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.

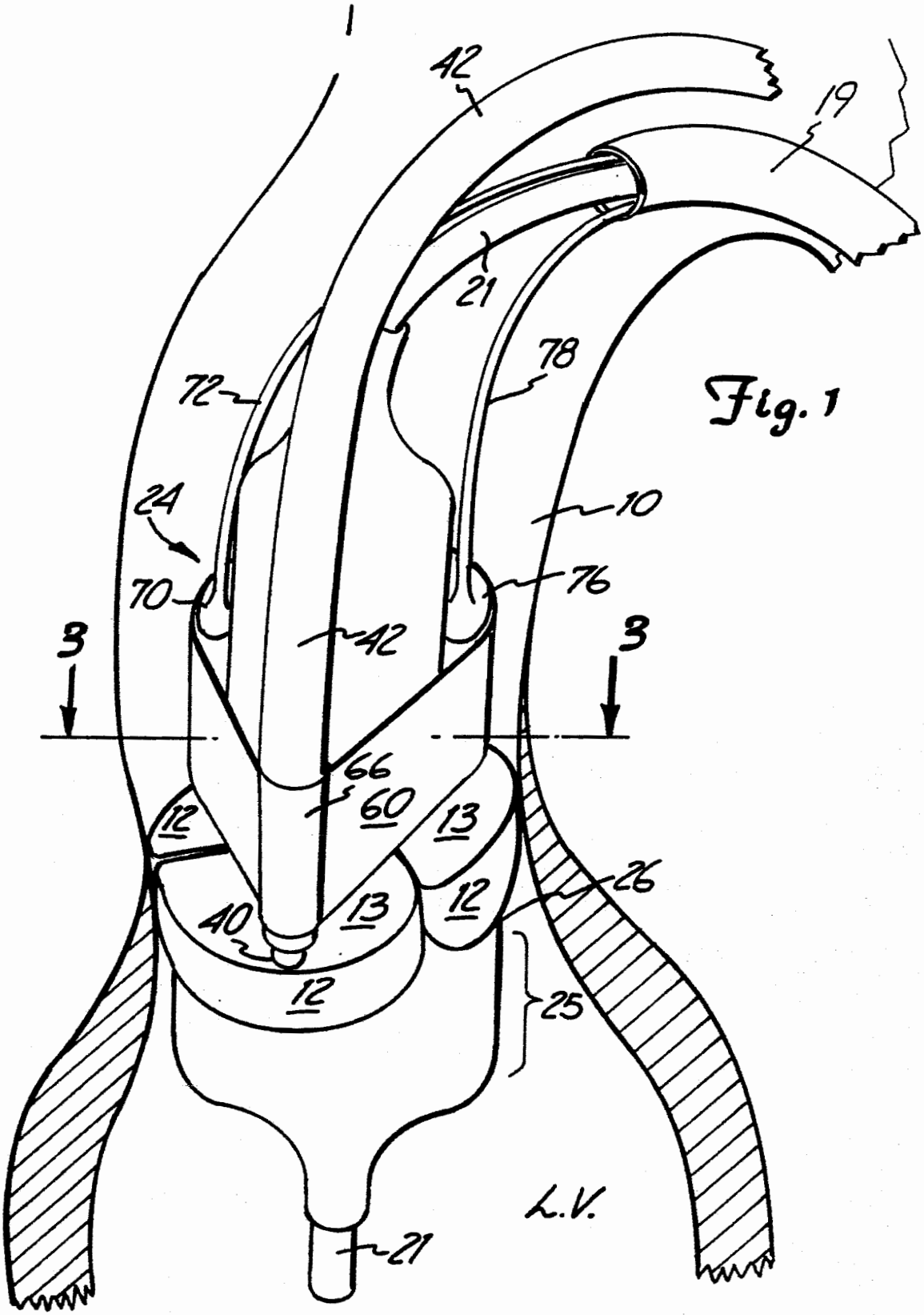


Fig. 1

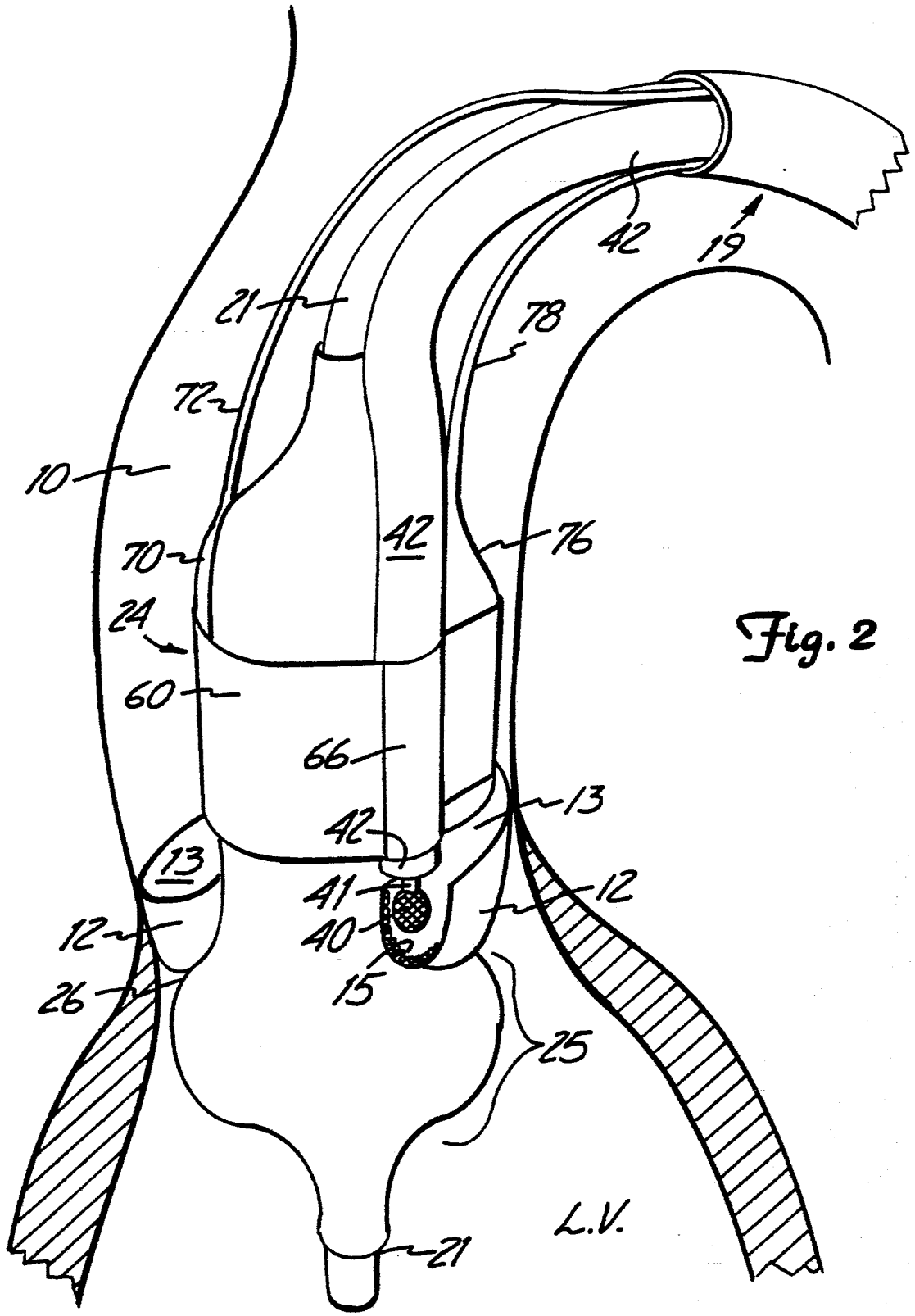


Fig. 2

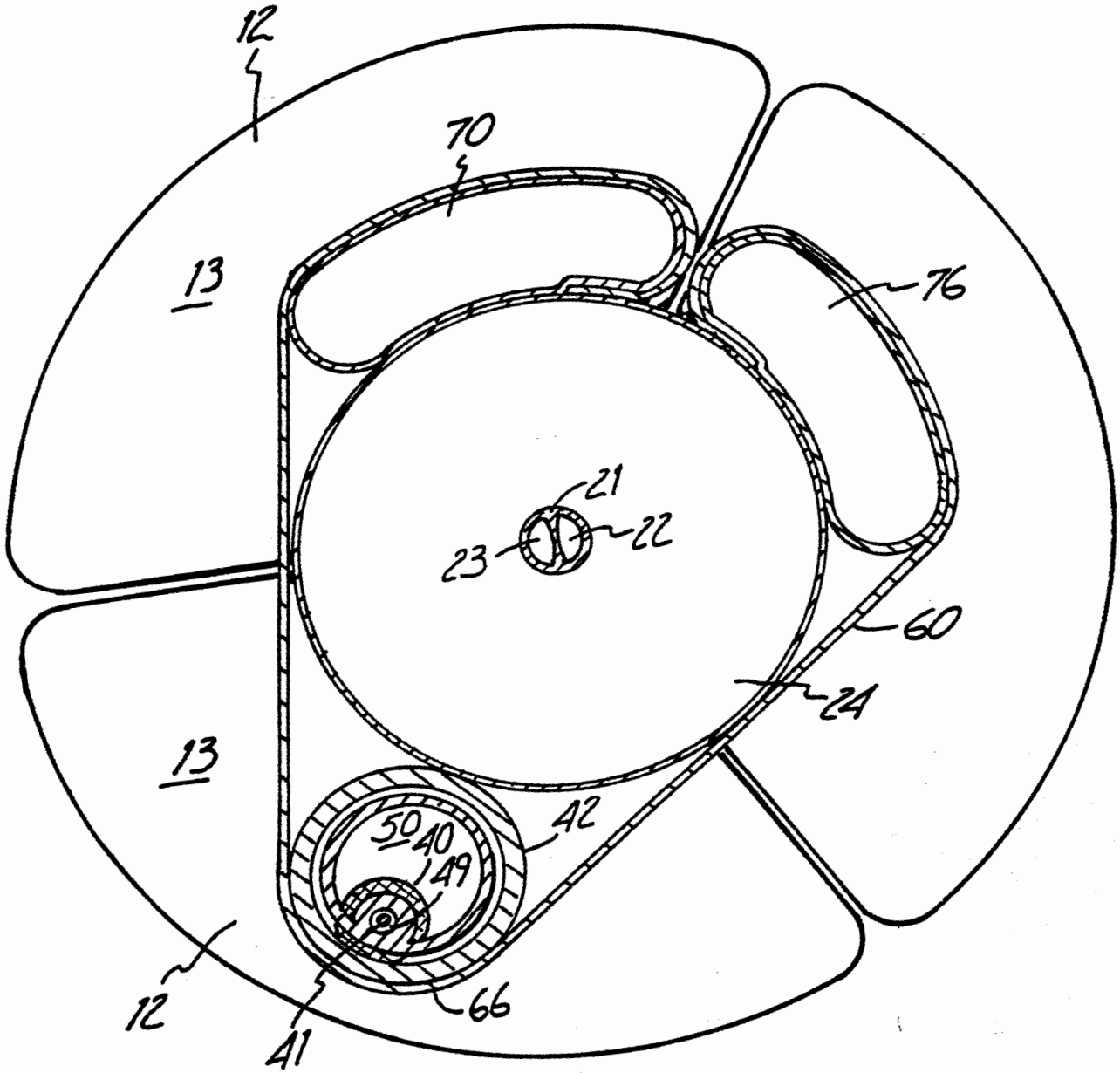


Fig. 3

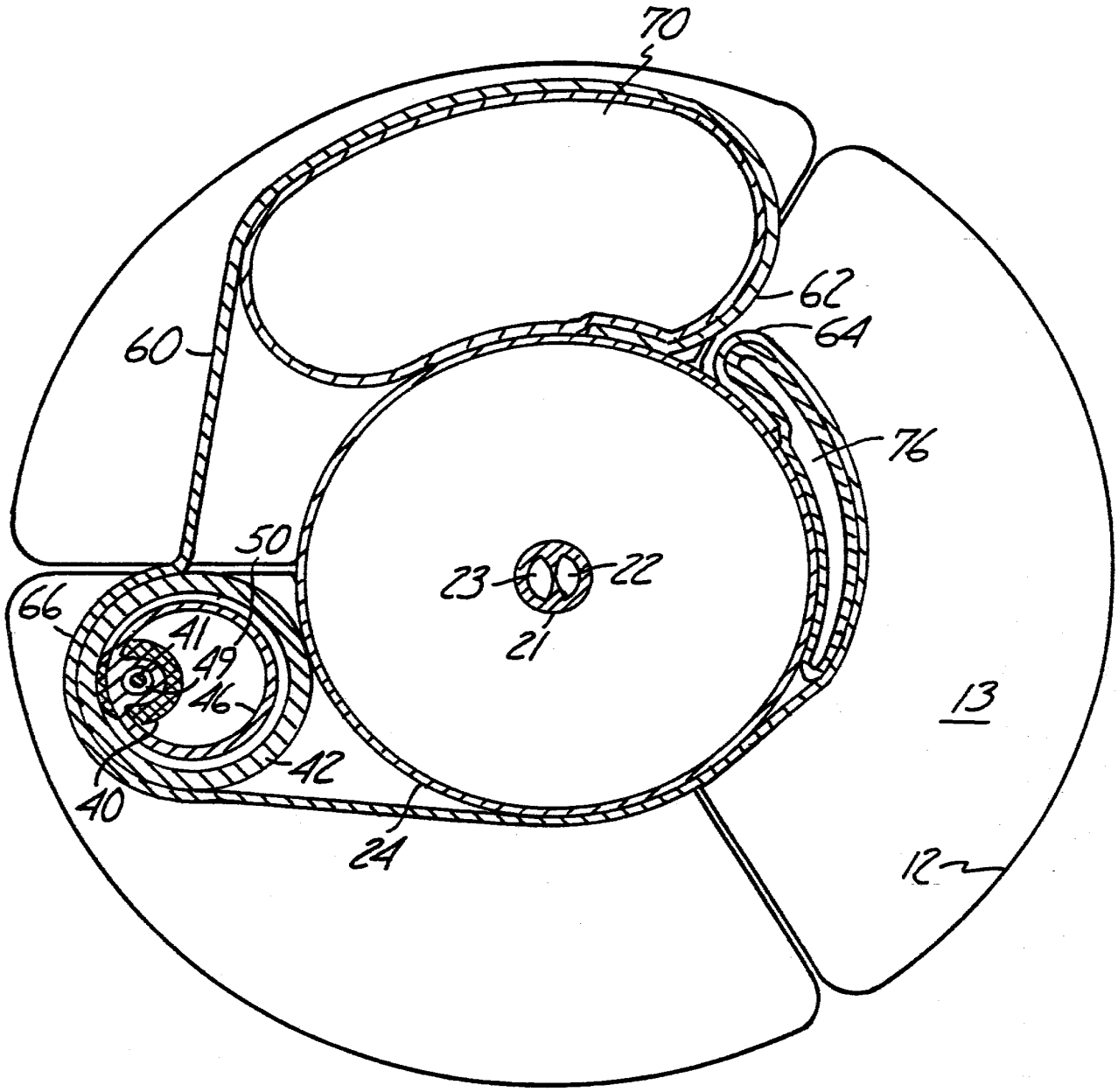


Fig. 4

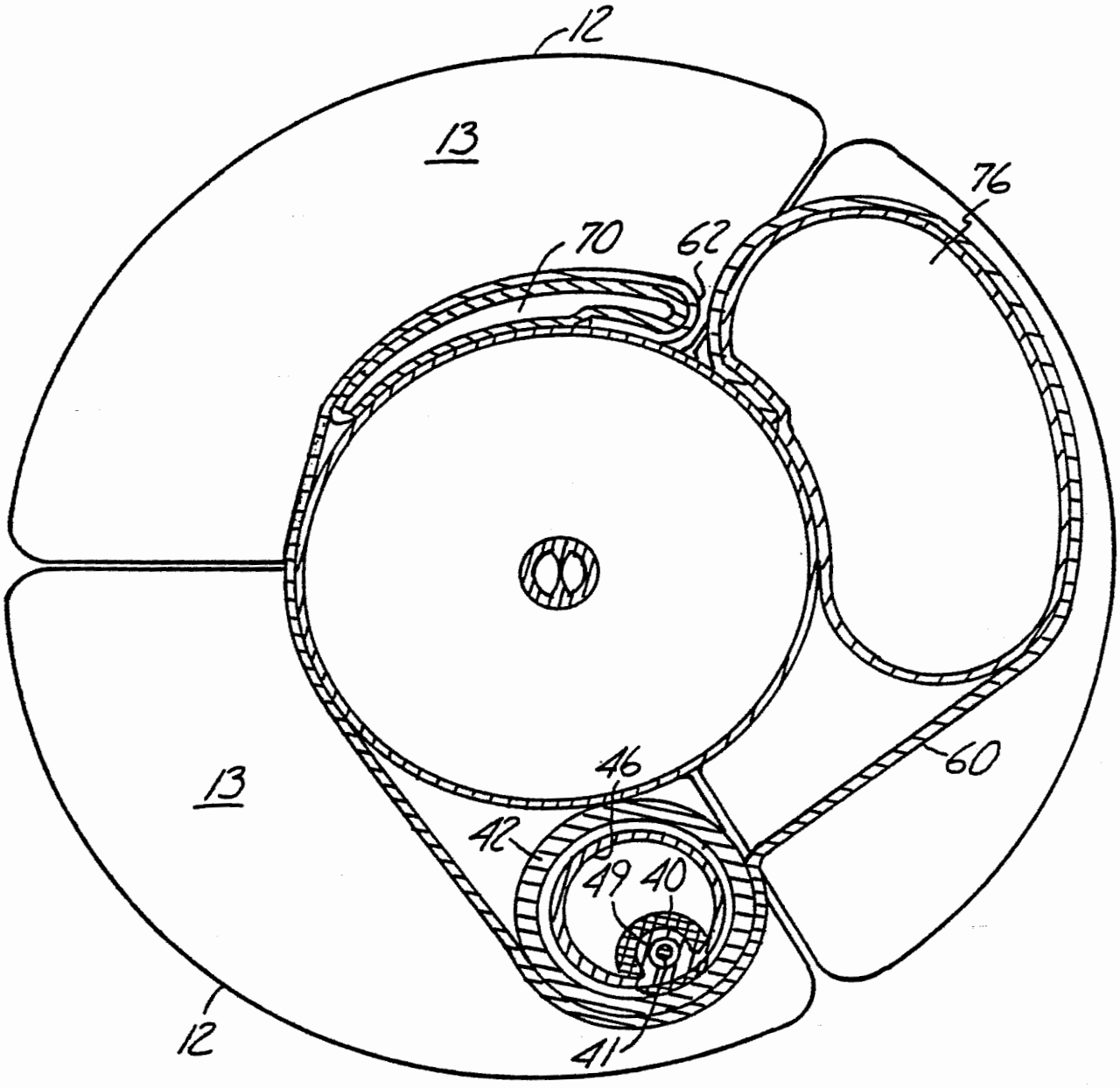


Fig. 5

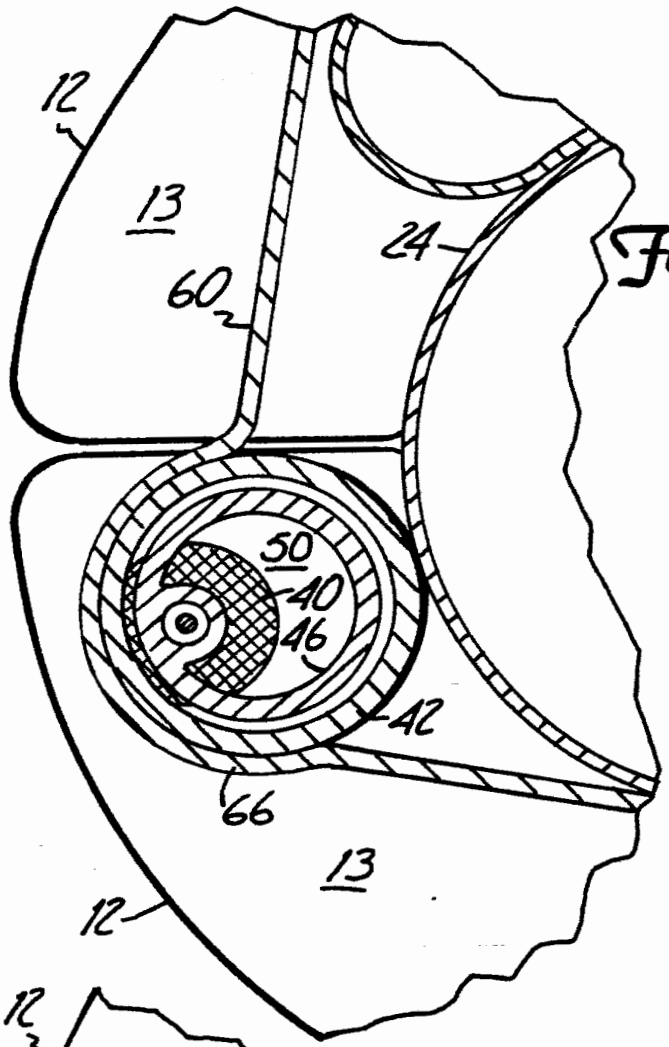


Fig. 7

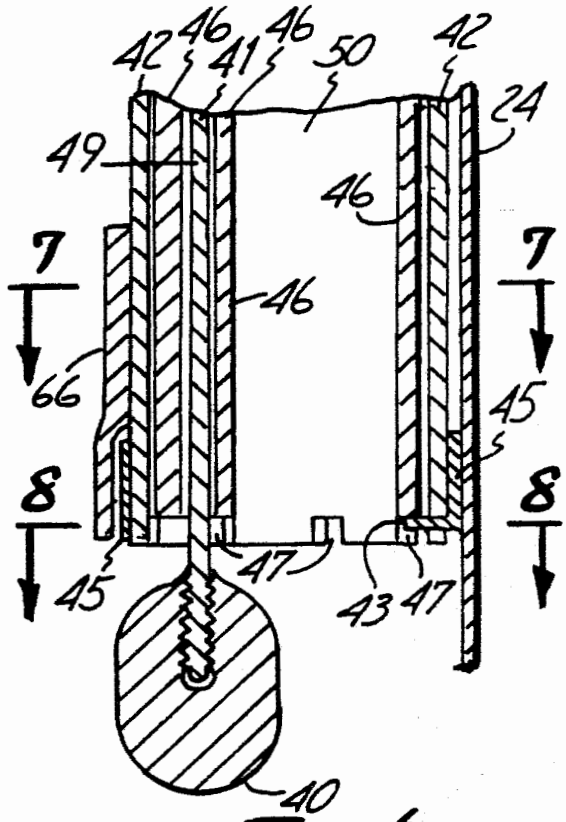


Fig. 6

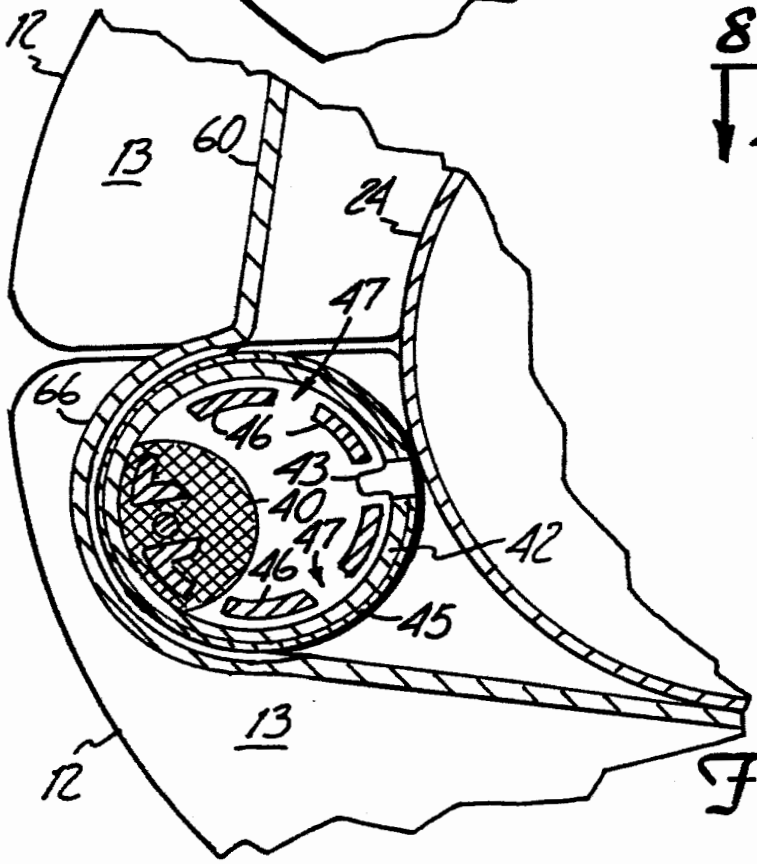


Fig. 8

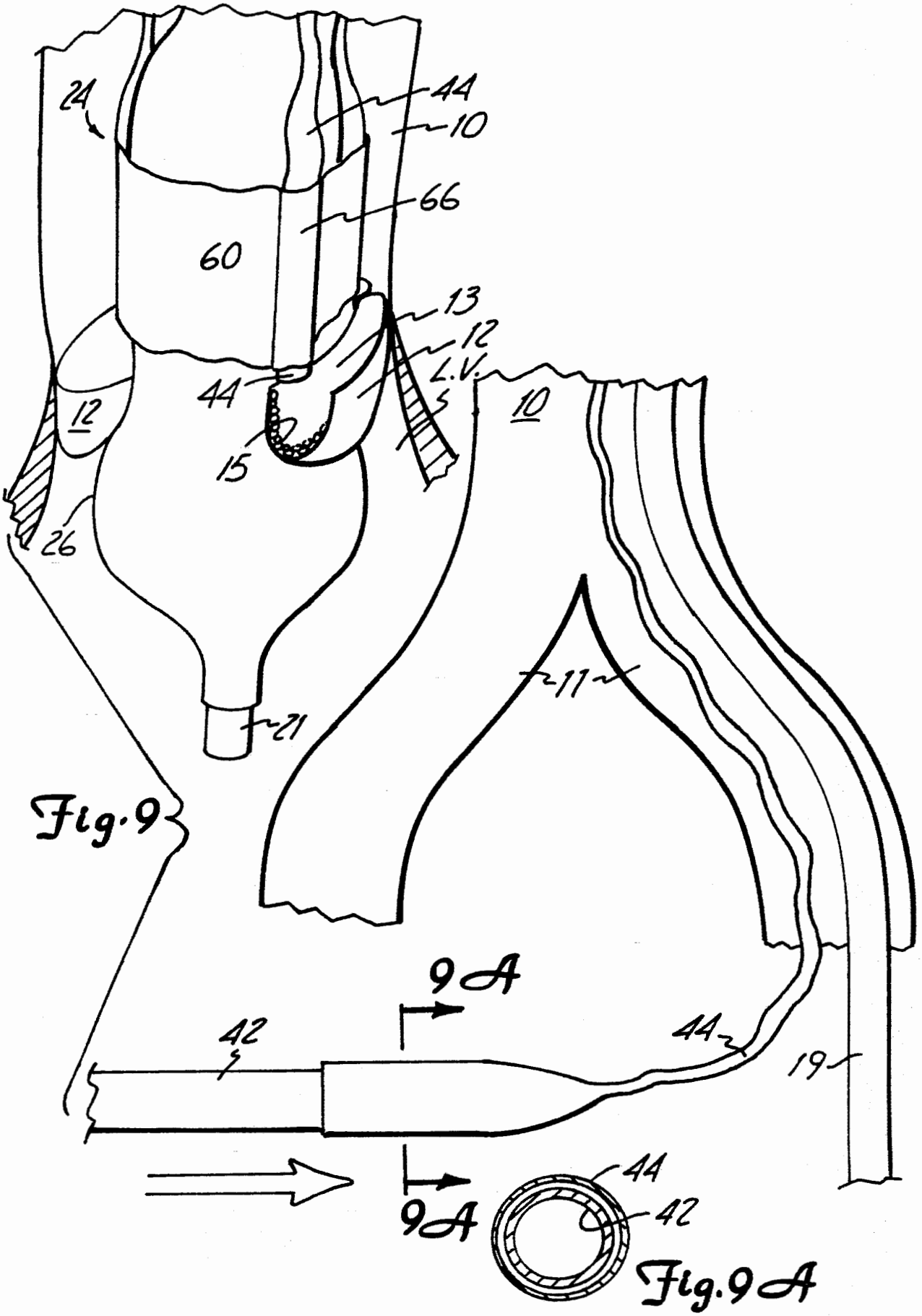


Fig. 9

Fig. 9A

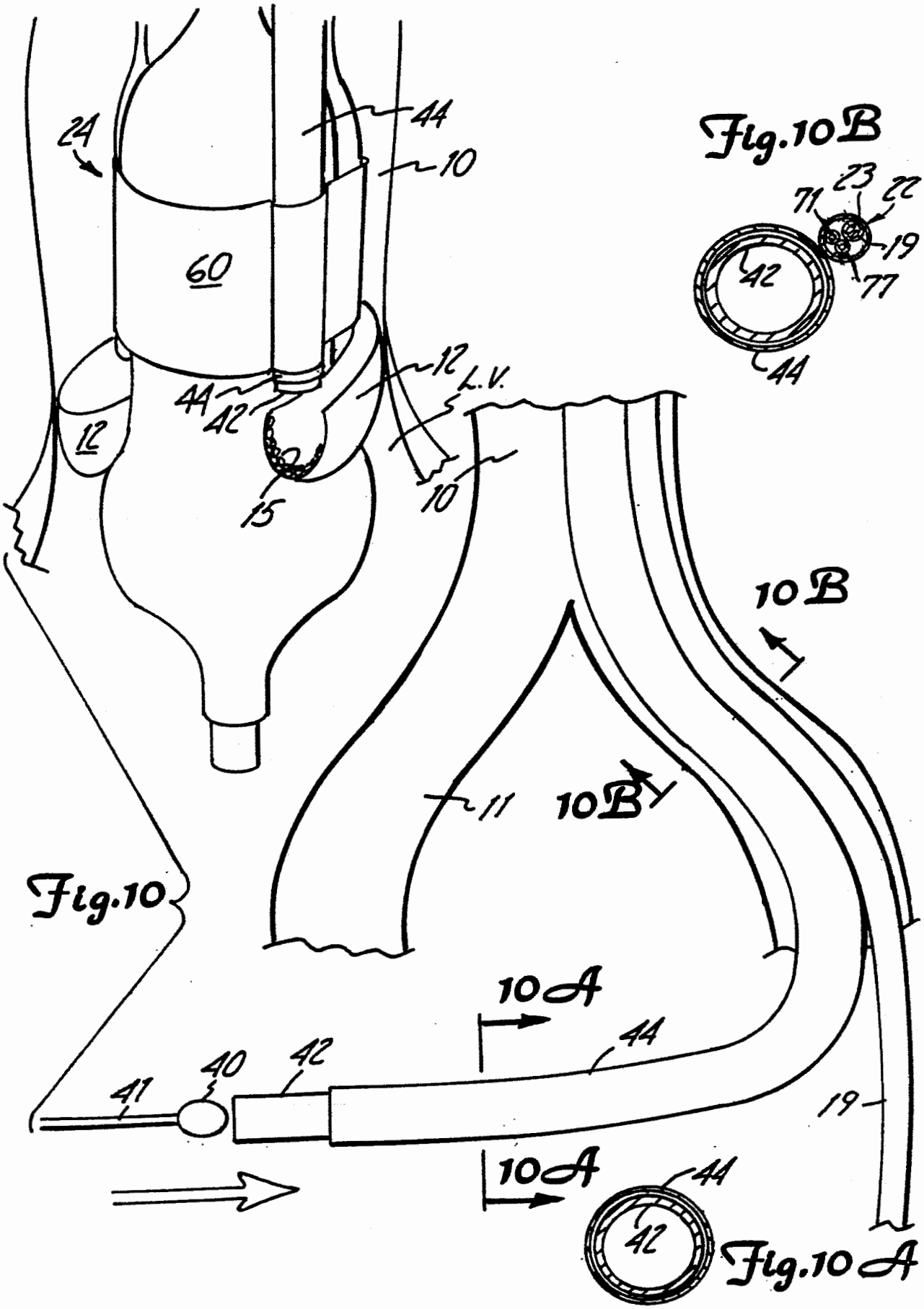
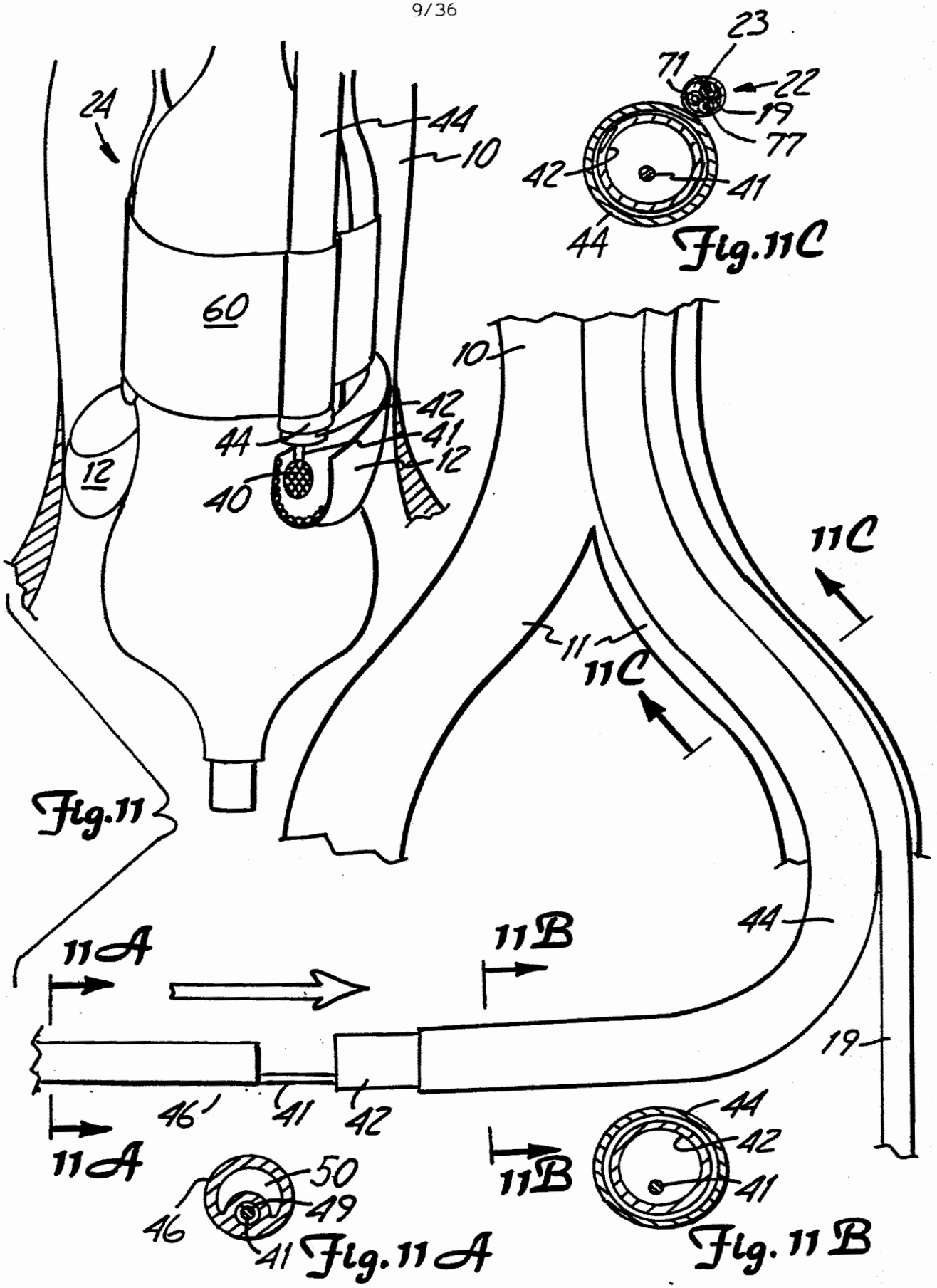


Fig.10

Fig.10B

Fig.10A



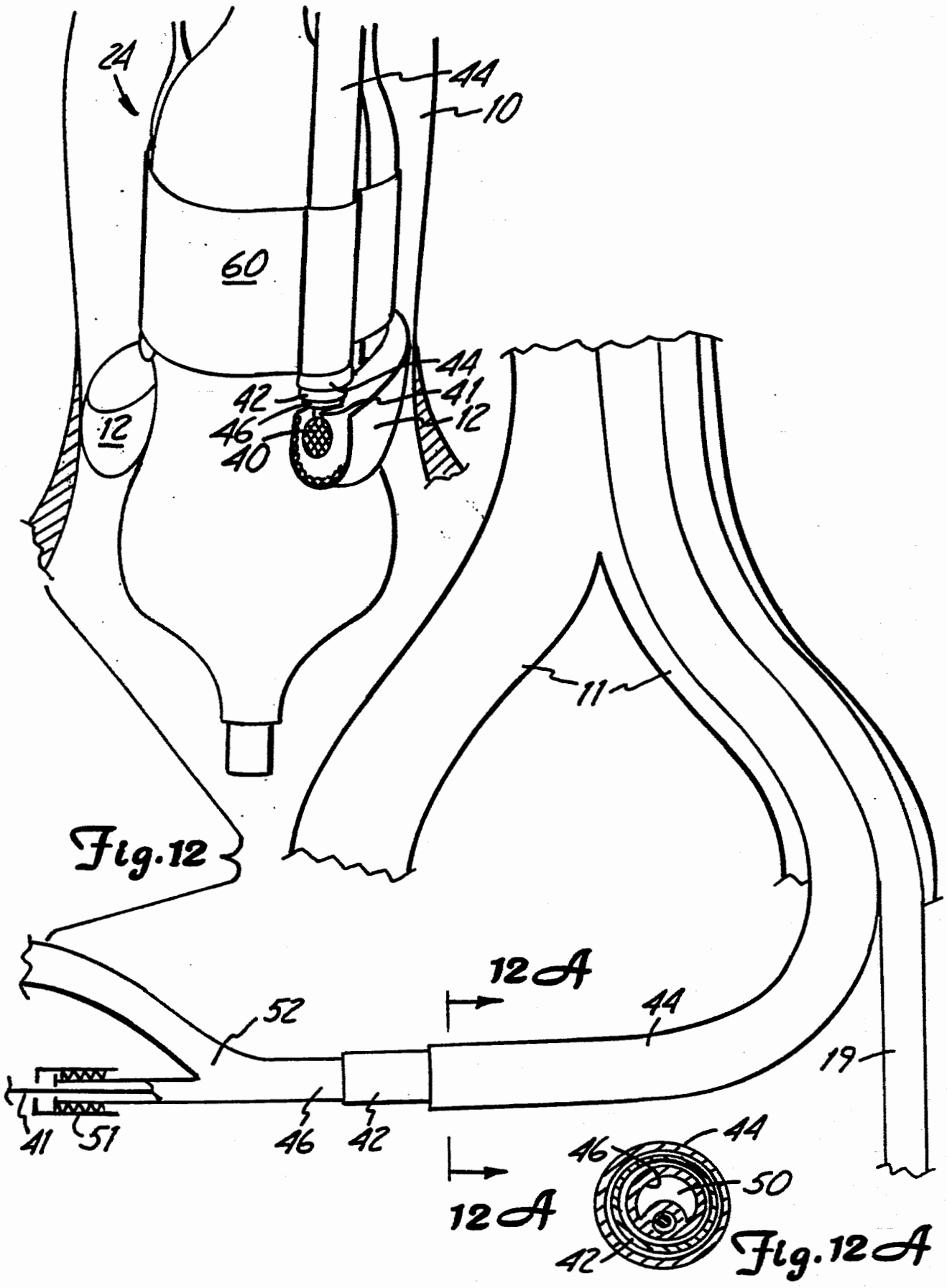
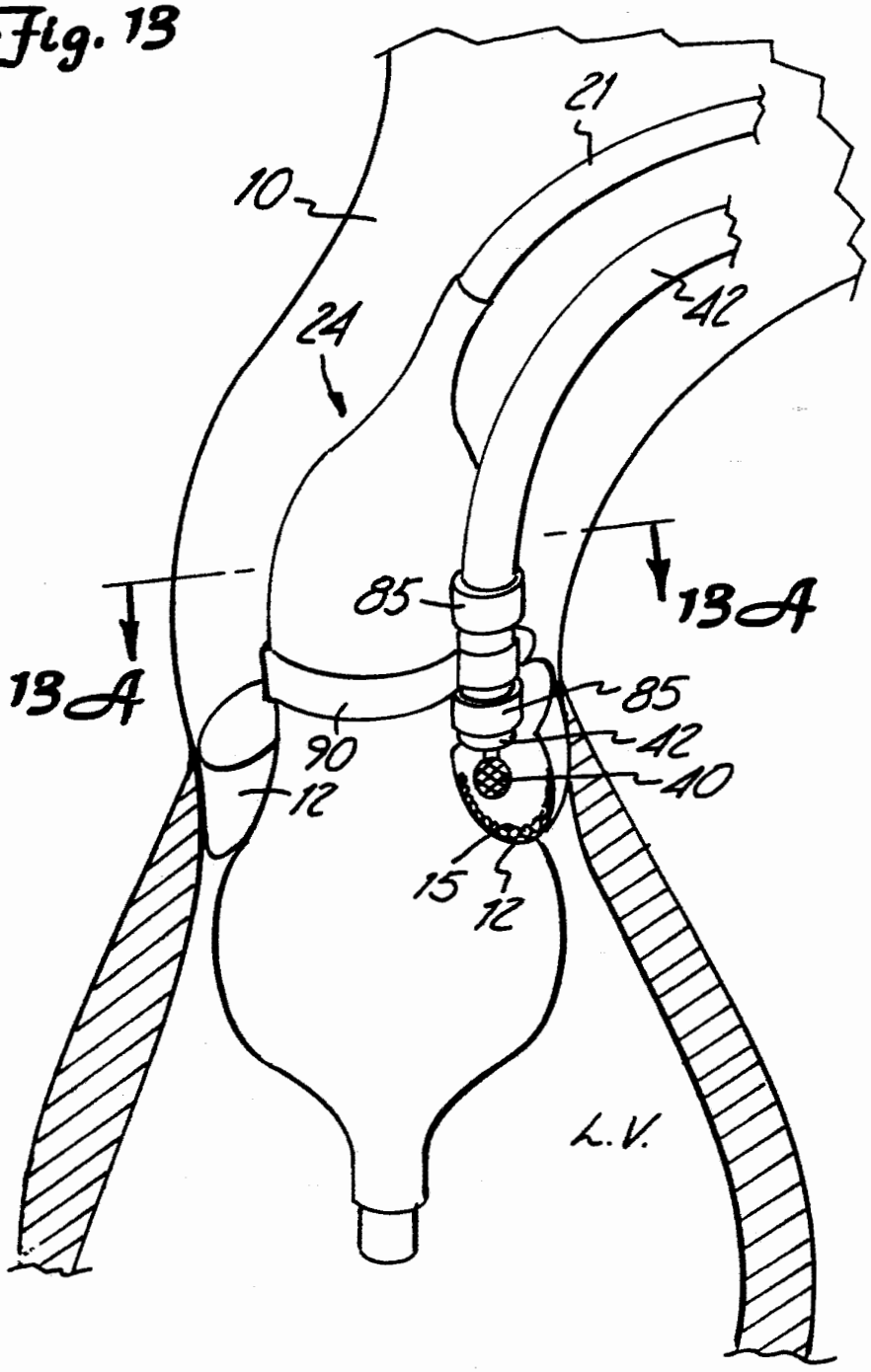


Fig. 12

Fig. 12A

Fig. 13



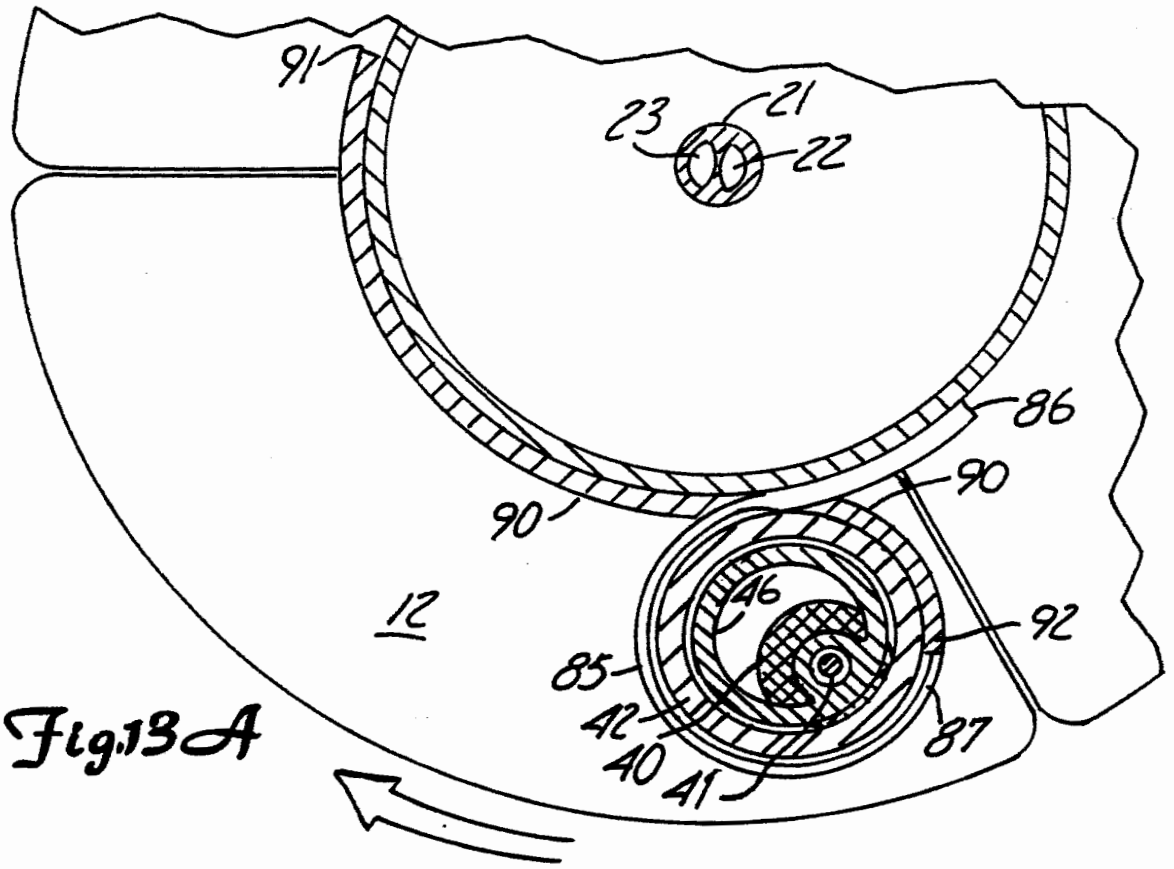


Fig. 13A

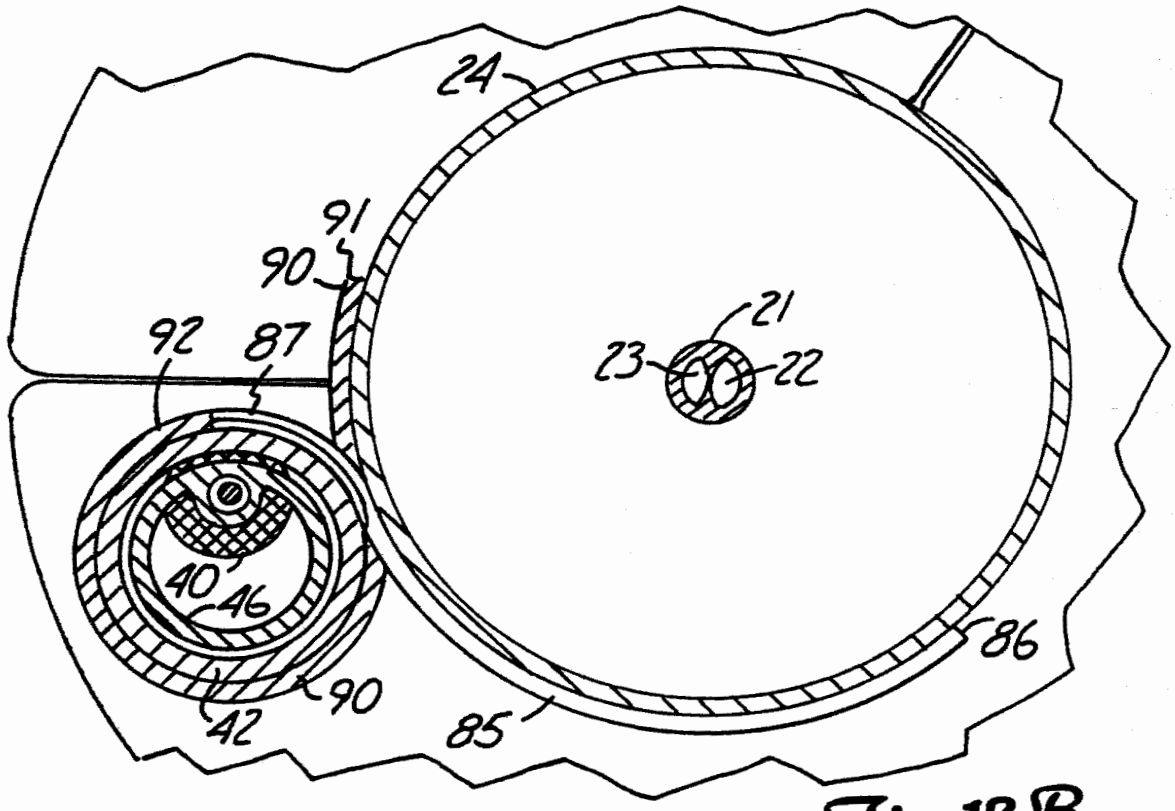
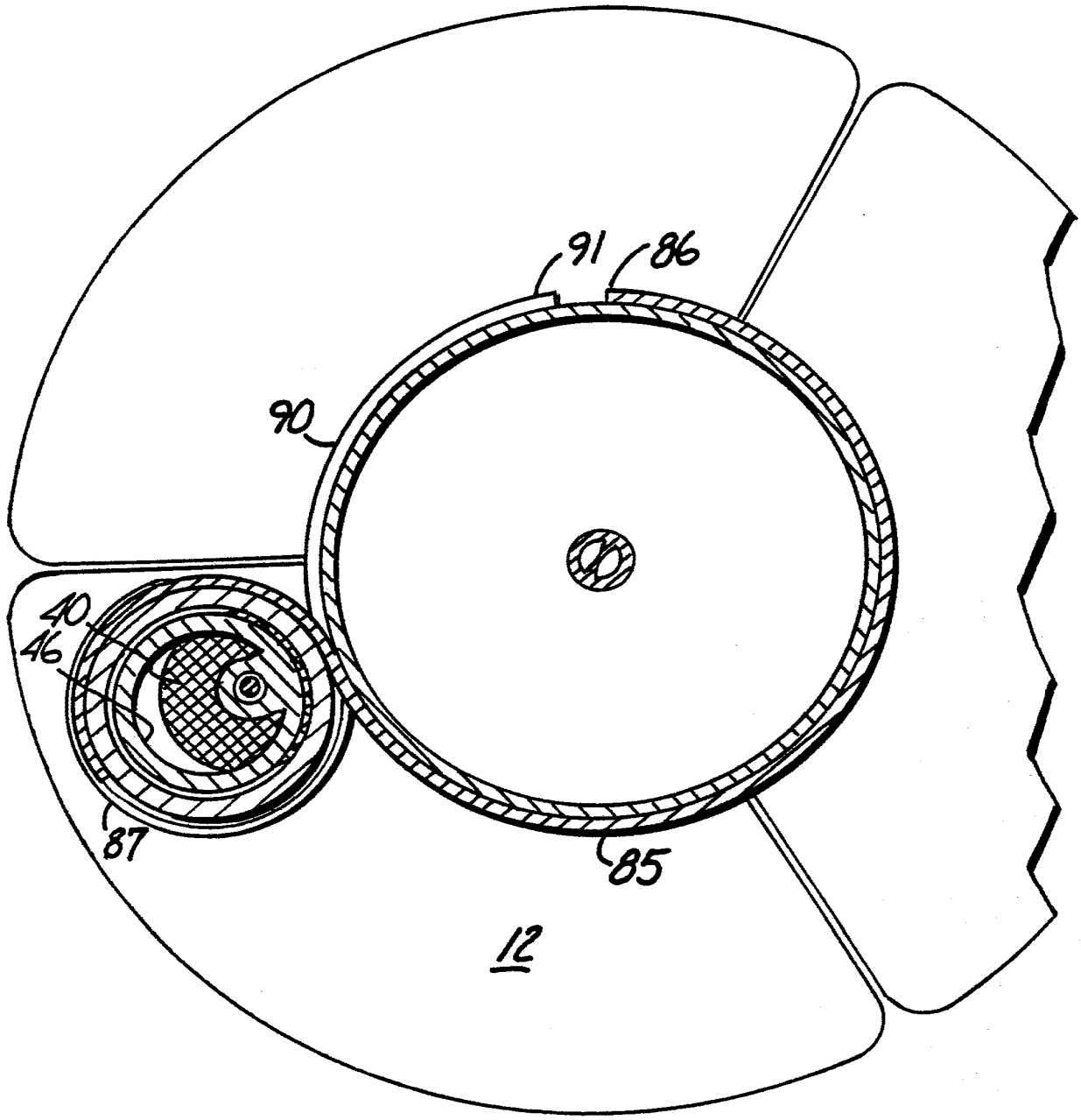


