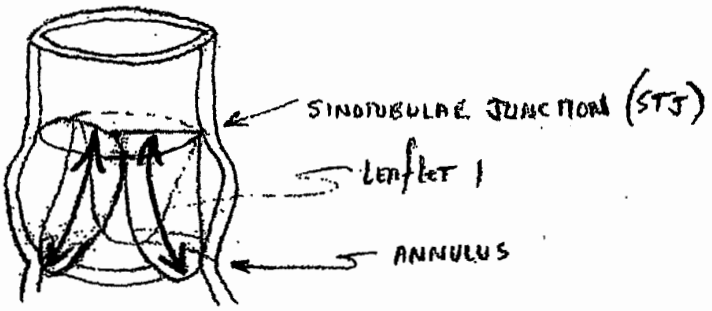

LEAFLET 1
RADIAL DIRECTION
LEAFLET 2
LEAFLET 3
CIRCUMFRENTIAL DIRECTION

FIG. 22

FIG. 23



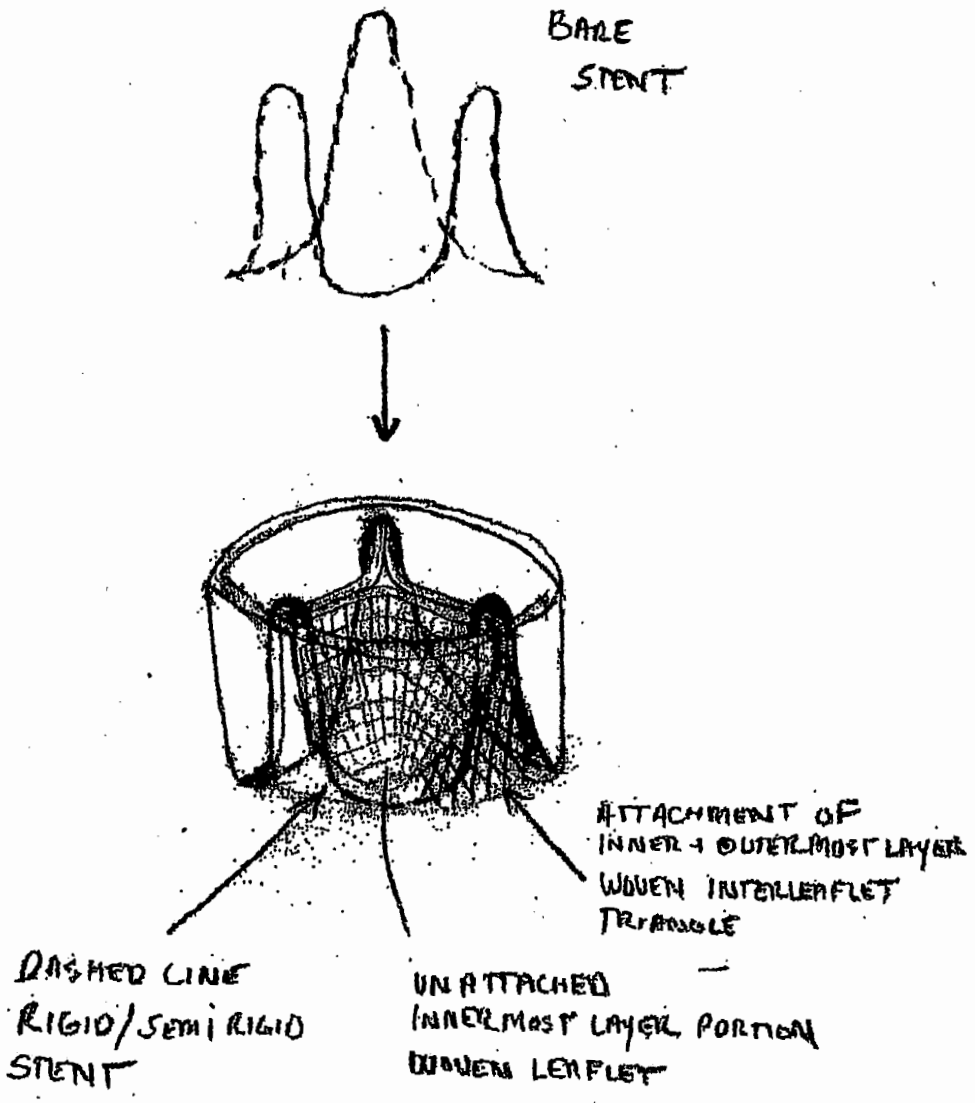

BARE STENT
ATTACHMENT OF INNER + OUTERMOST LAYER WOVEN INTERLEAFLET TRIANGLE
DASHED LINE RIGID/SEMI RIGID STENT
UNATTACHED INNERMOST LAYER PORTION WOVEN LEAFLET

FIG. 24

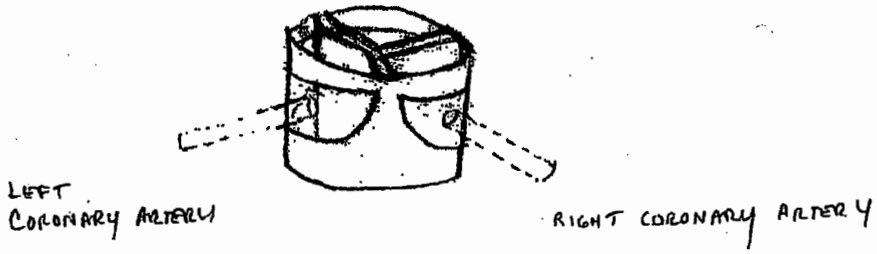


FIG. 25

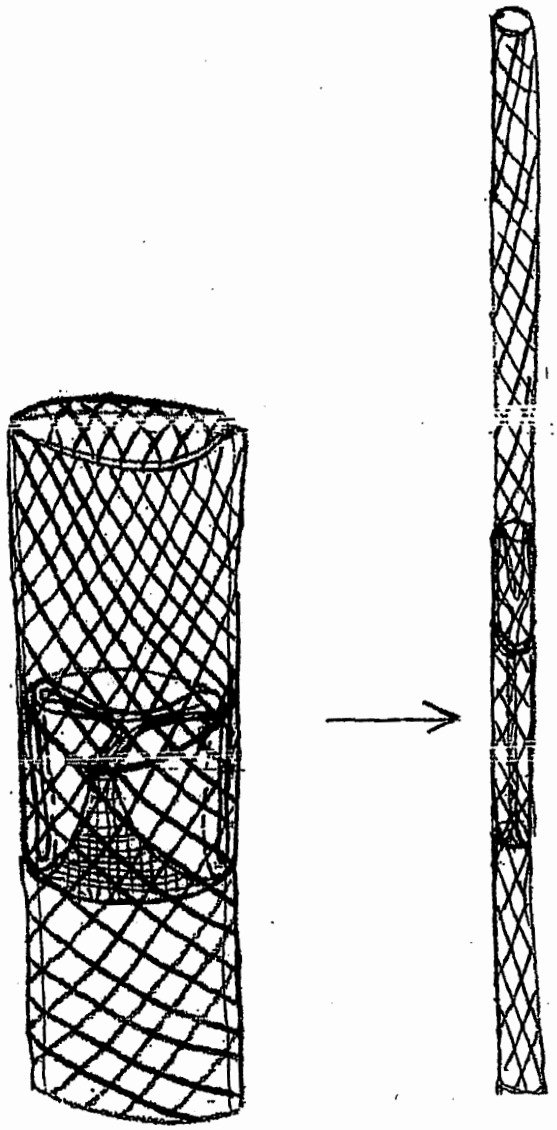


FIG. 26

INTERNATIONAL SEARCH REPORT

In...tional Application No
PCT/US 03/14160

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 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)
IPC 7 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)
WPI Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 172 295 A (BATTEN) 30 October 1979 (1979-10-30) the whole document	1,9-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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
20 August 2003	26/08/2003

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	Smith, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/14160

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 8
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:
see FURTHER INFORMATION sheet PCT/ISA/210

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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers 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.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 8

Text of claim incomplete.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 03/14160

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4172295 A	30-10-1979	NONE	

Form PCT/ISA/210 (patent family annex) (July 1992)

09-15-09

IFW

GreenbergTraurig

Manuel R. Valcarcel, Esq.
Tel. 305-579-0812
Fax 305-961-5812
mrv@gtlaw.com

September 14, 2009

VIA EXPRESS MAIL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Re: U.S. Patent Application No. 10/887,688
Invention: Percutaneously implantable replacement heart valve device and method of making same
Revocation/New Power of Attorney, Statement Under 3.73(b), Petition for Extension of Time, Response to Office Action Dated March 16, 2009, Declarations and Information Disclosure Statement
Our Ref. No. 051458.010100

Dear Sir:

Enclosed under cover of this transmittal letter are the following documents:

1. Revocation of Power of Attorney and New Power of Attorney executed by the assignee of the above-referenced application, appointing the undersigned, together with an executed Statement Under 37 CFR Section 3.73(b);

2. Petition for Extension of Time (three months) Under 37 CFR Section 1.136(a), including authorization to charge the small entity petition fee under 37 CFR Section 1.17(a)(3) ($555) and any other required fees to Deposit Account No. 50-1792;

3. Response to the office action dated March 16, 2009 in the above-referenced application, canceling 1 independent claim and 15 dependent claims, and adding 10 new independent claims, 3 new dependent claims and 6 multiple dependent claims (5 multiple dependent claims referring to 16 prior claims and 1 multiple dependent claim referring to 15 prior claims), including authorization to charge the small entity fee for 9 net additional independent claims in excess of 3 under 37 CFR Section 1.16(i) ($110 x9=$990), the small entity fee for 92 net additional claims in excess of 20 under 37 CFR 1.16(i) ($26 x 92=$2392) and the small entity multiple dependent claim fee under 37 CFR Section 1.16(j) ($195) (total claims fees $3,577) to Deposit Account No. 50-1792;

EXPRESS MAIL MAILING LABEL NO. EH 796550831 US

4. Supplemental Declaration Under 37 CFR Section 1.131 together with exhibits including Affidavits of Dr. Gervasio A. Lamas, M.D. and Dr. Paolo Angelini, M.D.;

5. Utility Patent Application Declaration; and

6. Information Disclosure Statement, Form PTO/SB/08a and copies of non-U.S. patent documents listed therein including authorization to charge the Information Disclosure Statement Fee under 37 CFR Section 1.17(p) ($180) to Deposit Account No. 50-1792.

Please charge all required fees noted above and any other required fees for the enclosed submission to Deposit Account No. 50-1792.

Please confirm receipt of the enclosed documents by date-stamping and returning the enclosed postage paid return postcard. Please direct all communications regarding the foregoing to the undersigned.

Respectfully submitted,

GREENBERG TRAURIG, P.A.

Manuel R. Valcarcel, Esq.
Reg. No. 41,360

EXPRESS MAIL MAILING LABEL NO. EH 796550831 US

MRV/mam
Enclosures

cc: David Paniagua, M.D.
R. David Fish
Endoluminal Technology LLC

MIA 180,806,014v1

PTO/SB/22 (8-00)
Approved for use through 10/31/2002 OMB 0651-0031
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 if displays a valid OMB control number

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 051458.010100

In re Application of Paniagua, et al.	
Application Number 10/887,688	Filed July 10, 2004
Group Art Unit 3738	Examiner: Miller, Cheryl L.

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows: (check time period desired):

- ☐ One month (37 CFR 1.17(a)(1)) $ _____
- ☐ Two months (37 CFR 1.17(a)(2)) $ _____
- ☒ Three months (37 CFR 1.17(a)(3)) $ 1110.00
- ☐ Four months (37 CFR 1.17(a)(4)) $ _____
- ☐ Five months (37 CFR 1.17(a)(5)) $ _____

☒ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: $ **555.00**

A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Commissioner has already been authorized to charge fees in this application to a Deposit Account.

☒ The Commissioner is hereby authorized to charge the fee and any additional fees which may be required, or credit any overpayment, to Deposit Account Number 50-1792.

I have enclosed a duplicate copy of this sheet.

I am the ☐ assignee of record of the entire interest.

☐ applicant.

☒ attorney or agent of record.

☐ attorney or agent under 37 CFR 1.34(a).
Registration number if acting under 37 CFR 1.34(a) _____.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

September 14, 2009
Date

Signature

Manuel Valcarcel, Esq.
Typed or printed name (Reg. 41,360)

Burden Hour Statement: This form is estimated to take 0.1 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

EXPRESS MAIL MAILING LABEL NO. EH 796550831 US

MIA 180,806,008v1

09/15/2009 RMEBRAHT 00000073 501792 10887688

04 FC:2253 555.00 DA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: Paniagua, et al.
Patent Application Serial No. 10/887,688
Filing Date: July 10, 2004
Title: Percutaneously Implantable Replacement Heart Valve Device and Method of Making Same

REVOCATION OF POWER OF ATTORNEY
AND
NEW POWER OF ATTORNEY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The undersigned assignee and owner of the above-referenced patent application hereby revokes all Powers of Attorney previously granted and hereby appoints **Manuel R. Valcarcel, attorney at law, of the firm of GREENBERG TRAURIG, P.A., with an address at 1221 Brickell Avenue, Miami, Florida 33131,** to transact all business in the United States Patent and Trademark Office in connection therewith. **The correspondence address in the above-referenced patent application shall remain the same, namely: Manuel Valcarcel, Esq., Greenberg Traurig, P.A., 1221 Brickell Avenue, Miami, Florida 33131.** Please direct all future correspondence to this address.

Date: September 3, 2009

Assignee/Owner:

ENDOLUMINAL TECHNOLOGY LLC

Signature: RDFish
Name: R. David Fish
Title: Managing Officer

cc: Manuel R. Valcarcel, Esq.
Greenberg Traurig, P.A.
1221 Brickell Avenue
Miami, Florida 33131

MIA 180,790,817v1

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Endoluminal Technology LLC

Application No./Patent No.: 10/887,688 Filed/Issue Date: July 10, 2004

Titled: Percutaneously implantable replacement heart valve device and method of making same

Endoluminal Technology LLC, a limited liability company
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☑ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

OR

B. ☑ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: D.Paniagua, E. Induni, C.Mejia and F. Lopez To: Endoluminal Technology Research, LLC
The document was recorded in the United States Patent and Trademark Office at
Reel 022532, Frame 0213, or for which a copy thereof is attached.

2. From: Endoluminal Technology Research, LLC To: Endoluminal Technology LLC
The document was recorded in the United States Patent and Trademark Office at
Reel 022532, Frame 0275, or for which a copy thereof is attached.

3. From: R. David Fish To: Endoluminal Technology LLC
The document was recorded in the United States Patent and Trademark Office at
Reel 022899, Frame 0819, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

RDFish
Signature

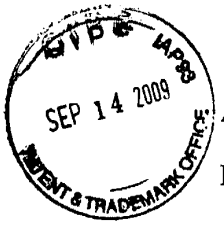
9.3.09
Date

R. David Fish
Printed or Typed Name

Managing Officer
Title

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No.: 051458.010100
First Named Inventor: Paniagua, David
Patent Application Serial No. 10/887,688
Filed: July 10, 2004
Art Unit: 3738
Examiner Name: Miller, Cheryl



UTILITY PATENT APPLICATION DECLARATION

As a below named inventor, I hereby declare that:

My mailing address, residence and citizenship are as stated below my name,

I believe I am an original, first and joint inventor of the subject matter claimed and for which a patent is sought on the invention entitled "Percutaneously Implantable Replacement Heart Valve Device and Method of Making Same," the specification, including the claims, of which was filed on July 10, 2004 as Application Serial No. 10/887,688, and as amended as attached hereto.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I hereby declare that the subject matter of the attached amendment was part of the invention and was invented before the filing date of the original application identified above for such invention.

I acknowledge the duty to disclose information that is known to me to be material to patentability in accordance with Title 37, Code of Federal Regulations, Section 1.56(a).

The benefit under Title 35, United States Code, Section 119 of United States provisional application(s), and/or Section 120 of any United States application(s) listed below has been claimed by or on behalf of the undersigned previously and said claim is reaffirmed, and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) that occurred between the filing date of the prior application and the filing date of this application:

Prior U.S. Application(s):

Serial No.	**Filing Date**	**Status: Patented, Pending, Abandoned**
10/037,266	January 4, 2002	Abandoned

Please direct all correspondence to the attorney of record:

Manuel Valcarcel, Esq.
Greenberg Traurig, P.A.
1221 Brickell Avenue
Miami, Florida 33131

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first joint inventor: David Paniagua

Inventor's signature: Date: September 5, 2009

Mailing Address: 3813 Drummond Street Houston Tx 77025

Citizenship: Costa Rica Residence (City, State, Country)(if different from mailing address):

Full name of second joint inventor: Eduardo Induni

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of third joint inventor: Carlos Mejia

Inventor's signature: Carlos Mejia A. Date: September 5, 2009

Mailing Address: 3503 Deal Street Houston Texas 77025

Citizenship: Colombia Residence (City, State, Country)(if different from mailing address):

Full name of third joint inventor: Francisco Lopez-Jimenez

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of fifth joint inventor: R. David Fish

Inventor's signature: Date: September __, 2009

Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first joint inventor: David Paniagua

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of second joint inventor: Eduardo Induni

Inventor's signature: Date: September _3_, 2009

Mailing Address: Resi Alajuela H 7 Alajuela 906 4050 Costa Rica

Citizenship: Costa Rica Residence (City, State, Country)(if different from mailing address):

Full name of third joint inventor: Carlos Mejia

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of third joint inventor: Francisco Lopez-Jimenez

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of fifth joint inventor: R. David Fish

Inventor's signature: Date: September __, 2009

Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first joint inventor: David Paniagua

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of second joint inventor: Eduardo Induni

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of third joint inventor: Carlos Mejia

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of third joint inventor: Francisco Lopez-Jimenez

Inventor's signature: Date: September 3, 2009

Mailing Address: 200 first St SW, Rochester, MN, USA

Citizenship: American. Residence (City, State, Country)(if different from mailing address):

Full name of fifth joint inventor: R. David Fish

Inventor's signature: Date: September __, 2009

Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first joint inventor: David Paniagua

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of second joint inventor: Eduardo Induni

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of third joint inventor: Carlos Mejia

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of third joint inventor: Francisco Lopez-Jimenez

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of fifth joint inventor: R. David Fish

Inventor's signature: RDFish Date: September 3, 2009

Address: 6349 Vanderbilt St. Houston, Texas 77005 (Residence)

Citizenship: USA Residence (City, State, Country)(if different from mailing address):

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of
Paniagua, et al.
Serial No. 10/887,688
Filed: July 10, 2004
Invention: Percutaneously Implantable Replacement Heart Valve Device and Method of Making Same

Examiner: Cheryl Miller
Group Art Unit 3738

RESPONSE TO OFFICE ACTION

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

In response to the Office Action dated March 16, 2009 in the above-referenced application, the undersigned, on behalf of the Applicant, submits the following Response to Office Action together with a summary of the telephonic interview held on June 9, 2009 between the examiner and the undersigned, which is attached as Appendix A to this Response, and a Supplemental Declaration under 37 CFR Section 1.131 including witness affidavits as supporting evidence, which is attached as Appendix B to this Response. An unmarked version of the claims is also provided as Appendix C, for examiner's convenience and ease of review of the claim amendments. A Revocation of Power of Attorney and New Power of Attorney executed on behalf of the assignee of the present application and a Statement Under 37 CFR Section 3.73(b) are also enclosed. Additionally, a Request for Extension of Time Under 37 CFR Section 1.136(a), a Utility Patent Application Declaration of the co-inventors and Information Disclosure Statement with a copy of the non-patent literature listed in same are enclosed. Authorization to charge Deposit Account No. 50-1792 for the applicable fees is included with the transmittal correspondence submitted with this Response to Office Action. Claim amendments begin on page 2. Remarks begin on page 19.

09/15/2009 RMEBRAHT 00000073 501792 10887688
01 FC:2201 990.00 DA
02 FC:2202 2392.00 DA
03 FC:2203 195.00 DA

AMENDMENTS TO THE CLAIMS

The following listing will replace all prior versions of the claims in the application:

1. (currently amended) A percutaneously implantable replacement heart valve device comprising:

an expandable stent member having an inner ~~space~~channel, and ~~a flexible, compressible artificial valve disposed within said inner space of said stent member affixed at one or more points on said artificial valve's outer surface to~~

a sheet of biocompatible material forming a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material being disposed within said inner channel of said stent member, said ~~artificial valve comprising a~~ sheet of biocompatible ~~material~~ material having two opposite ends joined to form an outer generally tubular portion having an inner space and having one or more folds defining ~~one~~an inner leaflet portion with two or more ~~cusps or~~unslit leaflets without ~~slits cut into said material or separate cusps or leaflets affixed thereto~~requiring suturing of said leaflets, said inner leaflet portion being disposed within said inner space of said outer generally tubular portion.

2. (currently amended) The percutaneously implantable replacement heart valve device of claim 1, wherein said expandable stent member is made of a metal or alloy of metals ~~selected from the group consisting of nickel-titanium alloy, titanium and stainless steel~~.

3. (currently amended) The percutaneously implantable replacement heart valve device of claim 1, wherein said sheet of biocompatible material ~~of said artificial valve~~ comprises mammal pericardium tissue.

4. (currently amended) The percutaneously implantable replacement heart valve device of claim 1, wherein said **sheet of** biocompatible ~~**material of said artificial valve comprises porcine pericardium tissue**~~ **material is disposed entirely within said inner channel of said stent member**.

5. (currently amended) The percutaneously implantable replacement heart valve device of claim 1, wherein said **sheet of** biocompatible material ~~**of said artificial valve is obtained from a juvenile animal pericardium**~~**comprises graft material**.

6. (currently amended) The percutaneously implantable replacement heart valve device of claim 1, wherein said **sheet of** biocompatible material ~~**of said artificial valve**~~ comprises **biological** ~~autologous~~ tissue ~~**obtained from the patient into whom said replacement heart valve device will be implanted**~~.

7. (currently amended) The percutaneously implantable heart valve device of claim 1, wherein said **sheet of** biocompatible material ~~**of said artificial valve**~~ comprises a synthetic biocompatible material.

8. (currently amended) The percutaneously implantable heart valve device of claim 7, wherein said synthetic biocompatible material is selected from the group consisting of polytetrafluoroethylene, polyester, **polyurethane,** metal, metal alloy **and metal foil,** including combinations thereof.

9. (original) The percutaneously implantable heart valve device of claim 1, wherein said stent member is self-expanding when implanted.

10. (original) The percutaneously implantable heart valve device of claim 1, wherein said stent member is balloon catheter expandable when implanted.

11. (canceled)

12. (canceled)

13. (canceled)

14. (canceled)

15. (canceled)

16. (canceled)

17. (canceled)

18. (canceled)

19. (canceled)

20. (canceled)

21. (canceled)

22. (canceled)

23. (canceled)

24. (canceled)

25. (canceled)

26. (canceled)

27. (currently amended) A percutaneously implantable replacement heart valve device comprising :

an expandable stent member having an inner ~~space and a flexible, compressible artificial valve made~~channel,

a first sheet of biocompatible ~~material and disposed within said inner space of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising a leaflet or cusp portion formed by folding of a first sheet portion of said biocompatible tissue material without cutting slits into said first sheet portion to form said cusps or leaflets, and an outer tubular cuff structure formed by folding a second sheet portion of biocompatible tissue material~~ material forming a first generally tubular portion having an inner space, said first generally tubular portion having a first border defined by a first border fold, and one or more additional folds, said first border fold and said one or more additional folds defining a cusp or leaflet portion having one or more unslit leaflets without requiring suturing of said leaflets, and

a second sheet of biocompatible material forming a second generally tubular portion having a folded border defining a cuff,

said first ~~sheet~~generally tubular portion and second ~~sheet~~generally tubular portion being affixed together to form a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure and having an outer generally tubular structure formed by said first generally tubular portion and said second generally tubular portion, said outer generally tubular structure having an inner space with said leaflets disposed within said inner space of said outer generally tubular structure, and

said first sheet of biocompatible material and said second sheet of biocompatible material being disposed within said inner channel of said stent member.

28. (currently amended) The percutaneously implantable replacement heart valve device of claim 27, wherein said ~~first sheet portion and said second sheet portions are~~

~~affixed together by suturing.~~ collapsible and expandable valve is attached to said expandable stent member at one or more attachment points, and wherein said one or more attachment points consist of attachment points disposed on said outer generally tubular structure.

29. (currently amended) The percutaneously implantable replacement heart valve device of claim ~~28, wherein said suturing is in the form of double continuous sutures~~27, wherein said first sheet of biocompatible material and said second sheet of biocompatible material are disposed entirely within said inner channel of said stent member.

30. (currently amended) A percutaneously implantable replacement heart valve device comprising :

a sheet of ~~flexible, compressible biocompatible material folded to form a tubular cuff portion having an inner tubular space and folded further to form an inner peripheral upstanding cusp or leaflet portion~~biocompatible material forming a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material having a first border with a fold defining a cuff portion, and having a second border opposite to said first border with a second border fold and one or more additional folds oriented perpendicularly in relation to said second border fold defining a leaflet portion having one or more leaflets formed by one or more of said folds without requiring slits in said sheet of biocompatible material to form said one or more leaflets, and without requiring suturing of said one or more leaflets, said sheet of biocompatible material forming a generally tubular structure having an inner space with said leaflets disposed

within said inner ~~tubular~~ space of said generally tubular ~~cuff portion~~ structure, said ~~cusps~~/leaflets opening in response to blood flow through said ~~tubular~~ inner space of said generally tubular ~~cuff portion~~structure in one direction and closing in response to blood flow in ~~the~~an opposite direction.

31. (currently amended) The device of claim 30, wherein said leaflet portion comprises a separate sheet of said ~~compressible~~ biocompatible material including one or more additional ~~lengthwise~~ pleats through which said leaflet portion is attached to said ~~tubular~~ cuff portion.

32. (currently amended) The device of claim 30, ~~wherein said biocompatible material further includes a folded edge through which said material is attached to~~further comprising an expandable stent having an inner channel, ~~said attachment being made to~~and wherein said sheet of biocompatible material is disposed within said inner channel of said expandable stent ~~member by suturing, and wherein said sheet of biocompatible material further comprises one or more folds through which said sheet of biocompatible material is affixed to said expandable stent~~.

33. (currently amended) A percutaneously implantable replacement heart valve device comprising :

an expandable stent member having an inner ~~space and a flexible, compressible artificial valve made of biocompatible material and~~channel, and

a sheet of biocompatible material forming a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material being disposed within said inner ~~space of said stent member affixed at one or more points on said artificial valve's~~

~~outer surface to~~channel of said stent member, said ~~artificial valve comprising a~~ sheet of biocompatible material having a first ~~inward fold disposed~~border fold, one or more additional folds parallel to ~~an edge of~~ said ~~sheet~~first border fold and one or more ~~inward folds spaced along said sheet perpendicular to said first inward fold, the free edge of said first inward fold defining a peripheral upstanding~~folds oriented perpendicularly in relation to said first border fold to form a leaflet ~~or cusp~~ portion with leaflets without cutting of slits in said sheet of biocompatible material to form said ~~cusps or leaflets said sheet having two opposite ends perpendicular to said first inward fold, said opposite ends being joined to define a tubular portion~~leaflets, and without requiring suturing of said leaflets, said sheet of biocompatible material being formed into a tubular structure having an inner space within which said ~~cusp or leaflet portion is~~leaflets are disposed, said ~~folded cusps or~~ leaflets ~~causing said valve to open~~opening in response to blood flow toward said leaflets in one direction and ~~close~~closing in response to blood flow in ~~the~~an opposite direction.

34. (currently amended) A percutaneously implantable replacement heart valve device ~~comprising~~including:

an expandable stent member having an inner ~~space and a flexible, compressible artificial valve having a generally tubular portion and a peripheral upstanding cusp or leaflet portion disposed within said inner space of said stent member and affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising a continuous uncut, unslit sheet of biocompatible tissue material having an upper border with an outward fold, a lower border with an inward fold, a first edge and a second edge, said first edge and second edge being disposed perpendicular to said upper border and said lower border, said first edge and said second edge being folded inwardly in~~

~~relation to eachother and said inward folds of said first edge and said second edge being joined to form said~~channel, and

a sheet of biocompatible material forming a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material having an upper border fold, a lower border fold, and one or more folds oriented perpendicularly in relation to said upper border fold forming one or more cusps or leaflets without requiring suturing of said leaflets, said sheet of biocompatible material further having two opposite ends coupled to form a generally tubular portion having an inner space~~,~~ with said ~~inward folds being~~cusps or leaflets disposed within said inner space of said generally tubular portion ~~to form said peripheral upstanding cusp or leaflet portion~~, said cusps or leaflets being unslit, said sheet of biocompatible material being disposed within said inner channel of said stent member.

35. (currently amended) A percutaneously implantable replacement heart valve device comprising:

an expandable stent member having an inner ~~space~~channel, and

~~a flexible, compressible artificial valve disposed within said inner space of said stent member, affixed at one or more points on said artificial valve's outer surface to said stent member, comprising a first single continuous uncut, unslit sheet of biocompatible tissue material having an upper border, a lower border opposite and parallel to said upper border, an inner fold disposed at said lower border, and two opposite edges perpendicular to said upper border and said lower border and folded inwardly in relation to eachother with the edge of said inward folds of said two opposite edges joined to eachother, and a second sheet of biocompatible tissue material having an upper border with an outward fold~~

~~and a lower border opposite and parallel to said upper border, and having two opposite edges perpendicular to said upper border and said lower border and joined to eachother, said upper border of said first sheet joined to said lower border of said second sheet.~~

a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said collapsible and expandable valve comprising a first sheet of biocompatible material having an upper border defined by an upper border fold, a lower border and one or more additional folds positioned on said sheet of biocompatible material between said upper border and said lower border and oriented inwardly in relation to eachother, said upper border fold and said one or more additional folds forming one or more leaflets without cutting of slits to form said one or more leaflets and without requiring suturing of said one or more leaflets, said first sheet formed into a generally tubular portion having an inner space with said one or more leaflets disposed within said inner space, and a second sheet of biocompatible material formed into a second generally tubular portion having an inner space and a cuff defined by a fold, said first sheet of biocompatible material being affixed to said second sheet of biocompatible material to define a generally tubular structure having a border defined by said cuff, with said one or more leaflets disposed within said inner space of said generally tubular structure, said first sheet of biocompatible material and said second sheet of biocompatible material being disposed within said inner channel of said stent member.

36. (currently amended) A percutaneously implantable replacement heart valve device ~~comprising~~including:

an expandable stent member having an inner ~~space~~channel, and ~~a flexible, compressible artificial valve~~

~~disposed within said inner space of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising a generally tubular portion and a cusp or leaflet portion, said generally tubular portion and said cusp or leaflet portion comprising a single folded unslit sheet of~~ a sheet of biocompatible ~~tissue~~ material disposed within said inner channel of said stent member, said biocompatible material having two or more folds to define a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said folded sheet of biocompatible material having a generally tubular portion having an inner space and a cusp or leaflet portion with leaflets disposed within said inner space of said generally tubular portion, said leaflets being unslit and formed by one or more of said folds without requiring suturing of said leaflets and without requiring affixation of said leaflets.

37. (currently amended) A percutaneously implantable replacement heart valve device ~~comprising an expandable stent member having an inner space and a flexible, compressible artificial valve disposed within said inner space of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising a single sheet of biocompatible material having one or more folds defining one or more cusps or leaflets without slits cut into said material.~~including:

an expandable stent member having an inner channel, and

a sheet of biocompatible material forming a collapsible and expandable valve capable of being percutaneously and transluminally implantable via an endovascular

procedure, said sheet of biocompatible material having one or more inward horizontal folds and one or more inward vertical folds defining one or more unslit cusps or leaflets without requiring suturing of said leaflets, said leaflets opening in response to blood flow in one direction and closing in response to blood flow in an opposite direction, said sheet of biocompatible material formed into a generally tubular structure having an inner space with said leaflets disposed within said inner space of said generally tubular structure, said sheet of biocompatible material being positioned within said inner channel of said stent member.

38. (new) A percutaneously implantable replacement heart valve device comprising:

a sheet of biocompatible material forming a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material having one or more folds to form a cuff portion and being formed into generally tubular structure having an inner space, said sheet of biocompatible material having two or more additional folds forming a cusp or leaflet portion with unslit leaflets without requiring suturing of said leaflets or affixation of said leaflets, wherein said leaflets open in response to blood flow in one direction and close in response to blood flow in an opposite direction, and

an expandable stent having an inner channel, said sheet of biocompatible material being disposed within said inner channel of said stent.

39. (new) A percutaneously implantable replacement heart valve device including:

an expandable stent member having an inner channel, and

a sheet of biocompatible material forming a collapsible and expandable valve, said

collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material disposed within said inner channel of said stent member, said sheet of biocompatible material being formed into a generally tubular structure having a top end fold, a bottom end fold, and one or more additional folds positioned between said top end fold and said bottom end fold forming leaflets defined by folds without requiring cutting of slits into said sheet of biocompatible material to form said leaflets or requiring suturing of said leaflets.

40. (new) A percutaneously implantable replacement heart valve device comprising:

an expandable stent member having an inner channel, and

a sheet of biocompatible material forming a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material having a first border portion with one or more first border folds, one or more additional folds oriented perpendicularly in relation to said first border portion, said sheet of biocompatible material being further formed into a generally tubular structure having an inner space with one or more unslit leaflets defined by one or more of said folds without requiring suturing of said leaflets and without requiring affixation of said leaflets, said leaflets disposed within said inner space of said generally tubular structure, said sheet of biocompatible material being disposed within said inner channel of said expandable stent member.

41. (new) The percutaneously implantable replacement heart valve device of claim 40, further comprising a further fold defining a second border parallel to said one or more first border folds.

42. (new) A percutaneously implantable replacement heart valve device including:

an expandable stent member having an inner channel, and

a sheet of biocompatible material forming a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material disposed within said inner channel of said stent member, said sheet of biocompatible material having two or more folds defining one or more unslit leaflets without requiring suturing of said leaflets.

43. (new) A percutaneously implantable replacement heart valve device comprising:

an expandable stent member having an inner channel, and

a sheet of biocompatible material forming a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material having an upper border defined by a first fold having an outer end portion oriented inwardly in relation to said upper border, said outer end portion having a further fold, a lower border defined by a second fold, a right end, a left end, and one or more additional folds positioned between said right end and said left end, said right end and said left end coupled to form a generally tubular structure with an inner space having unslit leaflets disposed within said inner space of said generally tubular structure without requiring suturing of said leaflets, said sheet being disposed within said inner channel of said stent member.

44. (new) A percutaneously implantable replacement heart valve device comprising:

an expandable stent member having an inner channel, and

a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said collapsible

and expandable valve consisting essentially of biocompatible sheet material disposed within said inner channel of said stent member, said biocompatible sheet material formed into a tubular structure having one or more folds defining one or more unslit leaflets without requiring suturing of said leaflets or affixation of said leaflets, said leaflets opening in response to blood flow toward said leaflets in one direction and said leaflets closing by means consisting of blood flow in an opposite direction.

45. (new) A percutaneously implantable replacement heart valve device comprising:

an expandable stent member having an inner channel, and

a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said collapsible and expandable valve consisting of biocompatible sheet material disposed within said inner channel of said stent member, said biocompatible sheet material formed into a generally tubular structure having one or more folds defining one or more unslit leaflets without requiring suturing of the leaflets.

46. (new) A percutaneously implantable replacement heart valve device consisting essentially of:

an expandable stent member having an inner channel, and

biocompatible sheet material forming a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material disposed within said inner channel of said stent member, said biocompatible sheet material formed into a generally tubular structure with two or more folds defining one or more unslit leaflets without requiring suturing of said leaflets.

47. (new) A percutaneously implantable replacement heart valve device consisting of:

an expandable stent member having an inner channel, and

biocompatible sheet material forming a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material being disposed within said inner channel of said stent member, said biocompatible sheet material being formed into a generally tubular structure with two or more folds defining one or more unslit leaflets without requiring suturing of said leaflets.

48. (new) A percutaneously implantable replacement heart valve device comprising:

a sheet of biocompatible material having a first border portion with one or more first border folds, a second border opposite said first border portion defined by a second border fold, and one or more additional folds oriented perpendicularly in relation to said first border portion and having two opposite outer free ends, said opposite outer free ends being coupled to form a generally tubular structure having an inner space to define a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said collapsible and expandable valve having one or more unslit leaflets defined by one or more of said folds, said one or more leaflets disposed within said inner space of said generally tubular structure, said leaflets opening in response to blood flow toward said leaflets in one direction and closing in response to blood flow in an opposite direction, and

an expandable stent having an inner channel, said sheet of biocompatible material being disposed within said inner channel of said expandable stent.

49. (new) The device of claim 27, wherein said first sheet has one or more additional pleats through which said first sheet is attached to said second sheet.

50. (new) The percutaneously implantable replacement heart valve device of claims 1, 27, 30, 33, 34, 35, 36, 37, 38, 39, 40, 42, 43, 46, 47 or 48, wherein said biocompatible material is affixed to said stent member with affixation points on a single plane.

51. (new) The percutaneously implantable heart valve device of claims 27, 30, 33, 34, 35, 36, 37, 38, 39, 40, 42, 43, 46, 47 or 48, wherein said biocompatible material of said valve comprises a synthetic biocompatible material selected from the group consisting of: polytetrafluoroethylene, polyester, polyurethane, metal, metal alloy and metal foil, including combinations thereof.

52. (new) The percutaneously implantable replacement heart valve device of claims 1, 27, 30, 33, 34, 35, 36, 37, 38, 39, 40, 42, 43, 46, 47 or 48, wherein said biocompatible material is dried prior to folding and rehydrated after folding.

53. (new) The percutaneously implantable replacement heart valve device of claims 1, 27, 30, 33, 34, 35, 36, 37, 38, 39, 40, 42, 43, 46, 47 or 48, wherein said biocompatible material is further folded to form one or more attachment pleats.

54. (new) The percutaneously implantable replacement heart valve device of claims 1, 27, 30, 33, 34, 35, 36, 37, 38, 39, 40, 42, 43, 46, 47 or 48, wherein said inner channel of said stent member has no inward projections coupled to and supporting said valve leaflets.

55. (new) The percutaneously implantable replacement heart valve device of claims 1, 27, 30, 33, 34, 35, 36, 37, 38, 39, 40, 42, 43, 46, 47 or 48, wherein said biocompatible material is photomechanically compressed prior to folding.

56. (new) The percutaneously implantable replacement heart valve device of claim 1, wherein said sheet of biocompatible material is attached to said expandable stent member at one or more attachment points on said sheet of biocompatible material, said one or more attachment points consisting of attachment points disposed on said outer generally tubular portion.

Remarks

Claims 1-10 and 27-37 remain in the application. Please cancel claims 11-26. New claims 38-56 have been added, and claims 1-8, and 27-37 have been amended.

A. Discussion of Claim Amendments and New Claims.

Below is a summary of the claim amendments and new claims, providing references to the present application and/or the parent application supporting the amendments. Where similar amendments are made in multiple claims, the explanation of support is provided in the discussion of the claim where the amendment is first made, but is not repeated with respect to later claims to reduce redundancy.

Claim 1 has been amended to refer to state that the suturing of leaflets is not required, distinguishing from Garrison (US 6,425,916)("Garrison") which requires suturing of the leaflets (see sutures 110 and Fig. 35 of Garrison). Support for suturing of leaflets not being required is in paragraph [0024] of the present application and paragraphs [0024] and [0027] as well as Figs. 3A and 3B of the present application and the parent application, among other portions of said applications. Additionally, new claim 56 has been added which depends on claim 1 and refers to the sheet of biocompatible material forming the valve is attached to the stent at one or more attachment points on the sheet of biocompatible material, said attachment points consisting of points on the outer generally tubular portion of the folded sheet, distinguishing from Bailey (US 6,458,153) ("Bailey") which has the stent attached to the valve *at the leaflet portion* via the reinforcement struts that are coupled to or are encased in the valve flaps in Bailey. Support for claim 56 is in paragraph [0037], last sentence, of the present application, among other parts of the present and past application.

Claim 2 has been amended to eliminate the Markush group.

Claim 3-7 have been amended to remove unnecessary wording.

Claim 4 has been amended to refer to the sheet of biocompatible material forming the valve being disposed *entirely* within the inner channel of the stent, distinguishing from Bailey which requires graft/valve material to be at least partially covering the outer surface of the stent (See Bailey at Col. 9, lines 5-7: "The outer graft member 11a encloses at least a portion of the ablumenal surface of the intermediate annular section 20 of the stent body member"). Support for the valve/biocompatible material being disposed entirely within the stent is in Figs. 5 and 6 and paragraph [0037] of both the present application and the parent application, among other portions of said applications.

Claim 5 has been amended to refer to graft material. Support for said amendment is in paragraph [0046] of both the present application and the parent application.

Claim 8 has been amended to refer to polyurethane and metal foil as synthetic materials. Support for said amendment is in paragraph [0046] of the present application.

Claim 27 has been amended as with claim 1, to state that suturing of leaflets is not required, distinguishing from Garrison, and to add further detail regarding the two sheets and noting that both sheets are disposed within the inner channel of the stent, which is supported by paragraph [0047] of the present application among other portions of the application. If Bailey is interpreted has disclosing two sheets as indicated by the examiner in the last sentence of the first paragraph of page 6 of the office action (referring to seams 29 and col. 9, lines 48-52 of Bailey), the two sheets are the inner graft member 11b and the outer graft member 11a, and the outer graft member 11a is disposed on the ablumenal surface of the stent body member, i.e., not *within* the stent. Claim 27 has *both* sheets of biocompatible material disposed within the inner channel of the stent.

Claim 28, which depends on claim 27, has been amended to refer to the attachment of the valve to the stent being at attachment points consisting of points on the generally tubular structure, distinguishing from Bailey which has the stent attached to the leaflet portion via the reinforcement struts that are coupled to or are encased in the valve flaps in Bailey. Support for claim 28 as amended is in paragraph [0037], last sentence, of the present application, among other parts of the present and past application.

Claim 29, which depends on claim 27, has been amended to refer to the first sheet of biocompatible material and second sheet of biocompatible material forming the valve being disposed *entirely* within the inner channel of the stent, distinguishing from Bailey which requires graft/valve material to be at least partially covering the outer surface of the stent (See Bailey at Col. 9, lines 5-7 of Bailey: "The outer graft member 11a encloses at least a portion of the ablumenal surface of the intermediate annular section 20 of the stent body member"). Support for the valve/biocompatible material being disposed entirely within the stent is in Figs. 5 and 6 and paragraph [0037] of both the present application and the parent application, among other portions of said applications.

Claim 30 has been amended to state that suturing of leaflets is not required, distinguishing from Garrison, and to add further detail regarding the position of folds to distinguish from Bailey and adding "unslit" to distinguish from Bessler (5,855,601) ("Bessler"). Support for the claim amendments relating to folds is included at paragraph [0047] of the present application and the figures referred to therein, among other portions of the application.

Claim 31 has been amended to eliminate unnecessary wording and to conform to revisions to Claim 30.

Claim 32 has been amended to add the stent element and refer to the sheet of biocompatible material being disposed within the stent. Reference is also made to one or more folds for affixing the valve to the stent, which is supported by paragraph [0053] of the present application and paragraph [0052] of the parent application among other portions of said applications.

Claim 33 has been amended to add further detail regarding the position of folds to distinguish from Bailey and Garrison. Support for the claim amendments relating to folds is included at Figs. 9A, 9B and 9C and paragraphs [0047] and [0053] of the present application among other portions of the application.

Claims 34 has been amended to replace "comprising" with "including" after the preamble per current MPEP interpretation of said term and to add further detail regarding the position of folds. Support for the claim amendments relating to folds is included at Figs. 9A, 9B and 9C and paragraphs [0047] and [0053] of the present application among other portions of the application.

Claim 35 has been amended to add further detail regarding the position of the folds. Support for the claim amendments relating to folds is included at Figs. 9A, 9B and 9C and paragraphs [0047] and [0053] of the present application among other portions of the application. Claim 35 also refers to a first sheet of biocompatible material and a second sheet of biocompatible materials, both of which are disposed within the stent.

Claim 36 has been amended to replace "comprising" with "including" after the preamble per current MPEP interpretation of said term and to state that suturing of leaflets is not required to distinguish from Garrison, and to state that affixation of leaflets is not required. Support for same is at paragraph [0024] of the present application, among other parts of the present application and prior application.

Claim 37 has been amended to replace "comprising" with "including" after the preamble per current MPEP interpretation of said term and to state that suturing of leaflets is not required to distinguish from Garrison, also stating that affixation of leaflets is not required and that the leaflets open in response to blood flow in one direction and close in response to blood flow in an opposite direction. Support for the opening and closing of the leaflets in response to blood flow is provided in paragraph [0024] of the present application and the parent application, among other parts of said applications.

Claim 38 is a new claim referring to the valve having at least two or more folds forming a leaflet portion without slits or sutures on the leaflets and where leaflets open in response to blood flow in one direction and close in response to blood flow in an opposite direction. Support for the claim amendments relating to folds is included at Figs. 9A, 9B and 9C and paragraphs [0047] and [0053] of the present application among other portions of the application.

Claim 39 is a new claim using "including" after the preamble, per current MPEP interpretation of said term and referring to positions of folds. Support for the claim amendments relating to folds is included at Figs. 9A, 9B and 9C and paragraphs [0047] and [0053] of the present application among other portions of the application.

Claims 40 and 41 are new claims detailing the position of folds and also refer to the suturing of leaflets or affixation of leaflets not being required. Support for the claim amendments relating to folds is included at Figs. 9A, 9B and 9C and paragraphs [0047] and [0053] of the present application among other portions of the application and support for suturing or affixation of leaflets not being required is at paragraph [0024] of the present application among other portions of the application.

Claim 42 is a new claim a new claim using "including" after the preamble, per current MPEP interpretation of said term, referring to one or more folds defining unslit leaflets which distinguishes from Bailey, and stating that suturing of leaflets is not required, which distinguishes from Garrison.

Claim 43 is a new claim detailing the position of folds. Support for the claim amendments relating to folds is included at Figs. 9A, 9B and 9C and paragraphs [0047] and [0053] of the present application among other portions of the application.

Claim 44 is a new claim referring to the valve as "consisting essentially of" a sheet of biocompatible material having folds defining unslit leaflets without requiring suturing of leaflets and referring to the closing by means *consisting of* blood flow in an opposite direction, which distinguishes from Bailey which has valve arms/reinforcement struts biasing the leaflets closed.

Claim 45 is a new claim referring to the valve "consisting of" a sheet of biocompatible material having folds defining unslit leaflets without requiring suturing of leaflets.

Claim 46 is a new claim using "consisting essentially of" after the preamble and referring to two or more folds defining unslit leaflets without requiring suturing of leaflets.

Claim 47 is a new claim using "consisting of" after the preamble.

Claim 48 is a new claim with further detail regarding the position of folds. Support for the claim amendments relating to folds is included at Figs. 9A, 9B and 9C and paragraphs [0047] and [0053] of the present application among other portions of the application.

Claims 50-55 are multiple dependent claims. Claim 50 adds the element of affixation to the stent with affixation points on a single plane, which is supported by paragraph [0053] of the present application and paragraph [0052] of the parent application; Claim 51 adds specific types of synthetic biocompatible material; Claim 52 adds the element of the biocompatible material

being dried prior to folding and being rehydrated after folding, which further helps impart the leaflet structure without suturing or slits, which is supported by paragraph [0051] of the present application and [0050]of the parent application; Claim 53 which refers to attachment pleats, which is supported by paragraph [0050] of the present application; and Claim 54 which refers to the stent having no inward projections supporting the valve leaflets, which is supported by Fig. 5 of both the present application and the parent application. Claim 55 refers to the biocompatible material being photomechanically compressed prior to folding, which affects structure by producing protein coagulation to make the material surface smoother, stronger more homogeneous and more biocompatible. Claim 55 is supported by [0049] of the present application.

Additionally, independent claims 1, 27, 30, 33-40 and 42-48 have been amended to state that the valve is collapsible and expandable and is capable of being percutaneously and transluminally implantable via an endovascular procedure. Support for same is provided at paragraphs [0058]-[0064] of the present application among other portions of the present application and the prior application.

B. Interview.

The undersigned thanks the examiner for the telephonic interview held on June 9, 2009. A summary of the interview between the undersigned and the examiner held telephonically on June 9, 2009 is provided as Appendix A to this Response.

C. Discussion of Office Action.

The Applicants have noted the examiner's Section 112, 102(b), 102(e) and 103 rejections of the claims and respectfully request reconsideration and withdrawal of said rejections based on the claim amendments and remarks contained in this response as well as the Applicant's

previously submitted Declaration under 37 CFR §1.131 and Supplemental Declaration under 37 CFR §1.131 and supporting witness affidavits enclosed with this response antedating Bailey (U.S. Patent Nos. 6,652,578B2 and 6,458,153B1).

(i) Priority with Respect to "Unslit" Valve Leaflets.

The Applicant respectfully requests that the examiner reconsider the position taken that the subject matter consisting of the valve body being unslit or uncut is new to the current application and was not part of the parent application. Paragraph [0023] of the specification in the Applicant's parent application Serial No. 10/037,266 notes in the last sentence as one of the flaws of prior tissue valves the fact that "most are constructed by cutting or suturing the tissue material, resulting in leaflets that do not duplicate the form and function of a real valve." The parent application discusses the valve material being unslit at paragraph [0027] ("the *folding* of the pericardium material to create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of valve leaflets. . . present invention also greatly reduces the risk of tearing of the cusps or leaflets, since they are integral to the valve rather than being attached by suturing."). Paragraphs [0024] and [0047] of the parent application reiterate that "[t]he cusp or leaflet portion of the valve means is formed *by folding* of the pericardium material used to create the valve . . . The *folded* design provides a number of advantages over prior designs, including improved resistance to tearing at suture lines." Suturing, sometimes combined with cloth reinforcement, is often required to help prevent tearing when leaflets are formed by slitting. Paragraph [0049] of the parent application, which discusses how the valve is made, states: "The valve is formed by taking a rectangular fragment of bovine pericardium and *folding* it in such a way that forms a three-leaflet or desired number of leaflet valve as shown in Figs. 3A and 3B. The *folding* of the pericardium material to create the cusps

or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of the valve leaflets. It also greatly reduces the risk of tearing of the cusps or leaflets, since they are integral to the valve rather than being attached by suturing." Figures 3A and 3B of the parent application also show the folding of the material, the material being unslit and without affixing of separate cusps or leaflets. Figure 3A clearly shows a sheet of material that has no slits. As shown in Figure 3A, the sheet is folded and then as shown in Figure 3B, the ends of the folded sheet are folded further to form the valve with cusps or leaflets resulting from the folds. There are only two possibilities: slit or unslit, and there is no support for slitting. If slitting was part of the Applicant's invention it would have had to have been disclosed to satisfy the written description, enablement and best mode requirements, as cutting or slitting require action to be taken on a structure and in fact, slitting would defeat the patentable improvements benefit of the Applicant's invention.

The examiner states that it is unclear whether the leaflets have slits or cuts as the leaflets appear to have an arcuate shape in Fig. 1, 2 and 3B. However, Fig. 3A clearly shows folding without any slitting or cutting, and the description of Fig. 3A in the description of the figures makes clear that Fig. 3A depicts the procedure for *folding the pericardium tissue starting material to create the replacement heart valve.* Fig. 3B has the same description and clearly shows folding, without any cutting of slits. The arcuate shape at the end is from the joining the ends of the sheet after folding, to form a tubular structure, not from slitting. The arcuate shape depicts the resulting three leaflets coapting naturally against eachother due to the folds shown by the dotted lines in Figure 3B followed by the joining of the resulting edges of the material together to form the tubular structure. In fact, the reason why the shape is arcuate is *because* of the folds without slits. If there were slits in the material the leaflets would not coapt properly

when the edges of the folded material are joined to form the tubular structure. It is respectfully submitted that the interpretation that unslit leaflets are not supported by the original application where there is absolutely no mention of any embodiment involving slitting, when the figures show unslit material and where the novel folding technique is expressly stated to be for the purpose of overcoming the flaws of past valves that include slit and/or sutured leaflets is an unreasonable interpretation.

(ii) Declaration under 37 C.F.R. Section 1.131.

Regarding the prior Declaration under 37 C.F.R. Section 1.131 that was submitted to antedate the Bailey U.S. Patent No. 6,652,578 date of December 31, 1999, which is the same date as applicable with respect to the Bailey 6,458,153 patent, the Applicant respectfully submits that the prior Declaration submitted with the response dated December 15, 2008, together with its supporting exhibits, which included a paper model of the folded, unslit valve that was included as Exhibit B and a stent/valve combination model that was included as Exhibit C, both of which are already on file and stored at the Patent Office, as well as the sketches provided as Exhibit D, each dating back prior to December 31, 1999 as declared by the co-inventors under penalty of perjury in paragraph 4 of the Declaration, clearly show that the inventors had already conceived and commenced efforts to reduce to practice the folded design of the valve with unslit leaflets, having inner and outer folds. Additionally, enclosed as Appendix B with this response is a Supplemental Declaration pursuant to 37 CFR Section 1.131 to antedate Bailey, including additional evidence in the form of two supporting witness affidavits, each from a very experienced, knowledgeable and renown medical doctor practicing in the field of cardiology who witnessed the invention prior to December 31, 1999 attesting to the valve having a folded design with cusps or leaflets formed by folding of the valve material rather than by cutting slits in the

valve material. The Affidavit of Dr. Lamas further notes that the valve had a tubular form with a fold at one end and one or more folds disposed inwardly in relation to the valve's interior space to form cusps or leaflets at or near the opposite end. Under MPEP Section 715.07(I)(F), support for a declaration may be provided in the form of supporting statements of witnesses. The two witness statements provide corroborating evidence of the invention by the Applicants prior to the Bailey filing date. As such, the Applicant respectfully submits that the previously submitted Declaration either alone or in combination with the enclosed Supplemental Declaration should be accepted as sufficient to demonstrate that prior to December 31, 1999, the inventors had conceived of and commenced efforts to reduce to practice their invention comprising the folded unslit valve device, and Applicant respectfully requests that the Examiner withdraw the rejections based on Bailey.

(iii) Section 112 First Paragraph Rejection of Claim 35.

Claim 35 has been amended to address the examiner's Section 112 first paragraph rejection.

(iv) Section 102 (b) and/or (e) Rejections of Claims 1, 2, 7-10, 27-28, 30-34 and 36-37.

With respect to claims 1, 2, 7-10, 27-28, 30-34 and 36-37, rejected by examiner based on Bailey (U.S. 6,458,153) ("Bailey"), reconsideration and withdrawal of said rejections is respectfully requested and it is respectfully submitted that contrary to the examiner's interpretation of Bailey, as stated at lines 11-13 of page 6 of the office action and at lines 7-8 of page 7 of the office action, that "Bailey discloses the sheet of tissue (11b) having an upper border (top of device in fig. 4) with an outward fold (material 11b is folded outwardly at 11a; col. 9, lines 20-24)," there is no such outward fold. The stent 12 is between 11b and 11a and 11b does

not fold over. The inner and outer graft material 11a and 11b in Bailey are described as being two separate sections of graft material, 11a being outside the stent and 11b being inside the stent, with 11a and 11b being connected to each other "through the interstices of the stent body member" (see col. 8, lines 16-19 of Bailey). The material 11b is not folded outwardly at 11a in Bailey, and there is no support for such a fold either in the text or the figures in Bailey. Additionally, with respect to the examiner's reference in the office action to Bailey disclosing folds at 27 and 29, it is respectfully submitted that 29 in Bailey refers to seams, not folds. See col. 9, lines 48-52, which states: "It is preferable to couple sections of the valve flaps 28, along *a longitudinal seam 29*, to the inner graft member 11b and the outer graft member 11a at points equidistant from the valve arms 24 in order to impart a more cusp-like structure to the valve flaps." Seams are where edges abut each other-they are not folds. With respect to 27 in Bailey, it is described in col. 9, lines 16-20 as "a pocket or envelope 27" "formed at the eversion point of the inner graft member 11b." It is not a fold. It is at most the pocket formed by the back or inner side of the "eversion point" interpreted by the examiner to constitute a fold in Bailey, if the "everted" 11b is considered to be a fold. Even if 27 in Bailey is interpreted as being a fold, it is a single fold. The Applicant's claims 27, 30, 33, 34, 35, 38, 39, 40, 42, 43, 46, 47 and 48 refer to a folded design having more than one fold. As such, it is respectfully submitted that the Applicant's claims as amended are not anticipated by Bailey.

Bailey uses graft material which covers at least a portion of either or both of the luminal and ablumenal surfaces of the stent and encapsulates valve arms/reinforcing struts that bias the leaflets. Graft material that is capable of endothelialization is required in Bailey because the stent does not function merely to maintain a semi-rigid patent channel at the implantation site. The valve leaflets are formed by sections of the graft material that are attached to the stent body

member. By contrast, as discussed below, the valve leaflets in the present invention are formed by portions of the sheet of biocompatible material that are disposed within the inner space of the generally tubular structure and that portion is not attached to the stent, as per new claim 56 and amended claim 28. Additionally, the leaflets in the Applicant's invention are not biased with reinforcement struts, but instead open and, in particular, *close*, based on blood flow. The closing function in Bailey is clearly based on biasing from the struts, as the leaflets are closed under zero strain and are already closed during diastole, as discussed below.

As shown in Figure 4 in Bailey, the valve arms 24 force the valve leaflets 28 to collapse into the center of the lumen of the stent valve 10, biasing the valve to its closed position. The flow regulator struts in Bailey are thus connected to or are part of the stent itself at one end, and are either coupled to or are encapsulated by the valve outer membrane and inner leaflet membrane and are responsible for both providing support to the valve leaflets and opening and closing of the valve leaflets. The stent's reinforcement struts are therefore an inner support to the valve leaflets and being encapsulated by graft material, actually form part of the leaflets. The stent in Bailey is not merely an outer support to maintain a semi-rigid patent channel at the implantation site as in the present invention, which has a stent with no inward projections supporting the leaflets.

In Bailey the stent functions as the valve body and the valve arms/reinforcing struts extending from the stent and encapsulated by the graft material to control the opening and closing of the valve. The graft material inside and outside of the stent fuses together to encapsulate the stent and the outer material fuses to the tissue where the stented valve is implanted. The inner and outer graft members are coupled to each other <u>through</u> the stent. See Bailey at Column 9, lines 12-19: "the graft member 11 consists of an outer or ablumenal graft

member 11a and an inner or lumenal graft member 11b. The outer graft member 11a *encloses at least a portion of the ablumenal surface of the intermediate annular section of the stent body member, while the inner graft member 11b is coupled, on the lumenal surface of the intermediate annular section of the stent body member 12, to the outer graft member 11a through the interstices 14 of the stent body member.*" (emphasis added). All embodiments of Bailey require graft member material on the outer surface of the stent, none have the complete valve entirely within the stent. While Bailey discloses that the graft material can be *attached* to the stent at its inner or outer surface or both, the graft material *covers* the inner and outer surface of the stent in all embodiments of Bailey. See col. 5, lines 45-47, col. 10 lines 55-58 and col. 11, lines 45-48 of Bailey (all have inner and outer graft members, which part of the biocompatible material valve elements) (see also col. 9, lines 52-55 of Bailey 6,458,153 stating that "it should be appreciated that graft member 11 should *cov*er at *least a portion of the ablumenal surface of the stent body member* . . . ").