Fig. 13B

Fig. 14



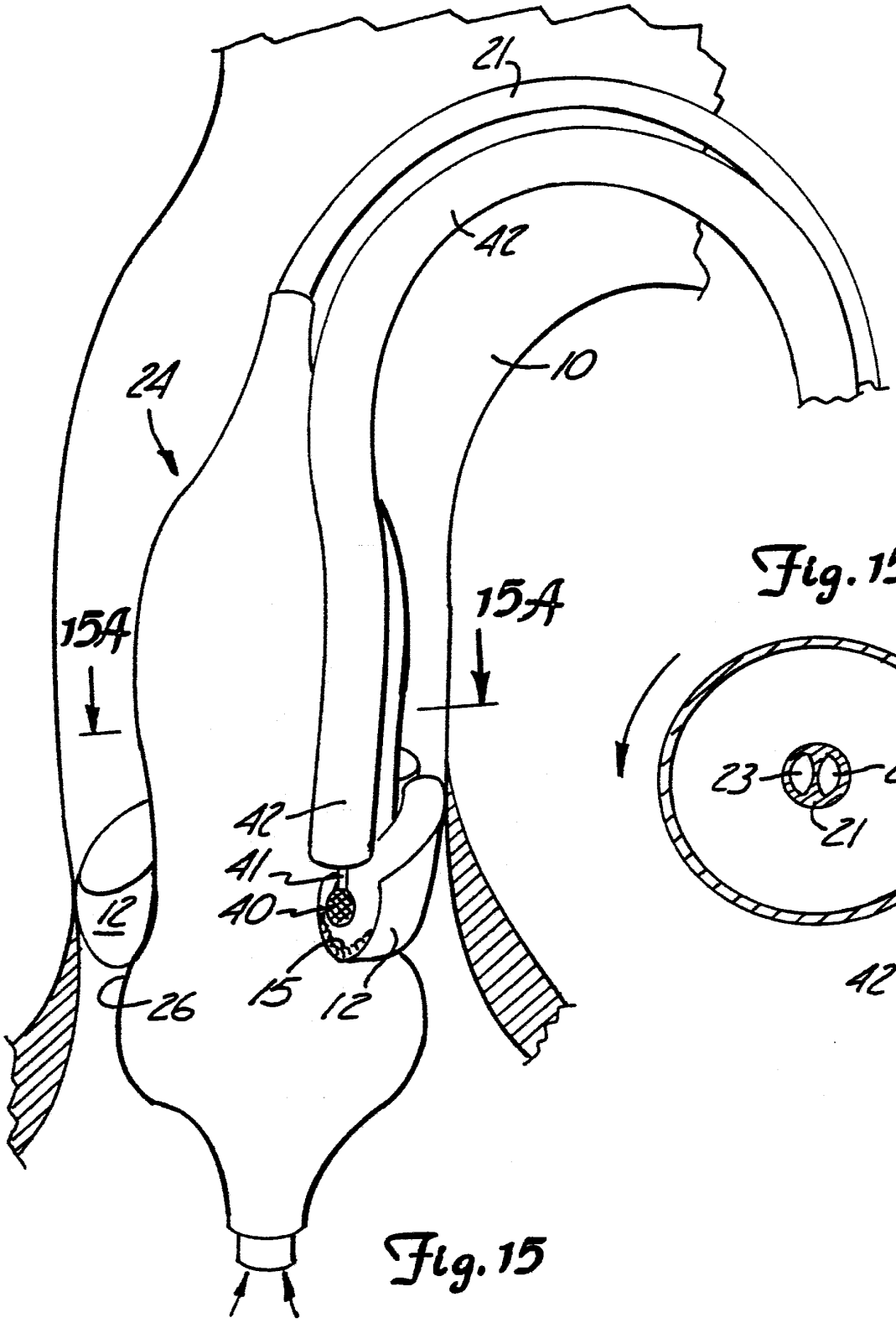


Fig. 15

Fig. 15A

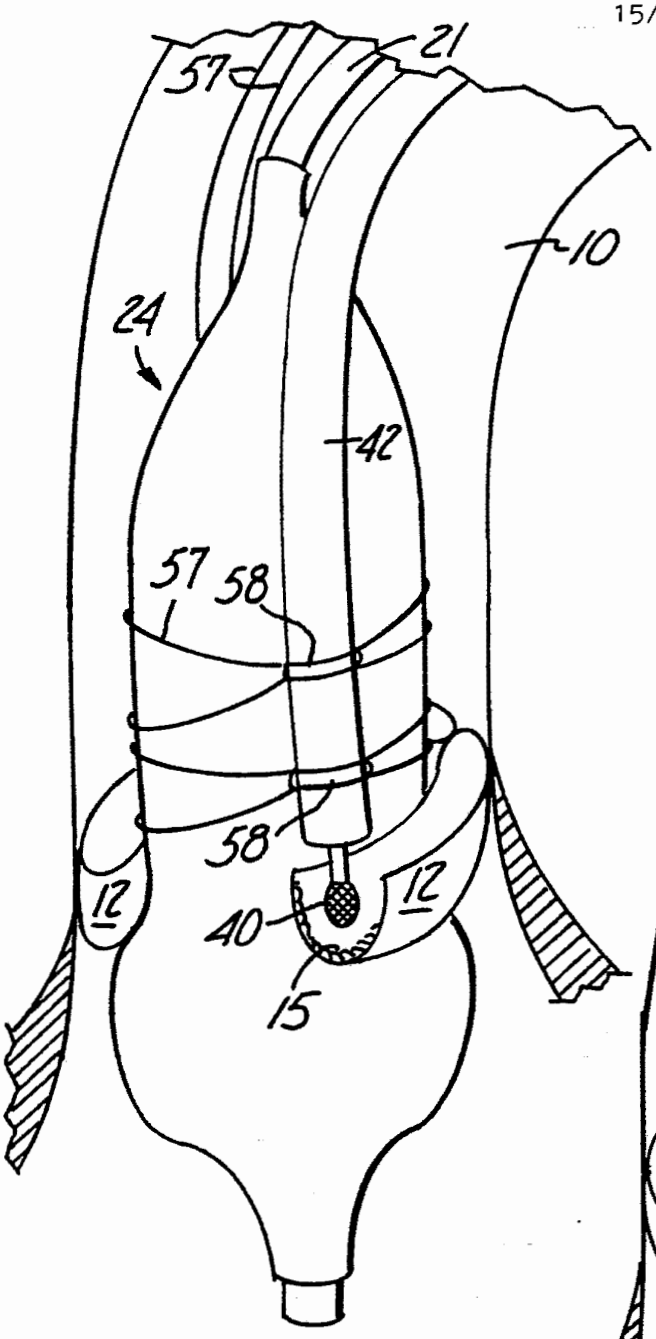


Fig. 16

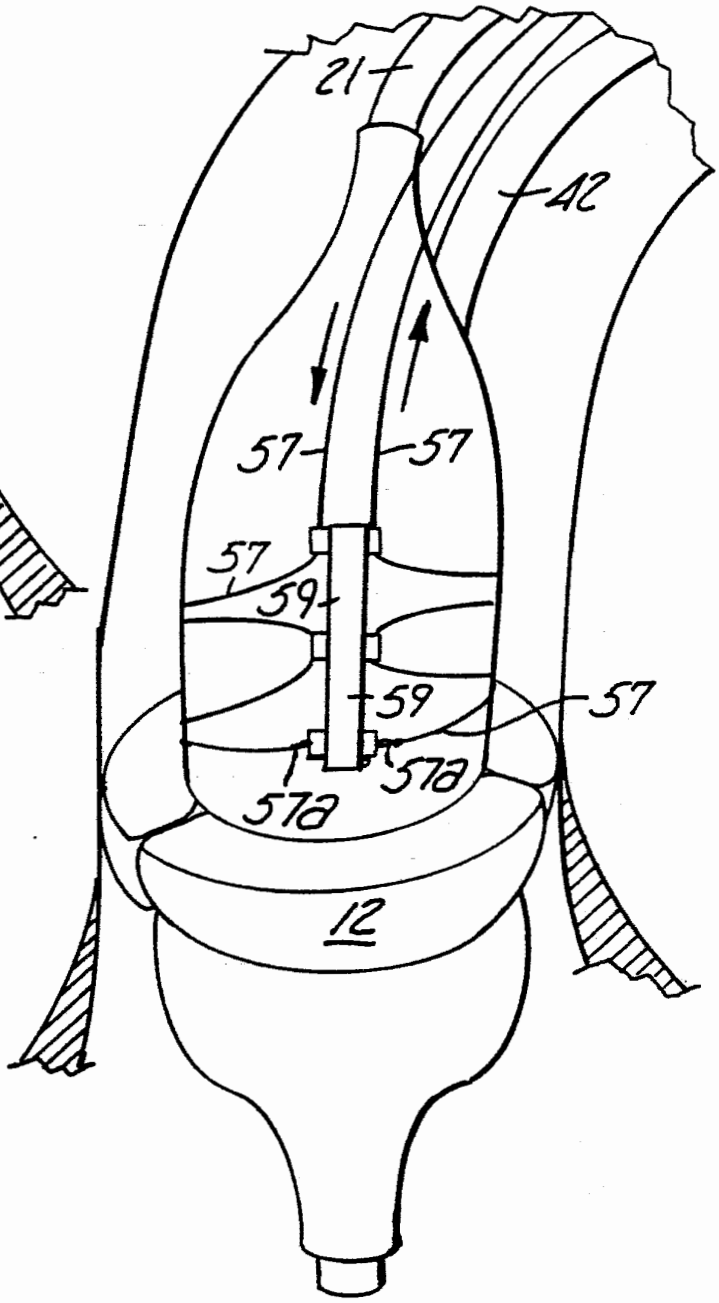


Fig. 16A

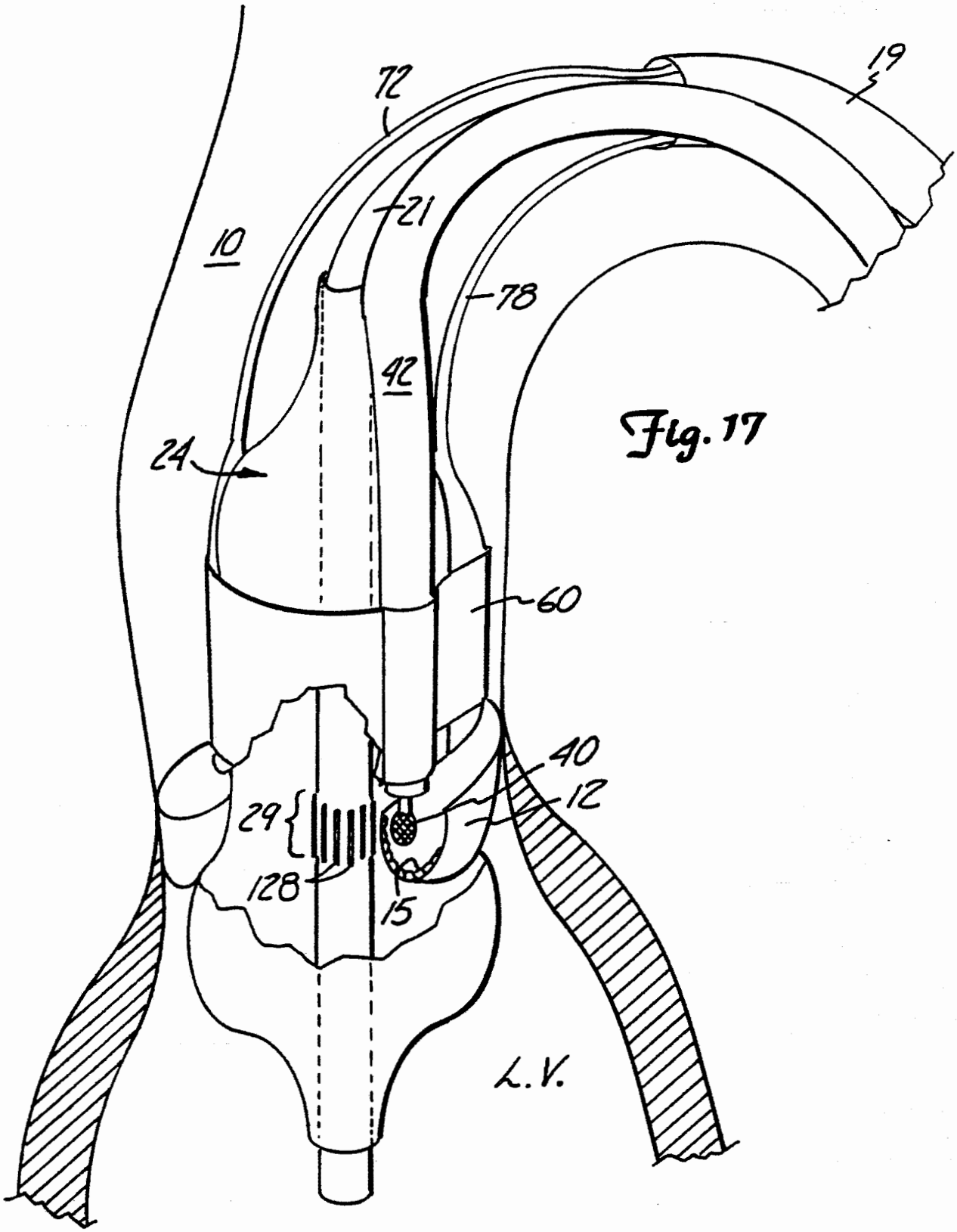


Fig. 17

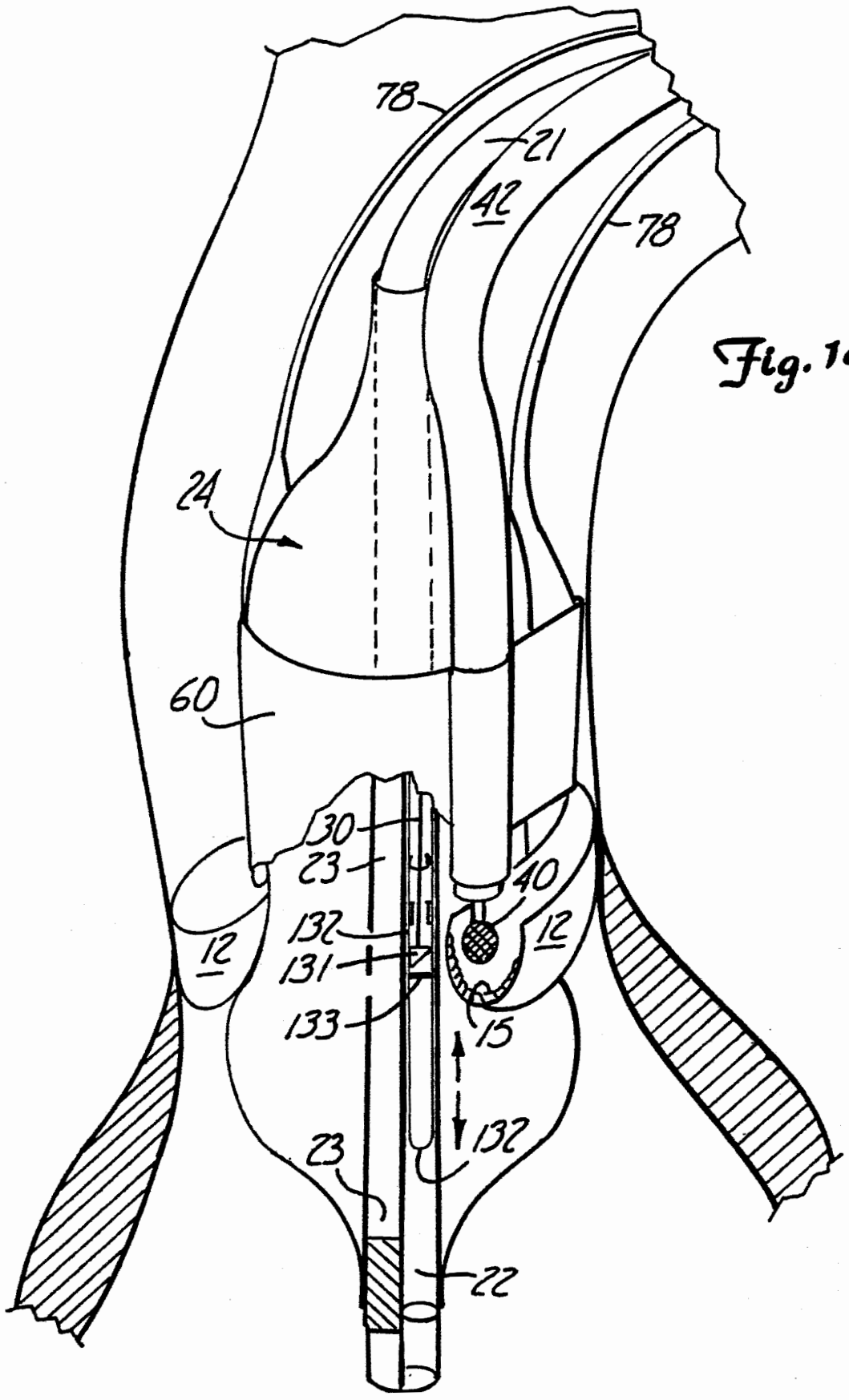
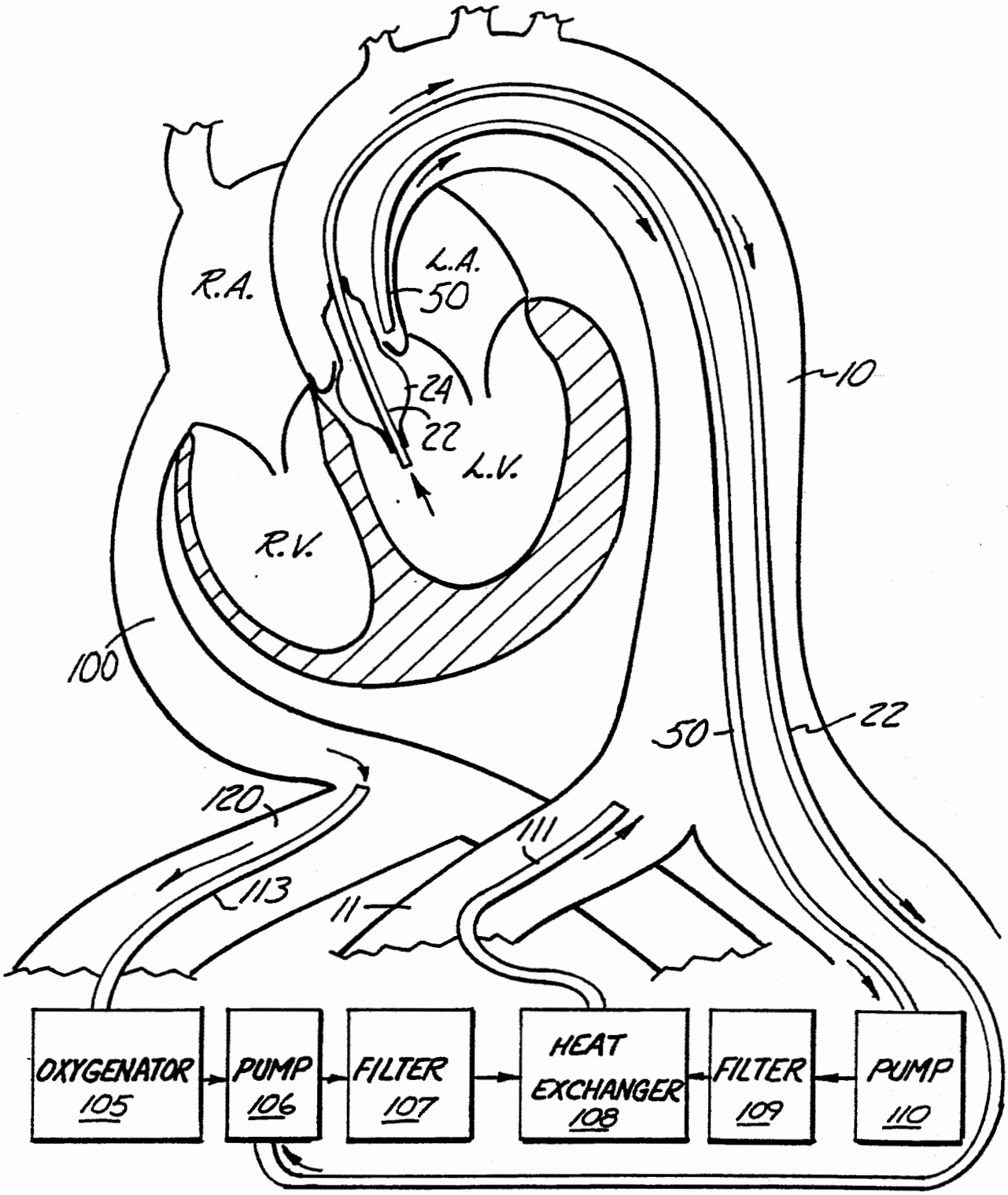


Fig. 18

Fig. 19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FILTER 107
HEAT EXCHANGER 108
FILTER 109
PUMP 110

Fig. 20

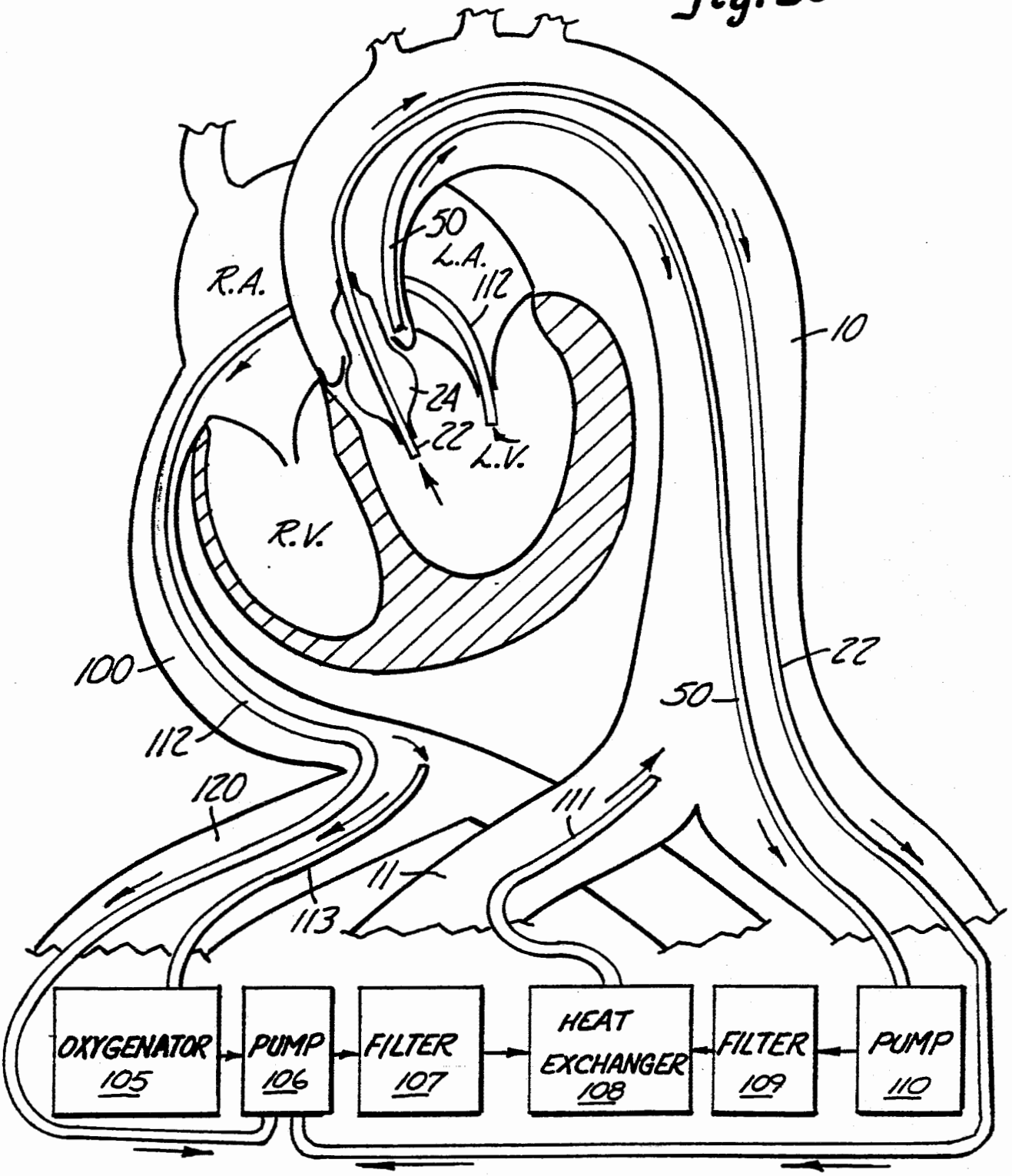
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Fig. 21

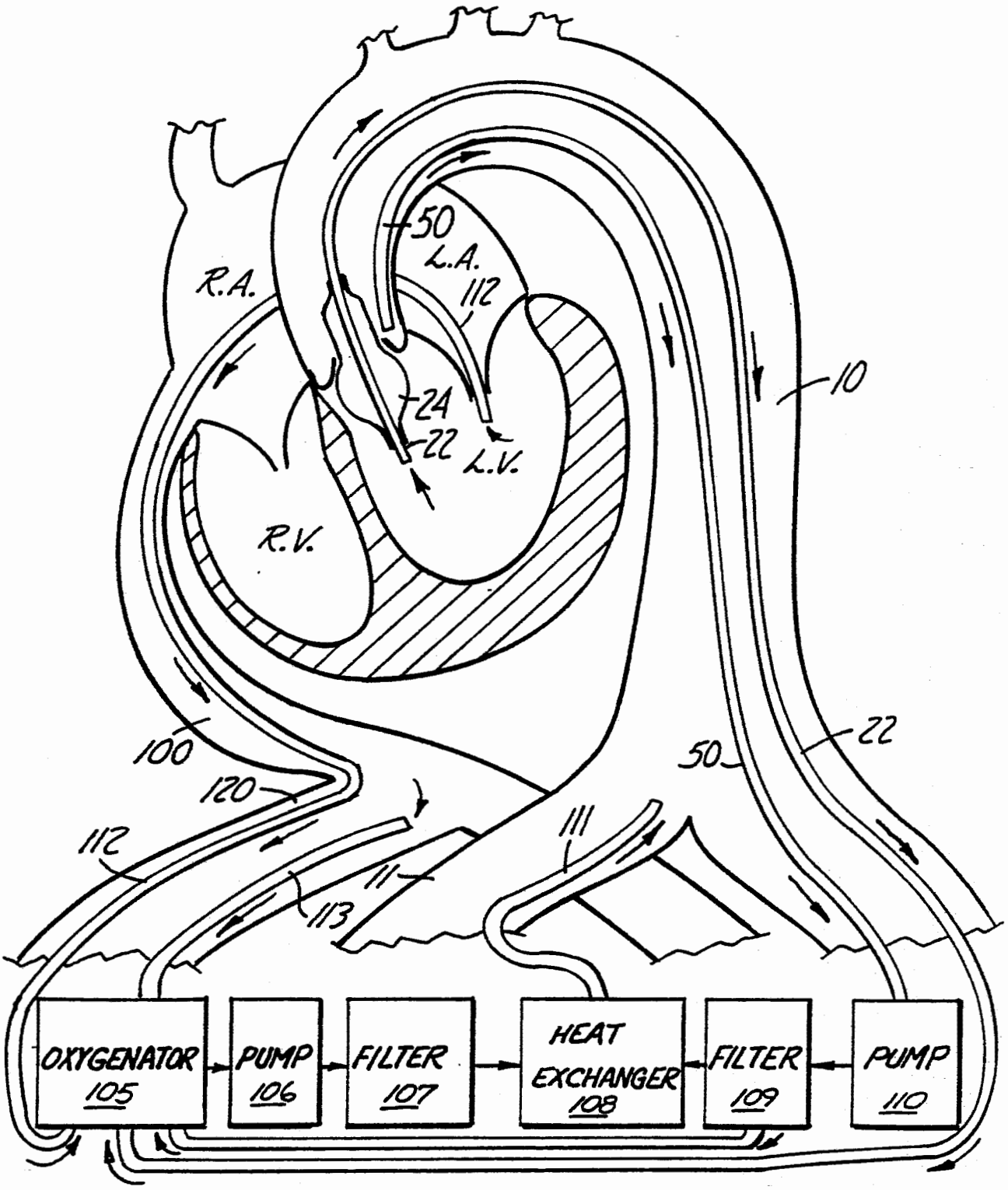
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Fig. 22

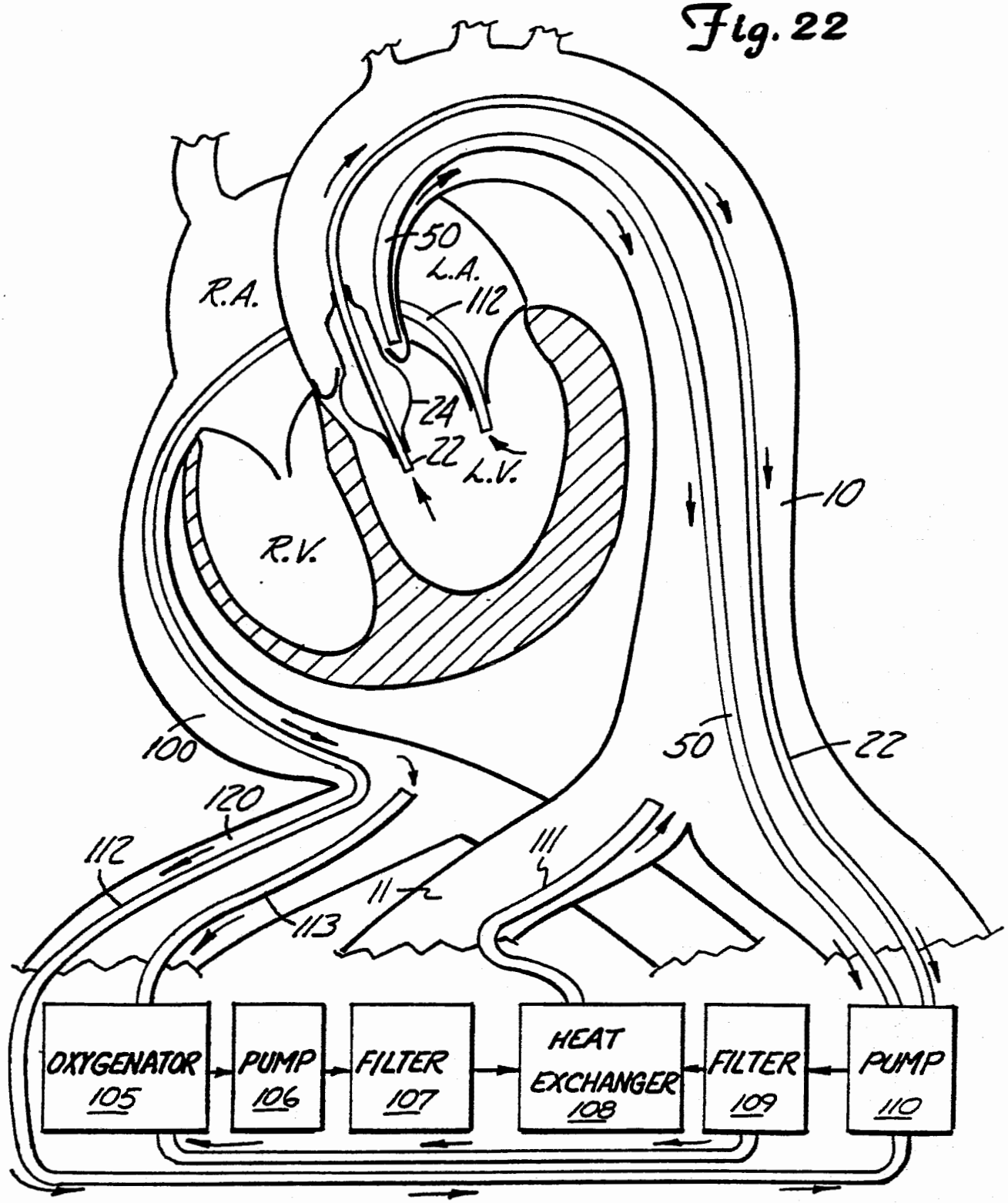
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Fig. 23

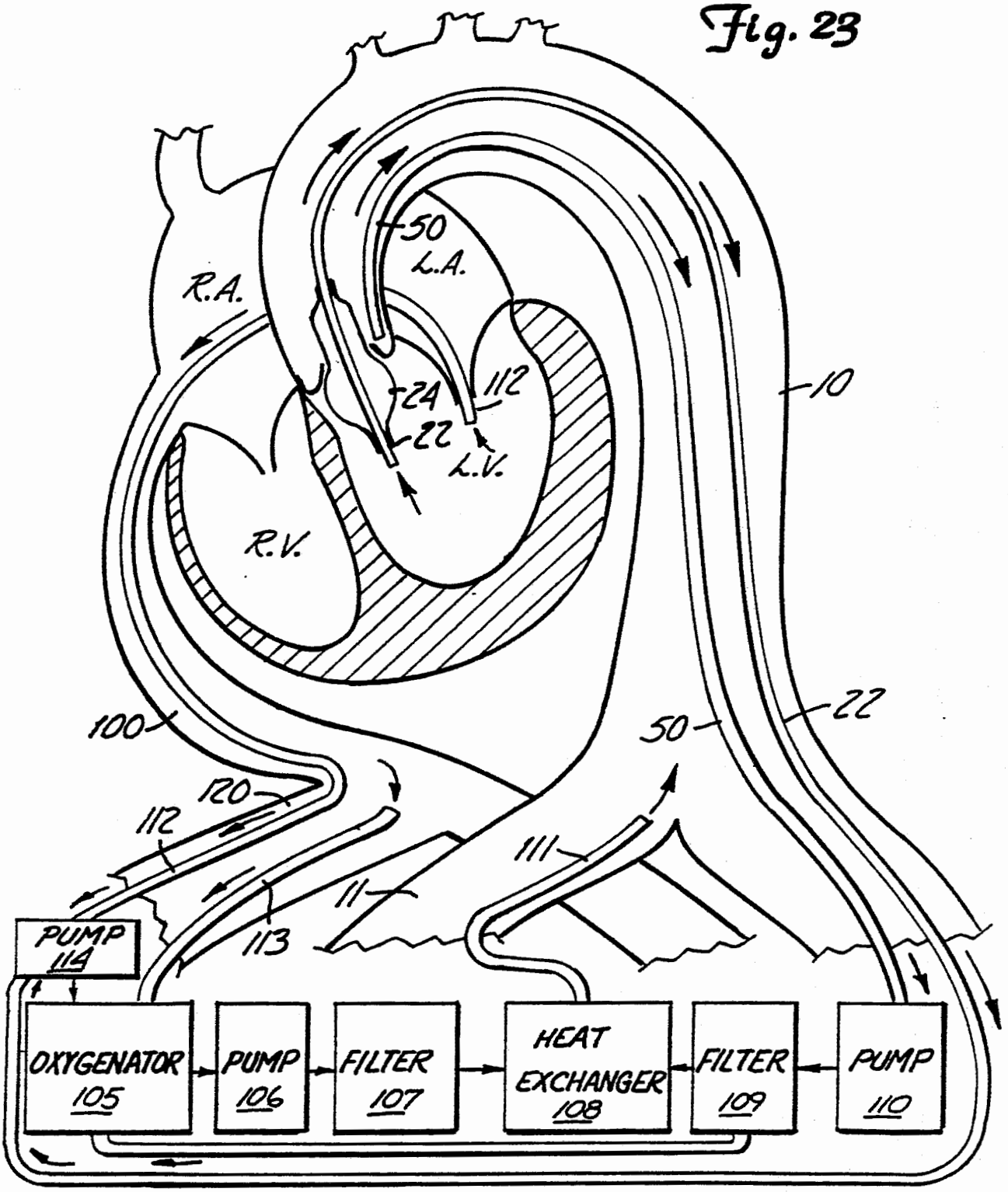
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Fig.24

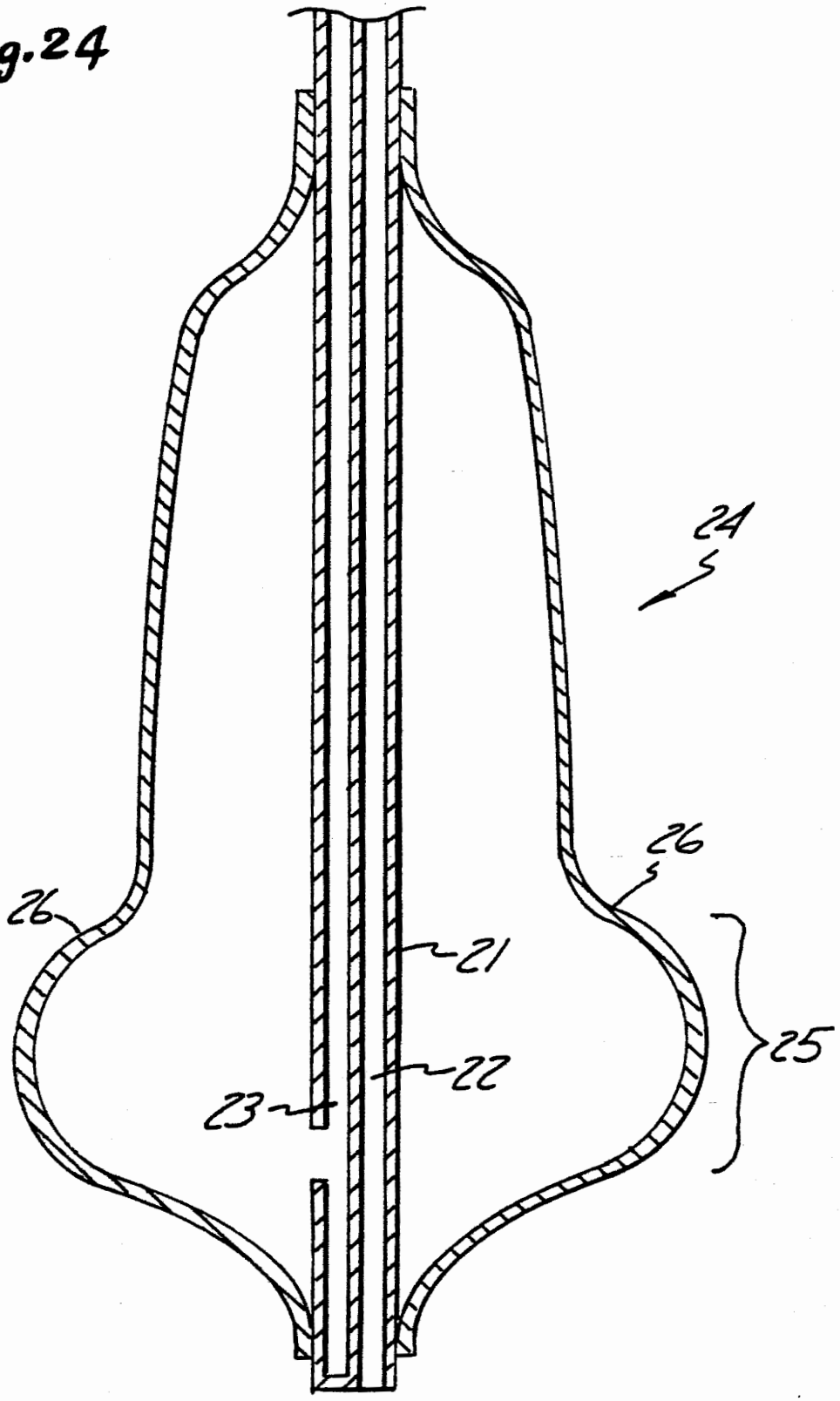


Fig. 25

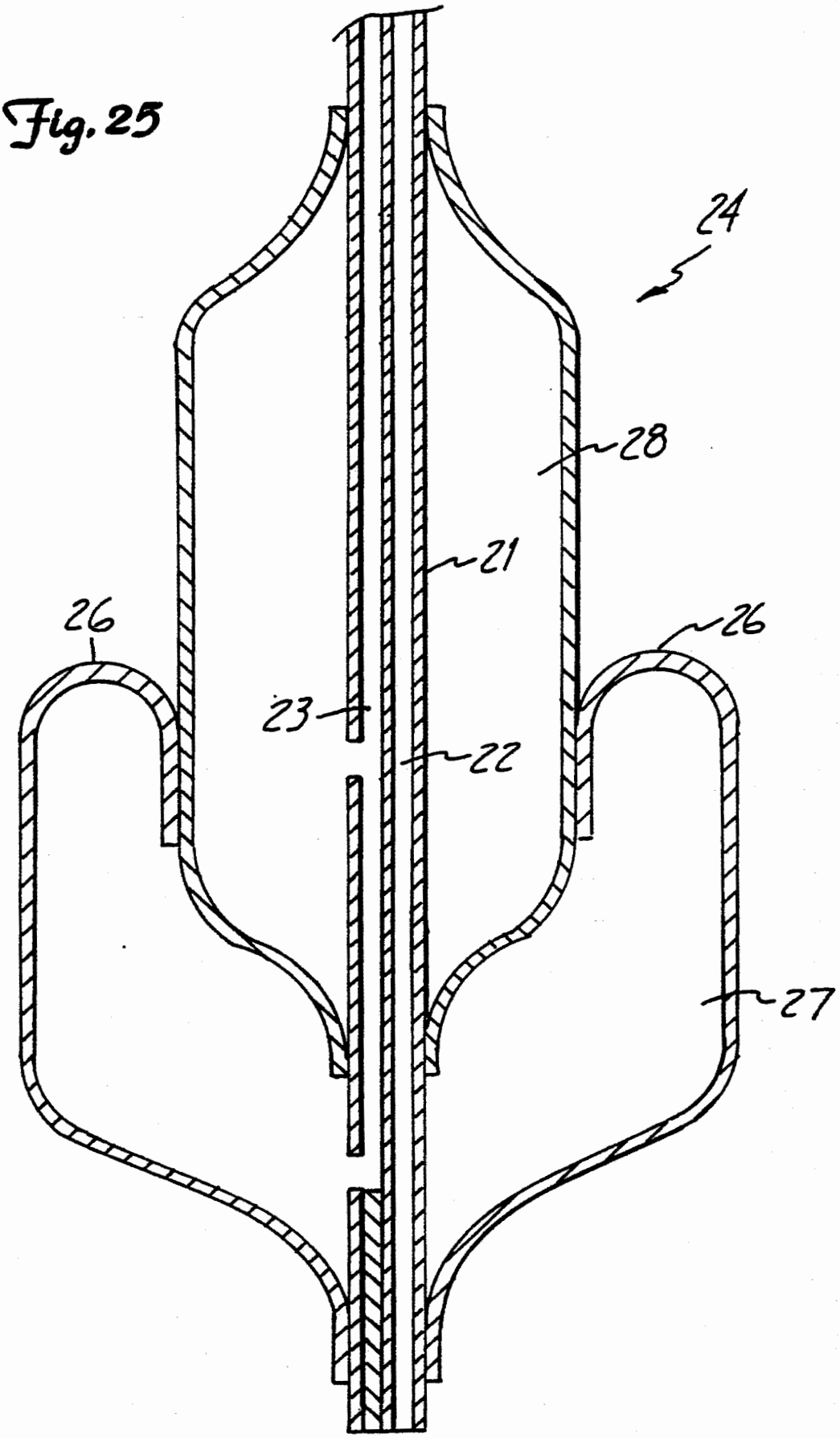


Fig.26

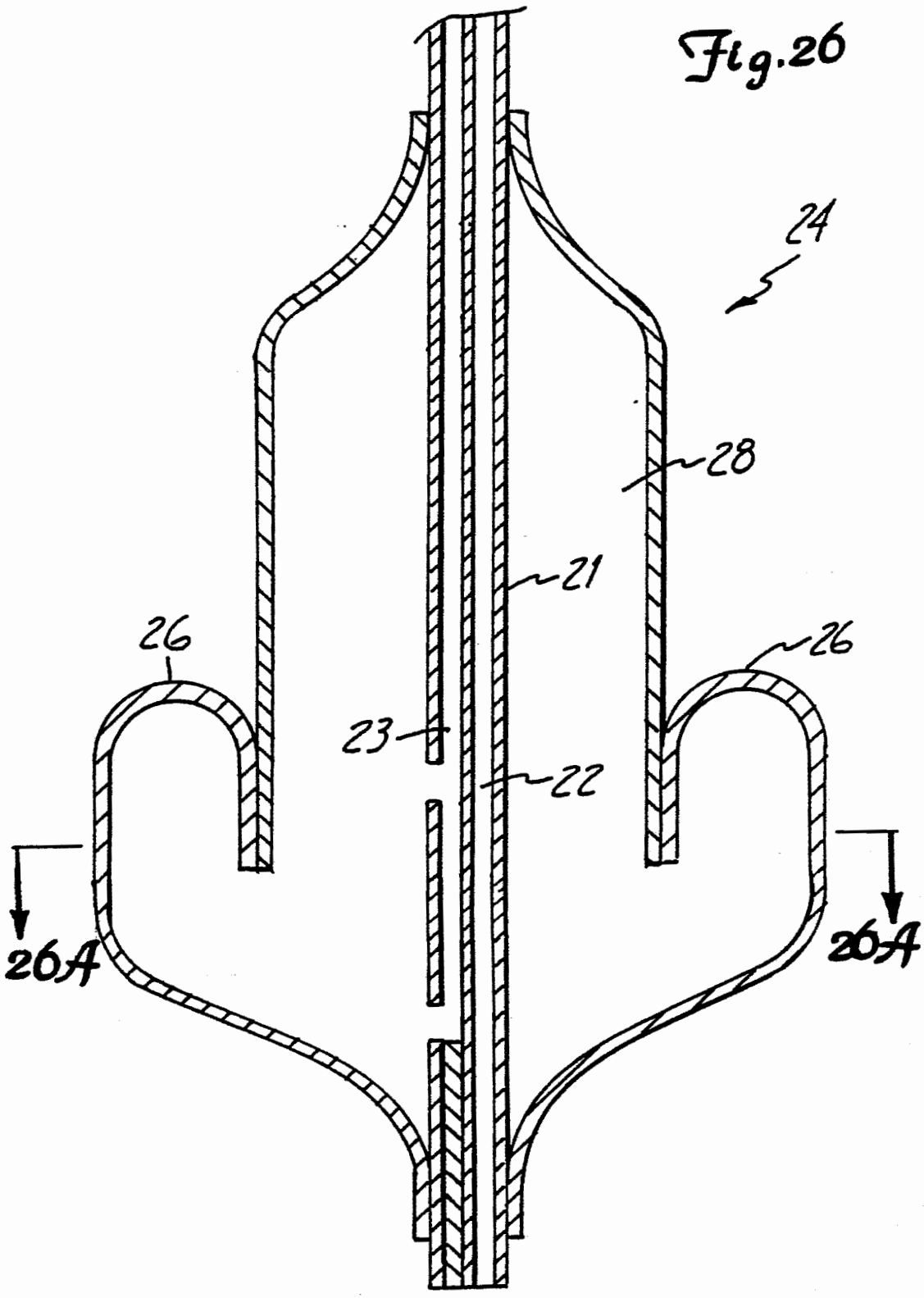
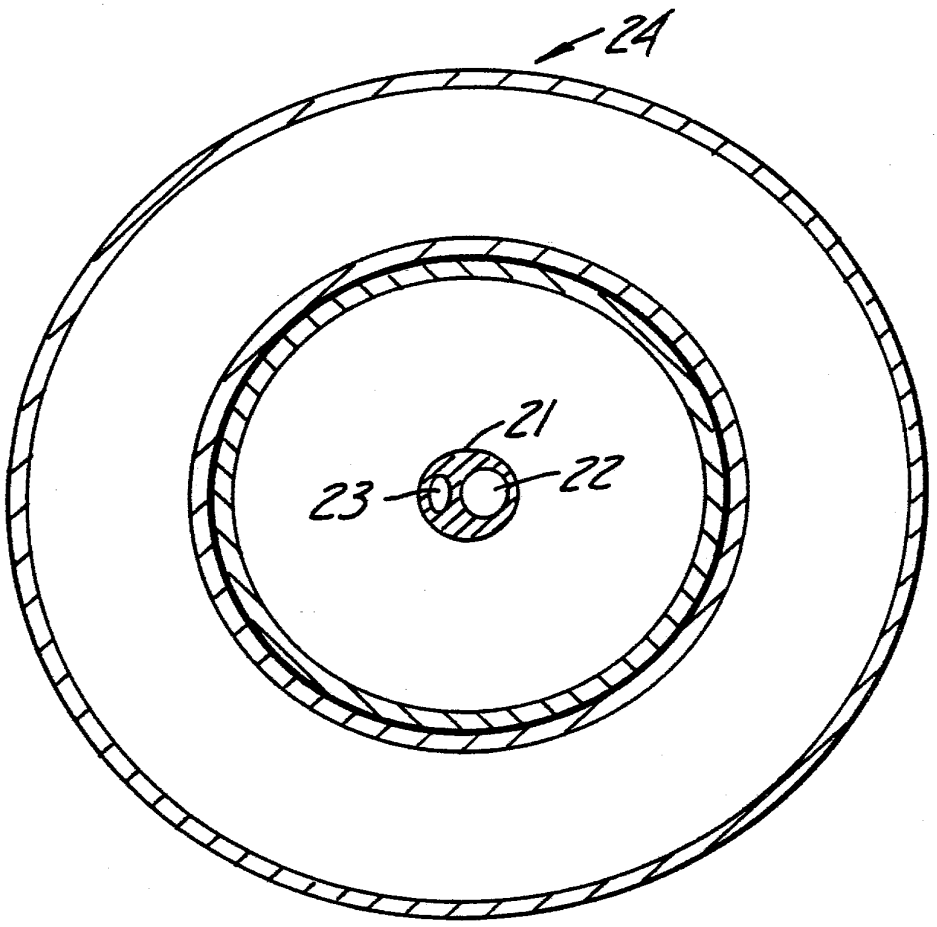


Fig. 26A



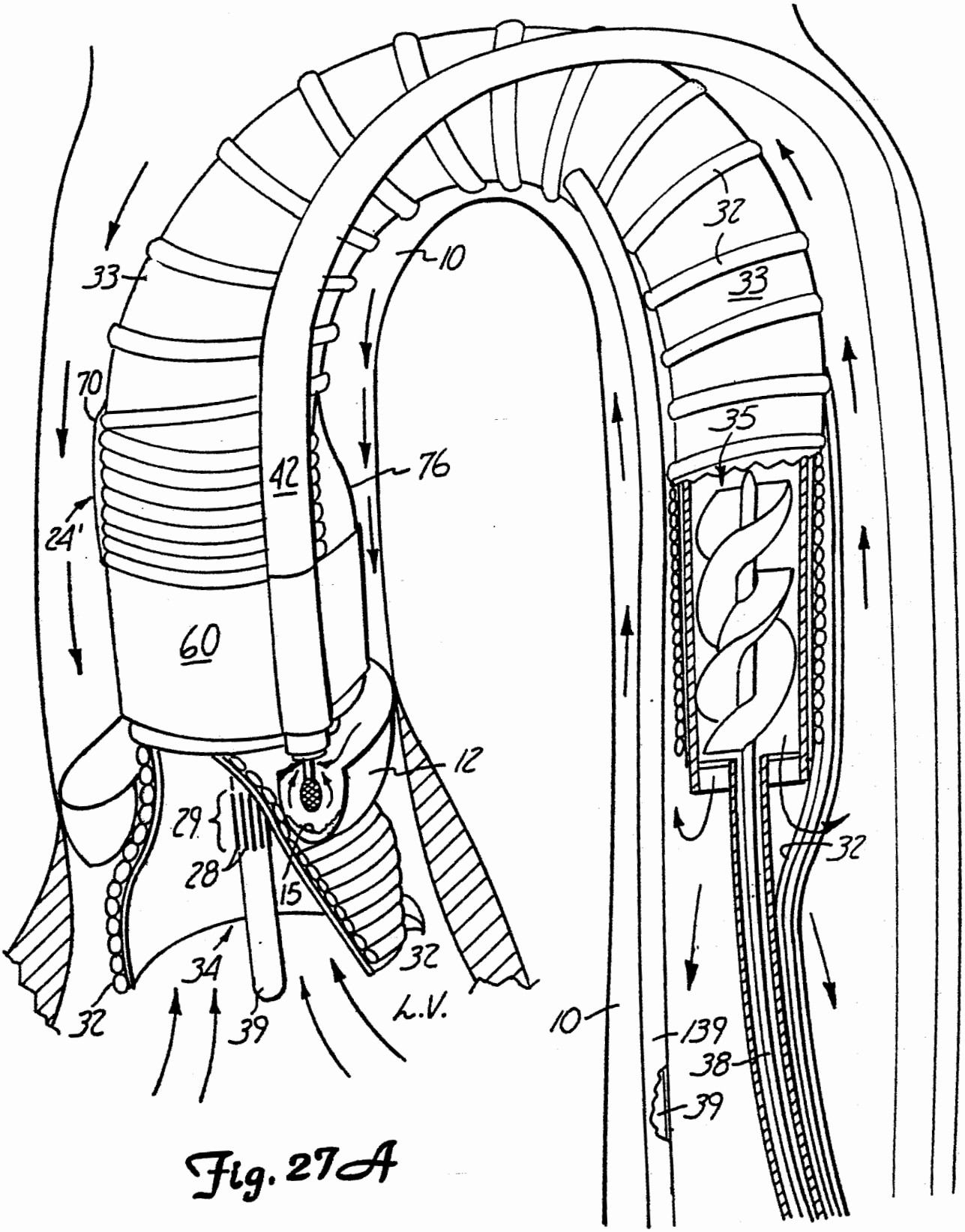
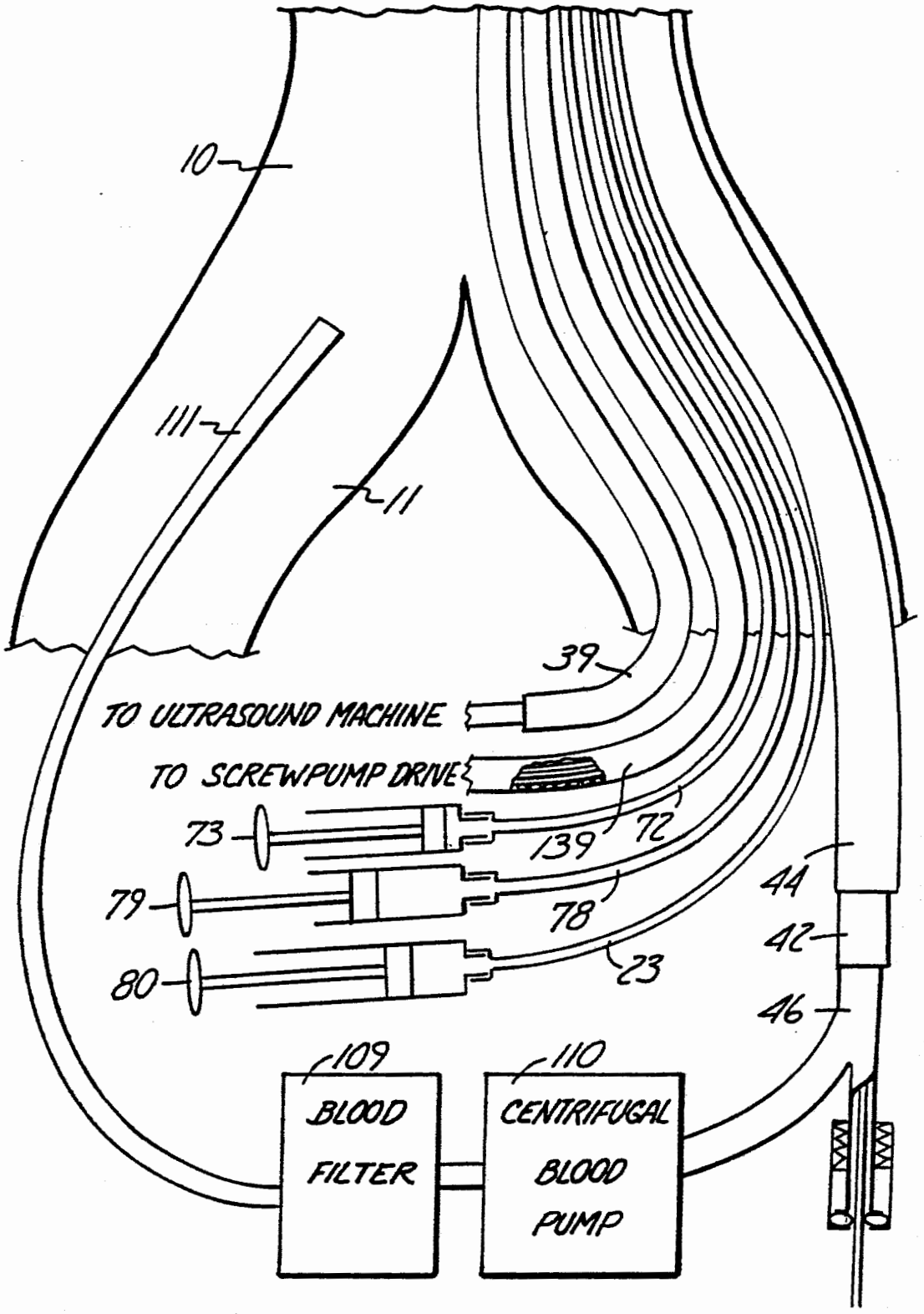


Fig. 27A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111
11
39
TO ULTRASOUND MACHINE
TO SCREWPUMP DRIVE
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46
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BLOOD FILTER
CENTRIFUGAL BLOOD PUMP

Fig. 27B

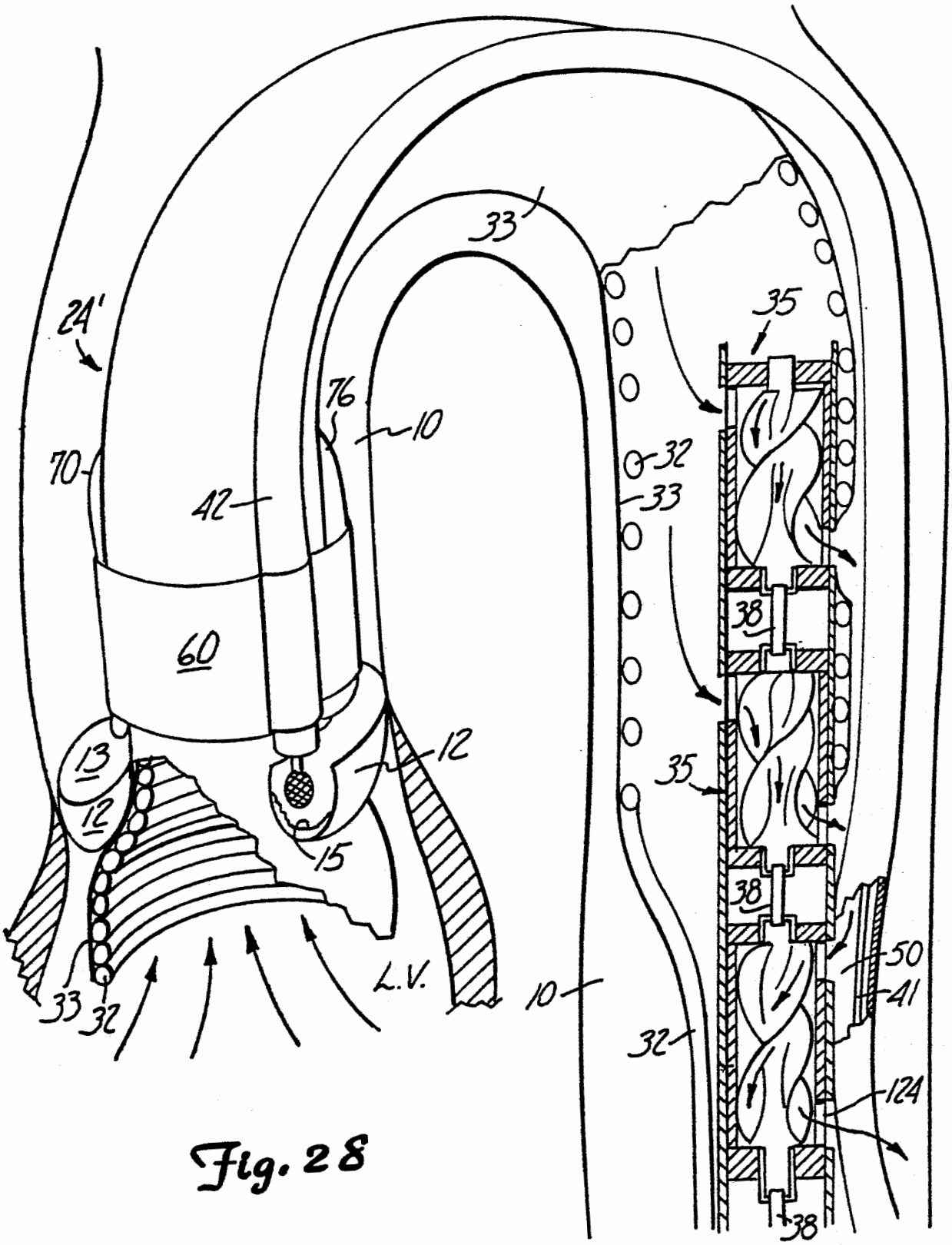
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Fig. 28

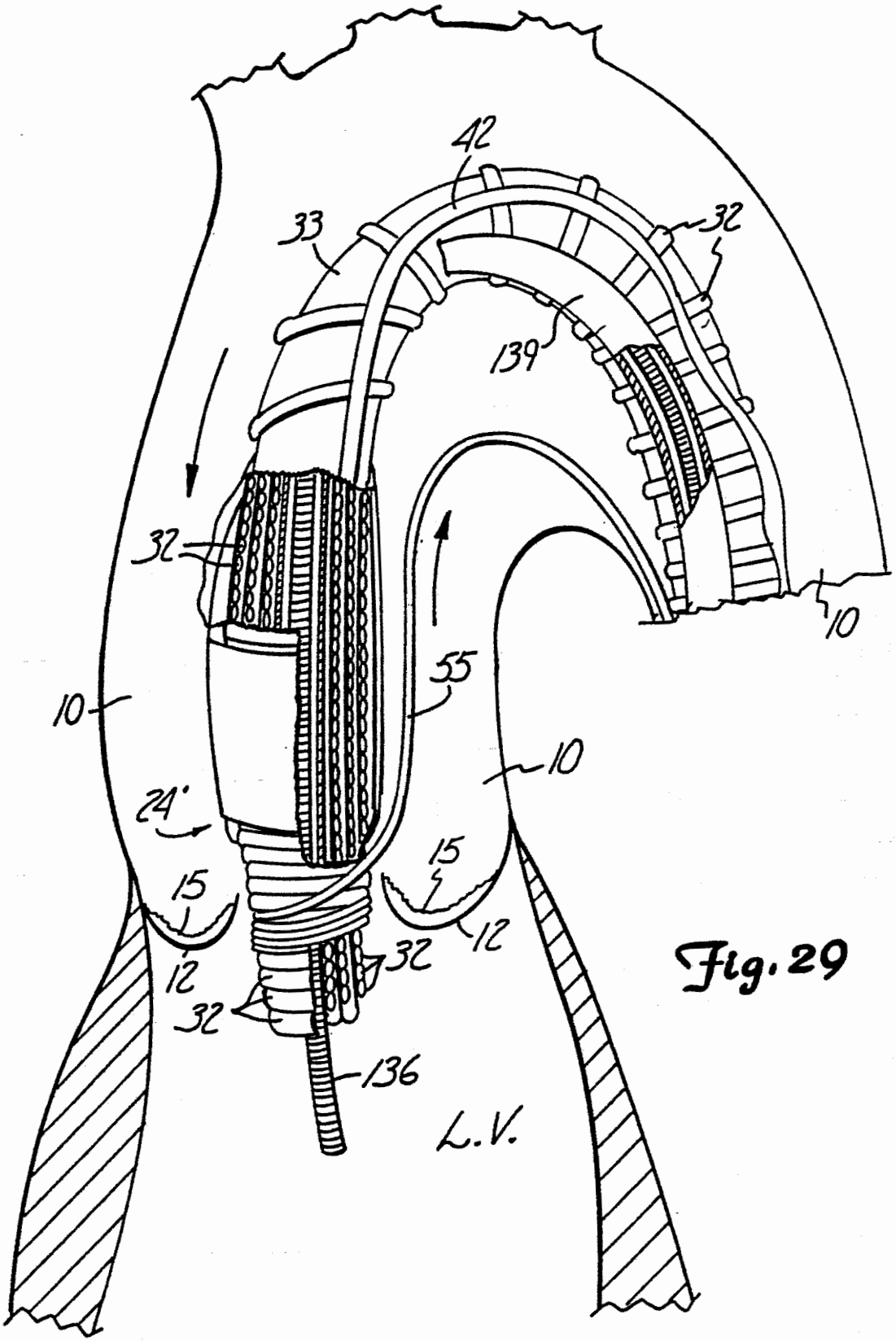


Fig. 29

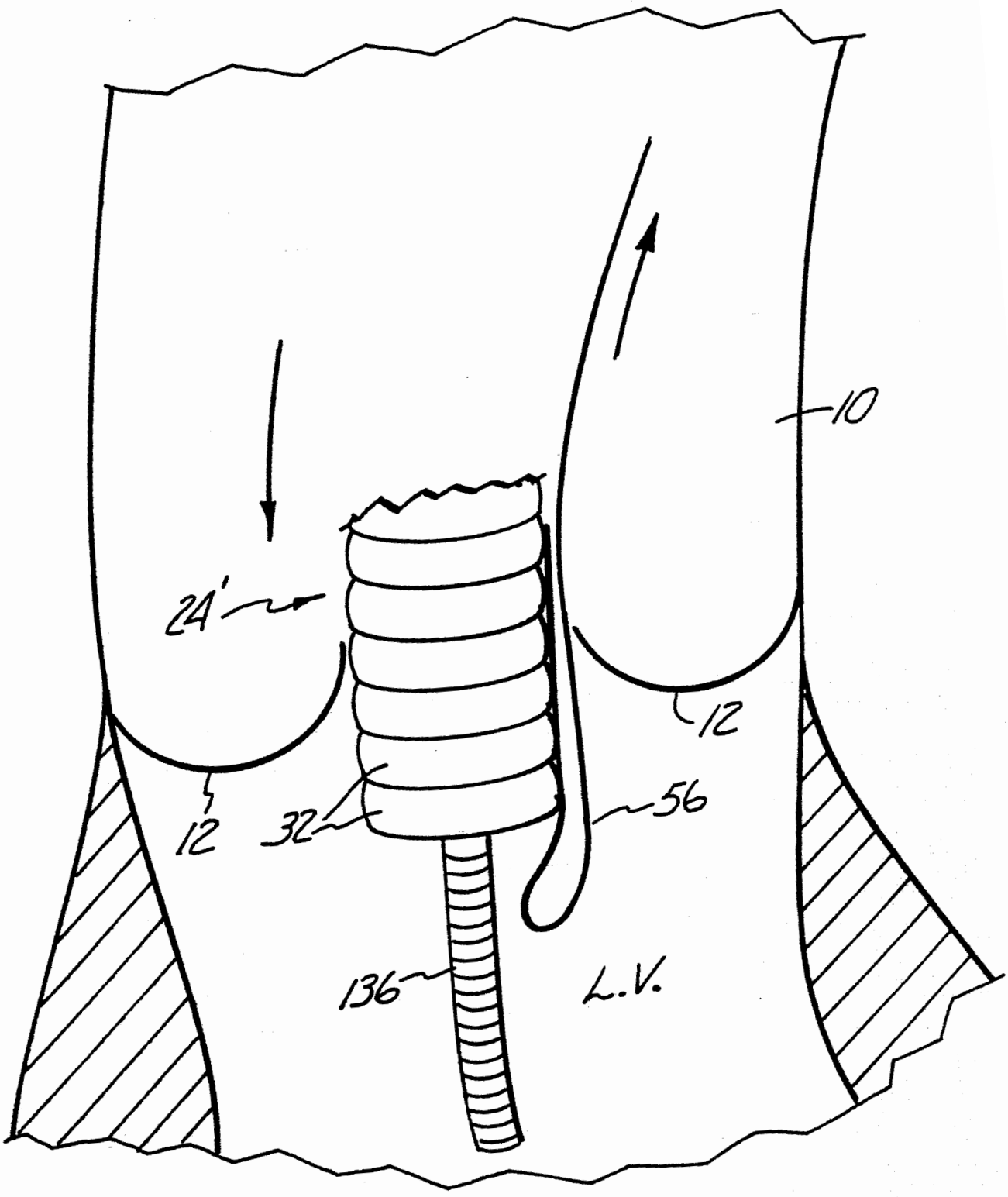
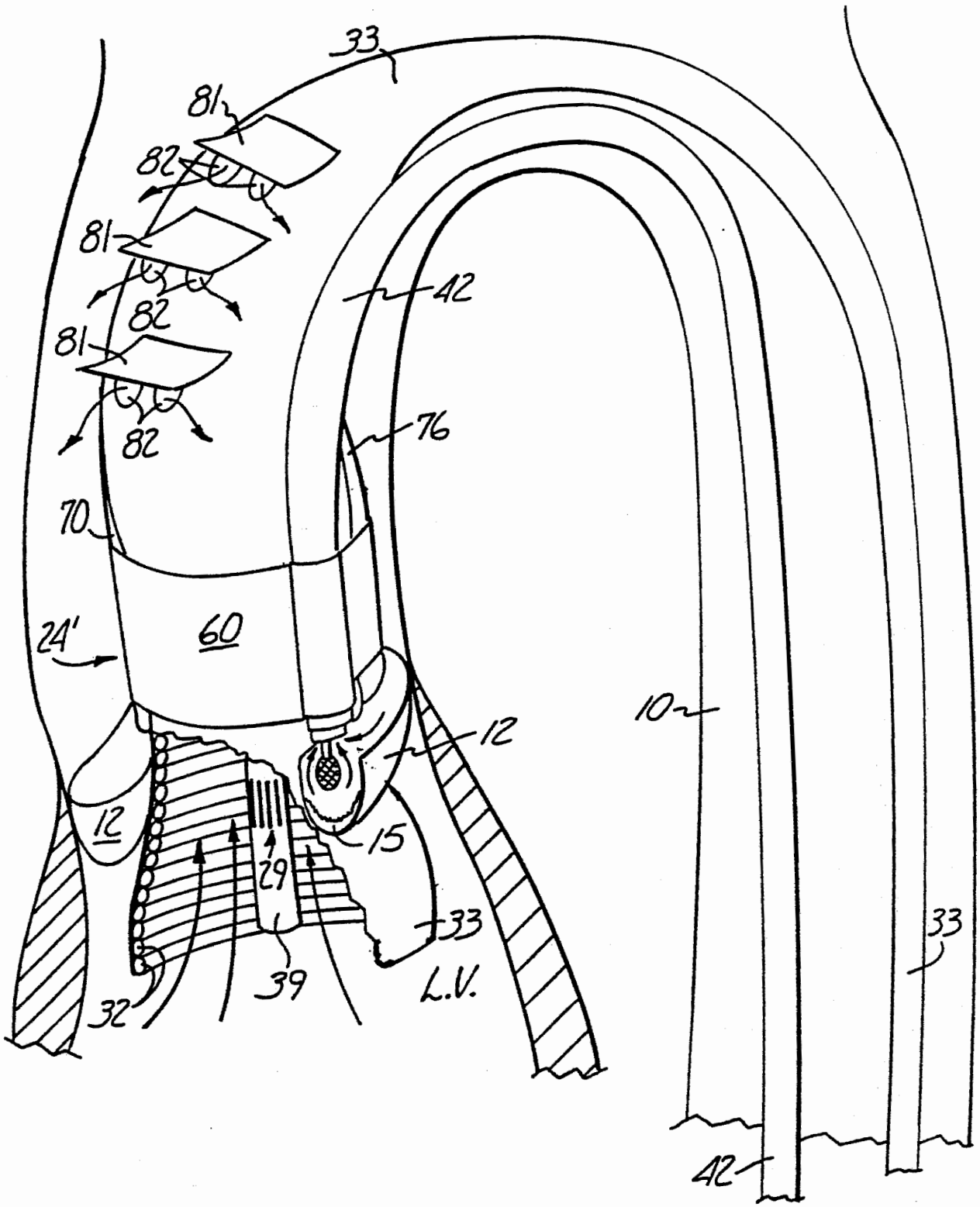


Fig.30

Fig. 31



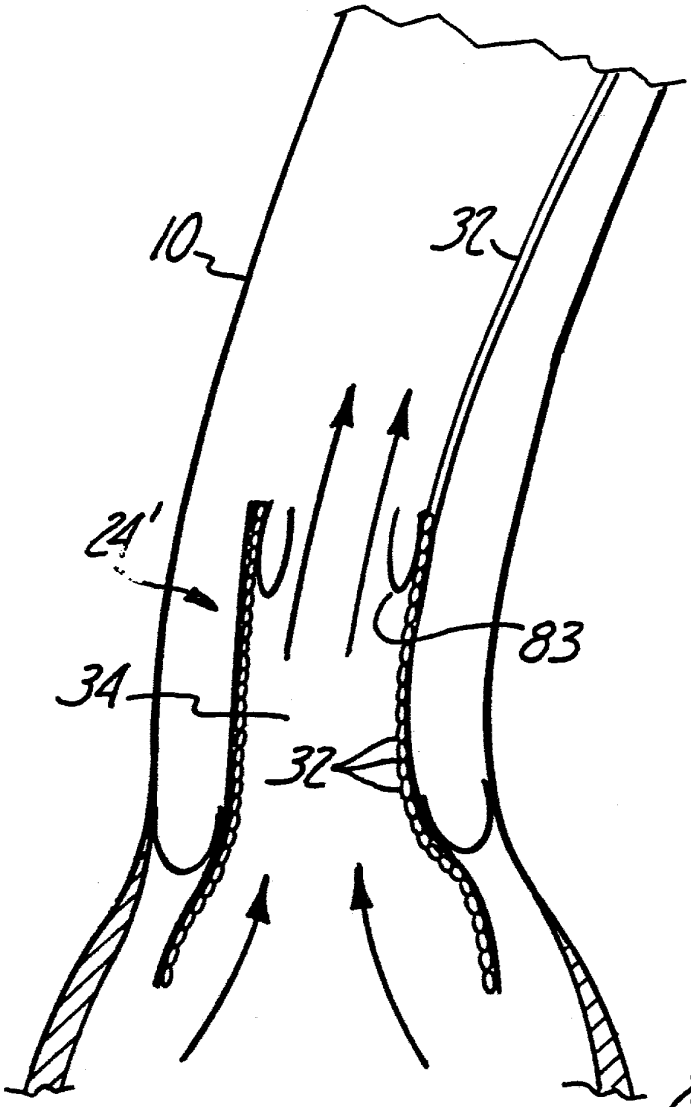


Fig. 32A

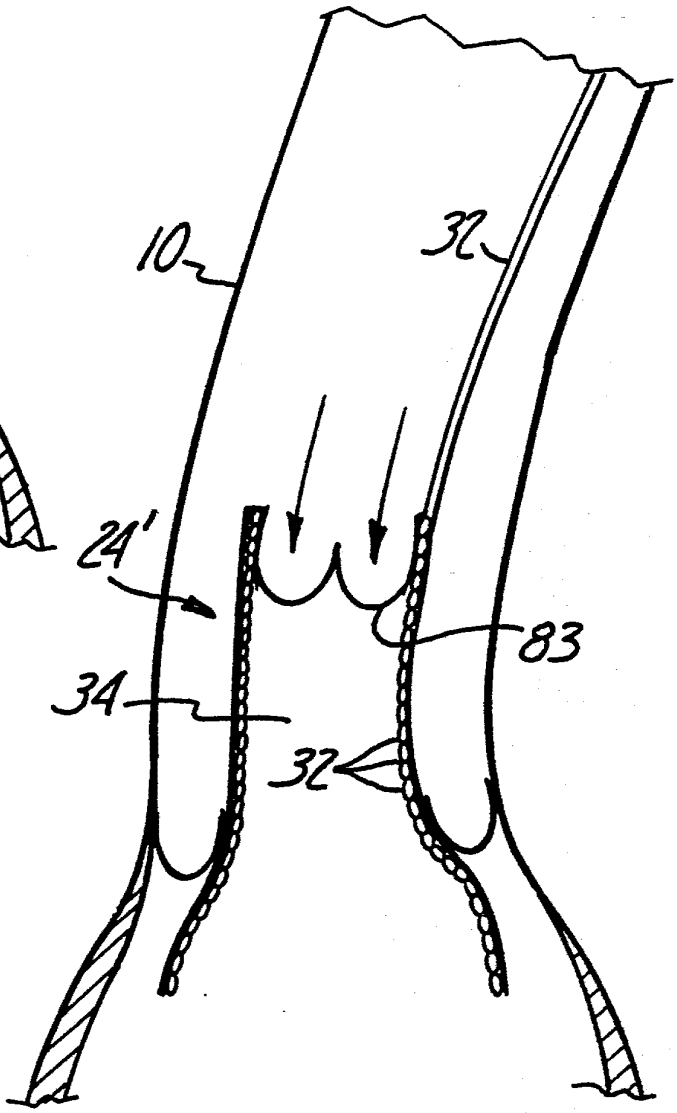


Fig. 32B

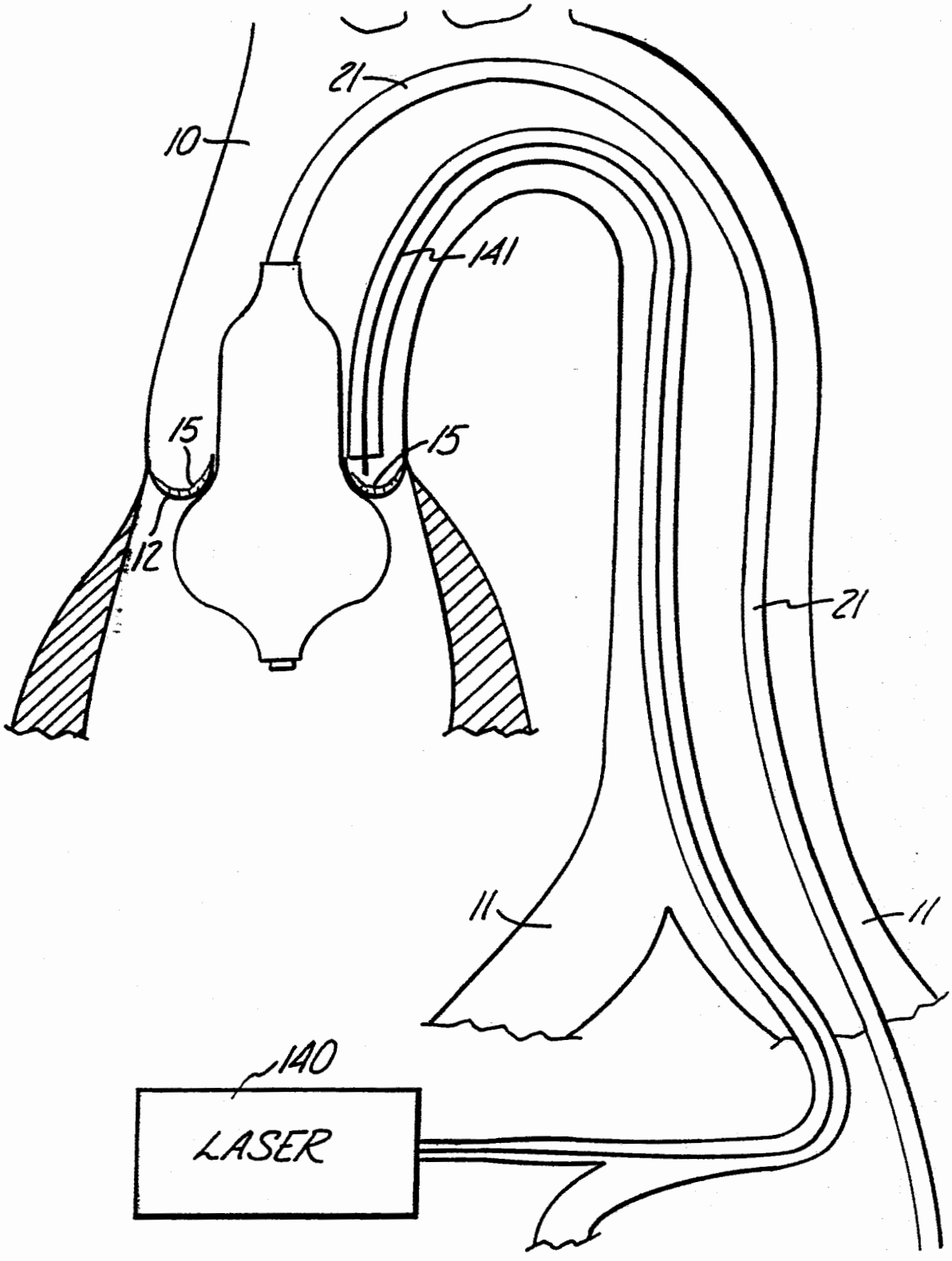


Fig. 33

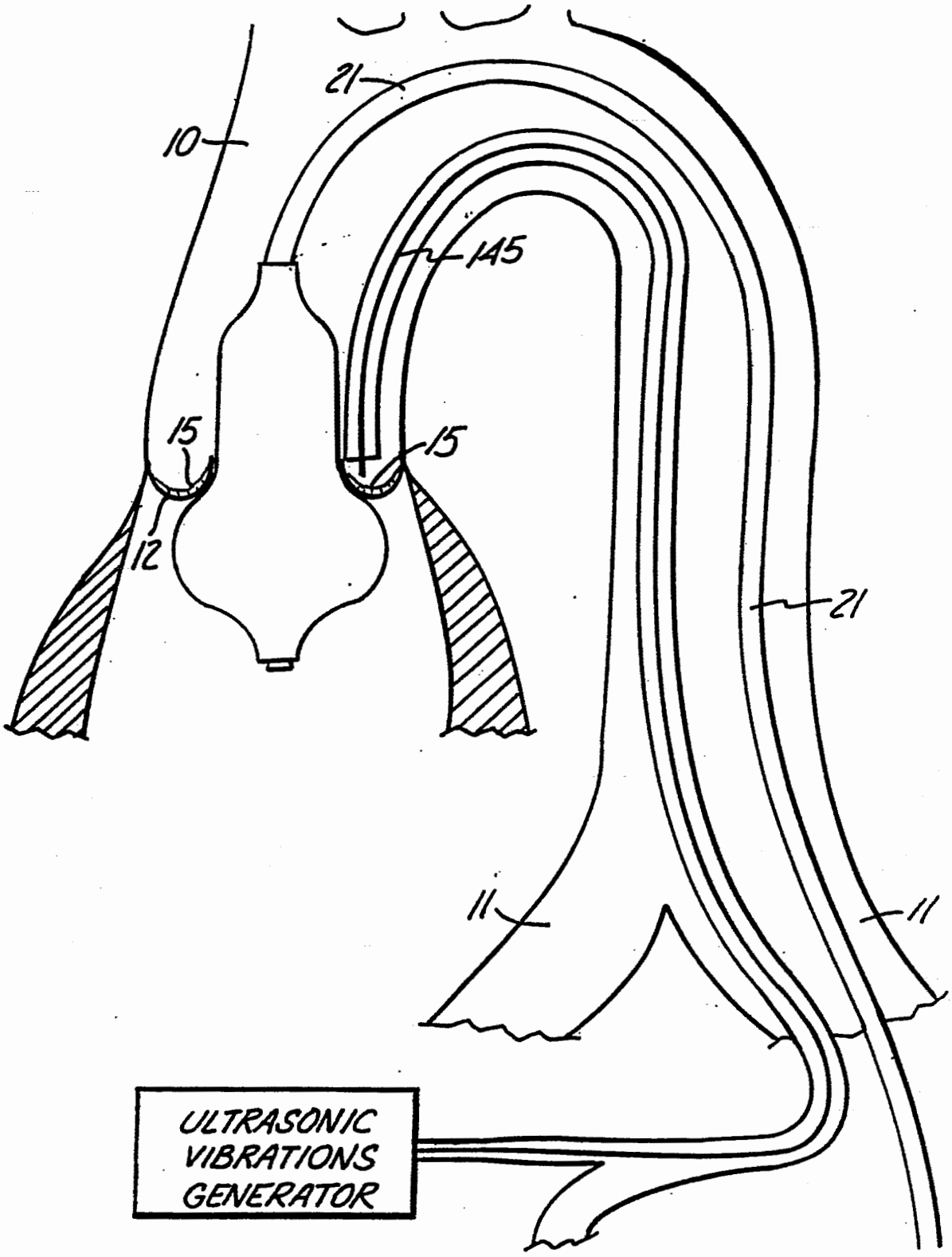


Fig. 34

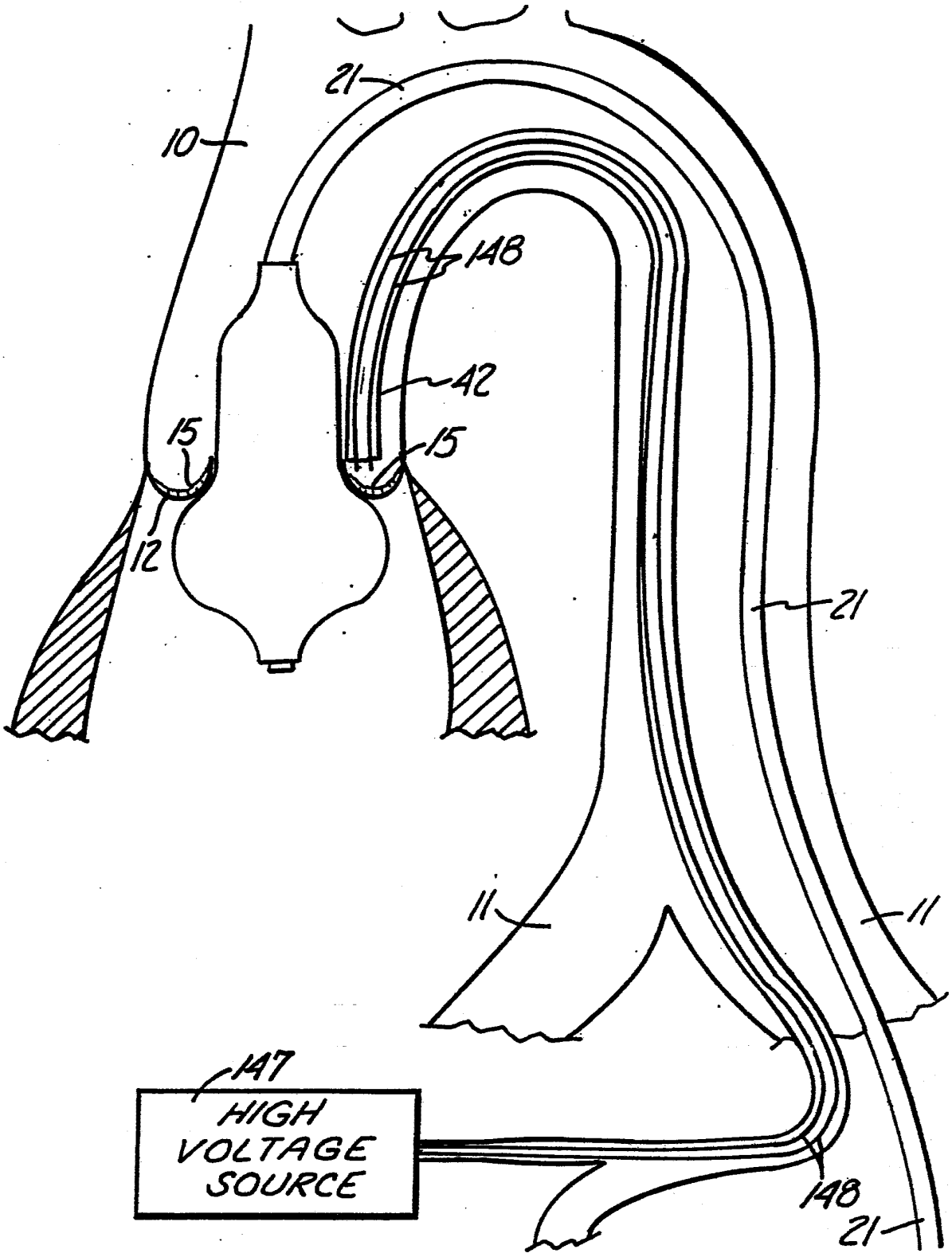


Fig. 35

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
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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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"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)	"&"	document member of the same patent family
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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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(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.

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

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

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

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

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

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

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

As a non-limiting example, the surgeon may choose a tubular implant having a tubular wall diameter of 28 millimeters at proximal end **76** while lumen **88** of the

tubular implant, as measured at ring-shaped component **78**, has a smaller diameter, thereby reducing effective orifice area to 466 millimeters^2, as seen in Figure 18A. Upon attachment of mitral valve **26**, the diameter of valve periphery edge **70** will be reduced, thereby increasing coaptation of leaflets **38** and **40**.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ring) located above the inner rim of the cardiac valve annulus **34** (Figure 22C). In embodiments, the proximal portion **76** of the tubular wall **74** of the tubular implant is attached below the inner rim of the cardiac valve annulus **34**, Figure 22B.

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

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

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

Embodiments, such as depicted in Figure 17E, are provided with a conical section helical spring **108** (*e.g.*, of titanium or nitinol wire) as a reinforcement component encased within tubular wall **74**. Tubular wall **74** comprises two layers **74a** and **74b** of serous tissue (peritoneum) with the respective basement layers facing each other and sandwiching helical spring **108** therebetween, mutually secured with biological glue or other suitable adhesive. In such a way, the smooth serous layer of the serous tissue face outward in contact with blood while the tough basement layers hold helical spring **108**. Helical spring **108** is sandwiched and glued between the

serous layers when slightly lengthened and released only when dry so as to bias the entire construct to a shortened configuration, substantially pleating the serous tissue. In such a way, helical spring **108** provides, in part, not only radial flexibility as described above, but also both axial extensibility and axial bendability to the tubular wall. Secured to the distal end of tubular wall **74** (by sutures) and engaging of the end of helical spring **108** is a slightly flexible and piercable ring-shaped component **78** of titanium mesh.

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

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

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

In the embodiments described above, the cardiac (e.g., mitral) valve is detached from the respective annulus substantially intact as a complete functioning unit where the leaflets of the valve are mutually associated through commissures of the valve as depicted in Figure 11. Such embodiments are exceptionally simple to implement. In embodiments, the cardiac valve is detached not intact, for example,

each leaflet separately. In such embodiments, for example, each leaflet is secured to the edge of the implant separately. Such embodiments allow repair or replacement of a damaged leaflet.

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

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

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

The present invention also provides for the manufacture of implants such as annuloplasty apparatus and cardiac valve augmenting implants such as described herein. Thus according to the teachings of the present invention there is also provided for the use of a sheet of an implantable material (as described hereinabove) for the manufacture of a cardiac valve augmenting implant, the implant including a wall

comprising the material, the wall delimited by two edges each having a shape of a closed curve and defining a lumen.

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

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

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

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

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

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

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

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

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

ventricular enlargement; connective tissue disorders such as Marfan's syndrome; and untreated syphilis.

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

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

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

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

WHAT IS CLAIMED IS:

1. An annuloplasty apparatus comprising:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

a) providing an sheet of implantable material; and

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

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

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

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

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

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

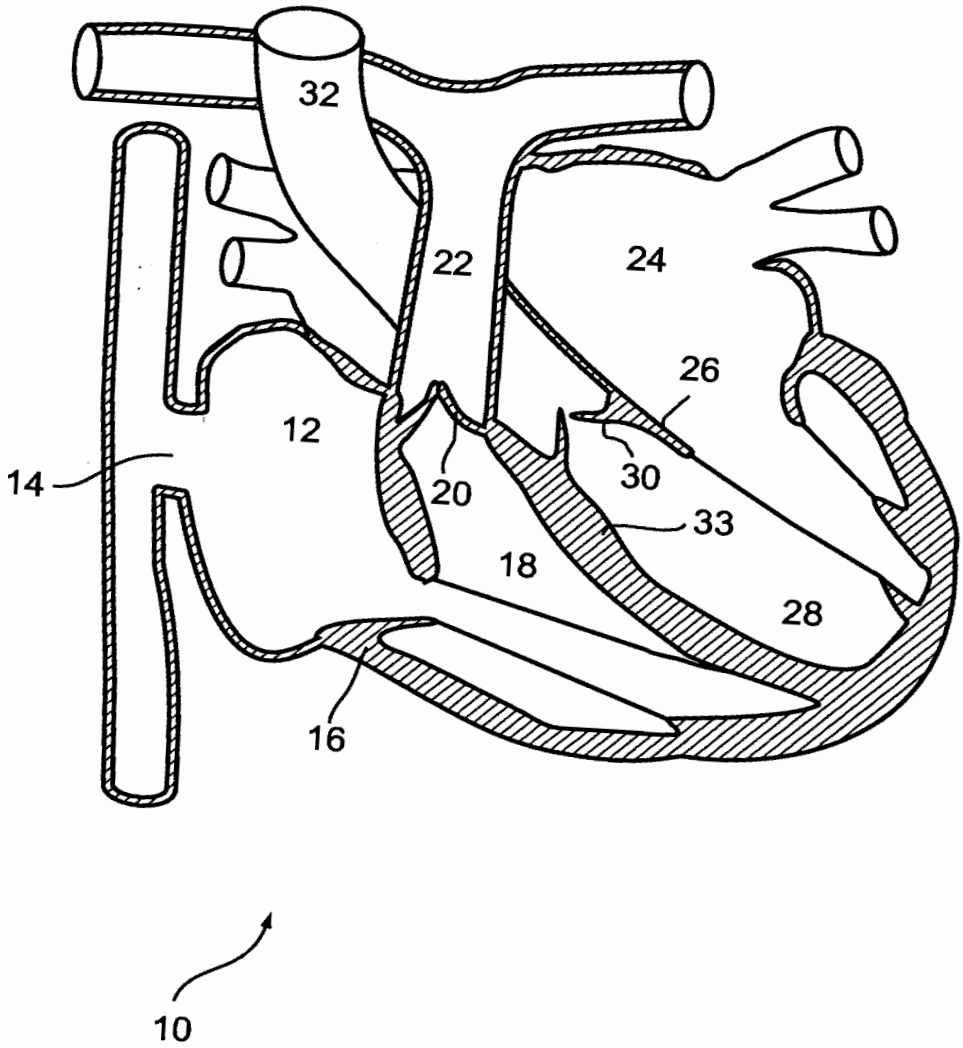

Fig. 1(Prior Art)

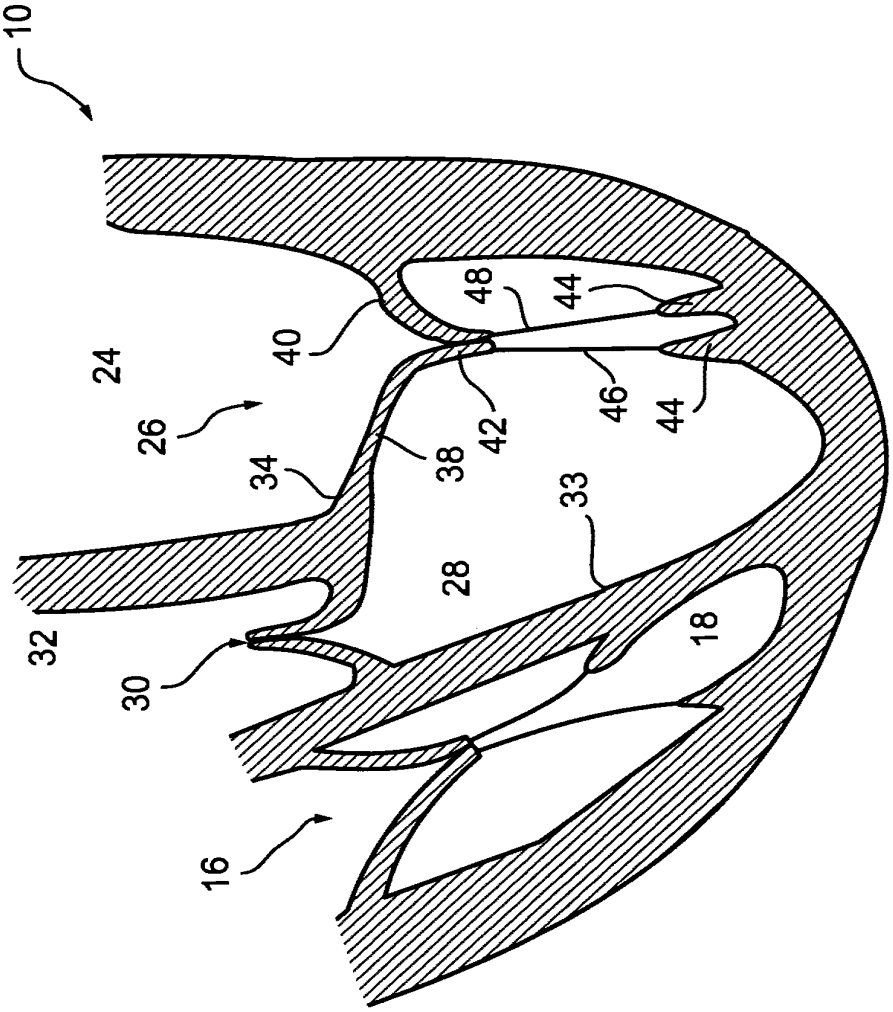

Fig. 2b (Prior Art)

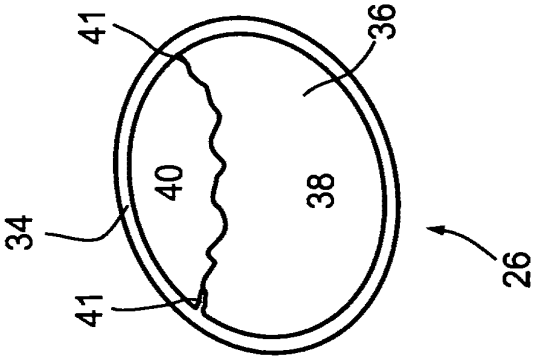

Fig. 2a (Prior Art)

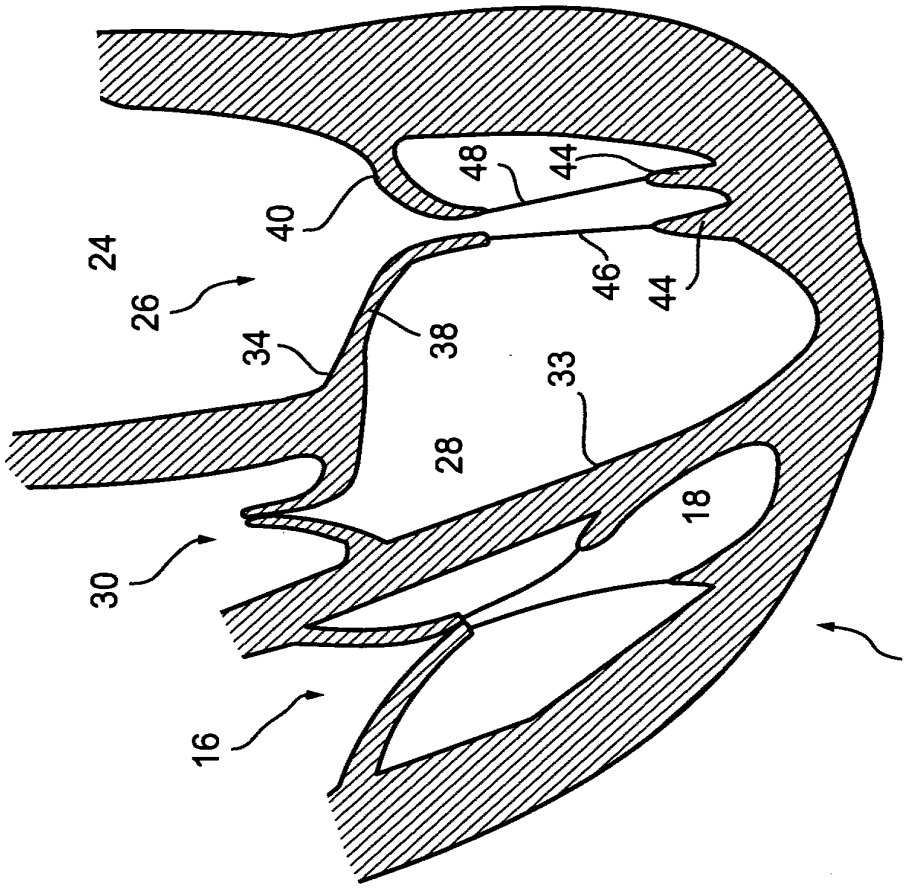

Fig. 3b (Prior Art)

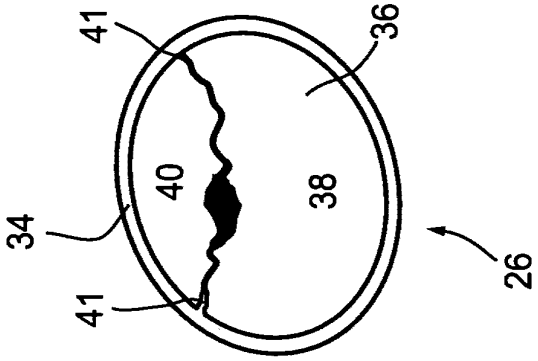

Fig. 3a (Prior Art)

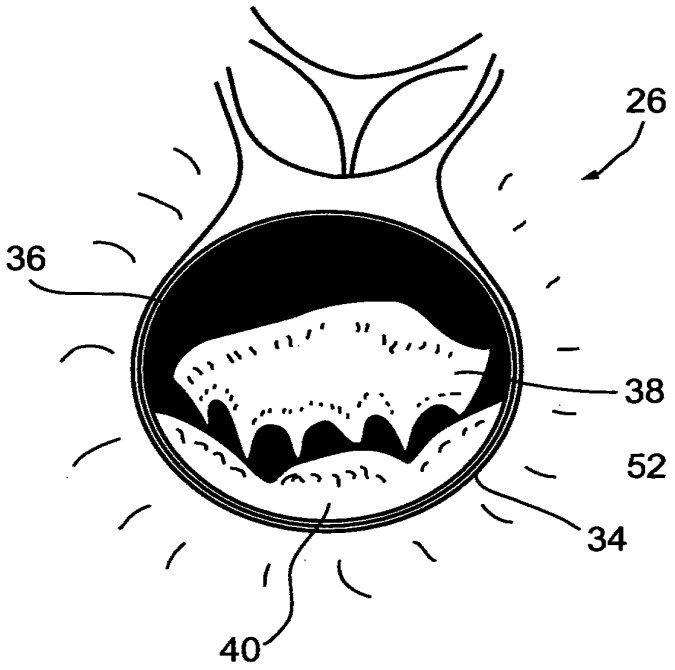

Fig. 4

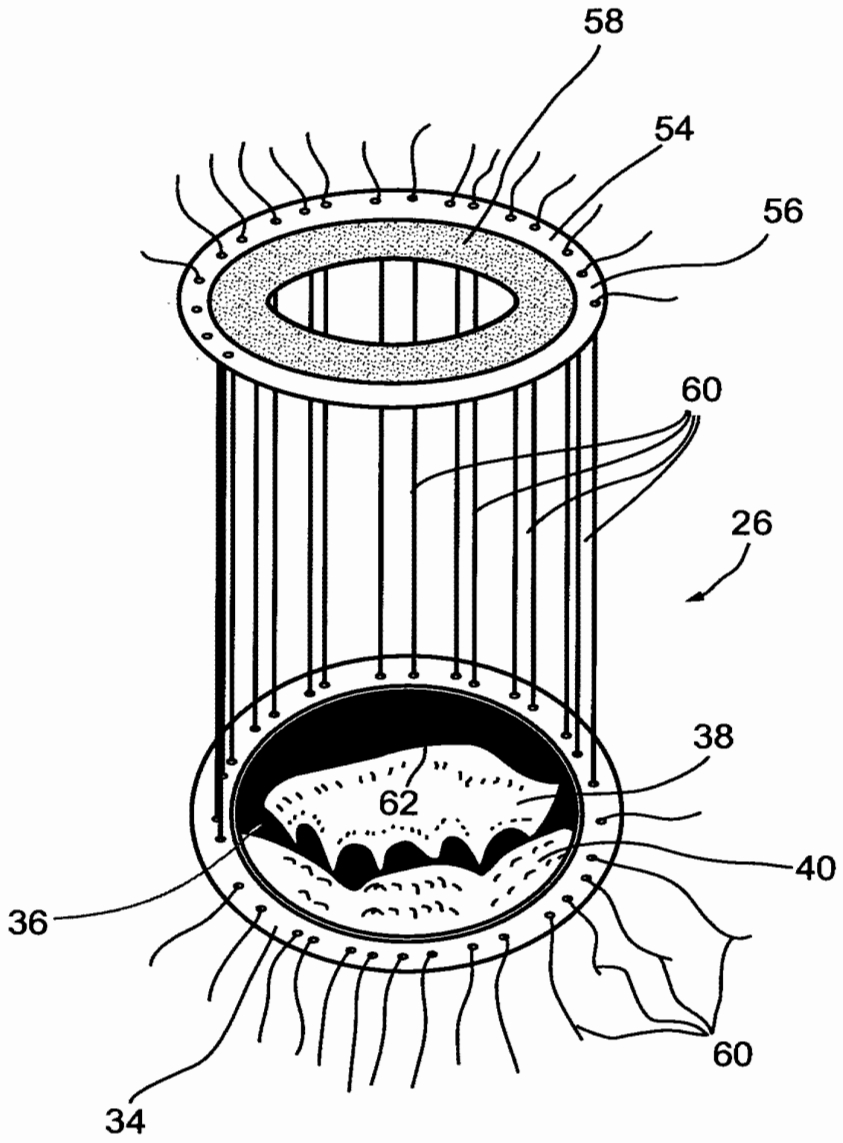

Fig. 5

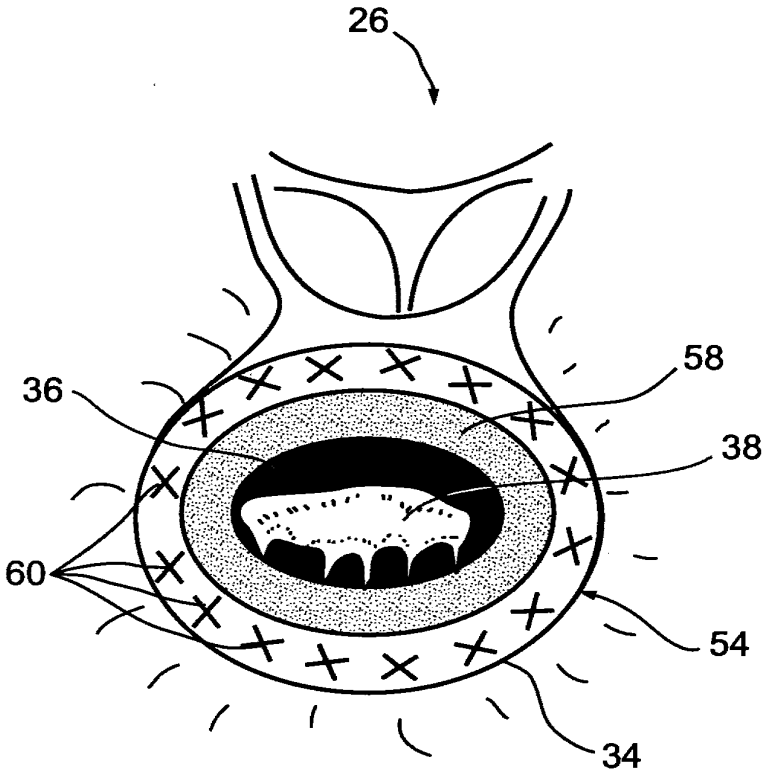

Fig. 6

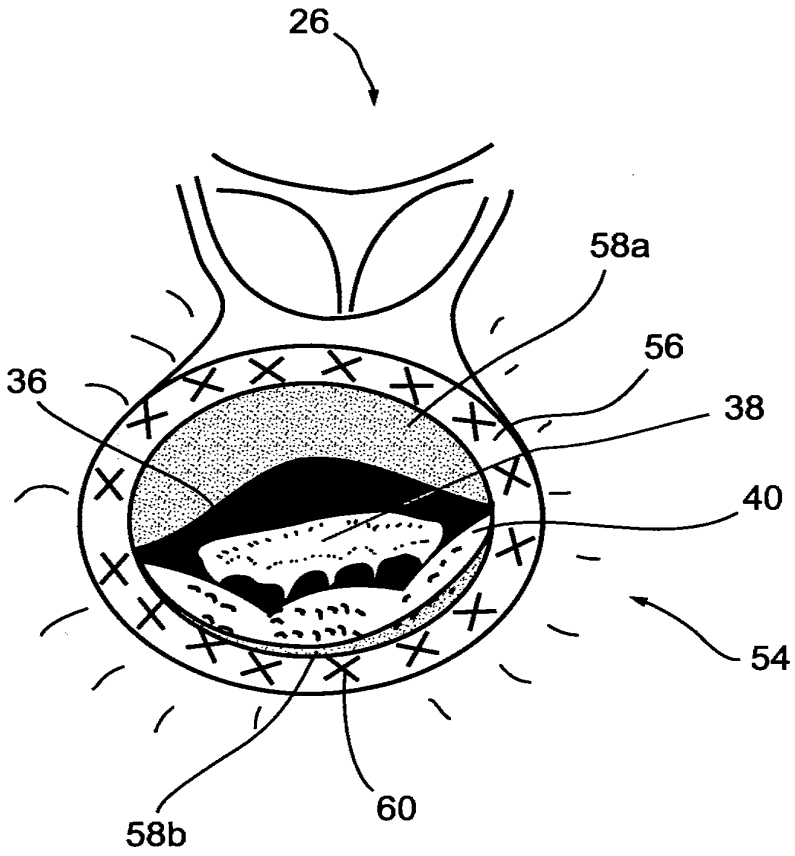

Fig. 7

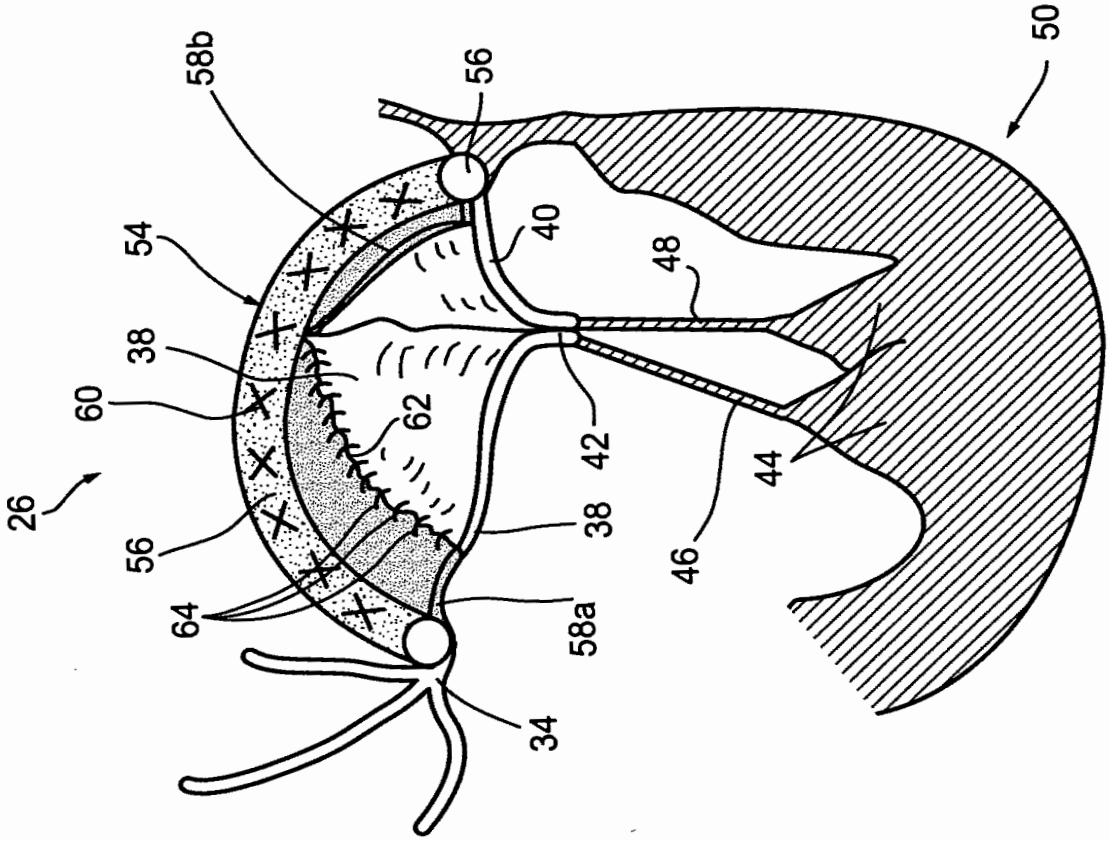
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Fig. 8b

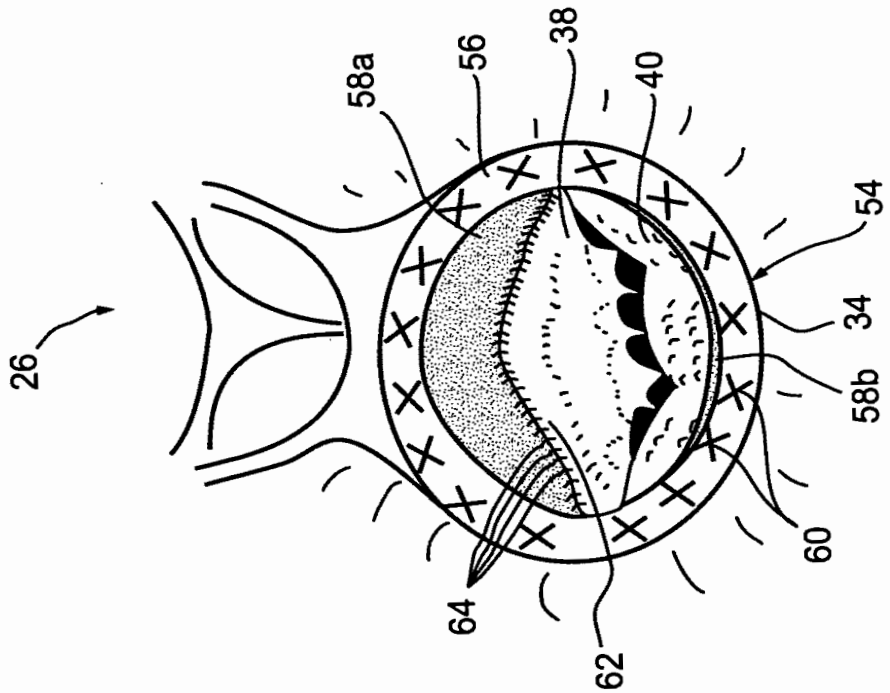
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Fig. 8a