The Applicant's invention, by contrast, does not have valve material on both sides of the stent to encapsulate the stent and does not have valve arms/reinforcing struts supporting the leaflets or biasing the leaflets to open and close. Instead, the sheet of biocompatible material forming the valve in the Applicant's invention is mounted within the stent and the leaflets open *and close* solely in response to directional blood flow. Claims 4 and 29 specifically refer to the biocompatible material being disposed *entirely* within the stent member, and claims 27 and 35, which refer to a valve made of two sheets of biocompatible material, *both* sheets are disposed within the stent. In Bailey the biocompatible material is at least partially outside the stent in all embodiments and if Bailey is interpreted as having two sheets, 11a and 11b, both are *not* disposed within the stent. Only one is.

The Applicant respectfully submits that the invention as claimed in the claims as amended is not anticipated or rendered obvious by Bailey. Bailey at most has one fold forming leaflets because it is not a folded design. It is a design using inner and outer grafts with a stent sandwiched between the two graft portions, one which is affixed to the *inner surface* of the stent and the other affixed to the *outer surface* of the stent. It is not a folded sheet of material. The valve material in the Applicant's invention is disposed entirely within the inner channel of the stent-there is no encapsulation of the stent between inner and outer graft members as in Bailey.

By having the valve material the inner surface and outer surface of the stent, the device disclosed in Bailey is more complicated in design and manufacture, since the stent and the valve must be connected to each other during creation of the valve portion (the valve material being partially inside and partially outside the stent and connected through the stent), whereas the Applicant's device allows for the valve to be created at one point in time and be coupled to the stent at a later point in time, also allowing for a variety of both valve materials and stent materials to be used.

With respect to claim 27, Bailey does not teach a compressible valve made from two sheets of biocompatible material, one sheet being folded to form a tubular structure with folded leaflets, and a second sheet being folded to form a tubular structure with a folded border defining a cuff, with the two sheets being affixed to have the leaflet layer within the outer cuff layer, with both sheets being disposed within the stent. As explained above, there is no border fold on the second border in Bailey, and if there are two sheets in Bailey, they are not both disposed within the stent.

Additionally, with respect to Applicant's amended claim 30, Bailey does not disclose a cuff fold at one end and a fold at an opposite end and one or more folds oriented perpendicularly in relation to the end folds.

Additionally, with respect to amended claim 28 and new claim 56, Bailey includes as an essential element a stent/valve that has "valve arms" or "regulator struts" that support the valve leaflet material and which control the opening and closing of the valve leaflets in Bailey, forcing separate valve flaps closed by applying a biasing force. (See Column 5, lines 61-63: "The stent body member is shaped to include the following stent sections: proximal and distal anchors, a [sic] intermediate annular section *and at least one valve arm or blood flow regulator struts*." (emphasis added)). Column 9, lines 7-10, referring to Figure 2 of Bailey, discloses a "valve body 26 and valve arms or flow regulator struts 24 coupled to the stent body member 12." The "*valve arms or regulator struts are coupled or formed integral with the stent body member* and are positioned adjacent the junction point between intermediate annular section and the proximal anchor flange 22 of the stent body member 12. The valve arms 24 are oriented radially inward toward the central longitudinal axis of stent body member 12 when in their zero strain state. The valve arms 24 are *attached or coupled* to *the valve flap portions 28 of the inner graft member leaflets* to bias the valve flap portions 28 to the closed position when under zero pressure differential across the stent valve 10." Bailey, Column 9 at lines 32-42 (emphasis added). Column 5, lines 58-60 in Bailey note that "the valve leaflets are preferably *formed* by sections of the graft material *attached to the stent body member.*" Column 6 lines 20-39 of Bailey further state that the valve arms are *"biased closed in a manner to that described for a surgically implanted replacement heart valve by Boretos, U.S. Pat No. 4,222,126.*" The valve regulator-struts are preferably configured to be positioned to radiate inward from the stent body

member toward the central longitudinal axis of the prosthesis . . . *The struts of the stent are encapsulated by the outer graft membrane. The valve regulator struts are encapsulated by the inner leaflet membrane and serve to bias the valve to the closed position*. The regulator struts also prevent inversion or prolapse *of the otherwise unsupported leaflet membrane* during increased supra-valvular pressure." (emphasis added). The reference made in Bailey to Boretos U.S. Patent No. 4,222,126 makes it further clear that in Bailey the regulator struts support the valve flaps and mechanically bias them.

By contrast the Applicant's invention as claimed in amended claim 28 and claim 56 has the stent attached to the valve only at the generally tubular portion, *not* at the leaflet portion. Additionally, as per claim 54, the Applicant's invention has folds forming leaflets without inward projections from the stent supporting the valve leaflets (as per new claim 54), and as claimed in claims 30, 33, 38 and 48, has leaflets opening in response to directional blood flow rather than by mechanical biasing, opening in response to blood flow in one direction *and closing* in response to blood flow in an opposite direction. The examiner asserts that the leaflets in Bailey help regulate blood flow in addition to the valve arms/reinforcing struts. While the valve flaps may help regulate blood flow because they are present and may form part of the valve mechanism, that is not the same as stating that the valve flaps themselves open in response to blood flow in one direction *and close* in response to blood flow in the other direction. They don't. They open and close in response to biasing by the valve arms/reinforcement struts. Bailey states that the valve arms/reinforcing struts bias the valve flaps closed under a zero strain load- this indicates that it is the mechanical biasing and *not* directional blood flow that closes the leaflets in Bailey. See, e.g., Bailey, col. 9, lines 31-34, col. 9, lines 36-47, and col. 11, lines 5-7. See also Column 10, lines 41-42 of Bailey, which state that during diastole, the valve leaflets are

already closed due to the reinforcement struts biasing the valve flaps closed. The negative pressure head of the diastole pushes against the closed leaflets, but the leaflets are already closed due to the biasing force of the reinforcement struts/valve arms in Bailey.

By contrast, in the Applicant's valve the leaflets open in response to blood flow in one direction and close in response to blood flow in an opposite direction without biasing, support or reinforcement of struts extending from the stent. The Applicant's invention does not include "valve arms" or "regulator struts" whether as part of the stent or as part of the valve. The Applicant's valve with folded cusps and leaflets provides more natural functioning, less susceptability to tearing and allows for effective opening and closing of the valve without the regulator struts required in Bailey to support and bias the flaps. The folded design claimed in the present application does not require struts that are affixed to the valve by suturing or encapsulation in the valve material for valve leaflet material support or valve opening and closing. It is precisely such suturing or encapsulation that the Applicant's folded design is intended to eliminate, resulting in less susceptibility to suture failure and/or tearing of the valve material. The valve in Bailey does not function to control blood flow without the valve regulator struts.

With respect to examiner's Section 102(b) rejection of claims 1, 2, 7, 9-10, 27, 30, 36 and 37 based on Garrison et al. (6,425,916), Garrison requires suturing of the leaflets: multiple sutures are made into the leaflets and the sutures are then pulled after deployment to invert the valve within the patient which can result in tearing of leaflets. The Applicant's invention uses a folded design that does not require any suturing of leaflets, much less pulling the valve to invert it after deployment in a patient. Additionally, in Garrison, the 6d valve portion that the examiner is interpreting as folded leaflets are externally exposed, whereas the present invention has leaflets

disposed within the inner space of the generally tubular valve body structure. The claims as amended include detail regarding the position of folds not disclosed in Garrison.

With respect to the rejection of claims 30 and 32 based on Bessler (U.S. 5,855,601), the claims as amended are not anticipated by Bessler. Bessler has slit leaflets and the stent is disposed on the inner side of the valve material, whereas the Applicant's invention has unslit leaflets and the stent is outside the valve material.

In view of the enclosed claim amendments, new claims and the foregoing remarks, the Applicant respectfully requests withdrawal of the examiner rejections and allowance of all claims in the present case. Nonetheless, should the examiner have any comments, questions or suggestions, the examiner is respectfully requested to telephone the undersigned at the telephone number listed below.

Respectfully submitted,

Date: September 14, 2009

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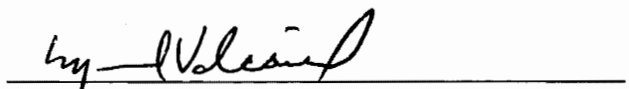

Manuel R. Valcarcel, Esq.
Reg. No. 41,360

APPENDIX A

INTERVIEW SUMMARY

Interview held telephonically on June 9, 2009 between examiner Cheryl Miller and attorney Manuel Valcarcel.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments:

Attorney for applicant argued that support for unslit valve material/unslit leaflets is provided in the parent application, including, but not limited to, in Figure 3A which depicts a sheet free of slits and Figure 3B which depicts folds, not slits. The arcuate shape shown in Fig. 3B was noted as not being the result of any slits, but rather the result of the joining the ends of the material to form a tubular structure which causes the material to appear arcuate. The applicants indicated they would respond with further explanation and references to the parent application which will be evaluated in more detail at that time. The examiner indicated she would consult with another examiner to get a second opinion. Applicant further noted that the previously submitted declaration clearly states in paragraph 4 and supporting exhibits that the folded unslit design for the valve was conceived prior to 12/31/99. A couple of prototypes were submitted as Exhibits B and C, which are not in the electronic file and the examiner will have to search for the location of the prototypes. The applicant argued that Bailey shows a valve material outside the stent, and that Garrison requires suturing of the valve leaflets and inversion of the leaflets when being implanted. Variations in claim wording such as use of "consisting essentially of" and "consisting of" for elements or after the preamble were discussed. Language such as "including" following the preamble, and the sheet of biocompatible material or valve, "disposed entirely within the inner space of the stent" was discussed which the examiner indicated potentially could overcome the Bailey rejections. Language such as "without suturing" the leaflets was discussed with regards to the Garrison reference. Applicant plans to file an official response which will be considered in more detail at that point in time. Adding reference to unslit leaflets in the claims rejected based on Bessler was also discussed as potentially overcoming Bessler. The examiner noted that the applicant may also want to consider claiming the location of the folds, or the inner and outer cuff or entire sheet positioned interior of the stent.

APPENDIX B

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

In the application of:)
)
Paniagua, et al.) Group Art Unit 3738
Serial No. 10/887,688)
Filed: 7/10/2004) Examiner: Miller, Cheryl L.
)

For: Percutaneously Implantable Replacement Heart Valve Device and Method of Making Same

DECLARATION UNDER 37 CFR 1.131

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia

Sir:

The undersigned co-inventors each hereby declare as follows:

1. I am a co-inventor of the invention claimed in the patent application identified above.

2. I was directly and personally involved in the conception and reduction to practice of the invention throughout the period from prior to December 31, 1999 until the filing date of U.S. Patent Application Serial No. 10/037,266 on January 4, 2002, of which the present application is a continuation in part.

3. Prior to December 31, 1999, the percutaneously implantable replacement heart valve device and method of making same described and claimed in the above-referenced application had been conceived by co-inventors David Paniagua and Francisco-Lopez Jimenez who were at the time cardiology fellows at Mount Sinai Medical Center in Miami Beach, Florida. Attached as Exhibit A is a copy of an electronic diary that was kept with respect to development of the invention by co-inventor Paniagua, with entries dating back to prior to December 31, 1999 indicating that the Applicants had by then already conceived of the invention. The dates for certain of the entries are blacked out but predate December 31, 1999.

4. Prior to December 31, 1999, co-inventors Eduardo Induni and David Paniagua conceived of the folded design of the valve means and the method of folding an unslit sheet of valve material to create a valve with cusps that are created by the folds without suturing separate leaflets or cutting of slits to create leaflets. Enclosed as Exhibit B is a replica of one of the co-inventors' initial paper models of the valve means created prior to December 31, 1999, showing a single piece folded design. Additionally, enclosed as Exhibit C is replica of one of the co-inventors' initial prototypes which was created prior to December 31, 1999, which includes the valve means with the folded design mounted in a stent. The original prototypes and related notes

from dating back prior to December 31, 1999 were lost when co-inventor Paniagua relocated from Miami to Houston and/or during Hurricane Ike. However, attached as Exhibit D are copies of sketches that were created prior to December 31, 1999 which show the co-inventors had already conceived of their folded sheet valve design, including valve cusps and leaflets formed by folding rather than by slitting material or affixing separate cusps or leaflets.

5. During the time period from prior to December 31, 1999 through January 4, 2002, the first prototypes and the method of making same of the invention were created and tested. As indicated in Exhibit A, during the time period from September 1999 through December 1999, anatomical studies were done with respect to porcine aortic and pulmonary valves as well as the aortic arch, including measurements of valve length, cusp length, vertical diameters, attachment points, interaction with other cusps, interaction with the Sino tubular junction and coronary ostium and observation of characteristics of the opening and closing, redundancy of tissue and sinus of Valsalva measurements and the initial prototypes were studied and tested. Durability and fatigue studies were conducted with regard to the valve material and folded design during the months prior to December 31, 1999. A protocol for in-vitro testing was written by Co-Inventor Paniagua in the early months of 2000. The in-vitro model consisted of a plastic hose tubing filled with a 30% solution of glycerol to resemble blood viscosity, a continuous pump, pressure recording instruments and pressure generating clamps. The study indicated excellent opening and closing profiles of the valve with no evidence of regurgitation even at pressures of 200 mmHg.

6. During the time period from prior to December 31, 1999 through January 4, 2002, which is the filing date of Patent Application Serial No. 10/037,266, to which the above-referenced application is a continuation in part and claims priority, we also worked with diligence toward reduction to practice of the invention by preparing a written description of the invention (see copy of a later draft dated April 22, 2001, attached hereto as Exhibit E).

7. During the time period from prior to December 31, 1999 through January 4, 2002, we also worked with diligence toward reduction to practice of the invention by conducting various tests and trials relating to preparation of the valve starting material, formation of the valve, optimal stent composition and configuration, attachment of the valve to the stent and attachment of the stented valve to an artery. See the attached entries from the electronic diary attached hereto as Exhibit A, which include entries relating to tests regarding preparation of the valve starting materials and formation of the valve in October, November and December 2000 and January, February, March, and June 2001. See also the attached entries from the electronic diary attached hereto as Exhibit A, which include entries pertaining to animal studies in June, September and November 2000 and April, 2001.

8. In August 2001, patent counsel was engaged to conduct a patent search directed to the invention and prepare and file a patent application for same. Enclosed as Exhibit F are copies of a search patent request letter dated August 29, 2001 which was sent to order a patent search for the invention, the invention being described in the letter. Said request letter was received by the patent search provider on August 30, 2001 as evidenced by the stamped confirmation of receipt attached to Exhibit G.

9. The patent search results were received on or about mid-September, 2001 and were reviewed by patent counsel, as well as by the undersigned, in the weeks that followed (bearing in mind that during such time period there were various office closures and disruptions due to the September 11, 2001 terrorist attacks and their immediate aftermath).

10. After the patent search results were reviewed and discussed with patent counsel, the patent application was prepared, reviewed, revised, figures for the application were prepared, and the application and figures were submitted on January 4, 2002. Attached as Exhibit H are copies of correspondence from patent counsel enclosing drafts of the patent application for the invention dated November 27, 2001 and December 28, 2001.

The undersigned co-inventors each hereby declare that all statements made herein of his own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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DAVID PANIAGUA

Signature: _____

Date: October 11, 2008

ACKNOWLEDGEMENT

COUNTY OF Harris)
) SS:
STATE OF Texas)

The foregoing Declaration was signed before me this 11 day of October, 2008 by David Paniagua. He is personally known to me or has produced _____ as identification.

Notary: _____
Print Name: ROSIE HIDALGO

[NOTARIAL SEAL]
Notary Public, _____

ROSIE HIDALGO
MY COMMISSION EXPIRES
AUGUST 18, 2009

My commission expires: 8/18/09

FRANCISCO LOPEZ-JIMENEZ

Signature: 

Date: October 10, 2008

ACKNOWLEDGEMENT

COUNTY OF Olmsted)
) SS: 016 78 3147
STATE OF MN)

The foregoing Declaration was signed before me this 10th day of October, 2008 by Francisco Lopez-Jimenez. He is personally known to me or has produced _____ as identification.

Notary: Vicki Virginia Yount
Print Name: Vicki Virginia Yount

[NOTARIAL SEAL]
Notary Public, _____

VICKI VIRGINIA YOUNT
Notary Public-Minnesota
My Commission Expires Jan 31, 2010

My commission expires: January 31, 2010

R. DAVID FISH

Signature: R. David Fish

Date: October 13, 2008

ACKNOWLEDGEMENT

COUNTY OF Harris)
) SS:
STATE OF Texas)

The foregoing Declaration was signed before me this 13th day of October, 2008 by R. David Fish. He is personally known to me or has produced _____ as identification.

Notary: Mary R. Jones [NOTARIAL SEAL]
Print Name: Mary R. Jones Notary Public, 10-13-08

My commission expires: 8-27-10

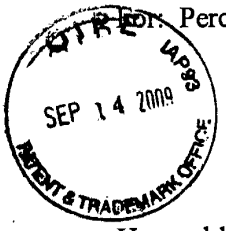
MIA 180,228,061v1

MARY R. JONES
NOTARY PUBLIC
STATE OF TEXAS
MY COMM. EXP. 8-27-10

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

In re the application of:	)	
	)	
Paniagua, et al.	)	Group Art Unit 3738
Serial No. 10/887,688	)	
Filed: 7/10/2004	)	Examiner: Miller, Cheryl L.
	)	

For: Percutaneously Implantable Replacement Heart Valve Device and Method of Making Same



SUPPLEMENTAL DECLARATION UNDER 37 CFR 1.131

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

The undersigned co-inventors each hereby declare as follows:

1. I am a co-inventor of the invention claimed in the patent application identified above.

2. This Supplemental Declaration supplements the prior Declaration Under 37 CFR 1.131 and the supporting evidence submitted as Exhibits A-H thereto filed on December 15, 2008 in the above-referenced application, a copy of which is attached hereto as Appendix A (the "Prior Declaration"), providing additional supporting evidence with respect to conception of the invention claimed in the above-identified patent application prior to December 31, 1999.

3. The events referenced herein and in the Prior Declaration took place in the United States, or a NAFTA country other than the United States or a WTO member country other than a NAFTA country.

4. Prior to December 31, 1999, the undersigned co-inventors conceived the invention claimed in the above-referenced application, more particularly, an unslit sheet of biocompatible material with folds to create a valve with unslit cusps or leaflets formed by folds

without suturing separate leaflets or cutting of slits to create leaflets. Prior to December 31, 1999, co-inventor David Paniagua created a paper model of the valve using an unslit sheet of paper with opposite edges joined to form a tubular valve structure with a fold at one end or border and one or more additional folds disposed inwardly in relation to the interior space of the tubular valve structure to form unslit cusps or leaflets at or near the opposite end without suturing of separate leaflets or cutting of slits to create leaflets. The valve model was mounted entirely within a stent. Attached as Exhibit I and Exhibit J, respectively, are the witness Affidavits of Dr. Gervasio A. Lamas, M.D. and Dr. Paolo Angelini, M.D. submitted as evidence supporting the occurrence of the above-described events prior to December 31, 1999.

5. The replica of a paper model of the valve that was submitted as Exhibit B to the Prior Declaration and the replica of a prototype of the valve mounted within a stent that was submitted as Exhibit C to the Prior Declaration, the originals of both of which were created prior to December 31, 1999, each further evidence conception of the valve comprising a folded unslit sheet of material forming a generally tubular structure with a fold at one end and one or more additional folds disposed within and inwardly in relation to the interior space of the tubular valve structure to form cusps or leaflets at or near the opposite end, with folds defining unslit cusps or leaflets without cutting or slitting of the material to create leaflets and without suturing of leaflets.

The undersigned co-inventors each hereby declare that all statements made herein of his own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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DAVID PANIAGUA

Date: September 7, 2009 Signature: _____

EDUARDO INDUNI

Date: September ___, 2009 Signature: _____

CARLOS MEJIA

Date: September 7, 2009 Signature: Carlos Mejia A.

FRANCISCO LOPEZ-JIMENEZ

Date: September ___, 2009 Signature: _____

R. DAVID FISH

Date: September ___, 2009 Signature: _____

DAVID PANIAGUA

Date: September ___, 2009 Signature: _____

EDUARDO INDUNI

Date: September 8, 2009 Signature: _____

CARLOS MEJIA

Date: September ___, 2009 Signature: _____

FRANCISCO LOPEZ-JIMENEZ

Date: September ___, 2009 Signature: _____

R. DAVID FISH

Date: September ___, 2009 Signature: _____

DAVID PANIAGUA

Date: September ___, 2009 Signature:_____

EDUARDO INDUNI

Date: September ___, 2009 Signature:_____

CARLOS MEJIA

Date: September ___, 2009 Signature:_____

FRANCISCO LOPEZ-JIMENEZ

Date: September 8, 2009 Signature:_____

R. DAVID FISH

Date: September ___, 2009 Signature:_____

DAVID PANIAGUA

Date: September ___, 2009 Signature:_____

EDUARDO INDUNI

Date: September ___, 2009 Signature:_____

CARLOS MEJIA

Date: September ___, 2009 Signature:_____

FRANCISCO LOPEZ-JIMENEZ

Date: September ___, 2009 Signature:_____

R. DAVID FISH

Date: September 7, 2009 Signature: RDFish

APPENDIX A

C/M NO. 051458.010100 Mailed December 15, 2008

APPLIC.NO. 10/887,688 Express Mail EM248929807US

The stamp of the Patent Office hereon may be considered the date on which papers indicated below were received.

Applic pgs. . . .Rule 53b New ☐ Contin ☐ Div ☐ CIP ☐/Rule 53c Prov. ☐/Rule 53d CPA ☐

☐ CIP . . . pgs ☐ TM ☐ Design ☐ . . . Dwgs ☐ inf. ☐ fml. ☐ Mailing Certif.

☐ Priority Claim ☐ Cert. Prior. Doc(s) ☐ PCT Cover Sheet WO. . . . . .

☐ Amend pgs . . . ☐ Prel. Amend pgs . . . ☐ Letter

☐ Response pgs . . . ☐ 37CFR1.116 ☐ Not. of Appeal

☐ Brief pgs . . . ☐ Appndx pgs. . . ☐ I.D.S. + . . . Refs.

☐ Assoc Pwr of Atty ☐ . . . Specimen ☐ Declaration

☐ Pet. for Ext. . . . Mo. ☐ Pet . . . . ☐ Check $ . . . .

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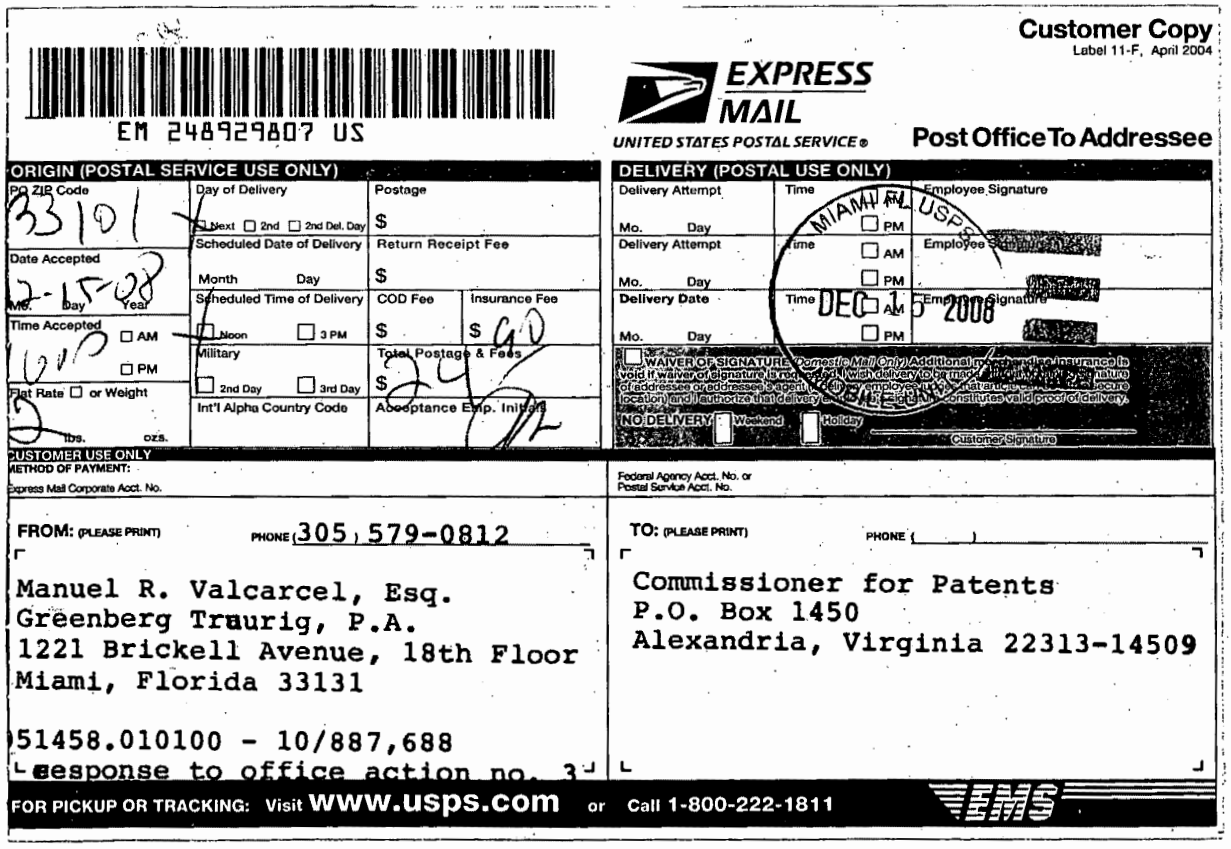
Response to office action no. 3



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Manuel R. Valcarcel, Esq.
Greenberg Traurig, P.A.
1221 Brickell Avenue, 18th Floor
Miami, Florida 33131

51458.010100 - 10/887,688
response to office action no. 3

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EMS

CARLOS MEJIA

Signature: Carlos Mejia D.

Date: October 10, 2008

ACKNOWLEDGEMENT

COUNTY OF HARRIS)
) SS:
STATE OF TEXAS)

The foregoing Declaration was signed before me this 10th day of October, 2008 by Carlos Mejia. He is personally known to me or has produced COLOMBIAN PASSPORT as identification.

Notary: R Hidalgo
Print Name: ROSIE HIDALGO

[NOTARIAL SEAL]
Notary Public,

ROSIE HIDALGO
MY COMMISSION EXPIRES
AUGUST 18, 2009

My commission expires: 8-18-09

EDUARDO INDUNI

Signature: _____

Date: October 10, 2008

ACKNOWLEDGEMENT

COUNTY OF HARRIS)
) SS:
STATE OF TEXAS)

The foregoing Declaration was signed before me this 11th day of October, 2008 by Eduardo Induni. He is personally known to me or has produced REPUBLICA OF COSTA RICA as identification.

Notary: RHidalgo
Print Name: ROSIE HIDALGO

[NOTARIAL SEAL]
Notary Public, _____

ROSIE HIDALGO
MY COMMISSION EXPIRES
AUGUST 18, 2009

My commission expires: 8/18/09

EXHIBIT A

St Lizy Project: A new percutaneous device to decrease Valvular insufficiency

[redacted]

David Paniagua and **Francisco Lopez-Jimenez** (cardiology fellows at that time) discussed the need to develop a percutaneous valve. This discussion took place in the cardiology fellow's room at Mount Sinai Medical Center in Miami Beach Florida.

After this initial discussion a careful and extensive literature search was started. All articles in the field were reviewed as well as all information regarding patents filed.

[redacted]

The candidate stents that we thought of using in our project were: balloon expandable and self-expandable stents. The balloon expandable stents have been used in the past in two animal experiments reported in the literature. One of them was in Denmark and the other in New York. No other study has been reported after these two original reports. No one has implanted a percutaneous valve in a human being. We believe that the main limitation of the balloon expandable stents is its bulky design.

Among the self-expandable stents, we decided to start using in the first phase the Wallstent and we were planning to use the Smart stent in the second phase. These self-expandable stents has never been used for percutaneous implantation of a valve.

[redacted] Boston, MA) that has been used in human since 1987. The main advantage of this stent is its protruding metal wires suitable for fixation in the arterial wall. The main limitation is that the length of the stent changes significant from the collapsed state to the expanded state.

[redacted] the particularity that the stent changes form with temperature. The Smart stent expands when it is in contact with body temperature. The main advantages on the other hand that its length in the collapse and expanded state is quite similar.

The valves that we thought of placing in the stent: porcine pulmonary valve, porcine aortic valve, a new special valve made of bovine pericardium or a valve made of smart materials.

David Fish suggested the utility of using Smart materials in the development of the valve.

Exhibit A

September to December 1999
Anatomical studies in animals
David Paniagua and his wife Elizabeth while in Houston, Texas studied more than 100 porcine aortic and pulmonary valves as well as the aortic arch. Carefull measurement of the valve length, cusp length, vertical diameters, attachment points, interaction with the other cusps, interaction with the Sino tubular junction, coronary ostium. Characteristics of the opening and closing, redundancy of the tissue, sinus of Valsalva measurements [redacted]

[redacted]

On a trip to Vienna, Austria; Francisco Lopez-Jimenez and David Paniagua discussed all the research synthesis. The pros and cons of different options were discussed and finally a strategy to develop our new percutaneous valve took place.

Porcine pulmonary valve

The main advantage of this valve is the thickness of the arterial wall is significantly less than the aortic wall.

Limitations Still bulky

Porcine aortic valve

Limitations Still bulky and the ostium of both coronaries

Bovine pericardium

We designed a new model of valve with special features to be suitable to use in the stent.

<u>The bovine pericardium</u>

Design

The horizontal length of the stent is equal to diameter x π.
The vertical length suffer a lot of modifications in the last 18 months

The process of management of the pericardium

The pericardium is membrane that surrounds the heart and isolates it from the rest of the chest wall structures.

The pericardium is a thin and very slippery, what makes it difficult for suturing in a millimetric precise way that is required for the valve that we were planning to develop.

[redacted] makes it possible to handle the way we needed.

Dry process

Since the pericardium is such a slippery material we started looking the way to [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] like a plastic paper and makes it easy to manipulate to suture the valve.

Hydrating process

Once the valve was done we hydrated the valve back again by placing it in a solution of water and 70% alcohol. In approximately 3 days the valve hydrate back again.

Converting the pericardium into a valve

David Paniagua and **Eduardo Induni** (a cardiovascular surgeon) discussed the best way to suture a flat pericardium and converted into a complete valve.

Many designs were made in paper until we developed a working model in that resembles the human valve.

See diagrams

Types of sutures

Sutures planes

Francisco Lopez-Jimenez introduced the trapezoid modification
We tested the trapezoid modification but it did not work. It introduces too much redundant tissue.

Attachment of the valve to the stent
3-point fixation on border of the stent

6-point fixation at each border of the stent

Fixation on both borders 18 points at each end following a single plane
36 fixation points following to adjacent vertical planes.

Fixation without any fold in the border resulted in tears, so we made a fold that resolved the problem.

Attachment of the valve to the aorta
R. David Fish suggested the possibility of attaching the mother stent to the subclavian artery using a daughter stent deployed first in the subclavian artery and attached to the mother stent that will be deployed in the descending aorta.

Hooks to the arterial wall Like the Ancure

Double stents

Acute Doppler studies in vitro

Francisco Lopez-Jimenez and David Paniagua performed the first Doppler studies in an in-vitro model.

The model consisted of a plastic hose tubing filled with a 30% solution of glycerol to resemble the blood viscosity, a continuous pump, pressure recording instruments and pressure generating clamps.

In this acute in vitro study we document excellent opening and closing profile of the valve. There was no evidence of regurgitation even at pressures of 200 mmHg.

See video

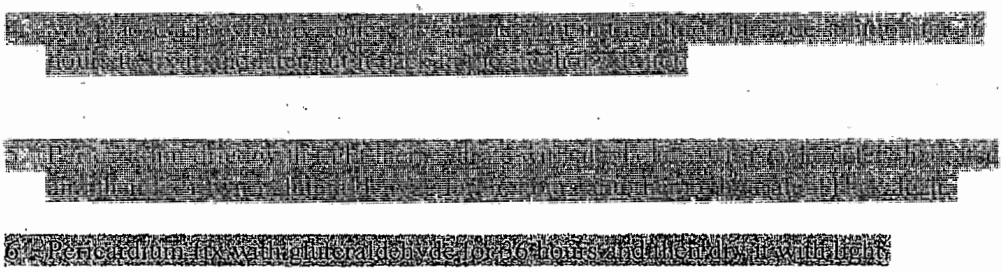
October 5th to 11th 2000

We studied different ways to fix the pericardium.

1- Piece of pericardium-- dried with light in our standard procedure then placed in glutaraldehyde for 36 hours and hydrate back in alcohol 70%. It looses resistant and it breaks easily.

2- Natural pericardium that was in alcohol solution for 2 months at least and we fix it with gluteraldehyde for 36 hours and then place in the alcohol solution with excellent results in terms of tissue resistance. We were not able to break it.

3 We fix a piece of diaphragm after drying it with light and then gluteraldehyde and we obtained the same result than with the pericardium.. The tissue resistance significant decreased and we were able to tear the tissue.



6 - Pericardium fix with glutaraldehyde for 36 hours and dried with light

Delivery device

Chronic studies in vitro

On Sep 17 2001, we created a chronic model to test the valve. The model consisted of a pump attached to an 18 mm tubing system that is also attached to a 3 liters container that is placed 180 cms above the pump.

The stented valve was placed at the bottom of a 180 cm water column to mimic the diastolic pressure.

Histological studies

Preservation of the pericardium several month in ETOH

Glutaraldehido

[redacted]

E-mails

[redacted]

Materials

Calf
The device Delivery system
Cook needle Wires
Pigtails Dilators 11 F, 14F, 16F, 18F, 20F
Contrast media
Balloons PTA of the aorta.

Heparin Plavix for the animal

Surgical equipment

Echo Doppler

[redacted]

Injector X ray tech
Person in charge of anesthesia, monitoring

Circulating person	Endotracheal tube	IV fluids
IV connections	angiocaths	4 liter of IV fluids

Ventilators Lamps

KYJELLY
ET TUBE
ANTIBIOTICS
HEPARIN
XYLOCAINE
BETADINE
KETAMINE
EMERGENCY DRUGS
PROPOFOL XYLAZINE
INJECTION T SPRAY
ALCOHOL

STERILE TOWELS T DRAPES
STERILE SURGICAL TRAY
RECTAL TEMP PROBE
STERILE BOWL FOR SALINE
NS SALINE D5RL
COLLOID
SYRINGES-DIFFERENT SIZES
NEEDLES- DIFFERENT SIZES
HEATING PAD
IV CATLETERS, TOURNIGUETS
VASCULAR CLAMPS
SUCTION CATLETERS
SCISSORS
SECADORA PELO

[redacted]

Carlos Mejia and David Paniagua meet to discuss and design the next experiment.

We reviewed the previous information in video tapes, all films were discussed with emphasis in how we can decrease the size of the valve to try to identify the optimal Dimension of the valves.

We are going to try a valve 10mm deep and the circumference of the valve is going to be 71 mm for a 24mm diameter stent. The width of each pocket is going to be 22 mm

We did the valve in a rubber model with 10 mm deep and it was competent, for this reason we decided to try it in the pericardium.

The change in dimension of the valve with hydration after it is place in alcohol is unpredictable at the present time.

We are going to make two valves

1- Following our previous method of drying the valve with light and sewing to the stent when it its dried and then hydrating it with alcohol. Same design than previously, with folds.
2- A valve with pericardium fixed with gluteraldehyde. No folds in the upper part.

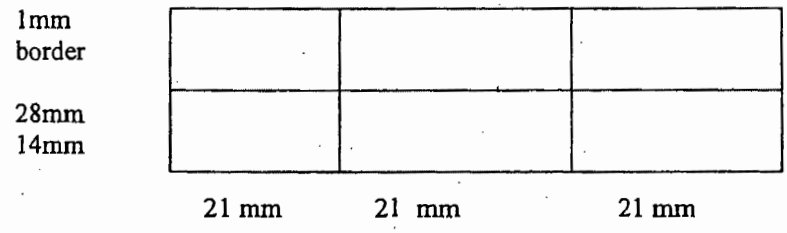
December 2 2000

Eduardo Induni, Carlos Mejia, David Paniagua review all the data collected so far in all the previous experiments and plan a strategy.
We found out that the material needs to be fix with gluteraldehyde before we implant the device. We study different concentrations of gluteraldehyde to fix the valve.

Finally we conclude that we the best is to fix the valve with 0.7% gluteraldehyde and keep it in this solution until the time to use it. At this moment we need to put the valve in normal saline before we implant it

January 2001

We designed a new valve with modification of its length. The pericardium was fixed with gluteraldehyde at 0.7% and later we did the valve and kept it in the same solution until the time to implant it.
During the creation of the valve constant hydration was maintain with frequent immersion of the pericardium in gluteraldehyde.



1 mm at each end to suture the valve.

February 2001

David Fish, Eduardo Induni and David Paniagua review the new stent-pericardium-valve and discussed the design improvement and decided to implant it in a new animal experiment.

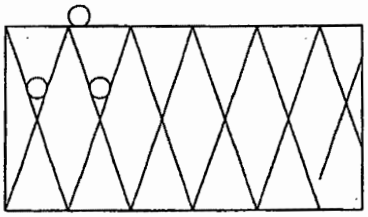
[redacted]

The valve required 7-0 prolene, 24-inch long 10 packs
3 to suture the valve and 7 to attach the valve to the stent.

The valve was attached to a 24 mm maximal diameter Wallstent.

We eliminate the folds at each end of the valve.

The valve was fixed in its **superior border** using two fixation planes with 18 fixation points at each plane.



○ Fixation points

18 fixation points at each plane

There are two rows of fixation point at the upper or proximal end of the stent and one row of fixation point at the lower or distal end of the stent.

Each fixation point was knotted 5 times in the upper plane and 7 knots in the lower plane.

The fixation of the **inferior border** of the valve to the stent was done with a single plane with 18 fixation points. Each fixation point was knotted 7 times using prolene 7-0.

The vertical fixation of the valve to the stent was done along the suture line of each cusp of the valve. We used 3 fixation points at each vertical suture line. Each fixation point was knotted 7 times.

The vertical fixation was mildly loose to allow easy collapsibility of the valve.

The approximate time to suture and attach the valve was 10 hours.

The stent-valve is maintained in 0.7% gluteraldehyde solution.

March 24, 2001

We plan to place the valve in a chronic in vitro model to evaluate its chronic function.

We will perform collapsibility test of the valve.

The delivery system that we plan to use is the AneuRx deployment device.

April 21, 2001

We did an animal experiment in Costa Rica, see description in animal studies.

June 9, 2001

Carlos Mejia and David Paniagua in Miami got together to discuss about the evolution of the valve.

We were discussing how to reduce the dimension to the optimal size of the valve and prevent valvular folds.

The last valve length was 65 mm after fixation, but if you pull it to its maximum length it grows 10 mm more up to 75 mm. Carlos decreased the length of the valve to 55 mm and 57 mm. We were concerned about the elastic recoil of the pericardium once implanted in the valve, because if it is not tense the pericardium makes folds, we want to achieve the optimal length that does not produce folds and that it is not so tight that causes so much elastic recoil that does not allow the stent to expand.

We had the idea of fixing the valve in the closing position using tiny metallic clips to keep the cusps close to each other.

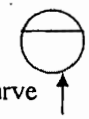
We tried the aortic valvuloplasty balloon to test if it can be used to expand the distal end of the stented valve in the case this extreme does not open.

We tried the consistency of different suture materials: Ticro 4-0, braided nylon and prolene. We discussed pros and cons of monofilament versus braided suture material.

June 12, 2001

At Carlos Mejia's' house we evaluated the design of the valve.

The new valve design includes the creation of a curve in each cusp of the valve



The other modification that we are doing in the handling process is to fix the pericardium in gluteraldehyde and transfer it to a solution of alcohol while making the valve and attaching it to the stent.

We changed the attachment position of the valve to be closer to the proximal and wider part of the Walstent, based on the previous experience during the animal study Alba.

We discussed the use of a pericardium piece fix in glutaraldehyde in a flat glass and the possibility of doing the valve with the natural pericardium and then fixing it with gluteraldehyde after mounting it in the stent.

One observation that we noted is that the material becomes whiter and apparently increases its elasticity

We obtained 1mm vascular clips to keep the cusps coapted while fixing them in gluteraldehyde.

June 13 2001

We evaluated the results of the use of metallic clips to keep both cusps adjacent to each other after 24 hours of fixation in gluteraldehyde. The results were very satisfactory to educate the material and make the primary position of the valve cusps adjacent to each other. After we removed the clips, there were no lesions to the valve. After doing this test, we use the metallic clips to keep both cusps together and immersed it in gluteraldehyde for 24 hours.

We evaluated different suture material that included praline 6-0 and Madrilène 6- 0 which is a braided suture.

We make more fixing fluid using gluteraldehyde 25% in a concentration of 3ml per 97 ml of fluid.

The pericardium of the first valve was in gluteraldehyde for 6 months approximately, then we put it in alcohol 60 during 2 to 3 days and after making the valve and placing in the transport fluid which consist of 60% alcohol.

June 16 2001

We were ready to perform another animal experiment in Costa Rica, but unfortunately all our equipment of dilator and the temporary delivery system was lost.

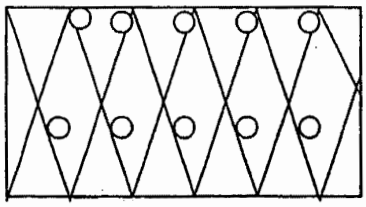
We developed a temporary delivery system that consisted of a central catheter big enough to let a 0.38 wire pass through its lumen, a cover sheath made of plastic material with a sliding device that allows to expose the stented valve.

Dr Eduardo Induni and David Paniagua discussed different ways to improve the collapsibility of the valve
The new observation was that the fixation points at the proximal part should be placed at the midpoint of the rhomboid structure to allow some mobility of the valve when we collapse it. This is true when using Wallstent material not smart materials

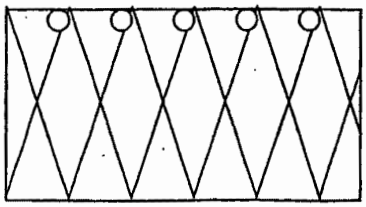
The other observation is that two planes of fixation point at the distal attachment of the valve to the stent causes a lot of tension to the valve when we are collapsing it.

One plane of fixation points will probably be enough to prevent systolic collapsed of the proximal edge of the valve

Proximal fixation points / expanded



Proximal fixation points sliding down



when stent collapses

○ ○ ○ ○ ○

○ Fixation points

18 fixation points at each plane

June 29, 2001

We discussed again the fixation points of the valve to the stent in such a way that they allow mobility of the stent over the valve without exerting too much tension. We believe this will allow better profile to the valve.

We also discussed the different suture materials and call Eduardo Induni and we make the decision that a braided suture is better than a monofilament, for this reason we are going to use mersilene which is a polyester braided suture.

[redacted]

September 8

Carlos Mejia and David Paniagua designed the in vitro model to test chronically the valve and list all the required material

September 22

The valve is mounted in the chronic testing model

[redacted]

EXHIBIT B

Previously Submitted

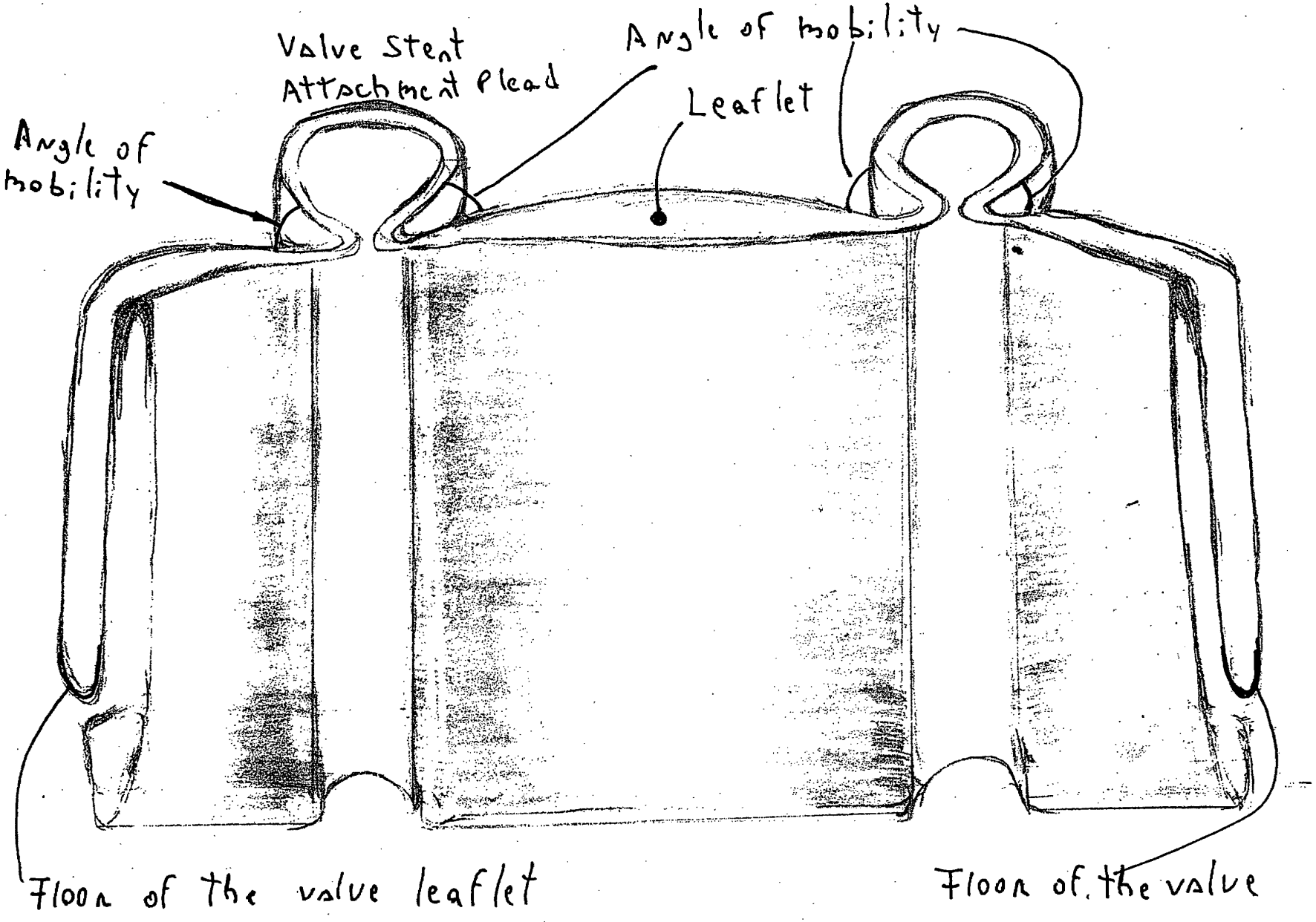
EXHIBIT C

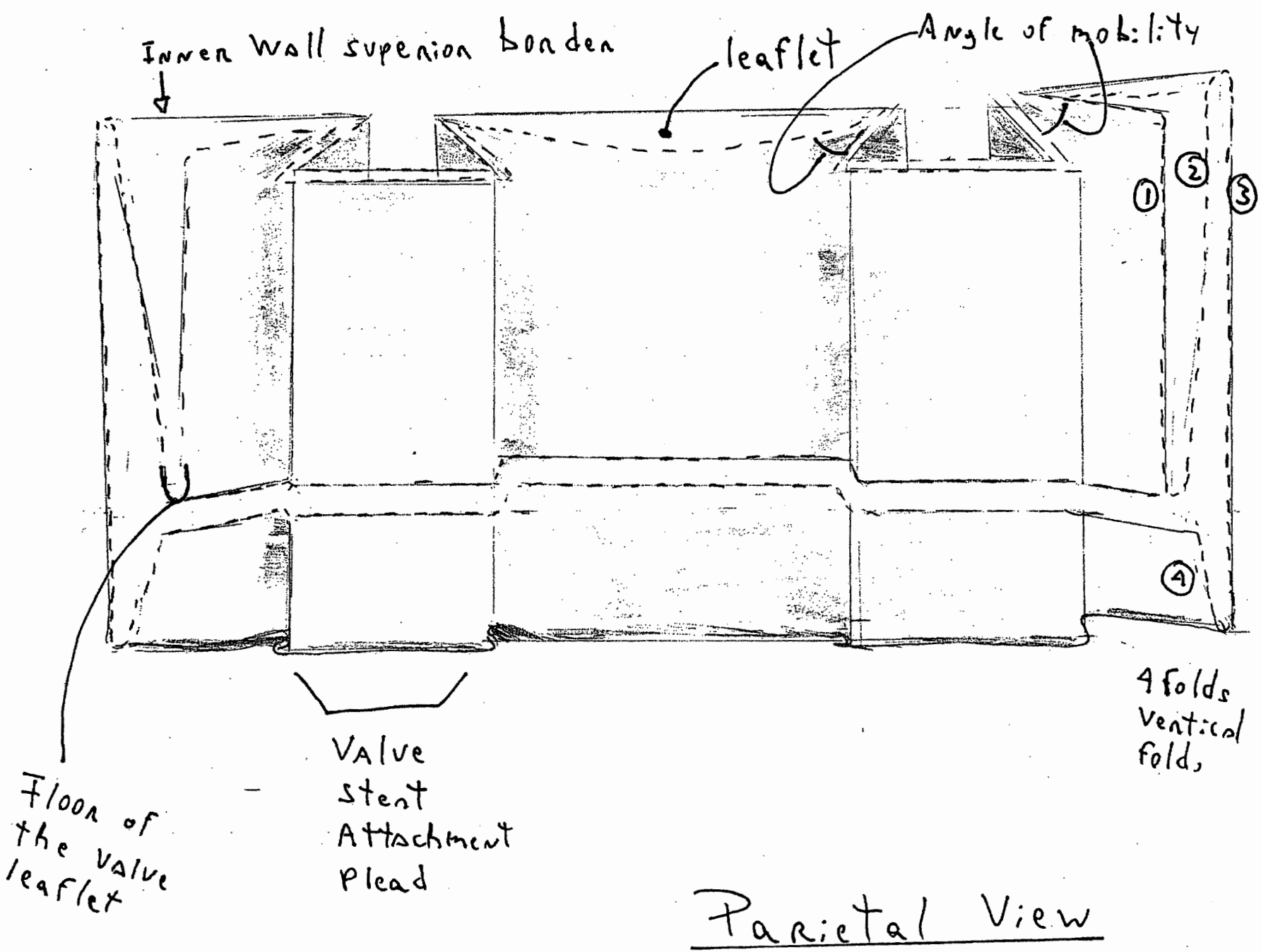
Please see the attached container labeled Exhibit C

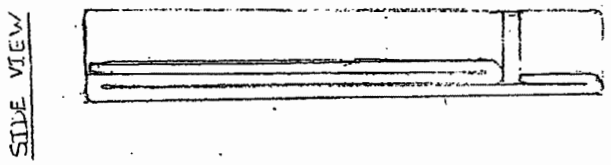
Previously Submitted

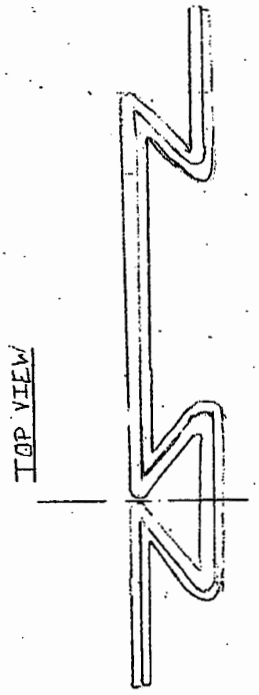
EXHIBIT D

Internal View






SIDE VIEW


TOP VIEW

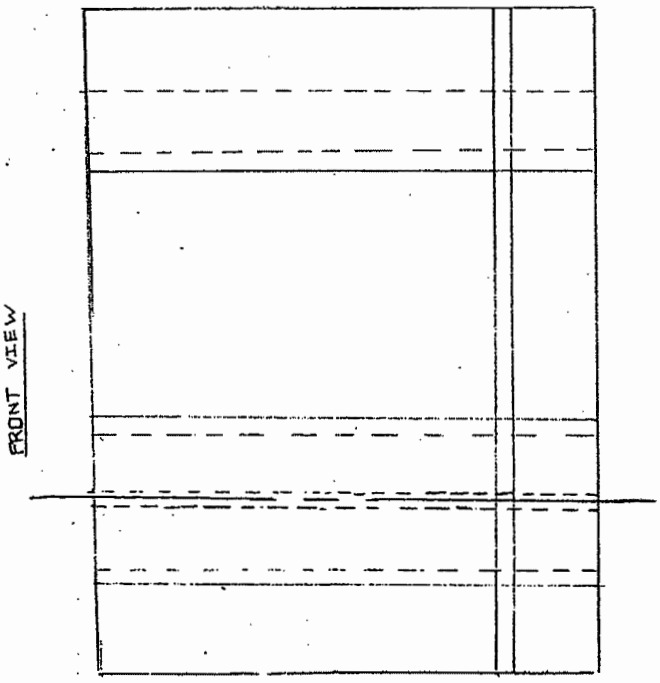

FRONT VIEW

EXHIBIT E

United States Patent

Paniagua, Induni, Mejia, Lopez, Fish, April 22, 2001

PERCUTANEOUS VALVE REPLACEMENT

Abstract

The invention relates to a new technique and a special type of device that allows percutaneous heart-valve replacement without the need for open-heart surgery.

The valve replacement system includes the following components:

(1) A system for removing a damaged heart valve
(2) a delivery system of the prosthetic valve device
(3) a prosthetic valve device
(4) an implantation technique

Inventors:

David Paniagua
Eduardo Induni
Carlos Mejia
Francisco Lopez
R. David Fish

U.S. Patent Documents

4056854	Nov.1977	Boretos et al.	623/2.
4631052	Dec., 1986	Kensey	606/159.
4883458	Nov., 1989	Shiber	606/159.
4966604	Oct., 1990	Reiss	606/159.
4979939	Dec., 1990	Shiber	606/159.
5007896	Apr., 1991	Shiber	606/159.
5011488	Apr., 1991	Ginsburg	606/159.
5026366	Jun., 1991	Leckrone	606/7.
5032128	Jul., 1991	Alonso	623/2.
5047041	Sep., 1991	Samuels	606/159.
5080660	Jan., 1992	Buelna	606/49.
5152771	Oct., 1992	Sabbaghian	606/159.

Foreign Patent Documents

WO91/17720	Nov., 1991	WO.
WO91/17118	Oct., 1992	WO.

Claims

What is claimed is:

1- An endovasculat system for delivering a heart valve.
2- An artificially percutaneous heart valve
3- An implantation technique

1. An endovascular system for delivering a replacement heart valve through an aortic passageway to or near to the location from which the natural heart valve has been removed, comprising:

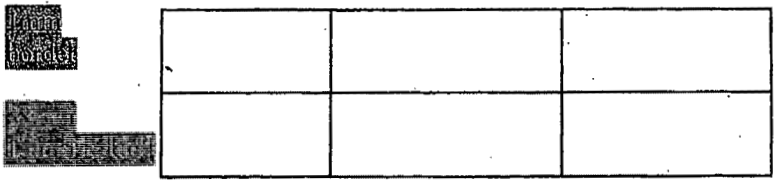
[redacted]

[redacted]

[redacted]

The horizontal length of the pericardium piece is equal to the desired diameter x π.
The vertical length suffer a lot of modifications in the last 18 months

[redacted]



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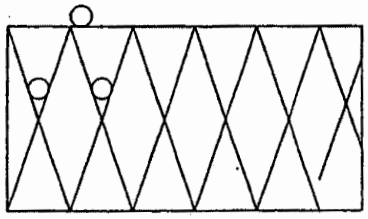

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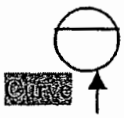
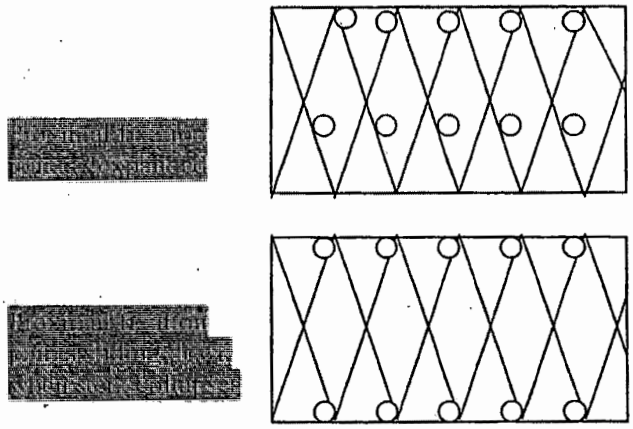
The new valve design includes the creation of active tricuspid portion of the valve



Curve

[redacted]

One plane of fixation points will probably be enough to prevent systolic collapse of the proximal edge of the valve



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Fixation points

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NEEDS DETAILED DESCRIPTION OF WHAT IS CLAIM

DESCRIPTION

FIELD OF THE INVENTION

This invention relates to devices and methods for percutaneous endovascular replacement of heart valves.

BACKGROUND

When a heart valve is malfunctioning in such a degree that interferes with normal cardiac function it may be necessary to replace it. Currently this requires a surgical procedure that involves open-heart surgery requiring general anesthesia, full cardiopulmonary bypass with complete cessation of cardiopulmonary activity. Usually after the surgical procedure seven to ten days of hospitalization and months of recuperation time are required. This valve replacement surgery is not free of complication and it is associated with a mortality rate in the best hands and circumstances of about five to six percent.

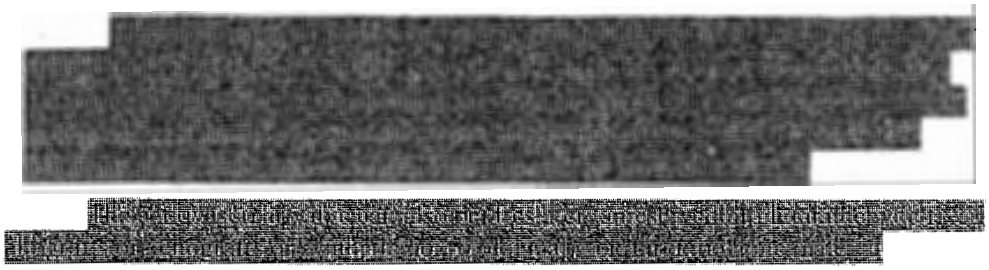
Endovascular procedures for valve replacement provide an alternative to open heart surgery and this is the goal of our new invention.

Previous endovascular treatments of disease heart-valves have focus in opening stenotic lesions in the mitral and aortic valve using specially designs balloons to dilate or split commissures in diseased aortic or mitral valves with commissural fusion and to crack calcific plaques in calcified stenotic aortic valves.

The success for the mitral valve has been rewarding but the aortic valve results have been discouraging This method provides only partial and temporary relief for a patient with a stenotic aortic valve and this method cannot be used to treat valves with leakage. Moreover, aortic valvuloplasty in a few cases may induce severe aortic leakage that is not compatible with life.

The method that we describe is to use a percutaneously endovascular valve replacement. supplantation. In this procedure, a delivery system is used to insert a biological or mechanical valve in the lumen of a central blood vessel via entry through the brachial or femoral artery. Vascular access is obtained using a needle or exposing the artery surgically and a guide wire is placed through the entry vessel and it is advanced to the desired placed under fluoroscopically guidance. Dilators are advanced over the wire to increase the lumen of the entry site preparing the artery to receive the delivery system of our heart-valve. The heart-valve is then advanced to the desired place and deployed under X-ray guidance.

This new technique of percutaneous endovascular heart-valve replacement, in contrast to open heart surgical procedures, would require only local anesthesia, partial or no cardiac bypass, one to two days hospitalization, and should have a reduced mortality rate as compared to open heart procedures.



RELEVANT LITERATURE

U.S. Pat. No. 3,671,979 to Moulopoulos, issued Jun. 27, 1972, describes a endovascularly inserted conical shaped umbrella-like valve positioned and held in place by an elongated mounting catheter at a supra-annular site to the aortic valve in a nearby arterial vessel. The conical end points toward the malfunctioning aortic valve and the umbrella's distal ends open up against the aorta wall with reverse blood flow, thereby preventing regurgitation.

U.S. Pat. No. 4,056,854 to Boretos, issued Nov. 8, 1977, describes a endovascularly inserted, catheter mounted, supra-annular valve in which the circular frame abuts the wall of the artery and attached flaps of flexible membrane extend distally in the vasculature. The flaps lie against the artery wall during forward flow, and close inward towards the central catheter to prevent regurgitation during reverse blood flow. The Boretos valve was designed to be positioned against the artery wall during forward flow, as compared to the mid-center position of the Moulopoulos valve, to reduce the stagnation of blood flow and consequent thrombus and embolic formation expected from a valve at mid-center position.

SUMMARY OF THE INVENTION

The invention relates to a new technique and a special type of device that allows percutaneous heart-valve replacement without the need for open-heart surgery.

The valve replacement system includes the following components:

1- A delivery system of the prosthetic valve device.
2- A prosthetic valve device.
3- An implantation technique

DESCRIPTION OF THE DRAWINGS

FIG. 1 Delivery system of the self-expanded stented valve.

FIG. 2 Initial deployment of the self-expanded stented valve.

FIG. 3 illustrates a bottom view of stented valve.

FIG. 4 illustrates a top view of the stented valve.

FIG. 5 illustrates a tissue laser wire used to cut the commisures of stenotic valve.

FIG. 6 illustrates a diagram of the relationships, dimensions and folds used to create the valve.

FIG. 7 illustrates a side view of a valve introducer.

FIG. 9 illustrates a side view of the attachment point of the valve to the stent.

FIG. 10 illustrates a top view showing the attachment points of the cusp of the valve.

FIG. 11 illustrates an aortic valve in the side position.

FIG. 12 illustrates an aortic valve from the top view.

FIG. 13 is a side cross-sectional view of the valve mounted in the self-expanded stent.

FIG. 14 illustrates a front view of the valve mounted in the stent in the open position.

FIG. 15A is a close-up side cross-sectional view of the mounting stent and FIG. 15B in the closed position.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

The present invention relates to the supplantation or replacement of a cardiac valve in a host through percutaneous endovascular means.

The valve replacement system includes
(1) a delivery device
(2) a prosthetic valve device
(3) an implantation technique.

GENERAL DESCRIPTION OF THE PROCEDURE

The Femoral artery is canulated using a Cook needle and a standard J wire is advance into the artery either perutaneously or after surgical exposure of the artery. An 8 F introducer is advanced into the femoral artery over the wire. The J wire is then withdraw and anticoagulation is started using heparin 60 U/Kg intravenously. Once vascular access is obtained an aortogram is performed for anatomical evaluation.

A special wire (Lunderquist or Amplatz superstiff) is advanced into the aortic arch and dilators progressively larger are advance over the wire, starting with 12 F all the way to 18 F after this the valve introducer device containing the prosthetic valve device is then inserted and used to transport the replacement valve over a guidewire to the desired position.

The stented-valve is released by pulling the cover sheath of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advance over the wire and repeat aortogram is performed to assess the competency of the valve.

When the device is used to treat severe leakage of the aortic valve, the native valve is left in placed and the prostetic stented valve is deployed below the subclavian artery.
When the device is used to treat aortic stenosis, first the stenotic valve needs to be opened using either aortic valvuloplasty or the new laser wire cutters and if this procedure induces aortic insufficiency the stented valve is placed to prevent the regurgitation.

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The prosthetic valve device can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation. In addition, with the development of longer-life, flexible, non thrombogenic synthetic valve alternatives to bioprosthesis', the prosthetic valve device will be indicated in all patients where the relative advantages of the life-span, the non-thrombogenic quality, and the ease of insertion of prosthetic valve devices outweigh the disadvantages of mechanical valves. Anticoagulation may be beneficial in certain clinical situations for either short or long term use.

All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

* * * * *

EXHIBIT F

GREENBERG
ATTORNEYS AT LAW
TRAURIG

Manuel R. Valcarcel
305-579-0812
valcarcelm@gtlaw.com

ATTORNEY-CLIENT PRIVILEGED
CONFIDENTIAL INFORMATION

August 29, 2001

VIA FACSIMILE (703) 413-4150
AND FED EX

Mr. Mark Miller
Just Files
2001 Jefferson Davis Highway
Suite 506
Arlington, VA 22202

Re: Novelty Search for Percutaneous heart valve replacement device and method
Our Reference No. 51458.010100

Dear Mr. Miller:

Please conduct a novelty search for the above-identified invention which is described below.

A. Replacement Heart Valve Device. The replacement heart valve device comprises a stent made of stainless steel or self-expanding nitinol, a completely newly designed biological valve disposed within the inner space of the stent, and a delivery system having a central part which consists of a hollow tube that allows a metallic wire to be advanced inside it. The stented valve is collapsed over this central metallic tubing and it is covered by a movable sheath. The sheath keeps the stented valve in the collapsed position. Once the cover sheath is moved backwards, the stented valve can be deployed.

The endovascular stented-valve is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow. Bioprostetic valves are presently a mainstay in aortic valve replacement and they are preferable in patients who cannot tolerate long-term anticoagulant therapy or are otherwise potentially noncompliant with a long term medical regimen.

In making of the valve initially, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a

solution of gluteraldehyde at a concentration of 0.07% during 36 hours, then the pericardium is transferred to a solution of ethanol at 60% before making the valve.

The valve is formed by taking a rectangular fragment of bovine pericardium and folding it in such a way that forms a three-leaflet valve.

The endovascular valve can also be fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts or synthetic non-biological, non-thrombogenic material.

B. Implantation Method.

The method for implanting said replacement heart valve device through an aortic passageway to, or near to, the location from which the natural heart valve has been removed comprises the following steps:

inserting the replacement heart valve device in the lumen of a central blood vessel via entry through the brachial or femoral artery using a needle or exposing the artery surgically; placing a guide wire through the entry vessel and advancing it to the desired position; advancing dilators over the wire to increase the lumen of the entry site, thereby preparing the artery to receive the heart-valve; and advancing the heart-valve to the desired place.

This new technique of percutaneous endovascular heart-valve replacement, in contrast to open heart surgical procedures, would require only local anesthesia, partial or no cardiac bypass, one to two days hospitalization, and should have a reduced mortality rate as compared to open heart procedures.

When the device is used to treat severe leakage of the aortic valve, the native valve is left in placed and the prosthetic stented valve is deployed below the subclavian artery. When the device is used to treat aortic stenosis, first the stenotic valve is opened using either aortic valvuloplasty or laser wire cutters and if this procedure induces aortic insufficiency the stented valve is placed to prevent the regurgitation.

The stented-valve is released by pulling the cover sheath of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advanced over he wire and an aortogram is performed to assess the competency of the valve.

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The prosthetic valve device can be used in any patient where

bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation.

Please do not hesitate to contact me at 305-579-0812 if you have any questions or need additional information to complete the search. Please let me know beforehand if the search will cost more than $400.00.

Sincerely,

GREENBERG TRAURIG, P.A.

Manuel R. Valcarcel, Esq.

MRV/ps

\\MIA-SRV01\VALCARCELM\1333881v01\8/29/01\51458.010100

EXHIBIT G

GREENBERG
ATTORNEYS AT LAW
TRAURIG

Manuel R. Valcarcel
305-579-0817
valcarcelm@gtlaw.com

ATTORNEY-CLIENT PRIVILEGED
CONFIDENTIAL INFORMATION

August 29, 2001

VIA FACSIMILE (703) 413-4150
AND FED EX

Mr. Mark Miller
Just Files
2001 Jefferson Davis Highway
Suite 506
Arlington, VA 22202

Re: Novelty Search for Percutaneous heart valve replacement device and method
Our Reference No. 51458.010100

Dear Mr. Miller:

Please conduct a novelty search for the above-identified invention which is described below.

A. Replacement Heart Valve Device. The replacement heart valve device comprises a stent made of stainless steel or self-expanding nitinol, a completely newly designed biological valve disposed within the inner space of the stent, and a delivery system having a central part which consists of a hollow tube that allows a metallic wire to be advanced inside it. The stented valve is collapsed over this central metallic tubing and it is covered by a movable sheath. The sheath keeps the stented valve in the collapsed position. Once the cover sheath is moved backwards, the stented valve can be deployed.

The endovascular stented-valve is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow. Bioprostetic valves are presently a mainstay in aortic valve replacement and they are preferable in patients who cannot tolerate long-term anticoagulant therapy or are otherwise potentially noncompliant with a long term medical regimen.

In making of the valve initially, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a

EXHIBIT H

GREENBERG
ATTORNEYS AT LAW
TRAURIG

Manuel R. Valcarcel
(305) 579-0812

November 27, 2001

ATTORNEY-CLIENT PRIVILEGED
CONFIDENTIAL COMMUNICATION

VIA HAND DELIVERY

David Paniagua, M.D.
1865 – 79th Street Causeway
Apartment 7-H
Miami Beach, Florida 33141

Re: Draft of patent application specification for percutaneously implantable heart valve replacement device and method of making same

Dear Dr. Paniagua:

Enclosed for your review and revision as appropriate is the draft of the nonprovisional patent application specification for your above-referenced invention. Please review the draft at your earliest convenience (please also review the draft with the other co-inventors) and provide your comments, revisions and additional text. Please note the descriptions of the figures in the draft and if you have drawings or clear digital photographs that provide the views described in the description of the drawings, please provide them. The photographs provided previously are not clear enough for use in the application. If you do not have such photographs, please let me know if you can provide an actual sample of the device so that a draftsman can prepare the figures.

Best regards,

GREENBERG TRAURIG, P.A.

Manuel R. Valcarcel, Esq.

MRV/ps
Enclosures

\\MIA-SRV01\VALCARCELM\1353475v01\11/27/01\51458.010100

Docket No. 51458.010100

NON-PROVISIONAL PATENT APPLICATION

SPECIFICATION

TO WHOM IT MAY CONCERN:

BE IT KNOWN THAT WE, David Paniagua, Eduardo Induni, Carlos Mejia, Francisco Lopez and R. David Fish, each citizens of the United States of America, have invented a new and useful percutaneously implantable replacement heart valve and method of making same, of which the following is the Specification.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is in the field of heart valve replacement. More specifically, the present invention is directed to a percutaneously implantable replacement heart valve and method of making same.

2. Description of Related Art

There have been numerous efforts in the field of heart valve replacement to improve both the durability and effectiveness of replacement heart valves as well as the ease of implantation. A brief description of heart valves and heart function follows to provide relevant background for the present invention.

There are four valves in the heart that serve to direct the flow of blood through the two sides of the heart in a forward direction. On the left (systemic) side of the heart are: 1) the mitral valve, located between the left atrium and the left ventricle, and 2) the aortic valve, located between the left ventricle and the aorta. These two valves direct oxygenated blood coming from the lungs through the left side of the heart into the aorta for distribution to the body. On the right (pulmonary) side of the heart are: 1) the tricuspid valve, located between the right atrium and the right ventricle, and 2) the pulmonary valve, located between the right ventricle and the pulmonary artery. These two valves direct de-oxygenated blood coming from the body through the right side of the heart into the pulmonary artery for distribution to the lungs, where it again becomes re-oxygenated to begin the circuit anew.

Heart valves are passive structures that simply open and close in response to differential pressures on either side of the particular valve. They consist of moveable "leaflets" that are designed simply to open and close in response to differential pressures on either side of the valve's leaflets. The mitral valve has two leaflets and the tricuspid valve has three. The aortic and pulmonary valves are referred to as "semilunar valves" because of the unique appearance

of their leaflets, which are more aptly termed "cusps" and are shaped somewhat like a half-moon. The aortic and pulmonary valves each have three cusps.

In general, the components of heart valves include the valve annulus, which will remain as a roughly circular open ring after the leaflets of a diseased or damaged valve have been removed; leaflets or cusps; papillary muscles which are attached at their bases to the interior surface of the left or right ventricular wall; and multiple chordae tendineae, which couple the valve leaflets or cusps to the papillary muscles. There is no one-to-one chordal connection between the leaflets and the papillary muscles; instead, numerous chordae are present, and chordae from each papillary muscle attach to both of the valve leaflets.

When the left ventricular wall relaxes so that the ventricular chamber enlarges and draws in blood, the leaflets of the mitral valve separate and the valve opens. Oxygenated blood flows in a downward direction through the valve, to fill the expanding ventricular cavity. Once the left ventricular cavity has filled, the left ventricle contracts, causing a rapid rise in the left ventricular cavitary pressure. This causes the mitral valve to close while the aortic valve opens, allowing the oxygenated blood to be ejected from the left ventricle into the aorta. The chordae tendineae of the mitral valve prevent the mitral leaflets from prolapsing back into the left atrium when the left ventricular chamber contracts.

The three leaflets, chordae tendineae, and papillary muscles of the tricuspid valve function in a similar manner, in response to the filling of the right ventricle and its subsequent contraction. The cusps of the aortic valve also respond passively to pressure differentials between the left ventricle and the aorta. When the left ventricle contracts, the aortic valve cusps open to allow the flow of oxygenated blood from the left ventricle into the aorta. When the left ventricle relaxes, the aortic valve cusps reapproximate to prevent the blood which has entered the aorta from leaking (regurgitating) back into the left ventricle. The pulmonary valve cusps respond passively in the same manner in response to relaxation and contraction of the right ventricle in moving de-oxygenated blood into the pulmonary artery and thence to the lungs for

re-oxygenation. Neither of these semilunar valves has associated chordae tendineae or papillary muscles.

Problems that can develop with heart valves consist of stenosis, in which a valve does not open properly, and/or insufficiency, also called regurgitation, in which a valve does not close properly. In addition to stenosis and insufficiency of heart valves, heart valves may need to be surgically repaired or replaced due to certain types of bacterial or fungal infections in which the valve may continue to function normally, but nevertheless harbors an overgrowth of bacteria (vegetation) on the leaflets of the valve that may embolize and lodge downstream in a vital artery. If such vegetations are on the valves of the left side (i.e., the systemic circulation side) of the heart, embolization may occur, resulting in sudden loss of the blood supply to the affected body organ and immediate malfunction of that organ. The organ most commonly affected by such embolization is the brain, in which case the patient suffers a stroke. Thus, surgical replacement of either the mitral or aortic valve (left-sided heart valves) may be necessary for this problem even though neither stenosis nor insufficiency of either valve is present. Likewise, bacterial or fungal vegetations on the tricuspid valve may embolize to the lungs resulting in a lung abscess and therefore, may require replacement of the tricuspid valve even though no tricuspid valve stenosis or insufficiency is present.

These problems are treated by surgical repair of valves, although often the valves are too diseased to repair and must be replaced. If a heart valve must be replaced, there are currently several options available, and the choice of a particular type of artificial valve depends on factors such as the location of the valve, the age and other specifics of the patient, and the surgeon's experiences and preferences. Currently in the United States over 100,000 defective heart valves are replaced annually, at an approximate cost of $30-50,000 per procedure, and thus it would be desirable if heart valves could be replaced using minimally invasive techniques and without having to repeat the procedure within a matter of years due to the lack of durability of the replacement heart valve. It would be especially advantageous if a defective heart valve

could be removed via an endovascular procedure, that is, a procedure where the invasion into the body is through a blood vessel such as the femoral artery. The procedure is then carried out percutaneously and transluminally using the vascular system to convey appropriate devices to the position in the body wherein it is desired to carry out the desired procedure. An example of such a procedure would be angioplasty, wherein a catheter carrying a small balloon at its distal end is manipulated through the body's vessels to a point where there is a blockage in a vessel. The balloon is expanded to create an opening in the blockage, and then the balloon is deflated and the catheter and balloon are removed from the vessel.

Endovascular procedures have substantial benefits both from the standpoint of health and safety as well as cost. Such procedures require minimal invasion of the human body, and there is consequently considerable reduction and in some instances even elimination, of the use of a general anesthesia and much shorter hospital stays.

Replacement heart valves can be categorized as either artificial mechanical valves, transplanted valves and tissue valves. Replacement heart valves are designed to optimize hemodynamic performance, thrombogenicity and durability. Another factor taken into consideration is the relative ease of surgical implantation.

Mechanical valves are typically constructed from nonbiological materials such as plastics, metals and other artificial materials which, while durable, are expensive and prone to blood clotting which increases the risk of an embolism. Anticoagulants taken to help against blood clotting can further complicate the patient's health due to increased risks for hemorrhages.

Transplanted valves are natural valves taken from cadavers. These valves are typically removed and frozen in liquid nitrogen, and are stored for later use. They are typically fixed in glutaraldehyde to eliminate antigenicity and are sutured in place, typically with a stent.

Artificial tissue valves are valves constructed from animal tissue, such as bovine or porcine tissue. Efforts have also been made at using tissue from the patient for which the valve will be constructed.

Most tissue valves are constructed by sewing the leaflets of pig aortic valves to a stent to hold the leaflets in proper position, or by constructing valve leaflets from the pericardial sac of cows or pigs and sewing them to a stent. The porcine or bovine tissue is chemically treated to alleviate any antigenicity. The pericardium is a membrane that surrounds the heart and isolates it from the rest of the chest wall structures. The pericardium is a thin and very slippery, which makes it difficult for suturing in a millimetricly precise way. The method of making the replacement heart valve of the present invention solves this problem through a process to dry the pericardium in such a way that makes it possible to handle and fold more easily.

For example, one prior replacement heart valve requires each sculpted leaflet to be trimmed in a way that forms an extended flap, which becomes a relatively narrow strand of tissue near its tip. The tip of each pericardial tissue strand is sutured directly to a papillary muscle, causing the strand to mimic a chordae tendineae. Each strand extends from the center of a leaflet in the valve, and each strand is sutured directly to either an anterior and posterior papillary muscle. This requires each leaflet to be positioned directly over a papillary muscle. This effectively rotates the leaflets of the valve about 90 degrees as compared to the leaflets of a native valve. The line of commissure between the leaflets, when they are pressed together during systole, will bisect (at a perpendicular angle) an imaginary line that crosses the peaks of the two papillary muscles, instead of lying roughly along that line as occurs in a native valve.

A different approach to creating artificial tissue valves is described in U.S. Patent Nos. 5,163,955 to Calvin, et al. and 5,571,174 and 5,653,749 to Love. Using a cutting die, the pericardial tissue is cut into a carefully defined geometric shape, treated with glutaraldehyde, then clamped in a sandwich-fashion between two stent components. This creates a tri-leaflet

valve that resembles an aortic or pulmonary valve, having semilunar-type cusps rather than atrioventricular-type leaflets.

U.S. Patent No. 3,671,979 to Moulopoulos describes an endovascularly inserted conical shaped umbrella-like valve positioned and held in place by an elongated mounting catheter at a supra-annular site to the aortic valve in a nearby arterial vessel. The conical end points toward the malfunctioning aortic valve and the umbrella's distal ends open up against the aorta wall with reverse blood flow, thereby preventing regurgitation.

U.S. Patent No. 4,056,854 to Boretos describes an endovascularly inserted, catheter mounted, supra-annular valve in which the circular frame abuts the wall of the artery and attached flaps of flexible membrane extend distally in the vasculature. The flaps lie against the artery wall during forward flow, and close inward towards the central catheter to prevent regurgitation during reverse blood flow. The Boretos valve was designed to be positioned against the artery wall during forward flow, as compared to the mid-center position of the Moulopoulos valve, to reduce the stagnation of blood flow and consequent thrombus and embolic formation expected from a valve at mid-center position.

The main advantage of tissue valves is that they do not cause blood clots to form as readily as do the mechanical valves, and therefore, they do not absolutely require systemic anticoagulation. The major disadvantage of tissue valves is that they lack the long-term durability of mechanical valves. Tissue valves have a significant failure rate, usually within ten years following implantation. One cause of these failures is believed to be the chemical treatment of the animal tissue that prevents it from being antigenic to the patient. In addition, the presence of extensive suturing prevents the artificial tissue valve from being anatomically accurate in comparison to a normal heart valve, even in the aortic valve position.

A shortcoming of prior artificial tissue valves has been the inability to effectively simulate the exact anatomy of a native heart valve. Although transplanted human or porcine aortic valves have the gross appearance of native aortic valves, the fixation process (freezing with

liquid nitrogen, and chemical treatment, respectively) alters the histologic characteristics of the valve tissue. Porcine and bovine pericardial valves not only require chemical preparation (usually involving fixation with glutaraldehyde), but the leaflets must be sutured to cloth-covered stents in order to hold the leaflets in position for proper opening and closing of the valve. Additionally, the leaflets of most such tissue valves are constructed by cutting or suturing the tissue material, resulting in leaflets that do not duplicate the form and function of a real valve.

SUMMARY OF THE INVENTION

The present invention is a replacement heart valve device and method of making same. The replacement heart valve device, in a preferred embodiment, comprises a stent made of stainless steel or self-expanding nitinol and a completely newly designed artificial biological tissue valve disposed within the inner space of the stent. The cusp or leaflet portion of the valve means is formed by folding of the pericardium material used to create the valve. The cusps/leaflets open in response to blood flow in one direction and close in response to blood flow in the opposite direction. Preferably the tubular portion of the valve means contains the same number of cusps as the native valve being replaced, in substantially the same size and configuration. The outer surface of the valve means is attached to the stent member.

The replacement heart valve device is preferably implanted using a delivery system having a central part which consists of a flexible hollow tube catheter that allows a metallic guide wire to be advanced inside it. The stented valve is collapsed over the central tube and it is covered by a movable sheath. The sheath keeps the stented valve in the collapsed position. Once the cover sheath is moved backwards, the stented valve can be deployed. The endovascular stented-valve, in a preferred embodiment, is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow.

The present invention also comprises a method of making a replacement heart valve device. In order to make the valve, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a

solution of gluteraldehyde, preferably at a concentration of about 0.07% during 36 hours, then the pericardium is transferred to a solution of ethanol, preferably at a concentration of about 60% before making the valve. The material is dried in order to make it easier to handle and fold. The valve is formed by taking a rectangular fragment of bovine pericardium and folding it in such a way that forms a three-leaflet valve. The valve can also be made from fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts or synthetic non-biological, non-thrombogenic material. The folding of the pericardium material to create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of the valve leaflets. The valve is rehydrated after being formed. The method of the present invention also greatly reduces the risk of tearing of the cusps or leaflets, since they are integral to the valve rather than being attached by suturing.

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The replacement heart valve device of the present invention can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation medication and treatment. The present invention can be practiced in applications with respect to each of the heart's valves.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 depicts a side perspective view of the replacement heart valve of the present invention in one embodiment without the stent.

Fig. 2 depicts the folds which form the leaflets or cusps of the replacement heart valve of the present invention in one embodiment.

Fig. 3 depicts the procedure for folding the pericardium tissue starting material to create the replacement heart valve of the present invention.

Fig. 4 depicts a side perspective view of the replacement heart valve of the present invention in one embodiment mounted within a stent.

Fig. 5 depicts a cross-sectional view of one embodiment of the replacement heart valve of the present invention mounted within a self-expanding stent, with the stent in the expanded position.

Fig. 6 depicts a side perspective view of one embodiment of the replacement heart valve of the present invention mounted within a self-expanding stent in the collapsed position.

Fig. 7 depicts the suture points of one embodiment of the replacement heart valve of the present invention.

Fig. 8 depicts the implantation/delivery system used with the present invention in a preferred embodiment.

DESCRIPTION OF A PREFERRED EMBODIMENT

The present invention comprises a percutaneously implantable replacement heart valve and a method for making same. The artificial heart valve device of the present invention is capable of exhibiting a variable diameter between a compressed or collapsed position and an expanded position. A preferred embodiment of the replacement heart valve according to the present invention is set forth in FIGS. 1 and 2. The replacement heart valve comprises a stent member __ and a flexible valve means __. The stent member is self-expanding and has a first cylindrical shape in its compressed or collapsed configuration and a second, larger cylindrical shape in its expanded configuration. The valve means comprises a generally tubular center portion and, preferably, a peripheral upstanding cusp or leaflet portion. The valve means is

disposed within the cylindrical stent member with the tubular portion transverse of and at some acute angle relative to the stent walls. The diameter of the tubular portion is substantially the same as the inside diameter of the stent member in its initial expanded configuration. The peripheral upstanding cusp or leaflet portion is disposed substantially parallel to the walls of the stent member similar to a cuff on a shirt. The center portion __ of the valve means __ is generally tubular in shape and comprises three leaflets __ as shown, although it is understood that there could be from two to four leaflets. The tubular portion of the valve means is attached to the stent member __ by a plurality of sutures __.

The leaflet portion of the valve means __ extends across or transverse of the cylindrical stent. The leaflets __ are the actual valve and allow for one-way flow of blood. The leaflet portion as connected to the rest of the valve resembles the cuff of a shirt. The configuration of the stent member __ and the flexible, resilient material of construction allows the valve to collapse into a relatively small cylinder __ as seen in FIG. 6. The replacement heart valve will not stay in its collapsed configuration without being restrained. Once the restraint is removed, the self-expanding stent member __ will cause the artificial heart valve to take its expanded configuration, as seen in FIG. __.

Stent Member

The stent member __ comprises self-expanding nickel-titanium alloy, also called "nitinol," in a sine wave-like configuration as shown in FIG. 1. An enlarged view of a preferred embodiment of the stent member for use in the replacement heart valve of the invention is depicted in FIG. 5. The stent member __ includes a length of wire __ formed in a closed zigzag configuration. The wire can be a single piece, stamped or extruded, or it could be formed by welding the free ends together as at __. The straight sections __ of the stent are joined by bends __. The stent is readily compressible to a small cylindrical shape and resiliently self-expandable to the shape shown in FIG. 5.

The stent members of the artificial heart valves of the present invention may be made from various metal alloys, titanium, titanium alloy, nitinol, stainless steel, or other resilient, flexible non-toxic, non-thrombogenic, physiologically acceptable and biocompatible materials. The configuration may be the zigzag configuration shown or a sine wave configuration, mesh configuration or a similar configuration which will allow the stent to be readily collapsible and self-expandable. When a zigzag or sine wave configured stent member is used, the diameter of the wire from which the stent is made should be from about [0.010 to 0.035] inches, preferably from about [0.012 to 0.025] inches. The diameter of the stent member will be from about [1.5 to 3.5 cm], preferably from about [1.75 to 3.00 cm], and the length of the stent member will be from about [1.0 to 10 cm], preferably from about [1.1 to 5 cm.]

The stent used in a preferred embodiment of the present invention is fabricated from a "shaped memory" alloy, nitinol, which is composed of nickel and titanium. Nitinol wire is first fashioned into the desired shape for the device and then the device is heat annealed. A meshwork of nitinol wire of approximately 0.008 inch gauge is formed into a tubular structure with a minimum central diameter of 20 min to make the stent. Away from its central portion, the tubular structure flares markedly at both ends in a trumpet-like configuration. The maximum diameter of the flared ends of the stent is approximately 30 mm. The purpose of the stent is to maintain a semi-rigid patent channel through the diseased cardiac valve following its implantation.

When the components of the replacement heart valve device are exposed to cold temperatures, they become very flexible and supple, allowing them to be compressed down and pass easily through the delivery sheath. A cold temperature is maintained within the sheath during delivery to the deployment site by constantly infusing the sheath with an iced saline solution. Once the valve components are exposed to body temperature at the end of the sheath, they instantaneously reassume their predetermined shapes, thus allowing them to function as designed.

Preferably the stent member carries a plurality of barbs extending outwardly from the outside surface of the stent member for fixing the heart valve in a desired position. More preferably the barbs are disposed in two spaced-apart, circular configurations with the barbs in one circle extending in an upstream direction and the barbs in the other circle extending in a downstream direction. It is especially preferable that the barbs on the inflow side of the valve point in the direction of flow and the barbs on the outflow side point in the direction opposite to flow. It is preferred that the stent be formed of titanium alloy wire or other flexible, relatively rigid, physiologically acceptable material arranged in a closed zigzag configuration so that the stent member will readily collapse and expand as pressure is applied and released, respectively.

Valve Means

The valve means is flexible, compressible, host-compatible, and non-thrombogenic. The valve can be, for example, fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts. Synthetic biocompatible materials such as polytetrafluoroethylene, polyester and the like may be used. The preferred material for the valve means is bovine pericardium tissue. The valve means is disposed within the cylindrical stent member with the tubular portion transverse of and at some acute angle relative to the stent walls. The diameter of the tubular portion is substantially the same as the inside diameter of the stent member in its initial expanded configuration. The peripheral upstanding cusp or leaflet portion is disposed substantially parallel to the walls of the stent member similar to a cuff on a shirt.

The cusp or leaflet portion of the valve means is formed by folding of the pericardium material used to create the valve. The cusps/leaflets open in response to blood flow in one direction and close in response to blood flow in the opposite direction. Preferably the tubular portion of the valve means contains the same number of cusps as the native valve being replaced, in substantially the same size and configuration.

Method of Making Replacement Heart Valve Device

The present invention also comprises a method of making a replacement heart valve device. In order to make the valve, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a solution of gluteraldehyde, preferably at a concentration of about 0.07% during 36 hours, then the pericardium is transferred to a solution of ethanol, preferably at a concentration of about 60% before making the valve. The valve is formed by taking a rectangular fragment of bovine pericardium and folding it in such a way that forms a three-leaflet or desired number of leaflet valve. FIG. 2 depicts the folds which form the cusps or leaflets, and FIG. 3 depicts the folding procedure. The folding of the pericardium material to create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of the valve leaflets. It also greatly reduces the risk of tearing of the cusps or leaflets, since they are integral to the valve rather than being attached by suturing.

In order to make the pericardium material less slippery and easier to fold, the pericardium is dried, preferably with artificial light using a 60-watt lamp with the pericardium material placed in a flat aluminum surface to dry it homogeneously. A photo drying machine can also be used. The final result is a homogeneous tissue that looks like plastic paper and makes it easy to manipulate to fold and suture the valve. Once the valve is formed it is re-hydrated by placing it in a solution of water and 70% alcohol. In approximately 3 days the valve is fully rehydrated.

Attachment of the Valve Means to the Stent Member

The valve means is then attached to the inner channel of the stent member by suturing the outer surface of the valve means' pericardium material to the stent member. Fig. 7 depicts preferred suture points of one embodiment of the present invention: 3-point fixation or 6-point fixation at each border of the stent. Other fixation schemes can be utilized, such as, by way of

non-limiting example, fixation on both borders 18 points at each end following a single plane and 36 fixation points following to adjacent vertical planes. The use of only one plane of fixation points helps prevent systolic collapse of the proximal edge of the valve means. A fold on the border of the pericardium material prevents tearing. The attachment position of the valve is preferably closer to the proximal and wider part of the stent.

The sequence of steps can vary. The pericardium material can be fixed in glutaraldehyde before attachment to the stent or the valve can be formed and then fixed with gluteraldehyde after mounting it in the stent. One observation noted is that the material becomes whiter and apparently increases its elasticity. 1mm vascular clips keep the cusps coapted while fixing them in gluteraldehyde. The use of metallic clips to keep both cusps adjacent to each other after 24 hours of fixation in gluteraldehyde helps to educate the material and make the primary position of the valve cusps adjacent to each other. After the clips are removed, there are no lesions to the valve.

Different suture materials can be used, including, in a preferred embodiment, prolene 6-0 and Mersilene 6-0 which is a braided suture.

Implantation of Replacement Heart Valve Device

The replacement heart valve device of the present invention is preferably used in surgical procedures involving the percutaneous and transluminal removal of the diseased or defective heart valve and the percutaneous and transluminal implantation of the new heart valve described above. The defective heart valve is removed by a suitable modality, such as, for example, laser, ultrasound, mechanical, or other suitable forms of delivery of energy, or phacoemulsion, including, but not limited to, laser lithotripsy, mechanical lithotripsy, electrohydraulic lithotripsy, and laser or mechanical ablation. To remove the native heart valve that is being replaced, a guidewire is inserted percutaneously and transluminally using standard vascular or angiography techniques. The distal end of the guidewire is manipulated to extend

through and across the defective heart valve. Then a catheter is advanced distally through the femoral artery to a point proximal to the defective heart valve, between the origin of the coronary artery and the origin of the right subclavian artery. The position of the distal end of catheter can be monitored by observation of radiopaque markers. Collector member is preferably inflated and occludes the aorta at a point between the origin of the coronary artery and the right subclavian artery. Next, a balloon and cutting tool are advanced through the catheter so that the cutting tool and uninflated balloon are distal to the defective heart valve. Optionally an additional step, such as balloon dilatation or atherectomy, may be required to provide a passageway through the heart valve. A catheter is also placed into the coronary sinus via a transjugular puncture. This catheter is used for infusion of blood or cardioplegia solution during the portion of the procedure when the aorta is occluded. The absence of valves in the cardiac venous system allows retrograde flow so that there will be an effluence of fluid from the coronary arteries. This flow of fluid is desired to prevent embolization of material into the coronary arteries during the procedure. Once the cutting tool is in place, the balloon is inflated and flexible shaft is rotated. Once the cutting tool has reached the appropriate rotation speed, the cutting tool is pulled proximally to remove the defective heart valve. The balloon and the cutting tool are spaced apart so that the inflated balloon will be stopped by the perimeter, unremoved portion of the defective heart valve, which will signal the physician that the valve has been removed, as well as protect the heart and aorta from damage from the valve removal device. Once it is determined that the defective heart valve has been removed, the cutting tool is slowed or stopped altogether and the balloon is deflated. The cutting tool and the deflated balloon are pulled proximally through catheter. Then, a catheter containing an artificial heart valve is inserted and the artificial heart valve is placed as described above.

The delivery and implantation system of the replacement artificial heart valve of the present invention percutaneously and transluminally includes a flexible catheter which may be inserted into a vessel of the patient and moved within that vessel. The distal end of the catheter,

which is hollow and carries the replacement heart valve of the present invention in its collapsed configuration, is guided to a site where it is desired to implant the replacement heart valve. The catheter has a pusher member disposed within the catheter lumen and extending from the proximal end of the catheter to the hollow section at the distal end of the catheter. Once the distal end of the catheter is positioned as desired, the pusher mechanism is activated and the distal portion of the replacement heart valve is pushed out of the catheter and the stent member partially expands. In this position the stent member is restrained so that it doesn't pop out and is held for controlled release, with the potential that the replacement heart valve can be recovered if there is a problem with the positioning. The catheter is them retracted slightly and the replacement heart valve is completely pushed out of the catheter and released from the catheter to allow the stent member to fully expand. If the stent member includes two circles of barbs on its outer surface as previously described, the first push and retraction will set one circle of barbs in adjacent tissue and the second push and release of the replacement heart valve will set the other circle of barbs in adjacent tissue and securely fix the replacement heart valve in place when the valve is released from the catheter.

Alternatively, or in combination with the above, the replacement heart valve could be positioned over a metallic guidewire that is advanced through the catheter. The replacement heart valve device of the present invention is preferably implanted percutaneously through an aortic passageway to, or near to, the location from which the natural heart valve has been removed. Referring to Fig. 8, the implantation system comprises a flexible hollow tube catheter with a metallic guide wire disposed within it. The stented valve is collapsed over the tube and is covered by a moveable sheath. The moveable sheath maintains the stented valve in the collapsed position. comprises the following steps: inserting the replacement heart valve device in the lumen of a central blood vessel via entry through the brachial or femoral artery using a needle or exposing the artery surgically; placing a guide wire through the entry vessel and advancing it to the desired position; advancing dilators over the wire to increase the lumen of

the entry site, thereby preparing the artery to receive the heart-valve; and advancing the heart-valve to the desired place. The stented-valve is released by pulling the cover sheath of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advanced over the wire and an aortogram is performed to assess the competency of the valve.

Before creation of the valve means and implantation, the patient is studied to determine the architecture of the patient's heart. Useful techniques include fluoroscopy, transesophageal echocardiography, MRI, and angiography. The results of this study will enable the physician to determine the appropriate size for the replacement heart valve.

In one procedure for implantation of the replacement heart valve device of the present invention, the femoral artery of the patient is canulated using a Cook needle and a standard J wire is advanced into the artery either percutaneously or after surgical exposure of the artery. An 8 F introducer is advanced into the femoral artery over the wire. The J wire is then withdrawn and anticoagulation is started using heparin 60 U/Kg intravenously. Once vascular access is obtained an aortogram is performed for anatomical evaluation. A special wire (Lunderquist or Amplatz superstiff) is advanced into the aortic arch and dilators progressively larger are advanced over the wire, starting with 12 F all the way to 18 F. After this the valve introducer device containing the prosthetic valve device is then inserted and used to transport the replacement valve over a guidewire to the desired position. The stented-valve is released by pulling the cover sheath of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advanced over the wire and repeat aortogram is performed to assess the competency of the valve.

When the device is used to treat severe leakage of the aortic valve, the native valve is left in place and the prosthetic stented valve is deployed below the subclavian artery. When the device is used to treat aortic stenosis, first the stenotic valve needs to be opened using either

aortic valvuloplasty or cutting and if this procedure induces aortic insufficiency the stented valve is placed to prevent the regurgitation.

Intravascular ultrasound or an angioscope passed intravascularly via either the venous system through the intra-atrial septum across the mitral valve and into the left ventricle or retrograde via the femoral artery would provide the added benefit of allowing constant high definition imaging of the entire procedure and high flow irrigation.

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The prosthetic valve device can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation. In addition, with the development of longer-life, flexible, non-thrombogenic synthetic valve alternatives to bioprosthesis, the prosthetic valve device will be indicated in all patients where the relative advantages of the life-span, the non-thrombogenic quality, and the ease of insertion of prosthetic valve devices outweigh the disadvantages of mechanical valves. Anticoagulation may be beneficial in certain clinical situations for either short or long term use.

This method of percutaneous endovascular heart-valve replacement, in contrast to open heart surgical procedures, requires only local anesthesia, partial or no cardiac bypass, one to two days hospitalization, and should result in a reduced mortality rate as compared to open heart procedures.

While the present invention has been shown and described herein in what is considered to be a preferred embodiment thereof, illustrating the results and advantages over the prior art obtained through the present invention, the invention is not limited to the specific embodiments

described above. Thus, the forms of the invention shown and described herein are to be taken as illustrative and other embodiments may be selected without departing from the spirit and scope of the present invention.

CLAIMS

Having thus described the invention, what is claimed is:

1. A percutaneously implantable replacement heart valve device comprising a self-expanding stent member and an artificial valve means made of biocompatible tissue material and disposed within the inner cavity of said stent member affixed at one or more points to said stent member, said valve means having cusps or leaflets formed by folding of said biocompatible tissue material.

2. The percutaneously implantable replacement heart valve of claim 1, wherein said stent member is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium, stainless steel [add others].

3. The percutaneously implantable replacement heart valve of claim 1, wherein said biocompatible tissue material of said valve means comprises bovine pericardium tissue.

4. The percutaneously implantable replacement heart valve of claim 1, wherein said biocompatible tissue material of said valve means comprises porcine pericardium tissue.

5. The percutaneously implantable replacement heart valve of claim 1, wherein said biocompatible tissue material of said valve means comprises autologous tissue obtained from the patient into whom said replacement heart valve will be implanted.

6. A method of making a percutaneously implantable replacement heart valve comprising the following steps:

obtaining a substantially rectangular segment of biocompatible tissue material;

soaking said biocompatible tissue material in a gluteraldehyde solution;

transferring said biocompatible tissue material from said gluteraldehyde solution to an ethanol solution;

drying said biocompatible tissue material;

folding said dried biocompatible tissue material to create cusps or leaflets and a cuffed tubular valve structure;

affixing said folded biocompatible tissue material to the inner cavity of a stent.

ABSTRACT

The present invention comprises a percutaneously implantable replacement heart valve device and a method of making same. The replacement heart valve device comprises a stent member made of stainless steel or self-expanding nitinol, a biological tissue artificial valve means disposed within the inner space of the stent member. An implantation and delivery system having a central part which consists of a flexible hollow tube catheter that allows a metallic wire guide to be advanced inside it. The endovascular stented-valve is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow. The present invention also comprises a novel method of making a replacement heart valve by taking a rectangular fragment of bovine pericardium treating, drying, folding and rehydrating it in such a way that forms a two- or three-leaflet/cusp valve with the leaflets/cusps formed by folding, thereby eliminating the extent of suturing required, providing improved durability and function.

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December 28, 2001

ATTORNEY-CLIENT PRIVILEGED
CONFIDENTIAL COMMUNICATION

VIA HAND DELIVERY

David Paniagua, M.D.
1865 – 79th Street Causeway
Apartment 7-H
Miami Beach, Florida 33141

Re: Revised draft of patent application specification for percutaneously implantable heart valve replacement device and method of making same

Dear Dr. Paniagua:

Enclosed for your review and revision is a revised draft of the nonprovisional patent application specification for your above-referenced invention. Please review the draft at your earliest convenience (please also review the draft with the other co-inventors) and provide your comments, revisions and additional text.

Best regards,

GREENBERG TRAURIG, P.A.

Manuel R. Valcarcel, Esq.

MRV/mp

Enclosure

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Docket No. 51458.010100

NON-PROVISIONAL PATENT APPLICATION

SPECIFICATION

TO WHOM IT MAY CONCERN:

BE IT KNOWN THAT WE, David Paniagua, Eduardo Induni, Carlos Mejia, Francisco Lopez and R. David Fish, ~~each citizens of the United States of America,~~ have invented a new and useful percutaneously implantable replacement heart valve **device** and method of making same, of which the following is the Specification.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is in the field of heart valve replacement. More specifically, the present invention is directed to a percutaneously implantable replacement heart valve and method of making same.

2. Description of Related Art

There have been numerous efforts in the field of heart valve replacement to improve both the durability and effectiveness of replacement heart valves as well as the ease of implantation. A brief description of heart valves and heart function follows to provide relevant background for the present invention.

There are four valves in the heart that serve to direct the flow of blood through the two sides of the heart in a forward direction. On the left (systemic) side of the heart are: 1) the mitral valve, located between the left atrium and the left ventricle, and 2) the aortic valve, located between the left ventricle and the aorta. These two valves direct oxygenated blood coming from the lungs through the left side of the heart into the aorta for distribution to the body. On the right (pulmonary) side of the heart are: 1) the tricuspid valve, located between the right atrium and the right ventricle, and 2) the pulmonary valve, located between the right ventricle and the pulmonary artery. These two valves direct de-oxygenated blood coming from the body through the right side of the heart into the pulmonary artery for distribution to the lungs, where it again becomes re-oxygenated to begin the circuit anew.

Heart valves are passive structures that simply open and close in response to differential pressures on either side of the particular valve. They consist of moveable "leaflets" that are designed simply to open and close in response to differential pressures on either side of the valve's leaflets. The mitral valve has two leaflets and the tricuspid valve has three. The

aortic and pulmonary valves are referred to as "semilunar valves" because of the unique appearance of their leaflets, which are more aptly termed "cusps" and are shaped somewhat like a half-moon. The aortic and pulmonary valves each have three cusps.

In general, the components of heart valves include the valve annulus, which will remain as a roughly circular open ring after the leaflets of a diseased or damaged valve have been removed; leaflets or cusps; papillary muscles which are attached at their bases to the interior surface of the left or right ventricular wall; and multiple chordae tendineae, which couple the valve leaflets or cusps to the papillary muscles. There is no one-to-one chordal connection between the leaflets and the papillary muscles; instead, numerous chordae are present, and chordae from each papillary muscle attach to both of the valve leaflets.

When the left ventricular wall relaxes so that the ventricular chamber enlarges and draws in blood, the leaflets of the mitral valve separate and the valve opens. Oxygenated blood flows in a downward direction through the valve, to fill the expanding ventricular cavity. Once the left ventricular cavity has filled, the left ventricle contracts, causing a rapid rise in the left ventricular cavitary pressure. This causes the mitral valve to close while the aortic valve opens, allowing the oxygenated blood to be ejected from the left ventricle into the aorta. The chordae tendineae of the mitral valve prevent the mitral leaflets from prolapsing back into the left atrium when the left ventricular chamber contracts.

The three leaflets, chordae tendineae, and papillary muscles of the tricuspid valve function in a similar manner, in response to the filling of the right ventricle and its subsequent contraction. The cusps of the aortic valve also respond passively to pressure differentials between the left ventricle and the aorta. When the left ventricle contracts, the aortic valve cusps open to allow the flow of oxygenated blood from the left ventricle into the aorta. When the left ventricle relaxes, the aortic valve cusps reapproximate to prevent the blood which has entered the aorta from leaking (regurgitating) back into the left ventricle. The pulmonary valve cusps

respond passively in the same manner in response to relaxation and contraction of the right ventricle in moving de-oxygenated blood into the pulmonary artery and thence to the lungs for re-oxygenation. Neither of these semilunar valves has associated chordae tendineae or papillary muscles.

Problems that can develop with heart valves consist of stenosis, in which a valve does not open properly, and/or insufficiency, also called regurgitation, in which a valve does not close properly. In addition to stenosis and insufficiency of heart valves, heart valves may need to be surgically repaired or replaced due to certain types of bacterial or fungal infections in which the valve may continue to function normally, but nevertheless harbors an overgrowth of bacteria (vegetation) on the leaflets of the valve that may embolize and lodge downstream in a vital artery. If such vegetations are on the valves of the left side (i.e., the systemic circulation side) of the heart, embolization may occur, resulting in sudden loss of the blood supply to the affected body organ and immediate malfunction of that organ. The organ most commonly affected by such embolization is the brain, in which case the patient suffers a stroke. Thus, surgical replacement of either the mitral or aortic valve (left-sided heart valves) may be necessary for this problem even though neither stenosis nor insufficiency of either valve is present. Likewise, bacterial or fungal vegetations on the tricuspid valve may embolize to the lungs resulting in a lung abscess and therefore, may require replacement of the tricuspid valve even though no tricuspid valve stenosis or insufficiency is present.

These problems are treated by surgical repair of valves, although often the valves are too diseased to repair and must be replaced. If a heart valve must be replaced, there are currently several options available, and the choice of a particular type of artificial valve depends on factors such as the location of the valve, the age and other specifics of the patient, and the surgeon's experiences and preferences. Currently in the United States over 100,000 defective heart valves are replaced annually, at an approximate cost of $30-50,000 per procedure, and

thus it would be desirable if heart valves could be replaced using minimally invasive techniques and without having to repeat the procedure within a matter of years due to the lack of durability of the replacement heart valve. It would be especially advantageous if a defective heart valve could be removed via an endovascular procedure, that is, a procedure where the invasion into the body is through a blood vessel such as the femoral artery. The procedure is then carried out percutaneously and transluminally using the vascular system to convey appropriate devices to the position in the body wherein it is desired to carry out the desired procedure. An example of such a procedure would be angioplasty, wherein a catheter carrying a small balloon at its distal end is manipulated through the body's vessels to a point where there is a blockage in a vessel. The balloon is expanded to create an opening in the blockage, and then the balloon is deflated and the catheter and balloon are removed from the vessel.

Endovascular procedures have substantial benefits both from the standpoint of health and safety as well as cost. Such procedures require minimal invasion of the human body, and there is consequently considerable reduction and in some instances even elimination, of the use of a general anesthesia and much shorter hospital stays.

Replacement heart valves can be categorized as either artificial mechanical valves, transplanted valves and tissue valves. Replacement heart valves are designed to optimize hemodynamic performance, thrombogenicity and durability. Another factor taken into consideration is the relative ease of surgical implantation.

Mechanical valves are typically constructed from nonbiological materials such as plastics, metals and other artificial materials which, while durable, are expensive and prone to blood clotting which increases the risk of an embolism. Anticoagulants taken to help against blood clotting can further complicate the patient's health due to increased risks for hemorrhages.

Transplanted valves are natural valves taken from cadavers. These valves are typically removed and frozen in liquid nitrogen, and are stored for later use. They are typically fixed in glutaraldehyde to eliminate antigenicity and are sutured in place, typically with a stent.

Artificial tissue valves are valves constructed from animal tissue, such as bovine or porcine tissue. Efforts have also been made at using tissue from the patient for which the valve will be constructed.

Most tissue valves are constructed by sewing the leaflets of pig aortic valves to a stent to hold the leaflets in proper position, or by constructing valve leaflets from the pericardial sac of cows or pigs and sewing them to a stent. The porcine or bovine tissue is chemically treated to alleviate any antigenicity. The pericardium is a membrane that surrounds the heart and isolates it from the rest of the chest wall structures. The pericardium is a thin and very slippery, which makes it difficult for suturing in a millimetricly precise way. The method of making the replacement heart valve of the present invention solves this problem through a process to dry the pericardium in such a way that makes it possible to handle and fold more easily.

For example, one prior replacement heart valve requires each sculpted leaflet to be trimmed in a way that forms an extended flap, which becomes a relatively narrow strand of tissue near its tip. The tip of each pericardial tissue strand is sutured directly to a papillary muscle, causing the strand to mimic a chordae tendineae. Each strand extends from the center of a leaflet in the valve, and each strand is sutured directly to either an anterior and posterior papillary muscle. This requires each leaflet to be positioned directly over a papillary muscle. This effectively rotates the leaflets of the valve about 90 degrees as compared to the leaflets of a native valve. The line of commissure between the leaflets, when they are pressed together during systole, will bisect (at a perpendicular angle) an imaginary line that crosses the peaks of the two papillary muscles, instead of lying roughly along that line as occurs in a native valve.

A different approach to creating artificial tissue valves is described in U.S. Patent Nos. 5,163,955 to Calvin, et al. and 5,571,174 and 5,653,749 to Love. Using a cutting die, the pericardial tissue is cut into a carefully defined geometric shape, treated with glutaraldehyde, then clamped in a sandwich-fashion between two stent components. This creates a tri-leaflet valve that resembles an aortic or pulmonary valve, having semilunar-type cusps rather than atrioventricular-type leaflets.

U.S. Patent No. 3,671,979 to Moulopoulos describes an endovascularly inserted conical shaped umbrella-like valve positioned and held in place by an elongated mounting catheter at a supra-annular site to the aortic valve in a nearby arterial vessel. The conical end points toward the malfunctioning aortic valve and the umbrella's distal ends open up against the aorta wall with reverse blood flow, thereby preventing regurgitation.

U.S. Patent No. 4,056,854 to Boretos describes an endovascularly inserted, catheter mounted, supra-annular valve in which the circular frame abuts the wall of the artery and attached flaps of flexible membrane extend distally in the vasculature. The flaps lie against the artery wall during forward flow, and close inward towards the central catheter to prevent regurgitation during reverse blood flow. The Boretos valve was designed to be positioned against the artery wall during forward flow, as compared to the mid-center position of the Moulopoulos valve, to reduce the stagnation of blood flow and consequent thrombus and embolic formation expected from a valve at mid-center position.

The main advantage of tissue valves is that they do not cause blood clots to form as readily as do the mechanical valves, and therefore, they do not absolutely require systemic anticoagulation. The major disadvantage of tissue valves is that they lack the long-term durability of mechanical valves. Tissue valves have a significant failure rate, usually within ten years following implantation. One cause of these failures is believed to be the chemical treatment of the animal tissue that prevents it from being antigenic to the patient. In addition,

the presence of extensive suturing prevents the artificial tissue valve from being anatomically accurate in comparison to a normal heart valve, even in the aortic valve position.

A shortcoming of prior artificial tissue valves has been the inability to effectively simulate the exact anatomy of a native heart valve. Although transplanted human or porcine aortic valves have the gross appearance of native aortic valves, the fixation process (freezing with liquid nitrogen, and chemical treatment, respectively) alters the histologic characteristics of the valve tissue. Porcine and bovine pericardial valves not only require chemical preparation (usually involving fixation with glutaraldehyde), but the leaflets must be sutured to cloth-covered stents in order to hold the leaflets in position for proper opening and closing of the valve. Additionally, the leaflets of most such tissue valves are constructed by cutting or suturing the tissue material, resulting in leaflets that do not duplicate the form and function of a real valve.

SUMMARY OF THE INVENTION

The present invention is a replacement heart valve device and method of making same. The replacement heart valve device, in a preferred embodiment, comprises a stent made of stainless steel or self-expanding nitinol and a completely newly designed artificial biological tissue valve disposed within the inner space of the stent. The cusp or leaflet portion of the valve means is formed by folding of the pericardium material used to create the valve. **Other forms of tissue and suitable synthetic materials can also be used for the valve, formed in a sheet of starting material. The folded design provides a number of advantages over prior designs, including improved resistance to tearing at suture lines.** The cusps/leaflets open in response to blood flow in one direction and close in response to blood flow in the opposite direction. Preferably the tubular portion of the valve means contains the same number of cusps as the native valve being replaced, in substantially the same size and configuration. The outer surface of the valve means is attached to the stent member.

The replacement heart valve device is preferably implanted using a delivery system having a central part which consists of a flexible hollow tube catheter that allows a metallic guide wire to be advanced inside it. The stented valve is collapsed over the central tube and it is covered by a movable sheath. The sheath keeps the stented valve in the collapsed position. Once the cover sheath is moved backwards, the stented valve can be deployed. The endovascular stented-valve, in a preferred embodiment, is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow. The stent can either be self-expanding or the stent can be expandable through use of a balloon catheter.

The present invention also comprises a method of making a replacement heart valve device. In order to make the valve, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a solution of gluteraldehyde, preferably at a concentration of about 0.07% during 36 hours, then the pericardium is transferred to a solution of ethanol, preferably at a concentration of about 60% before making the valve. The material is dried in order to make it easier to handle and fold. The valve is formed by taking a rectangular fragment of bovine pericardium and folding it in such a way that forms a three-leaflet valve. The valve can also be made in the same manner from fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts or synthetic non-biological, non-thrombogenic material. The folding of the pericardium material to create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of the valve leaflets. The valve is rehydrated after being formed. The method of the present invention also greatly reduces the risk of tearing of the cusps or leaflets, since they are integral to the valve rather than being attached by suturing.

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as

used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The replacement heart valve device of the present invention can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation medication and treatment. The present invention can be practiced in applications with respect to each of the heart's valves.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 depicts a side perspective view of the replacement heart valve device of the present invention in one embodiment ~~without~~with the ~~stent~~valve in the closed position.

Fig. 2 depicts the folds which form the leaflets or cusps of the replacement heart valve of the present invention in one embodiment.

~~Fig.~~Figs. 3 ~~depicts~~A and 3B depict the procedure for folding the pericardium tissue starting material to create the replacement heart valve of the present invention.

Fig. 4 depicts a side perspective view of the replacement heart valve device of the present invention in one embodiment represented as if implanted within an artery.

Fig. 45 depicts a side ~~perspective~~ view of one embodiment of the replacement heart valve device of the present invention ~~in one embodiment~~ mounted within a self-expanding stent, with the stent in the expanded position.

Fig. ~~5~~6 depicts a ~~cross-sectional~~side perspective view of one embodiment of the replacement heart valve device of the present invention mounted within a self-expanding stent, ~~with the stent~~ in the ~~expanded~~collapsed position.

~~Fig. 6 depicts a side perspective view of one embodiment of the replacement heart valve of the present invention mounted within a self-expanding stent in the collapsed position.~~

~~Fig.~~Fig. 7 ~~depicts~~depicts the suture points of one embodiment of the replacement heart valve device of the present invention.

Fig. 8 depicts the implantation/delivery system used with the present invention in a preferred embodiment.

DESCRIPTION OF A PREFERRED EMBODIMENT

The present invention comprises a percutaneously implantable replacement heart valve and a method for making same. The artificial heart valve device of the present invention is capable of exhibiting a variable diameter between a compressed or collapsed position and an expanded position. A preferred embodiment of the replacement heart valve device according to the present invention is set forth in ~~FIGS~~FIG. ~~1 and 2,~~5. The replacement heart valve device comprises a stent member ~~—~~100 and a flexible valve means ~~—~~200. The stent member 100 is preferably self-expanding although balloon-expandable stents can be used as well, and has a first cylindrical shape in its compressed or collapsed configuration and a second, larger cylindrical shape in its expanded configuration. ~~The~~Referring to FIG. 1, the valve means 200 comprises a generally tubular ~~center~~ portion 210 and, preferably, a peripheral upstanding cusp or leaflet portion~~.~~ 220. The valve means 200 is disposed within the cylindrical stent member 100 with the tubular portion 210 transverse of and at some acute angle relative to the stent walls. The diameter of the tubular portion 210 is substantially the same as the inside diameter of the stent member in its initial expanded configuration. The peripheral upstanding cusp or leaflet portion 220 is disposed substantially parallel to the walls of the stent member similar to a cuff on a shirt. The ~~center~~cusp or leaflet portion ~~—~~220 of the valve means ~~—~~200

is generally tubular in shape and comprises three leaflets —221, 222 and 223 as shown, although it is understood that there could be from two to four leaflets. The tubular portion of the valve means 200 is attached to the stent member —100 by a plurality of sutures —300, as depicted in FIG. 7.