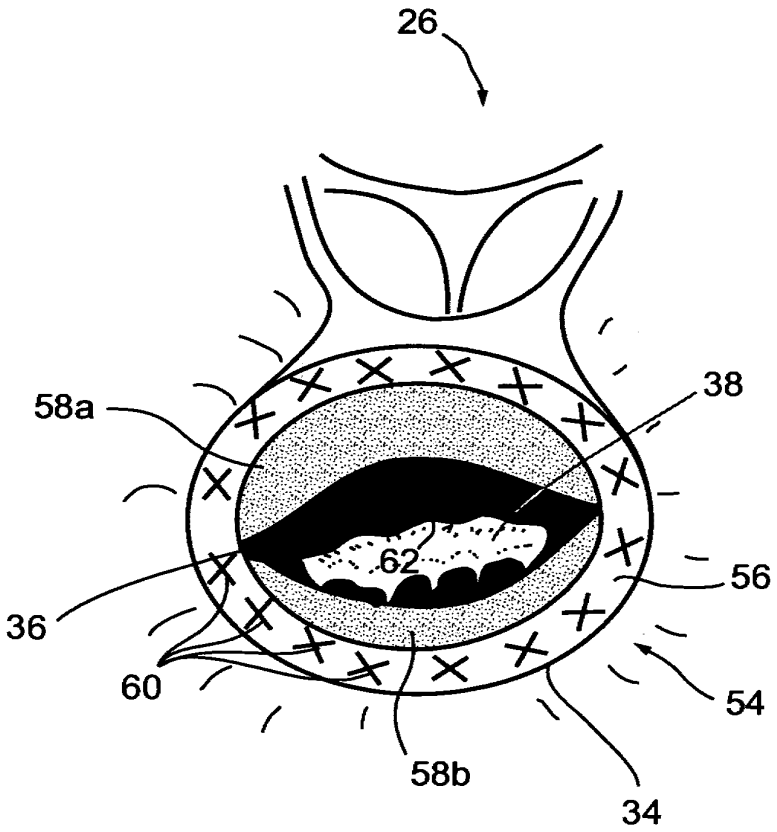

Fig. 9

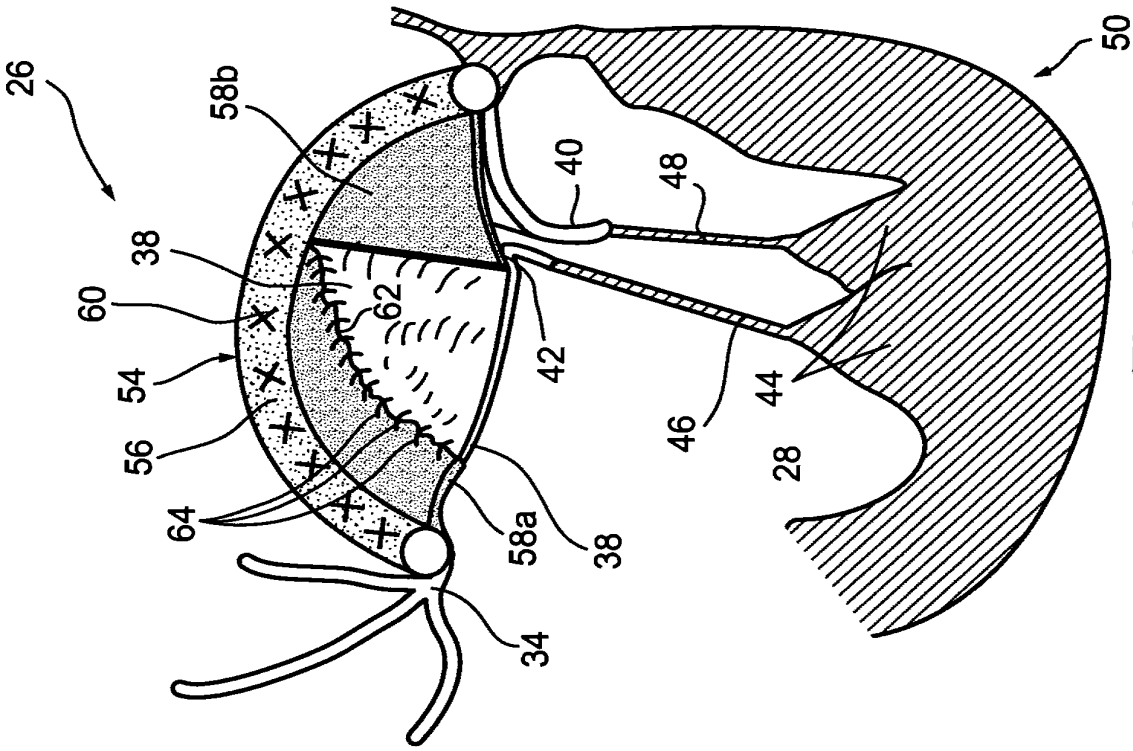

Fig. 10b

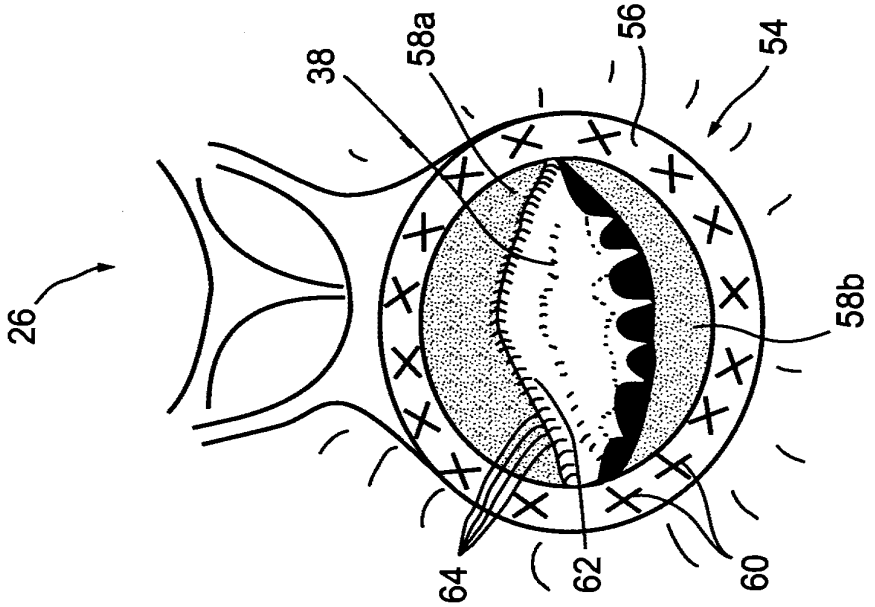

Fig. 10a

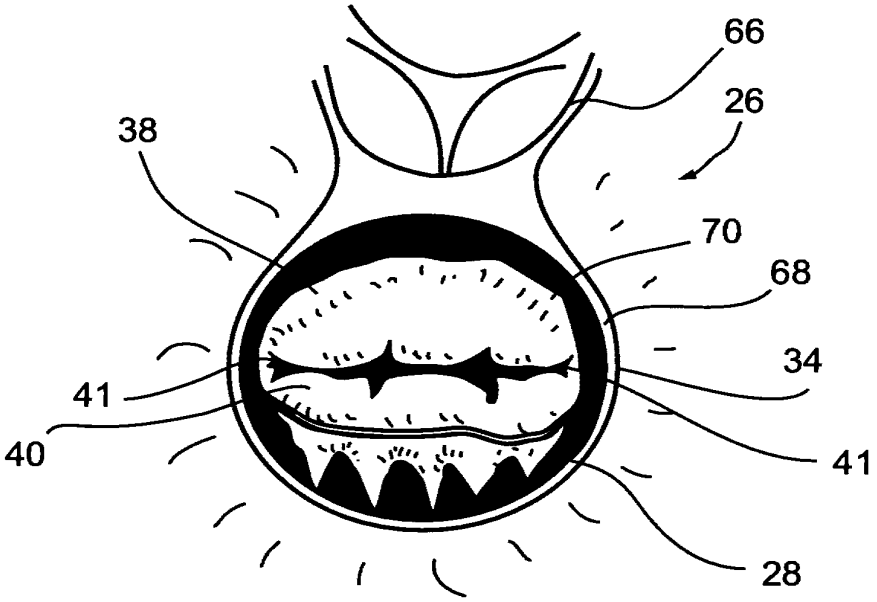

Fig. 11

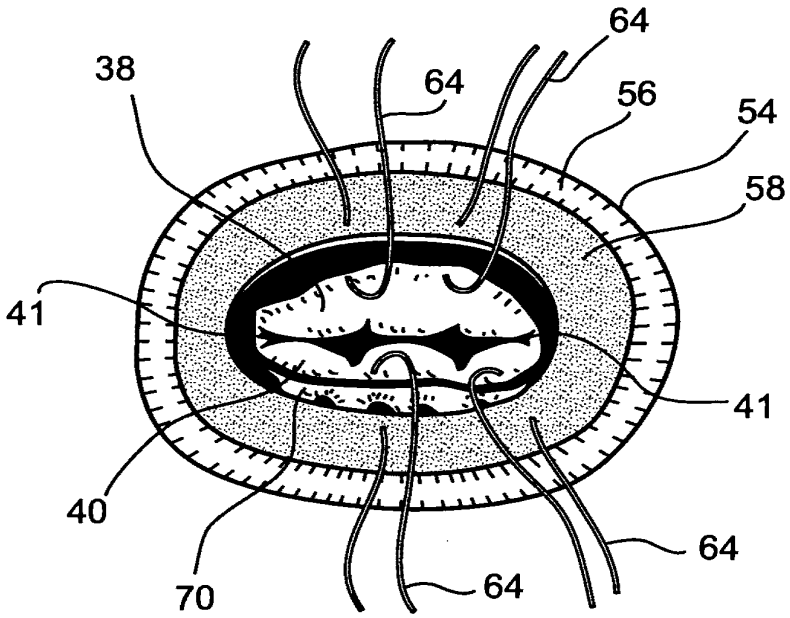

Fig. 12a

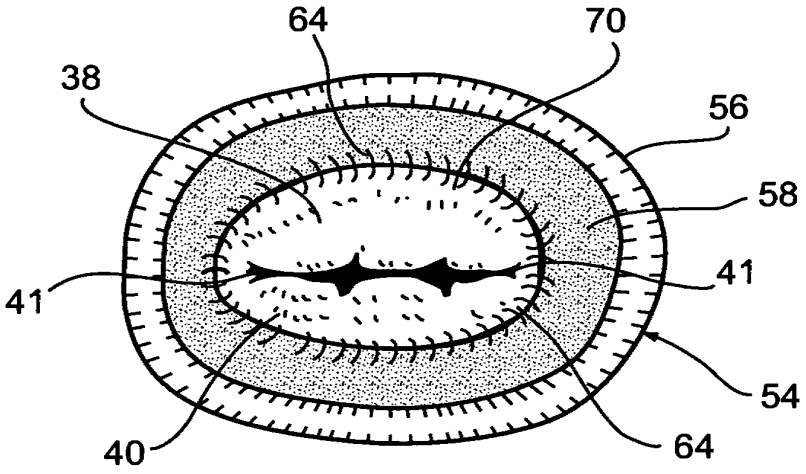

Fig. 12b

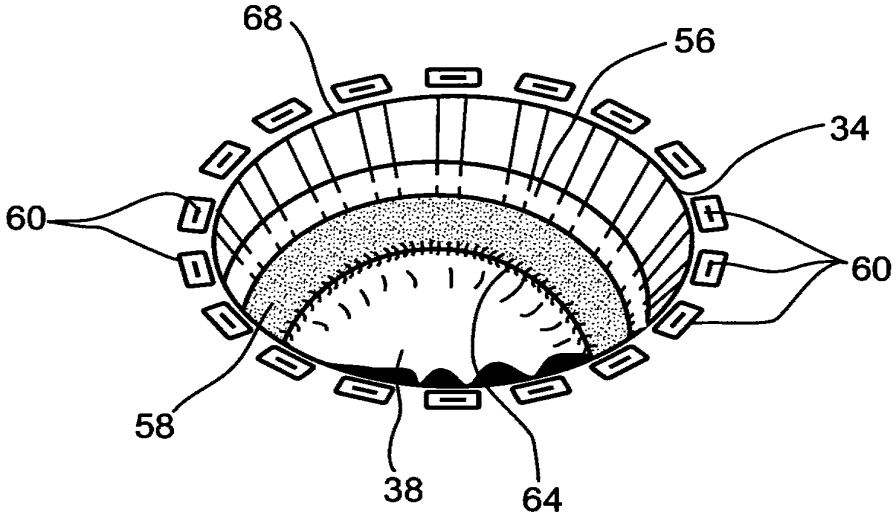

Fig. 12c

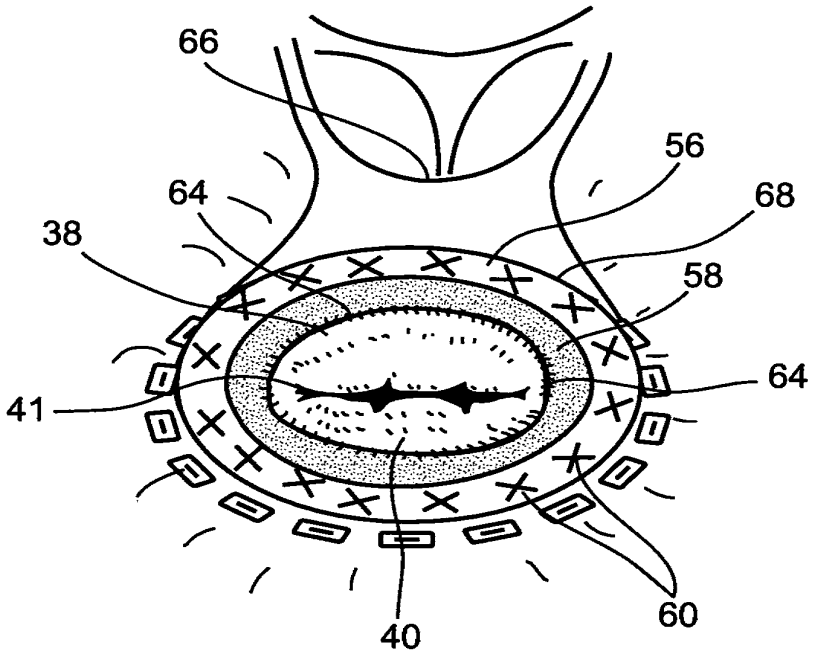

Fig. 12d

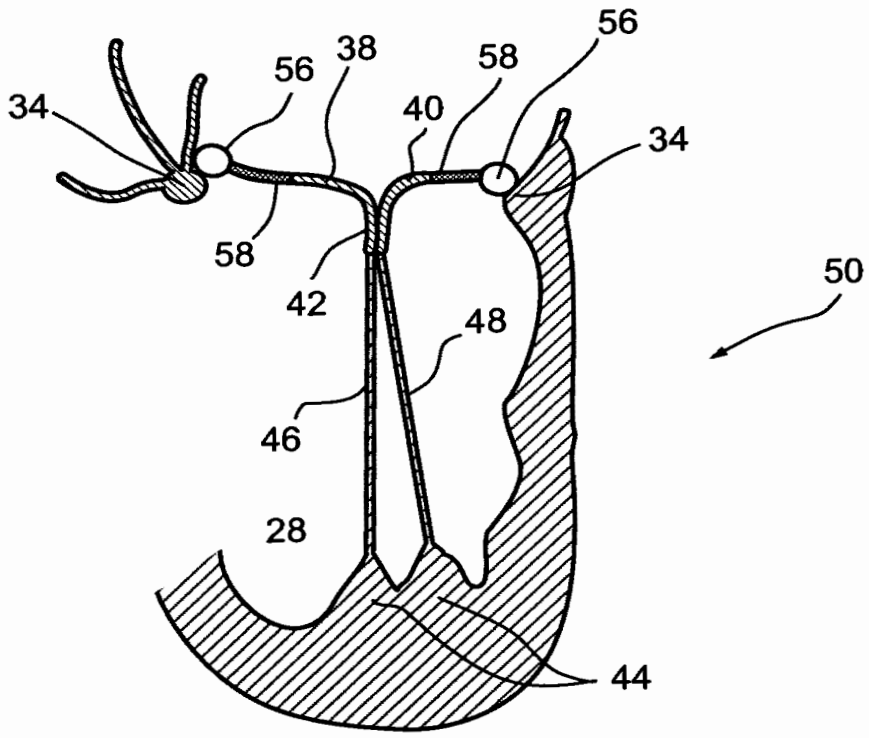

Fig. 12e

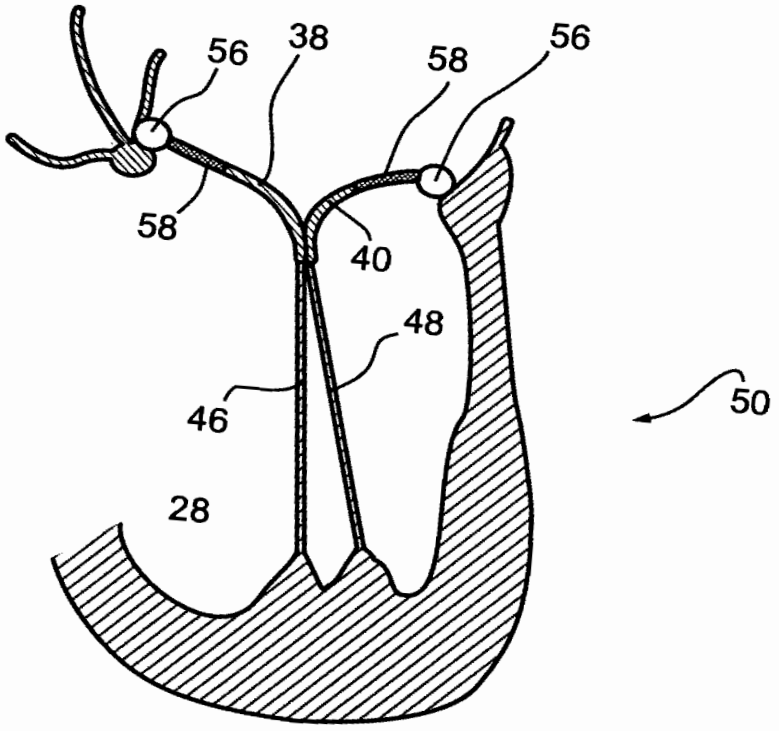

Fig. 12f

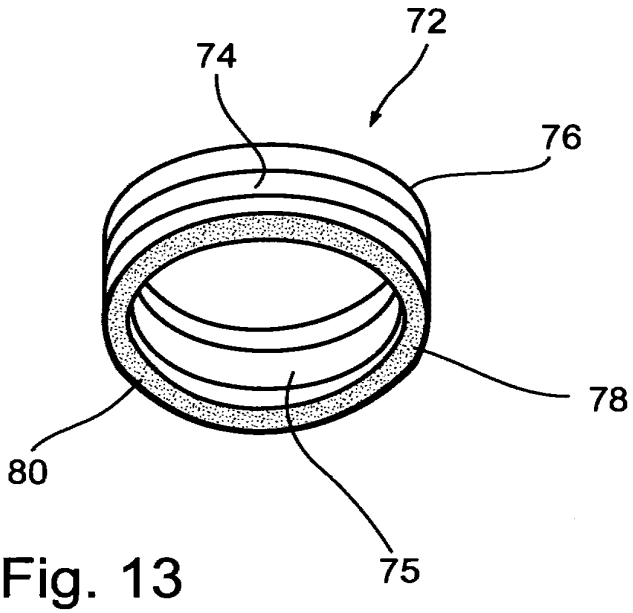

Fig. 13

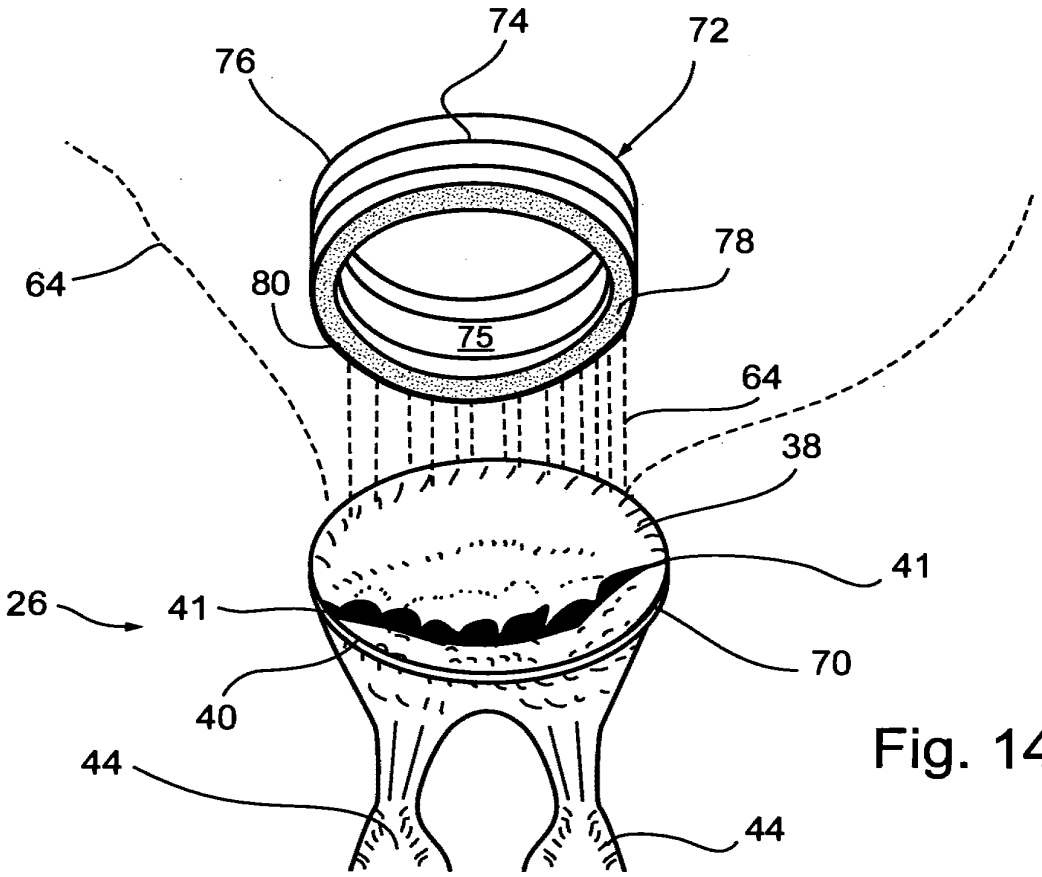

Fig. 14a

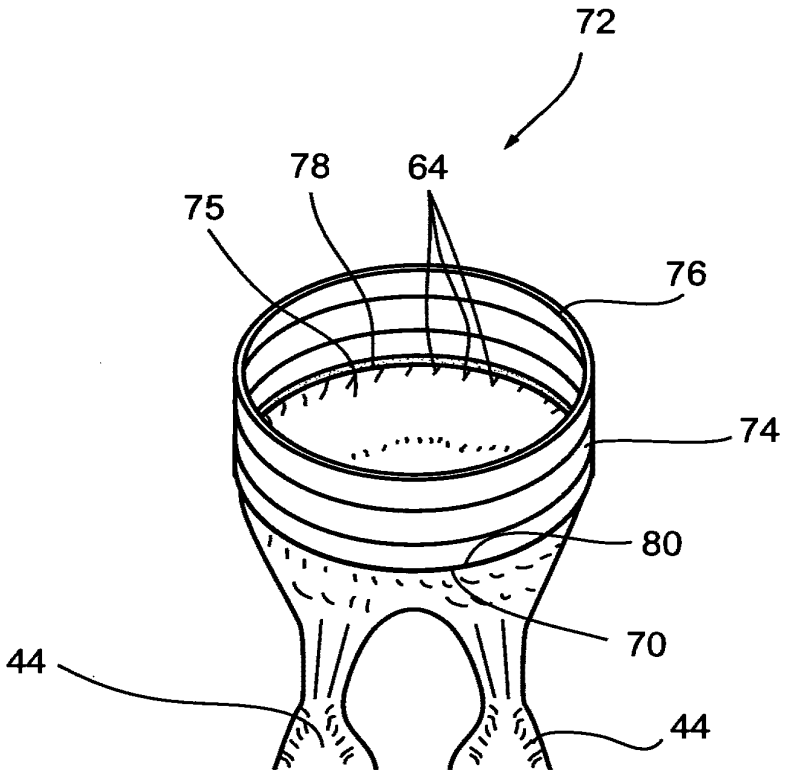

Fig. 14b

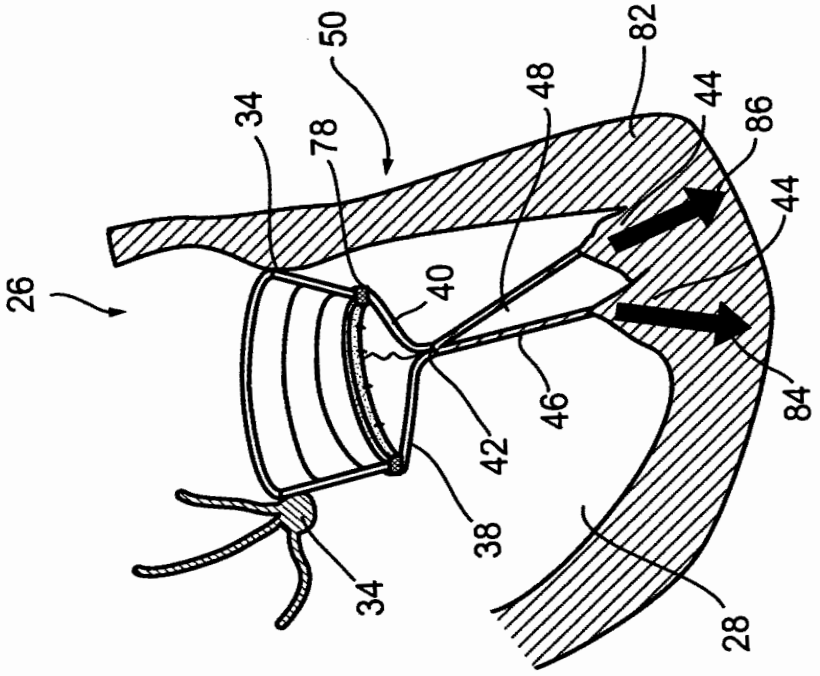
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Fig. 16

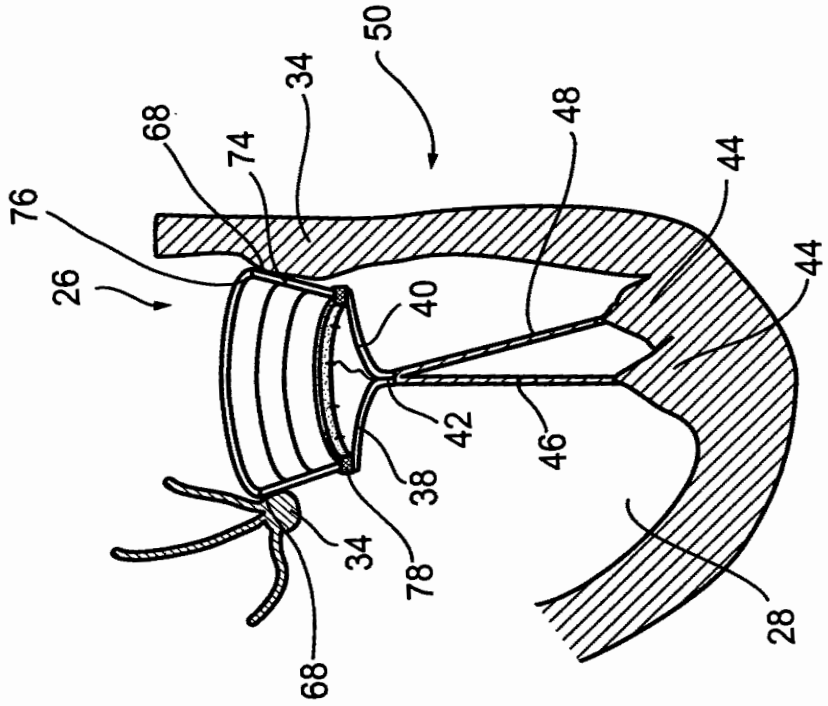
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Fig. 15

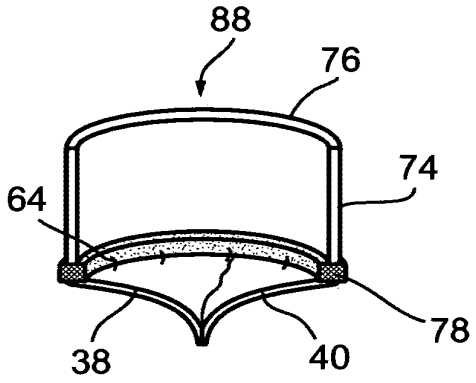

Fig. 17a

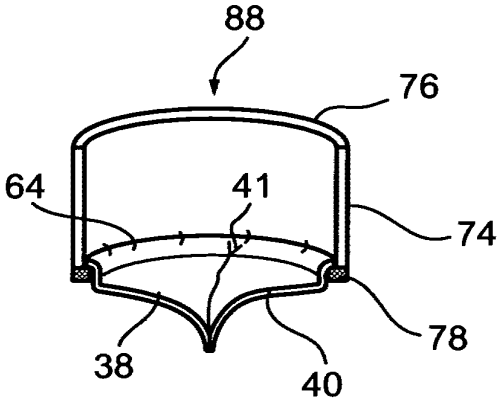

Fig. 17b

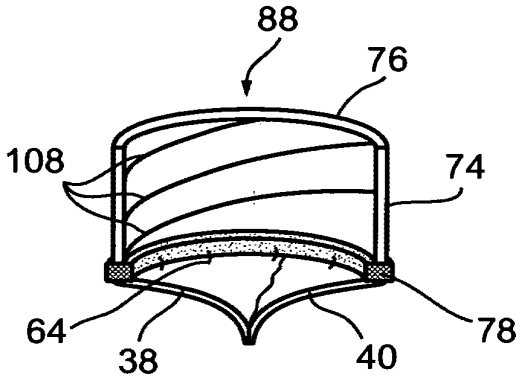

Fig. 17c

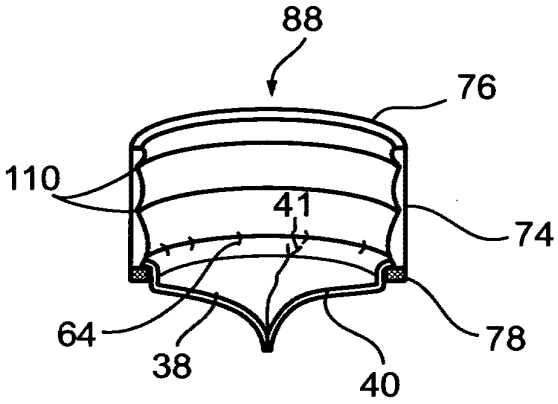

Fig. 17d

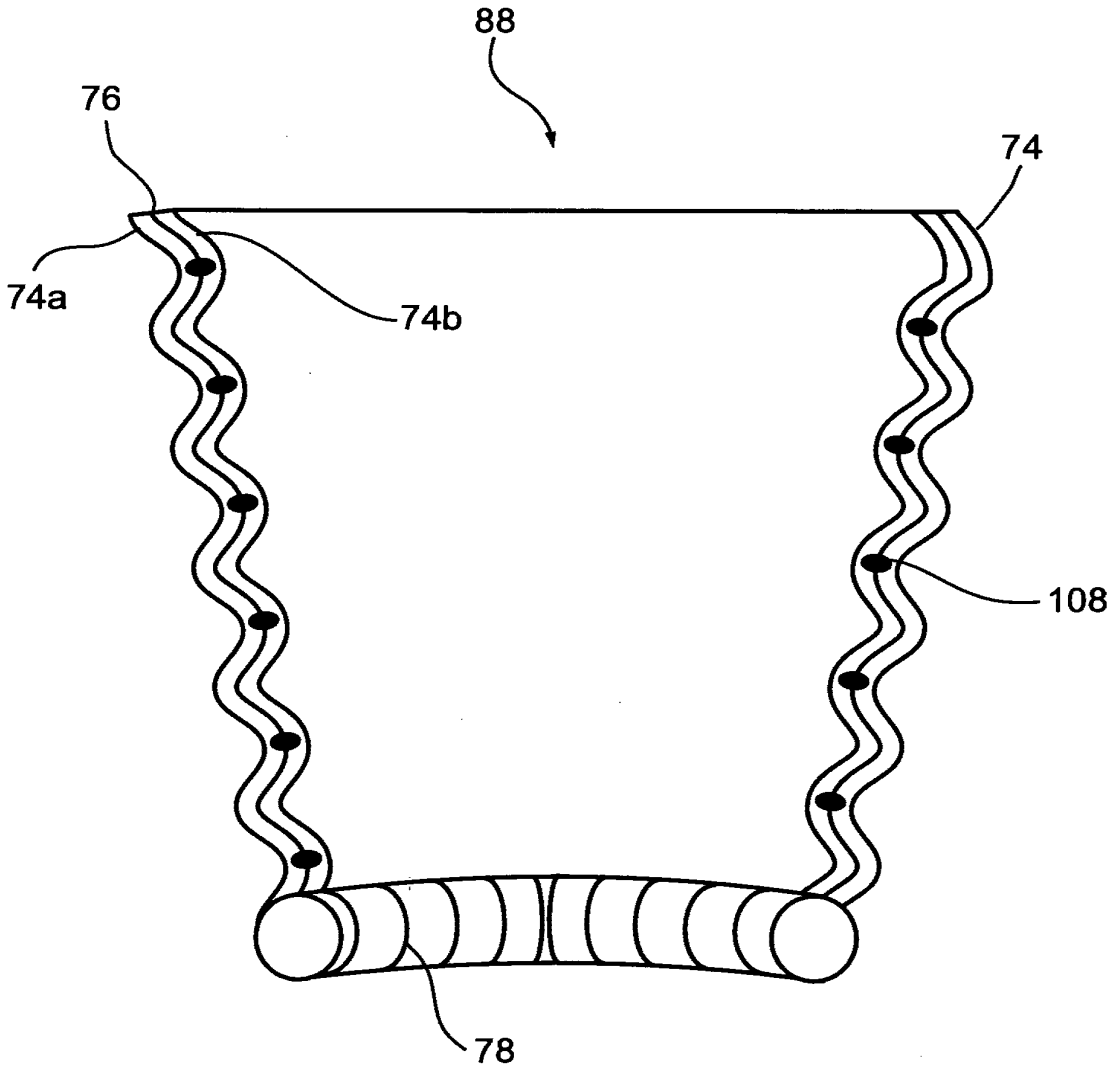

Fig. 17e

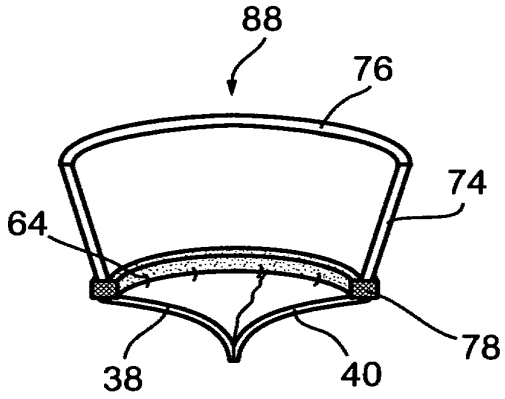

Fig. 18a

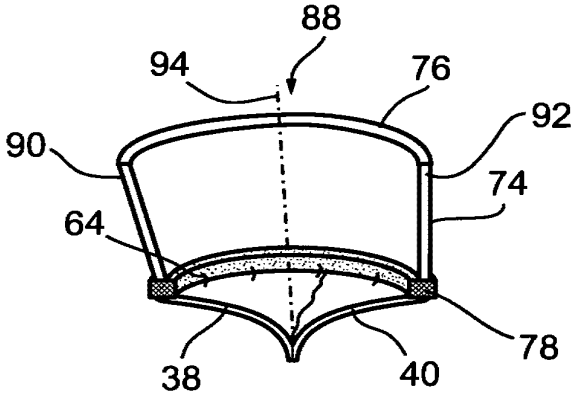

Fig. 18b

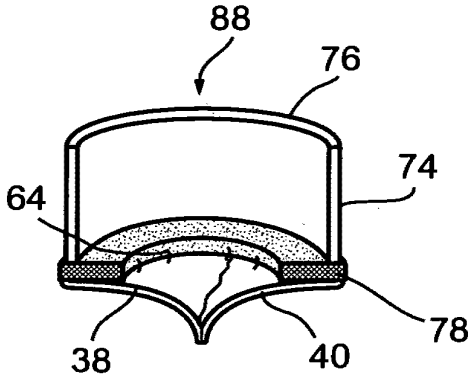

Fig. 18c

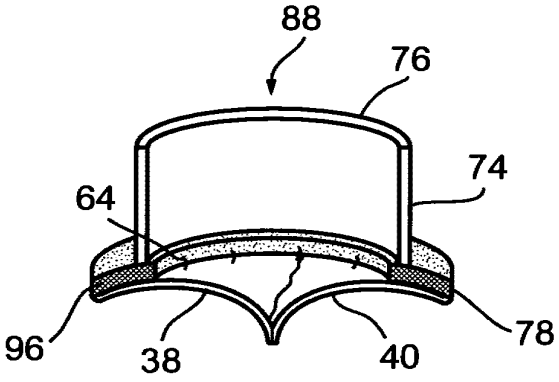

Fig. 18d

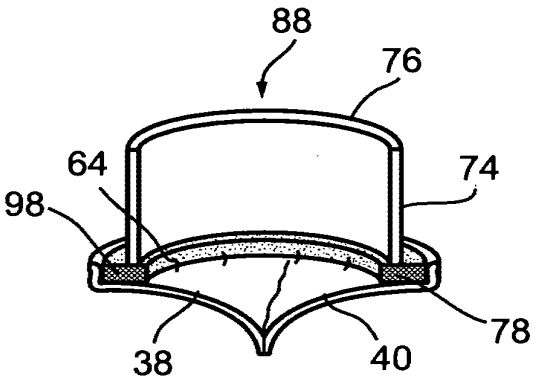

Fig. 19a

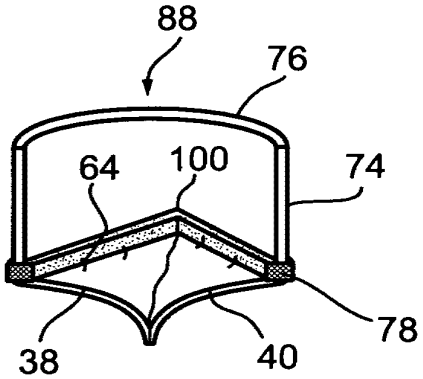

Fig. 19b

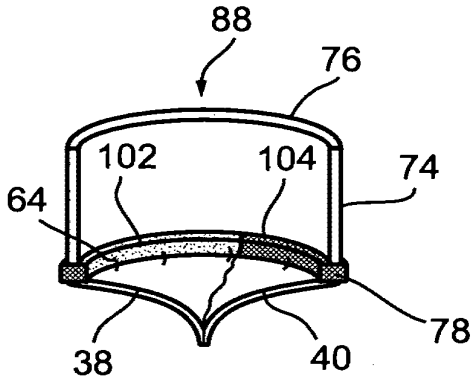

Fig. 19c

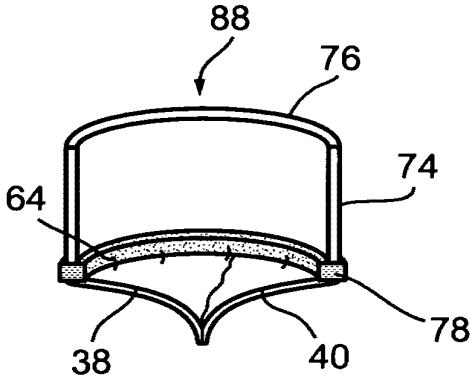

Fig. 19d

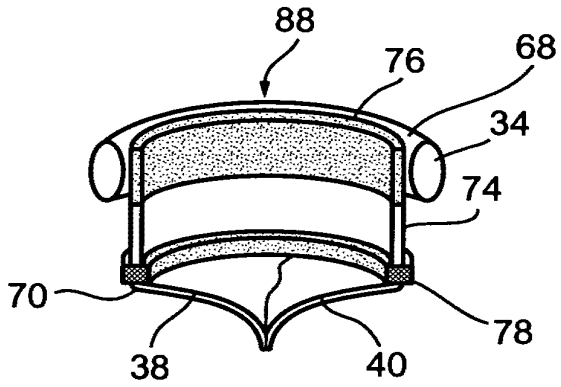

Fig. 20a

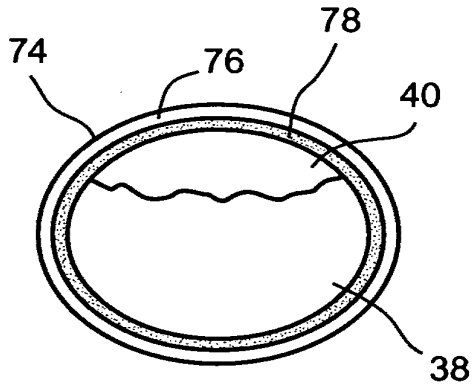

Fig. 20b

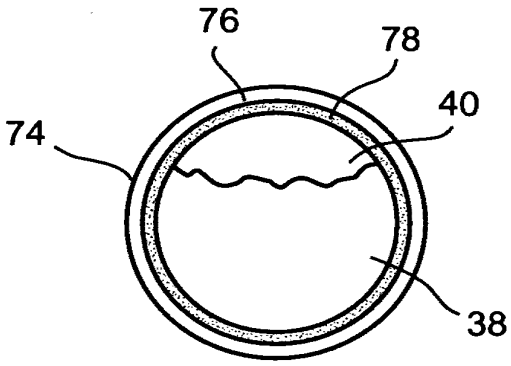

Fig. 20c

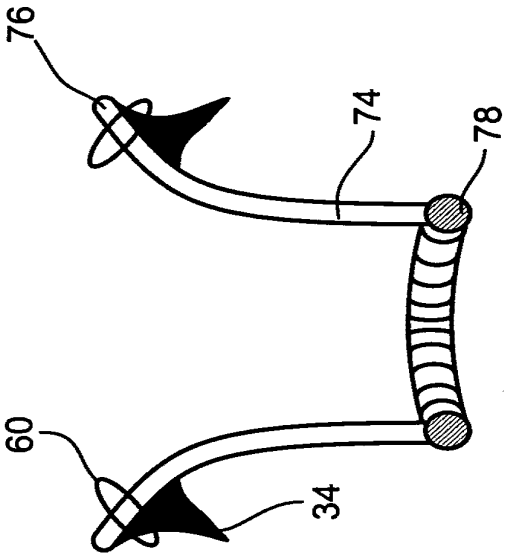

Fig. 22a

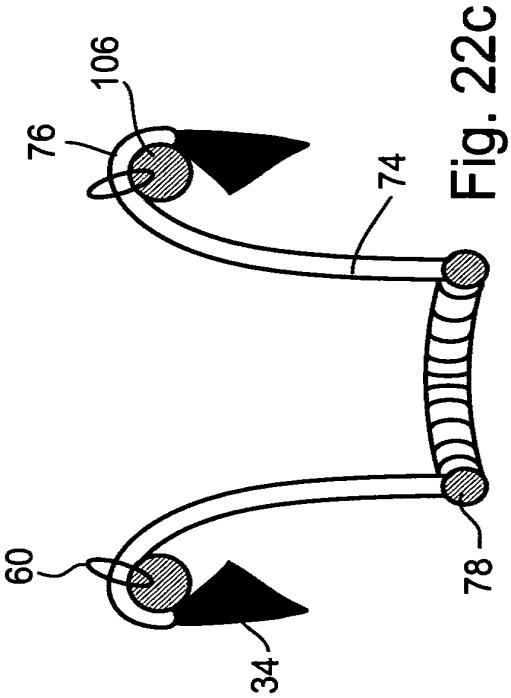

Fig. 22c

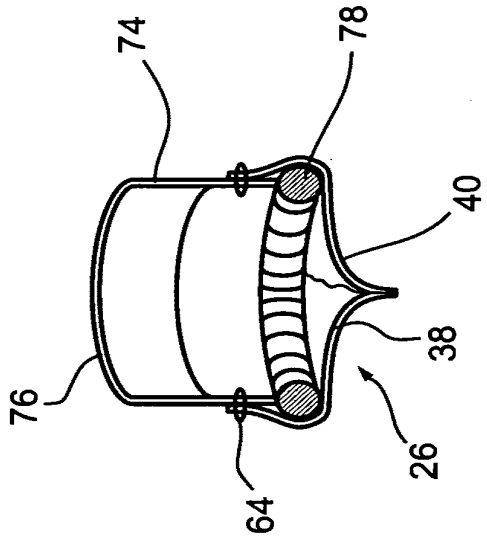

Fig. 21

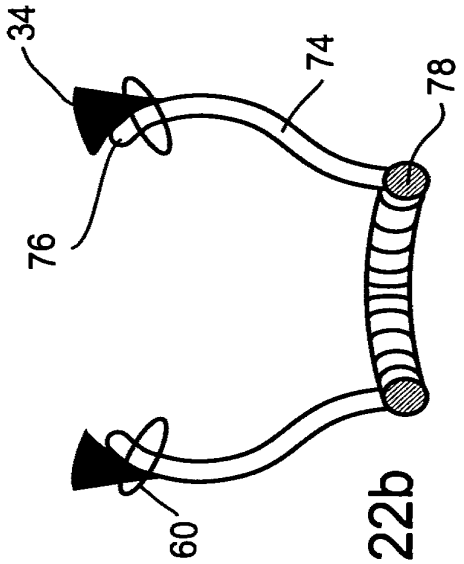

Fig. 22b

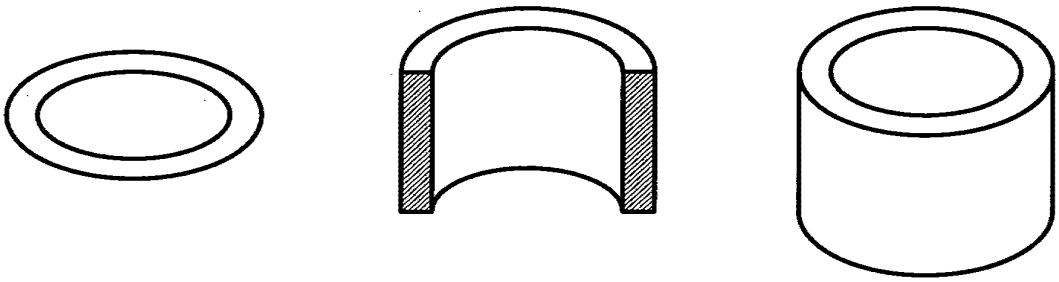

Fig. 23a

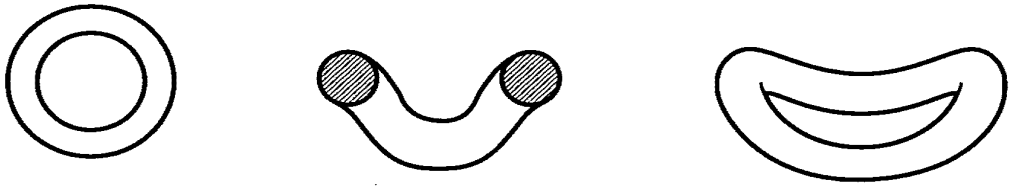

Fig. 23b

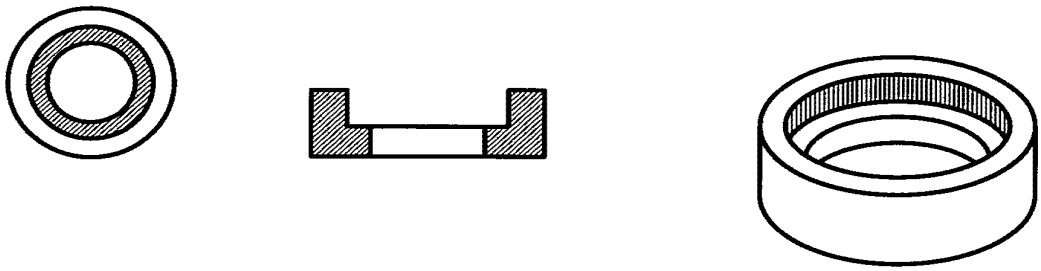

Fig. 23c

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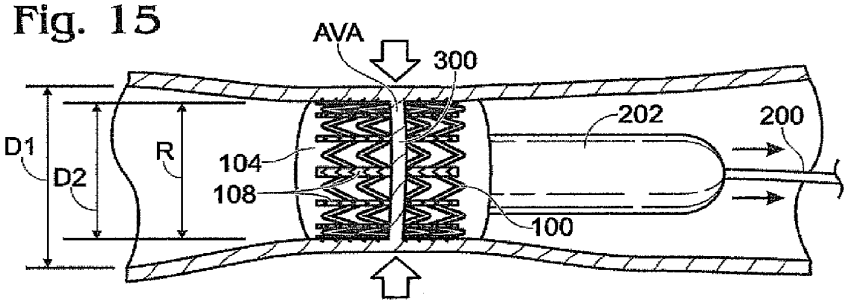
(54) Title: TRANSCATHETER HEART VALVE WITH MICRO-ANCHORS

Fig. 15



(57) Abstract: Various embodiments of methods and apparatus for treating defective heart valve are disclosed herein. In one exemplary embodiment, a transcatheter heart valve is disclosed that includes an expandable shape memory stent and a valve member supported by the stent. A plurality of micro-anchors can be disposed along an outer surface of the stent for engaging native tissue. The transcatheter heart valve can be configured to be advanced into a dilated valve annulus via a balloon catheter. The balloon can be inflated to expand the transcatheter heart valve from a collapsed diameter to an over-expanded diameter such that the micro-anchors engage tissue along the surrounding valve annulus. After engaging the tissue, the balloon can be deflated and the shape memory stent can retract or recoil toward its predetermined recoil diameter. As the stent recoils, the surrounding tissue is pulled inward by the stent such that the diameter of the valve annulus is reduced.

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TRANSCATHETER HEART VALVE WITH MICRO-ANCHORS

FIELD

[0001] The disclosed technology relates generally to methods and devices for improving valve function of a heart. For instance, embodiments of the disclosed technology can be used to treat aortic insufficiency in a human heart.

BACKGROUND

[0002] The aortic valve in the human heart is a one-way valve that separates the left ventricle from the aorta. The aorta is a large artery that carries oxygen-rich blood out of the left ventricle to the rest of the body. Aortic insufficiency is a condition in which the aortic valve does not fully close during ventricular diastole, thereby allowing blood to flow backward from the aorta into the left ventricle. This leakage of blood through the aortic valve back into the left ventricle is often referred to as aortic valve regurgitation.

[0003] Aortic insufficiency is typically caused by aortic root dilatation (annuloaortic ectasia), which is idiopathic in over 80% of the cases. Aortic insufficiency may also result from other factors, such as aging and hypertension. In any case, the regurgitation of blood resulting from aortic insufficiency substantially reduces the pumping efficiency of the left ventricle. Therefore, even during periods of rest, the heart must work hard simply to maintain adequate circulation through the body. Over time, this continuous strain on the heart can damage the left ventricle. For example, the additional strain on the heart may result in a thickening of the heart muscle (hypertrophy). When heart-wall thickening occurs due to aortic insufficiency, the geometry of the heart can be adversely affected and the heart can be permanently damaged.

[0004] Although aortic insufficiency is relatively common, the treatment of this condition still represents a substantial clinical challenge for surgeons and cardiologists. For example, because aortic insufficiency has a long latency period, afflicted patients may already be at significant risk for heart failure by the time the symptoms arise. In many cases, when patients are not monitored

well for aortic insufficiency and are left untreated, the patient's left ventricle may become irreversibly damaged before therapy can be delivered. Therefore, even if a defective aortic valve is replaced with a prosthetic valve, the patient may never fully recover and their survival rate may be substantially impaired.

[0005] Existing methods of treating aortic insufficiency suffer from a number of significant disadvantages. For example, open heart surgical valve replacement is often too traumatic for older and/or frail individuals. Replacement of the aortic valve using existing catheterization techniques is also challenging because it is difficult to anchor a prosthetic valve within a soft and dilated annulus. More particularly, when a prosthetic valve is delivered to the site of the aortic valve and expanded, it engages and continuously exerts an outward force against the aortic valve wall. This continuous outward pressure is necessary for anchoring the prosthetic valve within the native valve but may also cause the already-dilated native aortic annulus to become further expanded. The tissue along the annulus of a valve suffering from aortic insufficiency is typically soft and flexible (as opposed to being hard and calcified as with aortic stenosis) and therefore the further expansion of the aortic annulus may lead to dislodgement of the prosthetic valve. Such dislodgement could require delivery of a still larger valve or result in death of the patient. A prosthetic valve with a very large diameter may be delivered via a catheterization technique to reduce the possibility of dislodgement. However, it follows that such a valve would also have a large diameter in its crimped condition. The delivery of such a large-diameter prosthetic valve is much more challenging and dangerous than the delivery of a relatively small prosthetic valve of the type currently used to treat aortic stenosis.

[0006] Therefore, a need exists for new and improved methods and devices for treating aortic insufficiency.

SUMMARY

[0007] Embodiments of the disclosed technology are directed to percutaneous (e.g., catheter-based) and/or minimally invasive surgical (MIS) procedures for

treating aortic insufficiency. These less invasive therapies, which do not require open-heart surgery, provide patients with a more attractive option for early treatment of aortic insufficiency, thus mitigating or even avoiding the risk of damage to the left ventricle. These less invasive therapies also provide an urgently needed treatment option for patients who cannot be treated by open-heart surgery because they are too sick or frail to withstand the treatment. Unfortunately, at the present time, these "high-risk" patients are typically left untreated.

[0008] According to one exemplary embodiment disclosed herein, a system is provided for replacing the native aortic valve using a catheter-based approach. The system includes a transcatheter heart valve (THV), sometimes referred to herein as a "bioprosthesis." The transcatheter heart valve of this embodiment comprises a support structure, such as a stent, formed of, for example, a shape-memory material. The support structure can be configured to be radially compressible into a compressed state, expandable into an over-expanded state having a first diameter, and self-adjustable into a functional state having a second diameter less than the first diameter. The transcatheter heart valve can also include a flexible valve member or membrane, such as a prosthetic one-way valve member, within an interior of the support structure. In particular implementations, one or more grabbing mechanisms such as micro-anchors, are disposed on an outer surface of the support structure, where the grabbing mechanisms can be configured to penetrate or otherwise securably engage the support structure to surrounding native tissue, such as along a valve orifice when the support structure is expanded within the valve orifice.

[0009] In particular implementations, at least one of the one or more grabbing mechanisms comprises a projection having a hook, a sharpened barb, tree-shaped barbs, or an anchor-shaped barb. In some embodiments, at least one of the one or more grabbing mechanisms comprises a strip of projections disposed circumferentially around the support structure. In other implementations, at least one of the one or more grabbing mechanisms comprises a strip of projections disposed along a vertical axis of the support structure. At least one

of the one or more grabbing mechanisms can include a projection that changes shape after a period of time. For example, the projection can be initially held in an undeployed state by a resorbable material.

[0010] The support structure, the one or more grabbing mechanisms, or both the support structure and the one or more grabbing mechanisms can be formed of a shape memory alloy, such as of Nickel-Titanium (Nitinol), in some embodiments. The support structure can be constructed with sufficient radial strength to maintain the native aortic valve in a dilated condition such that the prosthetic valve member can effectively replace the function of the native aortic valve, but is configured such that its diameter is not substantially greater than the native valve's diameter.