The leaflet portion 220 of the valve means —200 extends across or transverse of the cylindrical stent 100. The leaflets —221, 222 and 223 are the actual valve and allow for one-way flow of blood. The leaflet portion 220 as connected to the rest of the valve resembles the cuff of a shirt. The configuration of the stent member —100 and the flexible, resilient material of construction allows the valve to collapse into a relatively small cylinder — as seen in FIG. 6. The replacement heart valve will not stay in its collapsed configuration without being restrained. Once the restraint is removed, the self-expanding stent member —100 will cause the artificial heart valve to take its expanded configuration, as seen in FIG. —5.

Stent Member

The stent member —100 preferably comprises a self-expanding nickel-titanium alloy stent, also called "nitinol," in a sine wave-like configuration as shown in FIG. ~~1,~~5. An enlarged view of a preferred embodiment of the stent member for use in the replacement heart valve of the invention is depicted in FIG. 5. The stent member —100 includes a length of wire —110 formed in a closed zigzag configuration. The wire can be a single piece, stamped or extruded, or it could be formed by welding the free ends together ~~as at~~ —. The straight sections —of the stent member 100 are joined by bends —. The stent is readily compressible to a small cylindrical shape as depicted in FIGS. 6 and 8, and resiliently self-expandable to the shape shown in FIG. 5.

The stent ~~members~~member 100 of the artificial heart ~~valves~~valve device of the present invention may be made from various metal alloys, titanium, titanium alloy, nitinol,

stainless steel, or other resilient, flexible non-toxic, non-thrombogenic, physiologically acceptable and biocompatible materials. The configuration may be the zigzag configuration shown or a sine wave configuration, mesh configuration or a similar configuration which will allow the stent to be readily collapsible and self-expandable. When a zigzag or sine wave configured stent member is used, the diameter of the wire from which the stent is made ~~should~~is ~~be~~preferably from about [0.010 to 0.035] inches and still, preferably from about [0.012 to 0.025] inches. The diameter of the stent member will be from about [1.5 to 3.5 cm], preferably from about [1.75 to 3.00 cm], and the length of the stent member will be from about [1.0 to 10 cm], preferably from about [1.1 to 5 cm.]

The stent used in a preferred embodiment of the present invention is fabricated from a "shaped memory" alloy, nitinol, which is composed of nickel and titanium. Nitinol wire is first fashioned into the desired shape for the device and then the device is heat annealed. A meshwork of nitinol wire of approximately 0.008 inch gauge is formed into a tubular structure with a minimum central diameter of 20 min to make the stent. Away from its central portion, the tubular structure flares markedly at both ends in a trumpet-like configuration. The maximum diameter of the flared ends of the stent is approximately 30 mm. The purpose of the stent is to maintain a semi-rigid patent channel ~~through~~ the diseased cardiac valve following its implantation.

When the components of the replacement heart valve device are exposed to cold temperatures, they become very flexible and supple, allowing them to be compressed down and pass easily through the delivery sheath. A cold temperature is maintained within the sheath during delivery to the deployment site by constantly infusing the sheath with an iced saline solution. Once the valve components are exposed to body temperature at the end of the sheath, they instantaneously reassume their predetermined shapes, thus allowing them to function as designed.

Preferably the stent member 100 carries a plurality of barbs extending outwardly from the outside surface of the stent member for fixing the heart valve device in a desired position. More preferably the barbs are disposed in two spaced-apart, circular configurations with the barbs in one circle extending in an upstream direction and the barbs in the other circle extending in a downstream direction. It is especially preferable that the barbs on the inflow side of the valve point in the direction of flow and the barbs on the outflow side point in the direction opposite to flow. It is preferred that the stent be formed of titanium alloy wire or other flexible, relatively rigid, physiologically acceptable material arranged in a closed zigzag configuration so that the stent member will readily collapse and expand as pressure is applied and released, respectively.

Valve Means

The valve means 200 is flexible, compressible, host-compatible, and non-thrombogenic. The valve means 200 can be made from various materials, for example, fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts. Synthetic biocompatible materials such as polytetrafluoroethylene, polyester and the like may be used. The preferred material for the valve means 200 is bovine pericardium tissue. The valve means 200 is disposed within the cylindrical stent member 100 with the tubular portion 210 transverse of and at some acute angle relative to the stent walls. The diameter of the tubular portion 210 is substantially the same as the inside diameter of the stent member 100 in its initial expanded configuration. The peripheral upstanding cusp or leaflet portion 220 is disposed substantially parallel to the walls of the stent member 100 similar to a cuff on a shirt.

The cusp or leaflet portion 220 of the valve means 200 is formed by folding of the pericardium material used to create the valve. FIGS. 3A and 3B depict the way the sheet of heart valve starting material is folded. The cusps/leaflets 221, 222 and 223 open in

response to blood flow in one direction and close in response to blood flow in the opposite direction. Preferably the ~~tubular~~cusp or leaflet portion 220 of the valve means 200 contains the same number of cusps as the native valve being replaced, in substantially the same size and configuration.

Method of Making Replacement Heart Valve Device

The present invention also comprises a method of making a replacement heart valve device. In order to make the valve, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a solution of gluteraldehyde, preferably at a concentration of about 0.07% during 36 hours, then the pericardium is transferred to a solution of ethanol, preferably at a concentration of about 60% before making the valve. The valve is formed by taking a rectangular fragment of bovine pericardium and folding it in such a way that forms a three-leaflet or desired number of leaflet valve~~. FIG. 2 depicts the folds which form the cusps or leaflets, and FIG.~~ as shown in FIGS. 3A and 3 ~~depicts the folding procedure~~B. The folding of the pericardium material to create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of the valve leaflets. It also greatly reduces the risk of tearing of the cusps or leaflets, since they are integral to the valve rather than being attached by suturing.

In order to make the pericardium material less slippery and easier to fold, the pericardium is dried, preferably with artificial light using a 60-watt lamp with the pericardium material placed in a flat aluminum surface to dry it homogeneously. A photo drying machine can also be used. The final result is a homogeneous tissue that looks like plastic paper and makes it easy to manipulate to fold and suture the valve. Once the valve is formed it is re-hydrated by placing it in a solution of water and 70% alcohol. In approximately 3 days the valve is fully rehydrated.

Attachment of the Valve Means to the Stent Member

The valve means 200 is then attached to the inner channel of the stent member 100 by suturing the outer surface of the valve means' pericardium material to the stent member. ~~Fig~~FIG. 7 depicts preferred suture points of one embodiment of the present invention: 3-point fixation or 6-point fixation at each border of the stent. Other fixation schemes can be utilized, such as, by way of non-limiting example, fixation on both borders 18 points at each end following a single plane and 36 fixation points following to adjacent vertical planes. The use of only one plane of fixation points helps prevent systolic collapse of the proximal edge of the valve means. A fold on the border of the pericardium material prevents tearing. The attachment position of the valve is preferably closer to the proximal and wider part of the stent.

The sequence of steps can vary. The pericardium material can be fixed in glutaraldehyde before attachment to the stent or the valve can be formed and then fixed with gluteraldehyde after mounting it in the stent. One observation noted is that the material becomes whiter and apparently increases its elasticity. 1mm vascular clips keep the cusps coapted while fixing them in gluteraldehyde. The use of metallic clips to keep both cusps adjacent to each other after 24 hours of fixation in gluteraldehyde helps to educate the material and make the primary position of the valve cusps adjacent to each other. After the clips are removed, there are no lesions to the valve.

Different suture materials can be used, including, in a preferred embodiment, prolene 6-0 and Mersilene 6-0 which is a braided suture.

Implantation of Replacement Heart Valve Device

The replacement heart valve device of the present invention is preferably used in surgical procedures involving the percutaneous and transluminal removal of the diseased or defective heart valve and the percutaneous and transluminal implantation of the new heart

valve described above. The defective heart valve is removed by a suitable modality, such as, for example, laser, ultrasound, mechanical, or other suitable forms of delivery of energy, or phacoemulsion, including, but not limited to, laser lithotripsy, mechanical lithotripsy, electrohydraulic lithotripsy, and laser or mechanical ablation. To remove the native heart valve that is being replaced, a guidewire is inserted percutaneously and transluminally using standard vascular or angiography techniques. The distal end of the guidewire is manipulated to extend through and across the defective heart valve. Then a catheter is advanced distally through the femoral artery to a point proximal to the defective heart valve, between the origin of the coronary artery and the origin of the right subclavian artery. The position of the distal end of catheter can be monitored by observation of radiopaque markers. Collector member is preferably inflated and occludes the aorta at a point between the origin of the coronary artery and the right subclavian artery. Next, a balloon and cutting tool are advanced through the catheter so that the cutting tool and uninflated balloon are distal to the defective heart valve. Optionally an additional step, such as balloon dilatation or atherectomy, may be required to provide a passageway through the heart valve. A catheter is also placed into the coronary sinus via a transjugular puncture. This catheter is used for infusion of blood or cardioplegia solution during the portion of the procedure when the aorta is occluded. The absence of valves in the cardiac venous system allows retrograde flow so that there will be an effluence of fluid from the coronary arteries. This flow of fluid is desired to prevent embolization of material into the coronary arteries during the procedure. Once the cutting tool is in place, the balloon is inflated and flexible shaft is rotated. Once the cutting tool has reached the appropriate rotation speed, the cutting tool is pulled proximally to remove the defective heart valve. The balloon and the cutting tool are spaced apart so that the inflated balloon will be stopped by the perimeter, unremoved portion of the defective heart valve, which will signal the physician that the valve has been removed, as well as protect the heart and aorta from damage from the valve removal

device. Once it is determined that the defective heart valve has been removed, the cutting tool is slowed or stopped altogether and the balloon is deflated. The cutting tool and the deflated balloon are pulled proximally through catheter. Then, a catheter containing an artificial heart valve is inserted and the artificial heart valve is placed as described above.

The delivery and implantation system of the replacement artificial heart valve of the present invention percutaneously and transluminally includes a flexible catheter 400 which may be inserted into a vessel of the patient and moved within that vessel as depicted in FIG. 8. The distal end 410 of the catheter, 400, which is hollow and carries the replacement heart valve device of the present invention in its collapsed configuration, is guided to a site where it is desired to implant the replacement heart valve. The catheter has a pusher member 420 disposed within the catheter lumen 430 and extending from the proximal end 440 of the catheter to the hollow section at the distal end 410 of the catheter. Once the distal end 410 of the catheter is positioned as desired, the pusher mechanism 420 is activated and the distal portion of the replacement heart valve device is pushed out of the catheter and the stent member 100 partially expands. In this position the stent member 100 is restrained so that it doesn't pop out and is held for controlled release, with the potential that the replacement heart valve device can be recovered if there is a problem with the positioning. The catheter 400 is ~~them~~then retracted slightly and the replacement heart valve device is completely pushed out of the catheter 400 and released from the catheter to allow the stent member 100 to fully expand. If the stent member 100 preferably includes two circles of barbs on its outer surface as previously described, the first push and retraction will set one circle of barbs in adjacent tissue and the second push and release of the replacement heart valve device will set the other circle of barbs in adjacent tissue and securely fix the replacement heart valve device in place when the ~~valve~~device is released from the catheter.

Alternatively, or in combination with the above, the replacement heart valve device could be positioned over a metallic guidewire that is advanced through the catheter. The replacement heart valve device of the present invention is preferably implanted percutaneously through an aortic passageway to, or near to, the location from which the natural heart valve has been removed. Referring to ~~Fig~~FIG. 8, the implantation system comprises a flexible hollow tube catheter 410 with a metallic guide wire 450 disposed within it. The stented valve device is collapsed over the tube and is covered by a moveable sheath 460. The moveable sheath 460 maintains the stented valve device in the collapsed position. The implantation method comprises the following steps: inserting the replacement heart valve device in the lumen of a central blood vessel via entry through the brachial or femoral artery using a needle or exposing the artery surgically; placing a guide wire 450 through the entry vessel and advancing it to the desired position; advancing dilators over the wire to increase the lumen of the entry site, thereby preparing the artery to receive the heart-valve; and advancing the heart-valve device to the desired place. The stented-valve device is released by pulling the cover sheath 460 of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advanced over the wire and an aortogram is performed to assess the competency of the valve.

Before creation of the valve means and implantation, the patient is studied to determine the architecture of the patient's heart. Useful techniques include fluoroscopy, transesophageal echocardiography, MRI, and angiography. The results of this study will enable the physician to determine the appropriate size for the replacement heart valve.

In one procedure for implantation of the replacement heart valve device of the present invention, the femoral artery of the patient is canulated using a Cook needle and a standard J wire is advanced into the artery either percutaneously or after surgical exposure of the artery. An 8 F introducer is advanced into the femoral artery over the wire. The J wire is then

withdrawn and anticoagulation is started using heparin 60 U/Kg intravenously. Once vascular access is obtained an aortogram is performed for anatomical evaluation. A special wire (Lunderquist or Amplatz superstiff) is advanced into the aortic arch and dilators progressively larger are advanced over the wire, starting with 12 F all the way to 18 F. After this the valve introducer device containing the prosthetic valve device is then inserted and used to transport the replacement valve over a guidewire to the desired position. The stented-valve is released by pulling the cover sheath of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advanced over the wire and repeat aortogram is performed to assess the competency of the valve.

When the device is used to treat severe leakage of the aortic valve, the native valve is left in place and the prosthetic stented valve is deployed below the subclavian artery. When the device is used to treat aortic stenosis, first the stenotic valve needs to be opened using either aortic valvuloplasty or cutting and if this procedure induces aortic insufficiency the stented valve is placed to prevent the regurgitation.

Intravascular ultrasound or an angioscope passed intravascularly via either the venous system through the intra-atrial septum across the mitral valve and into the left ventricle or retrograde via the femoral artery would provide the added benefit of allowing constant high definition imaging of the entire procedure and high flow irrigation.

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The prosthetic valve device can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and

patients unable to tolerate open heart procedures or life-long anticoagulation. In addition, with the development of longer-life, flexible, non-thrombogenic synthetic valve alternatives to bioprosthesis, the prosthetic valve device will be indicated in all patients where the relative advantages of the life-span, the non-thrombogenic quality, and the ease of insertion of prosthetic valve devices outweigh the disadvantages of mechanical valves. Anticoagulation may be beneficial in certain clinical situations for either short or long term use.

This method of percutaneous endovascular heart-valve replacement, in contrast to open heart surgical procedures, requires only local anesthesia, partial or no cardiac bypass, one to two days hospitalization, and should result in a reduced mortality rate as compared to open heart procedures.

While the present invention has been shown and described herein in what is considered to be a preferred embodiment thereof, illustrating the results and advantages over the prior art obtained through the present invention, the invention is not limited to the specific embodiments described above. Thus, the forms of the invention shown and described herein are to be taken as illustrative and other embodiments may be selected without departing from the spirit and scope of the present invention.

CLAIMS

Having thus described the invention, what is claimed is:

1. A percutaneously implantable replacement heart valve device comprising a ~~self-expanding~~-stent member and an artificial valve means made of biocompatible tissue material and disposed within the inner cavity of said stent member affixed at one or more points to said stent member, said valve means having cusps or leaflets formed by folding of **a substantially rectangular sheet of** said biocompatible tissue material.

2. The percutaneously implantable replacement heart valve **device** of claim 1, wherein said stent member is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium, stainless steel **[add others]**.

3. The percutaneously implantable replacement heart valve **device** of claim 1, wherein said biocompatible tissue material of said valve means comprises bovine pericardium tissue.

4. The percutaneously implantable replacement heart valve **device** of claim 1, wherein said biocompatible tissue material of said valve means comprises porcine pericardium tissue.

5. The percutaneously implantable replacement heart valve **device** of claim 1, wherein said biocompatible tissue material of said valve means comprises autologous tissue obtained from the patient into whom said replacement heart valve **device** will be implanted.

6. The percutaneously implantable heart valve device of claim 1, wherein said stent member is self-expanding when implanted.

7. The percutaneously implantable heart valve device of claim 1, wherein said stent member is balloon catheter expandable when implanted.

~~6.~~8. A method of making a percutaneously implantable replacement heart valve_ device comprising the following steps:

obtaining a substantially rectangular ~~segment~~sheet of biocompatible tissue material;

soaking said biocompatible tissue material in a gluteraldehyde solution;

transferring said biocompatible tissue material from said gluteraldehyde solution to an ethanol solution;

drying said biocompatible tissue material;

folding said dried biocompatible tissue material to create cusps or leaflets and a cuffed tubular valve structure;

affixing said folded biocompatible tissue material to the inner cavity of a stent.

9. The method of making a percutaneously implantable replacement heart valve device claim 8, wherein said biocompatible tissue material comprises bovine pericardium tissue.

10. The method of making a percutaneously implantable replacement heart valve device claim 8, wherein said biocompatible tissue material comprises porcine pericardium tissue.

11. The method of making a percutaneously implantable replacement heart valve device claim 8, wherein said biocompatible tissue material comprises autologous tissue obtained from the patient into whom said replacement heart valve device will be implanted.

12. The method of making a percutaneously implantable replacement heart valve device of claim 8, wherein said stent is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium, stainless steel, [add others].

13. The method of making a percutaneously implantable replacement heart valve device of claim 8, wherein said stent is self-expanding when implanted.

14. The method of making a percutaneously implantable replacement heart valve device of claim 8, wherein said stent is balloon catheter expandable when implanted.

ABSTRACT

The present invention comprises a percutaneously implantable replacement heart valve device and a method of making same. The replacement heart valve device comprises a stent member made of stainless steel or self-expanding nitinol, a biological tissue artificial valve means disposed within the inner space of the stent member. An implantation and delivery system having a central part which consists of a flexible hollow tube catheter that allows a metallic wire guide to be advanced inside it. The endovascular stented-valve is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow. The present invention also comprises a novel method of making a replacement heart valve by taking a rectangular fragment of bovine pericardium treating, drying, folding and rehydrating it in such a way that forms a two- or three-leaflet/cusp valve with the leaflets/cusps formed by folding, thereby eliminating the extent of suturing required, providing improved durability and function.

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EXHIBIT I

AFFIDAVIT OF DR. GERVASIO A. LAMAS, M.D.

STATE OF FLORIDA)
) SS
COUNTY OF MIAMI-DADE)

BEFORE ME, the undersigned authority, personally appeared DR. GERVASIO A. LAMAS, M.D., who after having been duly sworn, deposes and states the following:

1. My name is DR. GERVASIO A. LAMAS, M.D. and I am over eighteen years of age and otherwise *sui juris*.

2. I reside in Miami, Florida, U.S.A.

3. I am the Chief of Cardiology at the Columbia University Division of Cardiology at Mount Sinai Medical Center in Miami, Florida ("Mount Sinai Medical Center").

4. I am also the Director of Cardiovascular Research and Academic Affairs at Mount Sinai Medical Center.

5. I was also previously the Director of the Cardiology Fellowship Program at the University of Miami Miller School of Medicine and Interim Vice Chief of Clinical Affairs/Clinical Services for the Cardiovascular Division and Medical Director of the Cardiac Care Unit at the University of Miami Doctor's Hospital.

6. I received a Bachelor of Arts Degree in Biochemical Sciences (cum laude) from Harvard College and a Doctor of Medicine Degree (with honors) from New York University School of Medicine. I completed my internship, residency and cardiology training at the Brigham and Women's Hospital at Harvard Medical School and later served on the faculty of Harvard Medical School. I am board certified in Internal Medicine and Cardiovascular Diseases and am a fellow of the American College of Cardiology, the American Heart Association, the European Society of Cardiology and the Asian-Pacific Society of Cardiology. I have authored or

co-authored over 300 publications in the medical field and have been a licensed and practicing cardiologist for over thirty years.

7. Dr. David Paniagua, M.D. is personally known to me. Dr. Paniagua practiced as a cardiologist at Mount Sinai Medical Center from 1996-1999 while completing an interventional cardiovascular fellowship program for which I served as Program Director.

8. Prior to December 31, 1999, Dr. Paniagua informed me privately regarding his percutaneously implantable replacement heart valve invention, wherein a more durable valve less susceptible to tearing was made by folding biocompatible material such that the cusp or leaflet portion was formed by folding without cutting slits in the valve material to form the leaflets or suturing of separate leaflets onto the valve body.

9. Prior to December 31, 1999, Dr. Paniagua privately showed me a paper model of said valve mounted entirely within a stent. The model was shown to me in person by Dr. Paniagua in Miami, Florida. The valve was a folded design with cusps or leaflets formed by folding of the valve material rather than by cutting slits in the valve material or suturing of separate leaflets onto the valve body. The valve cusps or leaflets did not have slits or cuts. The valve instead had a tubular form with a fold at one end and one or more folds disposed inwardly in relation to the valve's interior space to form cusps or leaflets at or near the opposite end.

10. I do not have a financial or proprietary interest in the above-described invention.

11. The statements in this Affidavit are true, correct and based upon my personal knowledge.

FURTHER AFFIANT SAYETH NAUGHT. Dated this 7 day of September, 2009.

DR. GERVASIO A. LAMAS, M.D., Affiant

NOTARIAL ACKNOWLEDGMENT

STATE OF FLORIDA)
) SS:
COUNTY OF MIAMI-DADE)

The foregoing instrument was acknowledged before me this 3 day of September, 2009, by Dr. Gervasio A. Lamas, M.D., who is personally known to me, or has produced identification in the form of Driver License, and who did take an oath.

Beatriz Acevedo
Notary Signature
Print Name: Beatriz Acevedo
Notary Public, State of Florida
My Commission Expires: 7/26/2013
Commission Number: DD 910748

BEATRIZ ACEVEDO
MY COMMISSION # DD 910748
EXPIRES: July 26, 2013
Bonded Thru Notary Public Underwriters

[NOTARY SEAL]

MIA 180,741,915v1

EXHIBIT J

AFFIDAVIT OF DR. PAOLO ANGELINI, M.D.

STATE OF TEXAS)
) SS
COUNTY OF HARRIS)

BEFORE ME, the undersigned authority, personally appeared DR. PAOLO ANGELINI, M.D., who after having been duly sworn, deposes and states the following:

1. My name is DR. PAOLO ANGELINI, M.D. and I am over eighteen years of age and otherwise *sui juris*.

2. I reside in Houston, Texas, U.S.A.

3. I am a practicing cardiologist at the Texas Heart Institute St. Luke's Episcopal Hospital ("Texas Heart Institute") and with Leachman Cardiology Associates in Houston, Texas and am licensed to practice medicine in the State of Texas. I have been a practicing cardiologist for over thirty-five-years with specific focus on interventional cardiology and coronary anomalies.

4. I received a Doctor of Medicine degree from the University of Milan in Italy and completed an internship in internal medicine at the University of Milan. I completed my residency at the Instituto Nacional de Cardiologia, Mexico City, Mexico, and completed fellowship training in cardiology Baylor College of Medicine in Houston Texas. I am a member of the American College of Cardiology, the Houston Cardiology Society, the Texas Medical Society.

5. I am also a Clinical Professor of Cardiology at the Baylor College of Medicine, Baylor University, in Houston, Texas. I have authored or co-authored numerous publications in the field of interventional cardiology, particularly with regard to coronary angioplasty.

6. Dr. David Paniagua, M.D. is personally known to me. Dr. Paniagua practiced as a cardiologist at Texas Heart Institute in 1999-2000 while he was completing an interventional cardiovascular fellowship program there. I was practicing as a cardiologist at Texas Heart Institute during such period.

7. Prior to December 31, 1999, Dr. Paniagua informed me privately regarding his percutaneously implantable replacement heart valve invention, made by folding biocompatible material such that the cusp or leaflet portion was formed by folding without cutting slits in the valve material to form the leaflets or suturing of separate leaflets onto the valve body. This privileged communication occurred during the period January 1998 through June 1999, in the Animal laboratory of the Texas Heart Institute, where I was conducting dog experiments.

8. I do not have a financial or proprietary interest in the above-described invention.

9. The statements in this Affidavit are true, correct and based upon my personal knowledge.

FURTHER AFFIANT SAYETH NAUGHT. Dated this 25th day of August, 2009.

DR. PAOLO ANGELINI, M.D., Affiant

NOTARIAL ACKNOWLEDGMENT

STATE OF TEXAS)
) SS:
COUNTY OF HARRIS)

The foregoing instrument was acknowledged before me this 25th day of August, 2009, by Dr. Paolo Angelini, M.D., who is personally known to me, or has produced identification in the form of _____, and who did take an oath.

Notary Signature
Print Name: Renee Klaevemann
Notary Public, State of ~~Florida~~ Texas
My Commission Expires: August 9, 2012
Commission Number:

RENEE KLAEVEMANN
MY COMMISSION EXPIRES
AUGUST 9, 2012

[NOTARY SEAL]

MIA 180,744,103v1

APPENDIX C

UNMARKED VERSION OF CLAIMS

1. (currently amended) A percutaneously implantable replacement heart valve device comprising:

an expandable stent member having an inner channel, and

a sheet of biocompatible material forming a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material being disposed within said inner channel of said stent member, said sheet of biocompatible material having two opposite ends joined to form an outer generally tubular portion having an inner space and having one or more folds defining an inner leaflet portion with two or more unslit leaflets without requiring suturing of said leaflets, said inner leaflet portion being disposed within said inner space of said outer generally tubular portion.

2. (currently amended) The percutaneously implantable replacement heart valve device of claim 1, wherein said expandable stent member is made of a metal or alloy of metals.

3. (currently amended) The percutaneously implantable replacement heart valve device of claim 1, wherein said sheet of biocompatible material comprises mammal pericardium tissue.

4. (currently amended) The percutaneously implantable replacement heart valve device of claim 1, wherein said sheet of biocompatible material is disposed entirely within said inner channel of said stent member.

5. (currently amended) The percutaneously implantable replacement heart valve

device of claim 1, wherein said sheet of biocompatible material comprises graft material.

6. (currently amended) The percutaneously implantable replacement heart valve device of claim 1, wherein said sheet of biocompatible material comprises biological tissue.

7. (currently amended) The percutaneously implantable heart valve device of claim 1, wherein said sheet of biocompatible material comprises a synthetic biocompatible material.

8. (currently amended) The percutaneously implantable heart valve device of claim 7, wherein said synthetic biocompatible material is selected from the group consisting of polytetrafluoroethylene, polyester, polyurethane, metal, metal alloy and metal foil, including combinations thereof.

9. (original) The percutaneously implantable heart valve device of claim 1, wherein said stent member is self-expanding when implanted.

10. (original) The percutaneously implantable heart valve device of claim 1, wherein said stent member is balloon catheter expandable when implanted.

11. (canceled)

12. (canceled)

13. (canceled)

14. (canceled)

15. (canceled)

16. (canceled)

17. (canceled)

18. (canceled)

19. (canceled)

20. (canceled)

21. (canceled)

22. (canceled)

23. (canceled)

24. (canceled)

25. (canceled)

26. (canceled)

27. (currently amended) A percutaneously implantable replacement heart valve device comprising:

an expandable stent member having an inner channel,

a first sheet of biocompatible material forming a first generally tubular portion having an inner space, said first generally tubular portion having a first border defined by a first border fold, and one or more additional folds, said first border fold and said one or more additional folds defining a cusp or leaflet portion having one or more unslit leaflets without requiring suturing of said leaflets, and

a second sheet of biocompatible material forming a second generally tubular portion having a folded border defining a cuff,

said first generally tubular portion and second generally tubular portion being affixed together to form a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure and having an

outer generally tubular structure formed by said first generally tubular portion and said second generally tubular portion, said outer generally tubular structure having an inner space with said leaflets disposed within said inner space of said outer generally tubular structure, and

said first sheet of biocompatible material and said second sheet of biocompatible material being disposed within said inner channel of said stent member.

28. (currently amended) The percutaneously implantable replacement heart valve device of claim 27, wherein said collapsible and expandable valve is attached to said expandable stent member at one or more attachment points, and wherein said one or more attachment points consist of attachment points disposed on said outer generally tubular structure.

29. (currently amended) The percutaneously implantable replacement heart valve device of claim 27, wherein said first sheet of biocompatible material and said second sheet of biocompatible material are disposed entirely within said inner channel of said stent member.

30. (currently amended) A percutaneously implantable replacement heart valve device comprising:

a sheet of biocompatible material forming a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material having a first border with a fold defining a cuff portion, and having a second border opposite to said first border with a second border fold and one or more additional folds oriented perpendicularly in relation to said second border fold defining a leaflet portion having one or more leaflets formed by one or more of said folds without requiring slits in said sheet of biocompatible material to form said one or more leaflets, and without requiring suturing of said one or more leaflets, said sheet of biocompatible material forming a generally tubular structure having an inner space with said leaflets disposed

within said inner space of said generally tubular structure, said leaflets opening in response to blood flow through said inner space of said generally tubular structure in one direction and closing in response to blood flow in an opposite direction.

31. (currently amended) The device of claim 30, wherein said leaflet portion comprises a separate sheet of said biocompatible material including one or more additional pleats through which said leaflet portion is attached to said cuff portion.

32. (currently amended) The device of claim 30, further comprising an expandable stent having an inner channel, and wherein said sheet of biocompatible material is disposed within said inner channel of said expandable stent, and wherein said sheet of biocompatible material further comprises one or more folds through which said sheet of biocompatible material is affixed to said expandable stent.

33. (currently amended) A percutaneously implantable replacement heart valve device comprising:

an expandable stent member having an inner channel, and

a sheet of biocompatible material forming a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material being disposed within said inner channel of said stent member, said sheet of biocompatible material having a first border fold, one or more additional folds parallel to said first border fold and one or more folds oriented perpendicularly in relation to said first border fold to form a leaflet portion with leaflets without cutting of slits in said sheet of biocompatible material to form said leaflets, and without requiring suturing of said leaflets, said sheet of biocompatible material being formed into a tubular structure having an inner space within which said leaflets are disposed, said leaflets opening in

response to blood flow toward said leaflets in one direction and closing in response to blood flow in an opposite direction.

34. (currently amended) A percutaneously implantable replacement heart valve device including:

an expandable stent member having an inner channel, and

a sheet of biocompatible material forming a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material having an upper border fold, a lower border fold, and one or more folds oriented perpendicularly in relation to said upper border fold forming one or more cusps or leaflets without requiring suturing of said leaflets, said sheet of biocompatible material further having two opposite ends coupled to form a generally tubular portion having an inner space with said cusps or leaflets disposed within said inner space of said generally tubular portion, said cusps or leaflets being unslit, said sheet of biocompatible material being disposed within said inner channel of said stent member.

35. (currently amended) A percutaneously implantable replacement heart valve device comprising:

an expandable stent member having an inner channel, and

a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said collapsible and expandable valve comprising a first sheet of biocompatible material having an upper border defined by an upper border fold, a lower border and one or more additional folds positioned on said sheet of biocompatible material between said upper border and said lower border and

oriented inwardly in relation to eachother, said upper border fold and said one or more additional folds forming one or more leaflets without cutting of slits to form said one or more leaflets and without requiring suturing of said one or more leaflets, said first sheet formed into a generally tubular portion having an inner space with said one or more leaflets disposed within said inner space, and a second sheet of biocompatible material formed into a second generally tubular portion having an inner space and a cuff defined by a fold, said first sheet of biocompatible material being affixed to said second sheet of biocompatible material to define a generally tubular structure having a border defined by said cuff, with said one or more leaflets disposed within said inner space of said generally tubular structure, said first sheet of biocompatible material and said second sheet of biocompatible material being disposed within said inner channel of said stent member.

36. (currently amended) A percutaneously implantable replacement heart valve device including:

an expandable stent member having an inner channel, and

a sheet of biocompatible material disposed within said inner channel of said stent member, said biocompatible material having two or more folds to define a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said folded sheet of biocompatible material having a generally tubular portion having an inner space and a cusp or leaflet portion with leaflets disposed within said inner space of said generally tubular portion, said leaflets being unslit and formed by one or more of said folds without requiring suturing of said leaflets and without requiring affixation of said leaflets.

37. (currently amended) A percutaneously implantable replacement heart valve

device including:

an expandable stent member having an inner channel, and

a sheet of biocompatible material forming a collapsible and expandable valve capable of being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material having one or more inward horizontal folds and one or more inward vertical folds defining one or more unslit cusps or leaflets without requiring suturing of said leaflets, said leaflets opening in response to blood flow in one direction and closing in response to blood flow in an opposite direction, said sheet of biocompatible material formed into a generally tubular structure having an inner space with said leaflets disposed within said inner space of said generally tubular structure, said sheet of biocompatible material being positioned within said inner channel of said stent member.

38. (new) A percutaneously implantable replacement heart valve device comprising:

a sheet of biocompatible material forming a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material having one or more folds to form a cuff portion and being formed into generally tubular structure having an inner space, said sheet of biocompatible material having two or more additional folds forming a cusp or leaflet portion with unslit leaflets without requiring suturing of said leaflets or affixation of said leaflets, wherein said leaflets open in response to blood flow in one direction and close in response to blood flow in an opposite direction, and

an expandable stent having an inner channel, said sheet of biocompatible material being disposed within said inner channel of said stent.

39. (new) A percutaneously implantable replacement heart valve device including:

an expandable stent member having an inner channel, and

a sheet of biocompatible material forming a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material disposed within said inner channel of said stent member, said sheet of biocompatible material being formed into a generally tubular structure having a top end fold, a bottom end fold, and one or more additional folds positioned between said top end fold and said bottom end fold forming leaflets defined by folds without requiring cutting of slits into said sheet of biocompatible material to form said leaflets or requiring suturing of said leaflets.

40. (new) A percutaneously implantable replacement heart valve device comprising:

an expandable stent member having an inner channel, and

a sheet of biocompatible material forming a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material having a first border portion with one or more first border folds, one or more additional folds oriented perpendicularly in relation to said first border portion, said sheet of biocompatible material being further formed into a generally tubular structure having an inner space with one or more unslit leaflets defined by one or more of said folds without requiring suturing of said leaflets and without requiring affixation of said leaflets, said leaflets disposed within said inner space of said generally tubular structure, said sheet of biocompatible material being disposed within said inner channel of said expandable stent member.

41. (new) The percutaneously implantable replacement heart valve device of claim 40, further comprising a further fold defining a second border parallel to said one or more first border folds.

42. (new) A percutaneously implantable replacement heart valve device including:

an expandable stent member having an inner channel, and

a sheet of biocompatible material forming a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material disposed within said inner channel of said stent member, said sheet of biocompatible material having two or more folds defining one or more unslit leaflets without requiring suturing of said leaflets.

43. (new) A percutaneously implantable replacement heart valve device comprising:

an expandable stent member having an inner channel, and

a sheet of biocompatible material forming a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material having an upper border defined by a first fold having an outer end portion oriented inwardly in relation to said upper border, said outer end portion having a further fold, a lower border defined by a second fold, a right end, a left end, and one or more additional folds positioned between said right end and said left end, said right end and said left end coupled to form a generally tubular structure with an inner space having unslit leaflets disposed within said inner space of said generally tubular structure without requiring suturing of said leaflets, said sheet being disposed within said inner channel of said stent member.

44. (new) A percutaneously implantable replacement heart valve device comprising:

an expandable stent member having an inner channel, and

a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said collapsible and expandable valve consisting essentially of biocompatible sheet material disposed within said inner channel of said stent member, said biocompatible sheet material formed into a tubular structure having one or more folds defining one or more unslit leaflets without requiring suturing of said leaflets or affixation of said leaflets, said leaflets opening in response to blood flow toward said leaflets in one direction and said leaflets closing by means consisting of blood flow in an opposite direction.

45. (new) A percutaneously implantable replacement heart valve device comprising:

an expandable stent member having an inner channel, and

a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said collapsible and expandable valve consisting of biocompatible sheet material disposed within said inner channel of said stent member, said biocompatible sheet material formed into a generally tubular structure having one or more folds defining one or more unslit leaflets without requiring suturing of the leaflets.

46. (new) A percutaneously implantable replacement heart valve device consisting essentially of:

an expandable stent member having an inner channel, and

biocompatible sheet material forming a collapsible and expandable valve, said collapsible

and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material disposed within said inner channel of said stent member, said biocompatible sheet material formed into a generally tubular structure with two or more folds defining one or more unslit leaflets without requiring suturing of said leaflets.

47. (new) A percutaneously implantable replacement heart valve device consisting of:

an expandable stent member having an inner channel, and

biocompatible sheet material forming a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said sheet of biocompatible material being disposed within said inner channel of said stent member, said biocompatible sheet material being formed into a generally tubular structure with two or more folds defining one or more unslit leaflets without requiring suturing of said leaflets.

48. (new) A percutaneously implantable replacement heart valve device comprising:

a sheet of biocompatible material having a first border portion with one or more first border folds, a second border opposite said first border portion defined by a second border fold, and one or more additional folds oriented perpendicularly in relation to said first border portion and having two opposite outer free ends, said opposite outer free ends being coupled to form a generally tubular structure having an inner space to define a collapsible and expandable valve, said collapsible and expandable valve being percutaneously and transluminally implantable via an endovascular procedure, said collapsible and expandable valve having one or more unslit leaflets defined by one or more of said folds, said one or more leaflets disposed within said inner space of said generally tubular structure, said leaflets opening in response to blood flow toward

said leaflets in one direction and closing in response to blood flow in an opposite direction, and

an expandable stent having an inner channel, said sheet of biocompatible material being disposed within said inner channel of said expandable stent.

49. (new) The device of claim 27, wherein said first sheet has one or more additional pleats through which said first sheet is attached to said second sheet.

50. (new) The percutaneously implantable replacement heart valve device of claims 1, 27, 30, 33, 34, 35, 36, 37, 38, 39, 40, 42, 43, 46, 47 or 48, wherein said biocompatible material is affixed to said stent member with affixation points on a single plane.

51. (new) The percutaneously implantable heart valve device of claims 27, 30, 33, 34, 35, 36, 37, 38, 39, 40, 42, 43, 46, 47 or 48, wherein said biocompatible material of said valve comprises a synthetic biocompatible material selected from the group consisting of: polytetrafluoroethylene, polyester, polyurethane, metal, metal alloy and metal foil, including combinations thereof.

52. (new) The percutaneously implantable replacement heart valve device of claims 1, 27, 30, 33, 34, 35, 36, 37, 38, 39, 40, 42, 43, 46, 47 or 48, wherein said biocompatible material is dried prior to folding and rehydrated after folding.

53. (new) The percutaneously implantable replacement heart valve device of claims 1, 27, 30, 33, 34, 35, 36, 37, 38, 39, 40, 42, 43, 46, 47 or 48, wherein said biocompatible material is further folded to form one or more attachment pleats.

54. (new) The percutaneously implantable replacement heart valve device of claims 1, 27, 30, 33, 34, 35, 36, 37, 38, 39, 40, 42, 43, 46, 47 or 48, wherein said inner channel of said stent member has no inward projections coupled to and supporting said valve leaflets.

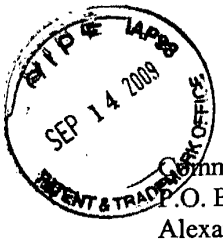
55. (new) The percutaneously implantable replacement heart valve device of claims 1, 27, 30, 33, 34, 35, 36, 37, 38, 39, 40, 42, 43, 46, 47 or 48, wherein said biocompatible material is photomechanically compressed prior to folding.

56. (new) The percutaneously implantable replacement heart valve device of claim 1, wherein said sheet of biocompatible material is attached to said expandable stent member at one or more attachment points on said sheet of biocompatible material, said one or more attachment points consisting of attachment points disposed on said outer generally tubular portion.

MIA 180,801,878v1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of Paniagua, et al.
Application Serial No. 10/887,688
Filing Date: 7/10/04



For: Percutaneously Implantable Replacement Heart Valve Device and Method of Making Same

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Submitted herewith on Form PTO-SB/08a is a listing of documents known to Applicant in order to comply with Applicant's duty of disclosure pursuant to 37 CFR §1.56. Copies of the listed documents are being submitted, if applicable, to comply with the provisions of 37 CFR §1.97-1.99. Please charge Deposit Account No. 50-1792 for the fee under 37 CFR §1.17(p) ($180) and any other fee due in connection with this submission.

The submission of any document herewith, which is not a statutory bar, is not intended as an admission that such document constitutes prior art against the claims of the present application. Applicant does not waive any rights to take any action which would be appropriate to antedate or otherwise remove as competent reference any document which is determined to be a prima facie prior art reference against the claims of the present application.

Applicant respectfully requests that the listed documents be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO-SB/08a be returned in accordance with MPEP § 609.

Respectfully submitted,

Date: September 14, 2009

Manuel R. Valcarcel, Esq.
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/887,688	07/10/2004	David Paniagua	51458.010100	4909

54353 7590 03/02/2010

MANUEL VALCACEL
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1221 BRICKELL AVENUE
MIAMI, FL 33131

EXAMINER	
MILLER, CHERYL L	
ART UNIT	**PAPER NUMBER**
3738	

MAIL DATE	DELIVERY MODE
03/02/2010	PAPER

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.

Office Action Summary	Application No.	Applicant(s)	
	10/887,688	PANIAGUA ET AL.	
	Examiner	Art Unit	
	CHERYL MILLER	3738	

-- 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 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *14 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ 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

4)☒ Claim(s) *1-10 and 27-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 27-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ 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).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

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).

a)☐ All b)☐ Some * c)☐ None of:

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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/14/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

The applicant has argued that Bailey (US 6,458,153) does not disclose 11a, 11b and 26 to be continuous. The examiner disagrees. Bailey discloses graft (sheet) *everted* (folded) into leaflets (26/28). See figure 10 which clearly shows leaflets (26/28) as a continuum of sheet (graft 11b) that is folded at 27, (see col.9, lines 19-27 which discussed *everting* the graft material, everting analogous to folding). Bailey's additional cuff fold is when 11a is a continuum of 11b (this is not shown in the figures, but is disclosed as an alternate embodiment, col.9, lines 20-24; as graft is disclosed to possibly cover entire length of the stent, col.9, lines 52-60, it is envisioned how such a passing through and eversion would occur).

The applicant has also argued that longitudinal seams 29 may not be considered perpendicular folds. The examiner disagrees. The seams 29 form folds in the sheet and are clearly seen in the figures.

The applicant has also argued that Bailey does not disclose the valve body entirely within the inner space of the stent. The examiner disagrees. When the valve body is considered 11b+26/28 (claim 1 for example), it is entirely within the stent. When the valve body is considered 11a+11b+26/28 (other claims), at least 11b+26/28 is within the valve body thus meets the claim (as the *entirety* of the sheet is not required by the claims to reside within the inner space).

The applicant has also argued that Bailey does not anticipate the claims as Bailey's device requires valve struts on the leaflets and thus the sheet is not within the stent inner channel. The examiner disagrees as the applicant's claims do not preclude the use of additional elements

such as struts. Although the struts help regulate the flow by helping the leaflets open and close by their bias, the leaflets themselves also help regulate the flow (as flow would not be regulated without the leaflets, if the struts were used alone). The struts need not be considered part of the "stent" as they are separate elements 24 and the stent is 12. The applicant argues the struts 24 are sutured to the leaflets. The examiner disagrees as they may be fused or adhered instead.

The applicant has argued that Garrison (US 6,425,916 B1) requires suturing of the leaflets (sutures 110, fig.35-37). The examiner disagrees. Without requiring suturing is a method step. Garrison's replacement valve does not have sutures in the end product. Sutures are not present upon purchasing or storing of the valve, nor are they present after implantation. The sutures are only used for delivery and are not *required*, that is the valve is *capable* of being implanted by other means without sutures. The applicant has also argued that Garrison does not disclose the leaflet portion within the outer tubular portion of the sheet. The examiner disagrees. Leaflet portion consists only of the arcuate lines to the free ends in fig.34. All other portions of the valve 6d are considered the tubular portion (including vertical folds/commissures). Thus, the semi-circular leaflets are within the commissures of the tubular portion.

The applicant has argued that Bessler (US 5,855,601) does not disclose unslit leaflets. The examiner disagrees. Bessler's leaflets themselves do not have slits, it is the tubular member that is slit *inbetween* the leaflets. The applicant has also argued that the sheet tubular portion is outside the stent (not within the inner channel). The examiner disagrees. The claims require the sheet to be within the inner channel. Some of the sheet (the leaflet portion) is within the inner channel. The claims do not require the entirety of the sheet to be within the inner channel, thus the fact that the outer cuff tubular portion is outside the stent is irrelevant.

Declaration

The declaration filed on December 15, 2008 and September 14, 2009 under 37 CFR 1.131 has been considered but is ineffective to overcome the Bailey (US 6,652,578 B2) reference. **Exhibits B and C were missing from the file, and unable to be evaluated.**

The evidence submitted is insufficient to establish a conception of the invention prior to the effective date of the Bailey reference. While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a complete disclosure to another. Conception is more than a vague idea of how to solve a problem. The requisite means themselves and their interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897). Portions of the declaration that are declared to have occurred prior to December 31, 1999 do not provide sufficient support for a valve being *unslit* and also *an inner and an outer fold*.

Priority

Applicants seem to disclose four separate embodiments, only one of which is supported by the parent application, thus all claims do not receive the same priority date.

Embodiment 1-seen in figures 3a, 3b, and disclosed in pgs.13-15 of the parent application; has 2 horizontal folds and some vertical folds.

Embodiment 2-seen in figures 9a-9c of the current application; has 2 horizontal folds, some vertical folds and additional curved folds 6, 7, 8 where attached to the valve portion.

Embodiment 3-disclosed on pg.18 of current application; has 2 separate sheets, the first being the valve body with 1 horizontal fold and the other sheet being the leaflet portion with no folds, the two attached together.

Embodiment 4-disclosed on pg.20 of the current application; has reinforcing tab at attachment location.

Thus the following claims receive the following priority dates:

January 4, 2002: claims 1-7, 9, 30, 32, 34, 36, 37, 38, 39, 40-42, 44-48, 56

July 10, 2004: claims 8, 10, 27-29, 31, 33, 35, 43, 49-55

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 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 1-10 and 27-56 are rejected under 35 U.S.C. 112, 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(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 27, 30, 33, 34, 35, 36, 37, 38, 39, 40, 42, 43, 44, 45, 46, and 47 each recite "without requiring suturing of said leaflets". This limitation is considered new matter. Applicants current specification discloses suturing the leaflets to the valve cuff portion, see pg.18 and 20, "leaflet layer is preferably attached to the outer cuff layer by curved or straight continuous suturing" and "leaflet layer is then attached to the cuff layer to form valve cusps in one of three preferred ways…."all which entail suturing. Further, both the current specification and the parent specification disclose the present invention "reducing the extent" of suturing of the leaflets, however no support was found for *elimination* (without requiring) of suturing (this

seems to be opposite of what is supported by the specification. Although fig.3a, 3b do not illustrate sutures, sutures are disclosed to be used and only a reduction in suturing is disclosed and a claim for without requiring sutures seems to be a contradiction to the specification and thus considered new matter. Claims 2-10, 28-29, 31-32, 41, and 49-56 depend upon the above claims and inherit all problems associated with them.

Claims 36, 40, 44 recite, "without requiring affixation of said leaflets", which is considered new matter for the same reasons stated above.

Claims 27 and 35 each require two separate sheets, each sheet having a border fold. There is no support for the claimed subject matter. The only embodiment using two separate sheets is disclosed at pg.18 of applicants specification (not shown in any figures) wherein the "leaflet forming layer made of a single piece of valve material attached to a separate piece forming the valve body having a folded cuff portion". Thus only the valve body has a border fold, the leaflet portion does not have a border fold.

Claim 33 recites, "one *or more* additional folds parallel to said first border fold" is considered new matter.

Claim 37 recites, "one or more *inward* horizontal folds", which is considered new matter.

Claim 40 recites, "one or more first border folds", which is considered new matter.

Claim 43 recites, "outer end portion having a further fold", which is considered new matter.

Claim 48 recites, "one or more first border folds" which is considered new matter.

Claim 53 is considered new matter as vertical folds have already been claimed in independent claims, thus additional pleats are not supported by the specification and are not for all embodiments in all independent claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> 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 1-10, 30-32, 34, 43, 48, and 50-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, and 34 recite "opposite ends", however it seems applicant instead intended to recite opposite *sides* as the ends relate to an inflow and outflow end.

Claim 43 recites "right end and left end", however is seems applicant instead intended to recite right and left *sides*.

Claim 48 recites, "outer free ends", however is seems applicant instead intended to recite free *sides*. Also, this limitation is indefinite since the free ends are attached to one another, thus no longer free. The claim requires the ends to be free and attached (not free) at the same time, which is considered indefinite as applicant is positively claiming both and intermediate and end product.

Claims 31 is an alteration of its independent claim 30. The leaflet portion cant be a continuous with (by a fold) the cuff and a separate sheet at the same time.

Claim 32 is unclear at "further comprises one or more folds", as it seems these folds have already been positively introduced into the independent claim 30, thus do not "further comprise".

Product by Process

Claims 52 and 55 are product by process claims. Patentable weight is given to the end product only, not its method of manufacture, see MPEP 2113.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 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 1-3, 5-10, 36, 37, 40, 42, 44-47, 50-52, and 54-56 are rejected under 35 U.S.C. 102(b) as being anticipated by Bessler et al. (US 5,855,601, cited previously). Bessler discloses a replacement heart valve device (see fig.1-5) comprising an expandable stent member (21 or 32) having an inner channel (lumen) and a sheet of biocompatible material (22 or 35) forming a valve and disposed within the inner channel (part of sheet, the leaflets, are disposed within the channel-*it is noted that the claims do not require the entirety of the sheet to be within the channel*), the sheet having two sides joined to form a tube (tube seen in figures) having an outer tubular portion (cuff 25) having an inner space (lumen) and having one or more folds (fold where cuff meets leaflets) with two or more unslit leaflets (24 or 36; *leaflets themselves are not slit; it is the sheet that is slit inbetween the leaflets*) without requiring suturing of the leaflets (24, 36 are not sutured to anything), the inner leaflet portion (24, 36) disposed within the inner space of the outer tubular portion (25; see figs.1-5). Bessler shows at least one horizontal fold, at the

bottom of the valve and one vertical fold (fold to form the tube). Bessler discloses the cuff (25) to be sutured to the stent (at 26 along one plane, see fig.1, 4). Bessler discloses the claimed materials for the stent (col.6, lines 3-8) and sheet (col.6, lines 18-31; col.4, lines 9-11).

Claims 1-10, 36-40, 42, 44-48, and 50-56 are rejected under **35 U.S.C. 102(b)** as being anticipated by Garrison et al. (US 6,425,916 B1, cited previously). See figures 32-38 and respective portions of the specification. Garrison discloses a valve device comprising an expandable stent member (111+26d+8d) having an inner space/channel (lumen) and a flexible compressible valve sheet (6d) disposed in the inner space/channel, the valve (6d) comprising a sheet of biocompatible material (col.10, lines 55-57; col.5, lines 45-60) having at least one fold (upper horizontal fold at border of 111), a lower fold (arcuate lines bordering leaflets) and three vertical fold perpendicular to the first upper fold (at commissures), the leaflets (arcuate inward portions seen in fig.34) being unslit and not *requiring* suturing (suturing the leaflets are a method step, and although sutures are used to deliver the valve of Garrison at 110, they are not *required*, that is the valve may be capable of being delivered without them, further, sutures are not present in the end product, during storage and after implantation). Garrison shows the leaflets (arcuate inward portions of fig.34) within the tubular portion/cuff of the sheet (*all portions of valve 6d besides the arcuate leaflets are considered the tubular portion, the leaflets shown positioned within the tubular portion as the three vertical folds are portions of the tubular portion*). Garrison discloses the stent to be made of the materials claimed that are self-expandable or balloon expandable materials (col.5, lines 4-7; col.10, lines 38-50, 59-61).

In the alternative to the above rejection, claims 1-10, 36-40, 42, 44-48, and 50-56 are rejected under **35 U.S.C. 102(e)** as being anticipated by Garrison et al. (US 6,425,916 B1, cited previously). See figures 32-38 and respective portions of the specification. Garrison discloses a valve device comprising an expandable stent member (111+26d+8d) having an inner space/channel (lumen) and a flexible compressible valve sheet (6d) disposed in the inner space/channel, the valve (6d) comprising a sheet of biocompatible material (col.10, lines 55-57; col.5, lines 45-60) having at least one fold (upper horizontal fold at border of 111), a lower fold (arcuate lines bordering leaflets) and three vertical fold perpendicular to the first upper fold (at commissures), the leaflets (arcuate inward portions seen in fig.34) being unslit and not *requiring* suturing (suturing the leaflets are a method step, and although sutures are used to deliver the valve of Garrison at 110, they are not *required*, that is the valve may be capable of being delivered without them, further, sutures are not present in the end product, during storage and after implantation). Garrison shows the leaflets (arcuate inward portions of fig.34) within the tubular portion/cuff of the sheet (all portions of valve 6d besides the arcuate leaflets are considered the tubular portion, the leaflets shown positioned within the tubular portion as the three vertical folds are portions of the tubular portion). Garrison discloses the stent to be made of the materials claimed that are self-expandable or balloon expandable materials (col.5, lines 4-7; col.10, lines 38-50, 59-61).

Claims 1-2, 4-10, 30-34, 36-48, 50-53, and 55-56 are rejected under **35 U.S.C. 102(b)** as being anticipated by Bailey et al. (US 6,458,153 B1; assuming all claims receive a priority date of July 10, 2004). Bailey discloses an implantable heart valve (figs.1-5 for example which

discloses graft may cover full stent length, col.9, lines 52-60) comprising an expandable stent (12 alone) and an inner flexible compressible valve (for claims 1, 2 and 4-10 sheet is 11b+26 which is entirely within the stent; for all other claims sheet is 11b+11a+26) made of biocompatible material (col.8, lines 37-40) disposed within the stent (12) the valve having leaflets without slits (see fig.2; valve body disclosed as a tubular graft 11b extension, col.9, lines 11-20). Bailey discloses the stent (12) to be made of the materials claimed (nitinol; col.8, lines 4-8). Bailey discloses the valve to be formed of biological or synthetic materials (col.8, lines 37-40). Bailey's valve is capable of self-expansion or balloon expansion (col.8, lines 4-8). Bailey discloses an outer cuff portion (considered 11a; which may be integral to 11b and 26; see col.9, lines 20-24, "11a may be *passed through* to the luminal surface..thereby *becoming* the inner graft 11b"; thus 11a and 11b may be continuous at a fold at the distal end of the stent). Bailey discloses the sheet of tissue (11b) having first horizontal fold (inverted at 27), second parallel horizontal fold (material 11a is folded inwardly to become 11b; col.9, lines 20-24). Vertical perpendicular folds of sheet may be considered 29. When the sheet is considered only 11b+26 (claim 1), the sheet is entirely within the stent. Referring to other claims (when sheet is considered 11a+11b+26 all continuous-the claims do not require the entire sheet to be within the stent, thus since portions 11b and 26 are within the stent they meet the claim). It is also noted that seams 29 attach the inner tube portion (26) to the outer tubular portion (11a, 11b), however the seams 29 are not considered to be on leaflets, but instead inbetween them.

In the alternative to the above rejection, claims 1-2, 4-10, 30-34, 36-48, 50-53, and 55-56 are rejected under **35 U.S.C. 102(e)** as being anticipated by Bailey et al. (US 6,458,153 B1; assuming all claims receive a priority date of January 4, 2002). Bailey discloses an implantable

heart valve (figs.1-5 for example which discloses graft may cover full stent length, col.9, lines 52-60) comprising an expandable stent (12 alone) and an inner flexible compressible valve (for claims 1, 2 and 4-10 sheet is 11b+26 which is entirely within the stent; for all other claims sheet is 11b+11a+26) made of biocompatible material (col.8, lines 37-40) disposed within the stent (12) the valve having leaflets without slits (see fig.2; valve body disclosed as a tubular graft 11b extension, col.9, lines 11-20). Bailey discloses the stent (12) to be made of the materials claimed (nitinol; col.8, lines 4-8). Bailey discloses the valve to be formed of biological or synthetic materials (col.8, lines 37-40). Bailey's valve is capable of self-expansion or balloon expansion (col.8, lines 4-8). Bailey discloses an outer cuff portion (considered 11a; which may be integral to 11b and 26; see col.9, lines 20-24, "11a may be *passed through* to the luminal surface..thereby *becoming* the inner graft 11b"; thus 11a and 11b may be continuous at a fold at the distal end of the stent). Bailey discloses the sheet of tissue (11b) having first horizontal fold (inverted at 27), second parallel horizontal fold (material 11a is folded inwardly to become 11b; col.9, lines 20-24). Vertical perpendicular folds of sheet may be considered 29. When the sheet is considered only 11b+26 (claim 1), the sheet is entirely within the stent. Referring to other claims (when sheet is considered 11a+11b+26 all continuous-the claims do not require the entire sheet to be within the stent, thus since portions 11b and 26 are within the stent they meet the claim). It is also noted that seams 29 attach the inner tube portion (26) to the outer tubular portion (11a, 11b), however the seams 29 are not considered to be on leaflets, but instead inbetween them.

Claim Rejections - 35 USC § 103

The following is a quotation of 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 34, 38, 39, 41, 43, and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bessler (US 5,855,601, cited previously). Bessler discloses the replacement valve substantially as claimed (see above), having at least on border fold (on the lower part of the valve where the cuff 25 meets the leaflets 24) and at least one perpendicular fold (where the sheet is folded into a tube). Bessler also shows in fig.4, a dotted line at the upper portion of the cuff, which would seemingly be for demarking an upper border fold, however it is not absolute as one is not disclosed. It would have been obvious to one having ordinary skill in the art at the time the invention was made to have an upper fold on the cuff to reinforce the area that is sutured to the stent (at 26, 38) to prevent tearing or fringing.

Conclusion

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 CHERYL MILLER whose telephone number is (571)272-4755. The examiner can normally be reached on Monday-Friday 7:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Corrine McDermott can be reached at 571-272-4754. 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.

/Cheryl Miller/
Examiner, Art Unit 3738

/Corrine M McDermott/
Supervisory Patent Examiner, Art Unit 3738

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	10/887,688
Filing Date	07/10/2004
First Named Inventor	Paniagua
Art Unit	3738
Examiner Name	Miller, Cheryl
Attorney Docket Number	051458.010100

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		US- 3,671,979	06-27-1972	Moulopoulos	
		US- 4,056,854	11-08-1977	Boretos et al.	
		US- 4,218,782	08-26-1980	Rygg	
		US- 4,222,126	09-16-1980	Boretos et al.	
		US- 4,759,758	07-26-1988	Gabbay	
		US- 5,163,955	11-17-1992	Love et al.	
		US- 5,509,930	04-23-1996	Love	
		US- 5,571,174	11-05-1996	Love et al.	
		US- 5,653,749	08-05-1997	Love et al.	
		US- 6,126,686	10-03-2000	Badylak et al.	
		US- 6,494,909 B2	08-08-2002	Greenhalgh	
		US- 6,626,938 B1	09-30-2003	Butaric et al.	
		US- 6,773,456 B1	08-10-2004	Gordon et al.	
		US- 7,331,993 B2	10-27-2005	White	
		US-			
		US-			
		US-			
		US-			
		US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
		WO 03/092554 A1	11-13-2003	White/The Gen. Hosp. Corp		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CM/

PTO/SB/08b (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	10/887,688
Filing Date	07/10/2004
First Named Inventor	Paniagua
Art Unit	3738
Examiner Name	Miller, Cheryl
Attorney Docket Number	051458.010100

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		CRIBIER, ALAIN, ET AL., Percut.Transcatheter Implant. of an Aortic Valve Prosthesis for Calcific Aortic Stensosis: First Human Case Descr., Circulation 2002, 3006-08, AHA, US.	
		PANIAGUA, DAVID, ET AL., Percutaneous Heart Valve In the Chronic In Vitro Testing Model, Circulation, 2002, pp.e51-52, Vol. 106, American Heart Association, US.	
		PANIAGUA, DAVID ET AL., First Human Case of Retrograde Transcatheter Implantation of an Aortic Valve Prosthesis, Texas Heart Institute Journal, 2005, pp.91-96, Vol. 32, US.	