[0011] The flexible membrane can be a valve assembly having an inlet side and an outlet side, the valve assembly being configured to allow flow from the inlet side to the outlet side but prevent flow from the outlet side to the inlet side. In some embodiments, the flexible membrane is configured to replace an aortic valve.

[0012] Embodiments of a prosthetic heart valve can comprise an inner and outer support structure that can be delivered separately from one another. For example, one embodiment comprises an outer support structure configured to be radially compressible, expandable into an over-expanded state having a first diameter, and self-adjustable into a functional state having a second diameter less than the first diameter. The prosthetic heart valve can also comprise one or more grabbing mechanisms disposed on an outer surface of the outer support structure, the one or more grabbing mechanisms being configured to penetrate or otherwise securably engage the outer support structure to surrounding native tissue, and an inner support structure configured to be radially compressible and expandable into an expanded state within the interior of the outer support structure, where a flexible valve member can be secured within an interior of the inner support structure.

[0013] As with other embodiments, embodiments comprising an inner and outer support structure can also include at least one grabbing mechanism that

comprises a projection having a hook, a sharpened barb, tree-shaped barbs, or an anchor-shaped barb. One or more of the outer support structure, the inner support structure, or the one or more grabbing mechanisms can be formed of a shape memory alloy. The flexible membrane can be configured to replace an aortic valve. The inner support structure can be configured to securably engage the interior of the outer support structure upon being expanded within the outer support structure.

[0014] In one exemplary method disclosed herein, the transcatheter heart valve can be "over-expanded" within a native aortic valve using a balloon catheter. More particularly, an expandable prosthetic heart valve can be positioned within a patient's aortic valve and expanded, such as by inflating a balloon of a balloon catheter around which the prosthetic heart valve is disposed, to an over-expanded diameter thereby causing one or more projections on an outer surface of the prosthetic heart valve to engage native tissue of the patient's aortic valve. The prosthetic heart valve can be allowed to retract toward a recoil diameter less than the over-expanded diameter (e.g., a "memorized" (if the support structure comprises a shape-memory alloy) or "recoil" diameter), such as by deflating the balloon. As the prosthetic heart valve recoils (reduces in diameter), the one or more projections are engaged with the native tissue of the patient's aortic valve, thereby reducing a diameter of the patient's native aortic valve. This can occur because the projections (*e.g.* micro-anchors) on the support structure are securely engaged with the tissue of the valve annulus. Conventional valves cannot undergo such over-expansion due to materials used and methods of manufacture.

[0015] In some embodiments, the expandable prosthetic heart valve comprises a support structure made of a shape memory alloy that causes the support structure to have the recoil diameter when the support structure is not acted on by any external force. In certain embodiments, the one or more projections include hooks, barbs, or anchors. At least one of the one or more projections changes its shape after penetrating the native tissue of the patient's aortic valve in some embodiments.

[0016] This exemplary method of implanting an over-expanded transcatheter heart valve has a number of advantageous features over known transcatheter heart valves. For example, unlike existing transcatheter heart valves, the over-expanded transcatheter heart valve does not apply an outward radial force on the native valve annulus after implantation. This is advantageous because, as discussed above, a regurgitating valve typically results from a diseased or aging valve annulus that is already substantially dilated. The application of a continuous outward radial force on a weakened and dilated annulus will usually dilate the annulus further. This could result in serious damage to the anatomical structure of the heart and, as the weakened aortic root dilates further, could eventually lead to dislodgement of the transcatheter heart valve.

[0017] By reducing the diameter of the surrounding annulus, it is also possible to replace the native aortic valve using a smaller transcatheter heart valve than would be typically required to treat aortic insufficiency. Due to the recoil of the support structure, the final diameter of the over-expanded transcatheter heart valve is substantially smaller than a conventional THV. A conventional THV must be expanded to a diameter that is capable of being securely maintained in a dilated valve annulus, whereas the over-expanded transcatheter heart valve constricts the annulus and therefore can have a smaller outer diameter. As a result of the smaller final diameter, the over-expanded transcatheter heart valve can also employ a smaller valve member. The smaller valve member allows the over-expanded transcatheter heart valve to be crimped to a much smaller diameter and have a smaller profile during advancement through the patient's vasculature. It will be recognized by those skilled in the art that a smaller diameter facilitates advancement of the transcatheter heart valve through a patient's vasculature.

[0018] Some methods for treating aortic insufficiency can comprise a two-stage delivery. For example, one method comprises positioning an outer stent within a patient's aortic valve, expanding the outer stent to an over-expanded diameter, thereby causing projections on the outer surface of the outer stent to engage tissue of the patient's aortic valve, allowing the outer stent to retract

toward a recoil diameter that is less than the over-expanded diameter while the projections are engaged with the tissue of the patient's aortic valve, thereby causing the diameter of the patient's native aortic valve to be reduced, positioning a prosthetic heart valve within the outer stent, and expanding the prosthetic heart valve while the prosthetic heart valve is positioned within the outer stent.

[0019] In some embodiments, the act of expanding the prosthetic heart valve comprises frictionally securing the prosthetic heart valve within the outer stent, engaging grooves provided within the outer stent with complementary members of the prosthetic heart valve, or engaging a snap mechanism that causes the prosthetic heart valve to be secured within the outer stent, and/or inflating a balloon of a balloon catheter around which the outer stent is disposed. In certain embodiments, the act of allowing the outer stent to retract comprises deflating the balloon of the balloon catheter. In some methods, the outer stent comprises a shape memory alloy. In some methods, the prosthetic heart valve comprises a compressible and expandable inner support structure and a valve membrane secured in an interior of the inner support structure

[0020] The foregoing and other features and advantages of the invention will become more apparent from the following detailed description, which proceeds with reference to the accompanying figures.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] FIG. 1 is an anatomic anterior view of a human heart, with portions broken away and in section to view the interior heart chambers and adjacent structures.

[0022] FIG. 2 is a perspective view of a transcatheter heart valve formed with a shape-memory stent in accordance with an embodiment of the disclosed technology.

[0023] FIG. 3 is a perspective view of another embodiment of a transcatheter heart valve formed with a shape memory support structure according to the disclosed technology.

[0024] FIG. 4 shows an elevation view of one embodiment of a projection (or micro-anchor) that can be used with embodiments of a transcatheter heart valve.

[0025] FIG. 5 illustrates an elevation view of another embodiment of a projection (or micro-anchor) that can be used with a transcatheter heart valve.

[0026] FIG. 6 illustrates an elevation view of another embodiment of a projection (or micro-anchor) that can be used with a transcatheter heart valve.

[0027] FIG. 7 illustrates an elevation view of another embodiment of a projection (or micro-anchor) that can be used with a transcatheter heart valve.

[0028] FIG. 8 illustrates an elevation view of another embodiment of a projection (or micro-anchor) that can be used with a transcatheter heart valve.

[0029] FIG. 9 illustrates an elevation view of another embodiment of a projection (or micro-anchor) that can be used with a transcatheter heart valve.

[0030] FIG. 10 is a perspective view of a transcatheter heart valve formed with a shape memory support structure in accordance with another embodiment of the disclosed technology.

[0031] FIG. 11 is a simplified side view of a balloon catheter delivery system that is configured to over-expand the shape memory support structure at a target area inside a patient's body in accordance with an embodiment of the disclosed technology.

[0032] FIGS. 12-15 are simplified sectional views of a transcatheter heart valve being deployed in accordance with an embodiment of the disclosed technology.

[0033] FIGS. 16-20 show simplified sectional views of one embodiment of a transcatheter heart valve being deployed in a two-stage process according to an exemplary method of the disclosed technology.

[0034] FIGS. 21-25 show perspective views of additional embodiments of projections (or micro-anchors) that can be used with a transcatheter heart valve.

[0035] FIG. 26 is an elevation view of another embodiment of a transcatheter heart valve according to the disclosed technology. In particular, the embodiment illustrated in FIG. 26 has two attachable sections.

DETAILED DESCRIPTION

[0036] As used in this application and in the claims, the singular forms "a," "an," and "the" include the plural forms unless the context clearly dictates otherwise. Additionally, the term "includes" means "comprises." Although the operations of exemplary embodiments of the disclosed method may be described in a particular, sequential order for convenient presentation, it should be understood that the disclosed embodiments can encompass an order of operations other than the particular, sequential order disclosed. For example, operations described sequentially may in some cases be rearranged or performed concurrently. Further, descriptions and disclosures provided in association with one particular embodiment are not limited to that embodiment, and may be applied to any embodiment disclosed herein. Moreover, for the sake of simplicity, the attached figures may not show the various ways in which the disclosed system, method, and apparatus can be used in combination with other systems, methods, and apparatuses.

[0037] In vertebrate animals, the heart is a hollow muscular organ having four pumping chambers as seen in FIG. 1. The left and right atria 2, 4 and the left and right ventricles 6, 8, are each provided with their own one-way valve. The natural heart valves are identified as the aortic 10, mitral (or bicuspid) 12, tricuspid 14, and pulmonary 16, and are each mounted in an annulus comprising dense fibrous rings attached either directly or indirectly to the atrial and ventricular muscle fibers. Each annulus defines a flow orifice.

[0038] The atria 2, 4 are the blood-receiving chambers, which pump blood into the ventricles 6, 8. The ventricles 6, 8 are the blood-discharging chambers. The synchronous pumping actions of the left and right sides of the heart constitute the cardiac cycle. The cycle begins with a period of ventricular relaxation, called ventricular diastole. The cycle ends with a period of ventricular contraction, called ventricular systole. The four valves 10, 12, 14, 16 ensure that blood does not flow in the wrong direction during the cardiac cycle; that is, to ensure that the blood does not back flow from the ventricles 6, 8 into the corresponding atria 2, 4, or back flow from the arteries into the

corresponding ventricles 6, 8. The mitral valve 12 is between the left atrium 2 and the left ventricle 6, the tricuspid valve 14 between the right atrium 4 and the right ventricle 8, the pulmonary valve 16 is at the opening of the pulmonary artery, and the aortic valve 10 is at the opening of the aorta. As discussed, in aortic insufficiency, the aortic valve 10 can become dilated, thus preventing the valve from fully closing. Embodiments of the present disclosure can be deployed to the aortic valve, specifically to the area of the aortic valve annulus, to treat aortic insufficiency.

[0039] FIG. 2 is a perspective view of an exemplary transcatheter heart valve 100 (also referred to as bioprosthesis 100). Bioprosthesis 100 includes a tubular support structure 102, a flexible membrane 104 (e.g., a valve member), a membrane support 106, and one or more grabbing mechanisms 108 affixed about a circumference of the support structure 102.

[0040] The support structure 102 in FIG. 2 can be formed of a shape memory material, such as Nitinol. In one exemplary embodiment, the support structure 102 can be radially compressed into a compressed state for delivery through the patient's vasculature, but can self expand to a natural, uncompressed or functional state having a preset diameter. In other words, the support structure 102 moves or tends toward a preset diameter when free of external forces. Furthermore, the support structure 102 can be expanded beyond its natural diameter to an over-expanded diameter. After the support structure 102 is in this over-expanded state, the support structure returns toward its preset diameter (or naturally recoils to the preset or recoil diameter).

[0041] The support structure 102 can be generally tubular in shape and has a longitudinal flow path along its structural axis. The support structure 102 can include a grated framework, such as a stent, configured to secure bioprosthesis 100 within or adjacent to the defective valve annulus of the heart. The support structure 102 further provides stability and prevents the bioprosthesis 100 from migrating after it has been implanted.

[0042] In alternative embodiments, the support structure 102 can comprise other shape memory alloys, or other materials capable of providing sufficient

support for the bioprosthesis 100. Such materials can include other metals, metal alloys such as stainless steel or cobalt chromium, and/or polymers. The support structure 102 can have configurations other than that shown in FIG. 2. For example, the support structure 102 can have a different shape, more or fewer vertical support bars, and/or additional structures for added stability. The support structure 102 can comprise a strut mesh and/or sleeve structure.

[0043] The flexible membrane 104 is a valve member that is positionable in the flow path of the support structure 102 and that is configured to permit flow in a first direction but substantially resist flow in a second direction. In certain implementations, the flexible membrane 104 comprises a biological tissue formed into a valve member. The biological tissue which forms the valve member can comprise pericardial tissue harvested from an animal heart, such as porcine, bovine, or equine pericardium. The flexible membrane 104 can also comprise, alternatively or additionally, biocompatible materials including synthetic polymers such as polyglycolic acid, polylactic acid, and polycaprolactone, and/or other materials such as collagen, gelatin, chitin, chitosan, and combinations thereof.

[0044] The membrane support 106 can be positionable in the flow path and affixed to the support structure 102. Membrane support 106 can comprise polyethylene terephthalate (PET) (e.g., Dacron), or any other suitable material. The membrane support 106 can be positioned such that it folds under and around the bottom of the flexible membrane 104. The membrane support 106 can be sutured or otherwise affixed to the flexible membrane 104. In some embodiments, the membrane support 106 can comprise a skirt on the exterior surface of the flexible membrane 104, and a thinner ribbon on the interior surface of the flexible membrane 104, within the flow path. In this embodiment, the ribbon and skirt structures of the membrane support 106 can be sutured together, with a portion of the flexible membrane between them. In some embodiments, the membrane support 106 can be a thin layer of material, such as a layer of PET that can be from about 0.01 mm thick to about 0.2 mm thick. In some embodiments, the thickness of the membrane support 106 can

vary from the center to the edge. For example, in one embodiment, the membrane support 106 can be about 0.07 mm thick at an edge, and about 0.05 mm thick at the center. In another specific embodiment, the membrane support 106 can be about 0.13 mm thick at the edge, and about 0.10 mm thick at the center. Additional details of the support structure 102, the flexible membrane 104, and the membrane support 106 are described in U.S. Patent Nos. 6,730,188 and 6,893,460, both of which are hereby incorporated herein by reference. Furthermore, U.S. Patent Nos. 6,730,188 and 6,893,460 describe additional prosthetic valve that can be modified according to the disclosed technology and used as part of any of the disclosed apparatus or systems or used with any of the disclosed methods or procedures.

[0045] In certain embodiments, grabbing mechanisms 108 are configured as strips of projections or micro-anchors 110. The grabbing mechanisms 108 can vary from implementation to implementation, but in certain implementations comprise any structure capable of at least partially penetrating and engaging the target tissue. For example, the projections 110 can be designed to at least partially penetrate and/or otherwise engage (*e.g.* by clamping or grabbing) the surrounding tissue upon over-expansion and to contract the aortic annulus and surrounding native tissue along with the support structure 102 upon recoil of the support structure 102. In other embodiments, the projections 110 may include barbed projections, umbrella projections, and/or hooks also designed to at least partially penetrate the tissue upon over-expansion and contract the aortic annulus and surrounding tissue upon recoil of the support structure 102.

[0046] As shown in FIG. 2, the grabbing mechanisms 108 can be positioned and coupled to the support structure 102 as vertical, or axial, strips of projections 110. In an alternative embodiment shown in FIG. 3, the grabbing mechanisms 109 can be positioned and coupled to the support structure 102 as one or more horizontal, or circumferential, strips of projections 111. For example, one or more strips of projections 111 can be disposed around the circumference of the support structure 102. Such grabbing mechanisms 109 can extend substantially around the circumference of the support structure 102,

and/or strips of projections 111 can extend only partially around the circumference of the support structure 102, such as horizontal arcs of projections. In some embodiments, projections can be provided in one or more localized areas of the support structure 102, in addition to or instead of being provided in linear strips. In certain embodiments, one or more strips of projections can be provided along one or more struts or wires of the support structure 102, substantially paralleling the angles of the support structure 102. In another embodiment, the strips can be disposed circumferentially around the support structure 102 and located along the commissural supports (e.g. portions of the support structure wherein adjacent prosthetic leaflets meet and attach to the support structure) of support structure 102.

[0047] Some implementations of the bioprosthesis 100 shown in FIGS. 2 and 3 can comprise only one grabbing mechanism 108, 109. Alternative embodiments can comprise two or more grabbing mechanisms 108, 109. Further, the grabbing mechanisms 108, 109 can be manufactured separately from the support structure 102 and attached to the support structure through a suitable means (e.g., sutures, adhesive, weld, snap-fit mechanism, friction, and the like). Alternatively, the grabbing mechanisms 108, 109 can be formed as an integral feature of the support structure. Each grabbing mechanism 108, 109 generally comprises one or more projections or micro-anchors 110, 111. The projections or micro-anchors 110 can have any suitable dimension. For instance, the projections 110 can have a length from approximately 1 mm to approximately 2 mm. Projections 110 can be smaller in some embodiments, such as having a length from about .001 mm to about 1 mm. Alternatively, projections 110 can be larger in some embodiments, such as having a length from about 2 mm to about 6.5 mm or larger. In some embodiments, a grabbing mechanism 108, 109 can include a plurality of projections 110, where at least a first projection can be a different size from a second projection. A single grabbing mechanism can include a plurality of sizes of projections.

[0048] In some embodiments, the projections can be formed of a shape memory material that is configured to change shape. For instance, in one

implementation, the projections can change shape after penetrating the tissue. For example, barbs at the tip of the projections can change in angle or configuration in relation to the projection after penetrating the tissue in order to more securely engage with the tissue. In another embodiment, the projections can change shape after expansion of the support structure 102. For example, the projections 110 can lay flat against the support structure 102 while the bioprosthesis is in its contracted configuration, and the projections can expand and the barbs can change shape to extend laterally outward from the projection to prevent the projection from slipping out of the tissue once the bioprosthesis 100 has been expanded.

[0049] In one variation, one or more projections can be configured with a delayed release mechanism, such that at least a portion of each projection changes shape after a period of time. This may be achieved by incorporating a resorbable material into the projection for temporarily holding the projection in a constrained condition. As the resorbable material is resorbed by the body, the projection becomes free to assume its relaxed condition. As the projection moves to its relaxed condition, its shape can change to more securely engage and hold the surrounding tissue. For example, barbs or hooks associated with the projection can initially be held against the main body portion of the projection until the resorbable material is resorbed. At that time, the barb or hook can extend outwardly from the main body portion, thereby creating a more secure attachment to the tissue in which the projection is inserted.

[0050] FIGS. 4-9 show elevation views of various embodiments of projections 400, 402, 404, 406, 408, 410 that can be used with embodiments of a transcatheter heart valve according to the present disclosure. In general, the projections 400, 402, 404, 406, 408 include a main body portion and one or more barbs. For instance, the illustrated projections include projection 400 with a single sharpened barb 401, projection 402 with a hook-shaped barb 403, projection 404 with an anchor-shaped (arrow head) barb 405, projection 406 with multiple branch-like barbs 407, projection 408 with multiple tree-shaped sharpened barbs 409, and hook-shaped projection 410. Suitable projections

further include spikes, staples, fasteners, tissue connectors, or any other suitable projection capable of engaging with a patient's native tissue. Embodiments of suitable projections 400, 402, 404, 406, 408, 410 can be designed to penetrate the aortic valve annulus and engage or lodge within the thickness of the aortic valve annulus such that when the bioprosthesis retracts toward its natural state, the projections pull the patient's native tissue inward towards the center of the flow path, substantially without dislodging from their engaged positions. The barbs can be formed on the projections 400, 402, 404, 406 408 by laser cutting or other appropriate manufacturing method. Suitable materials for projections include Nitinol, other shape memory alloys, stainless steel, cobalt chromium, titanium, Elgiloy, HDPE, nylon, PTFE, other biocompatible polymers, resorbable materials, and combinations thereof. Other suitable materials are known in the art, and the projections of the present disclosure are not limited to those discussed.

[0051] FIGS. 21-25 illustrate additional possible embodiments of projections 416, 418, 420, 422, 424. FIG. 21 shows a projection 416 that has a square cross-sectional base and a pyramidal pointed tip, wherein a cutout between the base and the tip can facilitate engagement within a patent's native tissue. FIG. 22 shows a pointed projection 418 that can extend at an angle from the surface of a support structure or bioprosthesis. FIG. 23 shows an asparagus tip-like projection 420. FIG. 24 shows a conical projection 422. FIG. 25 shows another embodiment of a tree-like projection 424.

[0052] FIG. 10 is a perspective view of another embodiment of a transcatheter heart valve 100a (also referred to as bioprosthesis 100a) according to the disclosed technology. Bioprosthesis 100a includes a support structure 102a having a tubular or cylindrical base, a flexible membrane 104a (e.g., valve member), a membrane support 106a and at least one grabbing mechanism 108a affixed about a circumference of the support structure 102a. The support structure 102a is expandable from a first reduced diameter to a second enlarged diameter, and has a flow path along a structural axis. The support structure 102a generally can include a tubular framework, such as a stent, which

primarily secures bioprosthesis 100a within or adjacent to the defective valve annulus of the heart. In this embodiment, the support structure 102a is configured to approximate the shape of the flexible membrane 104a such that the upper end of support structure 102a comprises peaks at the commissure supports and valleys (e.g. U-shaped cusps) between the commissure supports.

[0053] FIG. 26 is a perspective view of another embodiment of a transcatheter heart valve having two attachable sections 700, 702 that can be delivered separately. This embodiment can reduce the cross-sectional profile during delivery because each section 700, 702 can have a smaller delivery profile than the entire assembled bioprosthesis. In the illustrated embodiment, outer section 700 comprises an outer stent structure 710, and inner section 702 comprises an inner stent structure 720 and a valve member 722. In this embodiment, the inner stent structure 720 and the valve member 722 together form the expandable prosthetic heart valve. The outer section 700 can optionally include a temporary valve member 712, which can be thinner or less durable than the more permanent valve member 722. The temporary valve member 712 can be mounted on or otherwise secured to the outer stent structure 710 using any suitable mechanism (e.g., sutures, snaps, screws, friction, hooks, barbs, adhesives, and/or a slide structure). Furthermore, the temporary valve member 712 can be configured to have a diameter and flexibility suitable to receive the inner section 702 during valve delivery. The valve member 722 can be any valve as described herein and can be mounted to or otherwise secured to the inner stent structure 720 using any suitable means (e.g., sutures, snaps, screws, a slide structure, friction, hooks, barbs, and/or an adhesive).

[0054] In some embodiments, the outer section 700 can comprise a thin compressible member 712 that can facilitate securing the inner section 702 within the outer section 700. Such a compressible member 712 can create a tight seal between the outer section 700 and the inner section 702 as the inner section presses into the compressible material. Further details regarding a compressible member 712 are disclosed in U.S. Patent Application Publication No. 2008/0208327, which is hereby incorporated herein by reference.

[0055] According to one exemplary delivery procedure, and as more fully explained below in connection with FIGS. 16-20, the outer section 700 is delivered to the aortic valve first. The outer stent structure 710, like embodiments discussed above, can comprise a shape memory alloy such as Nitinol, and can have a predetermined recoil (or natural) diameter. The outer section 700 can be over-expanded to a diameter greater than its recoil diameter. For example, the outer section 700 can be disposed around a balloon catheter and delivered to the interior of the native heart valve. The balloon of the balloon catheter can then be inflated, causing the outer section 700 to expand to a diameter beyond its recoil diameter. In particular implementations, the outer section 700 comprises one or more grabbing mechanisms 708 configured to engage with the native tissue when the outer stent structure 710 is over-expanded. For example, the grabbing mechanisms 708 can be any of the grabbing mechanisms described above. Once the balloon of the balloon catheter is deflated and removed, the outer section 700 will contract to its memorized or recoil diameter. On account of the engagement of the grabbing mechanisms 708 to the surrounding tissue, the contraction of the outer section 700 will cause the size of the aortic annulus to be reduced as well. Inner section 702 can then be delivered and engaged with the outer section 700.

[0056] In an alternative method of delivering the two part bioprosthesis, the outer section 700 can be delivered to the interior of a native heart valve in a crimped state, and allowed to expand to its predetermined natural diameter, once positioned. A balloon can then be inserted within the outer section 700. When the balloon is expanded, the outer section can be over-expanded to a diameter greater than its natural diameter to allow the grabbing mechanisms of the outer section 700 to engage with the native valve tissue. When the balloon is deflated, contraction of the outer section 700 can cause the size of the aortic annulus to be reduced. When compared to the previous method, this can allow for delivering the outer section 700 in a smaller crimped state, because the outer section 700 is not crimped over the balloon for delivery; the balloon is not inserted until after the outer section 700 is first allowed to expand to its natural

diameter. Inner section 702 can then be delivered and engaged with the outer section 700.

[0057] FIG. 11 is a simplified illustration of a balloon catheter 200, which can be used to deliver and deploy a bioprosthesis (such as bioprosthesis 100 shown in FIG. 2 above) into a native heart valve. In one embodiment, the balloon catheter 200 advances the bioprosthesis 100 through an outer sheath of the delivery system over a guide wire 204. The balloon catheter 200 can also be configured to aid in the delivery and positioning of the bioprosthesis 100 within the native valve. For example, as shown in FIG. 11, the balloon catheter 200 can include a tapered nose cone tip 206 at its distal end that allows a balloon portion 202 and bioprosthesis 100 to cross easily into the native valve. The balloon portion 202 can be inflated (*e.g.*, using a controlled volume of saline), causing the bioprosthesis 100 to expand within and engage the native hart valve.

[0058] In one exemplary method, the guide wire 204 is inserted into the femoral artery of a patient, advanced through the aortic arch of a patient, and into the aortic valve. The balloon catheter 202 is advanced through the outer sheath of the delivery system, over the guide wire 204, and into the aortic valve. The bioprosthesis 100 is then positioned and secured within the native valve by inflating the balloon portion 202. FIGS. 12-15, described below, illustrate one exemplary procedure for deploying the bioprosthesis 100 into the native valve. The balloon portion 202 can then be deflated, and the balloon catheter 202 retracted from the patient's aorta and femoral artery. An exemplary delivery system designed to deliver the bioprosthesis 100 is the RETROFLEX II catheter assembly available from Edwards Lifesciences in Irvine, CA. Furthermore, although the operation described above is a percutaneous transfemoral procedure, it should be understood that embodiments of the disclosed technology include the use of a shorter catheter assembly or semi-rigid cannula for deploying a bioprosthesis in a minimally invasive surgical (MIS) procedure, such as a trans-apical procedure. In a transapical procedure, the catheter or cannula is inserted through a gap between the ribs and is advanced through a small incision formed along the apex of the heart. This technique

advantageously provides the surgeon with a direct line of access to the aortic valve. U.S. Patent Application Publication Nos. 2008/0065011, 2007/0005131, and 2007/008843 disclose further details regarding suitable delivery methods, and are hereby incorporated herein by reference.

[0059] FIGS. 12-15 are schematic cross-sectional views of a patient's aorta illustrating delivery of the support structure and valve of FIG. 2. As shown in FIG. 12, in one embodiment, the bioprosthesis 100 may be introduced into the patient's body using a percutaneous delivery technique with the balloon portion 202 of the balloon catheter 200 deflated, and the bioprosthesis 100 operably disposed thereon. The bioprosthesis can be contained in a radially crimped or compressed state. In embodiments using a self-expandable bioprosthesis 100, the bioprosthesis 100 can be held in a compressed state for delivery, by, for example, containing the bioprosthesis within an outer covering or sheath 201. The outer covering 201 can be removed or retracted, or the bioprosthesis 100 pushed through the outer covering 201, to allow the self-expandable bioprosthesis 100 to self-expand. In embodiments having a bioprosthesis that does not self-expand, such an outer covering may not be needed to retain the bioprosthesis in a crimped state, but can nonetheless be used if desired (*e.g.* to reduce friction during delivery).

[0060] In the embodiment illustrated in FIG. 12, the projections 110 of the grabbing mechanisms 108 are disposed around the outside circumference of support structure 102.

[0061] In the illustrated embodiment, the bioprosthesis 100 is introduced and positioned across the native aortic valve annulus (AVA) 300 by being inserted at least partially through native valve leaflets 302 and expanded. Because the AVA of an aortic valve suffering from aortic insufficiency is dilated, diameter D1 of the AVA 300 is expected to be larger than the diameter of a healthy AVA.

[0062] As shown in FIG. 13, outer sheath or covering 201 can be retracted or removed from over the bioprosthesis 100. In embodiments having a bioprosthesis 100 comprising a shape memory alloy, the bioprosthesis can

expand from its crimped or compressed diameter d to a predetermined or memorized diameter R once the sheath 201 is removed.

[0063] As shown in FIG. 14, the balloon portion 202 of the balloon catheter 200 is expanded to increase the diameter of the support structure 102 from its relaxed diameter R (FIG. 13) to an over-expanded diameter OE such that the outer diameter of the bioprosthesis 100 equals or exceeds the original diameter D1 of the AVA 300. In this manner, the AVA 300 may expand beyond the diameter D1 as well. During the expansion, the projections 110 of the grabbing mechanisms 108 are forced to contact and can penetrate or otherwise engage (*e.g.* clamp or grab) the target tissue, which may include the AVA 300 and some of the tissue surrounding the AVA. This causes the bioprosthesis 100 to adhere to the surrounding tissue.

[0064] Next, as shown in FIG. 15, the balloon portion 202 of the balloon catheter 200 can be deflated, and the balloon catheter 200 removed from the AVA 300. In embodiments where the support structure 102 is formed of a shape memory material, removing the expansion force of balloon 202 from support structure 102 allows the support structure 102 to return from an over-expanded diameter OE (FIG. 14) to a recoil or relaxed diameter R. The manufacture of the support structure (*i.e.*, stent) determines what the recoil diameter will be. For example, the recoil diameter of a support structure comprising a shape memory alloy can be the memorized or functional diameter of the support structure. The recoil diameter of a support structure comprising, for example, stainless steel and/or cobalt chromium can be that of the natural or resting diameter of the support structure, once it inherently recoils from being over-expanded by the balloon 202. As the diameter of bioprosthesis 100 decreases to the recoil diameter R, the diameter of the AVA 300 also decreases to a final diameter D2. The AVA 300 can decrease in diameter due to the projections 110 of the support structure 102 pulling the target tissue inward.

[0065] An existing bioprosthesis is generally configured to be radially expanded to a diameter capable of providing secure fixation in a dilated AVA. However, as discussed above, existing bioprostheses are not well suited for

treating aortic insufficiency due to the lack of firm tissue in the aortic annulus. Using existing technology, a larger bioprosthesis could be used to create a more secure fixation; however, a larger bioprosthesis cannot be easily crimped down for delivery via a catheterization technique. In contrast, embodiments of the present bioprosthesis 100 allow for the collapsed diameter of bioprosthesis 100 to be a smaller diameter because bioprosthesis 100 may be assembled with a smaller stent and a smaller valve member. This smaller size is possible because, rather than stretch the AVA, the present bioprosthesis advantageously reduces the diameter of the AVA during implantation. As a result, a smaller overall structure can be achieved which allows the support structure 102 of bioprosthesis 100 to be crimped to the smaller collapsed diameter and thus have a smaller profile for delivery through a patient's vasculature. For example, in some embodiments, bioprosthesis 100 can be crimped to a size of from about 4 French to about 7 French.

[0066] In alternative embodiments, the bioprosthesis 100 need not be operably disposed on the balloon 202 during delivery. For example, the bioprosthesis 100 can be crimped onto the catheter 200 at a different location than the balloon 202. The bioprosthesis can be allowed to self-expand once positioned within a patient's native aortic valve, and the balloon 202 can be positioned inside the self-expanded bioprosthesis 100 and inflated to then over-expand the bioprosthesis 100.

[0067] FIGS. 16-20 show simplified elevation views of one embodiment of a transcatheter heart valve being deployed in a two-stage process according to one method of the present disclosure. The illustrated method can be used, for example, to deliver the transcatheter heart valve assembly shown in FIG. 11. In the method illustrated in FIGS. 16-20, the outer section 700 can be deployed to the aortic valve separately from valve member 702. FIG. 16 shows the outer section 700 on a balloon 202, positioned inside the leaflets 302 of the aortic valve annulus 300. The outer section 700 can be a self-expanding stent, such as a stent comprising a shape memory alloy, or the outer section 700 can be simply balloon expandable, such as a stent comprising stainless steel, cobalt chromium

and/or other suitable biocompatible materials. FIG. 17 shows the balloon 202 in an inflated configuration, which can expand the outer section 700 such that grabbing mechanisms 708 engage with the native tissue of the leaflets 302 and/or the aortic valve annulus 300.

[0068] As shown in FIG. 18, the balloon 202 can be deflated and removed. The outer section 700 can reduce the diameter of the aortic valve annulus 300 as it retracts after the balloon 202 is removed. The outer section 700 can retract to a functional or memorized diameter if it comprises a shape memory alloy, or the outer section 700 can simply naturally recoil or retract due to the ductility of the material. The inner section 702 can be positioned within the outer section 700 using a catheter 200 and a balloon 202, as shown in FIG. 19. As shown in FIG. 20, the balloon 202 can be expanded, thus expanding the crimped inner section 702, allowing it to engage with the outer section 700.

[0069] The outer section 700 and the inner section 702 can be delivered on a single catheter 200 or on separate catheters. For example, a catheter 200 can include two expandable balloons, one distal to the other. A first balloon can be used to expand the outer section 700 then deflated and either guided through the lumen of the expanded outer section 700 or removed back through the lumen. The second balloon and inner section 702 can then be positioned within the outer section 700, and the second balloon can be expanded, allowing for the inner section 702 to engage with the outer section 700. The second balloon can then be deflated, and the catheter 200 removed, thus removing the first and second balloons. In alternative embodiments, separate catheters can be used, such that a first catheter is used to deliver a first balloon and the outer section 700 to the native valve, and a second catheter is used to deliver a second balloon and the inner section 702 to the native valve once the outer section has been deployed and the first catheter has been removed.

[0070] While FIG. 16 illustrates the outer section 700 being delivered while already crimped on the balloon 202, in alternative embodiments, the outer section 700 can be located at a different position on the catheter 200 than the balloon 202. For example, in some embodiments, a crimped outer section 700

can be delivered to a native aortic valve and allowed to self-expand, such as by removing an outer covering. The balloon 202 can then be positioned within the expanded outer section 700 and inflated, thereby over-expanding the outer section 700, allowing the grabbing mechanisms 708 to engage with the native tissue. The balloon can then be deflated and removed, and the inner section 702 can be delivered and engaged with the outer section 700.

[0071] It should be understood that embodiments of bioprosthesis 100 can be deployed using a non-inflatable, mechanical embodiment of delivery catheter 200. Furthermore, bioprosthesis 100 can be delivered using any suitable delivery method, including both transapical and femoral artery delivery methods. Additionally, although the disclosed embodiments concern aortic valve replacement, embodiments of the disclosed technology can be used to replace any dilated heart valve (e.g., a dilated mitral valve). Moreover, although bioprosthesis 100 is used as an exemplary embodiment of the disclosed technology, it should be understood that bioprosthesis 100 and bioprosthesis 100a may be considered interchangeable with one other, or with any other bioprosthesis made or adapted in accordance with the teachings of the disclosed technology.

[0072] Having illustrated and described the principles of the disclosed technology, it will be apparent to those skilled in the art that the disclosed embodiments can be modified in arrangement and detail without departing from such principles. In view of the many possible embodiments to which the principles of the disclosed technologies can be applied, it should be recognized that the illustrated embodiments are only preferred examples of the technologies and should not be taken as limiting the scope of the invention. Rather, the scope of the invention is defined by the following claims and their equivalents. I therefore claim all that comes within the scope and spirit of these claims.

I claim:

1. A prosthetic heart valve comprising:

a support structure configured to be radially compressible into a compressed state, expandable into an over-expanded state having a first diameter, and self-adjustable into a functional state having a second diameter less than the first diameter;

a flexible valve member secured within an interior of the support structure; and

one or more grabbing mechanisms disposed on an outer surface of the support structure, the one or more grabbing mechanisms being configured to penetrate or otherwise securably engage the support structure to surrounding native tissue.

2. The prosthetic heart valve of claim 1, wherein at least one of the one or more grabbing mechanisms comprises a projection having a hook, a sharpened barb, tree-shaped barbs, or an anchor-shaped barb.

3. The prosthetic heart valve of claim 1, wherein the support structure, the one or more grabbing mechanisms, or both the support structure and the one or more grabbing mechanisms are formed of a shape memory alloy.

4. The prosthetic heart valve of claim 1, wherein the flexible membrane is a valve assembly having an inlet side and an outlet side, the valve assembly being configured to allow flow from the inlet side to the outlet side but prevent flow from the outlet side to the inlet side.

5. The prosthetic heart valve of claim 1, wherein the flexible membrane is configured to replace an aortic valve.

6. The prosthetic heart valve of claim 1, wherein at least one of the one or more grabbing mechanisms comprises a strip of projections disposed circumferentially around the support structure.

7. The prosthetic heart valve of claim 1, wherein at least one of the one or more grabbing mechanisms comprises a strip of projections disposed along a vertical axis of the support structure.

8. The prosthetic heart valve of claim 1, wherein at least one of the one or more grabbing mechanisms includes a projection that changes shape after a period of time.

9. The prosthetic heart valve of claim 8, wherein the projection is initially held in an undeployed state by a resorbable material.

10. A prosthetic heart valve comprising:

an outer support structure configured to be radially compressible, expandable into an over-expanded state having a first diameter, and self-adjustable into a functional state having a second diameter less than the first diameter;

one or more grabbing mechanisms disposed on an outer surface of the outer support structure, the one or more grabbing mechanisms being configured to penetrate or otherwise securably engage the outer support structure to surrounding native tissue;

an inner support structure configured to be radially compressible and expandable into an expanded state within the interior of the outer support structure; and

a flexible valve member secured within an interior of the inner support structure.

11. The prosthetic heart valve of claim 10, wherein at least one of the one or more grabbing mechanisms comprises a projection having a hook, a sharpened barb, tree-shaped barbs, or an anchor-shaped barb.

12. The prosthetic heart valve of claim 10, wherein any one or more of the outer support structure, the inner support structure, or the one or more grabbing mechanisms are formed of a shape memory alloy.

13. The prosthetic heart valve of claim 10, wherein the flexible membrane is configured to replace an aortic valve.

14. The prosthetic heart valve of claim 10, wherein the inner support structure is configured to securably engage the interior of the outer support structure upon being expanded within the outer support structure.

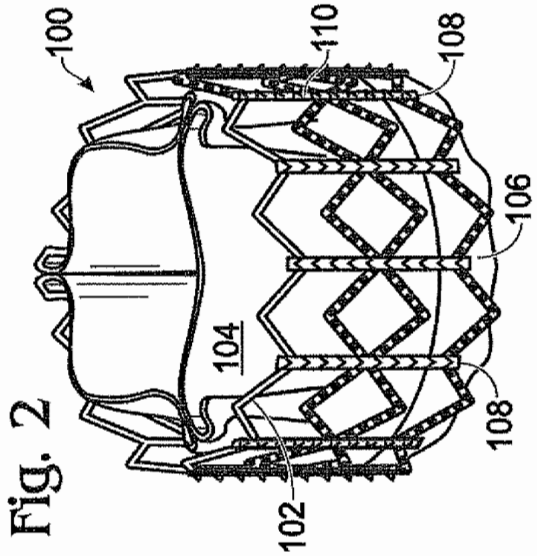


Fig. 2

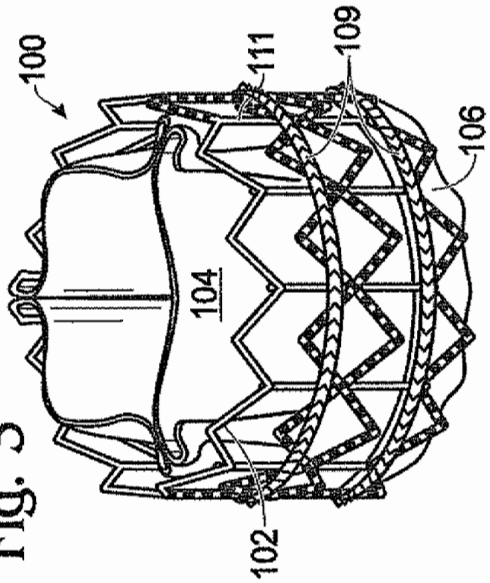


Fig. 3

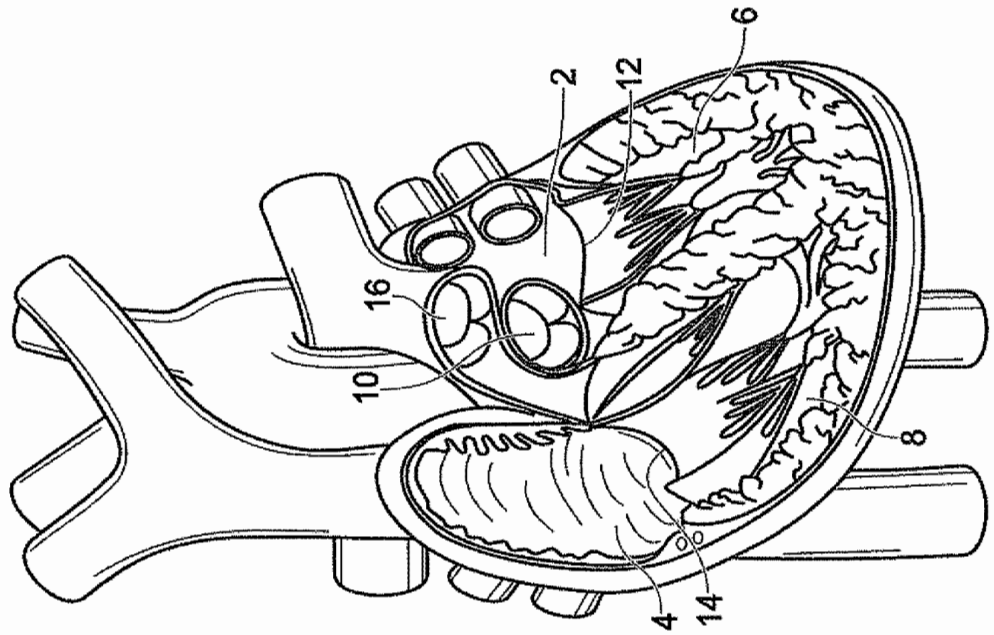


Fig. 1

Fig. 4

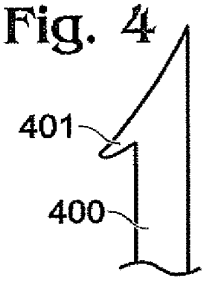


Fig. 5

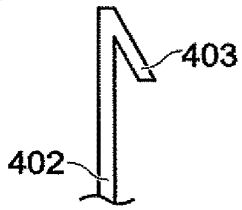


Fig. 6

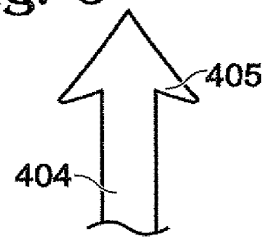


Fig. 7

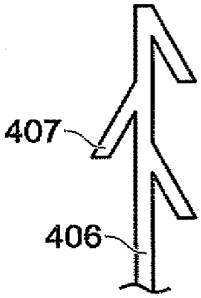


Fig. 8

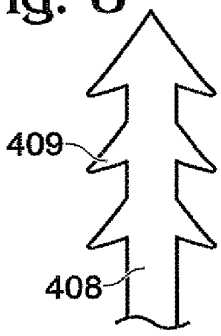
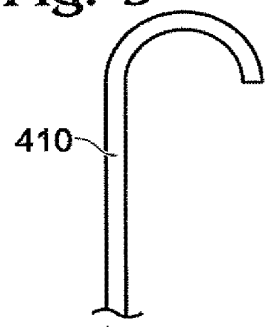


Fig. 9



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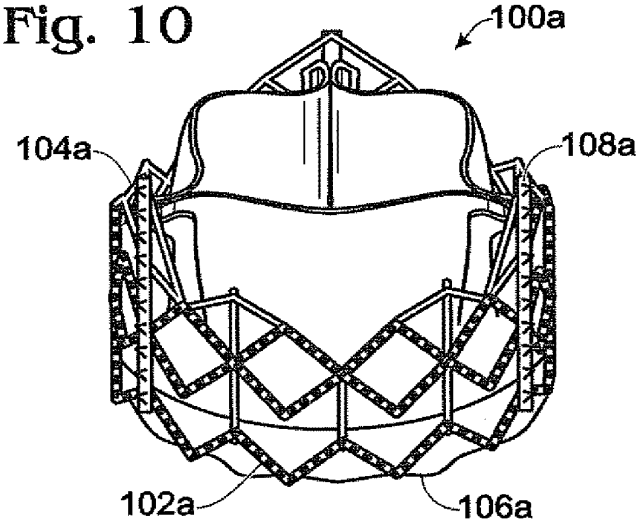

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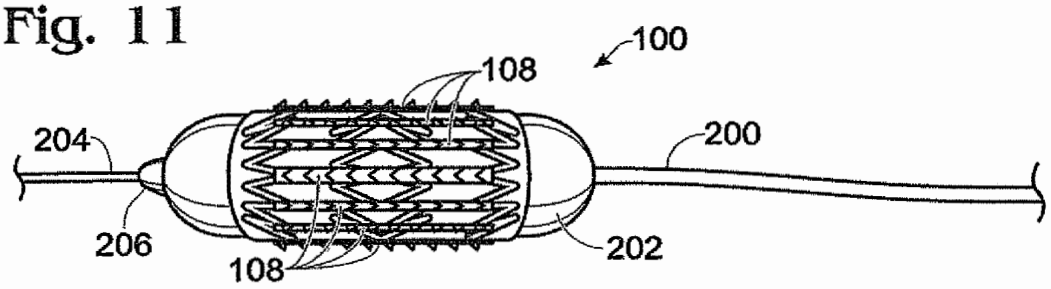
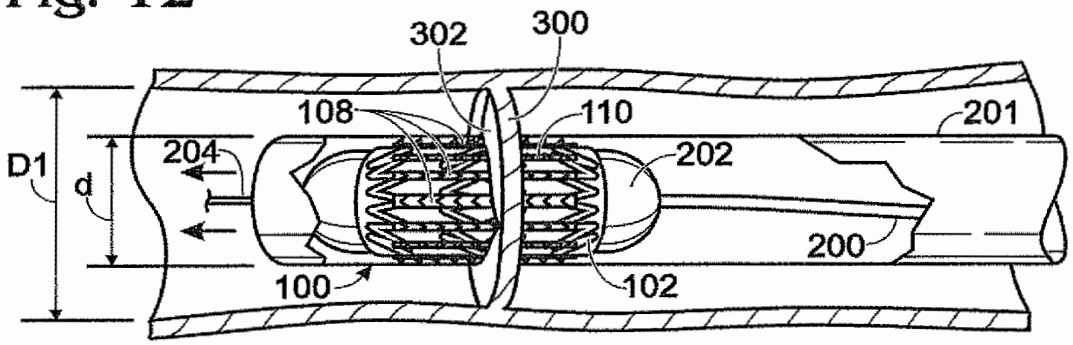


Fig. 12



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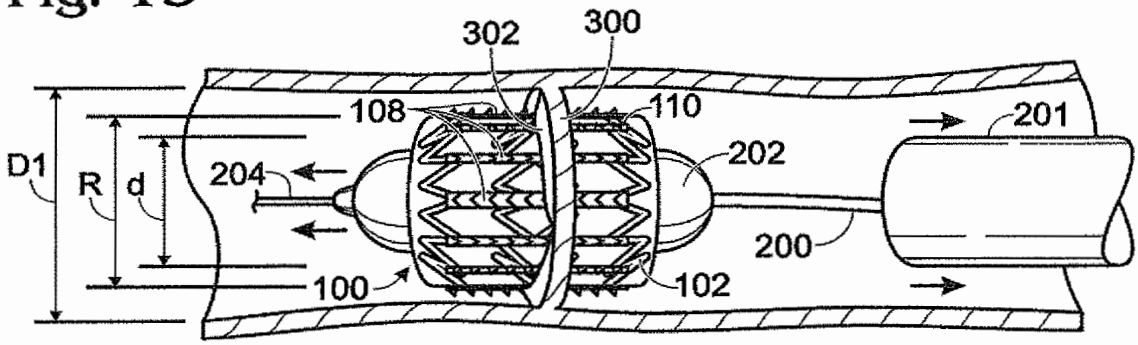
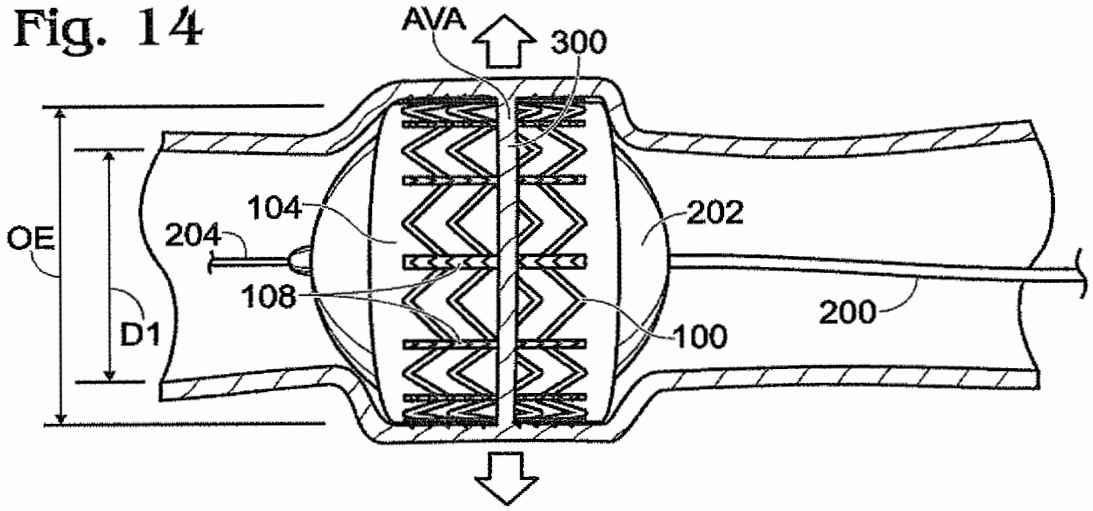


Fig. 14



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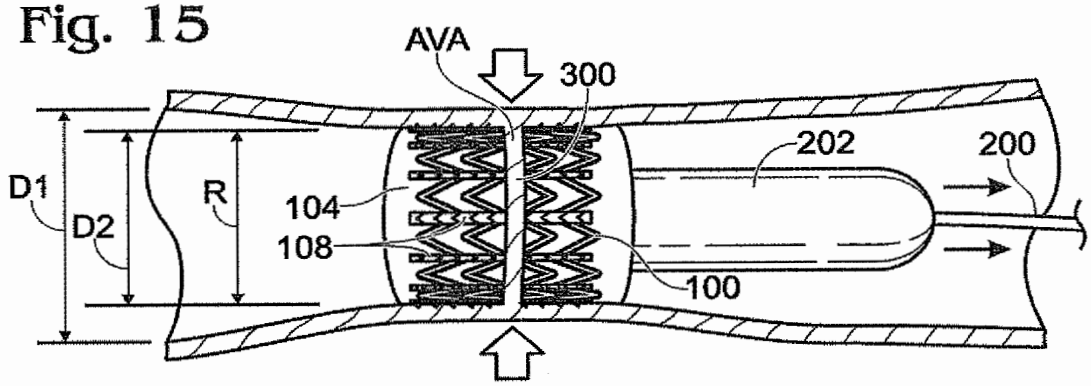

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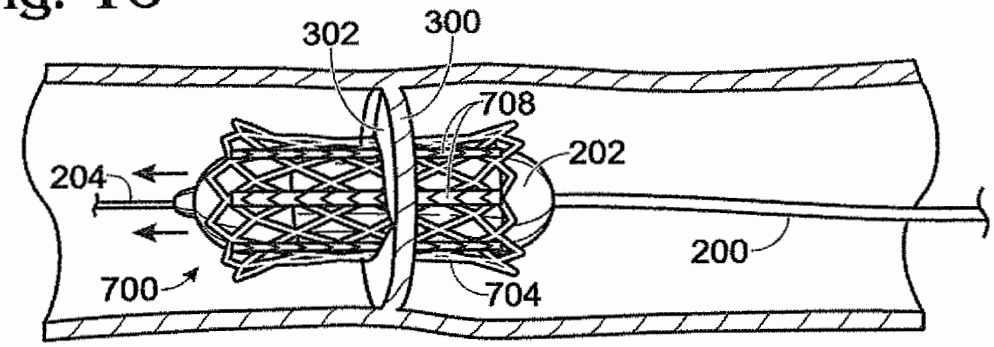


Fig. 17

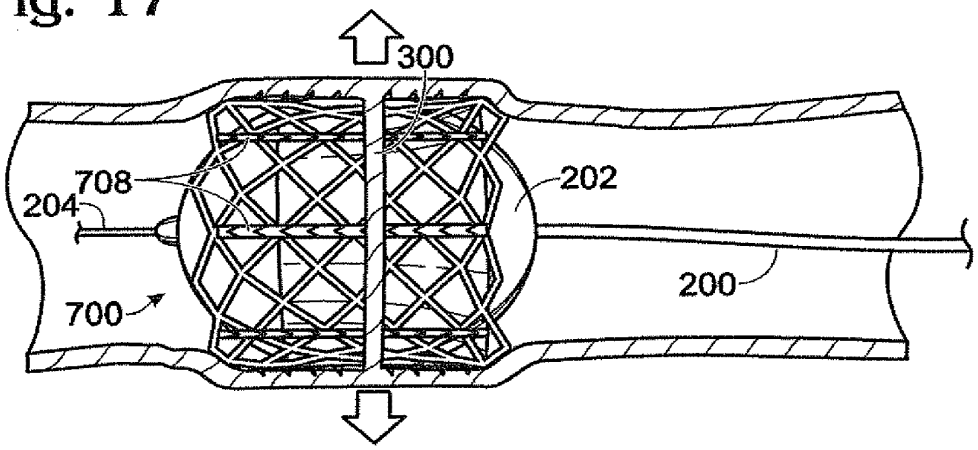


Fig. 18

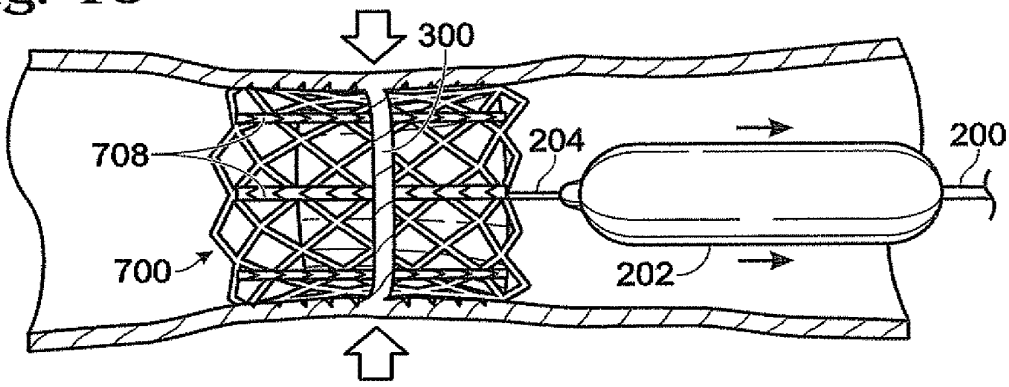


Fig. 19

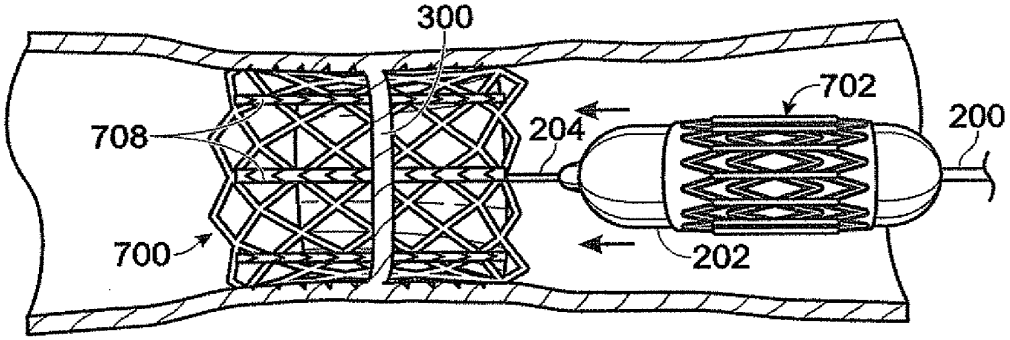


Fig. 20

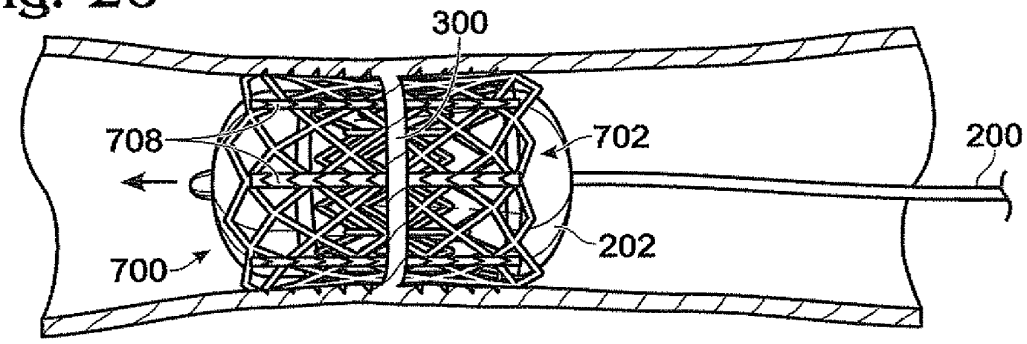


Fig. 21

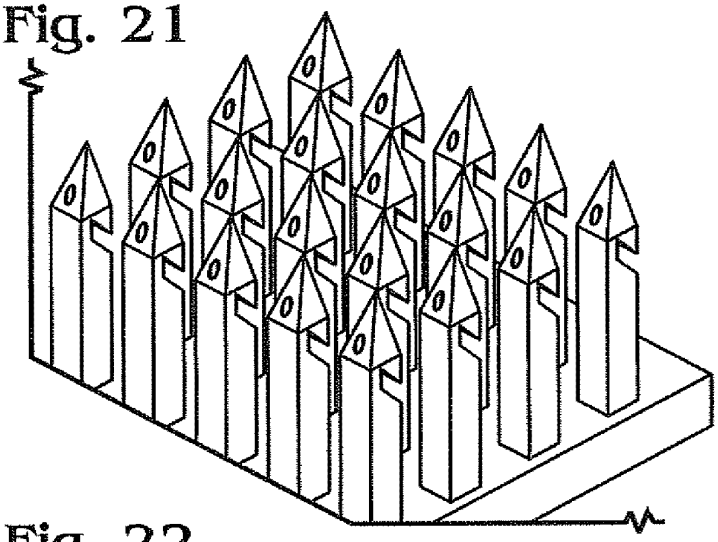


Fig. 22

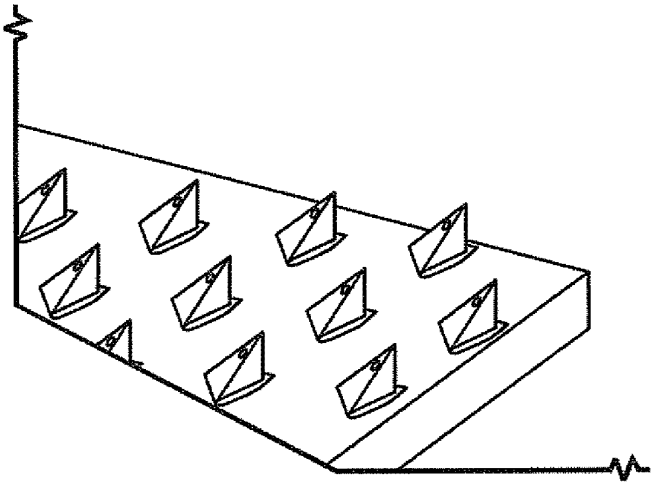


Fig. 23

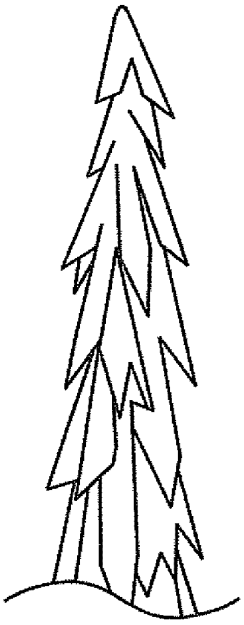


Fig. 24

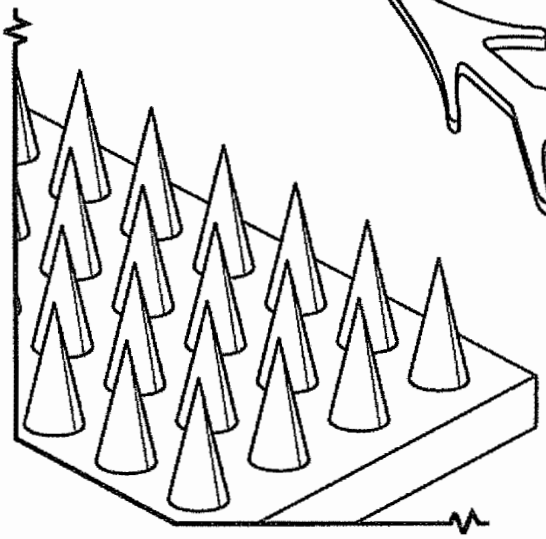


Fig. 25

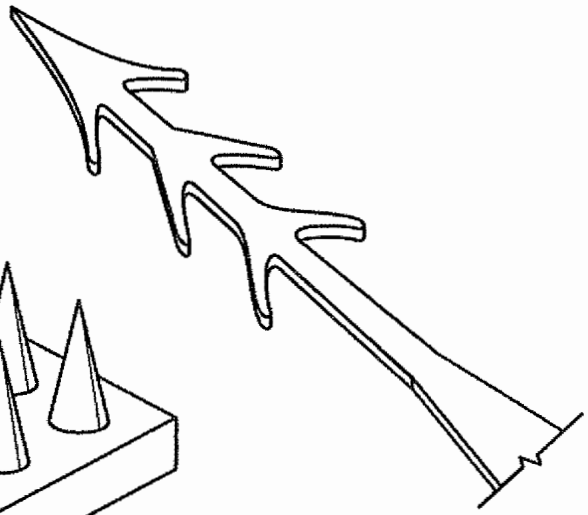
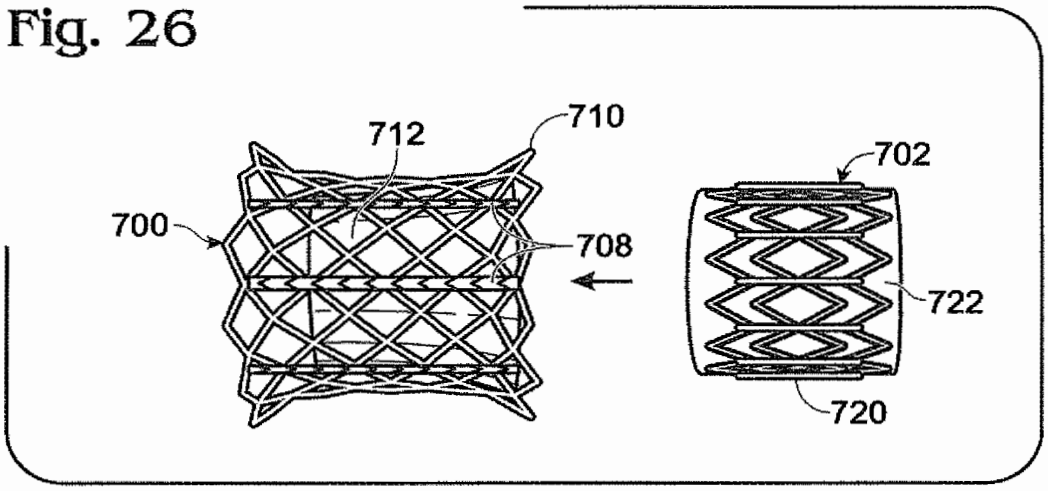


Fig. 26



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/080004

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61F2/24

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/053243 A (SADRA MEDICAL INC [US]; SALAHIEH AMR [US]; HILDEBRAND DANIEL [US]; SAU) 10 May 2007 (2007-05-10) paragraphs [0056], [0121]; figures	1-6
Y		7-14
A		10-13
Y	WO 2006/127756 A (EDWARDS LIFESCIENCES CORP [US]; ROWE STANTON J [US]; WOOD LARRY [US];) 30 November 2006 (2006-11-30) paragraphs [0012], [0061], [0062], [0067], [0088] - [0092]; figures	7-9
Y	US 2006/129235 A1 (SEGUIN JACQUES [GB] ET AL SEGUIN JACQUES [GB] ET AL) 15 June 2006 (2006-06-15) paragraph [0081] - paragraph [0082]; figures	10-14

-/--

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

[X] See patent family annex.

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 January 2009	23/01/2009

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

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/080004

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 2007/293942 A1 (MIRZAEE DARYUSH [US]) 20 December 2007 (2007-12-20) paragraphs [0034] - [0036], [0039]; figures	1,3-5
P,A		10,12,13
A	WO 2004/103223 A (CLEVELAND CLINIC FOUNDATION [US]) 2 December 2004 (2004-12-02) page 7, line 3 - line 9 page 16, line 6 - line 19 page 20, line 7 - page 21, line 14	1,10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/080004

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007053243 A	10-05-2007	AU 2006309251 A1	10-05-2007
		CA 2623814 A1	10-05-2007
		EP 1926455 A2	04-06-2008
WO 2006127756 A	30-11-2006	CA 2607744 A1	30-11-2006
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US 2007293942 A1	20-12-2007	NONE	
WO 2004103223 A	02-12-2004	CA 2526347 A1	02-12-2004
		EP 1626682 A1	22-02-2006

Electronic Patent Application Fee Transmittal

Application Number:	10887688
Filing Date:	10-Jul-2004
Title of Invention:	Percutaneously implantable replacement heart valve device and method of making same
First Named Inventor/Applicant Name:	David Paniagua
Filer:	Mark Lauren Yaskanin/Carol Donahue
Attorney Docket Number:	54813-10100

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 2 months with $0 paid	2252	1	245	245

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for continued examination	2801	1	405	405
		Total in USD ($)		**650**

Electronic Acknowledgement Receipt

EFS ID:	8138475
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:	23337
Filer:	Mark Lauren Yaskanin/Carol Donahue
Filer Authorized By:	Mark Lauren Yaskanin
Attorney Docket Number:	54813-10100
Receipt Date:	02-AUG-2010
Filing Date:	10-JUL-2004
Time Stamp:	18:17:16
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$650
RAM confirmation Number	5264
Deposit Account	082665
Authorized User	DONAHUE,CAROL S.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

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1		Response.pdf	530518 91f1a6be471835cc89e456aba32204c7636e1087	yes	33
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment After Final		1	1	
	Claims		2	4	
	Applicant Arguments/Remarks Made in an Amendment		5	33	
Warnings:					
Information:					
2	Request for Continued Examination (RCE)	RCE.pdf	697276 3dabd961d59a24145bfeb43e74709df5091bec2b	no	3
Warnings:					
Information:					
3	Extension of Time	Extension.pdf	331684 0cd360af553d9e96bdc81e5da5db1a4c69ab9cea	no	2
Warnings:					
Information:					
4	Information Disclosure Statement (IDS) Filed (SB/08)	Supp_IDS_1.pdf	614726 ce892b5feb2bc03125912f8681997f9f18f9f686	no	10
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5	Information Disclosure Statement (IDS) Filed (SB/08)	Supp_IDS_2.pdf	613027 2c1c42fab847c70fe46fc6e5d87b6d0cfe10868b	no	8
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Information:					

7	Information Disclosure Statement (IDS) Filed (SB/08)	Supp_IDS_4.pdf	613037 d748d60adb192e8dd7a7bcd4f5b82d1bbb436139	no	8
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8	Information Disclosure Statement (IDS) Filed (SB/08)	Supp_IDS_5.pdf	612811 7152eca729f4a36b1de69b88865cb4ddf4747400	no	8
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9	Foreign Reference	WO-1991-017720.pdf	857121 f24db653dcc46adde9c9d39603bd72c0b3a78fb6	no	21
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10	Foreign Reference	WO-1992-017118.pdf	2805645 638de26e8e8896033e8afee7df03039263f619e5	no	76
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11	Foreign Reference	WO-2007-138572.pdf	2881341 61a6766d1d18ad5e70fbf27b421bb8dd29f9cf18	no	71
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12	Foreign Reference	WO-2009-052188.pdf	1888039 9b53b000fcc1721e38d9a19c633caba20d12fe11	no	37
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Information:					
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15	NPL Documents	Sellaro_Effects_of_Collagen_Fiber_Medium_term_Fatigue.pdf	1073715 cd287a8777b23026c4a7be5a5777467a974dc692	no	12
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Information:					
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Warnings:					
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18	NPL Documents	Yasui_Determination_Collagen_Fiber_Orientation.pdf	725024 3eab612e51d5d59166ecb0dd25c2475a7750b877	no	7
Warnings:					
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19	NPL Documents	Cribier_Aoritc_Valve_Prosthesis.pdf	432972 84fc93303a328411e72023a86f7b0602fab356e5	no	4
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20	NPL Documents	Bonhoeffer_Percutaneous_insertion.pdf	582627 f8893183c6fb6cf60158ce59c83e421daa33902f	no	6
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21	NPL Documents	Bonhoeffer_Transcatheter_Implantation.pdf	585441 7fa67d034d657eb9462f6d95cd254cc84972e966	no	5
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24	NPL Documents	Breuer_Application_Tissue-Engineering_Principles.pdf	1193973 cb22dd9c8f73c41c122ec7c49fe1e12cfeaab050	no	12
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25	NPL Documents	Fish_Percutaneous_Heart_Valve_Replacement_Enthusiasm_Tempered.pdf	375136 d5049196713f8e9963b35ce8d9863ae8cd62b8e4	no	4
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26	Fee Worksheet (PTO-875)	fee-info.pdf	31960 c24d62f7183c64ad20c250fce70e9fa5b81925bd	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	24617345	

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re the Application of:	Group Art Unit: 3738
David PANIAGUA et al.	Confirmation No. 4909
Application No.: 10/887,688	Examiner: Cheryl L. MILLER
Filed: June 10, 2004	AMENDMENT AND RESPONSE
Atty. File No.: 54813-10100	**Filed Electronically**
Entitled: PERCUTANEOUSLY IMPLANTABLE REPLACEMENT HEART VALVE DEVICE AND METHOD OF MAKING SAME	**Certificate of EFS-Web Transmission** I hereby certify that this correspondence is being electronically transmitted to the U.S. Patent & Trademark Office by the EFS-Web system on 02 August 2010. Typed or printed name of person signing this certificate: Carol Donahue Signature: /Carol Donahue/

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Dear Sir:

In response to the March 2, 2010 Final Office Action (the "Office Action"), under separate cover Applicants herewith submit a Request for Continued Examination pursuant to 37 C.F.R. 1.114. In addition, along with this Amendment and Response, Applicants further request a two-month extension, thereby extending the period of reply from June 2, 2010 to August 2, 2010.

Please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

Applicants believe that all appropriate fees have been paid with this submittal. However, please credit any over payment or debit any under payment to Deposit Account No. 08-2665.

AMENDMENTS TO THE CLAIMS

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

Listing of Claims:

1.-56. **(Cancelled)**

57. **(New)** A percutaneously implantable replacement heart valve device for deployment in a patient, comprising:

a collapsible and expandable stent member including an inner channel; and

a single sheet of biocompatible pericardium tissue attached to the stent member by a plurality of sutures, the single sheet of biocompatible pericardium tissue partitioned by a transverse linear crease to form an outer cuff layer and an inner leaflet layer, the transverse linear crease oriented substantially parallel to a first edge and a second edge of the single sheet of biocompatible pericardium tissue, wherein the first edge includes a free edge of the inner leaflet layer, wherein at least portions of the inner leaflet layer reside substantially radially adjacent and in contact with the outer cuff layer within the stent member to form a contiguous double-layer folded construct, the inner leaflet layer partitioned by at least one additional linear crease oriented substantially perpendicular to the transverse linear crease to form two or more individual valve leaflets wherein the two or more individual valve leaflets are bordered in part by the at least one additional linear crease, the at least one additional linear crease located from the transverse linear crease to the free edge of the inner leaflet layer, wherein the inner leaflet layer resides in contact with the outer cuff layer at at least one point along each additional linear crease, wherein a first lateral edge of the single sheet of biocompatible pericardium tissue adjoins a second lateral edge of the single sheet of biocompatible pericardium tissue, wherein the single sheet of biocompatible pericardium tissue resides entirely within the inner channel of the stent member, and wherein after deployment in the patient, the contiguous double-layer folded construct with the inner leaflet layer located radially within the outer cuff layer resides as a single element within the inner channel of the stent member.

58. **(New)** The percutaneously implantable replacement heart valve device of Claim 57, wherein the single sheet of biocompatible pericardium tissue comprises one of treated bovine pericardium tissue or treated porcine pericardium tissue.

59. **(New)** The percutaneously implantable replacement heart valve device of Claim 57, wherein the stent member comprises a metal alloy.

60. **(New)** The percutaneously implantable replacement heart valve device of Claim 57, wherein the stent member comprises stainless steel.

61. **(New)** The percutaneously implantable replacement heart valve device of Claim 57, wherein the stent member comprises a shape memory alloy.

62. **(New)** The percutaneously implantable replacement heart valve device of Claim 61, wherein the shape memory alloy comprises nitinol.

63. **(New)** The percutaneously implantable replacement heart valve device of Claim 57, wherein the plurality of sutures includes sutures at axially distal and proximal ends of the contiguous double-layer folded construct.

64. **(New)** The percutaneously implantable replacement heart valve device of Claim 57, wherein the at least one point along each additional linear crease corresponds to a commissure.

65. **(New)** The percutaneously implantable replacement heart valve device of Claim 57, wherein the single sheet of biocompatible pericardium tissue forming the contiguous double-layer folded construct is continuous between the first edge to the transverse linear crease and back to the second edge.

REMARKS/ARGUMENTS

The present Amendment and Response comprises Applicants' reply to the Examiner's March 2, 2010 Final Office Action. Claims 1-56 are cancelled. New Claims 57-65 are added. Accordingly, Claims 57-65 are now pending in view of the above amendments. The Applicants believe that Claims 57-65 are consistent with the previously elected invention.

Applicants believe that no new matter has been added with regard to the new claims provided herein. Applicants do not donate or disclaim any claims or subject matter, and the Applicants expressly reserve the right to prosecute the original, cancelled claims, and/or any unclaimed subject matter in one or more future filed continuing applications.

Reconsideration of the application is respectfully requested in view of the new claims and the following remarks. Please note that the following remarks are not intended to be an exhaustive enumeration of the distinctions between any cited references and the claimed invention. Rather, the distinctions identified and discussed below are presented solely by way of example to illustrate some of the differences between the claimed invention and the cited references. In addition, the Applicants request that the Examiner carefully review any references discussed below to ensure that Applicants' understanding and discussion of the references, if any, is consistent with the Examiner's understanding. Also, Applicants' arguments related to each cited reference are not an admission that the cited references are, in fact, prior art.

I. Examiner's Interview

Applicants' Attorney expresses his sincere appreciation to Examiner Cheryl L. Miller for conducting a personal Examiner's Interview with co-inventor Dr. R. David Fish and the undersigned Applicants' Attorney on July 19, 2010.

An Interview Summary was prepared by the Examiner and mailed on July 26, 2010. Applicants are in general agreement with most of the Examiner's Interview Summary, including the claims, cited references, and models discussed. Here, Applicants' Attorney notes that both (A) a model of the pericardium tissue, and (B) a 3-D model representing the pericardium tissue mounted within a stent member were shown to the Examiner. In addition, Applicants believe that the disclosure of U.S. Pat. App. Pub. No. 2003/0130729 supports the wording of the claims as presented herein, including independent Claim 57 and dependent Claim 63. Moreover, Fig. 3B shows the free edge of the inner leaflet layer held in contact with the outer cuff layer at points marking the leaflet commissures. It will be understood by those skilled in the art that a form of imposing and securing this necessary contact as depicted in the figures is by means of a plurality of sutures, though other methods might be employed, and by whatever method, the orientation and operating position of the inner and outer layers as shown in the figures confers the functional benefits of the inventive percutaneously implantable heart valve.

Again, Applicants and Applicants' Attorney wish to express their appreciation to Examiner Miller for the courtesy of the personal Examiner's Interview of July 19, 2010.

II. Objection to Declaration

In the March 2, 2010 Office Action, the Examiner stated that the Declarations filed on December 15, 2008 and September 14, 2009 under 37 CFR 1.131 were ineffective to overcome

U.S. Patent No. 6,652,578 to Bailey. Applicants have cancelled Claims 1-56 and herein present new Claims 57-65. Subject matter for the claims as presented herein is limited to the disclosure associated with the Applicants' parent patent application, namely, U.S. Pat. App. No. 10/037,266 filed on January 4, 2002. However, the Applicants reserve the right to pursue any content associated with U.S. Pat. App. No. 10/887,688 filed on June 10, 2004.

On page 4 of the March 2, 2010 Office Action, the Examiner stated that "[p]ortions 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*." The claims as presented herein do not include the terms "unslit" and "an inner and an outer fold." Here, the Applicants respectfully note that the Applicants are not admitting or acquiescing to the Examiner's assertion set forth above in quotations. Rather, the Applicants have provided new claims that do not use such terminology.

Finally, the Examiner indicated in the March 2, 2010 Office Action that "Exhibits B and C were missing from the file, and unable to be evaluated." During the aforementioned Examiner's Interview, Dr. R. David Fish illustrated Exhibits B and C to Examiner Miller.

Based on the foregoing, the Applicants respectfully request the Examiner to reconsider the Applicants' Declaration under 37 CFR § 1.131 to overcome use of US 6,652,578 and US 6,458,153 both to Bailey as prior art available under 35 USC § 102(e).

III. Objection to Priority

The Examiner stated the application seems to disclose four separate embodiments, which encompassed different priority dates. Applicants have cancelled Claims 1-56 and present new Claims 57-65, and as noted above. Subject matter for the claims as presented herein is limited to

the disclosure associated with the Applicants' parent patent application U.S. Pat. App. 10/037,266 filed on January 4, 2002. Notwithstanding anything herein to the contrary or otherwise implied, the Applicants expressly reserve the right to pursue any content associated with U.S. Pat. App. No. 10/887,688, such as in one or more continuing patent applications, and the Applicants are not disavowing, donating, and/or abandoning their rights to any content associated with U.S. Pat. App. No. 10/887,688.

IV. Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected Claims 1-10 and 27-56 under 35 U.S.C. § 112, First Paragraph, as not conveying that the inventors possessed the invention at the time the application was filed.

Applicants have cancelled Claims 1-56 and presents new Claims 57-65 in an effort to expedite allowance of claims. However, Applicants do not acquiesce to the Examiner's rejection of these claims. Applicants' cancellation of the previously pending claims renders the Examiner's rejections moot.

V. Rejection Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected Claims 1-10, 30-32, 34, 43, 48 and 50-56 under 35 U.S.C. § 112, Second Paragraph, as not distinctly claiming the subject matter of the invention. Applicants have cancelled Claims 1-56 and presents new Claims 57-65 in an effort to expedite allowance of claims. However, Applicants do not acquiesce to the Examiner's rejection of these claims. Applicants' cancellation of the previously pending claims renders the Examiner's rejections moot.

VI. Product by Process Claims

In the March 2, 2010 Office Action, the Examiner stated that Claims 52 and 55 were product by process claims. Applicants have cancelled these claims and none of the claims presented herein are believed to be product by process claims. Notwithstanding this point, the Applicants believe that the underlying structure of the percutaneously implantable replacement heart valve device, at least as claimed herein, is novel and non-obvious.

VII. New Claims

The Applicants have added new independent Claim 57 and dependent Claims 58-65. The Applicants believe that the new claims are in accord with the previously made election. In addition, the Applicants believe that no new matter has been added by the addition of the new claims. Support for the new claims is discussed below.

Support for New Independent Claim 57

New independent Claim 57 is presented in this Amendment and Response. Support for the limitations in Claim 57 can be found in Applicants' parent patent application U.S. Pat. App. No. 10/037,266 filed on January 4, 2002. More particularly, support for the limitations of new independent Claim 57 can be found at least in Paragraphs [0024], [0037]-[0060] as well as original Claim 1, and Figures 1, 2, 3A, 3B, and 5 of U.S. Pat. App. Pub. No. 2003/0130729 that is the publication of the parent application of the present patent application. Claim 57 is reproduced below with comments in parentheses as to where support can be found in U.S. Pat. App. Pub. No. 2003/0130729:

57. A percutaneously implantable replacement heart valve device (*See ¶[0037]*) for deployment in a patient (*See ¶¶[0037]-[0060]*), comprising:

a collapsible and expandable stent member including an inner channel (*See ¶[0037]*); and

a single sheet (*See Fig. 3A, original Claim 1 and ¶[0024]*) of biocompatible pericardium tissue (*See original Claim 1*) attached to the stent member by a plurality of sutures (*See ¶[0037]*), the single sheet of biocompatible pericardium tissue partitioned by a transverse linear crease (*See original Claim 1 and Fig. 3A*) to form an outer cuff layer and an inner leaflet layer (*See Figs. 1 and 3B*), the transverse linear crease oriented substantially parallel to a first edge and a second edge (*See Figs. 1, 3A and 3B*) of the single sheet of biocompatible pericardium tissue, wherein the first edge includes a free edge of the inner leaflet layer (*See Figs. 1 and 3B*), wherein at least portions of the inner leaflet layer reside substantially radially adjacent and in contact with the outer cuff layer within the stent member (*See Figs. 1, 2, and 3B*) to form a contiguous double-layer folded construct (*See Figs. 1, 2, 3A, 3B and 5*), the inner leaflet layer partitioned by at least one additional linear crease oriented substantially perpendicular to the transverse linear crease to form two or more individual valve leaflets (*See Figs. 1, 2, 3B and 5*) wherein the two or more individual valve leaflets are bordered in part by the at least one additional linear crease (*See Figs. 1, 2, 3B and 5*), the at least one additional linear crease located from the transverse linear crease to the free edge of the inner leaflet layer (*See Figs. 1, 3B and 5*), wherein the inner leaflet layer resides in contact with the outer cuff layer

at at least one point along each additional linear crease (*See Figs. 1, 2, 3B, 5 and discussion below*), wherein a first lateral edge of the single sheet of biocompatible pericardium tissue adjoins a second lateral edge of the single sheet of biocompatible pericardium tissue (See *Figs. 1 and 3B*), wherein the single sheet of biocompatible pericardium tissue resides entirely within the inner channel of the stent member (*See Fig. 5)*, and wherein after deployment in the patient, the contiguous double-layer folded construct with the inner leaflet layer located radially within the outer cuff layer resides as a single element within the inner channel of the stent member (*See discussion below*).

With regard to support cited above for the limitations of Claim 57, the Applicants further note that the Applicants have included the limitations of "a collapsible and expandable stent member including an inner channel," and "wherein after deployment in the patient, the contiguous double-layer folded construct with the inner leaflet layer located radially within the outer cuff layer resides as a single element within the inner channel of the stent member." Support for a collapsible and expandable stent member can be found in the figures and in Paragraph [0037] of US 2003/0130729 corresponding to the present application. In addition, with regard to "wherein after deployment in the patient, the contiguous double-layer folded construct with the inner leaflet layer located radially within the outer cuff layer resides as a single element within the inner channel of the stent member," the Applicants note that an applicant need not include in the specification that which is already known and available to the public.

> It is well settled that the disclosure of an application embraces not only what is expressly set forth in words or drawings, but what would be understood by

> persons skilled in the art. As was said in Webster Loom Co. v. Higgins et al., 105 U.S. 580, 586, the applicant "may begin at the point where his invention begins, and describe what he has made that is new and what it replaces of the old. That which is common and well known is as if it were written out in the patent and delineated in the drawings."

In re Howarth, 654 F.2d 103, 106 (C.C.P.A. 1981), citing In re Chilowsky, 43 CCPA 775, 780, 229 F.2d 457, 460, 108 USPQ 321, 324 (1956). Here, Applicants assert that one of ordinary skill in the art would understand that, unless otherwise specified, a stent member would include an inner channel with the elements disclosed to be placed therein (i.e., the contiguous double-layer folded construct constituted of the biocompatible pericardium tissue), and not additional elements.

In addition to the foregoing, the Applicants note that the contact of the inner leaflet layer to the outer cuff layer occurs along lines corresponding to the at least one additional linear crease of Claim 57. Here, such contact is supported in U.S. Pat. App. Pub. No. 2003/0130729 in both closed (Fig. 1) and partially open (Fig. 2) operating configurations, with further support provided by Figs 3B and 5. In particular with reference to Fig. 3B, which depicts the disposition of the surfaces of the folded double-layer construct apart from the stent member, the inner leaflet layer is shown sharply retracted along axially oriented lines (corresponding to the at least one additional linear crease of Claim 57) into lines of contact with the outer cuff layer. Similarly, the free edge of the inner leaflet layer is shown held in contact with the outer cuff layer at points marking the leaflet commissures. It will be understood by those skilled in the art that the depiction of Fig. 3B necessitates, by evident mechanics, that these lines and/or points of contact are maintained during the operation of the valve, particularly in the closing action. In the art a well-understood form of imposing and securing this necessary contact as depicted in the figures is by means of a plurality of sutures, though other methods might be employed, and by whatever

method, the orientation and operating position of the inner and outer layers as shown in the figures confers the functional benefits of the inventive percutaneously implantable heart valve.

Based on the foregoing, the Applicants believe that the support for all limitations for new Claim 57 is supported by Applicants' parent patent application filed on January 4, 2002.

Support for New Dependent Claims 58-65

Support for the dependent claims can be found in U.S. Pat. App. Pub. No. 2003/0130729 as follows:

Claim 58:	*See ¶[0046] and original Claims 3 and 4*
Claims 59-62:	*See ¶[0041]*
Claim 63:	*See Figs. 1, 5 and 7*
Claim 64:	*See Figs. 1, 2, 3B and 5*
Claim 65:	*See Figs. 1, 3A and 3B*

VIII. PRIOR ART REJECTIONS

A. Recent Rejections Under 35 U.S.C. § 102(b) or (e) and § 103(a)

In the March 2, 2010 Office Action, the Examiner rejected Claims 1-3, 5-10, 36, 37, 40, 42, 44-47, 50-52 and 54-56, under 35 U.S.C. § 102(b) as being anticipated by United States Patent No. 5,855,601 to Bessler et al. ("Bessler"). In addition, the Examiner rejected Claims 34, 38, 39, 41, 43 and 48 under 35 U.S.C. § 103(a) as being unpatentable over Bessler. The Examiner also rejected Claims 1-10, 36-40, 42, 44-48 and 50-56, under 35 U.S.C. § 102(b), and alternatively under 35 U.S.C. § 102(e), as being anticipated by United States Patent No. 6,425,916 to Garrison et al. ("Garrison"). In addition, the Examiner rejected Claims 1-2, 4-10, 30-34, 36-48, 50-53 and 55-56, under 35 U.S.C. § 102(b), and alternatively under 35 U.S.C. § 102(e), as being anticipated by United States Patent No. 6,458,153 to Bailey et al. ("Bailey").

It is well recognized that claims are anticipated under 35 U.S.C. § 102 if, and only if, each and every element, as set forth in the claim is found in a single prior art reference. Vertegaal Bros. v. Union Oil Co. of Calif., 814 F.2d 628, 631 (Fed. Cir. 1987). Furthermore, "[t]he identical invention must be shown as a complete detail as contained in the . . . claim." Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236 (Fed. Cir. 1989). See MPEP § 2131. To constitute anticipation, all material elements of the claim must be found in one prior art source. In re Marshall, 198 U.S.P.Q. 344 (C.C.P.A. 1978). Additionally, the elements of the reference must be arranged as required by the claim. In re Bond, 15 U.S.P.Q. 2d 1566 (Fed. Cir. 1999). Applicant respectfully submits that the cited references do not teach all the material elements and do not arrange the elements as required by claim language in the newly added claims presented herein.

With regard to the obviousness rejections under 35 U.S.C. § 103(a), the U.S. Supreme Court, in KSR Int'l. Co. v. Teleflex Inc., 82 USPQ 2d 1385, 1391 (2007), reiterated the standard for determining obviousness under 35 U.S.C. § 103 as being the factual inquiries set forth in Graham v. John Deere Co. of Kansas City, 383 U.S. 1 (1966). In Graham, the Court stated that obviousness is determined by first determining the scope and content of the prior art, then ascertaining the differences between the invention, as claimed, and the prior art, and then resolving the level of ordinary skill in the prior art. Against this background, the obviousness or non-obviousness of the claimed subject matter is determined. Secondary considerations may also be utilized in this analysis to give light to the circumstances surrounding the origin of the subject matter sought to be patented. KSR Int'l Co., 82 USPQ 2d at 1391. When making any obviousness rejection, the Examiner must first acquire a thorough understanding of the claimed

invention by reading the specification and claims to understand what the Applicant is claiming as his invention. MPEP § 904.

To establish a prima facie case of obviousness under 35 U.S.C. §103(a), the Examiner must clearly articulate the reason(s) why the claimed invention would have been obvious (i.e., the analysis supporting the rejection must be made explicit.) See MPEP § 2142. "Rejections on obviousness cannot be sustained with mere conclusory statement; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." See MPEP § 2142; In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006); see also KSR Int'l Co., 82 USPQ 2d at 1396. To support a 103(a) rejection, the examiner must demonstrate that a person of ordinary skill in the art would have had reason to attempt to make the claimed device, or carry out the claimed process, and would have had a reasonable expectation of success in doing so. See Noelle v. Lederman, 355 F.3d 1343, 1351–52 (Fed. Cir. 2004); Brown & Williamson Tobacco Co. v. Philip Morris, Inc., 229 F.3d 1120, 1121 (Fed. Cir. 2000); see also KSR Int'l Co., 82 USPQ2d at 1391.

The Applicants note that they have cancelled Claims 1-56. However, Applicants do not acquiesce to the Examiner's rejection of these claims. Applicants' cancellation of the previously pending claims makes the Examiner's rejections moot. The new claims presented herein are distinguished over Bessler, Garrison and Bailey in the Applicants' remarks below, and are addressed in the order that they were cited in the USPTO Office Action dated March 2, 2010.

U.S. Pat No. 5,855,601 to Bessler

With regard to new independent Claim 57, Applicants believe that U.S. Pat No. 5,855,601 to Bessler fails to disclose at least those limitations shown in italics below:

57. A percutaneously implantable replacement heart valve device for deployment in a patient, comprising:

a collapsible and expandable stent member including an inner channel; and

a single sheet of biocompatible pericardium tissue attached to the stent member by a plurality of sutures, the single sheet of biocompatible pericardium tissue partitioned by a transverse linear crease to form an outer cuff layer and an inner leaflet layer, the transverse linear crease oriented substantially parallel to a first edge and a second edge of the single sheet of biocompatible pericardium tissue, *wherein the first edge includes a free edge of the inner leaflet layer, wherein at least portions of the inner leaflet layer reside substantially radially adjacent and in contact with the outer cuff layer within the stent member to form a contiguous double-layer folded construct, the inner leaflet layer partitioned by at least one additional linear crease oriented substantially perpendicular to the transverse linear crease to form two or more individual valve leaflets wherein the two or more individual valve leaflets are bordered in part by the at least one additional linear crease, the at least one additional linear crease located from the transverse linear crease to the free edge of the inner leaflet layer, wherein the inner leaflet layer resides in contact with the outer cuff layer at at least one point along each additional linear crease, wherein a first lateral edge of the single sheet of biocompatible pericardium tissue adjoins a second lateral edge of the single sheet of biocompatible pericardium tissue, wherein the single sheet of biocompatible pericardium tissue resides entirely within the inner channel of the stent member, and wherein after deployment in the patient, the contiguous double-layer folded construct with the inner leaflet layer located radially within the outer cuff layer resides as a single element within the inner channel of the stent member.*

Figures 1-4 of Bessler are shown below.

FIG. 1

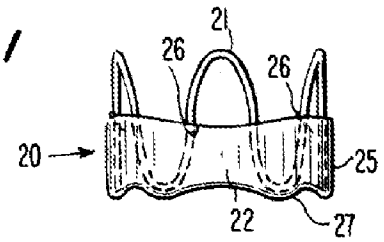


FIG. 2

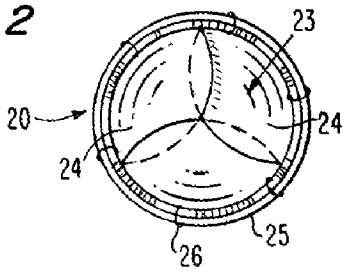


FIG. 3

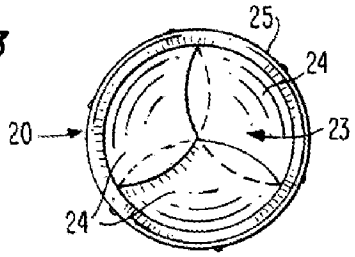
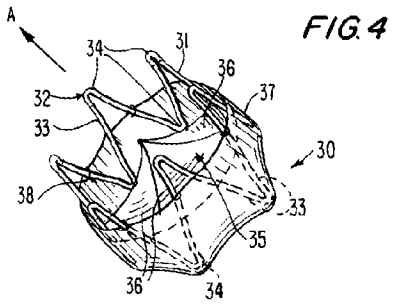


FIG. 4



Upon review of Bessler, it is apparent that Bessler fails to disclose one or more limitations as set forth in new independent Claim 57. More particularly, Bessler appears to disclose a stent member 21 and a flexible valve means 22. As can be seen in the figures of Bessler, at least portions of the valve means 22 reside on the ablumenal surface of the stent member 21. (See also Bessler, col. 5, ll. 24-27.) Claim 57 as presented herein and reproduced above recites the limitation that "*the single sheet of biocompatible pericardium tissue resides entirely within the inner channel of the stent member.*" Such configuration is not disclosed on Bessler.

With further reference to Bessler, the Applicants note that there does not appear to be any explanation within the specification of Bessler as to the form of attachment of the free edges of the leaflets (formed by "slitting") to the circumferential margin of the frame/valve. In the top and bottom views of Bessler (see Figs. 2 and 3) points are depicted that appear to mark the peripheral extent of the leaflet free edge meeting the circumferential inner aspect of the stent frame, but these are not annotated and are not otherwise indicated in Figs. 1 and 4. Upon review of Fig. 4 of Bessler, the leaflet free edges are shown carried down to the base of the valve (see Applicants' mark-up of Fig. 4 below).

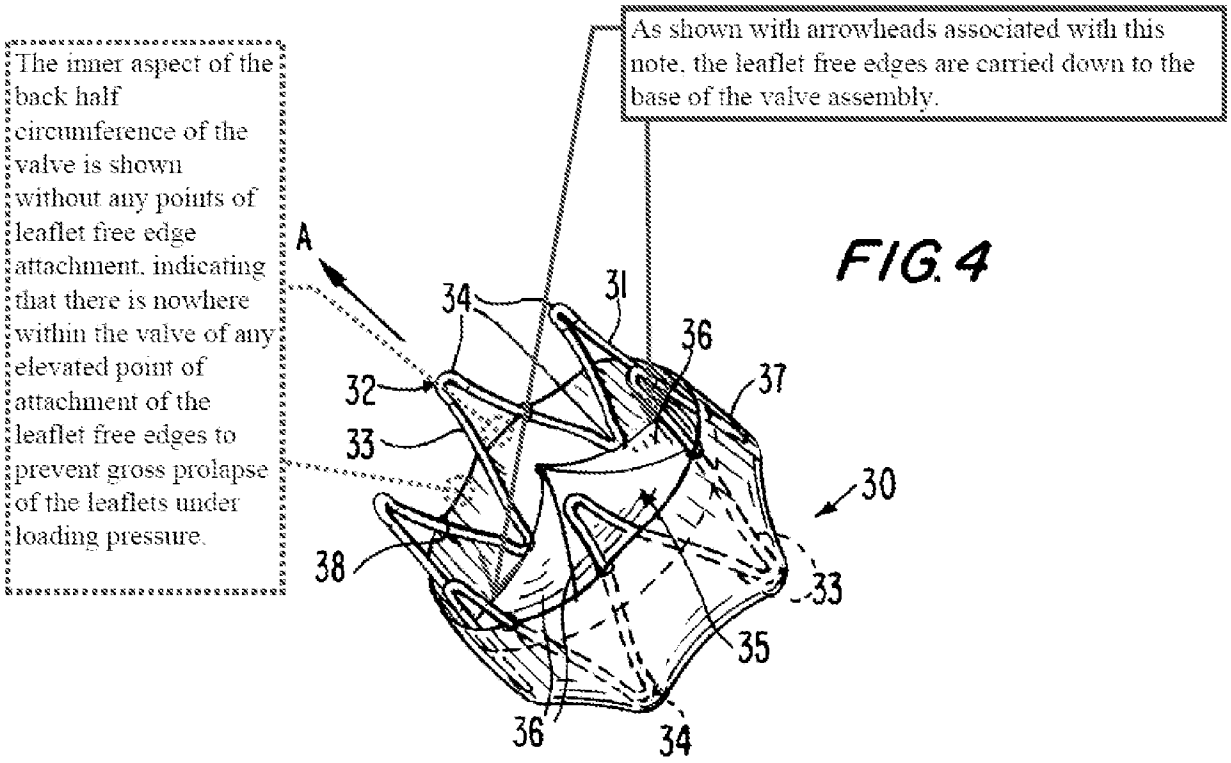


FIG. 4

The fact that the leaflet free edges are shown carried down to the base is consistent with the description of the valve construct as formed from a flexible membrane with slits to form (and delineate) leaflets. However, this means that there is no elevated point of attachment of the leaflet free edges to prevent gross prolapse of the leaflets under backflow loading pressure. Indeed, none of the figures associated with Bessler show the leaflet layer attached except for at the base of the valve. More particularly, while Bessler's further embodiment is shown in Fig. 4, none of the figures of Bessler, including Fig. 4, show how the leaflets are attached other than by base continuity with the cuff graft material that extends to the ablumenal surface of the stent member. Further distinguishing new Claim 57 over Bessler, the Applicants note that Claim 57 includes the combination of limitations that "*the transverse linear crease* [is] *oriented substantially parallel to a first edge ... of the single sheet of biocompatible pericardium tissue*"

and "*the first edge includes a free edge of the inner leaflet layer*." This combination of limitations is not disclosed in Bessler.

Bessler also fails to disclose the limitation that "*at least portions of the inner leaflet layer reside substantially radially adjacent and in contact with the outer cuff layer within the stent member to form a contiguous double-layer folded construct.*" Here, the Applicants note that Bessler appears to have a flexible valve means 22 within the stent member 21, wherein the flexible valve means 22 extends to the outside of the stent member 21 to form cuff portion 25. Accordingly, Bessler fails to disclose the limitation of "*at least portions of the inner leaflet layer reside substantially radially adjacent and in contact with the outer cuff layer within the stent member to form a contiguous double-layer folded construct*."

In addition to the foregoing, the Applicants note that Bessler discloses an "arcuate portion of the valve means" with one or more slits "to form leaflets" (Bessler, col. 3, ll. 65-66). In contrast, the Applicants disclose and are currently claiming "*two or more individual valve leaflets ... are bordered in part by the at least one additional linear crease ...*" Accordingly, the Applicants' currently claimed structure is different than that disclosed by Bessler.

Other limitations in italics as shown in reproduced Claim 57 are also believed to be novel over Bessler. For the foregoing reasons, the Applicants believe that Bessler fails to anticipate Claim 57 as presented herein.

U.S. Pat. No. 6,425,916 to Garrison

U.S. Pat. No. 6,425,916 to Garrison fails to disclose at least those limitations shown in italics below:

> 57. A percutaneously implantable replacement heart valve device for deployment in a patient, comprising:

> a collapsible and expandable stent member including an inner channel; and
> a single sheet of biocompatible pericardium tissue attached to the stent member by a plurality of sutures, *the single sheet of biocompatible pericardium tissue partitioned by a transverse linear crease to form an outer cuff layer and an inner leaflet layer, the transverse linear crease oriented substantially parallel to a first edge and a second edge of the single sheet of biocompatible pericardium tissue, wherein the first edge includes a free edge of the inner leaflet layer, wherein at least portions of the inner leaflet layer reside substantially radially adjacent and in contact with the outer cuff layer within the stent member to form a contiguous double-layer folded construct*, the inner leaflet layer partitioned by at least one additional linear crease oriented substantially perpendicular to the transverse linear crease to form two or more individual valve leaflets wherein the two or more individual valve leaflets are bordered in part by the at least one additional linear crease, *the at least one additional linear crease located from the transverse linear crease to the free edge of the inner leaflet layer, wherein the inner leaflet layer resides in contact with the outer cuff layer at at least one point along each additional linear crease*, wherein a first lateral edge of the single sheet of biocompatible pericardium tissue adjoins a second lateral edge of the single sheet of biocompatible pericardium tissue, wherein the single sheet of biocompatible pericardium tissue resides entirely within the inner channel of the stent member, and wherein after deployment in the patient, the contiguous double-layer folded construct with the inner leaflet layer located radially within the outer cuff layer resides as a single element within the inner channel of the stent member.

Garrison fails to disclose at least those limitations noted above, and in particular, Garrison does not disclose the combination of a "***single sheet of biocompatible pericardium tissue*** *partitioned by a transverse linear crease to form* ***an outer cuff layer and an inner leaflet layer***" as claimed in new independent Claim 57. Indeed, although Garrison mentions synthetic materials (Garrison, col. 5, ll. 50-60), the only written description of a "tissue" material of Garrison is found at col. 5, ll. 42-48, wherein Garrison states:

> The posts 32 support a valve portion 38 which performs the functions of the patient's malfunctioning native valve. Referring to FIGS. 10 and 11, the valve portion 38 is preferably a stentless tissue valve such as a tri-leaflet 39 stentless porcine valve. The valve portion 38 has a base 41 which is secured to the support structure 26 with sutures (not shown).

Figures 10 and 11 of Garrison are reproduced below:

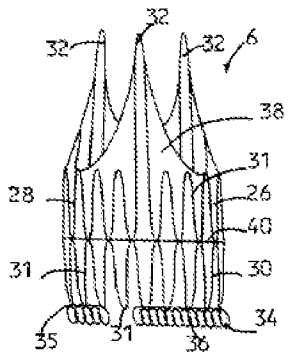


FIG. 10

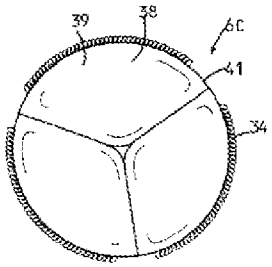
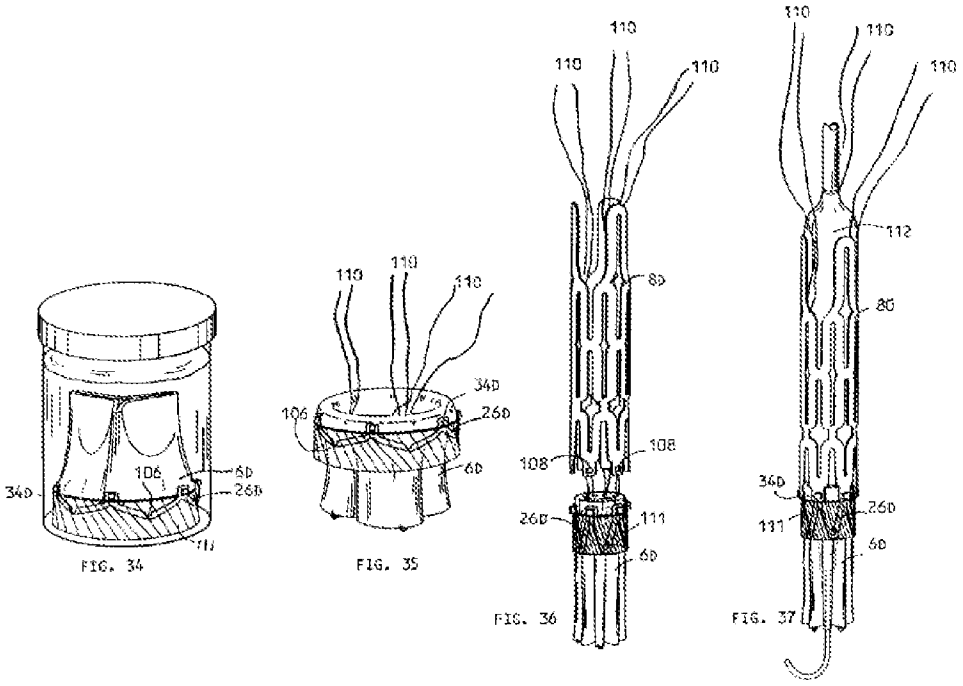


FIG. 11

Review of the text quoted above from Garrison reveals that Garrison uses "**a trileaflet 39 stentless porcine valve**." That is, Garrison does not disclose "*single sheet of biocompatible pericardium tissue"* as claimed in new Claim 57, but rather, Garrison discloses a preserved graft valve harvested from a porcine heart, wherein the porcine valve is "secured to the support structure 26 with sutures." (Garrison, col. 5, ll. 47.)

In addition, as noted above, Garrison fails to disclose that a single sheet of biocompatible pericardium tissue is "*partitioned by a transverse linear crease to form* ***an outer cuff layer and an inner leaflet layer.***" More particularly, while Garrison discloses a valve 6D shown in the figures of Garrison, there is no disclosure of an outer cuff layer and an inner leaflet layer that are both formed from a single sheet of pericardium material. Here, the Applicants direct the Examiner's attention to Figs. 34-37 of Garrison that are reproduced below. Upon review of the valve shown in Figs. 34 and 35, the Applicants note that the valve 6D is lacking "*an* ***outer cuff layer and an inner leaflet layer.***"



In addition to the foregoing, the Applicants also note that Garrison does not disclose some type of upper support structure for its versions of leaflets. That is, the valve 6D is connected to circumferential ring 111 and support structure 26D at its base. (Garrison, col. 10, ll. 40-42 and 58-59.) However, even after the valve 6D is inverted (Fig. 35) and the protrusions 34D of the support structure 26D are engaged with the holes 108 of the valve displacer 8D (Figs. 36 and 37), the upper portions of the valve 6D are not engaged with the valve displacer 8D. Garrison further states that after the balloon 112 is inflated to expand the valve 6D and valve displacer 8D, that the catheter 4D is removed and the sutures 110 (see Figs. 35-37) are "pulled to invert the valve as shown in Fig. 33." (Garrison, col. 11, ll. 29-30.) If the valve may be inverted by traction force on the leaflets, it should similarly prolapse under loading pressure back in the other direction down into the outlet of the heart chamber unless some form of mechanical hysteresis or "locking" mechanism is invoked to prevent it. Garrison appears to presume the readers' inference of such a mechanical effect without citation or explanation. However, in the

prior art such tissue membrane or whole graft valve configurations are free standing and upright as in Figs. 34 and 38 by virtue of internal frameworks or supports called "stents" in the surgical valve knowledge base. If Garrison is to rely on invoking "stentless" (surgical) valves as a component mechanism to explain the operation of valve 6D, it must be stated that none of the available "stentless" valves resemble valve 6D in configuration or operation. Rather, what Garrison depicts as valve 6D in Fig. 34 resembles a "stented" surgical valve, but is shown without any means of internal mechanical support. If Garrison asserts valve 6D as a novel and genuinely functional configuration, then the absolute lack of explanation of the mechanism by which it is to resist prolapse calls into question if and how it is enabled. See Fig. 33 of Garrison that is reproduced below.

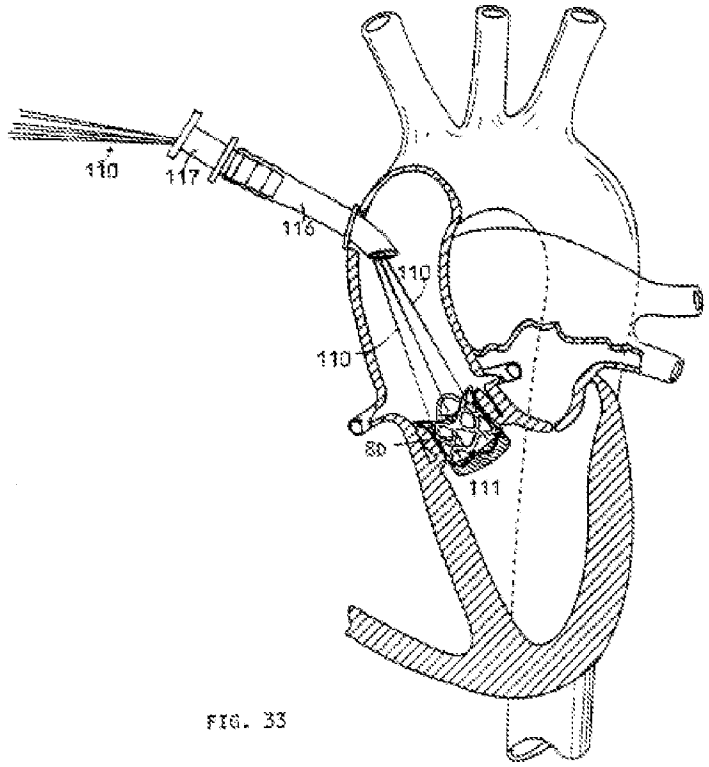


FIG. 33

Garrison goes on to state that "[a]n end of each suture 110 is then pulled to remove the sutures 110." (Garrison, col. 11, ll. 30-31.) Fig. 38 of Garrison is shown below illustrating Garrison's "valve and the valve displacer in the expanded condition." (Garrison, col. 4, ll. 5-6.)

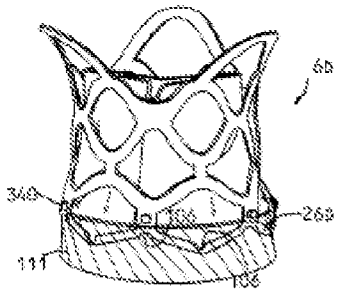


FIG. 38

Upon review of Garrison, including Fig. 38 above, it is apparent that there is no explanation as to how the valve 6D can be deployed, expanded and inverted to its operating position, and remain in such a position without prolapsing when in operation. In any event, Garrison does not disclose a valve construct wherein its inner leaflet layer resides *"substantially radially adjacent and in contact with the outer cuff layer within the stent member to form a contiguous double-layer folded construct,"* as claimed in new Claim 57. Therefore, whether in combination with a support structure or valve displacer, upon review of Garrison it can be seen that Garrison does not disclose pericardium tissue configured as claimed in new independent Claim 57. For the foregoing reasons, the Applicants believe that Garrison fails to anticipate Claim 57 as presented herein.

U.S. Pat No. 6,458,153 to Bailey

U.S. Pat No. 6,458,153 to Bailey fails to disclose at least those limitations shown in italics below:

57. A percutaneously implantable replacement heart valve device for deployment in a patient, comprising:

a collapsible and expandable stent member including an inner channel; and

a single sheet of biocompatible pericardium tissue attached to the stent member by a plurality of sutures, the single sheet of biocompatible pericardium tissue partitioned by a transverse linear crease to form an outer cuff layer and an inner leaflet layer, the transverse linear crease oriented substantially parallel to a first edge and a second edge of the single sheet of biocompatible pericardium tissue, wherein the first edge includes a free edge of the inner leaflet layer, wherein at least portions of the inner leaflet layer reside substantially radially adjacent and in contact with the outer cuff layer within the stent member to form a contiguous double-layer folded construct, the inner leaflet layer partitioned by at least one additional linear crease oriented substantially perpendicular to the transverse linear crease to form two or more individual valve leaflets wherein the two or more individual valve leaflets are bordered in part by the at least one additional linear crease, the at least one additional linear crease located from the transverse linear crease to the free edge of the inner leaflet layer, wherein the inner leaflet layer resides in contact with the outer cuff layer at at least one point along each additional linear crease, *wherein a first lateral edge of the single sheet of biocompatible pericardium tissue adjoins a second lateral edge of the single sheet of biocompatible pericardium tissue, wherein the single sheet of biocompatible pericardium tissue resides entirely within the inner channel of the stent member, and wherein after deployment in the patient, the contiguous double-layer folded construct with the inner leaflet layer located radially within the outer cuff layer resides as a single element within the inner channel of the stent member.*

The Applicants respectfully assert that Bailey fails to disclose a number of limitations of new Claim 57, including at least those limitations noted above in italics. More particularly, new independent Claim 57 includes the limitation that "*wherein after deployment in the patient, the contiguous double-layer folded construct with the inner leaflet layer located radially within the outer cuff layer resides as a single element within the inner channel of the stent member.*" Bailey fails to disclose this structure. That is, there is no question that Bailey insists on the valve regulator arms being present. Reference here is made to Figs. 3, 9 and 15 of Bailey shown below. Each of the embodiments described in Bailey uses valve leaflets 26 that are biased using valve arms 24.