Examiner Signature	/Cheryl Miller/	Date Considered	02/27/2010

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

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POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Application Number	10/887688
Filing Date	July 16, 2004
First Named Inventor	Pantaqua
Title	Percutaneously Implantable Replacement Heart Valve De
Art Unit	3738
Examiner Name	MILLER, Cheryl
Attorney Docket Number	54813-10100

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith: 23337

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified application to:

☒ The address associated with the above-mentioned Customer Number.

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☐	Firm or Individual Name				
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Applicant/Inventor.

OR

☒ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____

SIGNATURE of Applicant or Assignee of Record

Signature	RDFish	Date	4.16.2010
Name	R. David Fish	Telephone	713.705.6508
Title and Company	Managing Member, Endoluminal Technology, LLC		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. 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 1.11 and 1.14. This collection is estimated to take 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: ENDOLUMINAL TECHNOLOGY LLC

Application No./Patent No.: 10/887,688 Filed/Issue Date: 2004-07-10

Titled:
Percutaneously implantable replacement heart valve device and method of making same

ENDOLUMINAL TECHNOLOGY LLC , a Corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Inventors: Paniagua, Induni, Mejia, & Lopez To: Endoluminal Technology Research, LLC
The document was recorded in the United States Patent and Trademark Office at
Reel 022532 , Frame 0213 , or for which a copy thereof is attached.

2. From: (Merger) Endoluminal Technology Research, L To: Endoluminal Technology LLC
The document was recorded in the United States Patent and Trademark Office at
Reel 022532 , Frame 0275 , or for which a copy thereof is attached.

3. From: Inventor: R. David Fish To: Endoluminal Technology LLC
The document was recorded in the United States Patent and Trademark Office at
Reel 022899 , Frame 0819 , or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Mark L. Yaskanin/ 19 April 2010
Signature Date

Mark L. Yaskanin Patent Attorney
Printed or Typed Name Title

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.

Electronic Acknowledgement Receipt

EFS ID:	7436605
Application Number:	10887688
International Application Number:	
Confirmation Number:	4909
Title of Invention:	Percutaneously implantable replacement heart valve device and method of making same
First Named Inventor/Applicant Name:	David Paniagua
Customer Number:	54353
Filer:	Mark Lauren Yaskanin/Carol Donahue
Filer Authorized By:	Mark Lauren Yaskanin
Attorney Docket Number:	51458.010100
Receipt Date:	19-APR-2010
Filing Date:	10-JUL-2004
Time Stamp:	10:51:47
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	Power of Attorney	Signed_POA.pdf	541083 d0dc5a248a69396e7177455c8aaf0bff61b914d7	no	1

Warnings:	
Information:	

2	Assignee showing of ownership per 37 CFR 3.73(b).	Statement_Under_3-73b.pdf	430089 b5381022b02da63ee04700c971865f5c2b67e5a2	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	971172	

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.

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 NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/887,688	07/10/2004	David Paniagua	54813-10100

CONFIRMATION NO. 4909

23337
HOLME ROBERTS & OWEN LLP
1700 LINCOLN STREET, SUITE 4100
DENVER, CO 80203

POA ACCEPTANCE LETTER

OC000000041276480

Date Mailed: 04/27/2010

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/19/2010.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/gbien-aime/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/887,688	07/10/2004	David Paniagua	51458.010100

CONFIRMATION NO. 4909

54353
MANUEL VALCACEL
c/o GREENBERG TRAURIG, P.A.
1221 BRICKELL AVENUE
MIAMI, FL 33131

POWER OF ATTORNEY NOTICE

OC000000041276448

Date Mailed: 04/27/2010

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/19/2010.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/gbien-aime/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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.
10/887,688	07/10/2004	David Paniagua	54813-10100	4909

23337 7590 07/26/2010

HOLME ROBERTS & OWEN LLP
1700 LINCOLN STREET, SUITE 4100
DENVER, CO 80203

EXAMINER	
MILLER, CHERYL L	
ART UNIT	PAPER NUMBER
3738	

NOTIFICATION DATE	DELIVERY MODE
07/26/2010	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):

USPTO_Mail@hro.com

Interview Summary	Application No.	Applicant(s)	
	10/887,688	PANIAGUA ET AL.	
	Examiner	Art Unit	
	CHERYL MILLER	3738	

All participants (applicant, applicant's representative, PTO personnel):

(1) *CHERYL MILLER (Examiner)*. (3)*Dr. David Fish (Applicant)*.

(2) *Mark Yaskanin (Registration No.45,246)*. (4)_____.

Date of Interview: *19 July 2010*.

Type: a)☐ Telephonic b)☐ Video Conference
c)☒ Personal [copy given to: 1)☐ applicant 2)☒ applicant's representative]

Exhibit shown or demonstration conducted: d)☒ Yes e)☐ No.
If Yes, brief description: *3-D paper model of invention disclosed in parent application (10/037,266)*.

Claim(s) discussed: *Proposed new claims 57-65*.

Identification of prior art discussed: *Bailey (US 6,458,153), Garrison (US 6,425,916), Bessler (US 5,855,601)*.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *See Continuation Sheet*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

/Cheryl Miller/ Examiner, Art Unit 3738	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

———

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Newly proposed claims were presented. The claims appear to overcome Bessler. Claim 57's last clause using "only" (or sole element/component) appears to overcome Bailey due to the valve struts 24 used by Bailey in the figures for a specific purpose of support. The examiner will have to read Bailey in more depth to see if there is disclosure to an embodiment of use without valve struts 24. The Examiners interpretation of the Garrison reference was discussed. If applicant were to require in the claims the leaflet layer to be inside/within cuff layer lumen in the deployed configuration or possessing a double layer construct in the deployed configuration, this would seemingly overcome Garrison. The majority of the claims seem to receive the priority date of the parent application. Claim 63 having sutures attaching the two layers to one another and the concept of the sutures through the inner leaflet layer was discussed. The specification does not appear to clearly disclose sutures through the inner leaflet layer, however they may need to be present to function and have the structure of the shown embodiment of figure 3b, and 5. This will be further considered in the future. Applicant plans to file an RCE which will be considered at that point in time.

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Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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 contains a valid OMB control number.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	10887688	Filing Date	2004-07-10	Docket Number (if applicable)	54813-10100	Art Unit	3738
First Named Inventor	David PANIAGUA			Examiner Name	Cheryl L. MILLER		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 082665

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Signature of Registered U.S. Patent Practitioner			
Signature	/Mark L. Yaskanin/	Date (YYYY-MM-DD)	2010-08-02
Name	Mark L. Yaskanin	Registration Number	45246

This collection of information is required by 37 CFR 1.114. 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 1.11 and 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.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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 the Freedom of Information Act requires disclosure of these records.

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 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.

PTO/SB/22 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) **FY 2009** *(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)*	Docket Number (Optional) 54813-10100
Application Number 10887688	Filed 2010-07-10
For Percutaneously Implantable Replacement Heart Valve Device and Method of Making Same	
Art Unit 3738	Examiner Cheryl L. MILLER

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$130	$65	$
☑	Two months (37 CFR 1.17(a)(2))	$490	$245	$ 245.00
☐	Three months (37 CFR 1.17(a)(3))	$1110	$555	$
☐	Four months (37 CFR 1.17(a)(4))	$1730	$865	$
☐	Five months (37 CFR 1.17(a)(5))	$2350	$1175	$

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Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☑ attorney or agent of record. Registration Number 082665

☐ attorney or agent under 37 CFR 1.34.
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/Mark L. Yaskanin/	2010-08-02
Signature	Date
Mark L. Yaskanin	303.861.7000
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Application Number	10887688
Filing Date	2004-07-10
First Named Inventor	David PANIAGUA
Art Unit	3738
Examiner Name	Cheryl L. MILLER
Attorney Docket Number	54813-10100

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Signature	/Mark L. Yaskanin/	Date (YYYY-MM-DD)	2010-08-02
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(74) Agent: LEHMANN & REE; Grundtvigsvej 37, DK-1864 Frederiksberg C (DK).

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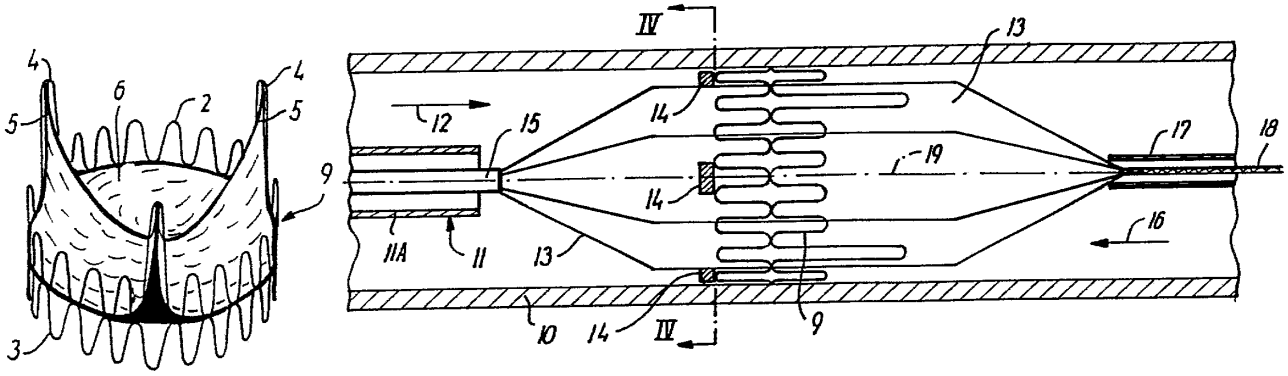
(54) Title: A VALVE PROSTHESIS FOR IMPLANTATION IN THE BODY AND A CATHETER FOR IMPLANTATING SUCH VALVE PROSTHESIS



(57) Abstract

A valve prosthesis (9) for implantation in the body by use of catheter (11) comprises a stent made from an expandable cylinder-shaped thread structure (2, 3) comprising several spaced apices (4). The elastically collapsible valve (6) is mounted on the stent as the commissural points (5) of the valve (6) is secured to the projecting apices (4). The valve prosthesis (9) can be compressed around the balloon means (13) of the balloon catheter (11) and be inserted in a channel, for instance in the aorta (10). When the valve prosthesis is placed correctly the balloon means (13) is inflated thereby expanding the stent and wedging it against the wall of aorta. The balloon means is provided with beads (14) to ensure a steady fastening of the valve prosthesis on the balloon means during insertion and expansion. The valve prosthesis (9) and the balloon catheter (11) make it possible to insert a cardiac valve prosthesis without a surgical operation comprising opening the thoracic cavity.

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A VALVE PROSTHESIS FOR IMPLANTATION IN THE BODY AND A CATHETER FOR IMPLANTATING SUCH VALVE PROSTHESIS.

Background of the Invention.

The present invention relates to a valve prosthesis, preferably a cardiac valve prosthesis, for implantation in the body by means of a technique of catheterization and of the type comprising a collapsible elastical valve which is mounted on an elastical stent.

Valve prostheses of this type are usually implanted in one of the channels of the body to replace a natural valve. In the present description the invention will be explained in connection with an cardiac valve prosthesis for implantation in aorta. However, it will be possible to use a valve prosthesis according to the invention in connection with implantation in other channels in the body by using the same technique as the one used for implantation of cardiac valve prosthesis. Such an implantation may e.g. comprise the implantation of:

1. a valve (for instance a cardiac valve) in the veins,
2. a valve in the oesophagus and at the stomach,
3. a valve in the ureter and/or the vesica,
4. a valve in the biliary passages,
5. a valve in the lymphatic system, and
6. a valve in the intestines.

An existing natural valve in the body is traditionally replaced with a valve prosthesis by a surgical implantation. However, a surgical implantation is often an exacting operation. Thus, today the implantation of cardiac valves are solely made by surgical technique where the choracic cavity is opened. The operation calls for the use of a heart and lung machine for extern circulation of the blood as the heart is stopped and opened during the surgical intervention and the artificial cardiac valves are subsequently sewed in.

Due to its exacting character it is impossible to offer such operation to certain people. For instance this is due to the fact that the person is physically weak because of age or illness. Moreover, the number of heart and lung machines available at a hospital will be a substantially limiting factor.

Cardiac valve prostheses that need no surgical intervention are known

as there are used for implantation by means of a technique of catheterization. Examples of such valve prostheses are described in US Patent specifications Nos. 3,671,979 and 4,056,854. However, both these valve prostheses are connected to means which lead to the surface of the patient either for a subsequent activation of the valve or for a subsequent reposition or removal of the valve prosthesis. With these valve prostheses it is impossible to make an implantation which makes it possible for the patient to resume a substantially normal life in the same way as it is possible in connection with a surgical implantation of a cardiac valve.

From US Patent specification No. 3,755,823 an elastic stent for a cardiac valve prosthesis is known. However, this valve prosthesis is not designed for implantation in the body by catheterization. Even though the Patent specification contains no detailed explanation the description indicates that this valve prosthesis is designed for implantation and sewering on by a surgical intervention.

Moreover, from the US Patent specifications Nos. 4,856,516 and 4,733,665 different shapes of expandable stents are known. These stents are made to be expanded by impression of a radially outward force coming from a balloon catheter or the like. These stents are made to reinforce the wall when there is a risk that the channel is closed and/or compressed.

It is the object of the present invention to provide a valve prosthesis of the type mentioned in the introductory part, which permits implantation without surgical intervention in the body and by using a catheter technique known per se and which makes it possible for the patient to resume a substantially normal life.

This is achieved according to the invention with a valve prosthesis of the type mentioned in the introductory part, which is characterized in that the stent is made from an expandable cylindrical support means and that the commissural points of the elastical collapsible valve are mounted on the cylinder surface of the support means for folding and expanding together with the cylindrical support means.

The collapsible elastic valve is mounted on the stent for instance by

gluing, welding or by means of a number of suitable sutures.

If the support means are made from a thread structure this can for instance be grate shaped, loop shaped or helical. This makes is possible to compress the stent and the collapsible valve mounted thereon for placing on the insertion catheter. The use of a non-self-expandable stent may e.g. be effected by a compression of the stent around the expansion arrangement of the catheter which preferably consists of a balloon. When using a self-expandable stent a catheter with an expansion arrangement is not used. In this case the stent is compressed and is inserted into an insertion or protection cap from which the stent is eliminated after implantation in order to obtain an expansion due to the stresses in the compressed support means which for instance may be made from plastics or metal. After the compression the entire outer dimension is relatively small which makes it possible to introduce the valve prosthesis through a channel in the body.

When the valve prosthesis is introduced and placed correctly the stent is expanded by self-expansion or by means of the expansion arrangement until the stent is given an outer dimension which is slightly larger than the channel in which it is placed. As the stent is elastic a contraction of the stent is prevented once it is expanded. The stiffness in the material of the support means contributes to maintain the expanded shape of the stent. After the expansion is made the expansion arrangement of the catheter is contracted and the catheter can be removed from the channel. The inlet opening can subsequently be closed and the patient will then be able to resume a normal life.

The valve prosthesis according to the invention does not require an actual operation but merely a small intervention to optionally expose the body channel, e.g. a vein, through which the insertion takes place. Thus patients for whom operation will be associated with high risk can be offered implantation of for instance cardiac valves. After the implantation has taken place the after-treatment will advantageously be shorter than normally which means fewer hospital days for the patient. Moreover, it is assumed that it will be possible to implantate the valve prosthesis under local anaesthetic.

The valve prosthesis can be used to replace a natural valve or to

establish a new valve function in one of the channels in the body which do not naturally contain a valve. For instance this goes for veins (arteries and veins) on a place without natural valves. The function of the valve prosthesis is then to ensure that the blood flows in one direction only. The valve is meant to be used in veins in the legs of persons suffering from varicose veins (varices).

In persons having varicose veins the blood flows in a wrong direction, viz. from the central veins in the centre of the leg towards the superficial veins. Among other things this is due to the changed pressure in the legs, upright working position and other conditions. A valve prosthesis according to the invention may easily be placed in the veins and prevent the flow of the blood in wrong direction.

Also, the valve prosthesis can be used in connection with diseases, for instance cancerous tumours, where too much humour is produced. If the humour is able to flow from the cancerous tumour through several channels it is possible to drain the humour in one desired direction through the channels of the body by an appropriate placing of the valve prostheses.

When the valve prosthesis is used as cardiac valve prosthesis in the aorta it is possible to mount it in three positions, viz. in the descending part of the aorta, in a position between the coronary arteries and the left ventricle of the heart or in the aorta in a position immediately after the mouth of the coronary arteries.

The cardiac valve prosthesis can also be used in other places than in the aorta. Thus the valve prosthesis can be used in the pulmonary artery and/or the right ventricle of the heart for replacing the pulmonary valves. Likewise the cardiac valve prosthesis can be used in the passage between the right auricle of the heart and the right ventricle of the heart (tricuspidalostium) and the passage between the left auricle of the heart and the left ventricle of the heart (mistralostium) for replacing the tricuspidal valve and the mitral valve, respectively.

Even though the cardiac valve preferably is meant to be used for patients suffering from aorta insufficiency and who can not be offered an open heart surgery the valve prosthesis can also be used for pa-

tients in connection with treatment of aorta stenosis. Several of the patients with aorta stenosis are elderly people who can not be offered a surgical cardiac operation. The patients are offered balloon dilatation of the aorta stenosis which may result in an aorta insufficiency as a side effect of the treatment.

As to these patients it is possible to insert a valve prosthesis in the descending or ascending part of the aorta thoracalis a few days or weeks before the balloon dilatation. As a result thereof the left ventricle is protected against weight if the subsequent balloon dilatation of the stenosis results in aorta insufficiency. In certain cases the weight (reflux) on the left ventricle is reduced by up to approximately 75%.

Furthermore, the stent may be made with a relatively great height and with a cylinder surface which is closed by a suitable material. Thus, a vascular prosthesis known per se is formed wherein the valve is mounted. This may facilitate the implantation of the valve prosthesis, for instance in the arcus aorta. Moreover, the great surface which abuts the inner wall of the channel contributes to ensure the securing of the valve prosthesis in the channel. This embodiment is also suitable as valve prosthesis which is inserted in veins. As veins have relatively thin and weaker walls than arteries it is desirable that the valve prosthesis has a greater surface to distribute the outward pressure which is necessary to secure the valve prosthesis.

Moreover, the invention relates to a balloon catheter for implantating a valve prosthesis according to the invention and comprising a channel for injection of a fluid for the inflation of the balloon means of the catheter and an insertion cap wherein the balloon means of the catheter and a collapsible valve prosthesis mounted thereon are located during the injection, characterized in that the balloon means are provided with a profiled surface which is made to ensure a steady fastening of the valve prosthesis during the elimination of the balloon means from the protection cap and the subsequent inflation for the expansion of the stent.

Different balloon catheters for implantating cores in the body are known. For instance such balloon catheters are known from US Patent

specifications Nos. 4,856,516, 4,733,665 and 4,796,629 and from DE publication No. 2,246,526. However, the known balloon catheters have a smooth or a slightly wavy surface. The use of such balloon catheter is disadvatageous for mounting a valve prosthesis in a channel having a large flow as for instance the aorta. A large humour flow is able to displace the stent on the smooth surface of the balloon and makes an accurate positioning difficult. This drawback has been remedied with the balloon catheter according to the present invention as the profiled surface prevent a displacement of the valve prosthesis in relation to the balloon means during introduction and the subsequent inflation of the balloon means.

In connection with the implantation any prior art technique may be used to supervise an accurate introduction and positioning of the valve prosthesis. Thus, guide wires for the catheter, X-ray supervision, injection of X-ray tracable liquids, ultrasonic measuring etc. may be used.

Description of the Drawings.

The invention will now be explained in details with reference to the accompanying schematical drawing, wherein

Fig. 1 shows a perspective view of a stent without a valve,
Fig. 2 a perspective view of a valve prosthesis according to the invention made from the stent shown in Fig. 1 having a biological valve mounted thereon,
Fig. 3 a partiel view through the aorta illustrating a partially inflated balloon catheter,
Fig. 4 a cross section through the embodiment shown in Fig. 9,
Fig. 5-7 views illustrating the introduction and implantation of a valve prosthesis of the invention in the aorta,
Fig. 8-10 views illustrating three possible positions of a cardiac valve prosthesis, and
Fig. 11-12 perspective views illustrating two further embodiments of a valve prosthesis having a closed cylindrical wall.

Fig. 1 shows a stent 1 made by support means in the form of two 0,55 mm surgical stainless steel wires 2,3. The wires are folded in 15

loops. Three loops 4 are 14 mm in height and intended to secure the commissural points 5 (see Fig. 2) from a biological cardiac valve 6 which is mounted in the stent 1. The remaining loops have a height of 8 mm. Each of the two folded wires 2,3 was bended to form rings 7,8 which were closed by welding the ends. The two rings are place on the top of each other as will appear from Fig. 1 and they are mutually secured by means of a number of sutures (not shown). By using a substantially cylindrical thread structure with projecting apices a reduction in weight is obtained compared to a stent which is exclusively cylindrical with the same loop heights for all the loops.

The biological valve 6 was removed from a slaughtered pig of 100 kg. The valve was cleaned before mounting in the stent 1. The cleaned valve has an outer diameter of 25-27 mm and the height of the three commissural points 5 is 8 mm. The valve 6 is mounted in the stent by means of a suitable number of sutures to form the cardiac valve prosthesis 9 shown in Fig. 2. The valve prosthesis produced is used for performing tests in pigs by implantation of cardiac valve prosthesis. However, the cardiac valve prosthesis for use in human beings has a corresponding form.

Fig. 3 shows a partiel view through the aorta 10. A balloon catheter 11 is introduced in the aorta according to the direction of an arrow 12. In the Figure shown the balloon means 13 of the balloon catheter is led out of the protection cap 11A and is partly inflated through a fluid channel 15, which is led to the surface of the patient. The balloon means 13 constitutes a tri-sectional balloon upon which the cardiac valve prosthesis is placed. In the form shown the cardiac valve prosthesis is expanded exactly to be in contact with the aorta 10. The balloon means 13 is provided with three projecting beads 14 which are engaged with the one side of the cardiac valve prosthesis 9. The blood flowing through the aorta according to the direction of an arrow 16 will thus cause the cardiac valve prosthesis 9 to abut on the beads 14 and the valve cannot be displaced in relation to the balloon means 13. Moreover, the balloon catheter used comprises a central channel 17 to receive a guide wire 18 which is used in a way known per se for supervising the introduction of the catheter through fluoroscopi. In the shown embodiment beads 14 are only used at one side of the valve prosthesis, but, however, it will often be desirable to use the beads in

pairs placed along lines parallel to the longitudinal axes 19 through the balloon means 13. In this case the spacing of the pair of beads 14 will correspond to the height of the loops of the stent. This makes it possible to make an effective fastening of a valve prosthesis on balloon means. Moreover, the fastening on the balloon means may be provided by using balloon means with an indentation in the surface (not shown).

Fig. 4 shows a cross section through the embodiment shown in Fig. 3 illustrating the placing of the beads 14 on the tri-sectional balloon means 13.

A balloon catheter of the above described type which was used in tests of implantating the cardiac valve prosthesis 9 in pigs had the following dimensions. Each of the three balloons is 60 mm in length and 15 mm in diameter. The total diameter for the three inflated balloons is 31 mm and in the balloon catheter used two beads 14 having a height of 3 mm are mounted on each side of the three balloons. The beads have a spacing of 15 mm. The protection cap 11A of the balloon catheter has an outer diameter of 13.6 mm and an inner diameter of 12.5 mm and a length of 75 cm. The balloon catheter is provided with a standard guide wire having a diameter of 0.9 mm and a length of 300 cm.

Figs. 5-7 show the valve prosthesis 9 at different steps in introducing and implantating in the aorta 10 by means of the catheter 11 having the inflatable balloon means 13. The cardiac valve prosthesis 9 is initially placed above the deflated balloon means 13 and compressed manually around the balloon means (Fig. 5), whereafter the outer diameter for the valve prosthesis is approximately 10 mm. After the introduction and positioning the balloon means 13 is inflated (Fig. 6) thereby contributing an outer dimension of approximately 30 mm to the cardiac valve prosthesis. To obtain an effective fastening in the aorta the outer dimension of the cardiac valve prosthesis is greater than the diameter of the aorta. This means that the prosthesis is tight against the inner wall of the aorta with a pressure which is sufficiently large to counteract a detachment due to the flow of the blood. The balloon catheter 11 may subsequently be removed from the aorta 10 (Fig. 7). Due to the stiffness of the metal the valve prosthesis will prevent a contraction. However, smaller contractions may occur (<10%

diameter reduction) after the deflation and removal of the balloon catheter 13. When the valve prosthesis is mounted as showed in Fig. 7 the patient will be able to resume a substantially normal life after a few days.

Figs. 8-10 show the positioning of the valve prosthesis 9 as cardiac valve prosthesis in the aorta 10 in three different positions. In a position between the coronary arteries 20 and the left ventricle of the heart 21 (Fig. 8). In a position immediately after the mouth of the coronary arteries in the ascending part of the aorta (Fig. 9). In a position in the descending part of the aorta 10. The positioning of the valve prosthesis is chosen in accordance with the diagnose of the illness of the patient. By placing the cardiac valve prosthesis as shown in Fig. 8 there is a risk of detachment and/or covering the mouth of the coronay arteries, and therefore it is preferred to use a higher stent which for instance comprises several rings 7,8 placed on top of each other. This allows a fixation of the prosthesis at a place after the mouth of coronary arteries even though the valve itself is in the position between the coronary arteries and the left ventricle. Fig. 8 and 9 show how a contrast medium 23 is injected by means of a so-called pigtail catheter for registration of the tightness of the implantated valve prosthesis 9.

A specific embodiment for a valve prosthesis and a balloon catheter for implantating the valve prosthesis has been explained above. However, it is obvious that it is possible to modify the valve prosthesis depending on the desired use, and moreover, it is possible to modify the catheter used in the implantation. Thus the stent of the valve prosthesis may be made solely of one closed ring folded in a number of loops or with three or more mutually secured loop-shaped rings placed on top of each other. Moreover, it is possible to make the stent having a thread structure which in stead of loops is grate shaped, helical or is formed otherwise if only it is ensured that the form of the stent permits the compression and expansion of the stent and fastening of the collapsible valve. In stead of a biological valve it might be possible to use other collapsible valves, such as valves made from synthetic materials, e.g. polyurethane. It is also possible to use valves with more or fewer flaps than three.

It is possible to make the valve prosthesis with a closed cylinder surface as illustrated in Figs. 11 and 12. In both Figures the support means of the valve prosthesis is made of an elongated tubular means 24 having a closed cylinder surface. This valve prosthesis is intended to expand by self-expansion or by means of a catheter according to the invention. This prosthesis is especially suitable for placing in veins and other channels where only a small pressure is exerted against the wall of the channel. In Fig. 11 the valve 6 is mounted at the end of the tubular means 24. In Fig. 12 an embodiment is showed where the valve 6 is mounted in a central position in the tubular means 24.

An explanation of a method of implantating a valve prosthesis according to the invention is given below:

- a valve prosthesis 9 made of a stent 1 and a collapsible valve 6, as described above,
- the valve prosthesis 9 is placed on a deflated balloon means and is manually compressed thereon,
- the balloon means 13 and the valve prosthesis are drawn into an insertion cover 11A,
- a guide wire 18 is inserted into the left ventricle of the heart through the central opening 17 of the balloon catheter under continuous fluoroscopi,
- the insertion cover 18 conveys the guide wire 18 to a point in the channel in immediate vicinity of the desired position of the valve prosthesis,
- the balloon means 13 is pushed out of the protection cap 11A and the valve prosthesis is positioned in the desired position if necessary by use of further registration means to ensure an accurate positioning,
- the balloon means 13 is inflated with a certain overstretching of the channel,
- the balloon means 13 is deflatated, and
- the balloon means 13, the guide wire 18 and the protection cap 11A are drawn out and the opening in the channel, if any, wherein the valve prosthesis is inserted can be closed.

C L A I M S.

1. A valve prosthesis, preferably a cardiac valve prosthesis, for implantation in the body by means of a technique of catheterization and of the type comprising a collapsible elastical valve which is mounted on an elastical stent, c h a r a c t e r i z e d in that the stent is made from an expandable cylindrical support means and that the commissural points of the elastical collapsible valve are mounted on the cylinder surface of the support means for folding and expanding together with the cylindrical support means.

2. A valve prosthesis according to claim 1, c h a r a c t e r i z e d in that the support means is made of a thread structure.

3. A valve prosthesis according to claim 2, c h a r a c t e r i z e d in that the thread structure comprises several spaced apices projecting from the one side of the cylindrical structure and in direction along the longitudinal axis of the cylinder and that the commissural points of the valve are attached to the projecting apices.

4. A valve prosthesis according to claim 3, c h a r a c t e r i z e d in that the elastically collapsible valve is a biological trilobate valve.

5. A valve prosthesis according to claim 4, c h a r a c t e r i z e d in that the stent is made from a stainless steel wire folded in a number of loops and bended according to a circle and welded to form a closed ring, that the stent comprises two or more such closed rings which are mutually connected end to end to form the cylindrical thread structure, that three of the loops in the external ring are folded with a greater height than the remaining loops to form the apices to which the commissural points of the biological valve are attached.

6. A valve prosthesis according to claim 5, c h a r a c t e r i z e d in that each of the rings of the stent is made from a wire having a diameter of 0.55 mm and a loop height of approximately 8 mm and approximately 14 mm for the three greater loops, and that the cylindrical thread structure produced and the collapsible valve mounted thereon in a folded state have an outer diameter of approximately 10 mm and in

expanded state an outer diameter of approximately 30 mm.

7. A valve prosthesis according to claim 5, c h a r a c t e r i z e d in that three or more mutually attached rings placed on top of each other are used and that the stent is made to be fixed through the expansion at one point in the channel where the valve prosthesis is inserted, which point is different from the point where the valve is mounted in the stent.

8. A valve prosthesis according to any of the preceding claims, c h a r a c t e r i z e d in that the cylinder surface of the support means is closed to form a tubular element.

9. A balloon catheter for use in implantating a valve prosthesis according to any of the preceding claims and comprising a channel for injection of a fluid for the inflation of the balloon means of the catheter and an insertion cap wherein the balloon means of the catheter and a collapsible valve prosthesis mounted thereon are located during the injection, c h a r a c t e r i z e d in that the balloon means are provided with a profiled surface which is made to ensure a steady fastening of the valve prosthesis during the elimination of the balloon means from the protection cap and the subsequent inflation for expanding the stent.

10. A balloon catheter according to claim 9, c h a r a c t e r i z e d in that the profiling of the surface is made by beads or buds on the surface of the balloon means.

11. A balloon catheter according to claim 10, c h a r a c t e r i z e d in that the beads are placed in pairs in a number from four to eight along lines parallel with the longitudinal axis of the balloon means and with a spacing corresponding to the height of the stent used.

12. A balloon catheter according to claim 9, c h a r a c t e r i z e d in that the profiling of the surface is made by an indentation which is formed in the surface of the balloon means with an extension corresponding to the height of the stent used.

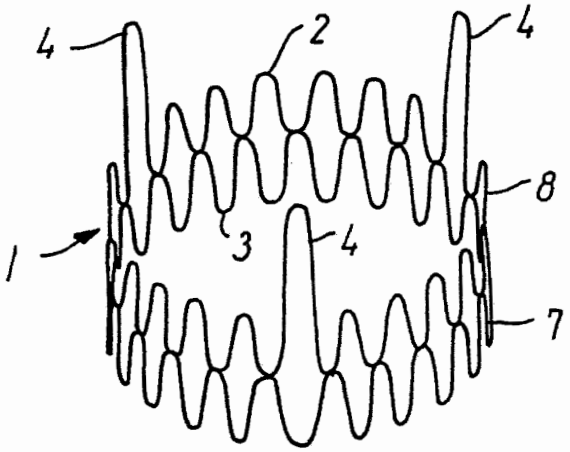

FIG. 1

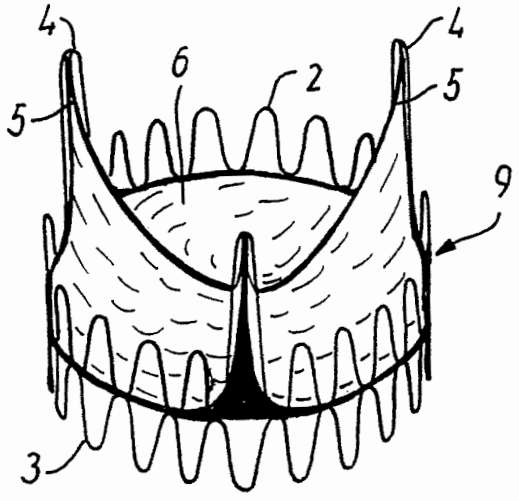

FIG. 2

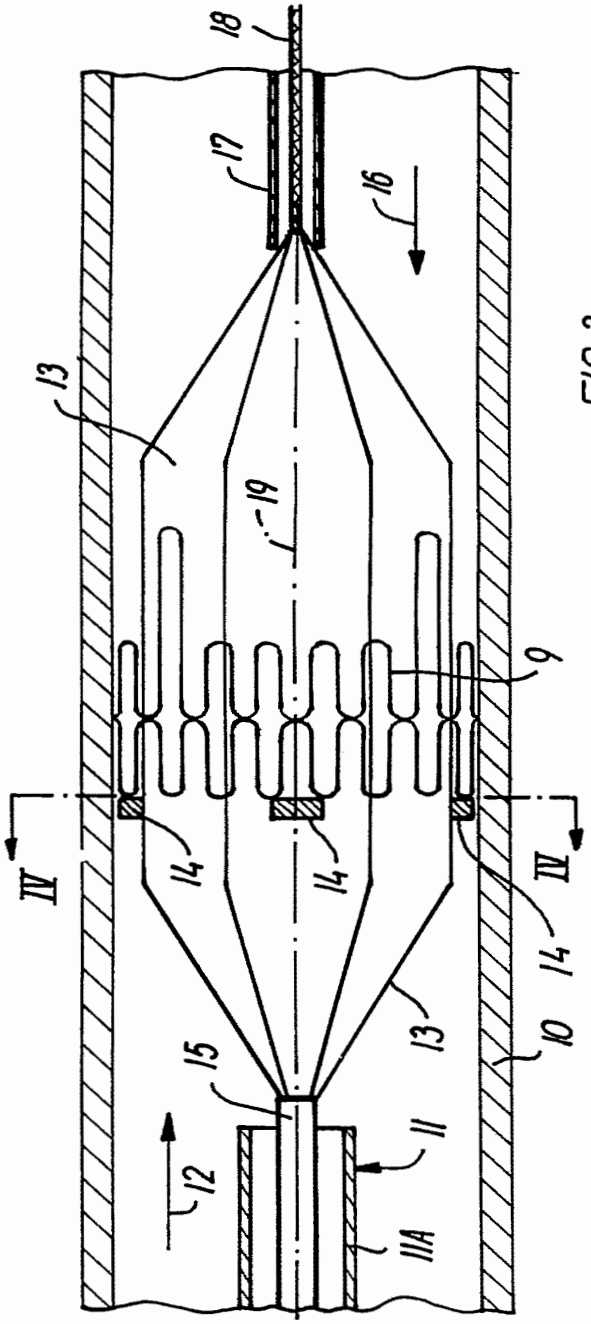

FIG.3

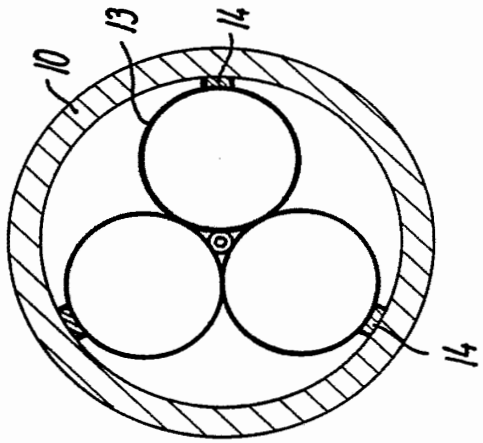

FIG.4

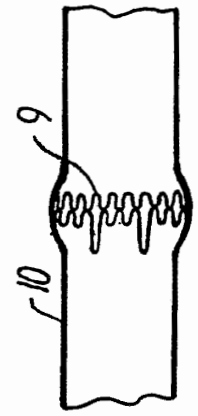

FIG.7

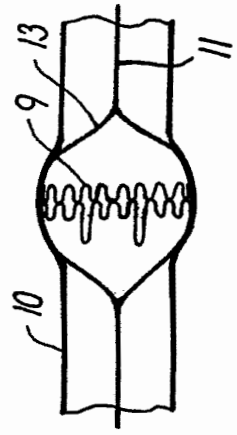

FIG.6

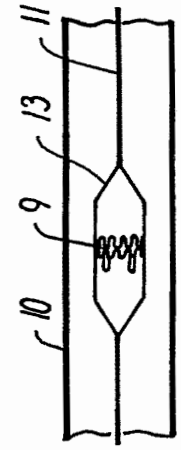

FIG.5

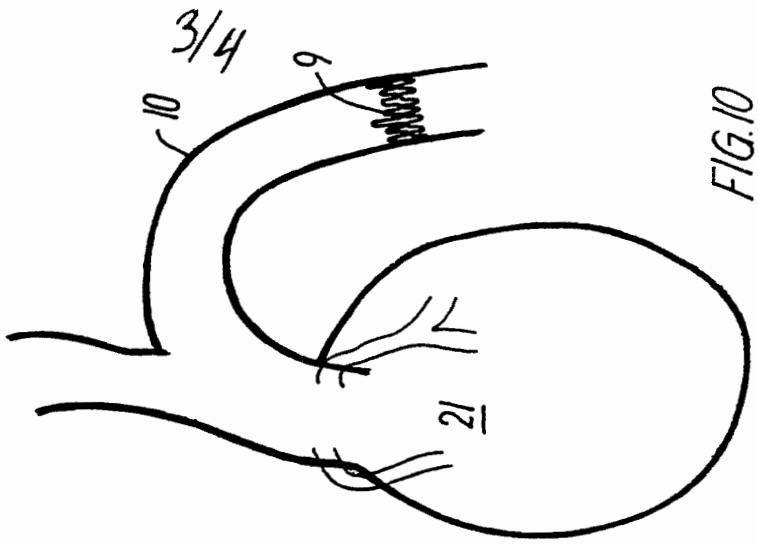

FIG.10

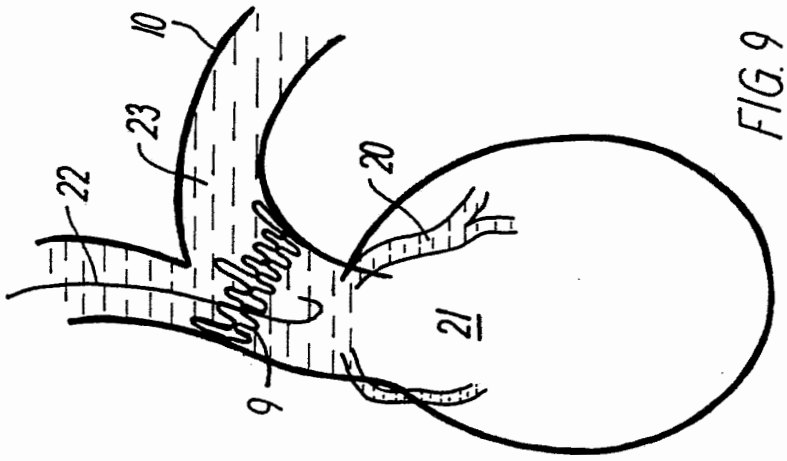

FIG.9

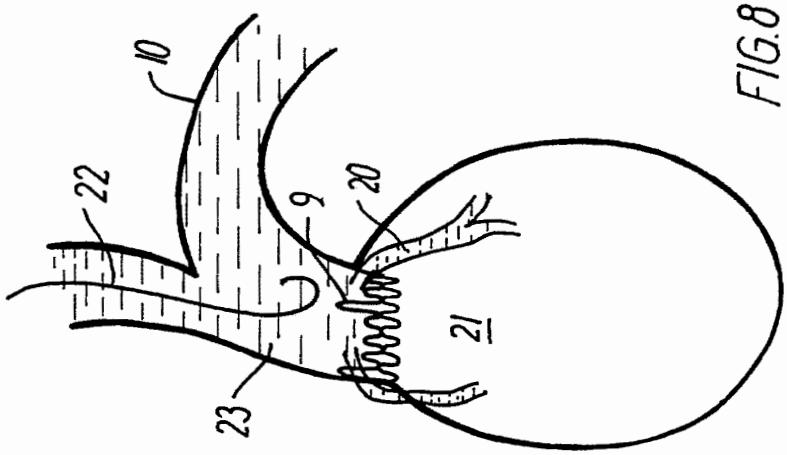

FIG.8

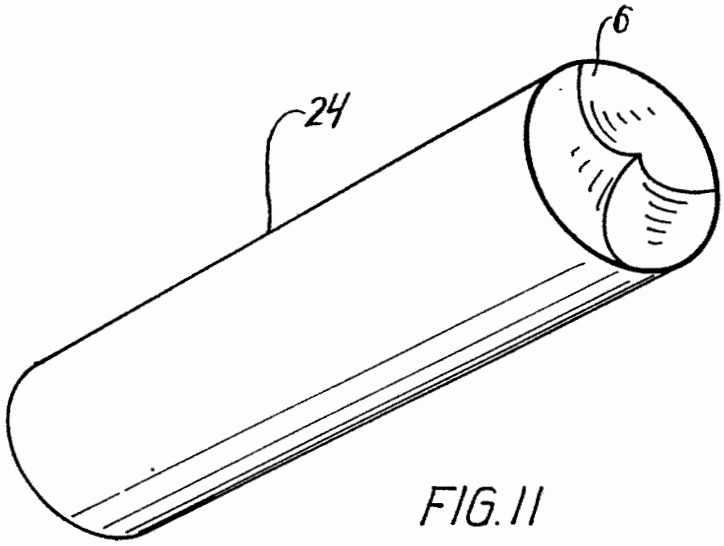

FIG. 11

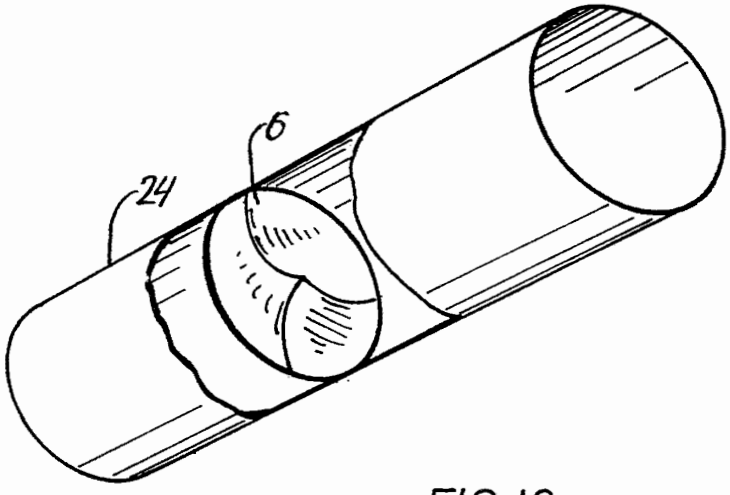

FIG. 12

INTERNATIONAL SEARCH REPORT

International Application No PCT/DK 91/00134

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 F 2/24, A 61 M 25/10

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	A 61 B; A 61 F; A 61 M

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	GB, A, 2056023 (DONALD NIXON ROSS) 11 March 1981, see figures 2,3 --	1-5,8
A	US, A, 3671979 (MOULOPOULOS) 27 June 1972, see figures 2B,5 --	1,9
A	Derwent's abstract, No. 87-190 867/27, SU 1 271 508, publ. week 8727 (GORKII KIROV MEDICAL INS) --	1

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* Special categories of cited documents: [10]

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"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
14th August 1991	1991 -08- 21
International Searching Authority	Signature of Authorized Officer
SWEDISH PATENT OFFICE	Leif Karnsäter

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers....., because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim numbers....., 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. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

Claims 1-8 concerning a valve prosthesis.
Claims 9-12 concerning a catheter.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ 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 the claims. It is covered by claim numbers:

4. ☒ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additonal fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional seach fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. PCT/DK 91/00134

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the Swedish Patent Office EDP file on 91-06-27
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A- 2056023	81-03-11	US-A- 4343048	82-08-10
US-A- 3671979	72-06-27	NONE	

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A1

(11) International Publication Number: WO 92/17118

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(22) International Filing Date: 30 March 1992 (30.03.92)

(30) Priority data:
680,705 4 April 1991 (04.04.91) US

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(74) Agents: KAIHOI, Gregory, P. et al.; Fredrikson & Byron, 1100 International Centre, 900 Second Avenue South, Minneapolis, MN 55402 (US).

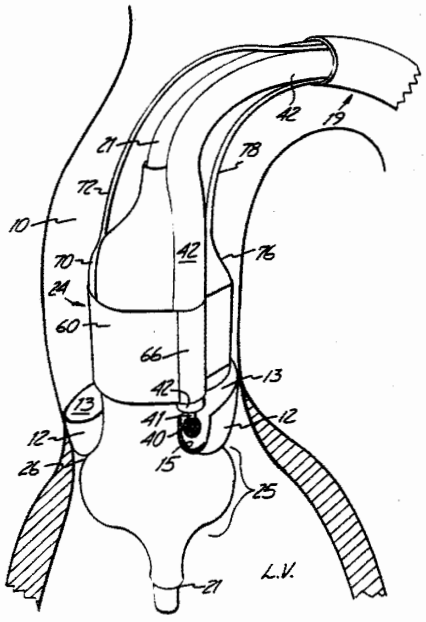
(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), SE (European patent).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: METHOD AND APPARATUS FOR IN VIVO HEART VALVE DECALCIFICATION

(57) Abstract

A method and apparatus for in vivo removal of calcified deposits from an aortic valve. The apparatus includes an anchoring balloon catheter (24) fixatable across the aortic valve, a tool (40) for removing the deposits (15), and attachment means (60) for securing the tool (40) with respect to the anchoring balloon (24) and the aortic valve. The method involves advancing an anchoring balloon catheter (24) through the aorta (10) and positioning it across the aortic valve, inflating the anchoring balloon (24) to fixate it with respect to the aorta (10) and aortic valve, and then operating a deposit removal tool (40) secured to the anchoring balloon (24) to remove the deposits (15).



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METHOD AND APPARATUS FOR IN VIVO HEART VALVE DECALCIFICATION

FIELD OF THE INVENTION

The invention relates to a method and apparatus for removing, in vivo, calcified deposits from heart valves.

BACKGROUND OF THE INVENTION

Calcific aortic stenosis (i.e., the buildup of calcified deposits on the superior surface of the aortic heart valve) accounts for a large percentage of aortic stenosis cases. This condition is characterized by the buildup of calcified nodules on the upper or superior surface of the aortic valve leaflets. These nodules decrease the flexibility of the leaflets, thereby limiting their mobility and capacity to fully open to permit adequate blood flow. Absent anatomic correction, advanced aortic stenosis carries a poor prognosis.

Three techniques have been employed to correct aortic stenosis: valve replacement, intraoperative decalcification (debridement) of the heart valve, and balloon valvuloplasty.

Valve replacement during open heart surgery is currently standard therapy for symptomatic aortic stenosis. Ten year survival rates for isolated aortic valve replacement are generally very good, even in elderly patients. However, this technique requires

that the patient be healthy enough to undergo open heart surgery. The operative mortality for this procedure, particularly among the elderly, is also significant--variously reported at between about 5% and 12%. In addition, a patient receiving a replacement valve typically must take anticoagulation drugs for the rest of his or her life--not all patients are capable of doing this. Moreover, some patients have an aortic root that is not large enough to easily accommodate conventional replacement valves. Thus, there are a significant number of patients for whom valve replacement is either impossible, impractical, or undesirable.

Intraoperative mechanical debridement (decalcification) of the aortic valve to treat aortic stenosis was successfully used for many years prior to the advent of mechanical replacement valves. In this technique, the aorta is entered surgically (as in a valve replacement procedure) but rather than replace the valve the surgeon manually removes the calcified deposits, using suitable surgical tools. The debridement techniques, although for some time completely forsaken in favor of valve replacement procedures, has enjoyed some recent revival, particularly for patients having a small aortic root and/or contraindications for anticoagulation therapy. In addition to mechanical tools, recently ultrasonic debridement has also been demonstrated to be effective to remove calcific deposits. Nevertheless, these techniques still require the patient to be healthy enough to survive and recuperate from thoracic surgery, and involve all of the costs and risks attendant with such surgery.

The third technique for correcting aortic stenosis involves percutaneous balloon aortic

valvuloplasty (BAV). In this procedure, an inflatable balloon catheter is advanced to the aortic valve and inflated to compress and fracture the calcified nodules in an attempt to increase leaflet mobility. Although this procedure eliminates many of the risks and disadvantages attendant with the preceding two techniques, restenosis is very common within one year, limiting the technique's usefulness to temporarily mitigating symptoms for those patients who are poor surgical candidates or refuse surgery.

SUMMARY OF THE INVENTION

The invention provides a method and apparatus for in vivo removal of calcified deposits from an aortic valve. The apparatus includes an anchoring balloon catheter fixatable across the aortic valve, a tool for removing the deposits, and attachment means for securing the tool with respect to the anchoring balloon and the aortic valve.

The attachment means preferably includes means for positioning the deposit removal tool with respect to the anchoring balloon. In one embodiment the distal end of a guiding catheter is secured to the anchoring balloon, and positioning of the tool is accomplished by selectively moving the distal end of the guiding catheter about the anchoring balloon and by moving the tool around within the guiding catheter.

One embodiment for securing the guiding catheter with respect to the anchoring balloon while allowing selective movement of the guiding catheter employs a circumferential band having first and second ends respectively attached to the anchoring balloon, with the distal end of the guiding catheter attached to an intermediate portion of the band. Positioning balloons are interposed between the circumferential band and the anchoring balloon. The positioning

balloons work in concert, so that as one balloon is inflated, the other is deflated, thereby changing the relative position of the intermediate portion of the band and the associated distal end of the guiding catheter. Thus, when a first of the balloons is being inflated (with the second balloon being simultaneously deflated), the distal end of the guiding catheter will move clockwise about the anchoring balloon, and when the second balloon is being inflated (with the first balloon being simultaneously deflated), the distal end of the guiding catheter will move counterclockwise about the anchoring balloon.

The deposit removal tool may be positioned within the guiding catheter by providing a coaxial positioning catheter within the guiding catheter. The positioning catheter preferably includes an off-center lumen in which the elongated shaft of the removal tool is closely received. Thus, by rotating the positioning catheter within the guiding catheter, the position of the removal tool can be selectively controlled.

The removal tool may comprise any effective device, including any one of a variety of rotatable cutting, scraping or abrading devices, an ultrasonic vibrations generator or a wire capable of conveying ultrasonic vibrations and being connected to an ultrasonic vibrations generator, an optical fiber connected to a laser outside of the body, a pair of electrodes connected to a high voltage source outside of the body, or any other suitable device.

In a modified embodiment of the invention, the anchoring balloon catheter utilized in the invention comprises an inflatable tube that has a proximal, generally straight portion, and a distal, helically coiled portion. The turns of the helical coil may be

spaced from one another slightly, or successive turns may abut one another. Means may also be provided for securing the turns of the coil to one another, such as by providing an outer or inner skin to which the turns adhere.

The method of the invention involves removing, in vivo, deposits from an aortic valve's superior surface. The method comprises the steps of advancing an anchoring balloon catheter through the aorta and positioning it across the aortic valve, inflating the anchoring balloon to fixate it with respect to the aorta and aortic valve, and then operating a deposit removal tool secured to the anchoring balloon to remove the deposits.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a perspective view in partial cross-section of the apparatus of the invention fixated in the aortic valve of a heart;

Figure 2 is a perspective view in partial cross-section similar to Figure 1 with one of the valve leaflets removed for clarity and with the guiding catheter shown in a moved position;

Figure 3 is a cross-section of Figure 1 taken along line 3-3 thereof;

Figure 4 is a cross-sectional view similar to Figure 3 shown in a moved position;

Figure 5 is another cross-sectional view similar to Figure 3 showing a second moved position;

Figure 6 is a cross-sectional broken-away view of a modified embodiment of the invention;

Figure 7 is a cross-sectional view of Figure 6 taken along line 7-7 thereof;

Figure 8 is a cross-sectional view of Figure 6 taken along line 8-8 thereof;

Figure 9 is a somewhat schematic representation

of another embodiment of the apparatus of the invention in the process of being introduced into a patient;

Figure 9A is a cross-sectional view of Figure 9, taken along line 9A-9A thereof;

Figure 10 is a view similar to Figure 9 after the guiding catheter has been introduced into the otherwise flaccid sheath;

Figures 10A and 10B are cross-sectional views of Figure 10, taken respectively across lines 10A-10A and 10B-10B thereof;

Figure 11 is a view similar to Figure 9 after the tool has been introduced into the guiding catheter;

Figures 11A, 11B and 11C are cross-sectional views of Figure 11, taken respectively across lines 11A-11A, 11B-11B and 11C-11C thereof;

Figure 12 is a view similar to Figure 9 after the positioning catheter has been introduced into the guiding catheter over the tool shaft;

Figure 12A is a cross-sectional view of Figure 12, taken across line 12A-12A thereof;

Figure 13 is a perspective view of another modified embodiment of the invention;

Figure 13A is a cross-sectional view, partially broken away, of Figure 13 taken along line 13A-13A thereof;

Figure 13B is a cross-sectional view similar to Figure 13A shown in a moved position;

Figure 14 is a cross-sectional view similar to Figure 13B showing a modified embodiment of the invention;

Figure 15 is a modified embodiment of the invention;

Figure 15A is a cross-sectional view of Figure 15, taken along line 15A-15A thereof;

Figure 16 is yet another modified embodiment of the invention;

Figure 16A is a view of the other side of the embodiment shown in Figure 16;

Figure 17 is a perspective view of yet another embodiment of the invention;

Figure 18 is a perspective, partially broken-away view of a yet one more embodiment of the invention;

Figure 19 is a schematic illustration of a cardiopulmonary support/bypass system utilized in conjunction with the decalcification apparatus of the invention;

Figure 20 shows a modified arrangement of the cardiopulmonary support system of Figure 19;

Figure 21 shows a modified arrangement of the cardiopulmonary support system of Figure 19;

Figure 22 shows a modified arrangement of the cardiopulmonary support system of Figure 19;

Figure 23 shows a modified arrangement of the cardiopulmonary support system of Figure 19;

Figure 24 is a cross-sectional view of an anchoring balloon of the invention;

Figure 25 is a cross-sectional view of a modified embodiment of the anchoring balloon of the invention;

Figure 26 is a cross-sectional view of another modified embodiment of an anchoring balloon of the invention;

Figure 26A is a cross-sectional view of Figure 26, taken along line 26A-26A thereof;

Figure 27A is a perspective, broken-away view in partial cross-section showing yet another embodiment of the apparatus of the invention;

Figure 27B shows the distal ends of the various

catheters utilized in the embodiment of Figure 27A;

Figure 28 shows a modified version of the embodiment of Figure 27A;

Figure 29 shows the embodiment of Figure 27A inserted into position prior to inflation of the anchoring balloon;

Figure 30 shows an alternate embodiment, partially broken away, similar to Figure 29;

Figure 31 shows another modified embodiment of the invention;

Figures 32A and 32B show yet another modified embodiment of the invention; and

Figures 33-35 show alternate deposit removal tools usable with the apparatus of the invention.

BEST MODE FOR CARRYING OUT THE INVENTION

Figure 1 shows in perspective, partial cross-sectional view an anchoring balloon catheter 24 of the invention secured in the aorta 10, with its distal portion 25 inserted past the leaflets 12 of the aortic valve. In Figure 2, a portion of the valve leaflets 12 in the foreground has been omitted to reveal better the position and shape of the distal portion 25 of the anchoring balloon catheter 24 and the deposits 15 on the superior surface 13 of the leaflets. In this view, it can be seen that the distal portion 25 of the anchoring balloon is preferably of a larger diameter, having a shoulder 26 that contacts the inferior surface of the valve leaflets 12 to accurately and securely position the anchoring balloon 24, with respect to the valve leaflets 12, providing support to the leaflets to stabilize their positions and to outline the inferior surface of the leaflets 12 in contact with the balloon inflated with radiographic contrast solution. The anchoring balloon catheter 24 also includes a central

catheter 21 having preferably at least a pair of lumens, one 22 for passage of the anchoring balloon catheter 24 over a guide wire (not shown) and/or injection or withdrawal of fluids therethrough, and a second 23 for inflation of the balloon 24.

Attachment means is provided to secure a deposit removal tool 40 to the inflatable anchoring balloon catheter 24. The attachment means may comprise a variety of configurations. A preferred embodiment is depicted in Figures 1-5. In this embodiment, the attachment means includes means for selectively positioning the deposit removal tool 40 with respect to the anchoring balloon 24 so that the physician can guide the tool 40 carefully to the calcification deposit 15 which is to be removed. Again, the preferred embodiment illustrated in Figures 1-5 shows a preferred mechanism for achieving this selective control.

In this preferred embodiment, a circumferential band 60 having first and second ends 62 and 64, respectively, is attached to the anchoring balloon 24. The circumferential band 60 also includes an intermediate portion 66, which is attached to a guiding catheter 42. The deposit removal tool 40 in turn is disposed within the guiding catheter 42.

As mentioned above, preferably means is provided for selectively moving the guiding catheter 42 about the periphery of the anchoring balloon 24. In this preferred embodiment, a pair of positioning balloons 70 and 76 are disposed between the circumferential band 60 and the anchoring balloon 24, each located adjacent the ends 62 and 64 of the circumferential band 60. As illustrated in Figures 3-5, the guiding catheter 42 can be moved about the periphery of the anchoring balloon 24 by selectively inflating and

deflating the positioning balloons 70 and 76.