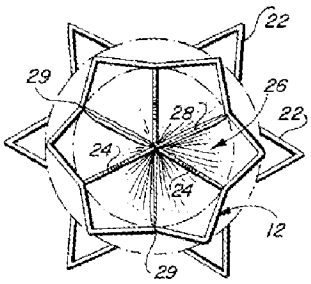


Fig. 3

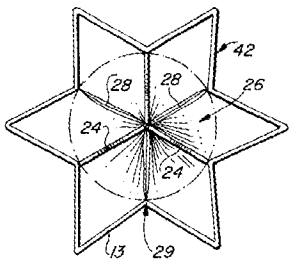


Fig. 9

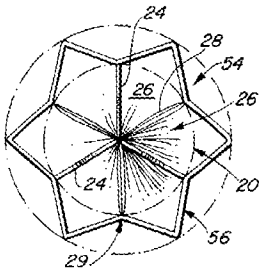


Fig. 15

In addition, the specification of Bailey states: "The stent body member is shaped to include the following stent sections: … **and at least one valve arm or blood flow regulator struts**" (Bailey, col. 5, ll. 51-54)(emphasis added); "[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..." (Bailey, col. 6, ll . 10-12)(emphasis added); and **"[c]ertain elements are common to each of the preferred embodiments of the invention, specifically, each embodiment includes ... at least one biasing arm** [] [that] projects from the stent body member and into the central annular opening of the stent body member" (Bailey, col. 7, ll . 58-67)(emphasis added). Accordingly, Bailey requires use of at least one biasing arm within the inner channel of the stent body member. In contrast, in new independent Claim 57 the Applicants claim "*a collapsible and expandable stent member including an inner channel*" wherein "*after deployment in the patient, the contiguous double-layer folded construct with the inner leaflet layer located radially within the outer cuff layer resides as a single element within the inner channel of the stent member.*" Therefore, Bailey fails to anticipate the claimed invention. Furthermore, Bailey teaches away from a collapsible and expandable stent member including an inner channel wherein after deployment in the patient, the contiguous double-layer folded construct with the inner leaflet layer located radially within the outer cuff layer resides as a single element within the inner channel of the stent member, because Bailey requires at least

one biasing arm **to close** the valve leaflets. Here, the Applicants direct the Examiner's attention to Bailey, wherein when discussing the struts, Bailey states:

> 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.

(Bailey, col. 6, ll. 23-26.)(Emphases added.) Here, it is clear that Bailey recognized the necessity to provide some type of mechanism to prevent prolapse of the leaflet membrane when closing. However, if the valve arms or blood flow regulator struts "serve to bias the valve to the closed position," then such biasing force must be overcome by the heart when attempting to pump blood through the valve. Accordingly, the valve arms or blood flow regulator struts of Bailey not only cause resistance to blood flow, but they add a level of complexity associated with interconnecting the leaflet-membrane to the valve arms or blood flow regulator struts, as well as crimping and deploying the valve. The invention disclosed and claimed herein by the Applicants overcomes these issues because, among other things, the contiguous double-layer folded construct, as claimed in Claim 57, provides a cuff mechanism for affixing the leaflet free edges and forming continuous and complete cusps that resist reverse blood flow while forward blood flow acts on the tissue material without valve arms or blood flow regulator struts connected to the tissue and biased in a closed position.

Bailey also makes it clear that the valve arms or blood flow regulator struts are part of the stent member. More particularly, Bailey states:

> Valve arms or regulator struts 24 **are coupled or formed integral with the stent body member 12** and are positioned adjacent the junction point between intermediate annular section 20 and the proximal anchor flange 22 of the stent body member 12.

(Bailey, col. 9, ll. 25-29.)(Emphasis added.) Therefore, the Applicants' limitations reciting "*a collapsible and expandable stent member including an inner channel,*" and "*wherein after deployment in the patient, the contiguous double-layer folded construct with the inner leaflet layer located radially within the outer cuff layer resides as a single element within the inner channel of the stent member*" clearly distinguish the claimed invention over Bailey.

In addition to the foregoing, the Applicants assert that Bailey does not enable a device that does not include the valve arms or blood flow regulator struts. That is, Bailey does not enable its tissue assembly to operate properly as a valve without the valve arms or blood flow regulator struts. MPEP § 2121.01 states that in order for a cited art document to anticipate a claim, the cited art must provide an enabling disclosure of the claimed subject matter. This section of the MPEP goes on to state that the mere naming or description of the subject matter is insufficient; rather, the cited art must demonstrate that the public was in possession of the claimed subject matter before the date of invention. In other words, the cited art must describe the claimed subject matter in such detail as to enable one of ordinary skill in the art to make the claimed subject matter without undue experimentation. In the present case, Bailey fails to enable one of ordinary skill in the art to make one or more embodiments that does not include at least one valve arm or blood flow regulator strut. That is, while Bailey discloses a construct that uses a plurality of valve arms or flow regulator struts 24, Bailey provides information insufficient to enable one of ordinary skill in the art to practice the invention without undue experimentation *if* the valve arms or regulator struts are *not* present.

In addition to the foregoing, the Applicants further distinguish over Bailey because each of the embodiments of Bailey requires use of graft material on the exterior of the stent member. In contrast, Applicants note that Claim 57 includes the limitation "*wherein the single sheet of*

biocompatible pericardium tissue resides entirely within the inner channel of the stent member." For Bailey's Chamber-to-Vessel Configuration, Bailey states "[i]n accordance with one embodiment of the present invention, the graft member 11 consists of an outer or ablumenal graft member 11*a* and an inner or lumenal graft member 11*b*. **The outer graft member 11*a* encloses at least a portion of the ablumenal surface** of the intermediate annular section 20 of the stent body member, while the inner graft member 11*b* is coupled, on the lumenal surface of the intermediate annular section 20 of the stent body member 12, to the outer graft member 11*a* through the interstices 14 of the stent body member." (Bailey, col. 9, ll . 2-11)(emphasis added). Bailey further states that "**the graft member 11 should cover at least a portion of the ablumenal surface of the stent body member 12 in order to exclude the anatomic valves**, but may also cover portions or all of the stent valve member 12, including the distal anchor section 16, the intermediate annular section 20, the transition section 18 and/or the proximal anchor flange 22, on either or both of the lumenal and ablumenal surfaces of the stent body member." (Bailey, col. 9 ll . 53-60)(emphasis added).

For Bailey's Chamber-to-Chamber Configuration, Bailey states "[t]hus, like the CV valve stent 10, described above, the CC valve stent 40 if formed of a stent body member 12 and a graft member 11, **with the graft member having lumenal 11*b* and ablumenal 11*a* portions which cover at least portions of the lumenal and ablumenal surfaces of the stent body member 12**, respectively." (Bailey, col. 10, ll . 52-58)(emphasis added).

For Bailey's Vessel-to-Vessel Configuration, Bailey states "[t]hus, like the CV valve stent 10, described above, the VV valve stent 50 is formed of a stent body member 12 and a graft member 11, **with the graft member having lumenal 11*b* and ablumenal 11*a* portions which**

cover at least portions of the lumenal and ablumenal surfaces of the stent body member 12, respectively." (Bailey, col. 11, ll . 43-49)(emphasis added).

Since Bailey only teaches embodiments with both ablumenal and lumenal positioned graft material, Claim 57 as presented herein is further distinguishable over Bailey because Bailey fails to disclose use of a single sheet of biocompatible pericardium tissue that resides entirely within the inner channel of the stent member.

In addition to the foregoing, the Applicants respectfully assert that although Bailey requires graft material on the ablumenal surface of the stent member, Bailey fails to explain how this can be integrated with the inner graft material as a single graft member. For example, Bailey states "[a]lternatively, portions of the outer graft member 11a may be passed through to the lumenal surface of the stent body member 12, thereby becoming the inner graft member 11b and everted to form the valve body 26." (Bailey, col. 9, ll. 20-24) However, Bailey fails to explain how this is done. That is, there are no drawings or explanation as to how "the outer graft member 11a" can be "passed through to the lumenal surface of the stent body member 12." Here, the Applicants note that the foregoing structure is never shown in Bailey. To the contrary, and as reproduced below, Bailey illustrates a series of embodiments in Figures 1, 7 and 13 of a stent body member 12 having pointed: (a) interstices 14 and proximal anchor flanges 22 (Bailey, Fig. 1); (b) distal anchor flanges 42 and proximal anchor flanges 44 (Bailey, Fig. 7); and (c) distal anchor sections 52 and proximal anchor sections 54 (Bailey, Fig. 13). However, none of the embodiments show the graft material extending around or actually passing through the foregoing structures and no explanation is provided in Bailey as to how the graft material is passed through to the lumenal surface of the stent body member.

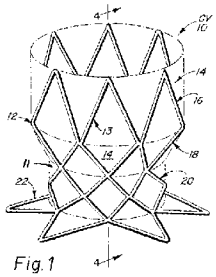


Fig. 1

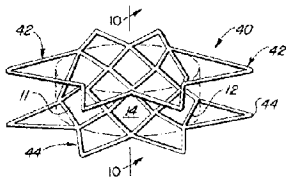


Fig. 7

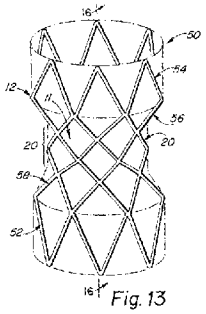


Fig. 13

Per the MPEP 2121.04, while pictures and drawings may be sufficiently enabling, they "must show all the claimed structural features and how they are put together." Jockmus v. Leviton, 28 F.2d 812, (2d Cir. 1928). Here, the Applicants respectfully assert while Bailey requires graft material on the ablumenal surface of the stent member and that Bailey must also use graft material to form the valve leaflets, Bailey does not explain nor show how to achieve the integration of both graft member configurations with a single graft member.

Summarizing the above, Bailey fails to disclose at least the limitations of:

- *a collapsible and expandable stent member including an inner channel,* and *wherein after deployment in the patient, the contiguous double-layer folded construct with the inner leaflet layer located radially within the outer cuff layer resides as a single element within the inner channel of the stent member;*
- *a single sheet of biocompatible pericardium tissue;*
- *wherein a first lateral edge of the single sheet of biocompatible pericardium tissue adjoins a second lateral edge of the single sheet of biocompatible pericardium tissue;* and
- *wherein the single sheet of biocompatible pericardium tissue resides entirely within the inner channel of the stent member.*

For the foregoing reasons, the Applicants believe that Bailey fails to anticipate Claim 57 as presented herein.

B. Previously Cited References

A number of references were previously cited in rejections in the present and parent patent applications. Without undertaking an exhaustive discussion of each references, the Applicants note at least the following differences between the limitations of Claim 57 presented herein and the references.

U.S. Pat. No. 5,545,215 to Duran

Duran discloses a surgically implantable valve. Among other things, Duran fails to disclose a collapsible and expandable stent member, wherein the single sheet of biocompatible pericardium tissue resides entirely within the inner channel of the stent member.

U.S. Pat. No. 5,855,597 to Jayaraman

Jayaraman discloses a valve in the form of two different embodiments. A first embodiment takes the form of a tube with slits at its end. A second embodiment includes a pocket sewed to a tube that is then turned inside out. However, Jayaraman fails to disclose at least the transverse linear crease and at least one additional linear crease oriented substantially perpendicular to the transverse linear crease, the inner leaflet layer partitioned by the at least one additional linear crease to form the two or more individual valve leaflets, the at least one additional linear crease located from the transverse linear crease to the free edge of the inner leaflet layer.

U.S. Pat. No. 5,782,914 to Schankereli

Schankereli discloses a method for preparing graft material from animal tissue, but fails to disclose the valve structure as claimed in Claim 57.

U.S. Pat. App. Pub. No. 2003/0153974 to Spenser

Spenser discloses a percutaneously deliverable implantable prosthetic valve. The Applicants note that Spenser has a filing date of October 11, 2001. Accordingly, the Applicants believe that their Declaration under 37 CFR 1.131 is sufficient to swear behind use of Spenser as a reference. Notwithstanding this point, among other things, Spenser fails to disclose a single sheet of biocompatible pericardium tissue partitioned as claimed in Claim 57.

For at least the foregoing reasons, the Applicants believe that Duran, Jayaraman, Schankereli, and Spenser all fail to disclose the structure recited by the Applicants in Claim 57 as presented herein.

CONCLUSION

In view of the foregoing, Applicants believe the claims as amended are in allowable form. In the event that the Examiner finds remaining impediment to a prompt allowance of this application that may be clarified through a telephone interview, or which may be overcome by an Examiner's Amendment, the Examiner is requested to contact the undersigned attorney.

Applicants believe no additional fees other than those fees tendered are due for this submission. However, please credit any over payment or debit any under payment to Deposit Account No. 08-2665.

Respectfully submitted,

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

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

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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	2	6264691		2001-07-24	Gabbay	
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	8	6312462		2001-11-06	McDermott et al.	

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	Art Unit	3738
	Examiner Name	Cheryl L. MILLER
	Attorney Docket Number	54813-10100

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	Art Unit	3738
	Examiner Name	Cheryl L. MILLER
	Attorney Docket Number	54813-10100

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	30	6702826		2004-03-09	Liddicoat et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	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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	43	6986735		2006-01-17	Abraham et al.	
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	50	7077862		2006-07-18	Vidlund et al.	

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OR

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☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Mark L. Yaskanin/	Date (YYYY-MM-DD)	2010-08-02
Name/Print	Mark L. Yaskanin	Registration Number	45246

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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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	2	3014024		1961-12-19	Lieberman et al.	
	3	3029819		1962-04-17	Edward	
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	49	5282847		1994-02-01	Trescony et al.	
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	1	1991/017720	WO		1991-11-28	Andersen et al.		☐
	2	1992/017118	WO		1992-10-15	Kaihoi et al.		☐
	3	2007/138572	WO		2007-12-06	Mor Research Applications Ltd.		☐
	4	2009/052188	WO		2009-04-23	Edwards Lifesciences Corporation		☐

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	1	CRIBIER, Alain et al., "Percutaneious Transcatheter Implantation of an Aoritc Valve Prosthesis for Calcific Aortic Stenosis: First Human Case Description" Circulation J of the Amer Heart Assoc, originally published online Nov 25, 2002	☐
	2	BONHOEFFER, Philipp M.D. et al., "Percutaneous Insertion of the Pulmonary Valve" J of the Amer College of Cardiology, Vol 39, No 10, Elsevier Science, Inc. 2002, pp 1664-1669, London, UK, and Paris, FR	☐

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	8	NOORLANDER, Maril L. et al., "A Quantitative Method to Determine the Orientation of Collagen Fibers in the Dermis" The J. of Histochemistry & Cytochemistry, Vol 50(11): 2002, pp. 1469-1474	☐
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	12	SHEN, Ming et al., "Protein adsorption in glutaraldehyde-preserved bovine pericardium and porcine valve tissues" The Annals of Thoracic Surgery, 2001; 71:409-409	☐
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Signature	/Mark L. Yaskanin/	Date (YYYY-MM-DD)	2010-08-02
Name/Print	Mark L. Yaskanin	Registration Number	45246

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	2	7164145		2007-01-16	Shakespeare	
	3	7166570		2007-01-23	Hunter et al.	
	4	7216301		2007-05-08	Stevens et al.	
	5	7214242		2007-05-08	Abraham et al.	
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	8	7309461		2007-12-18	Kujawski et al.	

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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

	9	7354702		2008-04-08	Dai et al.	
	10	7427291		2008-09-23	Liddicoat et al.	
	11	7431725		2008-10-07	Stack et al.	
	12	7481838		2009-01-27	Carpentier et al.	
	13	7510571		2009-03-31	Spiridigliozzi et al.	
	14	7510575		2009-03-31	Spenser et al.	
	15	7524330		2009-04-29	Berreklouw	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20010049558		2001-12-06	LIddicoat et al.	
	2	20020005073		2002-01-17	Tompkins et al.	

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	3	20020028243		2002-03-07	Masters	
	4	20020029783		2002-03-14	Stevens et al.	
	5	20020037940		2002-03-28	Koob et al.	
	6	20020042621		2002-04-11	Liddicoat et al.	
	7	20020095167		2002-07-18	Liddicoat et al.	
	8	20020095994		2002-07-25	Vesley et al.	
	9	20020128708		2002-09-12	Northup et al.	
	10	20030078659		2003-04-24	Yang	
	11	20030102000		2003-06-05	Stevens et al.	
	12	20030130727		2003-07-10	Drasler et al.	
	13	20030130729		2003-07-10	Paniagua et al.	

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	14	20030130731		2003-07-10	Vidlund et al.	
	15	20060178740		2006-08-10	Stacchino et al.	
	16	20030187362		2003-10-02	Murphy et al.	
	17	20030204023		2003-10-30	Koob et al.	
	18	20030212460		2003-11-13	Darois et al.	
	19	20030212462		2003-11-13	Gryska et al.	
	20	20030217415		2003-11-27	Crouch et al.	
	21	20040024452		2004-02-05	Kruse et al.	
	22	20040055608		2004-03-25	Stevens et al.	
	23	20040059418		2004-03-25	McKay et al.	
	24	20040098092		2004-05-20	Butaric et al.	

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	Attorney Docket Number	54813-10100

	25	20040193261		2004-09-30	Berreklouw	
	26	20040243153		2004-12-02	Liddicoat et al.	
	27	20040243229		2004-12-02	Vidlund et al.	
	28	20050027369		2005-02-03	Eldridge et al.	
	29	20050096673		2005-05-05	Stack et al.	
	30	20050142163		2005-06-30	Hunter et al.	
	31	20050147562		2005-07-07	Hunter et al.	
	32	20050147599		2005-07-07	Hunter et al.	
	33	20050147643		2005-07-07	Hunter et al.	
	34	20050148512		2005-07-07	Hunter et al.	
	35	20050158274		2005-07-21	Hunter et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		☐

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Examiner Signature		Date Considered	

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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	First Named Inventor	David PANIAGUA
	Art Unit	3738
	Examiner Name	Cheryl L. MILLER
	Attorney Docket Number	54813-10100

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Mark L. Yaskanin/	Date (YYYY-MM-DD)	2010-08-02
Name/Print	Mark L. Yaskanin	Registration Number	45246

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 1 hour 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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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 record s.

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/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

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

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5326371		1994-07-05	Love et al.	
	2	5332402		1994-07-26	Teitelbaum	
	3	5336616		1994-08-09	Livesey et al.	
	4	5360443		1994-11-01	Barone et al.	
	5	5374539		1994-12-20	Nimni et al.	
	6	5376110		1994-12-27	Tu et al.	
	7	5383927		1995-01-27	De Goiceochea et al.	
	8	5413601		1995-05-09	Keshelava	

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	9	5476506		1995-12-19	Lunn	
	10	5480424		1996-01-02	Cox	
	11	5500015		1996-03-19	Deac	
	12	5522879		1995-06-04	Scopelianos	
	13	5522881		1996-06-04	Lentz	
	14	5545215		1996-08-13	Duran	
	15	5549664		1996-08-27	Hirata et al.	
	16	5549666		1996-08-27	Hata et al.	
	17	5571170		1996-11-05	Palmaz et al.	
	18	5571173		1996-11-05	Parodi	
	19	5578071		1996-11-26	Parodi	

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	20	5578072		1996-11-26	Barone et al.	
	21	5582168		1996-12-10	Samuels et al.	
	22	5591229		1997-01-07	Parodi	
	23	5713953		1998-02-03	Vallana et al.	
	24	5728152		1998-03-17	Mirsch, II et al.	
	25	5741333		1998-04-21	Frid	
	26	5769780		1998-06-23	Hata et al.	
	27	5782914		1998-07-21	Schankereli	
	28	5787887		1998-08-04	Klingenbeck-Regn	
	29	5861028		1999-01-19	Angell	
	30	5895420		1999-04-20	Mirsch, II et al.	

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	Attorney Docket Number	54813-10100

	31	5931969		1999-08-03	Carpentier et al.	
	32	5957949		1999-09-28	Leonhardt et al.	
	33	5961539		1999-10-05	Northup et al.	
	34	5961549		1999-10-05	Nguyen et al.	
	35	5972030		1999-10-26	Garrison et al.	
	36	5976179		1999-11-02	Inoue	
	37	6010531		2000-01-04	Donlon et al.	
	38	6029671		2000-02-29	Stevens et al.	
	39	6053938		2000-04-25	Goldmann et al.	
	40	6091984		2000-07-18	Perelman et al.	
	41	6102944		2000-08-15	Huynh et al.	

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	42	6117169		2000-09-12	Moe	
	43	6125852		2000-10-03	Stevens et al.	
	44	6129756		2000-10-10	Kugler	
	45	6162245		2000-12-19	Jayaraman	
	46	6168619		2001-01-02	Dinh et al.	
	47	6197143		2001-03-06	Bodnar	
	48	6214055		2001-04-10	Simionescu et al.	
	49	6254629		2001-07-03	Inoue	
	50	6254630		2001-07-03	Inoue	

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☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Mark L. Yaskanin/	Date (YYYY-MM-DD)	2010-08-02
Name/Print	Mark L. Yaskanin	Registration Number	45246

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PTO/SB/06 (07-06)
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

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ 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 **08/02/2010**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 9	Minus	** 20	= 0	X $26 =	0	OR	X $ =	
Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $110 =	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 ($)	ADDITIONAL FEE ($)		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.

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Legal Instrument Examiner:
/RUTH M. LLOYD/

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

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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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4060081		1997-11-29	Yannas et al.	
	2	5171273		1992-12-15	Silver et al.	
	3	5746775		1998-05-05	Levy et al.	
	4	5862806		1999-01-26	Cheung	
	5	6352708		2002-03-05	Duran et al.	
	6	6432712		2002-08-13	Wolfinbarger, Jr. et al.	
	7	6471723		2002-10-29	Ashworth et al.	
	8	6569200		2003-05-27	Wolfinbarger, Jr. et al.	

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	Attorney Docket Number	54813-10100

	9	6719788		2004-04-13	Cox	
	10	7008763		2006-03-07	Cheung	
	11	7018404		2006-03-28	Holmberg et al.	
	12	7053051		2006-05-30	Hendriks et al.	
	13	7138226		2006-11-21	Vincek et al.	
	14	7381218		2008-06-03	Schreck	
	15	7585321		2009-09-08	Cribier	
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	1	20020091441		2002-07-11	Guzik	
	2	20060134079		2006-06-22	Sih et al.	
	3	20060193885		2006-08-31	Neethling et al.	
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	1	ANDERSEN, H.R. et al., "Transluminal implantation of artificial heart valve" European Heart Journal, 1992, 13, pp. 704-708	☐
	2	CALE, A.R. et al., "Revisited: a descending thorasic aortic valve to treat prosthetic valve insufficiency" Ann Thorac Surg, May 1993, 55(5), pp. 1218-2	☐
	3	CERROLAZA, M et al., "A comparison of the hydrodynamical behaviour of three heart aortic prostheses by numerical methods"	☐
	4	ZIOUPOS, P. et al., "Mechanical and Optical anisotrophy of bovine pericardium" Med Biol Eng Comput, 1992 Jan; 30 (1); pp. 76-82	☐
	5	FISHBEIN, M.C. et al., "Cardiac pathology after aortic valve replacement using Hufnagel trileaflet prostheses: study of 20 necropsy patients" Ann Heart J., April 1975, 89(4), pp. 443-448	☐
	6	GLOECKNER, D. Claire et al., "Mechanical Evaluation and Design of a Multilayered Collagenous Repair Biomaterial" J. of Biomedical Materials Research Part A, Vol. 52 Iss 2, PP 365-373, Published online Aug. 15, 2000, Wiley Periodicals, Inc.	☐
	7	HANLON, JG et al., "Pre-use intraoperative testing of autologous tissue for valvular surgery: a proof of concept study" J. Heart Valve Dis, Nov 1999; 8(6); pp. 614-23	☐
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	12	LIAO, K X et al., "Two-dimensional mechanical and ultrastructural correlates of bovine pericardium for prosthetic valves" ASAIO Trans, June 1, 1991, 37(3); M341-51	☐
	13	LS, Yu et al., "New Polyurethane valves in new soft artificial heart" ASAIO Trans 1989 Jul-Sep; 35(3), pp. 301-304	☐
	14	MOAZAMI, N. et al., "Transluminal aortic valve placement. A feasibility study with a newly designed collapsible aortic valve" ASAIO J, Sept-Oct 1996, 42(5):M 381-5	☐
	15	NIENABER C., M.D. et al., "Reconstruction of Thoracic Aortic Dissection By Stent-Graft Placement" N. Eng. J. Med, May 20, 1999, Col. 340, No. 20	☐
	16	NUNN, D.B., "Structural Failure of Dacron Arterial Grafts" Seminars in Vascular Surgery, Col 12, No. 1 (March), 1999, pp. 88-91	☐
	17	POHL, M. et al., "In vitro testing of artificial heart valves; comparison between Newtonian and non-Newtonian fluids" Artif Argns, Jan 1996; 20(1); pp. 37-46	☐
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	19	SACKS, M S et al., "Collagen fiber architecture of bovine pericardium" ASAIO J, July 1, 1994, 40(3):M632-7	☐
	20	SACKS, M S et al., "A small angle light scattering device for planar connective tissue miscrostructural analysis" Ann Biomed Eng, July 1, 1997, 254(4); 678-89	☐
	21	SACKS, Michael S, "Incorporation of experimentally-derived fiber orientation into a structural constitutive model for planar collagenous tissues" J. Biomech Eng, April 1, 2003, 125(2); 280-7	☐
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	23	SCHOEN, Frederick J., "Tissue heart valves: Current challenges and future research perspectives" J of Biomedical Materials Research, Vol 47, Iss 4, December 15, 1999, pp. 439-465	☐
	24	SHANDAS, Robin PhD et al., "A Method for Determining the Reference Effective Flow Areas for Mechanical Heart Valve Prostheses" Circulation April 25, 2000	☐
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	28	WIEGNER, A W et al., "Mechanical and structural correlates of canine pericardium" Circ Res, Sept 1, 1981m 49(3); 807-14	☐
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	31	WERNER, S. et al., "Testing the Hydrodynamic properties of heart valve prostheses with a new test apparatus", Biomed Tech (Berl) 1994 Sep; 30(9); pp. 204-210	☐
	32	COLLINS, J. J., Jr, "The Evolution of artificial heart valve" N. Engl J Med, 1991 Feb 28; 324(9):624-6	☐

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	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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Examiner Signature		Date Considered	

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	Art Unit	3738
	Examiner Name	Cheryl L. MILLER
	Attorney Docket Number	54813-10100

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

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☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Mark L. Yaskanin/	Date (YYYY-MM-DD)	2010-08-13
Name/Print	Mark L. Yaskanin	Registration Number	45246

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Application Number:	10887688
Filing Date:	10-Jul-2004
Title of Invention:	Percutaneously implantable replacement heart valve device and method of making same
First Named Inventor/Applicant Name:	David Paniagua
Filer:	Mark Lauren Yaskanin/Carol Donahue
Attorney Docket Number:	54813-10100

Filed as Large Entity

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Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

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EFS ID:	8218796
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:	23337
Filer:	Mark Lauren Yaskanin/Carol Donahue
Filer Authorized By:	Mark Lauren Yaskanin
Attorney Docket Number:	54813-10100
Receipt Date:	13-AUG-2010
Filing Date:	10-JUL-2004
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Application Type:	Utility under 35 USC 111(a)

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27	NPL Documents	Vyavahare_Mechanics_of_Bioprosthetic.pdf	603983 d9140785f6c37c4ebc0c6c67dddc5b833f9dce5	no	7
Warnings:					
Information:					
28	NPL Documents	Wiegner_Mechanical_and_structural_Correlates.pdf	2297229 96e7a6cc92ff1c1b3608d71dbf41f07420727836	no	9
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29	Information Disclosure Statement (IDS) Filed (SB/08)	Supp_IDS_6.pdf	615467 2ae6463df6127da75cb5f870b28692aa56117f03	no	9
Warnings:					
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30	NPL Documents	Zioupos_Anisotropic_Elasticity.pdf	15680386 f08432932351a38c9e402937644f10ff8ac832cc	no	9
Warnings:					
Information:					
31	NPL Documents	Corden_Influence_of_Open_Leaflet_Geometry.pdf	3120701 d5ee06d8ea93a23065e895465fa8f846a58b2deb	no	15
Warnings:					
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32	NPL Documents	Werner_Testing_Hydrodynamic_Properties.pdf	31526 51794f8eb90d6bc5d52a7cd9eed12da331852247	no	1
Warnings:					
Information:					
33	NPL Documents	Collins_Evolution_of_artificial_heart.pdf	597234 1b2acdd6677ccd15d758e0dbd359078be06ad1d2	no	3
Warnings:					
Information:					
34	NPL Documents	Lax_Estimation_of_Ejection_Fraction.pdf	465199 3dc7e34ea659168378c5229ac44957bc9c21e4de	no	8
Warnings:					
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35	NPL Documents	Simionescu_Mapping_Glutaraldehyde-treated_ARTICLE.pdf	12862309 46f0ddd8d9e9a9dcf7c4c0d5534d96a246963cb4	no	8
Warnings:					

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36	Fee Worksheet (PTO-875)	fee-info.pdf	29910 cb612255ae95b05bdb7eb1c54f8bcba4e1d32e98	no	2
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(54) Title: TARGETED ANTICALCIFICATION TREATMENT

(57) Abstract: Methods for providing biomaterials with increased resistance to calcification by treating with cell-targeted agents and/or with matrix-targeted agents. Cell-targeted agents are used which block calcium channels or which prevent oxidative damage to cells and/or inhibit enzymes. Other treatments of biomaterials may remove cell-derived calcium-binding components or target extracellular matrices, as by cleaving proteins with cyanogen bromide or reducing disulfide bonds to produce sulfhydryl groups which are thereafter alkylated. Combinations of the foregoing different treatments are also effective in increasing the calcification resistance of cardiovascular tissues that were previously subjected to chemical fixing and/or other anticalcification treatments.

TARGETED ANTICALCIFICATION TREATMENT

The present invention relates generally to treating biomaterials destined for implantation in a human patient so as to render such materials resistant to calcification, and more particularly relates to methods for targeting anticalcification treatment to particular biological tissue that has been previously fixed, i.e. chemically cross-linked, so as to render it more resistant to calcification following its implantation in the human patient. Still more particularly, the invention relates to treatments of this type that are targeted to specific biomaterials of a certain character that have heretofore been difficult to effectively render resistant to calcification.

Background of the Invention

Degenerative calcification of glutaraldehyde-fixed biological tissues used for bioprosthetic heart valve (BHV) fabrication is presently considered to be a major cause of long-term failure of these implants in a clinical setting. Mitigation of calcification has been investigated (a) by subsequently treating glutaraldehyde-treated tissues with a variety of compounds and (b) by employing fixation procedures which do not employ glutaraldehyde. The results obtained thus far indicate that the type of tissue and its precise composition may be important in determining its susceptibility to calcification. Collagen concentration, for example, varies from about 90% (w/w) in pericardium, to about 40% in aortic cusps, and to only about 25% in aortic wall tissue. On the other hand, elastin accounts for only 1-5% in pericardium and about 10-15% in cusps whereas it may account for up to about 50% of aortic wall tissue. Furthermore, cell types and numbers differ significantly between these three tissues.

Anticalcification treatment of glutaraldehyde fixed tissues such as that disclosed in U.S. Patent No.

4,976,733 and the treatment of tissues not cross-linked by glutaraldehyde in Nos. 5,447,536 and 5,733,339 were shown to be quite effective in reducing calcification of collagenous tissues, such as pericardium and porcine aortic leaflets; however, elastin-containing aortic wall tissue has proven to be less susceptible to reduction of calcification by the above-mentioned treatments. As a result, the investigation has continued for other anticalcification treatments that would specifically target tissue relatively low in collagen, for example tissue having relatively greater amounts of elastin.

Although, the molecular mechanisms of BHV calcification are not well understood, additional elements, e.g. the presence of injured or devitalized cells, are now considered to be important along with the character of cross-linked extracellular matrix. For example, cell injury induced by fixation protocols can lead to impairment of normal calcium homeostasis, followed by a massive calcium influx, and such can, in turn, lead to cell death and calcification of cell remnants. Cross-linked extracellular matrix, on the other hand, can induce calcium deposition per se or, as a consequence of cell-mediated propagation, can induce calcification into the surrounding matrix. Therefore, the molecular substrates that can promote deposition of calcium salts in BHV and other implanted organs may generally be divided into two categories: (a.) cell-derived elements, such as lipid membranes which may contain calcium-transporting channels and calcium ATPases, integrins, cadherins, selectins and annexins, as well as cytoskeletal protein structures present in the close vicinity of devitalized cells, cell enzymes, calmodulin, mitochondria, the cell nucleus and other calcium-binding components, and (b.) extracellular matrix calcium-binding components, such as elastin-associated microfibrillar proteins (EAMF), collagens, proteoglycans, proteolytic enzymes, such as metalloproteinases (MMPs), matrix phosphatases, and other non-collagenous proteins.

A common element that appears to characterize these calcifiable substrates is the ubiquitous presence of one or more high affinity calcium-binding sites or calcium-trapping pockets which, by means of carboxyl and/or hydroxyl groups, attract and immobilize calcium ions. The three-dimensional conformation of these sites is stabilized in the "correct" shape by intramolecular bridges, such as disulfide bonds, and hydrophobic interactions. [See *Guidebook to the Calcium-binding Proteins,* Celio et al., eds., Oxford University Press, Oxford, UK, p. 15-21, 1996]

Summary of the Invention

Anticalcification methods have now been devised that take into consideration the character of these molecular substrates that account for calcium deposition in tissues. These new methods accordingly target or challenge such substrates with specific compounds in such a way as to reduce or inhibit overall tissue calcification, without compromising any previously obtained cross-linking or calcification resistance that may have been obtained as a result of treatment with other reagents.

These methods of treatment generally fall into two main classes: cell-targeted treatments and matrix-targeted treatments. The cell-targeted class of treatment includes three general categories; however, in some instances treatments from different classes or from different categories within one class may be used in combination and, as such, may produce an effect that is greater than the effect produced by either class or category of treatment alone. Generally, it has been found that progression from reversible, physiological calcium-binding towards the irreversible deposition of calcium salts into or onto these substrates can be effectively stopped by treatments that destabilize, modify and/or destroy the original conformation of high affinity calcium-binding sites and/or by treatments that

permanently block the access and influx of counterions into otherwise unaltered sites.

In the class of treatment that targets cells, injured cells are protected from degeneration and calcium overload by treating tissue containing such cells to reduce calcium influx into the cells or prevent oxidative and/or enzymatic damage. One may use a calcium channel blocking agent, such as nifedipine (NIF) or diltiazem hydrochloride (DIL), an antioxidant, or an agent, such as captopril (CAP), that inhibits damaging enzymes. Potential cell-related calcification substrates, such as the cytoskeletal proteins actin, myosin, troponin and actinin, can also be removed, extracted or inactivated by using an appropriate extractant, such as a high potassium salt/MgATP mixture (KMA).

In the other class of treatment which targets the extracellular matrix, the structure of calcium-binding components, such as EAMF and MMPs and the like, in extracellular matrices can be appropriately modified to reduce the capacity thereof either to calcify per se or to induce calcification in adjacent components. For example, treatment with a suitable cleaving agent, such as cyanogen bromide (CB), will effect partial cleavage of proteins at methionine residues, whereas protein disulfide bonds can be effectively broken by treatment with a suitable reducing agent, such as dithiothreitol (DTT), and then alkylated with a suitable reactant, such as N-ethylmaleimide (NEM).

Detailed Description of the Preferred Embodiments

As mentioned above, it was known that certain tissues, such as the wall of aortic root tissue, have not heretofore been rendered as successfully resistant to calcification as a result of present anticalcification treatments or non-glutaraldehyde cross-linking, as have, for example, tissues containing significantly higher amounts of collagen. However, as indicated, it has now been found that these and other such tissues can be treated by specific cell-targeted and matrix-targeted

anticalcification treatments that are indeed effective. It has been found that the irreversible deposition of calcium salts into or onto these substrates can be effectively stopped by the use of different treatments within these two classes, which may be used individually or in combination with one another. One category of treatment permanently blocks the access and influx of counterions into such sites in cells. A second category of treatment provides antioxidants which prevent oxidative damage and inhibit the action of enzymes that promote calcification of cells. A third category extracts cell-related potential calcification sites. Another category of treatment destabilizes, modifies and/or destroys the original conformation of such high affinity calcium-binding sites and is principally effective against calcification in matrices.

Tissues and biomaterials generally that can benefit from this technology may be characterized as being constituents of either biologic or synthetic origin which, once implanted in a human, are expected to directly or indirectly suffer the effects of calcification while implanted in a patient. Because these biomaterials are expected to be susceptible to concomitant calcium overload, oxidative damage and/or enzymatic hydrolysis, the incorporation of protective agents into these biomaterials provides them with reduced susceptibility towards calcification as well as increased biostability and durability.

Biological tissues, as a result of modified extracellular matrix components or injured cells or both, will frequently present calcifiable substrates to which attention needs to be given; they may be cardiovascular tissues or non-cardiovascular tissues. Examples of the former group include cardiac valves with or without associated stents, i.e. aortic, mitral, pulmonary and tricuspid valves, pericardium and blood vessels, such as (a) arterial segments of large, medium or small caliber, e.g. aortic, carotid or coronary, and (b) venous segments

of large, medium or small caliber with or without accompanying venous valves, e.g. saphenous, jugular or cavae. Examples of the non-cardiovascular tissue group include tendons, ligaments, articulations, aponeuroses, cartilages, organ capsules and sheaths, membranes, such as fasciae and dura matter, conduits, such as esophagus, trachea, hepatic ducts and ureter, and cavitary organs from the digestive and urinary tracts. Such implanted tissue may be heterologous, homologous or autologous, i.e. of animal or human origin. Overall, the biomaterials which may be treated prior to implantation may be whole tissues, organs or products thereof which are composed of extracellular matrix components, both with and without cells, and they may be in solid, liquid or gel form, e.g. in the form of sheets, sponges or fibers. They may also be products of tissue engineering or of guided tissue regeneration, wherein scaffolds and scaffolds with cells are used.

The biomaterials which are to be treated by the invention may have been previously chemically processed for removal of selected components, such as antigenic determinants, cell remnants, lipids, sugars and the like. As earlier indicated, such tissues may also have been chemically fixed or cross-linked using glutaraldehyde or other procedures. These tissues may also be further processed by pre- or post-fixation treatments with various anticalcification compounds, e.g. 2-aminooleic acid, phosphonates, detergents, ions and dyes; moreover, these biomaterials may be freeze-dried or dehydrated tissues. They may also be tissues or organs that were preserved by deep-freezing in the presence of cryoprotectants, as well as tissues or organs preserved in antibiotic-containing cold solutions.

In accordance with the first treatment category mentioned above, lipid membranes from injured cells which may contain naturally occurring calcium channels and calcium ATPases, integrins, cadherins, selectins and annexins may be protected from calcium overload and/or

degeneration by treating such tissue with a calcium channel blocking agent and/or an antihypertensive agent that is capable of preventing oxidative damage and inhibiting the action of enzymes which have been reported to cause calcification. Examples of one group of suitable calcium-channel blocking agents include nifedipine (NIF), i.e., 1,4-Dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylic acid dimethyl ester, nimodipine, nisoldipine, nitredipine, nicardipine, nilvadipine, amlodipine, lacidipine, verapamil, diltiazem hydrochloride (DIL), i.e., 1,5-Benzothiazepin-4(5*H*)one, 3-(acetyloxy)-5-[2- (dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-monohydrochloride, trifluoperazine, bepridil, cinnarizine, fendiline, flunarizine, lidoflazine, phenylamine, pryanodine, ruthenium red and veratridine.

Useful in the second category of treatment are agents capable of preventing oxidative damage, which may also have antihypertensive properties; such agents include captopril (CAP), i.e., 1-(3-Mercapto-2-methyl-1-oxopropyl)-L-proline, quinalapril, enalapril, lisinopril and zofenopril. Other examples include allopurinol, nicotinamide, ebselen, resveratrol, xanthine, diphenyl phenylene diamine, chlorpromazine, manitol, catalase, peroxidase, desferroxamine, polyphenols, N-acetyl cysteine, ubiquinol, butylated hydroxytoluene, probucol, alpha-tocopherol, trolox, superoxid dismutase, thiourea, taurine, propyl galate, histidine, vitamin C, beta-carotene, beta-mercaptoethanol, reduced glutathion, reduced glutathion monoisopropyl esther, reducible dyes (phenazine methosulfate, nitroblue tetrazolium chloride, tiazolyl blue, methylene blue, toluidine blue), N-tert butyl phenyl nitrone, antioxidant peptides (anserine, carnosine, carcinine), Val-Phe-aldehyde, PMSF, leupeptin benzamidine, soybean trypsin inhibitor. Some compounds, such as CAP, are both antioxidants and inhibitors of metal-containing enzymes.

Combinations of agents from the foregoing two groups may advantageously be employed.

Either as an alternative to, or in addition to, the above treatments, it may be desirable and feasible as a third treatment category, to remove potential cell-related calcification substrates, e.g. cytoskeletal proteins such as actin, myosin, troponin and actinin, as well as cell enzymes, calmodulin, mitochondria, cell nuclei and other calcium-binding or calcium-trapping components. Such tissue is treated using a compound which functions as a suitable cell extractant, e.g. a high concentration potassium salt/MgATP mixture (KMA), to remove, extract and/or inactivate such substrates that are prone to calcium salt accumulation or inducing same, and such treatment of walls with KMA showed 52-56% reduction in wall calcification following 8 weeks implantation in the rat subdermal model of calcification. Other suitable cell extractants may also be used. Such extraction treatments may be advantageously used in combination with treatment by proteolytic enzyme inhibitors, such as PMSF, leupeptin, benzamidine and soybean trypsin inhibitor.

With respect primarily to sites in extracellular matrices where there also are calcium-binding components, e.g. fibrillin, other EAMF proteins, collagens, proteoglycans, proteolytic enzymes, such as MMPs, phosphatases, and non-collagenous proteins, such as laminin, fibronectin, thrombospondin, tenascin, osteonectin, osteopontin and matrix Gla-protein, the other main class of matrix-targeted treatment is used. It has been found that such protein components can be effectively modified in such way as to reduce their capacity to calcify per se or to induce calcification in adjacent or related components. One preferred treatment is to use an appropriate cleaving agent, such as cyanogen bromide(CB), to cleave such proteins at methionine (Met) residues; alternative cleaving agents are well known in the art and include hydroxylamine, N-bromosuccinimide,

N-chlorosuccinimide, thiocyanobenzoic acid, ortho-iodosobenzoic acid and trifuoroperazine. By use of such a modification regimen, the configuration of methionine-containing proteins is changed, and their ability to thereafter bind calcium salts or to induce or promote such binding is very significantly reduced. It has also been found that effective modification to the same end can be effected by breaking intramolecular bridges within proteins, e.g., by altering hydrophobic interactions and/or breaking disulfide bonds. Such modifications can be effected by reduction with dithiothreitol (DTT) or similar well known reducing agents, such as ammonium sulfite, dithioerythritol, sodium sulfite, tri-n-butylphosphine and beta-mercaptoethanol, and then preventing the reversal of such reduction by reacting with a reagent that will bond with a sulfhydryl group. Examples of suitable blocking reagents include alkylating reactants, such as N-ethylmaleimide (NEM), dithiobis-(2-nitrobenzoic acid), iodoacetamide, iodoacetate, p-hydroxymercuri-benzoate and the methanethiosulfonates. Because there may be more proteins with Met residues than there are proteins with disulfide bonds in such extracellular matrices, treatment with CB or an equivalent cleaving agent may be preferred. However, both these modifications have advantageous effects in reducing calcification resulting from the presence of EAMF proteins, MMPs and the like, and the combination of these two treatments may produce the most desirable effect.

Treatments are carried out using the cell-targeted agents at appropriate concentrations, temperatures, pH and durations as generally known in this art for use of such reagents. CAP or similar agents may be used at a concentration of from 1-200 mM (preferably 25-75 mM), at about 15-40°C, and at about pH 6-8 for about 2-72 hours. NIF, DIL and related calcium channel blocking agents would be used at concentrations of about 0.1-50 mM (preferably about 5-25 mM) under otherwise similar

conditions. Cell extractants are used at a similar pH and for a similar duration at temperatures in the range of about 0-20°C. KMA may be used at a KCl concentration between about 0.4 M and about 1.5 M and usually between 0.5-0.8 M and MgATP at concentrations between 0.01-10 mM and usually between about 0.05-8 mM. Although any sequence of treatments with agents from the three categories of cell-targeted agents may generally be used, when such a combination of treatments are employed, the following sequences are most often used: Category 1 followed by Category 2; Category 2 followed by Category 1; Category 3 followed by Category 2; Category 3 followed by Category 1; and Category 3 followed by Category 1 and Category 2.

A cleaving agent, such as CB, is used at a concentration of about 1-200 mM (preferably about 10-50 mM), at a similar pH and temperature as for CAP, but for a shorter duration of about 1-24 hours, e.g., about 3 hours. A reducing agent, such as DTT, might be employed at a concentration of about 1-200 mM (preferably about 25-75 mM) and at other conditions as for CAP, and treatment with such an agent is preferably followed by treatment with a blocking agent, such as NEM, at a similar concentration and about the same temperature and pH as for CAP, but for a duration of about 12-48 hours, e.g., 24 hours. When combinations of the two classes of treatment are employed, it is preferred that the matrix-targeted class of treatment precede the cell-targeted treatment. For example, treatment with CB, or treatment with DTT preferably followed by reaction with an alkylating agent, would usually be carried out prior to treatment with a Category 2 agent, with optional treatment thereafter with a Category 1 agent.

The aforementioned treatments are usually carried out in a buffered aqueous solution, e.g. using a borate buffer or HEPES, PIPES, MOPSO or the like. Washing is carried out following the anticalcification treatment and prior to sterilization. Normal saline or a buffered

aqueous solution, as described above, may be used at about 0-40°C for 15 minutes to 4 hours, with the optional inclusion of up to about 25% isopropanol or another lower alkanol. When a combination of treatment steps is used, washing or rinsing between steps is desirable but not always necessary so long as there is washing prior to sterilization.

The anticalcification treatment may be applied to tissue that is not cross-linked, such as cryopreserved homografts, or to tissue that is cross-linked. When the treatment is applied to cross-linked tissues, it is generally performed after fixation treatment of the biological tissue, although it may be performed previous thereto, or even both before and after. However, when a cell extractant or a reducing agent is used, treatment is preferably carried out prior to fixation. When the present treatment is carried out in combination with another type of anticalcification treatment, such as treating with 2-aminooleic acid as described in the '733 patent, the present treatment is preferably carried out subsequent thereto, except for treatment with a cell extractant or a reducing agent, which is preferably carried out prior to such other type of anticalcification treatment.

It is also important that such targeted methods of anticalcification treatment, when carried out following fixing, do not adversely affect the desirable cross-linking of tissue that has been previously effected, and tests to date show this be true. These treatments also do not appear to have any adverse effect upon the anticalcification properties of the overall tissue, which properties may have been the result of a previously administered anticalcification treatment or non-glutaraldehyde cross-linking, such as described in the aforementioned three U.S. patents that have been proven to provide excellent calcification resistance for porcine valves leaflets.

The foregoing is felt to be important because calcification may concomitantly occur, both in BHV and in other biomaterials, in a variety of different substrates, e.g. in cells and in extracellular matrix. As a result, sequential treatment using several targeted treatment methods that are compatible with one another may very well be important in achieving the overall desired effect. For example, it may be desirable to treat cell-containing BHV tissue to block calcium channels and/or reduce oxidizing and/or enzymatic damage, and/or extract or inactivate certain proteins, such as actin and myosin, in combination with modifying proteins in the extracellular matrix that may have a propensity to bind calcium per se or to induce calcification (as by partially cleaving such proteins and/or reducing cyclizing S-S bonds followed by alkylating); as a result of such treatment, overall calcification of BHV tissue is found to be very effectively reduced. Moreover, testing has shown that treatment with two agents in categories one and two, i.e. a combination of a calcium-channel-blocking agent and an antioxidant and/or enzyme inhibitor, may be more effective than either treatment alone. Furthermore, certain of the treatments described with respect to one class may also have some beneficial effects upon targets from the other class. For example, treatment with CAP, in addition to protecting targeted cells, also inhibits the action of MMPs and phosphatases; similarly, treatment with CB or by DTT/NEM may also have an anticalcification effect upon certain cell-derived substrates.

The following examples illustrate the effectiveness of treatments carried out using some of the preferred embodiments of the invention.

EXAMPLE 1 - Cell Targeted Treatment

Multiple samples of porcine aortic roots were fixed and treated as follows:

(a) Glutaraldehyde - Samples were treated with 0.2% glutaraldehyde in phosphate-buffered saline, pH 7.4,

for 12 days at room temperature. Tissues were then sterilized for 24 hours at 37°C using 1% glutaraldehyde, 20% isopropanol in phosphate-buffered saline, pH 7.4, followed by 24 hours incubation at 40°C in 0.2% glutaraldehyde in phosphate-buffered saline, pH 7.4, and then stored in the same solution;

(b) Glutaraldehyde plus 2-aminooleic acid - additional samples were treated with 0.2% glutaraldehyde in phosphate-buffered saline, pH 7.4, for 12 days at room temperature followed by incubation in an aqueous buffered solution of 2-aminooleic acid according to the '733 patent, and then rinsed. Tissues were then sterilized for 24 hours at 37°C in 1% glutaraldehyde, 20% isopropanol in borate-buffered saline, pH 7.4, followed by 24 hours incubation at 40°C in 0.2% glutaraldehyde in borate-buffered saline, pH 7.4, and stored in the same solution;

(c) Glutaraldehyde plus 2-aminooleic acid plus CAP - additional samples were treated with 0.2% glutaraldehyde in phosphate-buffered saline, pH 7.4, for 12 days at room temperature, followed by treatment with aminooleic acid (as above), followed by incubation in 50 mM CAP in borate-buffered saline, pH 7.4, in 10% isopropanol for 24 hours at 37°C and then rinsed. Tissues were then sterilized for 24 hours at room temperature in 1% glutaraldehyde, 20% isopropanol in borate-buffered saline, pH 7.4, followed by 24 hours incubation at 40°C in 0.2% glutaraldehyde in borate-buffered saline, pH 7.4, and stored in the same solution;

(d) Glutaraldehyde/AOA plus NIF - additional tissues were treated as in Example 1 group(b) (in which tissues were glutaraldehyde-fixed, then treated with 2-aminooleic acid). Tissues were then rinsed and incubated in 5 mM NIF in borate buffer saline, pH 7.4, containing 20% isopropanol for 24 hours at

37°C. After rinsing in borate buffer saline, pH 7.4, containing 20% isopropanol, tissues were sterilized in 1% glutaraldehyde 20% isopropanol in borate buffer saline, pH 7.4 for 24 hours at 37°C, followed by 24 hours incubation at 40°C in 0.2% glutaraldehyde in borate buffer saline, pH 7.4, and then stored in the same solution.

(e) EDC(sulfo-NHS)-type fixation - Additional tissues first fixed according to the teaching of the '339 patent using EDC plus sulfo-NHS and hexanediamine and/or suberic acid in HEPES buffer, and then sterilized according to U.S. patent number 5,911,951, e.g., by incubation for 24 hours at 40°C in 25 mM EDC, 20% isopropanol in 10 mM HEPES, pH 6.5, and stored in the same solution;

(f) EDC(sulfo-NHS)-type fixation plus CAP - Additional tissue was fixed with EDC(sulfo-NHS) as indicated above and then further incubated in 50 mM CAP in 10 mM HEPES, pH 6.5, in 10% isopropanol for 24 hours at 37°C and then rinsed. Tissues were then sterilized according to the '951 patent and stored in the same solution; and

(g) EDC/sulfo-NHS-fixed plus NIF - additional tissues were fixed as in Example 1 group(e) (in which tissues were fixed using the EDC/sulfo-NHS process). Tissues were then rinsed and incubated in 5 mM NIF in HEPES buffered saline, pH 6.5, containing 20% isopropanol, for 24 hours at 37°C. After rinsing in HEPES buffer saline, pH 6.5, containing 20% isopropanol, tissues were sterilized according to the `951 patent and stored in the same solution.

Following undergoing the foregoing treatments, the sterilized roots were washed in normal saline, and cusps were dissected away from the aortic walls. For calcification studies, 20 wall coupons and 20 cusp halves were randomly selected from each experimental condition; they were implanted subdermally in three-week old, male

Wistar rats. Samples were explanted at 4 and 8 weeks, and calcium was quantitated by Atomic Absorbtion Spectrophotometry (AAS). Selected samples from each experimental condition were processed for histology and stained with hematoxylin and eosin (H&E) for cells, and with von Kossa reagent for calcium deposits. The results are set forth in the table that follows.

RESULTS

Table 1

	Mean ± SEM (milligrams calcium/gram dry tissue)			
	Walls		Cusps	
Treatment	4-week	8-week	4-week	8-week
Group a	64.0 ± 5.0	114.0 ± 16	53.0 ± 4.0	155 ± 30
Group b	50.1 ± 6.0	99.6 ± 5.0	5.2 ± 1.0	5.6 ± 1.0
Group c	5.2 ± 2.0	21.5 ± 3.0	3.7 ± 1.0	3.5 ± 1.0
Group d	7.8 ± 4.0	18.7 ± 7.0	2.7 ± 1.3	2.3 ± 0.6
Group e	63.2 ± 6.0	100.0 ± 7.0	2.8 ± 0.9	2.9 ± 1.0
Group f	2.6 ± 1.1	8.0 ± 3.0	1.7 ± 0.3	1.9 ± 0.6
Group g	0.3 ± 0.1	8.9 ± 3.0	0.5 ± 0.3	0.7 ± 0.2

The results indicate that post-fixation treatment of wall tissue with CAP, i.e., groups (c) and (f), significantly reduces the calcification compared to wall tissue of groups (b) and (e). In (b), wall tissue samples had been fixed and then treated with 2-aminooleic acid, and in group (e), wall tissue samples had been fixed according to the '339 patent. Moreover, the treatment does not compromise the earlier established calcification resistance of the cusps created by such prior treatment, but instead it may actually slightly improve the resistance of the cusps. Similar results were obtained in the case of post-fixation treatments with 5 mM NIF, i.e. groups (d) and (g), and are also obtained when 5 mM DIL is used.

In all samples screened from each experimental condition, histology revealed the absence of inflammatory reactions (H&E), while von Kossa reagent staining essentially confirmed the calcium analysis results. Alternatively, a pre-fixation treatment to accomplish actin and myosin extraction using KMA was shown to reduce the number of such cells in calcification-prone areas in the wall tissue, but it proved less effective than those treatments detailed in the above-reported tests in increasing calcification resistance.

The foregoing results suggest that targeting cell calcification by treating with calcium-blocking agents or oxidative damage-preventing agents or with other modifying or extracting agents can significantly reduce aortic wall calcification.

EXAMPLE 2 - Extracellular Matrix Targeted Treatments

Multiple samples of porcine aortic roots were fixed and treated as follows.

(a) Glutaraldehyde - Samples as treated as in case of group(a) for Example 1.

(b) Glutaraldehyde plus aminooleic acid - Samples as treated as in case of group(b) for Example 1.