In Figure 3, both of the positioning balloons 70 and 76 are partially inflated, and the guiding catheter 42 is in a generally central position. In Figure 4, one of the positioning balloons 70 has been fully inflated and the other positioning balloon 76 deflated, causing the guiding catheter 42 to have moved to its most clockwise location. In Figure 5, the first positioning balloon 70 is fully deflated, and the second positioning balloon 76 is fully inflated, causing the circumferential band 60 to pull the guiding catheter 42 to its most counterclockwise position. Thus, by selectively inflating and deflating the positioning balloons 70 and 76, the guiding catheter 42 can be moved through a range of positions about the anchoring balloon 24. The size of the positioning balloons and the diameter of the anchoring balloon will dictate what total range of motion is possible. Preferably, the range of motion should be at least about 120°, allowing the deposit removal tool 40 to fully service one of the three leaflets 12 of the aortic valve without repositioning the anchoring balloon 24. To remove deposits from the other leaflets 12, the anchoring balloon 24 can be partially deflated and then rotated to a new position corresponding to one of the other leaflets 12.

Figures 3-8 depict a secondary positioning means that allows some control over the radial position of the deposit removal tool 40. In this embodiment, a positioning catheter 46 is disposed within the guiding catheter 42. The positioning catheter 46 includes an off-center lumen 49 in which the shaft 41 of the deposit removal tool 40 is carried. By rotating the positioning catheter 46 with respect to the guiding catheter 42, the deposit removal tool 40 can be

adjusted radially inwardly and outwardly with respect to the anchoring balloon 24. Some limited control over the circumferential position of the tool 40 is also provided.

Figures 6-8 illustrate a particularly preferred embodiment in which the positioning catheter 46 includes indexing slots 47 at its distal end. The guiding catheter 42 in turn carries a tab 43 extending radially inwardly (the tab 43 may, e.g., extend radially inwardly from a metal ring 45 carried by the guiding catheter 42). As the positioning catheter 46 is advanced through the guiding catheter 42 to its most distal position, the tab 43 of guiding catheter 42 will engage a corresponding slot 47 in the positioning catheter 46. This prevents rotational movement of the positioning catheter 46 with respect to the guiding catheter as the tool is being utilized. Where it is desired to change the rotational position of the positioning catheter 46, it can be withdrawn slightly, rotated, and then again advanced to engage the tab 43 in the desired slot 47 corresponding to the desired position.

Figures 9-12 illustrate another modification of the invention which includes a collapsable sheath 44, and illustrate its use in the process of introducing the device of the invention into the patient. In Figure 9, the aorta 10 is shown schematically dividing into the left and right iliac arteries 11. The anchoring balloon catheter 24 with its catheter 21 has been inserted into the iliac artery 11, and advanced through the aorta to the aortic valve, where the anchoring balloon 24 is inflated. In this embodiment, a flaccid sheath 44 is connected directly to the circumferential band 60. This flaccid sheath allows final assembly of the entire unit inside the

body--i.e., the anchoring balloon with the flaccid sheath 44, the circumferential band 60 and the positioning balloons 70 and 76 (all deflated and furled about the catheter 21 of the anchoring balloon 24) can first be inserted into the aorta 10 via the iliac artery 11. The guiding catheter, positioning catheter and deposit removal tool can then be inserted, after the anchoring balloon catheter is in position. The flaccid nature of this sheath 44 therefore allows the deflated anchoring balloon 24 with attachment means to be furled into a relatively small diameter unit for insertion through the narrower iliac artery 11 into the wider aorta 10. Once the anchoring balloon 24 has entered the aorta 10 (and, preferably, reached its position in the aortic valve), the anchoring balloon 24 can be inflated and the rest of the unit assembled by inserting the guiding catheter 42 through the sheath 44 to its position adjacent the anchoring balloon 24, followed by the deposit removal tool and the positioning catheter. To ease insertion of the guiding catheter into the sheath 44, the sheath can be of a larger diameter proximally, narrowing at its most distal portion to a diameter that closely receives the guiding catheter therein.

In Figure 9, the guiding catheter 42 has been advanced only slightly into the sheath 44. In Figure 10, the guiding catheter 42 is fully advanced, and the deposit removal tool 40 is about to be introduced. Note that Figures 10A and 10B illustrate the cross-sectional configuration of the device, and show catheter 19 with four lumens--one each 71 and 77 for inflating and deflating the positioning balloons 70 and 76, one 23 for inflating the anchoring balloon itself, and one 22 for passing through a guide wire or injecting or withdrawing fluids such as contrast or

blood. The catheter 19 is formed from catheter 21 of the anchoring balloon catheter 24 and catheters 72 and 78 of the positioning balloons 70 and 76, respectively.

In Figure 11 the deposit removal tool 40 has been fully advanced through the guiding catheter 42 and the positioning catheter 46 is about to be advanced over the shaft 41 of the deposit removal tool 40. Figure 11A depicts the tool's shaft 41 closely received in the off-center lumen 49 of the positioning catheter 46. Figure 12 shows the positioning catheter 46 fully advanced through the guiding catheter 42. A "Y" connector 52 may be provided on the proximal end of the positioning catheter 46 to allow fluid to be injected or withdrawn through the main lumen 50 of the positioning catheter 46, while the elongated shaft 41 of the tool 40 exits through a sealing fitting 51. In most applications, the main lumen 50 will be utilized to withdraw fluid from the area immediately adjacent the deposit removal tool, thereby removing any particles or debris cut away by the tool. This lumen 50 may also be used, however, for injecting fluids, such as contrast solutions used in radiographic imaging.

Figures 13-14 depict an alternate embodiment for providing attachment means to secure the tool 40 with respect to the anchoring balloon 24 and for permitting selected positioning of the deposit removal tool 40 with respect to the anchoring balloon 24. In this embodiment, a set of circumferential straps is provided. In the embodiment illustrated, a set of upper and lower circumferential straps 85 is attached with a first end 86 secured to the anchoring balloon 24 and a second end 87 attached to the guiding catheter 42. A middle strap 90 similarly has a first

end 91 attached to the anchoring balloon 24 and a second end 92 attached to the guiding catheter 42. The middle strap 90 is wound about the anchoring balloon 24 in a direction opposite that of the upper and lower straps 85. The guiding catheter 42 may then be rotated to move it circumferentially about the anchoring balloon 24. Referring to Figures 13A-13B, as the guiding catheter is rotated clockwise, the middle strap 90 will wind up on the guiding catheter 42, while the upper and lower straps 85 will unwind from the guiding catheter 42; as this occurs, the guiding catheter 42 will move clockwise about the anchoring balloon 24 from the position illustrated in Figure 13A to the position illustrated in Figure 13B. Figure 14 shows a slightly modified arrangement of this embodiment where the straps 85 and 90 are somewhat longer, permitting movement of the guiding catheter 42 substantially entirely around the anchoring balloon 24.

Figures 15 and 15A show another simplified embodiment of the invention. In this embodiment guiding catheter 42 is attached directly to the wall of the anchoring balloon 24. Positioning of the tool is accomplished merely by rotating the anchoring balloon 24 itself with respect to the aortic valve, and by rotating the positioning catheter 46 within the guiding catheter 42.

Figures 16-16A show yet another embodiment for controllably positioning the guiding catheter with respect to the anchoring balloon (Figure 16A showing the back side of Figure 16). In this embodiment a pair of cords 57 can be manipulated to move the guiding catheter 42 about the periphery of the anchoring balloon 24. Each cord 57 is attached at its distal end 57a to a pulley strip 59 that in turn is

attached to the anchoring balloon (Figure 16A). The cord is then threaded through a series of pulleys on a pair of pulley rings 58 carried by the guiding catheter 42 and pulleys on the fixed pulley strip 59. By pulling on one of the cords 57 while releasing the other the guiding catheter will be pulled around the anchoring balloon in one direction; by pulling on the other cord, the guiding catheter will be pulled around in the other direction.

In practice, the decalcification procedure of the invention proceeds as follows. Access to the aorta 10 is obtained, typically through percutaneous or cut-down entry into the femoral artery with a guide wire. The guide wire is advanced through the femoral and iliac arteries and the aorta to the aortic valve and then across the aortic valve into the left ventricle (L.V.). A deflated anchoring balloon catheter 24 is then advanced over the guide wire to a position across the aortic valve with the distal tip of the balloon in the left ventricle (L.V.). The anchoring balloon 24 is then inflated and slightly retracted to engage the shoulder 26 of the anchoring balloon 24 against the inferior surface of the calcified valve leaflets 12. (Depending on the situation and the type of anchoring balloon catheter utilized, cardiopulmonary support/bypass may be necessary once the balloon is inflated, and this can be accomplished as described below.)

When utilizing the embodiment having the collapsable guiding catheter sheath 44 attached to the anchoring balloon 24, the guiding catheter 42 may then advanced through the sheath 44 to proper position adjacent the anchoring balloon 24. The deposit removal tool 40, together with the positioning catheter 46, may then be advanced through the guiding

catheter 42 to their proper positions. One or both of the positioning balloons 70, 76, may then be inflated to circumferentially locate the guiding catheter 42 and, hence, the deposit removal tool 40 as desired. The positioning catheter may also be rotated to further position the removal tool 40. The tool 40 in turn may also be slightly advanced or withdrawn as necessary. Operation of the removal tool 40 can then be commenced, with blood and dislodged calcification deposits being sucked up through the main lumen 50 of the positioning catheter 46. When deposits from a particular leaflet 12 have been removed, the anchoring balloon 24 can be deflated partially and rotated to position the removal tool 40 adjacent one of the other leaflets 12. When the calcification deposits have been removed, the entire device may be removed essentially by reversing the process of inserting the device.

During the procedure, conventional radiographic imaging techniques may be utilized to allow the physician to view the relative locations of the anchoring balloon 24, deposit removal tool 40, and the calcified deposits which are to be removed from the aortic valve leaflets. Preferably, the components of the anchoring balloon and removal tool and associated catheters are either radio-opaque or marked with radio-opaque markers so that they will be visible by conventional radiographic imaging techniques. Visualization of the anchoring balloon and positioning balloons and the inferior surface of the leaflets in contact with the anchoring balloon 24 is further facilitated by using radiographic contrast solution for inflation of the balloons 24, 70 and 76. Contrast may also be injected either through the lumen 22 of the anchoring balloon 24, or through the main lumen 50

of the positioning catheter 46.

In addition, known ultrasound imaging techniques may also be utilized. N. Bom and J. Roelandt have edited a reference book entitled "Intravascular Ultrasound," (Kluwer Academic Publishers 1989), containing a variety of articles detailing techniques, developments, and clinical perspectives on intravascular ultrasound procedures. Figure 17 illustrates one possible embodiment utilizing a phased array ultrasound transducer 29 (containing many small acoustic elements 128) mounted on the catheter 21 of the anchoring balloon 24. This transducer 29 will generate a cross-sectional view of the aortic valve and the location of the calcified deposits to be removed. The details of such ultrasound techniques for intravascular imaging are well-known, as described in the above-mentioned text. Ultrasound preferably is used in conjunction with and not to the exclusion of conventional radiographic imaging.

Figure 18 shows another embodiment of the invention where an ultrasound catheter 132 is positioned inside one of the lumens of the catheter 21 of the anchoring balloon 24, preferably the lumen 22. The ultrasound catheter 132 shown in Figure 18 operates on a principle different from the one shown in Figure 17. Instead of a phased array transducer, the ultrasound catheter 132 includes an echo transducer 133 and a mirror 31 rotated by a flexible shaft 30. This embodiment is advantageous in that it allows the ultrasound catheter 132 to be advanced or retracted in the lumen 22 of the anchoring balloon 24 to provide a cross-sectional image at the desired more distal or more proximal position. As these types of ultrasound catheters and procedures are described in greater detail in the Bom reference identified above,

further description is not necessary here.

During performance of the decalcification procedure, it is desirable to provide cardiopulmonary support/bypass for the patient, as an anchoring balloon 24 of the type depicted in Figure 1 substantially occludes the aortic valve. Figures 19-23 depict several variations for providing such support.

Figure 19 depicts in schematic form a first variation. Blood is ejected/withdrawn from the left ventricle through the central lumen 22 of the anchoring balloon catheter 24 and delivered to a first pump 106. That pump 106 in turn delivers the blood through a filter 107 to a heat exchanger 108 and then through percutaneous catheter 111 back to the iliac artery 11 and the aorta 10. Blood and calcification deposit debris loosened by the removal tool 40 are aspirated into the main lumen 50 of the positioning catheter containing the tool shaft by a second pump 110. Debris is filtered out by a second filter 109, after which the blood is sent through the heat exchanger 108 and the return catheter 111 back to the aorta 10.

To assure adequate extracorporeal circulation an additional blood withdrawal catheter 113 is percutaneously introduced into the iliac vein 120. Blood withdrawn through this catheter 113 should be oxygenated before being returned to the body. This may be accomplished by a conventional oxygenator 105 which in turn passes the blood through pump 106 to filter 107, and heat exchanger 108, whereupon the blood may be returned to the aorta 10 through the return catheter 111.

In order to maintain blood flow through the heart sufficient to significantly reduce the risk of

cardiac asystole, particularly in light of the relatively small size of the central lumen 22 of the anchoring balloon catheter 24, a supplemental catheter 112 may be advanced percutaneously through the vena cava 100 to the left ventricle (L.V.) by way of the right atrium (R.A.) and the left atrium (L.A.), as shown in Figure 20. To achieve this positioning of the catheter 112, the catheter must pass through the thin septum between the right atrium (R.A.) and left atrium (L.A.), such as is commonly done in mitral balloon valvuloplasty (see, e.g., T. Bashore, "Invasive Cardiology Principles and Techniques" (B.C. Decker Inc.) at pp. 147ff). This catheter 112 may be of substantial diameter in comparison to the central lumen 22 of the anchoring balloon catheter 24. Blood ejected/withdrawn through this catheter 112 passes from pump 106 through filter 107 to heat exchanger 108 and then through the return catheter 111 back to the aorta 10. Catheters 112 and 113 may be arranged in a double lumen catheter, which may be a side by side double lumen, a coaxial double lumen, or even a single lumen catheter that has holes in a wall thereof in an intermediate portion, defining the distal "end" of the vein access catheter 113.

The foregoing blood paths through the lumen 22 of the anchoring catheter 24 and through catheter 112 usually will allow sufficient cardiac output to prevent cardiac asystole.

Figure 21 depicts an alternate arrangement for external blood flow. In this configuration, the blood withdrawn from the left ventricle of the heart (through the larger catheter 112 and through the central lumen 22 of the anchoring balloon catheter 24) is passed directly to the oxygenator 105 before being returned (via pump 106, filter 107 and heat exchanger

108) to the aorta 10 through return catheter 111. In yet another configuration shown in Figure 22, all of the blood withdrawn from the heart is first passed through pump 110 and the second filter 109 before being sent to the oxygenator 105.

In yet a further embodiment shown in Figure 23, an additional pump 114 is provided upstream from the oxygenator but separate from the second pump 110, thereby permitting separate control of the blood withdrawn by the main lumen 50 of the catheter containing the deposit removal tool. Other equivalent arrangements may also be utilized. The arrangements depicted in Figures 19-23 demonstrate, however, that cardiac function and coronary circulation can be maintained even while the decalcification procedure is being performed. Rapid cardiac pacing at about 180-200 beats per minute also may be employed to lower cardiac output, particularly when the trans-septal approach to the left ventricle (L.V.) is not used.

Figures 24-26A depict possible configurations for the anchoring balloon of the invention. Figure 24 shows in cross section the anchoring balloon depicted in Figure 1 and many of the other figures. The balloon includes a distal portion 25 that is of a larger diameter than the rest of the balloon, thereby providing a shoulder 26 for engaging and supporting the inferior surface of the valve leaflets 12--the balloon is inserted past the leaflets 12 and then inflated as it is withdrawn to allow the shoulder 26 to seat against the inferior surface of the valve leaflets 12.

In Figure 25 the anchoring balloon 24 includes an enhanced shoulder 26 formed by constructing a distal chamber 27 which is in fluid communication with the main chamber 28. The enhanced shoulder 26

provides an even more secure engagement against the inferior surface of the valve leaflets 12. Figure 26 shows a modified version of the balloon of Figure 25 wherein the main chamber is merged with the distal chamber, but the enhanced shoulder 26 is preserved. Figure 26A shows a cross-section of the anchoring balloon catheter 24 with the catheter 21 having two lumens, the lumen 22 through which a guide wire may be advanced or withdrawn and through which fluid may be withdrawn or injected, and the lumen 23 which communicates with the interior of the balloon to inflate and deflate it. Any of the embodiments of Figures 24-26A can be modified so that the shoulder portion is manufactured from a thin layer of stretchable material (such as silicone) and the remaining portion of the balloon from a substantially non-stretchable material (or a stretchable material that is reinforced so that it will not stretch beyond a certain point). With this construction, the balloon can be controllably inflated so that the thin, stretchable shoulder portion 26, which engages and supports the leaflets 12 of the aortic valve, will conform very closely to the shape of the leaflet, giving close, uniform support to the leaflet.

Figures 27A-30 depict an alternate embodiment of the invention that may partially or entirely eliminate the need for the cardiopulmonary support/bypass system depicted in Figures 19-23. In this embodiment, the anchoring balloon 24'consists of an inflatable tube 32 coiled into a helical configuration and held in this helical configuration by an inner sheath or skin 33, defining a large bore lumen 34. The helical anchoring balloon 24' allows its large bore lumen 34 to present a substantially open passageway distally and proximally, allowing blood to continue flowing through

the balloon even when it is inflated and holding the valve leaflets 12 in position for the decalcification procedure. If desired, a rotating screw-type pump 35 may be secured in the proximal portion of the balloon to maintain circulation through the aorta 10 while the procedure is being performed. Such screw-type pumps are well known, such as the HEMOPUMP® brand pump available through Johnson & Johnson. (Figure 28 shows that multiple screw pumps may be used in parallel to increase the volume of blood pumped. Figure 28 also shows that one of the screw pumps--e.g., the proximal one--may be used to pump blood from the main lumen 50 of the positioning catheter through the filter 124 at the proximal end of such screw pump.)

A catheter 39 (Figure 27A) is disposed in the central portion of the distal end of the helical anchoring balloon 24'. The catheter 39 is carrying the phased array ultrasound transducers 29, described previously. The ultrasound catheter 39 desirably exits the large bore lumen 34 through the skin 33 intermediate of the position of the screw pump 35 and the distal end of the helical anchoring balloon 24'. To allow assembly of the catheter into the helical anchoring balloon 24' after insertion of the balloon into the patient, a flaccid sheath 39a may be attached to the skin 33 at the point of entry of the catheter into the large bore lumen 34. Thus, the deflated, furled balloon may be first inserted; once in position, it can be inflated, and the catheter 39 can then be inserted through the flaccid sheath 139 to its position as shown in Figure 27A. A guide wire 136 may also be advanced via the flaccid sheath 139 or via the lumen of the catheter 39 as necessary.

Figure 27B shows the proximal end of the various catheters and lumens attached to the configuration in

Figure 27A, including the catheter 39 (containing leads for the ultrasound transducer 29), the drive shaft 139 for the screw pump 35, a syringe (or similar inflation device) 80 with catheter 23 for inflating the anchoring balloon, inflation devices 73 and 79, respectively, for the first and second positioning balloons, a blood pump 110 for withdrawing blood through the main lumen 50 of the positioning catheter 46, a blood filter 109 and a return catheter 111 to return filtered blood back to an artery (usually the aorta).

Figure 29 depicts the configuration of the device shown in Figure 27A and B immediately after it has been advanced over the guide wire 136, but prior to being inflated/unfurled. In Figure 29, the helical anchoring balloon 24' is in a deflated, furled configuration (the view shows in partial cross-section the layers of helical tubes 32 furled upon one another). A release string 55 may be provided to maintain the distal end of the device in a furled configuration; when the string is withdrawn, it releases the balloon to be inflated. Figure 30 shows a modified embodiment where a release strap 56 is adhesively attached to the distal portion of the furled helical anchoring balloon 24' (rather than the string 55) to keep it in furled configuration. When the strap is withdrawn, it similarly releases the balloon to be inflated.

Figure 31 depicts yet another embodiment of the invention that facilitates blood flow through the helical anchoring balloon catheter 24' while the procedure is being performed. A series of check valve flaps 81, covering orifices 82 in the skin 33 of the anchoring balloon, is provided proximally of the aortic valve to permit blood to flow outwardly through

such orifices 82 into the aorta during systole. During diastole, the valve flaps 81 close, similarly to the function of the aortic valve itself, to prevent reflux of the blood into the left ventricle. (Check valves of this type would also be usable with the anchoring balloon catheter 24 of Figure 1.) Figures 32A and 32B show alternate embodiments wherein the helical anchoring balloon 24' in its proximal portion includes a preferably trileaflet valve 83 similar in shape and function to the natural aortic valve.

Although most of the figures depict the deposit removal tool as being a conventional rotatable burr or similar cutting or abrasive device, any other suitable tool may also be employed. Figures 33-35 depict three other possibilities. In Figure 33, a laser 140 (preferably located external to the patient) is connected to a fiber-optic strand 141 which has a distal end positionable adjacent the calcified deposits to be removed. In Figure 34, an ultrasonic vibration generator 144 (e.g., of the type that generates vibrations in the range of 20,000 Hz) is connected to a wire 145 having a distal tip positionable adjacent the calcified deposits, the wire 145 being capable conveying ultrasonic vibrations. In Figure 35 a high voltage source 147 is connected to a pair of electrically conductive wires 148 having distal tips positionable adjacent the calcified deposits for generating an arc to destroy the deposits. Tools of other suitable configurations may similarly be utilized.

The components of the anchoring balloon catheter 24 of the invention may be manufactured from any suitable materials, including conventional plastics, silicones, etc. that are biocompatible and possess the desired flexibility/rigidity properties, as the case

may be, to perform the desired functions. Such materials are well known, being utilized commonly in current balloon catheters and other intravascular devices. The helical balloon of the invention may be manufactured by any suitable techniques, such as by winding tube 32 into a coiled configuration (as by winding it upon a mandrel) and then securing the turns by either applying an outer skin (or an inner skin, if desired). Such a skin may be formed by applying a thin layer of adhesive, by securing a thin layer of flexible plastic, or by any other suitable means.

While a preferred embodiment of the present invention has been described, it should be understood that various changes, adaptations and modifications may be made therein without departing from the spirit of the invention and the scope of the appended claims.

WHAT IS CLAIMED IS:

1. Apparatus for in vivo removal of deposits from an aortic heart valve, comprising:

an anchoring balloon catheter fixatable across the aortic valve;

a deposit removal tool; and

attachment means for securing the tool with respect to the anchoring balloon and the aortic valve.

2. The apparatus of claim 1 wherein the attachment means includes positioning means for adjustably positioning the deposit removal tool with respect to the anchoring balloon.

3. The apparatus of claim 1 further comprising a guiding catheter through which the deposit removal tool may be advanced toward the aortic valve, the guiding catheter including a distal end portion secured to the anchoring balloon catheter by the attachment means.

4. The apparatus of claim 3 wherein the attachment means comprises a circumferential band having first and second ends respectively attached to the anchoring balloon, and an intermediate portion operatively connected to the guiding catheter.

5. The apparatus of claim 4 wherein the attachment means further includes positioning balloon means for selectively moving the guiding catheter about the anchoring balloon in response to inflation and deflation of the positioning balloon means.

6. The apparatus of claim 5 wherein the positioning balloon means comprises two positioning balloons interposed between the circumferential band and the anchoring balloon.

7. The apparatus of claim 6 wherein each positioning balloon is located adjacent an end of the circumferential band.

8. The apparatus of claim 6 wherein the positioning means includes means for selectively inflating and deflating the positioning balloons whereby the guiding catheter will move clockwise about the anchoring balloon when one of the positioning balloons is inflated, and the guiding catheter will move counterclockwise about the anchoring balloon when the other positioning balloon is inflated.

9. The apparatus of claim 8 wherein the means for inflating and deflating the positioning balloons are operable syncronously so that when one of the balloons is being deflated the other is being inflated.

10. The apparatus of claim 3 wherein the deposit removal tool includes an elongated shaft.

11. The apparatus of claim 10 further comprising a positioning catheter carried within the guiding catheter, the positioning catheter being rotatable with respect to the guiding catheter and including an off-center lumen in which the shaft of the deposit removal tool is closely received, whereby rotation of the positioning catheter allows selective positioning of the deposit removal tool.

12. The apparatus of claim 1 wherein the deposit removal tool includes a distal tip portion, an elongated shaft portion extending proximally from the tip, and a catheter disposed about the shaft portion, the catheter having a distal end adjacent the distal tip portion through which dislodged deposits and blood may be aspirated.

13. The apparatus of claim 12 further comprising means for filtering and returning the aspirated blood to the patient.

14. The apparatus of claim 1 wherein the deposit removal tool comprises a rotatable cutting

device.

15. The apparatus of claim 1 wherein the deposit removal tool comprises a rotatable abrading device.

16. The apparatus of claim 1 wherein the deposit removal tool comprises an ultrasonic vibrations generator and a wire capable of conveying such ultrasonic vibrations connected to the generator and having a distal end locatable adjacent the aortic valve.

17. The apparatus of claim 1 wherein the deposit removal tool comprises a high voltage power source and a pair of electrical discharge electrodes positionable adjacent the aortic valve.

18. The apparatus of claim 1 wherein the deposit removal tool comprises a laser and an optical fiber connected to the laser.

19. The apparatus of claim 4 including a collapsable guiding catheter insertion sleeve having a distal end portion attached to the intermediate portion of the circumferential band.

20. The apparatus of claim 19 wherein the collapsable insertion sleeve is wider proximally than it is in its distal end portion, so that it receives the guiding catheter closely only in the distal end portion, allowing easy insertion and withdrawal of the guiding catheter through the insertion sleeve.

21. The apparatus of claim 3 wherein the attachment means comprises first and second straps, each having a first end attached to the anchoring balloon and a second end attached to the guiding catheter, the straps being attached so that as the guiding catheter is rotated with respect to the anchoring balloon one of the straps will wind up on the guiding catheter and the other will unwind off the

guiding catheter, causing the guiding catheter to move about the periphery of the anchoring balloon.

22. The apparatus of claim 21 wherein the first strap comprises two such straps straddling the second strap.

23. The apparatus of claim 1 wherein the anchoring balloon catheter includes an inflatable balloon having proximal and distal portions, the distal portion of the balloon being inflatable to a diameter larger than the proximal portion.

24. The apparatus of claim 23 wherein the valve is of the type having multiple leaflets with superior and inferior surfaces, the distal and proximal portions of the balloon defining a shoulder that is engagable with the inferior surface of the valve leaflets to support the leaflets as deposits are removed from the superior surface thereof.

25. The apparatus of claim 24 wherein the proximal portion of the balloon is generally elongated and cylindrical in shape and having an outer surface, the shoulder being formed by attaching a secondary distal balloon portion to the outer surface of the proximal balloon portion.

26. The apparatus of claim 24 wherein the balloon has a longitudinal axis, the shoulder portion of the balloon being made of a stretchable material so that it can conform to the inferior surface of the leaflet, other portions of the balloon being constructed to be substantially non-stretchable in a direction perpendicular to the longitudinal axis.

27. The apparatus of claim 1 wherein the anchoring balloon catheter comprises an inflatable helically coiled tube and securing means for securing windings of the helically coiled tube with respect to one another in a desired configuration.

28. The apparatus of claim 27 wherein the securing means comprises a flexible skin attached to the turns of the coil.

29. The apparatus of claim 1 further including a cardiopulmonary bypass system comprising a vein access catheter insertable into a vein to allow removal of blood therefrom, oxygenator means for oxygenating such blood, an artery access catheter insertable into an artery, and pump means for returning the blood through the artery access catheter to the artery.

30. The apparatus of claim 29 wherein the anchoring balloon catheter includes a catheter having proximal and distal ends and a lumen, the lumen being open at the distal end of the catheter, the proximal end of the catheter lumen being operatively connected to the pump means so that when the anchoring balloon catheter is fixated across the aortic valve blood may be removed through such lumen and returned to the artery.

31. The apparatus of claim 29 wherein the cardiopulmonary bypass system includes a filter and a heat exchanger through which the blood passes before it is returned to the artery.

32. The apparatus of claim 29 further including a left ventricle access catheter insertable through the iliac vein, vena cava, through the right atrium and left atrium to the left ventricle, the left ventricle access catheter being operatively connectable to the pump means to allow blood flow from the left ventricle and its return to the artery.

33. The apparatus of claim 32 wherein the vein access catheter and the left ventricle access catheter are arranged in one catheter.

34. The apparatus of claim 33 wherein the

vein access catheter and the left ventricle access catheter are arranged in a single lumen catheter having orifices in a wall thereof to define a distal end of the vein access catheter.

35. The apparatus of claim 33 wherein the vein access catheter and the left ventricle access catheter are arranged in a double lumen catheter.

36. The apparatus of claim 33 wherein the vein access catheter and the left ventricle access catheter are arranged in a co-axial double lumen catheter.

37. The apparatus of claim 1 further including ultrasound transducing means disposed within the anchoring balloon for imaging the aortic valve, the location of the deposit removal tool, and the location of the deposits to be removed.

38. The apparatus of claim 37 wherein the ultrasound transducing means comprises a phased array transducer comprised of an array of individual acoustic elements.

39. The apparatus of claim 37 wherein the ultrasound transducing means comprises an echo transducer and a rotatable mirror element positionable in the anchoring balloon catheter.

40. The apparatus of claim 37 wherein the anchoring balloon catheter includes a catheter lumen, the ultrasound transducing means being carried by a catheter positionable within the lumen of the anchoring balloon catheter and being movable distally and proximally within the lumen.

41. The apparatus of claim 37 wherein the anchoring balloon catheter includes a central catheter, the ultrasound transducing means being carried by the central catheter.

42. The apparatus of claim 3 wherein the

positioning means includes a pair of cords attached distally to the anchoring balloon, and pulleys mounted on the guiding catheter and the anchoring balloon, the cords being threaded through the pulleys so that pulling on a first of the cords and releasing the second cord will cause the guiding catheter to move clockwise about the anchoring balloon and, pulling the second cord and releasing the first cord will cause the guiding catheter to move counterclockwise about the anchoring balloon.

43. The apparatus of claim 1 wherein the anchoring balloon catheter includes a catheter having a distal end and a lumen, the lumen being open at the distal end of the catheter, and has a check valve opening into the aorta.

44. The apparatus of claim 1 wherein the anchoring balloon comprises an inflatable helically coiled tube defining a distally open lumen.

45. The apparatus of claim 44 wherein the helically coiled tube includes a thin skin thereon to hold windings of the helically coiled tube in position with respect to one another.

46. The apparatus of claim 45 wherein the anchoring balloon includes check valve means for permitting blood to flow through the lumen out of the heart's left ventricle and substantially preventing blood from flowing through such lumen back into the left ventricle.

47. The apparatus of claim 46 wherein the check valve means is disposed on the skin of the helically coiled tube.

48. The apparatus of claim 46 wherein the check valve means comprises a leaflet-type valve disposed across the lumen of the anchoring balloon.

49. The apparatus of claim 48 wherein the

leaflet-type valve is disposed across the lumen at the proximal end of the anchoring balloon.

50. The apparatus of claim 44 further comprising a screw-type pump means disposed in the lumen for pumping blood across the aortic valve.

51. The apparatus of claim 50 wherein the screw-type pump means comprises two or more screw-type pumps operating in parallel, each having an intake drawing blood distally from the lumen and an outlet discharging the blood proximally into the aorta.

52. The apparatus of claim 50 further comprising a second screw-type pump means for withdrawing blood from adjacent the deposit removal tool, and for filtering such blood and returning it to the aorta.

53. The apparatus of claim 52 wherein the second screw-type pump means includes catheter means defining a blood flow path that is operatively isolated from the open lumen of the anchoring balloon and the first screw-type pump means, the catheter means including a distal end located adjacent the deposit removal tool and a proximal portion connected to an inlet of the second screw-type pump means, the second screw-type pump means further including an outlet to the aorta.

54. The apparatus of claim 3 wherein the attachment means securing the tool to the anchoring balloon prevents any substantial movement of the guiding catheter with respect to the anchoring balloon catheter, the tool being positionable with respect to the aortic valve by rotating the anchoring balloon catheter.

55. Apparatus for in vivo removal of deposits from an aortic valve, comprising:

an anchoring balloon catheter fixatable across

the aortic valve;

a deposit removal tool having an elongated shaft;

a guiding catheter through which the tool may be advanced toward the aortic valve, the guiding catheter including a distal end portion;

a circumferential band having first and second ends respectively attached to the anchoring balloon, and an intermediate portion operatively connected to the guiding catheter;

a pair of positioning balloons interposed between the circumferential band and the anchoring balloon for selectively moving the guiding catheter about the anchoring balloon in response to inflation and deflation of the positioning balloons;

means for selectively inflating and deflating the positioning balloons whereby the guiding catheter will move clockwise about the anchoring balloon when one of the positioning balloons is inflated, and the guiding catheter will move counterclockwise about the anchoring balloon when the other positioning balloon is inflated; and

a positioning catheter carried within the guiding catheter, the positioning catheter being rotatable with respect to the guiding catheter and including an off-center lumen in which the shaft of the deposit removal tool is closely received, whereby rotation of the positioning catheter allows selective positioning of the deposit removal tool.

56. A method of removing deposits from an aortic valve's superior surface, comprising;

advancing an anchoring balloon through the aorta and positioning it across the aortic valve;

inflating the anchoring balloon to fixate it with respect to the aorta and aortic valve; and

operating a deposit removal tool secured to the

anchoring balloon to remove the deposits.

57. The method of claim 56 including the step of advancing the deposit removal tool through the aorta after the anchoring balloon has been inflated.

58. The method of claim 57 wherein the step of advancing the deposit removal tool comprises advancing the tool through a catheter that has its distal end secured with respect to the anchoring balloon.

59. The method of claim 56 wherein the step of advancing the anchoring balloon includes the step of simultaneously advancing the deposit removal tool and the anchoring balloon through the aorta.

60. The method of claim 56 including the steps of withdrawing blood through a lumen of the anchoring balloon catheter, utilizing a pump if necessary, oxygenating such blood if necessary, and then returning such blood to an artery.

61. The method of claim 56 further comprising withdrawing blood adjacent the deposit removal tool.

62. The method of claim 61 further comprising filtering such blood and returning it to an artery.

63. The method of claim 56 further comprising the steps of advancing a blood removal catheter through the vena cava to the right atrium and through the atrial septum to the left atrium and into the left ventricle, and then removing blood from the left ventricle through such catheter and returning such blood to an artery while the anchoring balloon is positioned across the aortic valve.

64. The method of claim 56 further comprising the steps of providing cardiopulmonary bypass support by inserting a vein access catheter

into an artery, withdrawing blood through the vein access catheter, oxygenating the blood and returning it to the artery through the artery access catheter.

65. The method of claim 56 further comprising the step of imaging the area adjacent the anchoring balloon.

66. The method of claim 65 wherein the imaging step comprises radiographic imaging.

67. The method of claim 65 wherein the imaging step includes imaging with ultrasound utilizing an ultrasound transducer carried by the anchoring balloon.

68. A method of removing deposits from the aortic valve of a heart, comprising;

advancing a deflated, furled anchoring balloon through the aorta and positioning it across the aortic valve, the anchoring balloon including a collapsable guiding catheter sheath;

inflating the anchoring balloon to fixate it with respect to the aorta and aortic valve; and

advancing a guiding catheter and a deposit removal tool through the guiding catheter sheath after the anchoring balloon has been inflated; and

operating the deposit removal tool secured to the anchoring balloon to remove the deposits.

69. The method of claim 68 further comprising withdrawing blood from the left ventricle of the heart through a catheter, and returning such blood to the aorta.

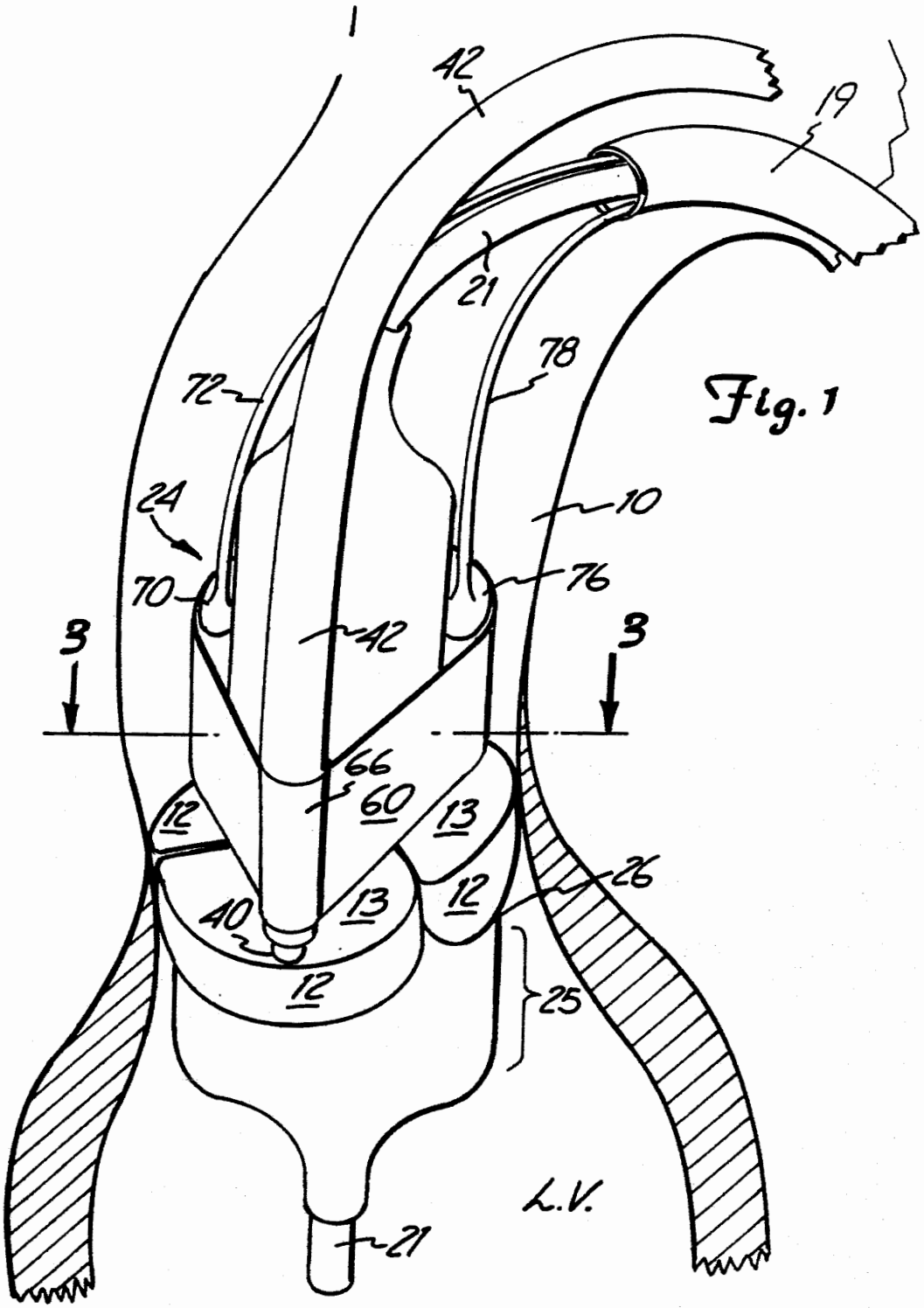


Fig. 1

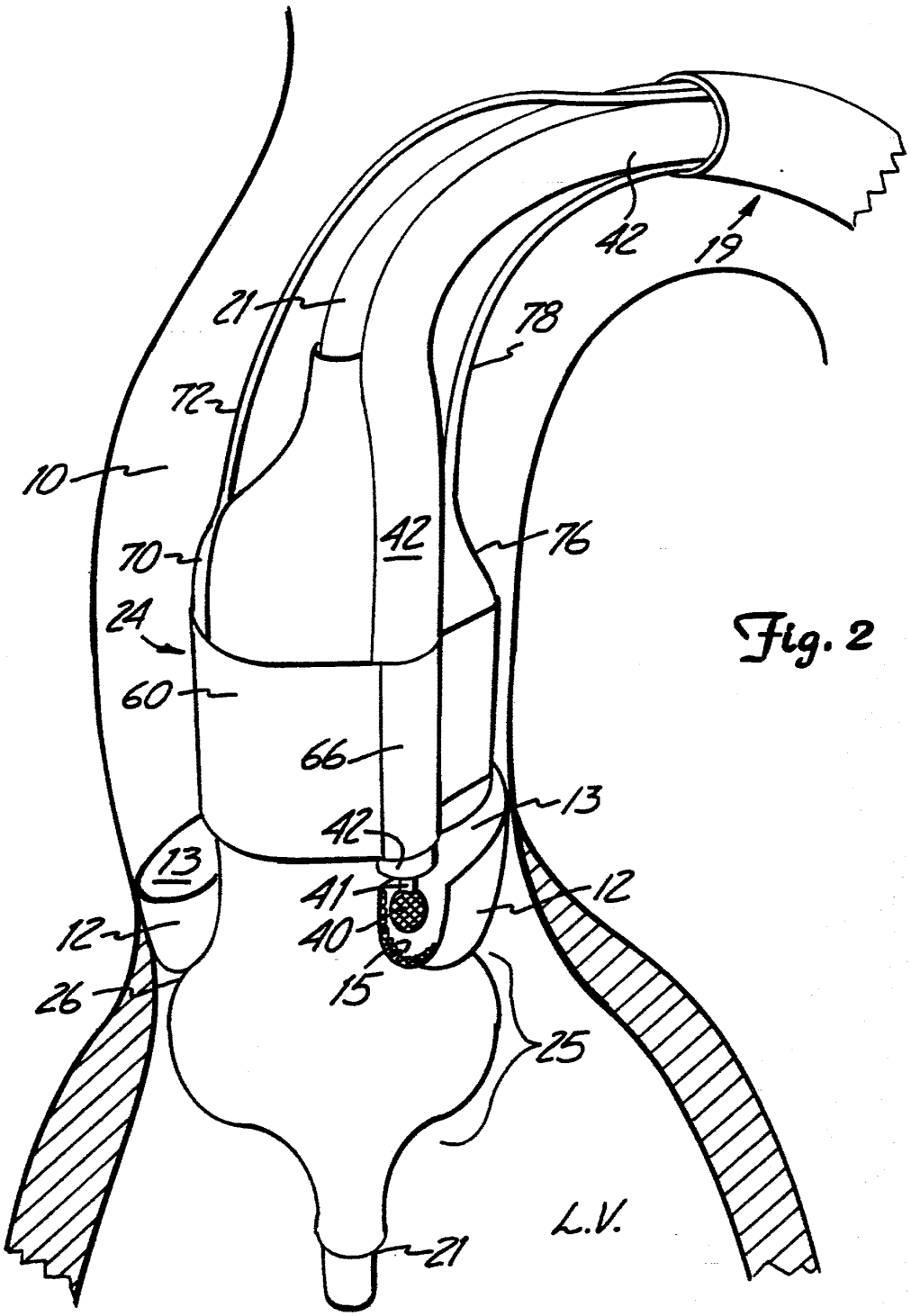


Fig. 2

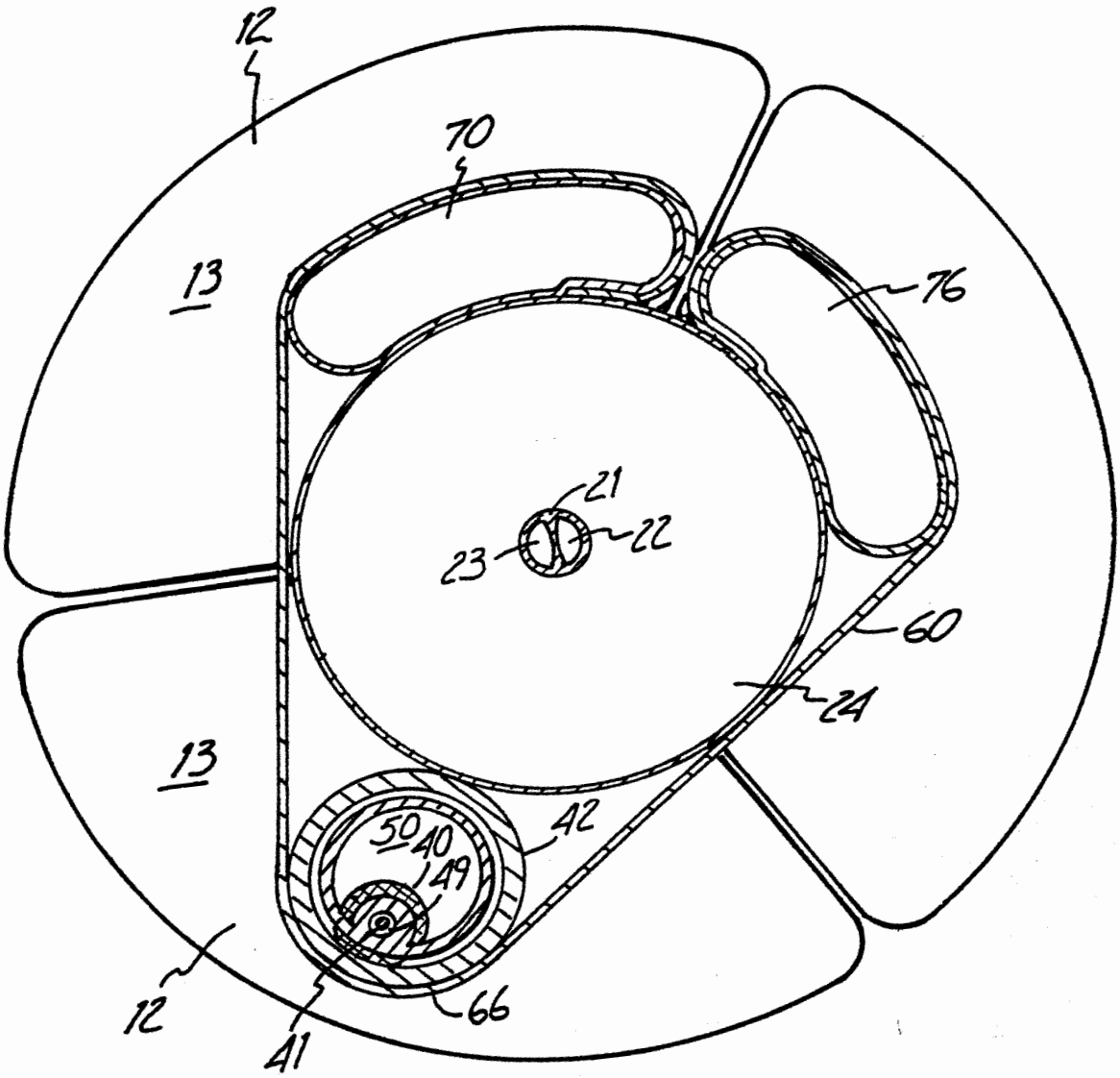


Fig. 3

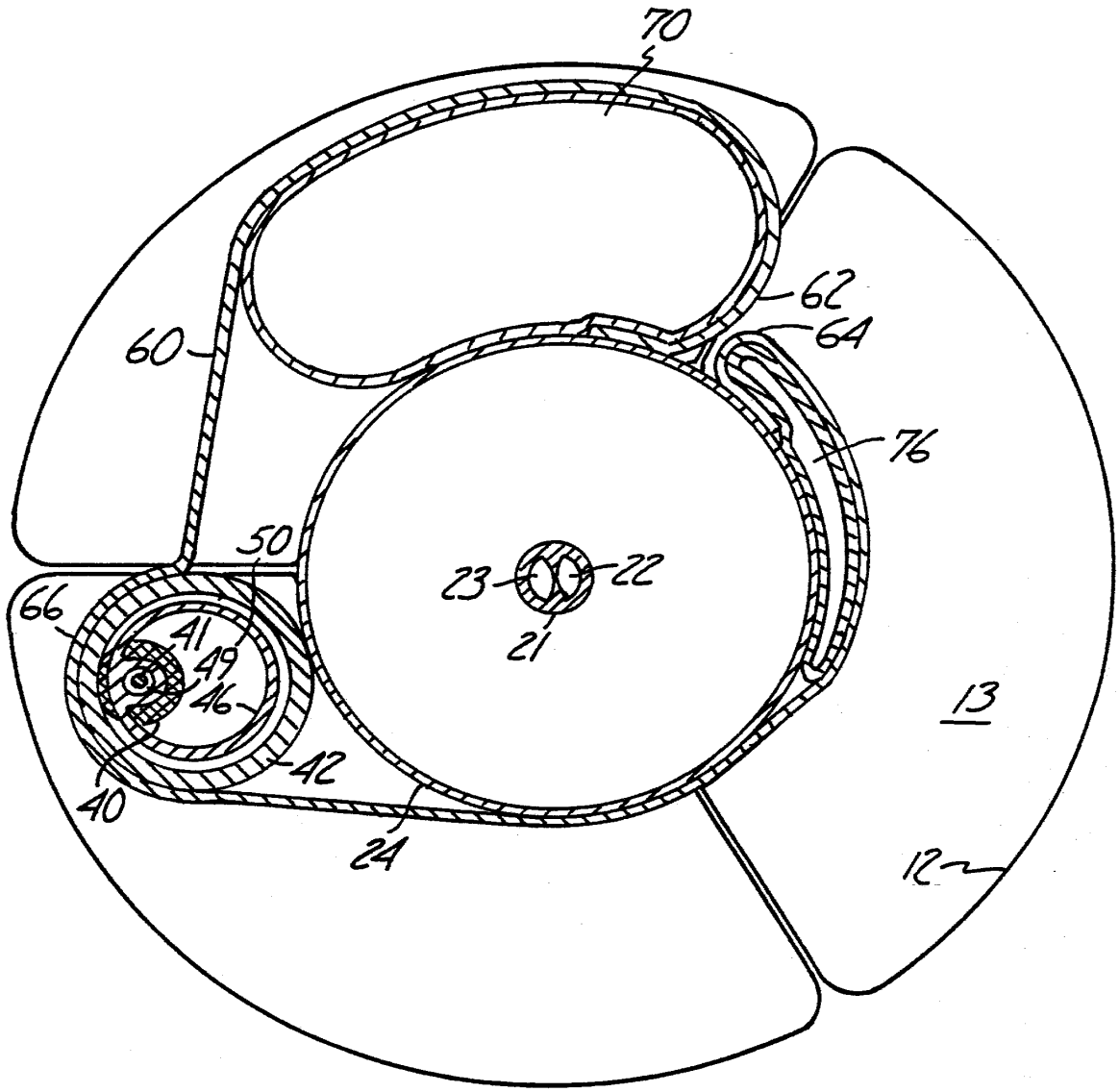


Fig. 4

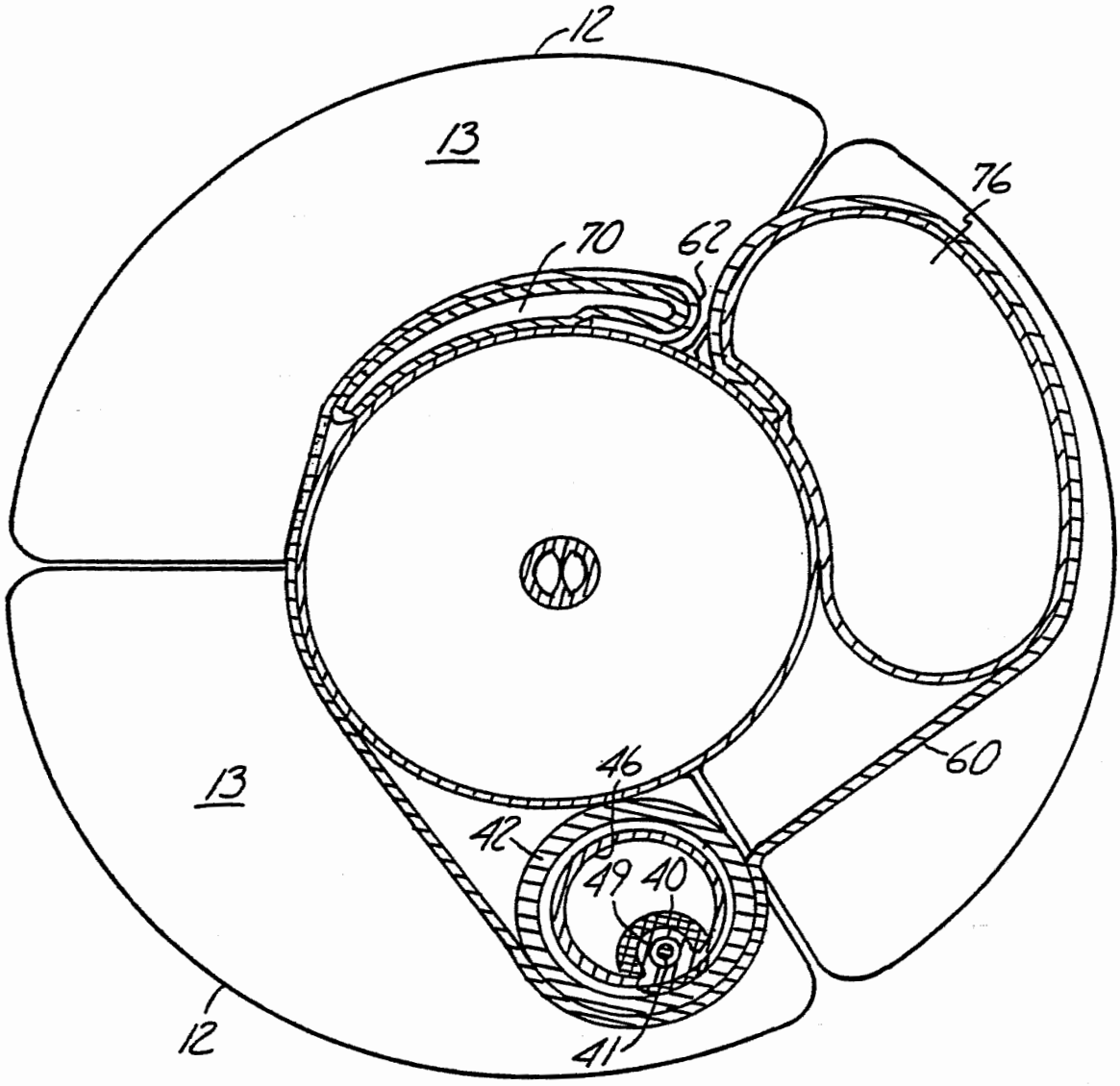


Fig. 5

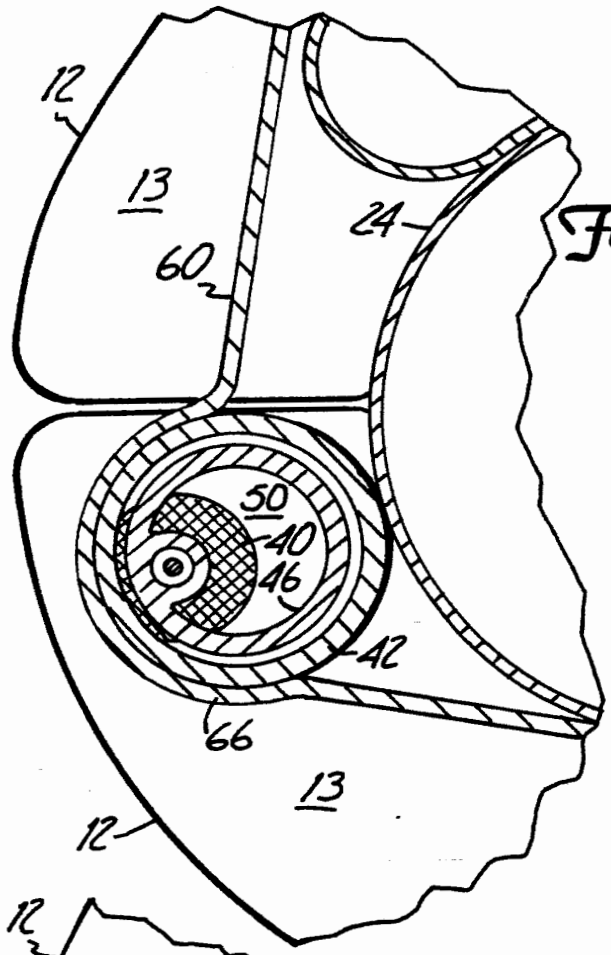


Fig. 7

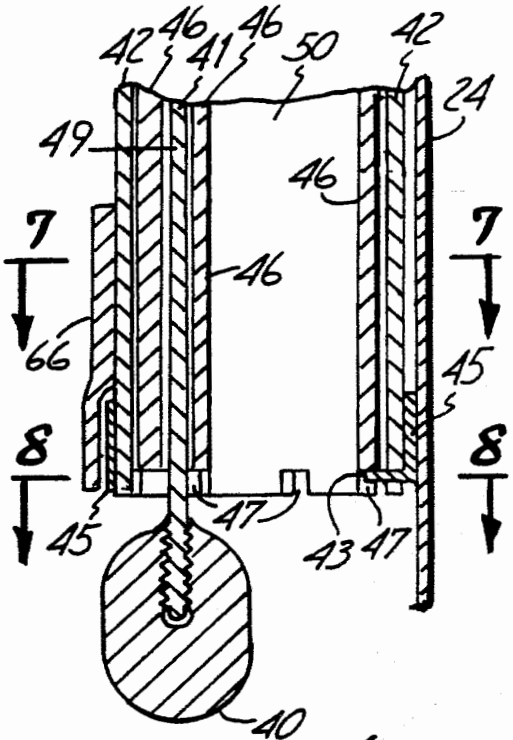


Fig. 6

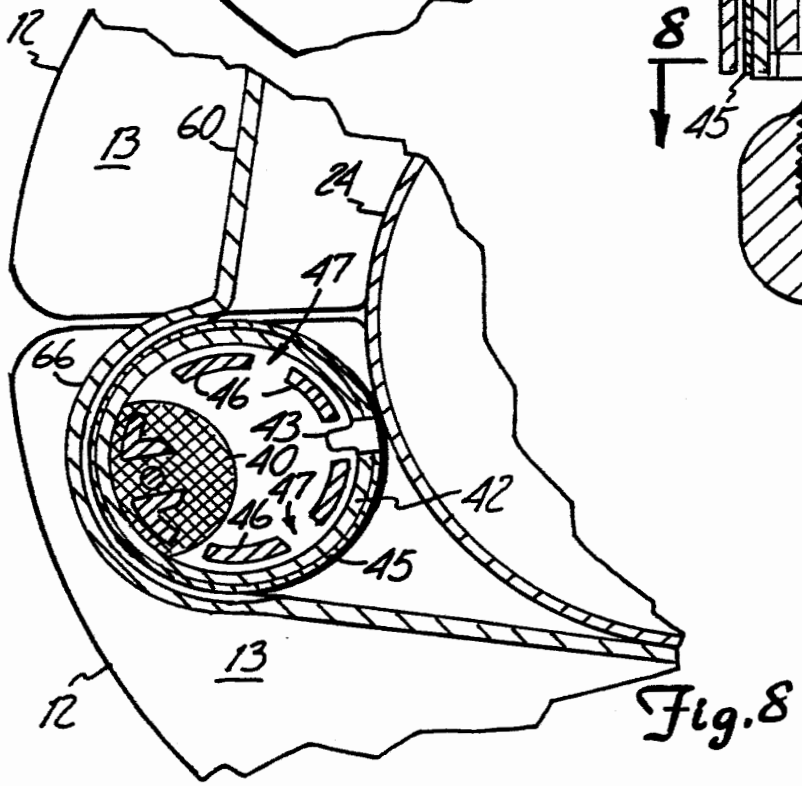


Fig. 8

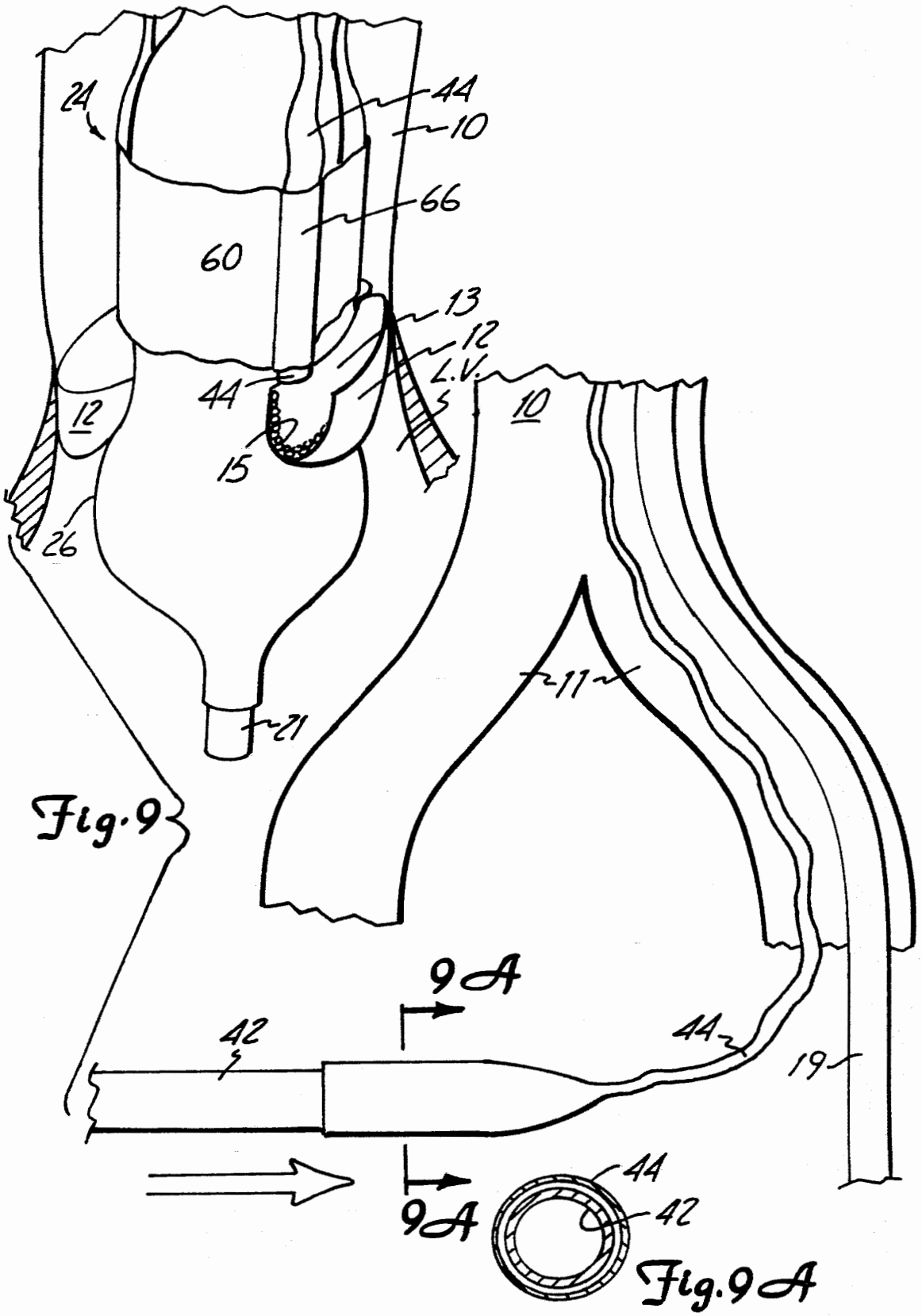
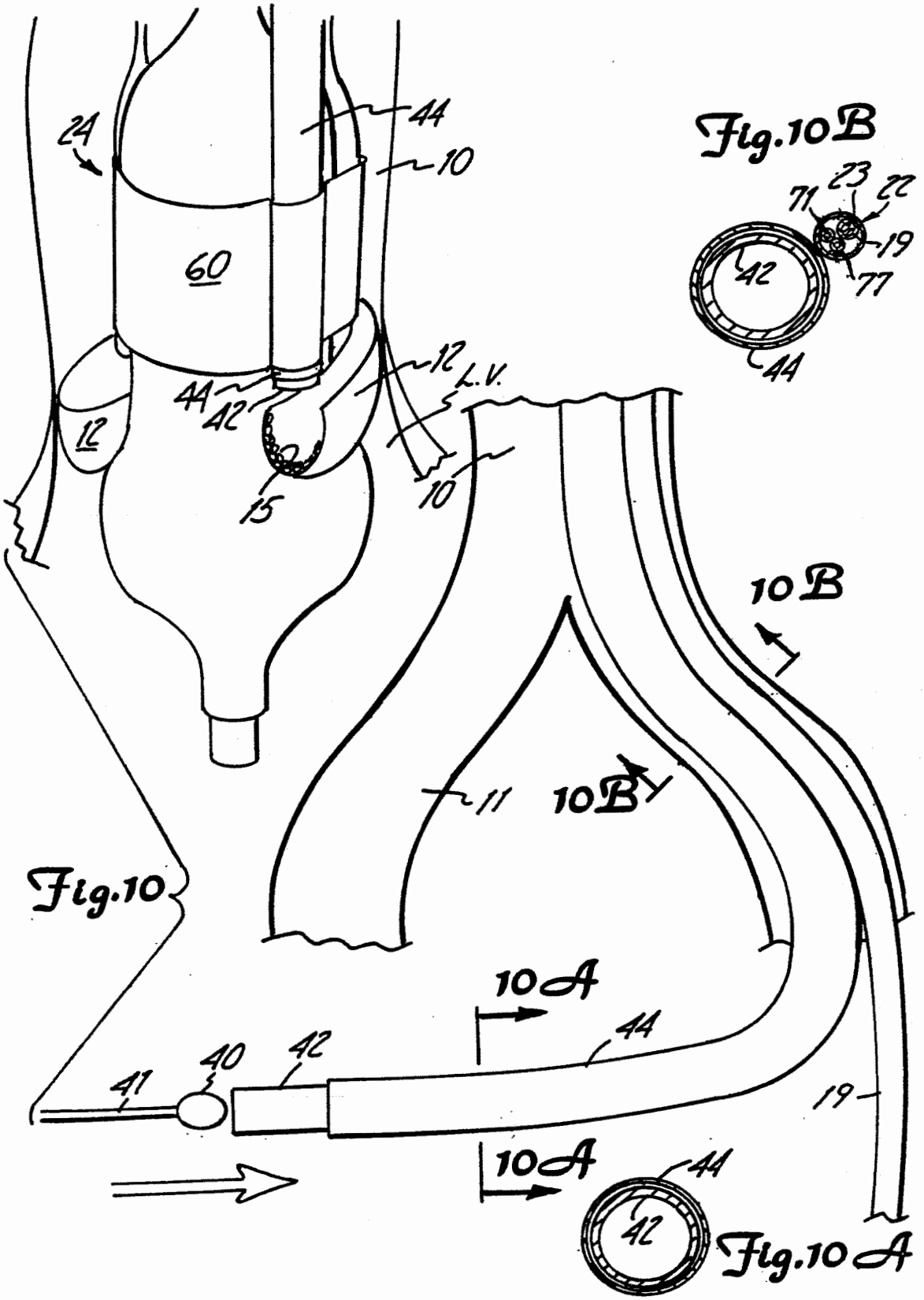


Fig. 9

Fig. 9A



SUBSTITUTE SHEET

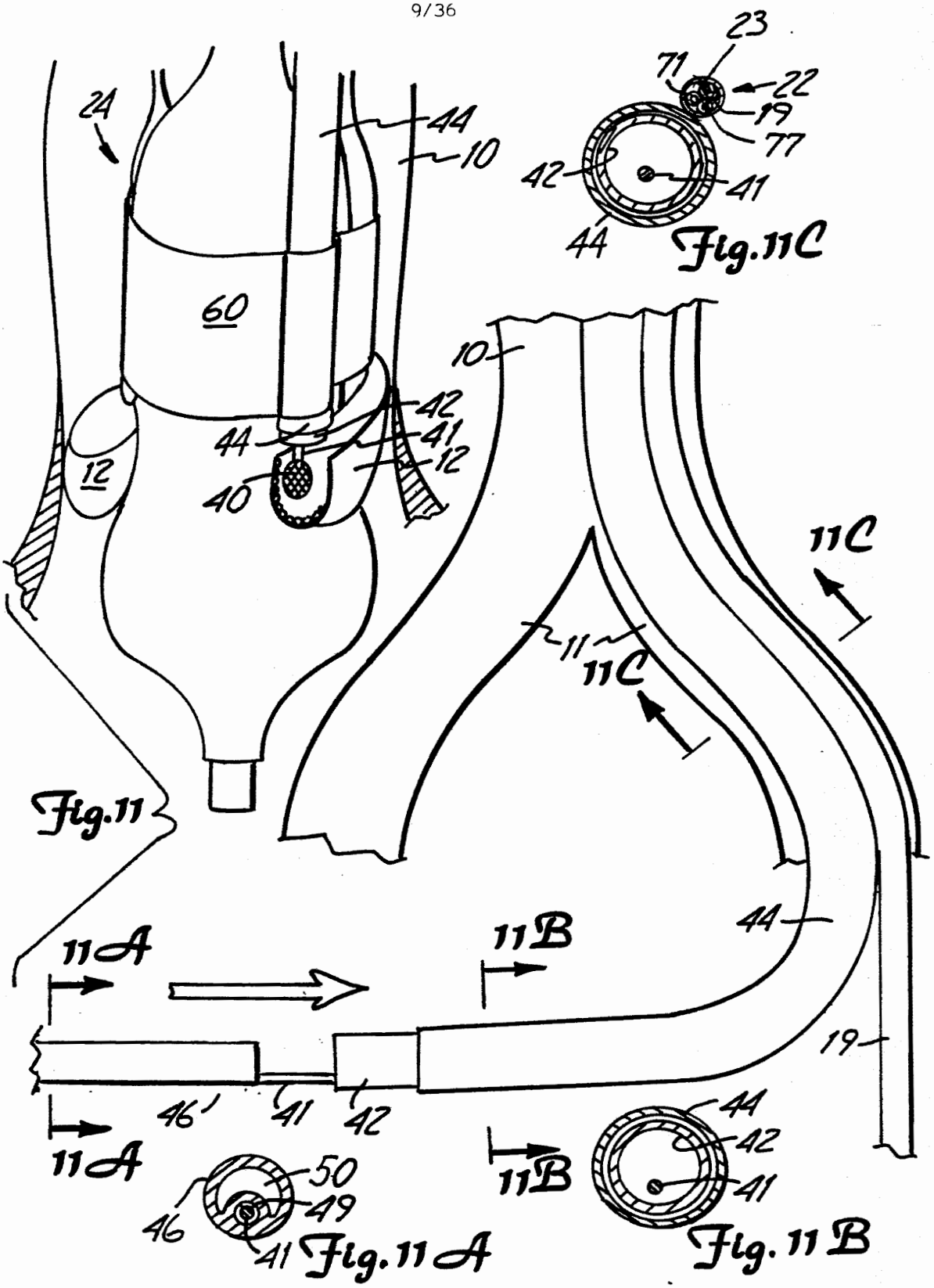

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Fig.11
Fig.11A
Fig.11B

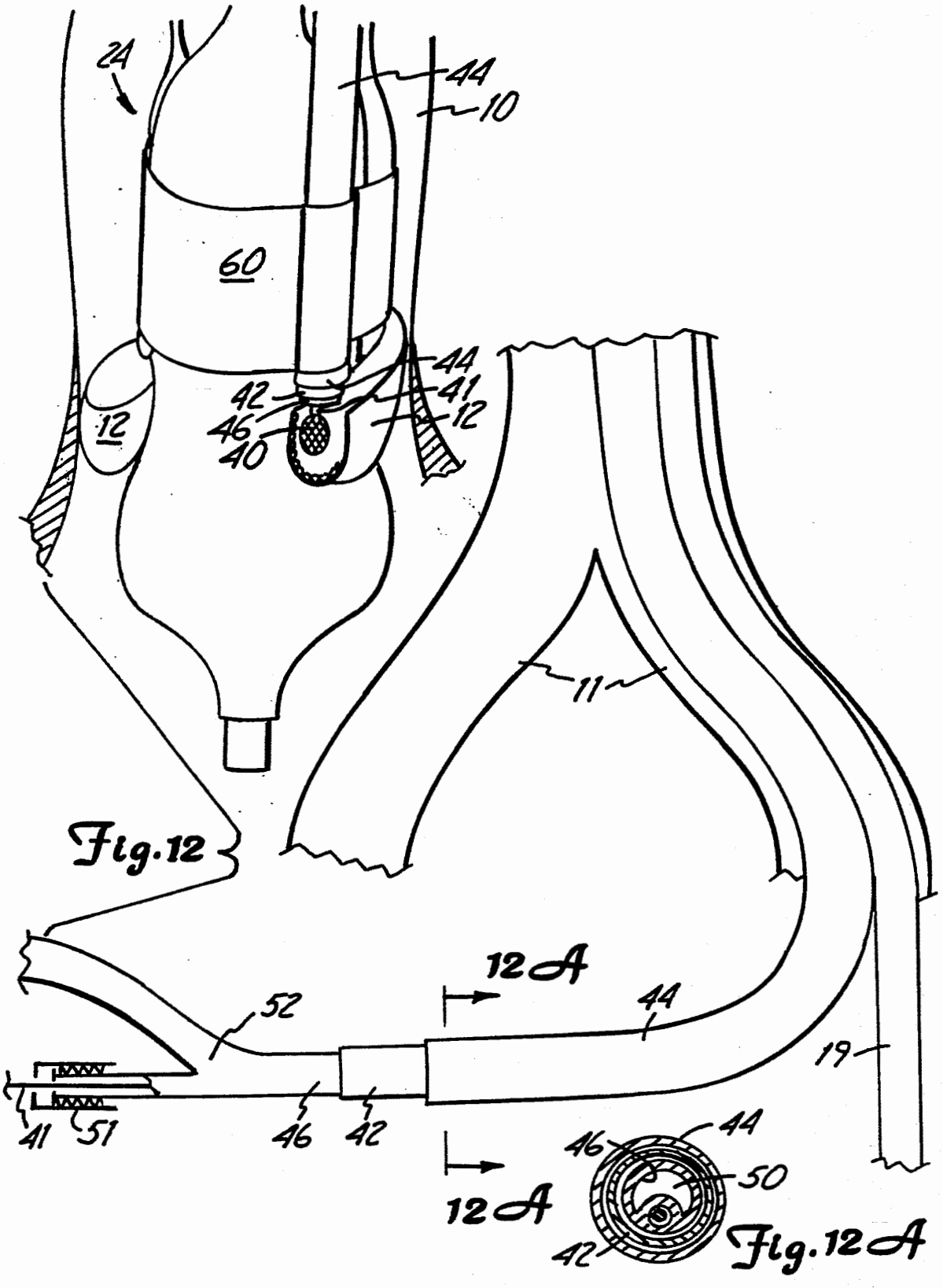
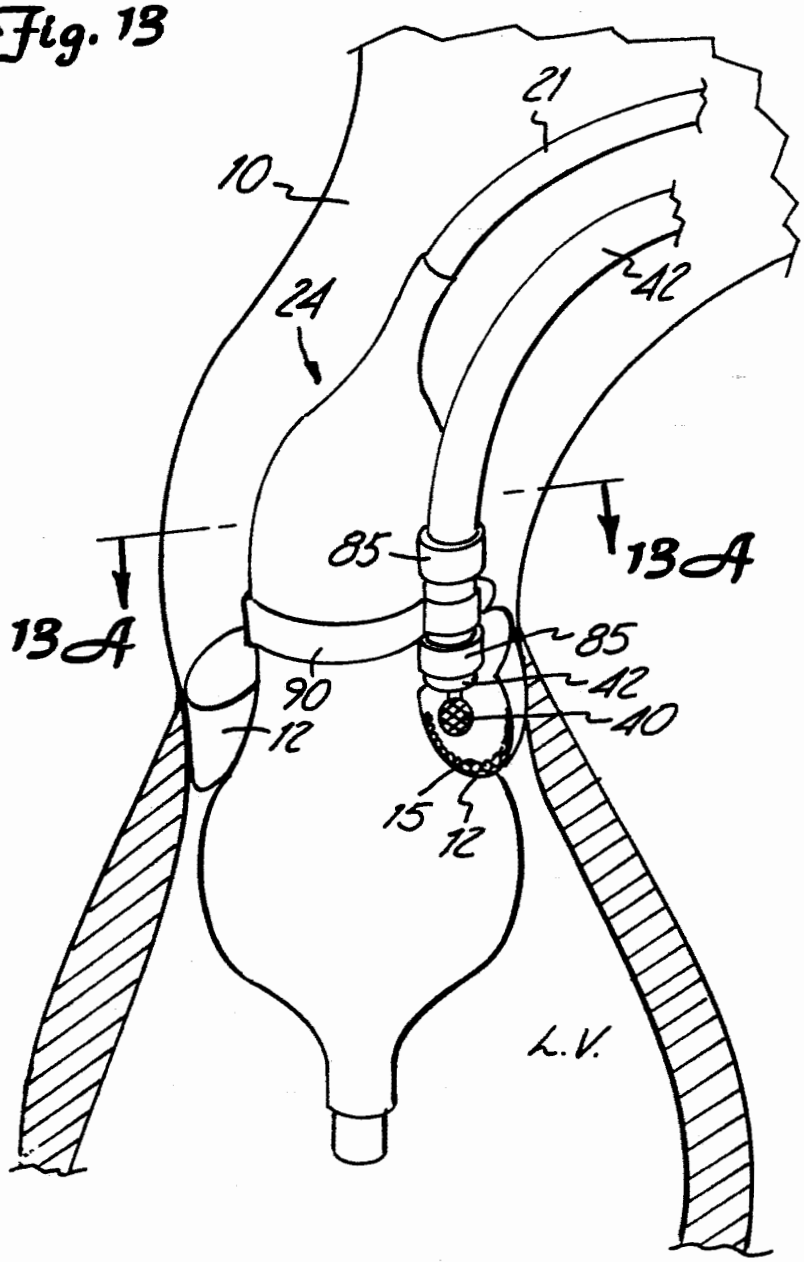


Fig. 12

Fig. 12A

Fig. 13



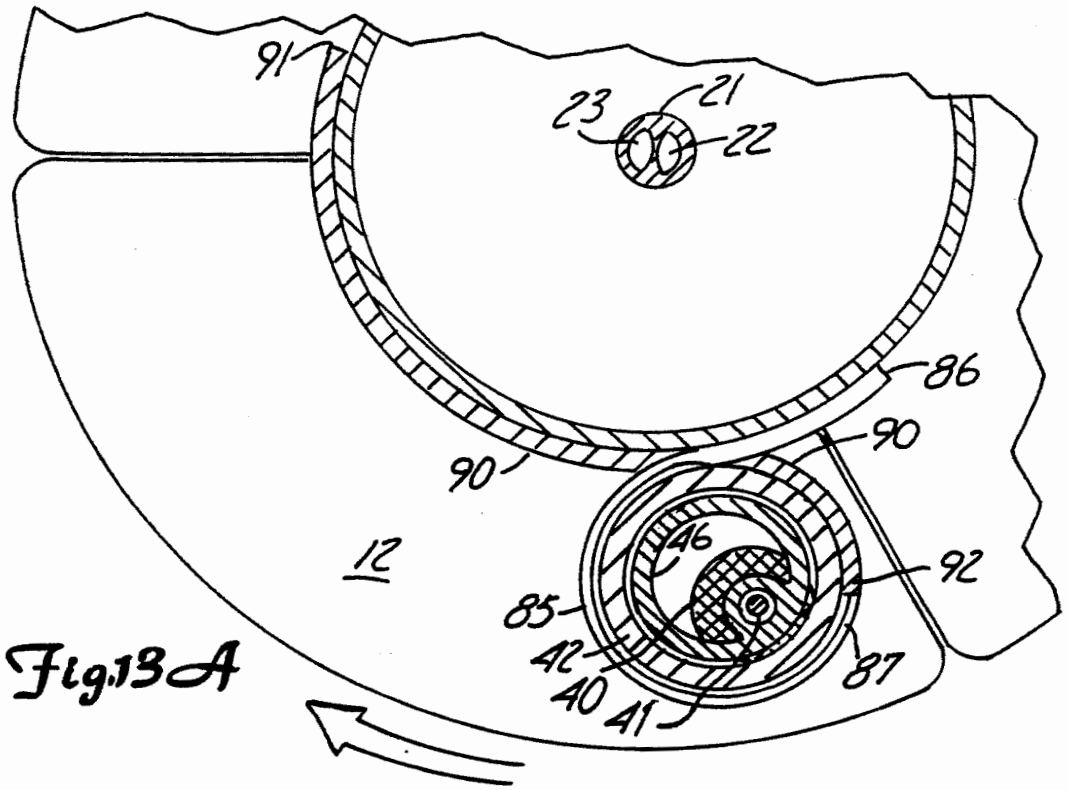


Fig. 13A

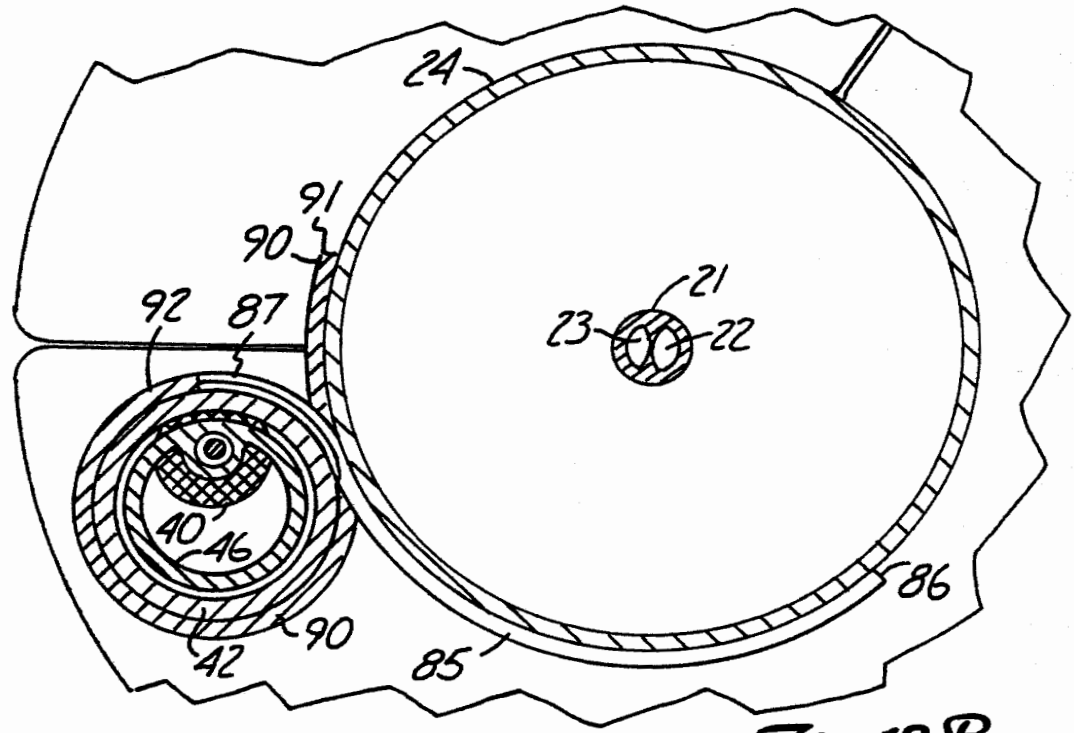
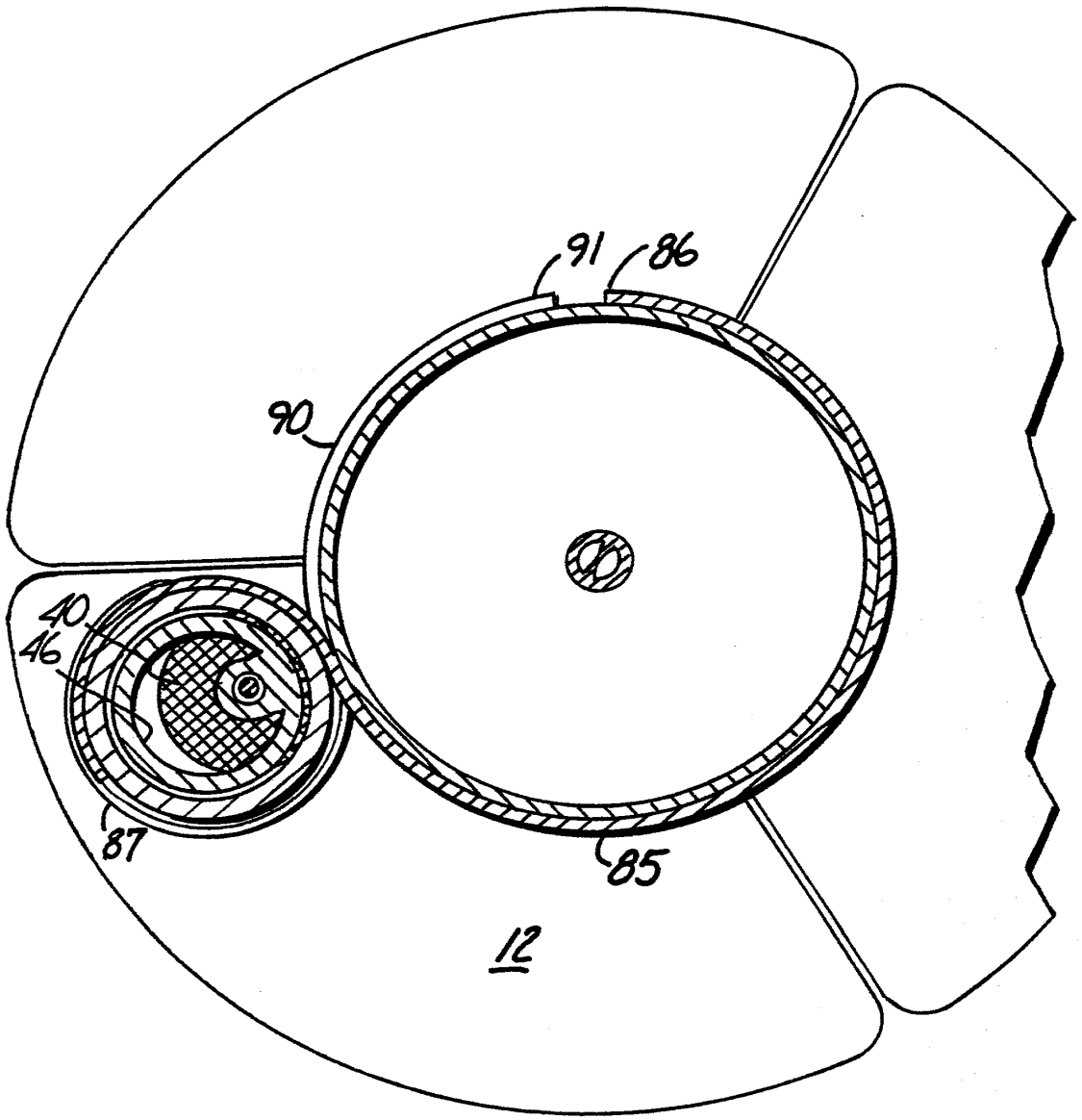


Fig. 13B

Fig. 14



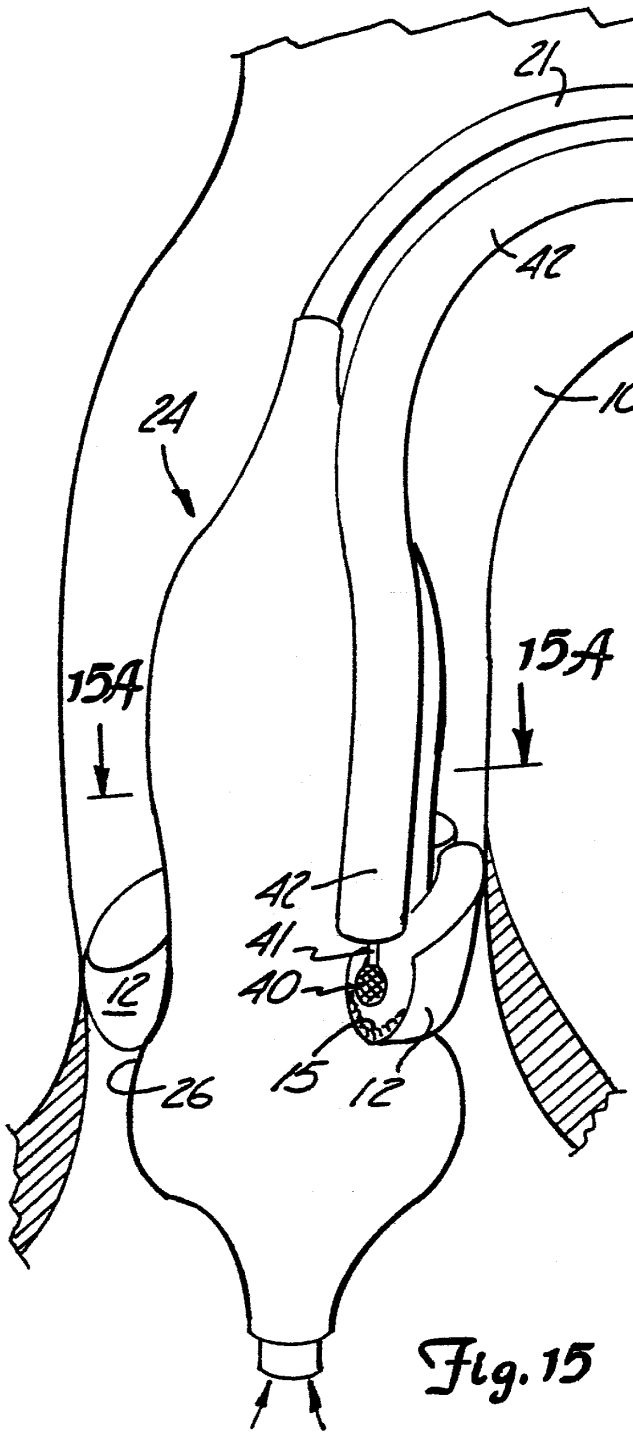


Fig. 15

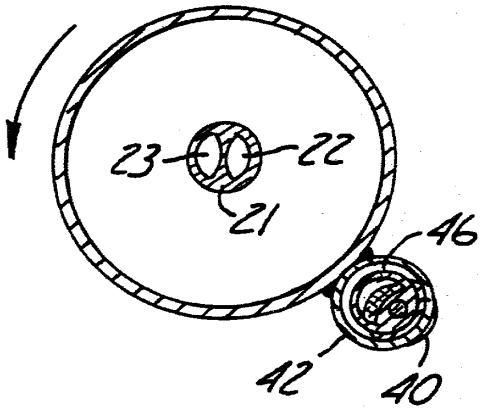


Fig. 15A

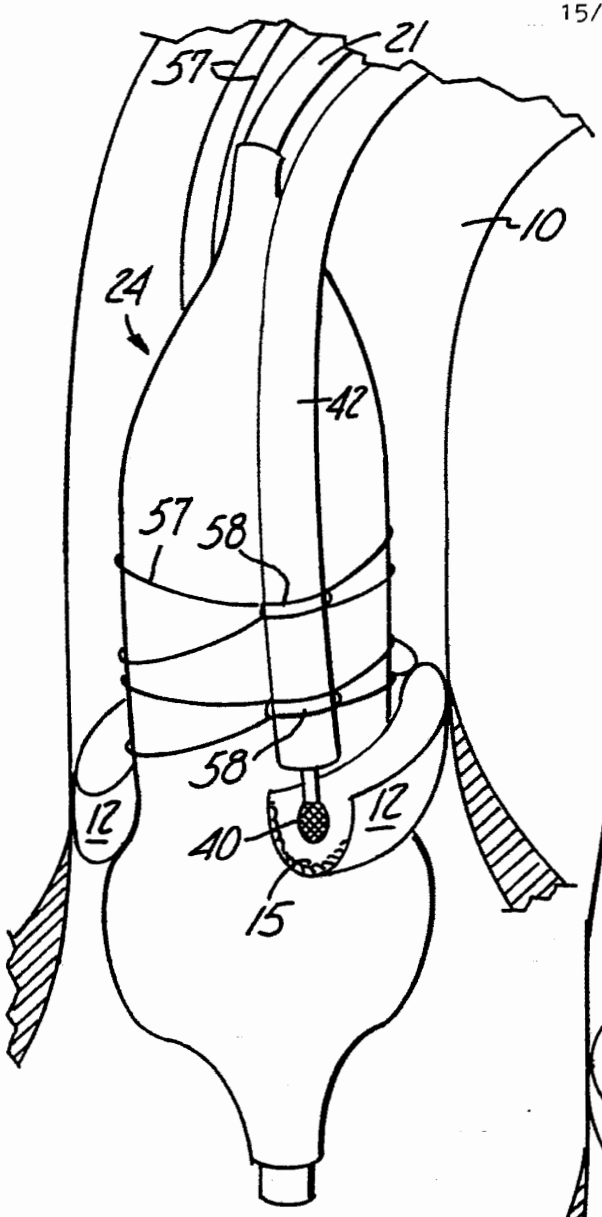


Fig. 16

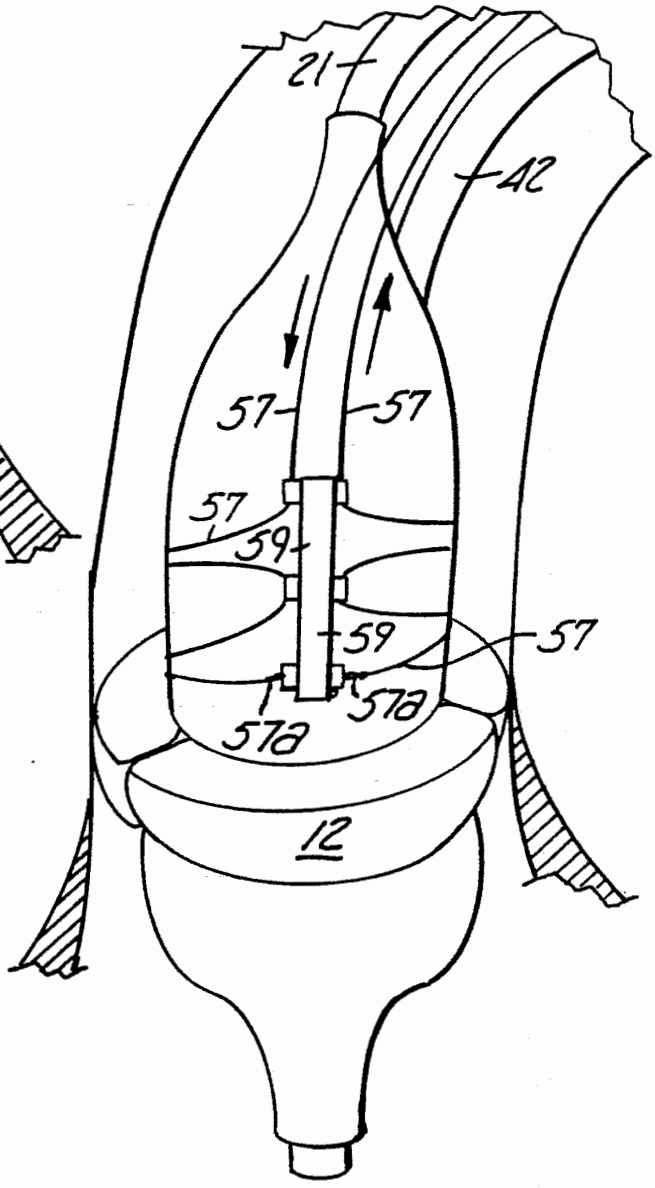


Fig. 16A

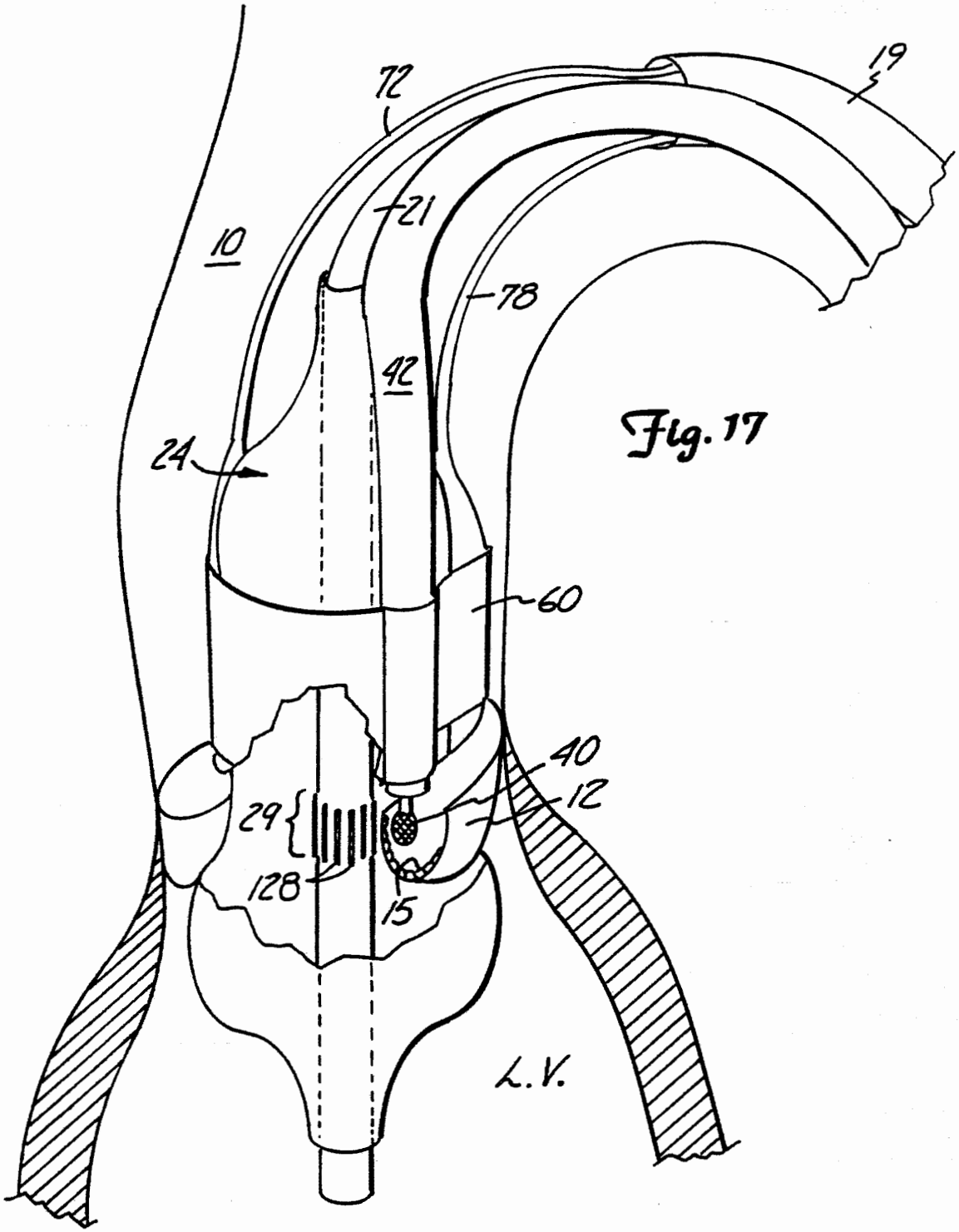


Fig. 17

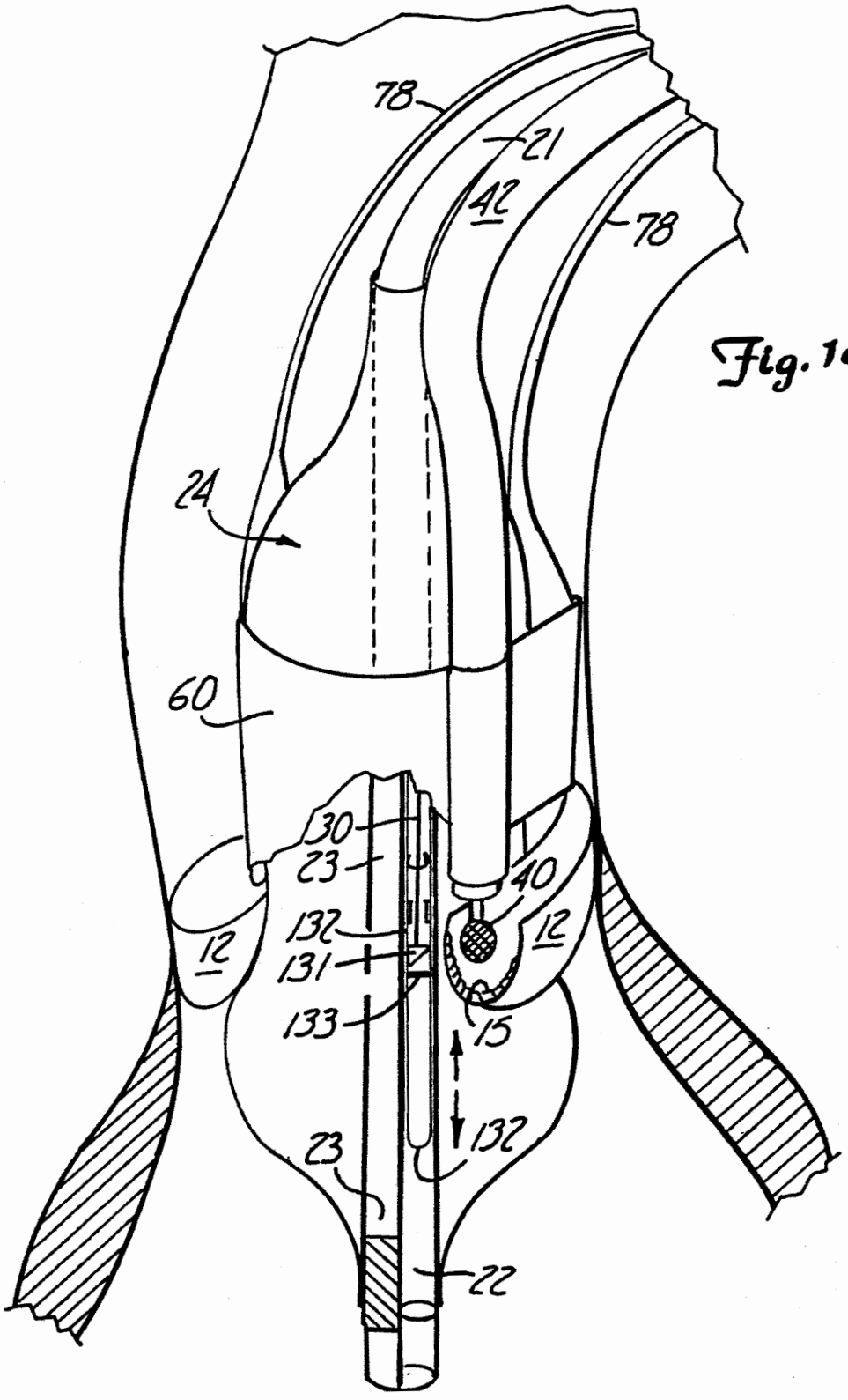
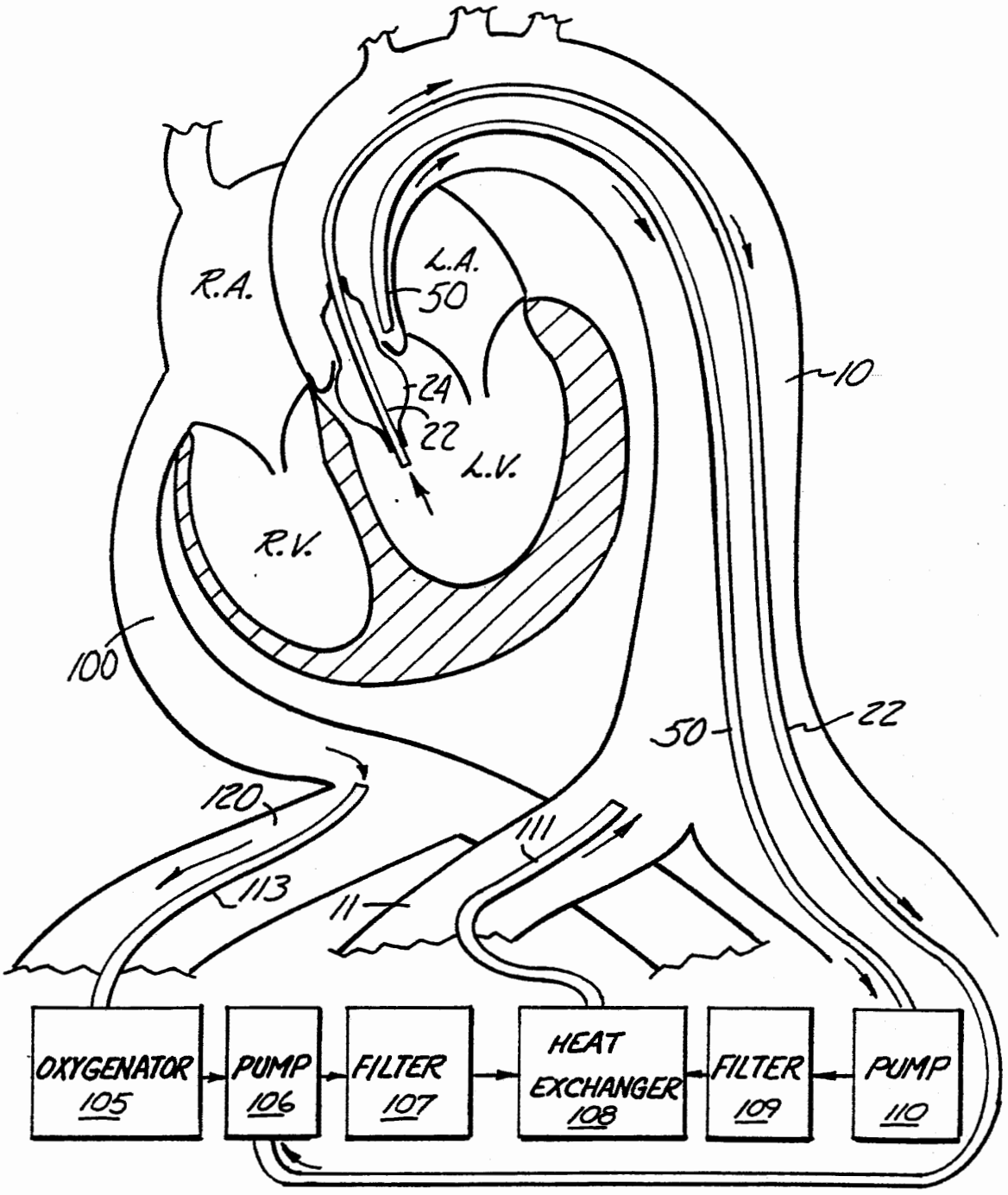


Fig. 18

Fig. 19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FILTER 107
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FILTER 109
PUMP 110

Fig. 20

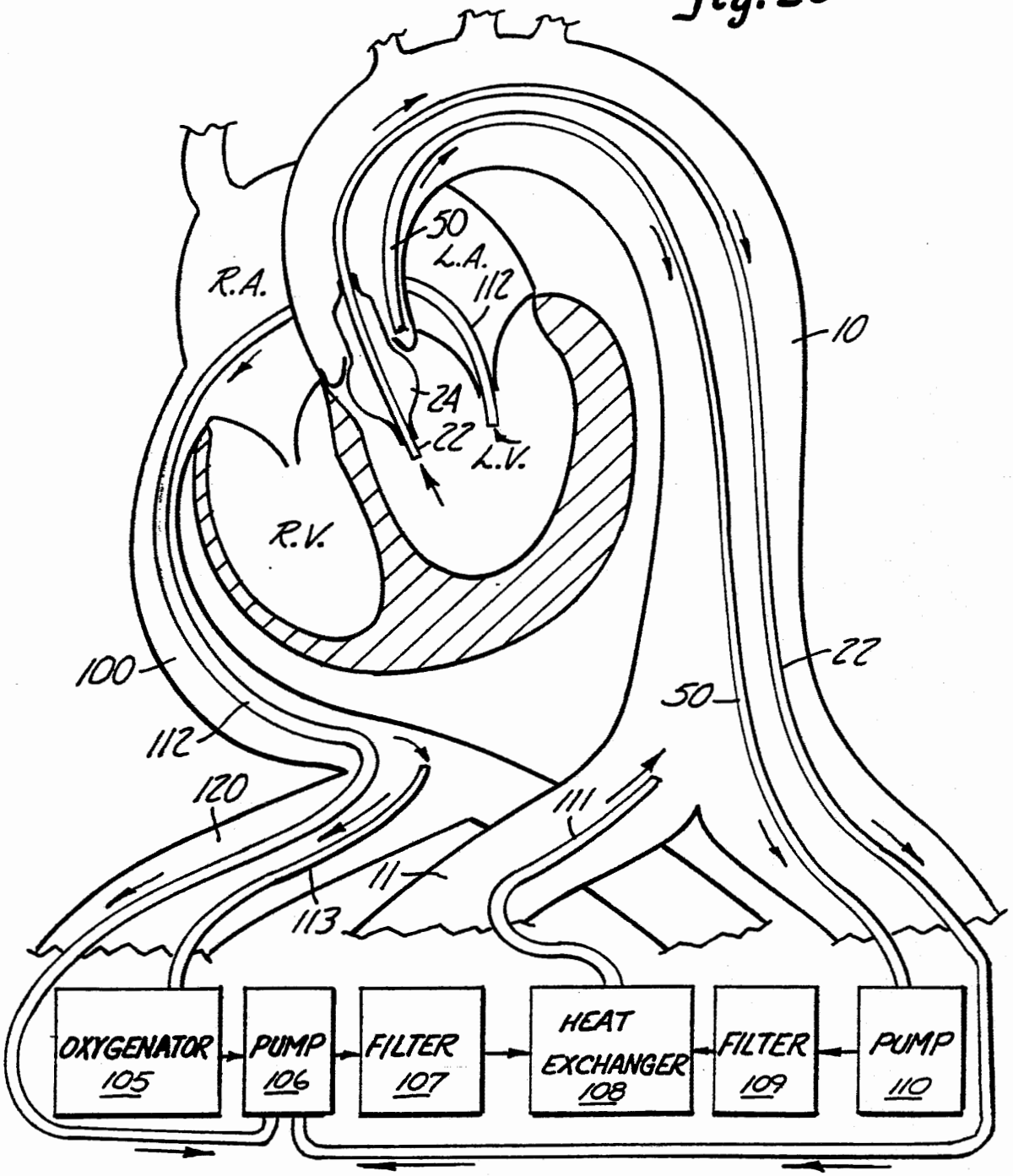
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Fig. 21

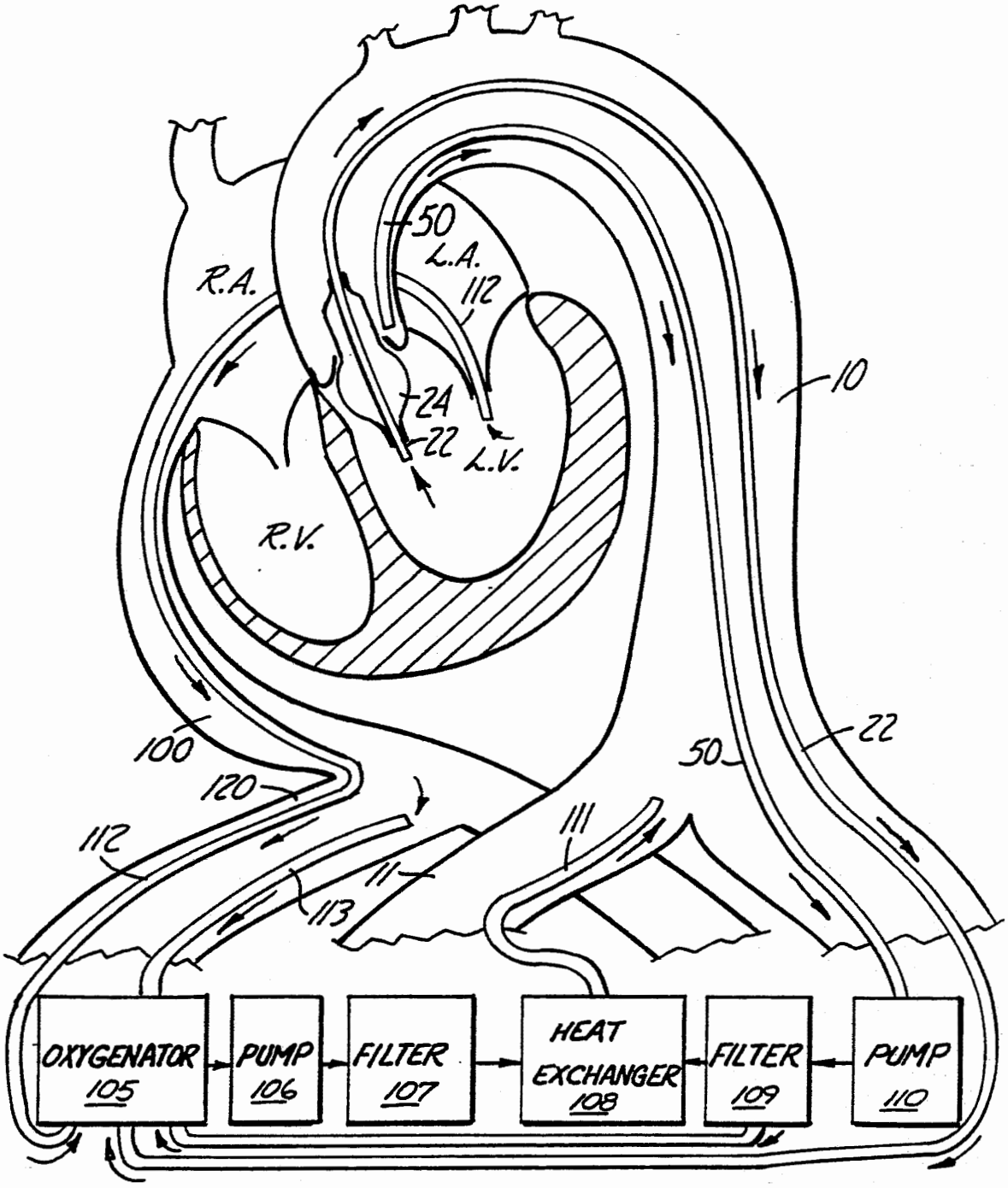
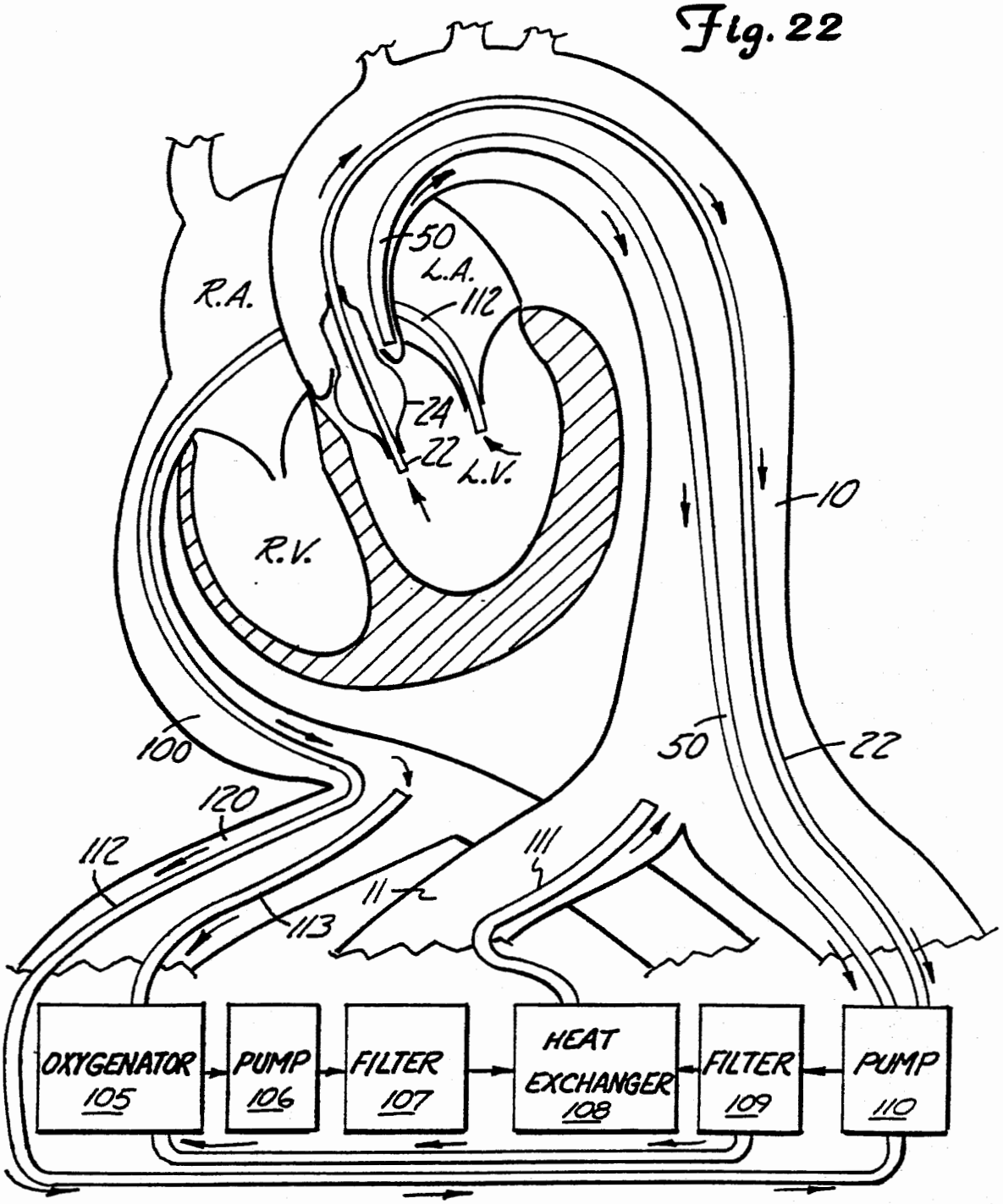


Fig. 22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FILTER 107
HEAT EXCHANGER 108
FILTER 109
PUMP 110

Fig. 23

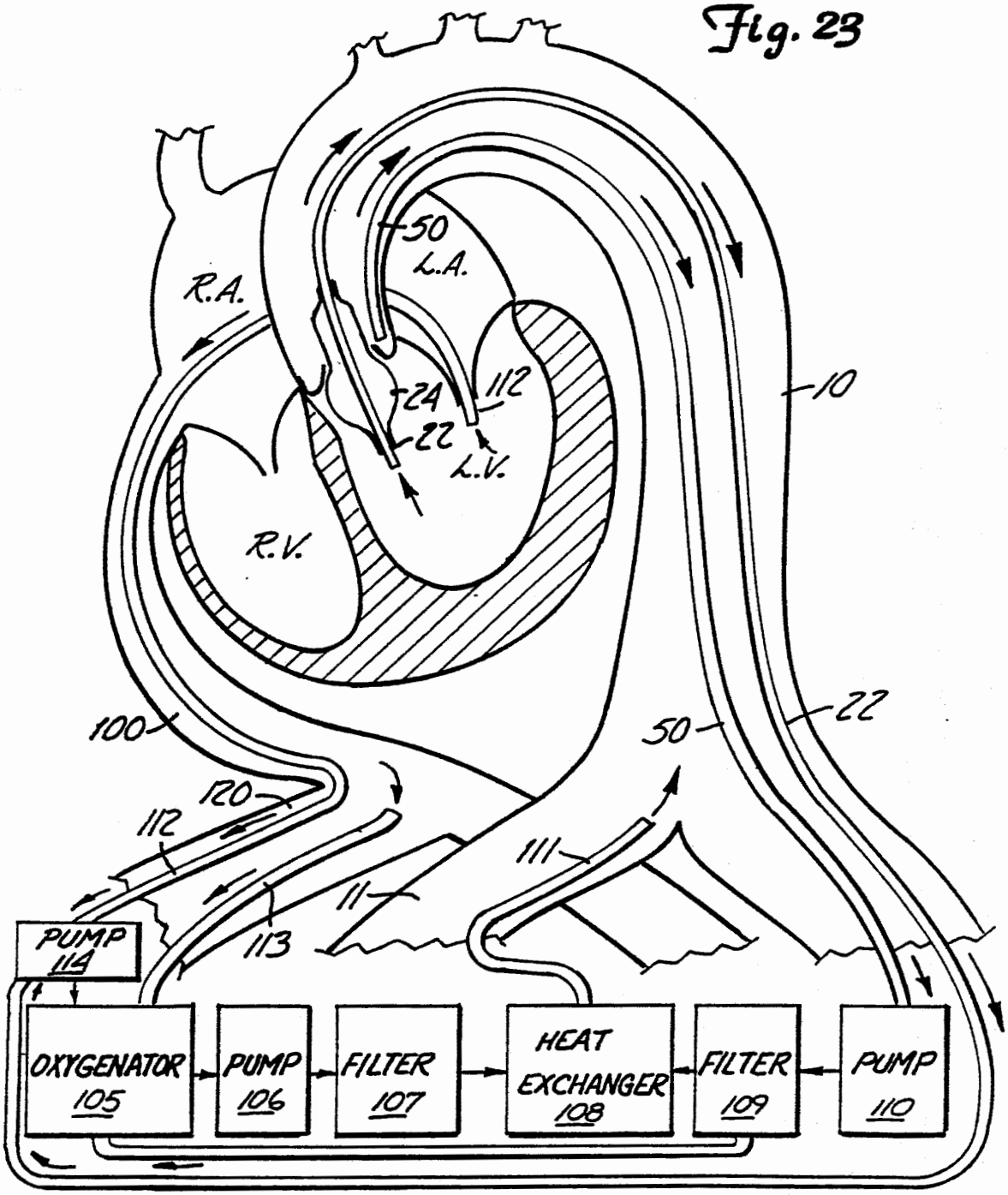
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Fig.24

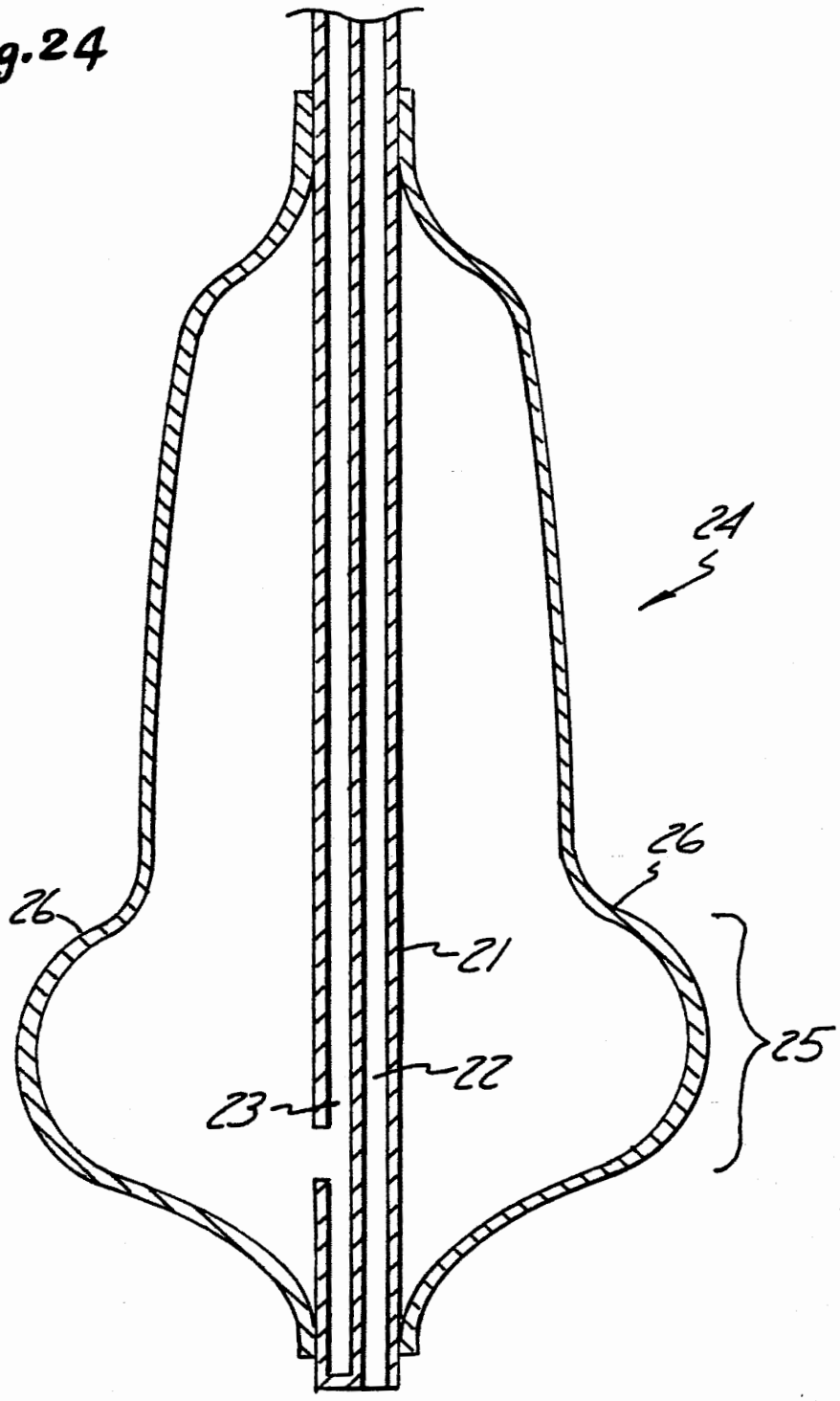


Fig. 25

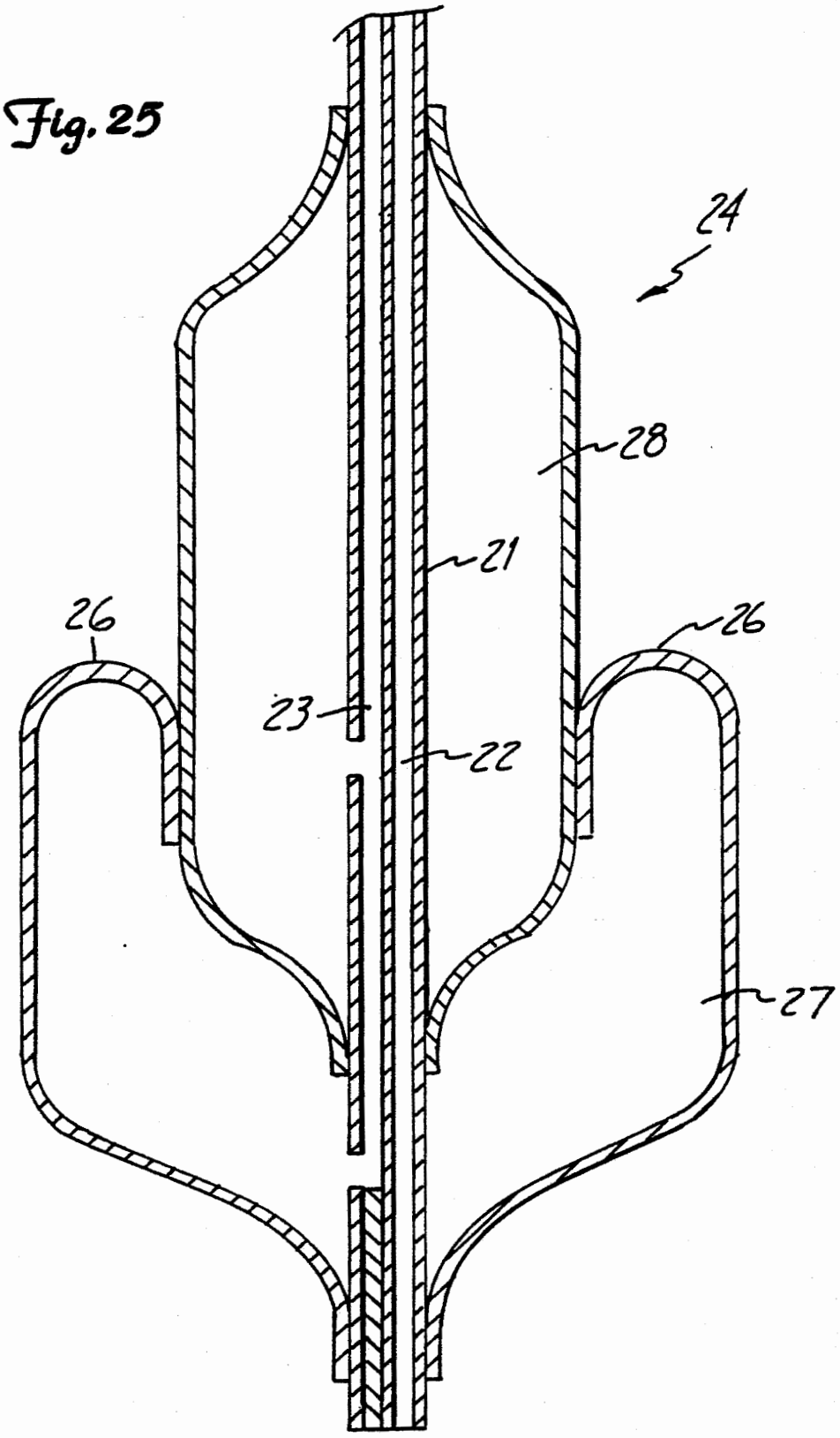


Fig.26

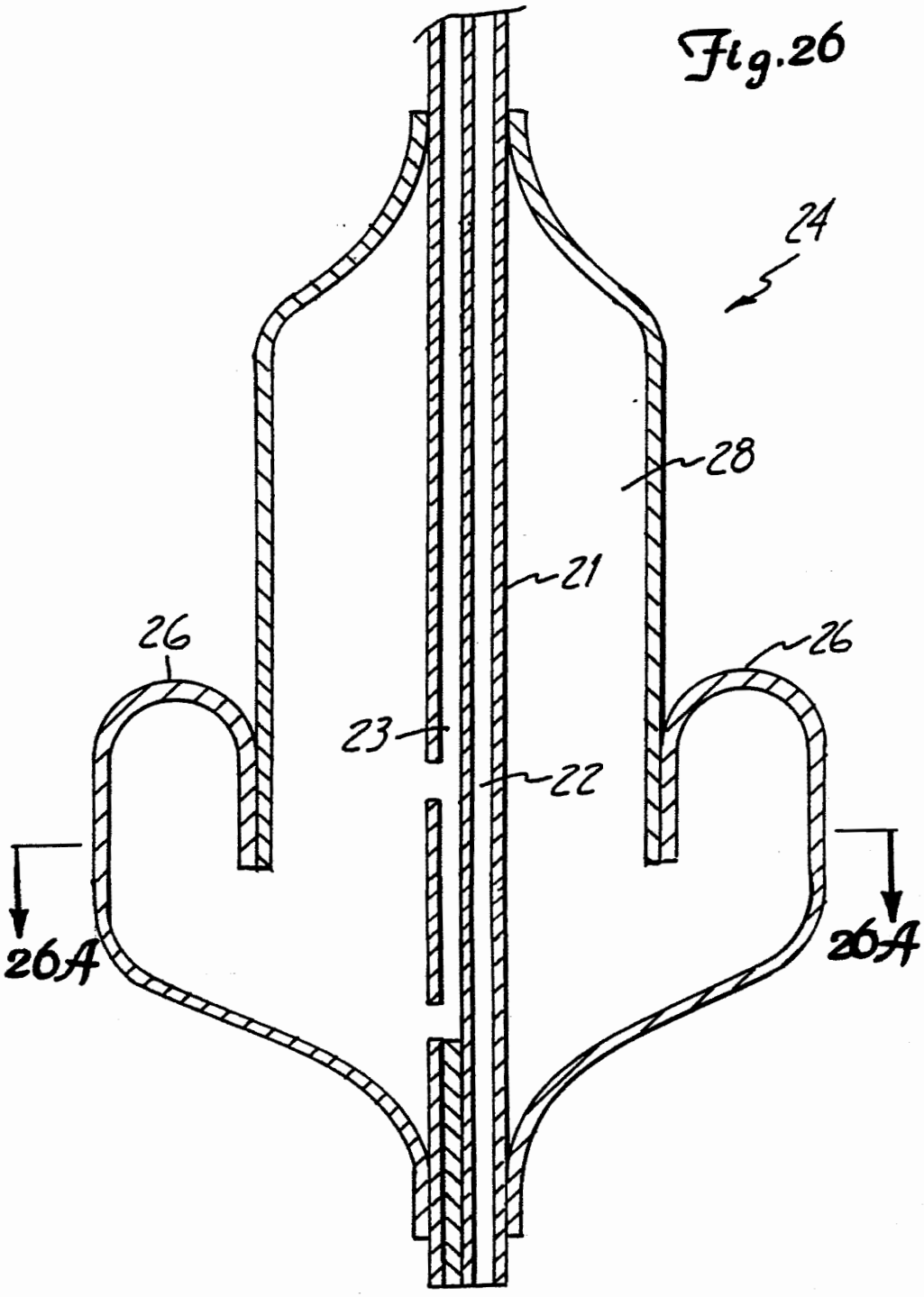
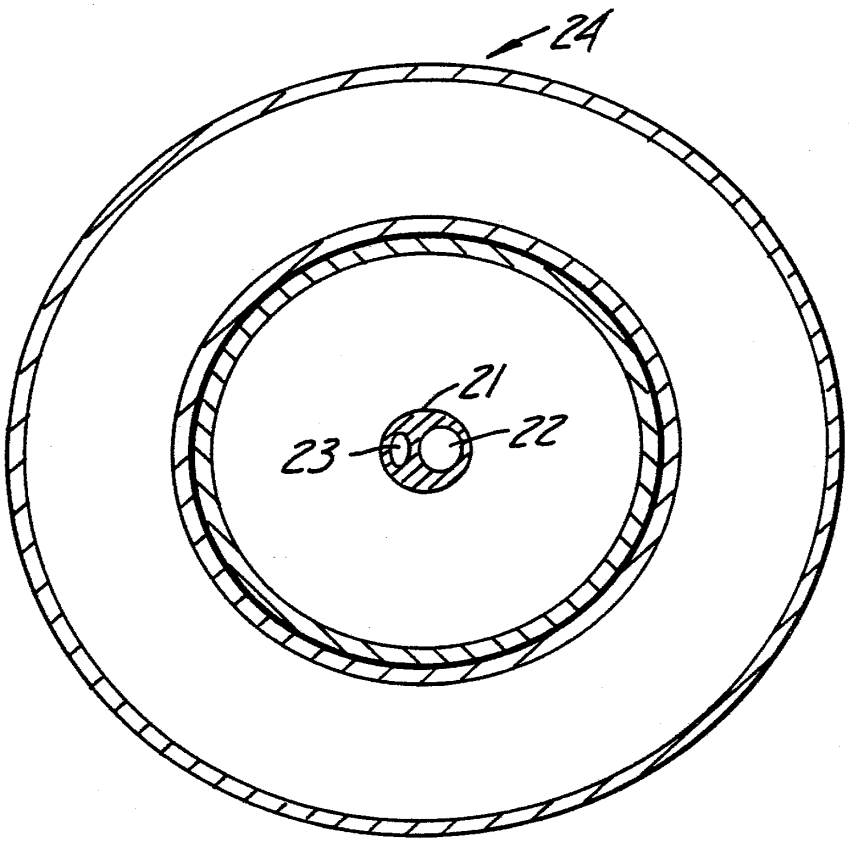


Fig. 26A



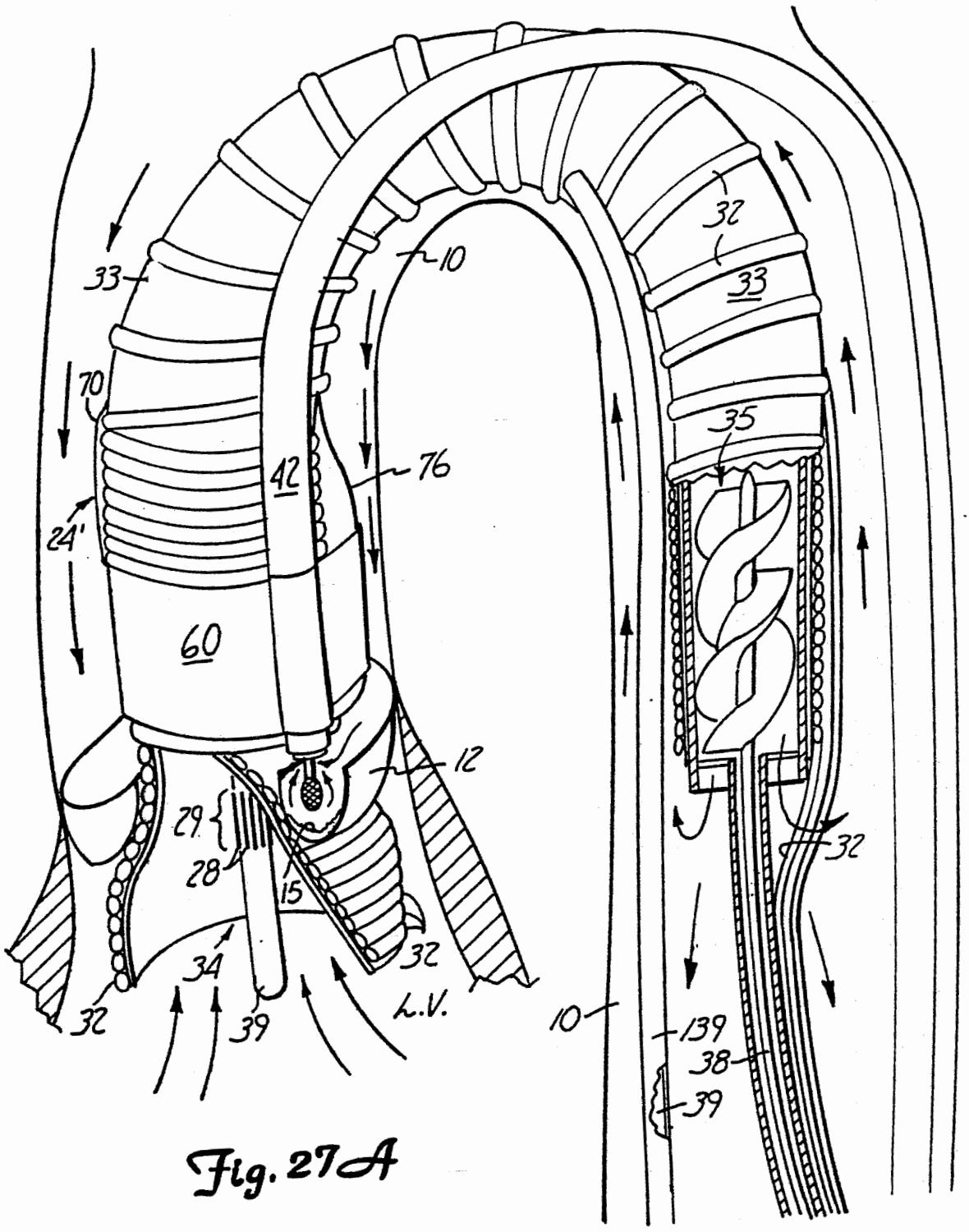


Fig. 27A

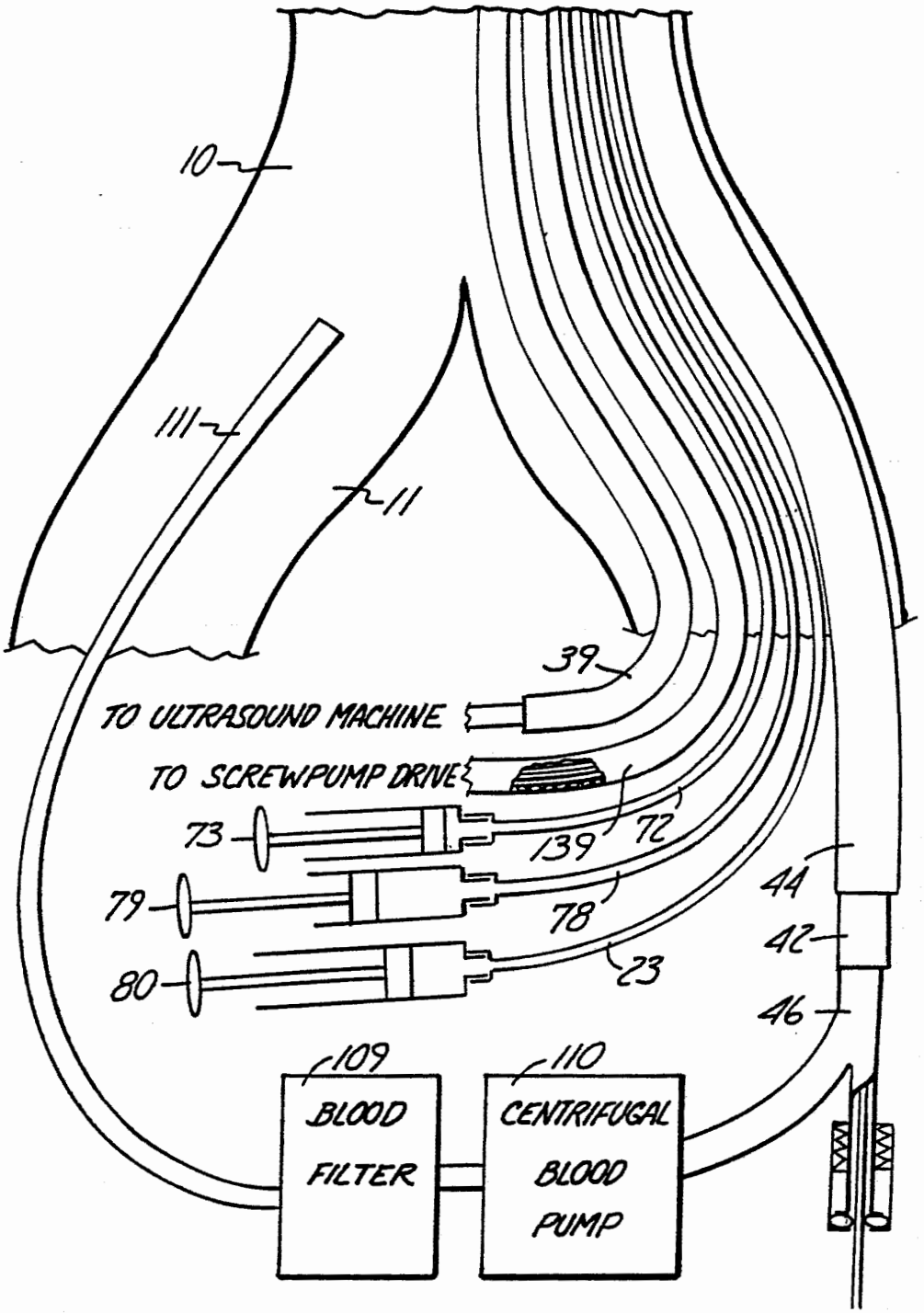


Fig. 27B

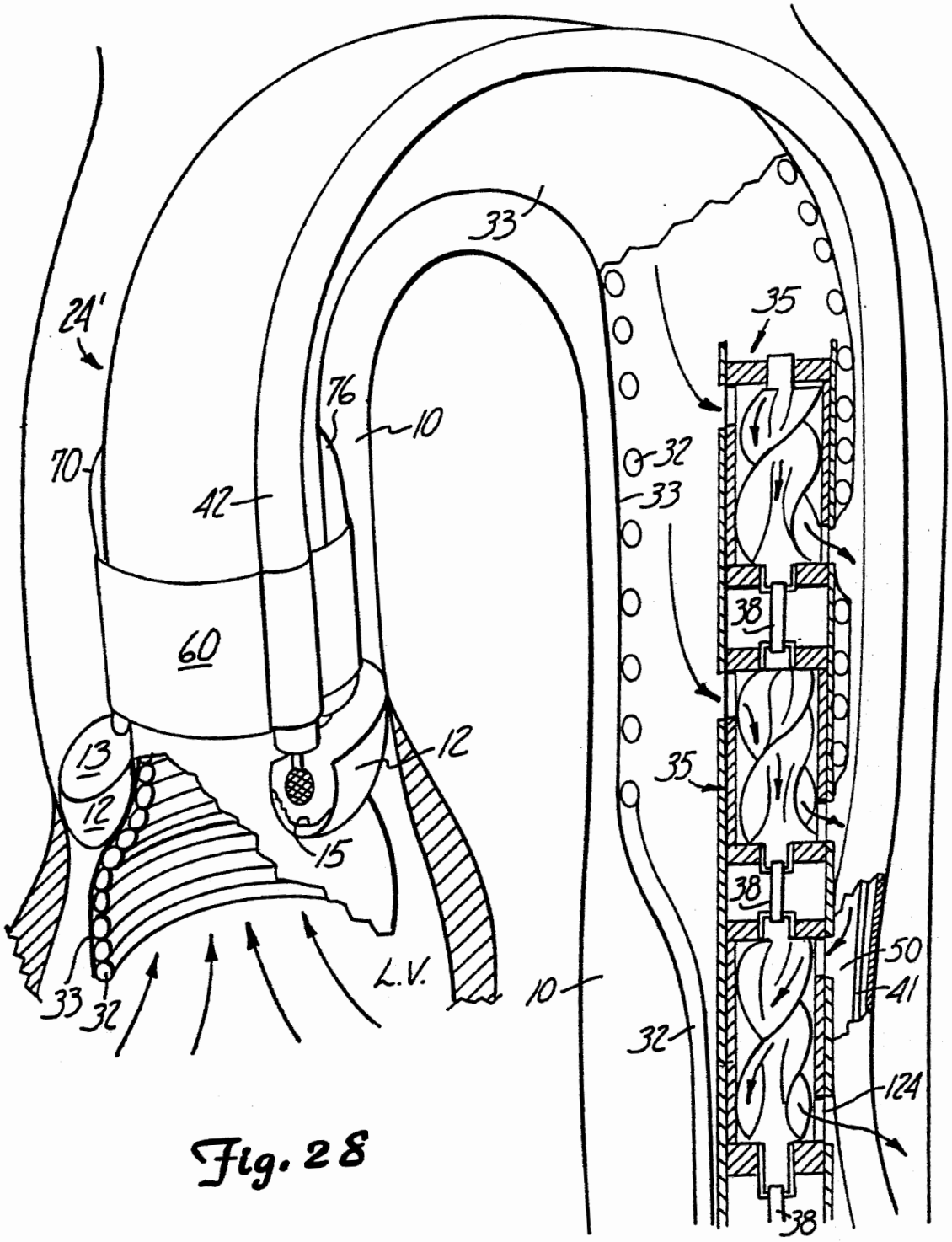

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Fig. 28

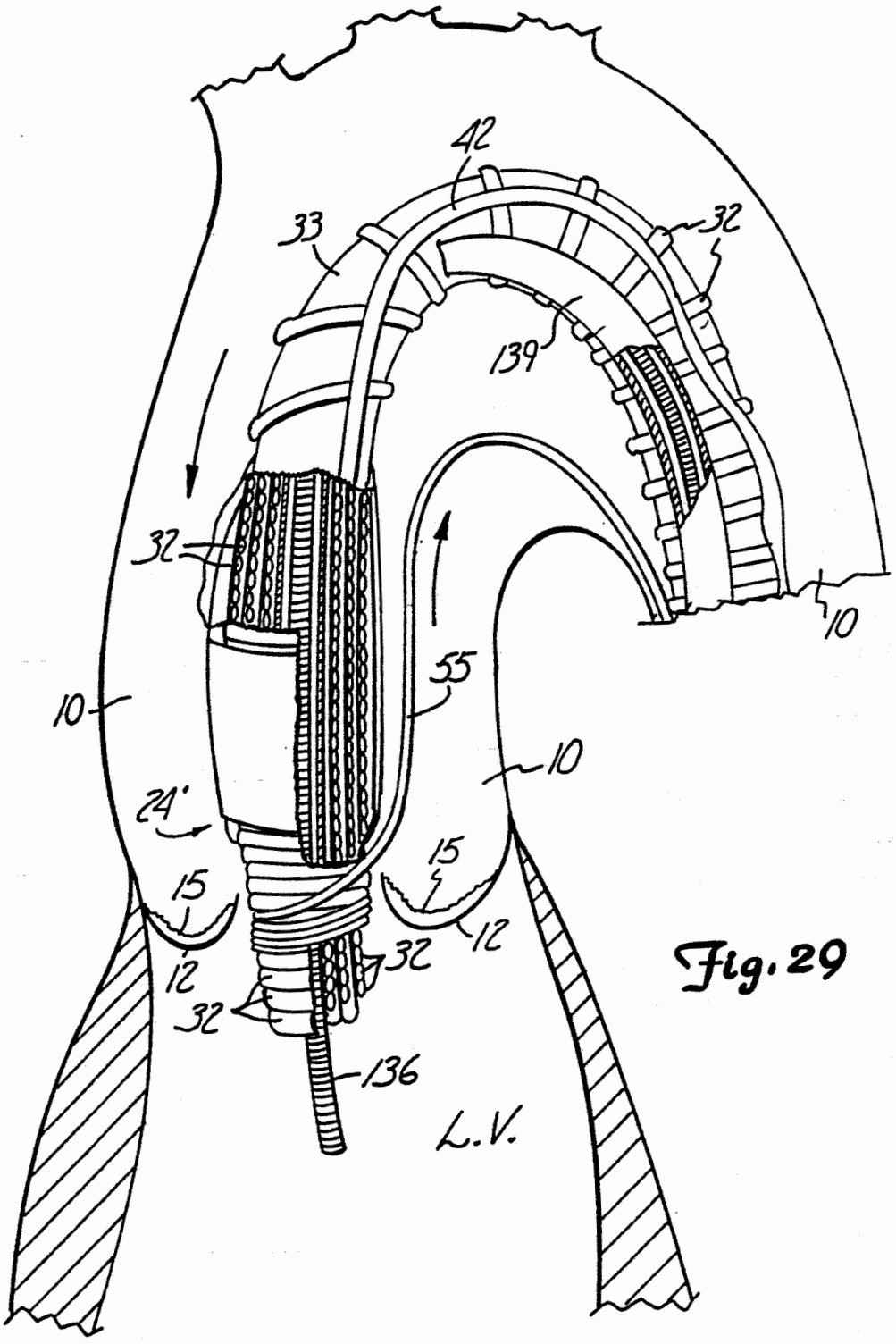


Fig. 29

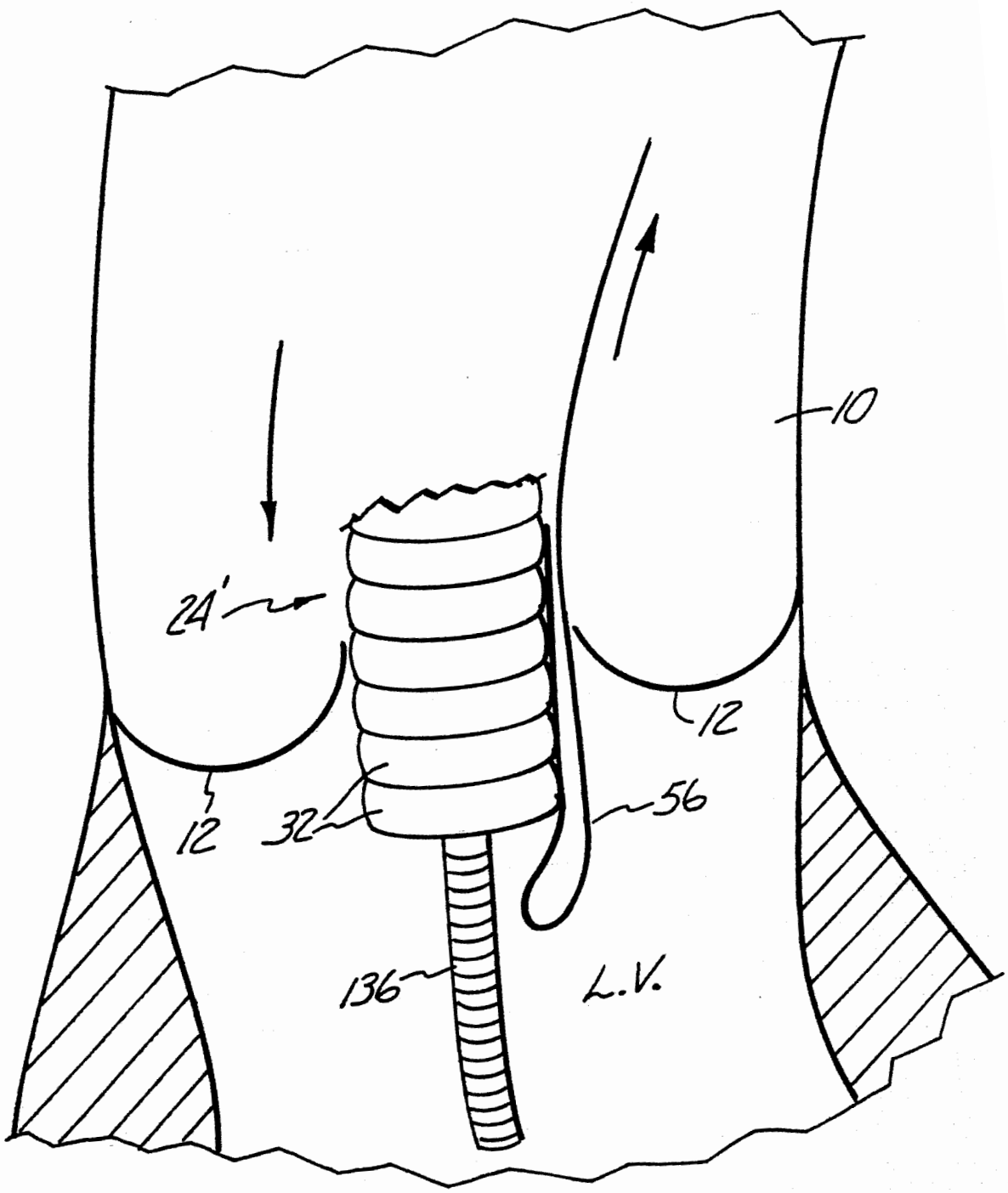
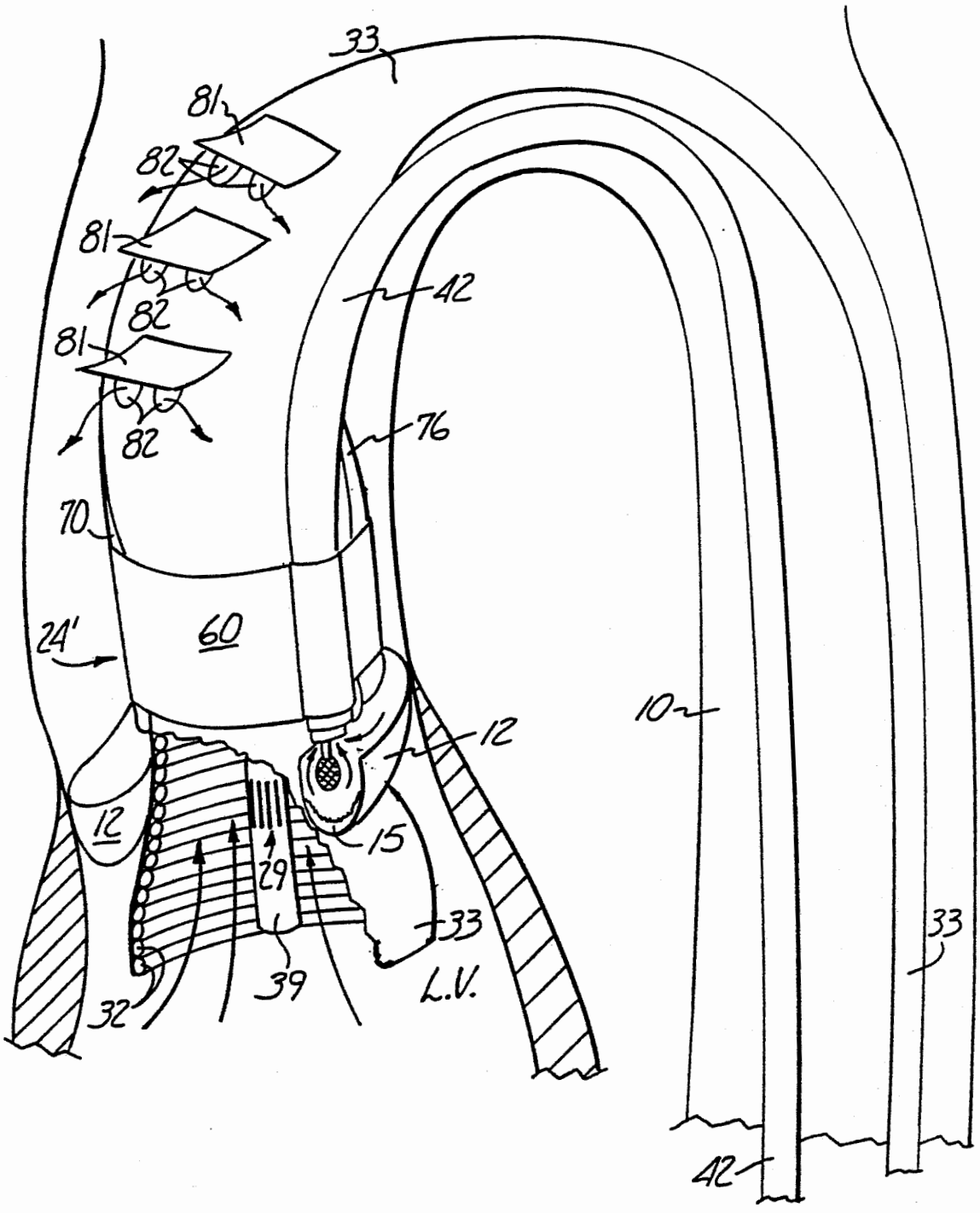


Fig.30

Fig. 31



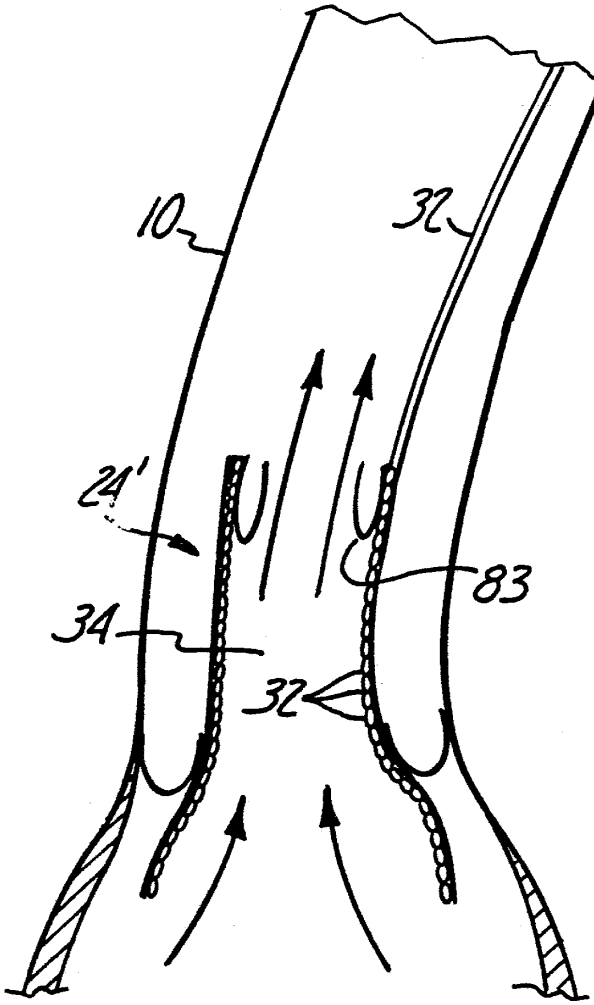


Fig. 32A

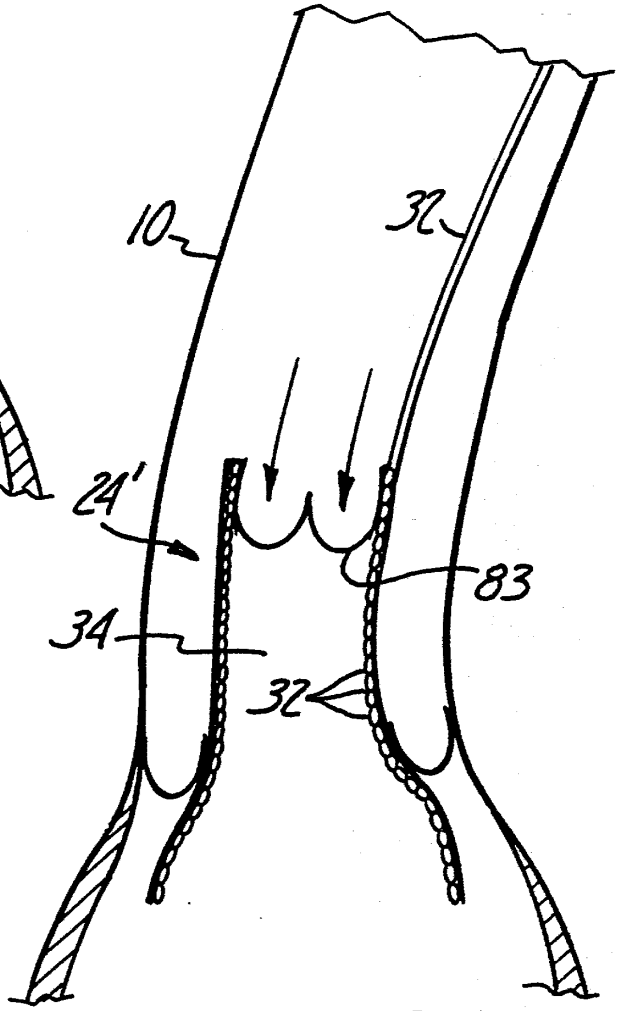


Fig. 32B

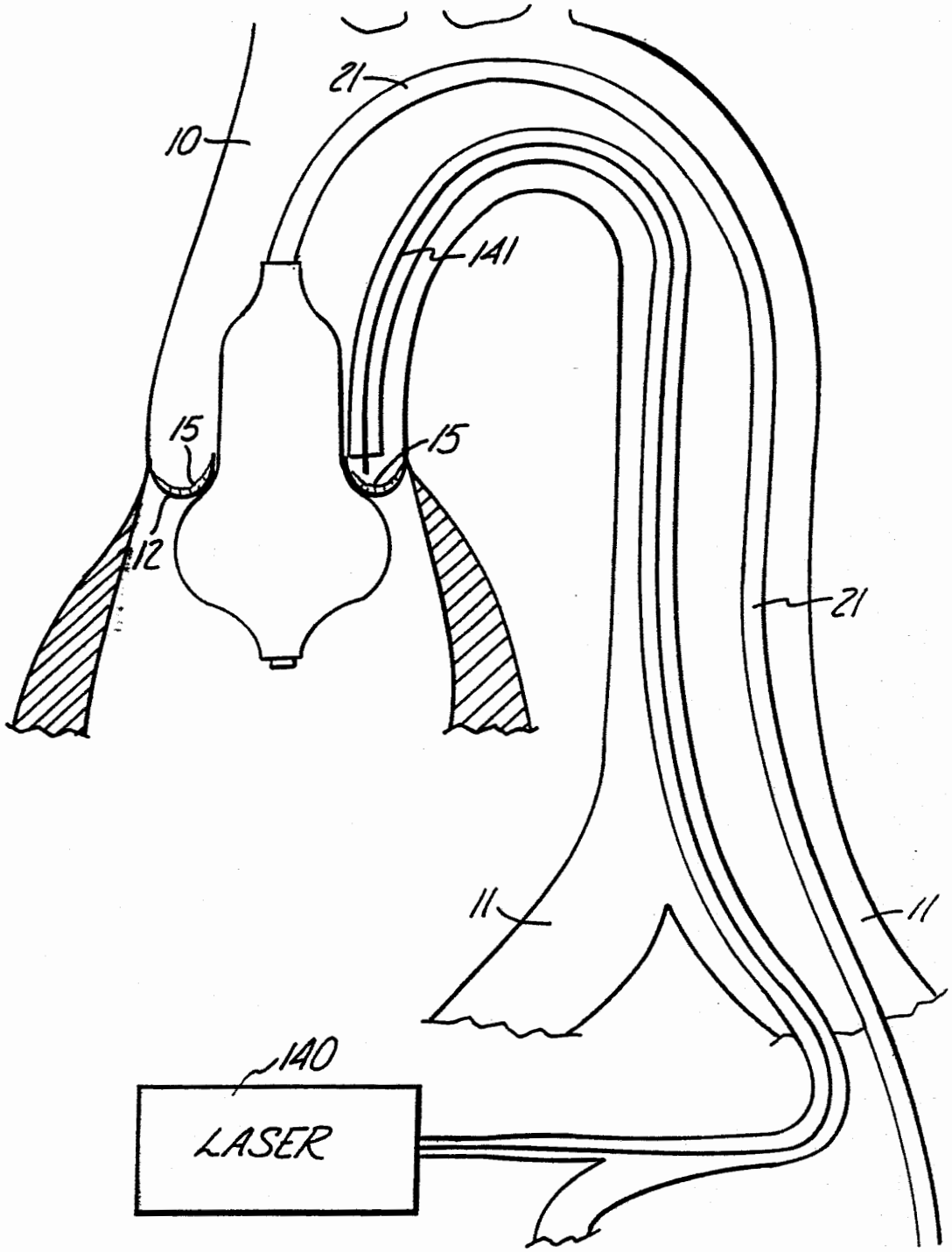


Fig. 33

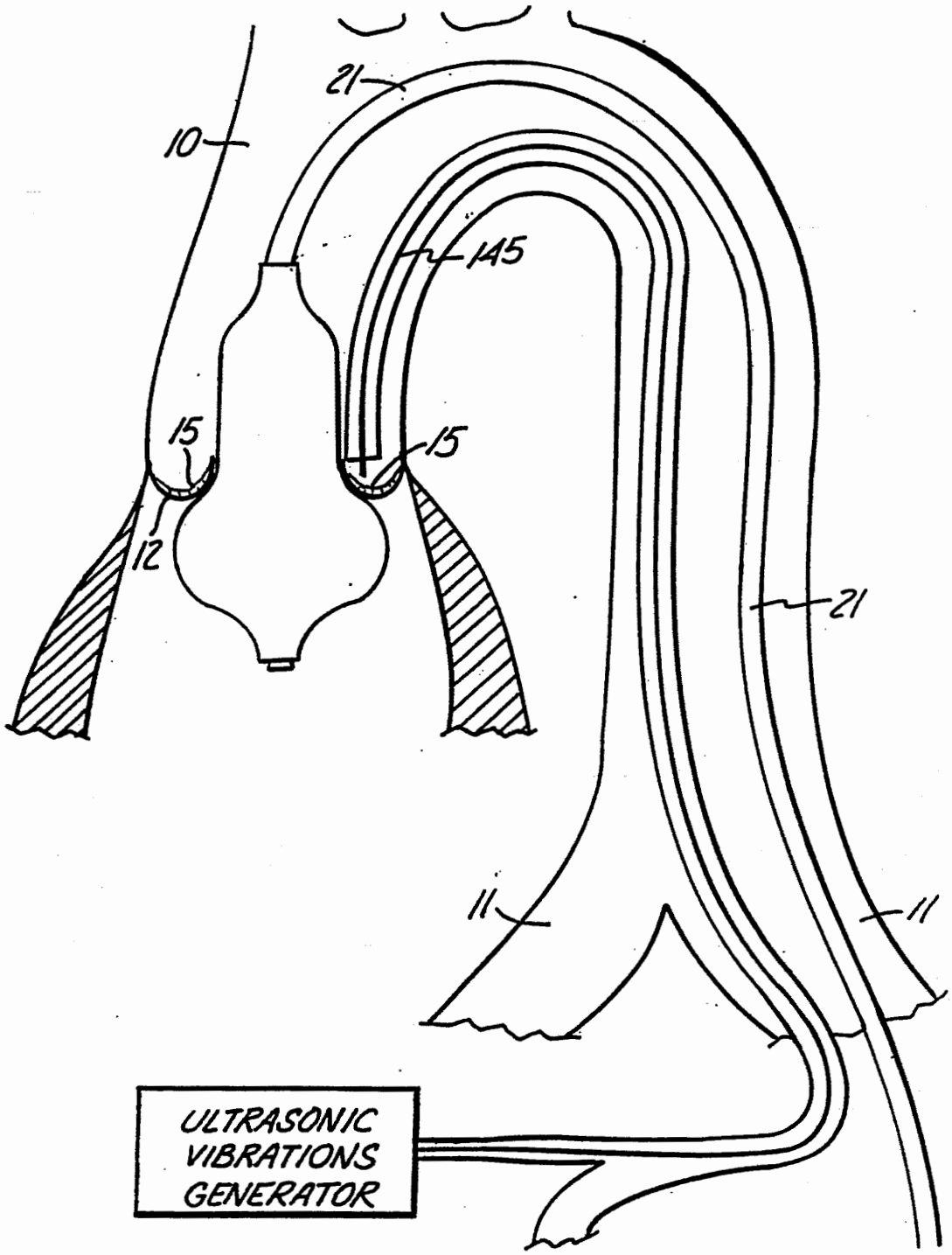


Fig. 34

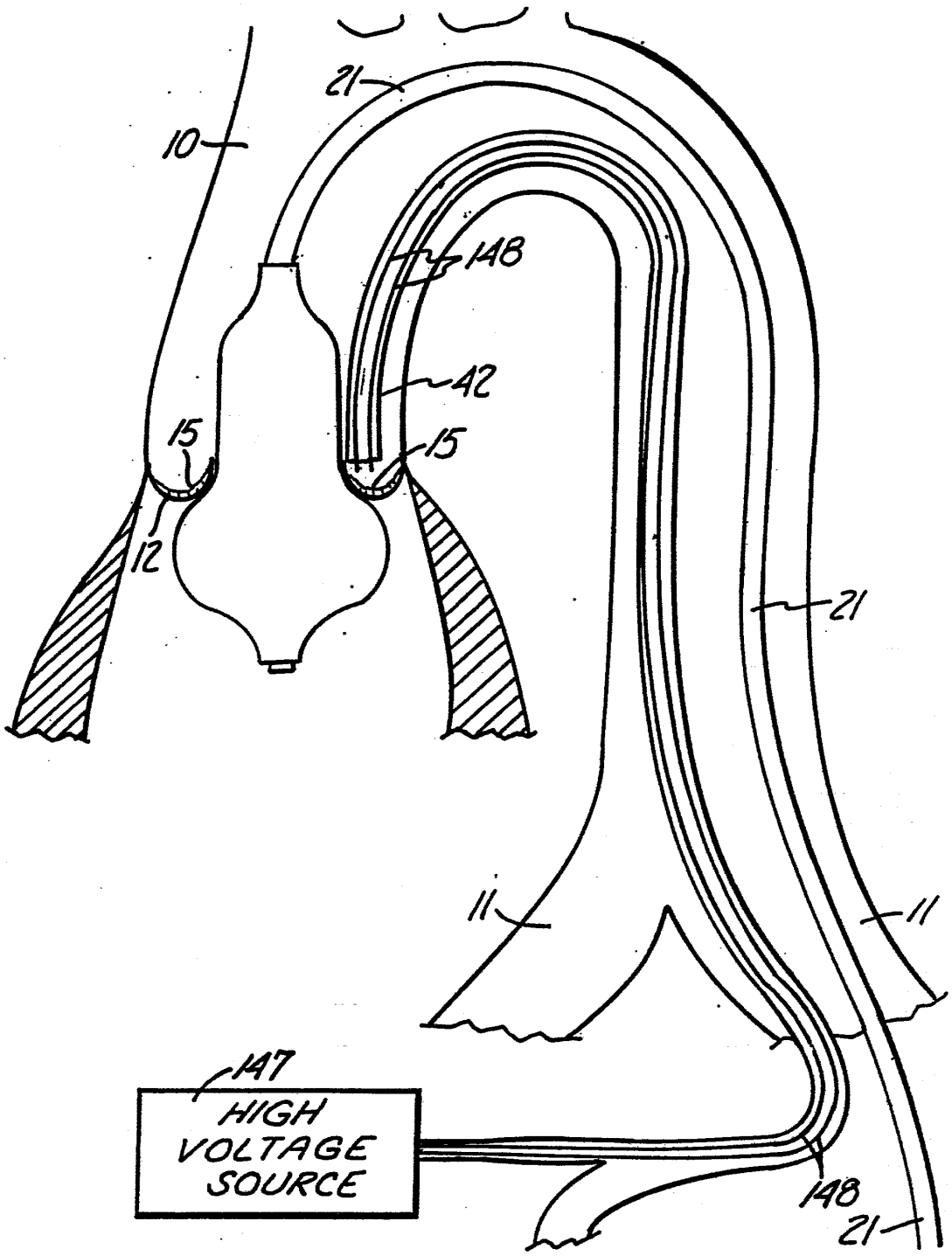


Fig. 35

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/02599

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61B 17/20; A61M 31/00,29/00; A61D 1/02
US CL :604/96,22,53; 606/159; 606/194
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)

U.S. : 604/95,97-99,101,103,104,113,128,171,173,264,280,283, 604/28,49-52; 606/160,167-171,180,191-192

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 practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	See Attached Sheet.	

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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"O"	document referring to an oral disclosure, use, exhibition or other means		
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Date of the actual completion of the international search 16 JULY 1992	Date of mailing of the international search report 15 SEP 1992
Name and mailing address of the ISA/ Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer RONALD STRIGHT, JR. Telephone No. (703) 308-2113

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/02599

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US,A 5,009,659 (HAMLIN ET AL) 23 APRIL 1991 (SEE ENTIRE DOCUMENT)	1-3,10,12-15,43,54
X	US,A 4,894,051 (SHIBER) 16 JANUARY 1990 (SEE COL. 6, LINES 8-10)	1-3, 10, 12,14-18
X	US,A 4,979,951 (SIMPSON) 25 DECEMBER 1990 (SEE ENTIRE DOCUMENT)	1-3, 10, 12, 14
X,P	US,A 5,092,873 (SIMPSON ET AL) 03 MARCH 1992 (SEE ENTIRE DOCUMENT)	1-3, 10, 12, 14, 23-24
X,E	US,A 5,100,424 (JANG ET AL) 31 MARCH 1992 (SEE ENTIRE DOCUMENT)	1-3, 10, 12, 15, 37, 40, 41
X	US,A 4,784,636 (RYDELL) 15 NOVEMBER 1988 (SEE ENTIRE DOCUMENT)	1-3, 10, 12-14 43, 54
A,P	US,A 5,078,722 (STEVENS) 07 JANUARY 1992 (SEE ENTIRE DOCUMENT)	50-53
A	PROGRESS IN CARDIOLOGY, JULY 1990, (SHAWL ET AL), PERCUTANEOUS CARDIOPULMONARY BYPASS SUPPORT IN THE CATHETERIZATION LABORATORY: TECHNIQUE AND COMPLICATIONS, PP. 195-203.	29-36
X A	INTERNATIONAL JOURNAL OF CARDIAC IMAGING, VOLUMN 4, NOS. 2-4 1989, (BOM ET AL), EARLY AND RECENT INTRALUMINAL ULTRASOUND DEVICES, PP. 79-88. (SEE ENTIRE DOCUMENT)	1-13, 12, 14,37,40,41 38-39
A	US,A 4,785,795 (SINGH) 22 NOVEMBER 1988 (SEE FIGURES 3 AND 4)	23,24
A	US,A 4,762,130 (FOGARTY ET AL) 09 AUGUST 1988 (SEE ENTIRE DOCUMENT)	27,28,44,45
A	US,A 3,438,375 (ERICSON) 15 APRIL 1969 (SEE ENTIRE DOCUMENT)	27,28,44,45
X,P	US,A 5,026,367 (LECKRONE ET AL) 25 JUNE 1991 (SEE ENTIRE DOCUMENT)	1-3,18

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60/814,572	19 June 2006 (19.06.2006)	US
60/832,162	21 July 2006 (21.07.2006)	US
60/832,142	21 July 2006 (21.07.2006)	US
60/860,805	24 November 2006 (24.11.2006)	US

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(74) Agents: **G.E. EHRLICH (1995) LTD.** et al.; 11 Menachem Begin Street, 52521 Ramat Gan (IL).

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Published:

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(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.

WO 2007/138572 A2

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.