(c) Glutaraldehyde plus 2-aminooleic acid plus CB - Samples were treated with 0.2% glutaraldehyde in phosphate-buffered saline, pH 7.4, for 12 days at room temperature, followed by treatment with aminooleic acid (as above), followed by incubation in 18.8 mM CB in borate-buffered saline, pH 7.4, for 3 hours at 37°C, and then rinsed. Tissues were sterilized for 24 hours at room temperature in 1% glutaraldehyde, 20% isopropanol in borate-buffered saline, pH 7.4, followed by 24 hours incubation at 40°C in 0.2% glutaraldehyde in borate-buffered saline, pH 7.4, and stored in the same solution.

(d) EDC(sulfo-NHS)-type fixation - Samples were treated as in case of group (e) for Example 1.

(e) EDC(sulfo-NHS)-type fixation plus CB - Additional tissue was fixed using EDC and sulfo-NHS as

indicated above and then further incubated in 18.8 mM CB in 10 mM HEPES, pH 6.5, for 3 hours at 37°C. Tissues were then sterilized according to the '951 patent and stored in the same solution.

Following the foregoing treatments, the sterilized roots were washed in normal saline, and cusps were dissected away from the aortic walls. For calcification studies, 20 wall coupons and 20 cusp halves were randomly selected from each experimental condition and were implanted subdermally in three-week old, male Wistar rats. Samples were explanted at 4 and 8 weeks, and calcium was quantitated by AAS. Selected samples from each experimental condition were processed for histology and stained as in Example 1. The results are tabulated in the table which follows.

RESULTS

Table 2

	Mean ± SEM (milligrams calcium/gram dry tissue)			
	Walls		Cusps	
Treatment	4-week	8-week	4-week	8-week
Group a	65.5 ± 6.0	111.0 ± 14	58.0 ± 5.0	165 ± 28
Group b	58.3 ± 5.0	109.5 ± 5.0	5.2 ± 1.0	5.1 ± 1.2
Group c	7.9 ± 3.0	22.6 ± 3.0	3.5 ± 0.8	3.8 ± 1.0
Group d	60.0 ± 6.0	102.0 ± 8.0	2.5 ± 0.8	5.0 ± 1.0
Group e	8.9 ± 1.1	20.2 ± 3.0	4.2 ± 1.0	3.3 ± 0.8

The results indicate that post-fixation treatment with CB, i.e., groups (c) and (e), reduces the calcification of wall tissue that has been either treated with glutaraldehyde and 2-aminooleic acid or fixed according to the '339 patent, without increasing calcification of the corresponding cusps. Studies on calcification of purified elastic fibers obtained from aortic walls confirmed the efficacy of CB treatment as an anticalcification treatment. Moreover, shrinkage temperature for the fixed cusps was not significantly

affected by the CB treatment, indicating that cross-link density was not significantly reduced by treatment with CB. Histology revealed little, if any, inflammatory reactions in all samples screened from each experimental condition, and von Kossa staining confirmed the calcium quantitation results. Alternative testing showed that similar post-fixation modification of aortic wall tissue with DTT/NEM was also effective in reducing calcification; however, it was not as effective in one particular test as treatment with CB, which is presently preferred.

The results of this testing indicate that matrix components, such as EAMF proteins, MMPs, and other calcium-binding components can be effectively chemically modified in a manner so as to reduce aortic wall calcification.

EXAMPLE III - Combination of Targeted Treatments

Multiple samples of porcine aortic wall segments were fixed and treated as follows.

(a) Glutaraldehyde/AOA - additional tissue was treated as in Example 1 group(b) (in which the tissues were glutaraldehyde-fixed, then treated with aminooleic acid, followed by sterilization).

(b) Glutaraldehyde/AOA plus CAP plus NIF - additional tissue was treated as in Example 1 group(c) (in which tissues were glutaraldehyde-fixed, then treated with aminooleic acid, followed by treatment with the CAP). Tissues were then rinsed and incubated for 24 hours at 37°C in 5 mM NIF in borate buffer saline, pH 7.4, containing 20% isopropanol. After rinsing in borate buffer saline, pH 7.4, containing 20% isopropanol, tissues were sterilized for 24 hours at 37°C in 1% glutaraldehyde and 20% isopropanol in borate buffer saline, pH 7.4, followed by 24 hours incubation at 40°C in 0.2% glutaraldehyde in borate buffer saline, pH 7.4, and stored in the same solution.

(c) Glutaraldehyde/AOA plus CB plus CAP - additional tissue was treated as in Example 2 group(c) - (in which tissues were glutaraldehyde-fixed, then treated with aminooleic acid, and then treated with CB). Tissues were further rinsed and incubated for 24 hours at 37°C in 50 mM CAP in borate buffer saline, pH 7.4, containing 10% isopropanol. After rinsing, the tissues were sterilized for 24 hours at 37°C in 1% glutaraldehyde and 20% isopropanol in borate buffer saline, pH 7.4, followed by 24 hours incubation at 40°C in 0.2% glutaraldehyde in borate buffer saline, pH 7.4, and stored in the same solution.

(d) Glutaraldehyde/AOA plus CB plus NIF - additional tissue was treated as in Example 2 group(c) - (in which tissues were glutaraldehyde-fixed, then treated with aminooleic acid, and then treated with CB). Tissues were further rinsed and incubated for 24 hours at 37°C in 5 mM NIF in borate buffer saline, pH 7.4, containing 20% isopropanol. After rinsing, the tissues were sterilized for 24 hours at 37°C in 1% glutaraldehyde and 20% isopropanol in borate buffer saline, pH 7.4, followed by 24 hours incubation at 40°C in 0.2% glutaraldehyde in borate buffer saline, pH 7.4, and stored in the same solution.

(e) EDC/sulfo-NHS - additional tissue was treated as in Example 1 group(e) (in which tissues were fixed with the EDC sulfo-NHS process, followed by sterilization).

(f) EDC/sulfo-NHS plus CAP plus NIF - additional tissue was treated as in Example 1 group(f) (in which tissues were fixed with the EDC sulfo-NHS process, then treated with CAP). Tissues were then rinsed and incubated for 24 hours at 37°C in 5 mM NIF in HEPES buffered saline, pH 6.5, containing 20% isopropanol. After rinsing in HEPES buffer saline, pH 6.5, containing 20% isopropanol, tissues were

sterilized according to the `951 patent and stored in the same solution.

(g) EDC/sulfo-NHS plus CB plus CAP - additional tissue was treated as in Example 2 group(e) (in which tissues were fixed with the EDC sulfo-NHS process, then treated with CB). Tissues were then rinsed and incubated for 24 hours at 37°C in 50 mM CAP in HEPES buffered saline, pH 6.5, containing 10% isopropanol. After rinsing in HEPES buffer saline, pH 6.5, containing 10% isopropanol, tissues were sterilized according to the `951 patent and stored in the same solution.

(h) EDC/sulfo-NHS plus CB plus NIF - additional tissue was treated as in Example 2 group(e) (in which tissues were fixed with the EDC sulfo-NHS process, then treated with CB). Tissues were then rinsed and incubated for 24 hours at 37°C in 5 mM NIF in HEPES buffered saline, pH 6.5, containing 20% isopropanol. After rinsing in HEPES buffer saline, pH 6.5, containing 20% isopropanol, tissues were sterilized according to the `951 patent and stored in the same solution.

Following the above-mentioned treatments, the sterilized wall segments were washed in normal saline, and 20 wall coupons were randomly selected from each experimental group and implanted subdermally in rats; they were analyzed for calcification after 4 and 8 weeks as described in Example 1. The results are set forth in the table that follows:

RESULTS

Table 3

Treatment	Mean ± SEM (milligrams calcium/gram dry tissue) Walls 4-week	8-week
Group a	49.9 ± 8.0	114.9 ± 12.0
Group b	4.4 ± 3.5	4.2 ± 2.1
Group c	3.9 ± 2.6	12.0 ± 8.8
Group d	1.4 ± 0.9	3.8 ± 2.9
Group e	65.4 ± 7.0	103.0 ± 9.0
Group f	1.8 ± 1.2	7.1 ± 3.1
Group g	2.3 ± 0.7	6.7 ± 3.0
Group h	3.4 ± 1.5	4.9 ± 3.7

The results indicate that post-fixation treatments with CAP followed by NIF, as well as treatments which employ CB followed by CAP or NIF, significantly reduce calcification of wall tissue that has earlier been either treated with glutaraldehyde and aminooleic acid or fixed according to the `399 patent. Histology performed on samples randomly selected from each experimental group revealed the absence of inflammatory reactions, and von Kossa staining confirmed the calcium quantitation results.

By comparing the 8-week calcium results from Example 3 with the comparable results in Examples 1 and 2, the data indicate that the effect of certain combinations of targeted treatments can reduce wall calcification to a higher extent than either treatment alone. For example, calcification of glutaraldehyde- and aminooleic acid-treated walls at 8-week post-implantation was reduced to 22.6±3 milligrams of calcium/gram dry tissue by treatment with CB alone (Example 2, group c) and to 18.7±7.0 milligrams of calcium/gram dry tissue by treatment with

NIF alone (Example 1, group d), while treatment with CB, followed by treatment with NIF, reduced calcium levels to 3.8±2.9 milligrams of calcium/gram dry tissue (Example 3, group d).

These data suggest that the major determinants of wall calcification are related to both cells and components of the extracellular matrix. As a result, it now appears that multiple targeting of relevant calcifying substrates can still further significantly reduce aortic wall calcification.

Although the invention has been described with regard to certain preferred embodiments which constitute the best mode presently known to the inventors for carrying out the invention, it should be understood that various changes and modifications that would be obvious to one having the ordinary skill in this art may be made without deviating from the scope of the invention as set forth in the claims appended hereto. For example, although various sequences of treatment are set forth, in many instances, the steps can be carried out in different sequences and still obtain the advantageous anticalcification characteristics in the ultimate products. Although washing between steps is considered desirable to avoid any potential interaction between reagents, if there is no such interaction expected, such washing step may be omitted. Moreover, some reagents may be fully compatible with each other, in which case a combination of treatments may be performed simultaneously, and as such, simultaneous treatment is often considered to be the equivalent of sequential treatment with agents from certain categories. Likewise, although the working examples show treatment of cardiovascular tissues, i.e. porcine aortic roots with walls and cusps or porcine aortic wall segments alone, such was done for purposes of allowing reasonable comparison, and it should be understood, as set forth in the description, that the invention is considered to be applicable to a wide variety of biomaterials destined for

implantation in mammals, particularly humans, where calcification is considered to be a distinct problem because of its adverse effect on ultimate lifetime.

The disclosures of the previously enumerated U.S. patents are expressly incorporated by reference.

Particular features of the invention are set forth in the claims that follow.

CLAIMS:

1. A method for the treatment of biomaterials destined for implantation in mammals, including humans, which method comprises:

(a) treating said biomaterial with an effective amount of a cell-targeted agent, which agent (i) decreases calcification by blocking calcium channels, (ii) prevents oxidative or selective enzymatic damage and/or (iii) removes cell-derived calcium-binding components; followed by washing said treated biomaterial; or

(b) treating said biomaterial with an effective amount of a matrix-targeted agent which chemically modifies proteins in matrix-derived components thereof that bind calcium or that induce calcification in adjacent components, followed by washing said treated biomaterial; or

(c) sequentially treating said biomaterial with a combination of (a) followed by (b) or of (b) followed by (a) with an intermediate washing step being optional,

whereby said treated and washed biomaterial thereafter resists *in vivo* calcification.

2. The method according to claim 1 wherein treating is carried out according to step (a)(ii) using a concentration of between about 1 and about 200 mM of an antihypertensive agent which prevents oxidative and/or enzymatic damage.

3. The method according to claim 2 wherein a concentration of captopril between about 25 and about 75 mM is employed.

4. The method according to any one of claims 1-3 wherein treating is carried out in accordance with step (a)(i) using a concentration of between about 0.1 and about 50 mM of a calcium channel-blocking agent.

5. The method according to claim 4 wherein a concentration of between about 5 and about 25 mM of nifedipine or diltiazem hydrochloride is used.

6. The method of any one of claims 1-5 wherein treating is carried out according to step (b) using a protein cleaving agent at a concentration of between about 1 and about 200 mM.

7. The method according to claim 6 wherein a concentration of about 10 and about 50 mM of cyanogen bromide is used.

8. The method according to claim 6 wherein, following treatment according to step (b), said biomaterial is treated according to step (a)(i).

9. The method according to claim 6 wherein, following treatment in accordance with step (b), said biomaterial is treated in accordance with step (a)(ii), and optionally then treated according to step (a)(i).

10. The method according to any one of claims 1-9 wherein treating is carried out according to step(a)(iii) using KMA at a KCl concentration of between about 0.5-0.8 M and MgATP at a concentration of between about 0.05 and about 8 mM.

11. The method according to any one of claims 1-10 wherein step (b) is carried out using a reducing agent at a concentration of between about 1 and about 200 mM.

12. The method according to claim 11 wherein step (b) is carried out using a concentration of between about 25 and about 75 mM of DTT and is followed by treatment with an alkylating agent.

13. A method for the treatment of chemically cross-linked cardiovascular tissues prior to implantation in the human body, which method comprises:

(a) treating said tissue with an effective amount of a cell-targeted agent which decreases calcification by blocking calcium channels, and then washing said treated tissue; or

(b) treating said tissue with an effective amount of a cell-targeted agent which decreases calcification by preventing oxidative and enzymatic damage, and then washing said treated tissue; or

(c) treating said tissue with an effective amount of KMA which removes cell-derived calcium binding proteins, and then washing said treated tissue; or

(d) treating said tissue with an effective amount of a matrix-targeted agent which chemically modifies proteins in matrix-derived components that bind calcium or that induce calcification in adjacent components, and then washing said treated tissue; or

(e) sequentially treating said tissue with a combination of at least two of steps (a), (b), (c) and (d) with intermediate washing being optional between any sequence of two such steps ; and

(f) sterilizing said treated and washed tissue,

whereby said treated, washed and sterilized tissue thereafter resists *in vivo* calcification.

14. The method according to claim 13 wherein treating is carried out according to step (a) using a concentration of between about 5 and about 25 mM of nifedipine or diltiazem hydrochloride.

15. The method according to either claim 13 or 14 wherein treating is carried out in accordance with step (b) using a concentration of captopril between about 25 and about 75 mM.

16. The method according to claim 15 wherein, following treatment in accordance with step (b), said biomaterial is treated in accordance with step (a).

17. The method of any one of claims 13-16 wherein treating is carried out according to step (d) using a concentration of between about 25 and about 75 mM of DTT followed by treatment with an alkylating agent.

18. The method of any one of claims 13-17 wherein treating is carried out according to step (d) using a concentration of about 10 and about 50 mM of cyanogen bromide.

19. The method according to claim 13 wherein following treatment according to step (d), said biomaterial is treated according to step (b) and following treatment according to step (b), said biomaterial is optionally treated according to step (a).

20. The method according to claim 13 wherein there is sequential treatment of said tissue in the form of one of the following combinations: (a) followed by (b); (b) followed by (a); (c) followed by (b); (c) followed by (a); or (c) followed by (a) and (b).

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(54) Title: NATURAL TISSUE-DERIVED DECELLULARIZED MATRIX AND METHODS OF GENERATING AND USING SAME

(57) Abstract: Decellularized tissue-derived extracellular matrices (ECM) and methods of generating and using same are provided. The method of generating a decellularized matrix includes the steps of: (a) subjecting the tissue to washes and a hypertonic buffer; (b) subjecting the tissue to an enzymatic proteolytic digestion with an enzyme such as trypsin; and (c) removing all cellular components from the tissue using a detergent solution which includes Triton-X-100 and ammonium hydroxide. Specifically, there is provided a decellularized myocardium-derived matrix which is completely devoid of all cellular components and hence non-immunogenic in a subject, exhibits suitable structural and mechanical properties for cardiac tissue engineering or replacement therapy of damaged cardiac tissue, and is capable of remodeling upon seeding of cells.

NATURAL TISSUE-DERIVED DECELLULARIZED MATRIX AND METHODS OF GENERATING AND USING SAME

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to a method of generating a decellularized extracellular matrix (ECM) from a natural tissue such that the decellularized matrix is devoid of cellular components and hence non-immunogenic when implanted in a subject, preserves the mechanical properties of the original tissue ECM and upon seeding with cells is capable of tissue remodeling. Specifically, the present invention relates to a myocardium-derived decellularized matrix suitable for myocardial tissue regeneration.

Cardiovascular disease (CVD), and particularly, coronary artery disease (CAD) such as atherosclerosis, is the main cause of death among women and men in the Western World. Atherosclerosis is a process that leads to a group of diseases characterized by a thickening of artery walls and narrowing of the internal space of coronary arteries. It accounts for nearly 75 % of all deaths from CVD. Treatment options for patients with CAD include drugs, percutaneous transluminal coronary angioplasty or coronary artery bypass grafting (CABG). Bypass grafting is usually performed with autologous vascular conduits which replace or bypass diseased or occluded vessels. However, in cases of limited availability of suitable autologous vascular conduits, synthetic or natural-derived decellularized grafts can be used.

Heart failure is among the main contributors to morbidity and mortality in the Western world. The main reason for the morbidity and mortality associated with heart failure is the inability of cardiomyocytes to proliferate and regenerate following injuries such as caused by myocardial infarction (MI). Thus, the only efficient remedy for patients with acute loss of cardiac function or patients with congenital or acquired heart disease is heart transplantation. Since the demand for heart transplantation exceeds beyond the availability of donated hearts, there is a need to develop engineered cardiac tissues. The ideal cardiac tissue engineered graft should be functionally and morphologically similar to the native healthy heart tissue, integrate into the heart tissue, remain viable over time and improve the function of the damaged heart. Such an artificial heart graft should be contractile, electro-

physiologically stable, flexible yet mechanically stable, readily vascularized *in vivo* and of autologous nature (*i.e.*, non-immunogenic). However, to date, such an ideal cardiac tissue equivalent has not been reported.

Synthetic, natural or decellularized tissue grafts are designed to mimic the natural tissue extracellular matrix (ECM) which serves as a network supporting the attachment and proliferation of cells. The natural ECM includes molecules such as the collagen family (as a major macromolecule), elastic fibers, glycosoaminoglycans (GAG) and proteoglycans, and adhesive glycoproteins.

Synthetic tissue grafts used in the art include synthetic polymers such as polyglycolic acid (PGA), polylactic-plyglycolic acid co-polymer (PLGA), epsilon-caprolactone-co-L-lactide sponge reinforced with knitted poly-L-lactide fabric (PCLA), polydimethylsiloxane (PDMS), 1,3-trimethylene carbonate (TMC) and D,L-lactide (DLLA). Although such synthetic polymers offer good control over chemical and physical properties of the scaffold, such polymers might rapidly loose these properties and/or release inflammatory products *in vivo* upon degradation (Shachar and Cohen, 2003; Zimmermann and Eschenhagen, 2003). In addition, while synthetic polymers of vascular grafts have proved to be efficient when designed as large-diameter conduits (e.g., with an internal diameter larger than 5 mm), it has been difficult to develop narrower vascular grafts because of biological reactions at the blood-material and tissue-material interfaces.

Natural scaffold materials for cardiac tissue engineering include primarily ECM proteins, such as collagen and Matrigel® hydrogels, laminin and gelatin. The natural non-ECM alginate polysaccharide has also been studied as biomaterial for cardiac tissue engineering. Natural ECMs were shown to be superior to synthetic polymers in recruiting and repopulating cells *in-vivo* (Badylak et al, 2001). Indeed, natural tissue-derived ECMs were used in tissue engineering of heart valves (Steinhoff et al, 2000; Cebotari et al, 2002; Vesely I, 2005) and atrial septal occluder (Jux et al, 2003). However, to date, there is no report of a natural, decellularized ECM which is derived from a myocardium tissue.

Due to their bio-mechanical and non-immunogenic properties between different vertebrates, decellular ECM and collagen have become the biomaterials-of-choice for tissue engineering. The gel form of the commercially available type I collagen was used as a polymer scaffold for tissue engineered cardiac constructs

[Rasidic et al., 2003; Zimmermann et al., 2002; Kofidis et al., 2002]. Prior attempts to generate decellularized ECM from natural tissues involved subjecting the tissues to enzymatic cellular digestion (e.g., using trypsin), hypotonic, hypertonic and/or low ionic strength buffers, detergent and chemical digestion (e.g., using SDS, Triton-X-100, ammonium hydroxide, peracetic acid) and non-micellar amphipatic molecules such as polyethylene glycole (PEG) (See for example, U.S. Pat. Appl. Nos. 20040076657, 20030014126, 20020114845, 20050191281, 20050256588 and U.S. Pat. Nos. 6,933,103, 6,743,574, 6,734,018 and 5,855,620; which are fully incorporated herein by reference). However, to date, there is no report of natural tissue - derived decellularized ECM which is completely devoid of cellular components and thus non-immunogenic in a subject, preserves the unique mechanical properties of the original tissue ECM prior to decellularization and which upon seeding with cells is subject to biological remodeling.

There is thus a widely recognized need for, and it would be highly advantageous to have, a method of decellularizing natural tissues devoid of the above limitations.

SUMMARY OF THE INVENTION

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

According to another aspect of the present invention there is provided a scaffold formed by the method.

According to yet another aspect of the present invention there is provided a scaffold comprising a myocardium-derived decellularized ECM which is completely devoid of cellular components.

According to still another aspect of the present invention there is provided an engineered tissue comprising the scaffold and a population of at least one cell type seeded and proliferated therein.

According to yet an additional aspect of the present invention there is provided a method of *ex vivo* forming a tissue, the method comprising: (a) seeding the scaffold with at least one type of cells; and (b) providing the cells with growth conditions so as to allow the cells to populate in the scaffold; thereby *ex vivo* forming the tissue.

According to still an additional aspect of the present invention there is provided a method of *ex vivo* forming a myocardial tissue, the method comprising: (a) seeding the scaffold with at least one type of cells; and (b) providing the cells with growth conditions so as to allow the cells to populate in the scaffold; thereby *ex vivo* the forming the myocardial tissue.

According to a further aspect of the present invention there is provided a method of *in vivo* forming of a tissue, the method comprising implanting the scaffold in a subject thereby *in vivo* forming the tissue.

According to yet a further aspect of the present invention there is provided a method of *in vivo* forming a myocardial tissue, the method comprising implanting the scaffold in a subject thereby *in vivo* forming the myocardial tissue.

According to further features in preferred embodiments of the invention described below, the method further comprising: (d) subjecting the tissue resultant of step (a) to a nuclease treatment to thereby obtain nucleic acid – free tissue.

According to still further features in the described preferred embodiments step (d) is effected following or concomitant with step (b).

According to still further features in the described preferred embodiments the hypertonic buffer comprises 1 – 1.2 % NaCl.

According to still further features in the described preferred embodiments the hypertonic buffer comprises 1.1 % (w/v) NaCl.

According to still further features in the described preferred embodiments the enzymatic proteolytic digestion comprises trypsin digestion.

According to still further features in the described preferred embodiments the trypsin is provided at a concentration selected from the range of 0.05-0.25 % (w/v).

According to still further features in the described preferred embodiments the trypsin is provided at a concentration of 0.05 % (w/v).

According to still further features in the described preferred embodiments the enzymatic proteolytic digestion is effected for about 24 hours.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present

invention, suitable methods and materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

BRIEF DESCRIPTION OF THE DRAWINGS

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

In the drawings:

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

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

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

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

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

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

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

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

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

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

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

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

FIGs. 10a-e are fluorescent photomicrographs depicting cardiac fibroblast cells cultured on the decellularized matrices of the present invention. Cardiac fibroblasts were stained with the DiO stain, following which the fibroblasts were

seeded on the decellularized matrices. Shown are the stained cells on the decellularized matrices at various time points after seeding: Figure 10a – 10 hours (Magnification x 20); Figure 10b – 4 days (Magnification x 10); Figure 10c – 12 days (Magnification x 4); Figure 10d – 18 days (Magnification x 4; Figure 10e – 24 days (Magnification x 4). Note that three weeks after seeding the matrices began to shrink and formed dense cell populated spheres (Figures 10d and e).

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

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

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

FIGs. 14a-b are photomicrographs of H&E staining depicting a natural (Figure 14a) and a decellularized (Figure 14b) artery. Arrows mark the elastin fibers. Note

that the decellularized artery preserves the collagen and elastin structure of the natural artery tissue. Magnification is x 4.

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

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

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

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

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

FIGs. 20a-f are photomicrographs of H&E staining (Figures 20a-c) or SMC actin immunostaining (Figures 20d-f) of decellularized artery scaffolds following 4

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

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

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

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

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

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

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

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

DESCRIPTION OF THE PREFERRED EMBODIMENTS

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

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

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

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

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

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

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

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

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

The phrase "completely devoid of any cellular components" as used herein refers to being more than 99 % (e.g., 100 %) devoid of the cellular components present in the natural (e.g., native) tissue. As used herein, the phrase "cellular components" refers to cell membrane components or intracellular components which make up the cell. Examples of cell components include cell structures (e.g.,

organelles) or molecules comprised in same. Examples of such include, but are not limited to, cell nuclei, nucleic acids, residual nucleic acids (e.g., fragmented nucleic acid sequences), cell membranes and/or residual cell membranes (e.g., fragmented membranes) which are present in cells of the tissue. It will be appreciated that due to the removal of all cellular components from the tissue, such a decellularized matrix cannot induce an immunological response when implanted in a subject.

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

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

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

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

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

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

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

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

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

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

embodiment of this aspect of the present invention, proteolytic digestion is effected using trypsin.

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

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

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

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

Following incubation in the digestion solution, the digested cellular components are removed from the tissue. Removal of the digested components from the tissue can be effected using various wash solutions, such as detergent solutions

(e.g., ionic and non ionic detergents such as SDS Triton X-100, Tween-20, Tween-80) which can be obtained from e.g., Sigma (St Louis, MO, USA) or Biolab (Atarot, Israel, Merck Germany).

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

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

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

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

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

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

Although as described hereinabove, incubation with the detergent solution enables the removal of cell nuclei, proteins and membrane, the method according to this aspect of the present invention optionally and preferably includes an additional step of removing nucleic acids (as well as residual nucleic acids) from the tissue to

thereby obtain a nucleic acid – free tissue. As used herein the phrase "nucleic acid – free tissue" refers to a tissue being more than 99 % free of any nucleic acid or fragments thereof as determined using conventional methods (e.g., spectrophotometry, electrophoresis essentially as described in Example 1 of the Examples section which follows). Such a step utilizes a DNase solution (and optionally also an RNase solution). Suitable nucleases include DNase and/or RNase [Sigma, Bet Haemek Israel, 20 μg/ml in Hank balance salt solution (HBSS)]. It will be appreciated that the nuclease treatment is effected following or concomitant with the proteolytic digestion described in step (b).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

For *ex vivo* tissue formation the scaffold is seeded with cells and is further subjected to growth conditions (e.g., culture medium with growth factors, amino acids, serum, antibiotic and the like, incubation temperature, % of CO_2) which enable

the cells seeded thereon to populate and thus form the tissue-of-interest (e.g., a cardiac tissue, nerve tissue, bladder wall, testicular sac, kidney and the like).

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

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

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

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

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

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

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

EXAMPLES

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

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

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

EXAMPLE 1

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

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

Materials and Experimental Methods

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

Preliminary washes - To remove residual blood, the myocardium tissue segments were washed at room temperature by agitation in large amounts (e.g., 50 ml per gram tissue segment) of EDTA (0.5-10 mM, pH-7.4) in saline. Solution was changed every 30 minutes, at least four or five times, until there was no evident blood. Myocardium tissue segments were then agitated for two hours in a hypertonic buffer

consisting of 1.1 % NaCl – 0.02 % EDTA. Incubation of the myocardium tissue segments in the hypertonic buffer induces an osmotic pressure which results in diffusion of water out of the cells and/or the intercellular space, resulting in increased intercellular space, thus enhancing accessibility of tissue substrates for the subsequent enzymatic digestion.

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

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

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

Lyophilization and sterilization - Matrices were washed several times in large volumes of double-distilled sterile water to remove remaining salts. The matrices were then spread in 6-cm tissue culture plastic dishes, and excess water was removed. For lyophilization, the matrices were snap-frozen in liquid nitrogen and lyophilized for 12 hours. Dry matrices were then cut into the desired shape and size (e.g. ~11-13 mm squares or disks, suitable for placing in 24-well culture plates). Lyophilized matrices were sterilized in cold ethylene-oxide gas and ventilated for at least one

week before further use. Alternatively, matrices were exposed to ultra-violet light radiation for a few hours under sterile condition, desiccated with silica gel beads to prevent re-hydration by air moisture. Alternatively, non-lyophilized matrices were soaked overnight in 70 % ethanol, washed with sterile water and kept in PBS at 4 °C. Under these sterilization methods shelf life of decellularized matrices was practically eternal.

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

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

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

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

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

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

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

Experimental Results

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

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

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

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

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

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

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

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

EXAMPLE 2

ASSESSMENT OF ACELLULARIZED MATRIX COMPONENTS AND MECHANICAL PROPERTIES

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

Materials and Experimental Methods

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

and compared to standard hydroxyprolin (Fluka) and collagen type I (Sigma) curves, prepared along with the sample.

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

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

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

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

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

Experimental Results

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

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

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

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

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

EXAMPLE 3

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

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

Materials and Experimental methods

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

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

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

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

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

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

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

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

Experimental Results

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

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

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

The cells populated on the decellularized matrices of the present invention are viable - Viability of cells seeded on the scaffolds was quantitated using the alamarBlue® assay. After seeding medium was changed every 2-3 days. Every second medium change scaffolds were gently moved to new wells to prevent artifact results caused by the outgrowth of fibroblasts from the matrix onto the culture dish. The density and distribution of the cardiac fibroblasts in the scaffolds was shown by

the DiO staining (Figures 10a-e) and the histochemical H&E staining (Figures 11a-d). The viability of cells on each scaffold, which was measured two days after seeding, was denoted 100 %. Further measurements for each scaffold were related to it's own initial viability value. As is shown in Figures 12a-b, both cardiac fibroblasts and cardiomyocytes were highly viable (80 % or more) for the first three weeks post seeding. In addition, at four weeks post seeding, ~77 % and ~68 % of the cardiac fibroblasts or the cardiomyocytes, respectively, remained viable.

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

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

EXAMPLE 4

ARTERY-DERIVED DECELLULARIZED MATRICES

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

Materials and Experimental Methods

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

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

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

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

Static seeding - For the static seeding, cells were trypsinized, centrifuged and resuspended in 50 μL of fresh medium. Sterilized scaffolds were ventilated for a few

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Experimental Results

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

the absence of cell nuclei from both the outer and the luminal sides of the processed decellularized artery-derived matrices (Figures 16a-d).

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

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

Centrifugal seeding and dynamic culturing results in efficient penetration of SMCs to the scaffolds - To determine the optimal conditions for SMC and endothelial seeding and growth on the decellularized scaffolds, several seeding and culture techniques were utilized. These include static seeding followed by static culturing, centrifugal seeding followed by static culturing and centrifugal seeding followed by

dynamic culturing. The efficiency of the various seeding and culturing techniques was evaluated using histological (e.g., H&E staining) and immunohistochemical (e.g., using α-smooth muscle actin immunostaining) analyses. As is shown in Figures 20a-f, centrifugal seeding resulted with better penetration of SMCs into the scaffolds than a static seeding, whereas a dynamic environment resulted in even greater penetration and alignment of the cells along the elastin fibers.

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

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

showing that cells cultured in a dynamic environment proliferate better when compared to cells cultured in a static environment.

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

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

The decellularized matrices of the present invention are non-immunogenic when implanted in a subject - To eliminate any possible complications when using scaffolds as vascular grafts *in vivo*, the immune reaction against the decellularized scaffolds was tested in C57 black mice following implantation of patches of 0.5 cm x 0.8 cm. The implanted patches were harvested at different time points (one and two weeks post-implantation) and the immune response was examined by histological analysis of inflammatory or immune cells and by RT-PCR analysis of pro-inflammatory factors (TNF-α and IL-1β) of RNA extracted from the lymph nodes of the implanted animals. One and two weeks post surgery the surrounding tissues of the sham mice (not shown) presented similar results to those observed in animals implanted with the polymers (*i.e.*, the decellularized matrices of the present invention) (Figures 26a-d). These included several granulocytes and elongated fibroblasts (typical for a wound healing response). Furthermore, RT-PCR analysis of the

proinflammatory factors TNF-α and IL-1β revealed no increase in the proinflammatory factors between one to two weeks and was similar in the sham-operated mice (data not shown).

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

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

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

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

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

Analysis and Discussion

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

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

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

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

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

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

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad

scope of the appended claims. All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention.

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WHAT IS CLAIMED IS:

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

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

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

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

thereby generating the decellularized ECM of the tissue.

2. The method of claim 1, further comprising:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

thereby *ex vivo* forming the tissue.

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

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

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

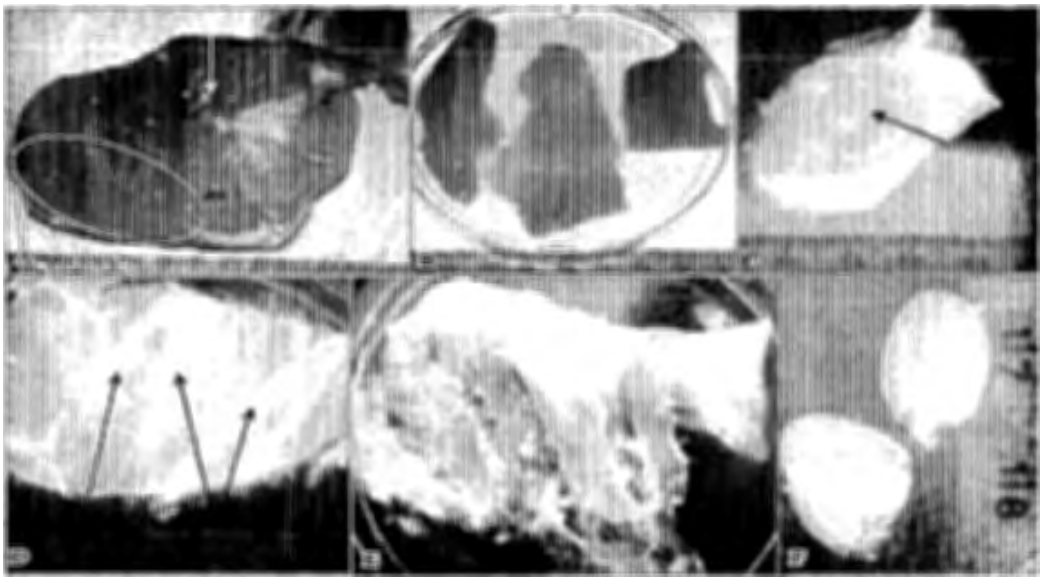
thereby *ex vivo* the forming the myocardial tissue.

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

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

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

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



Figs. 1a-f

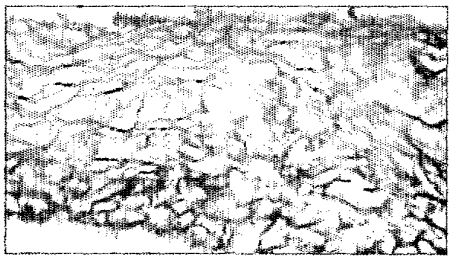
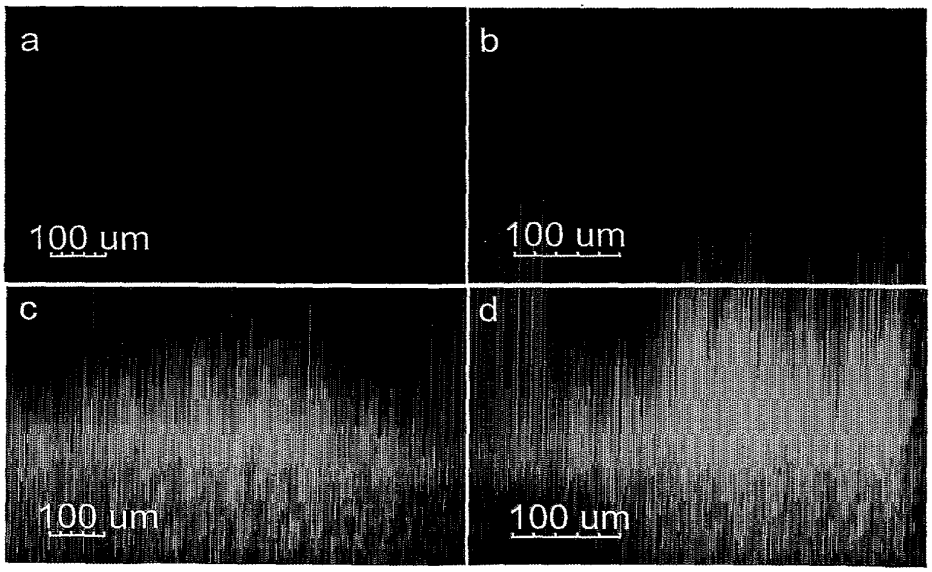
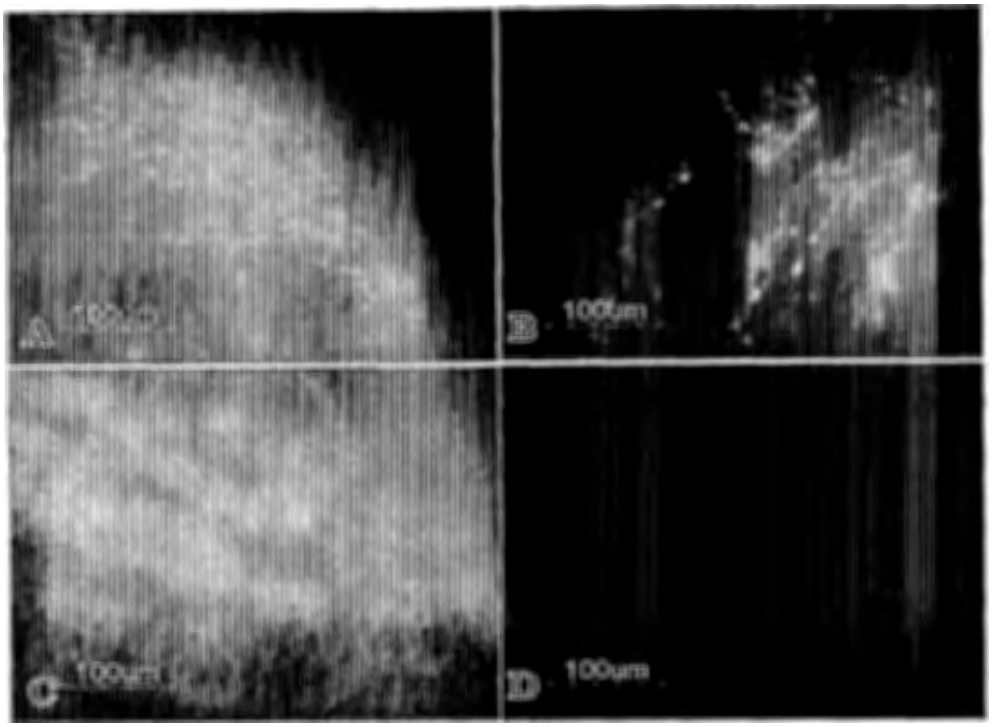


Fig. 2



Figs. 3a-d



Figs. 4a-d

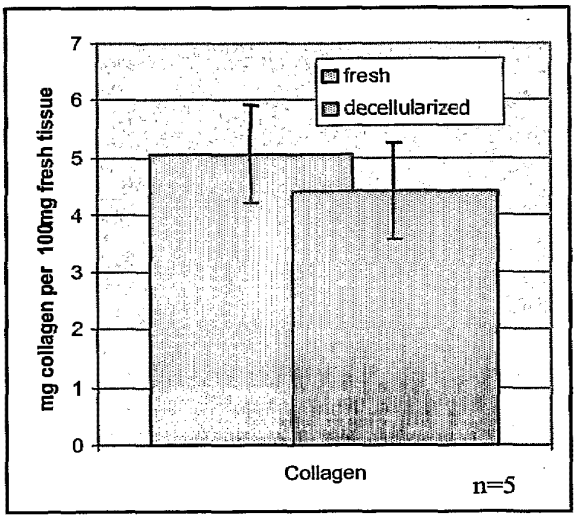


Fig. 5a

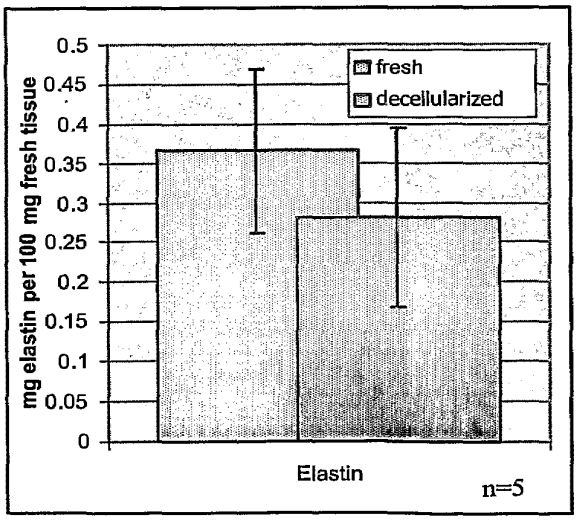


Fig. 5b

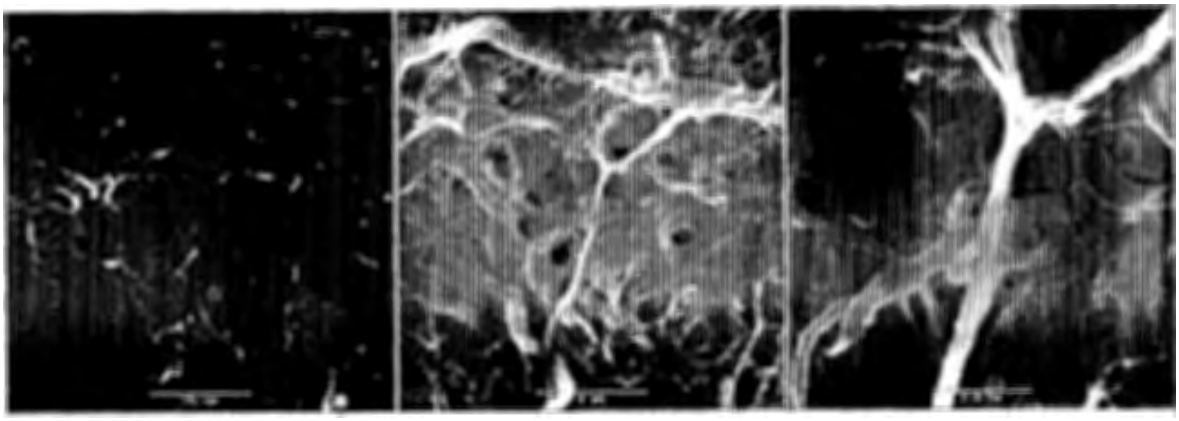


Fig. 6a Fig. 6b Fig. 6c

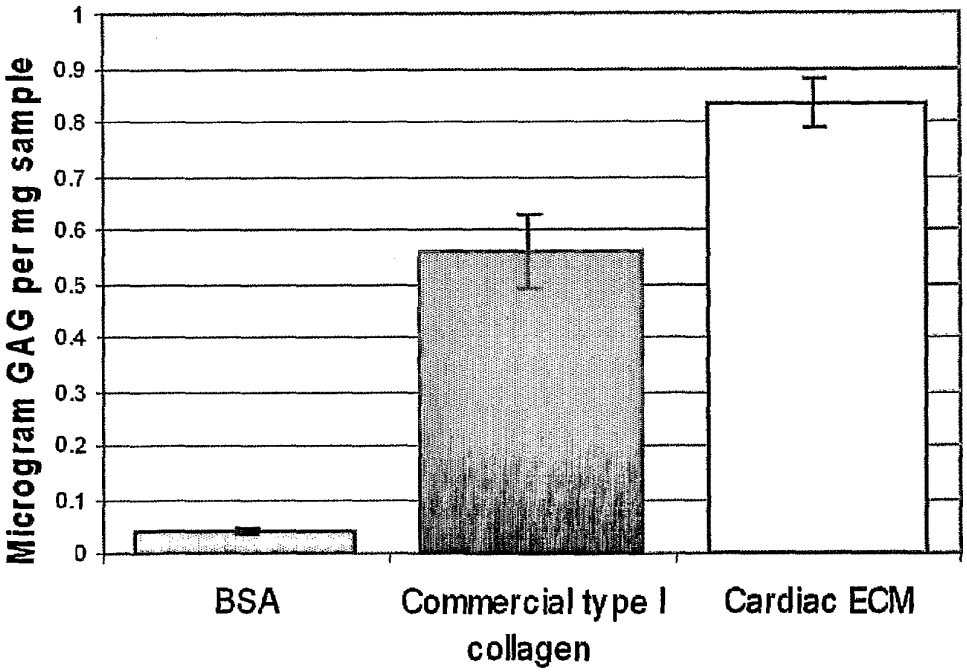


Fig. 7

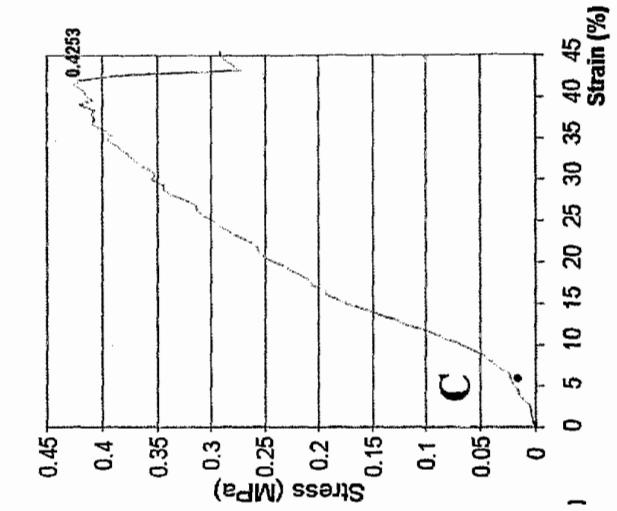


Fig. 8c

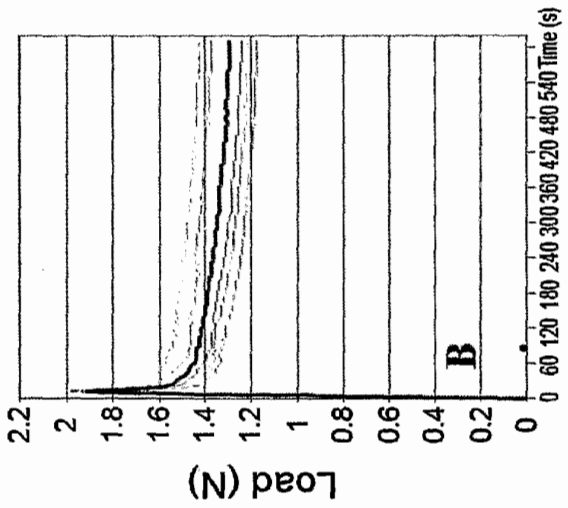


Fig. 8b

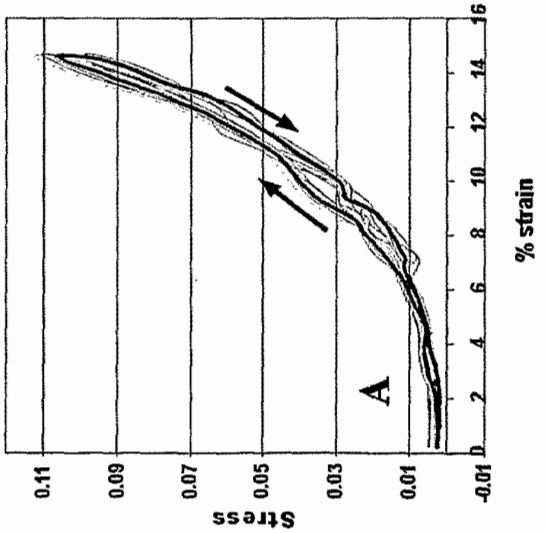


Fig. 8a

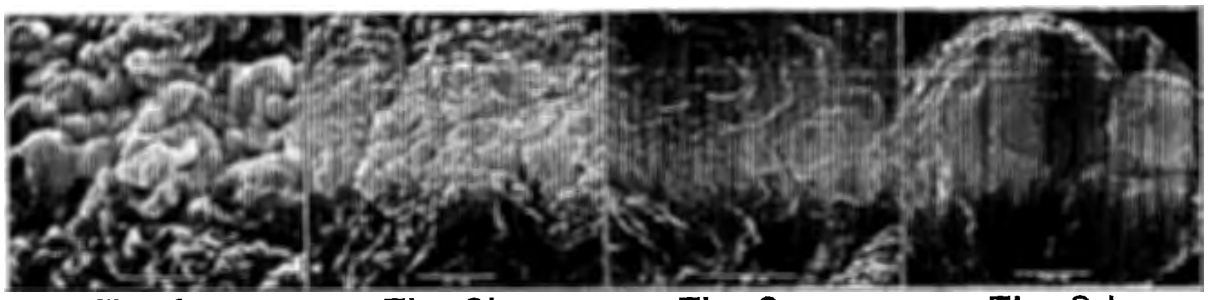
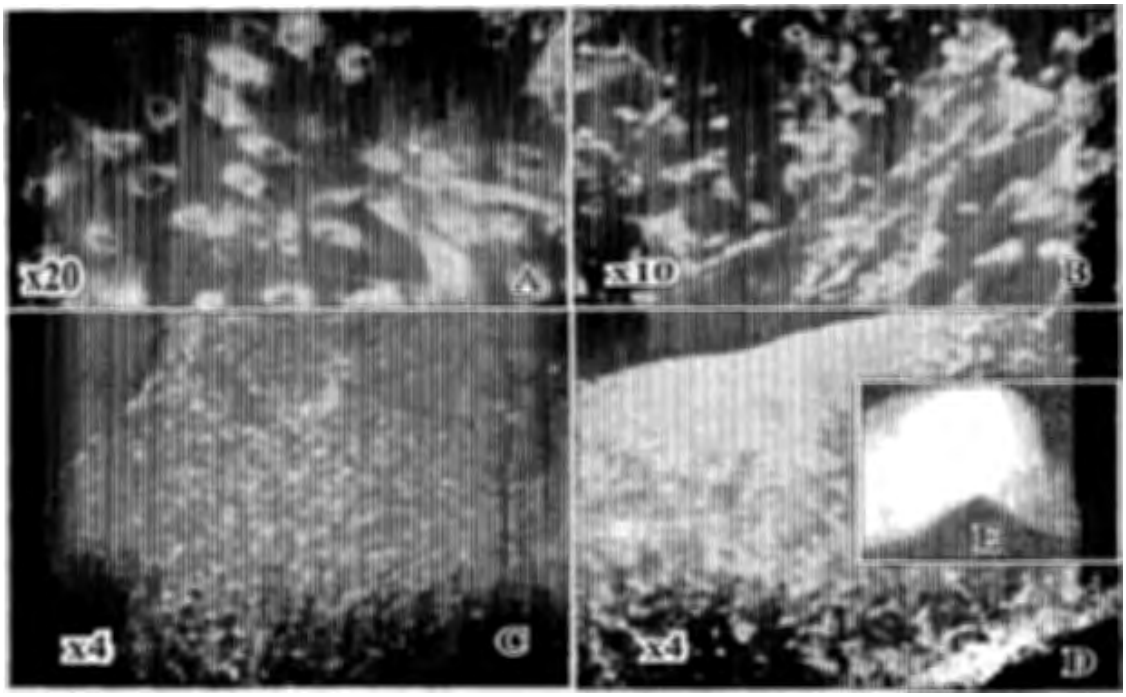
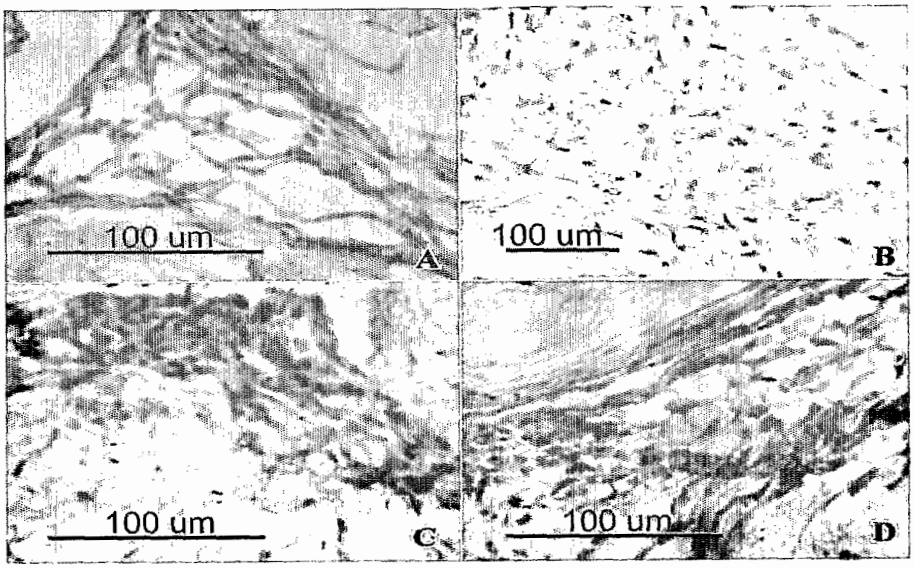


Fig. 9a Fig. 9b Fig. 9c Fig. 9d

Fig. 9e Fig. 9f Fig. 9g



Figs. 10a-e



Figs. 11a-d

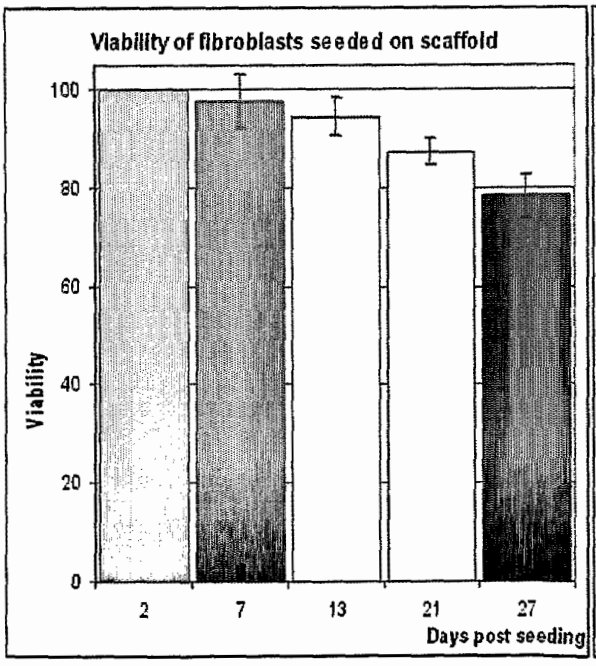


Fig. 12a

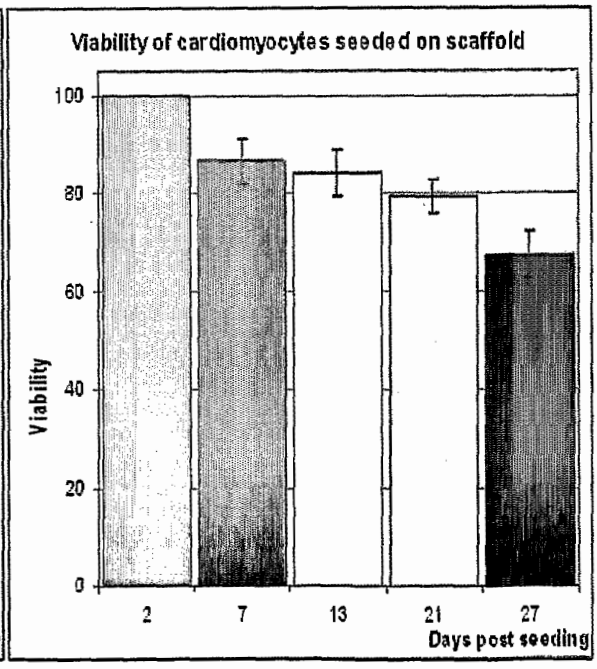


Fig. 12b

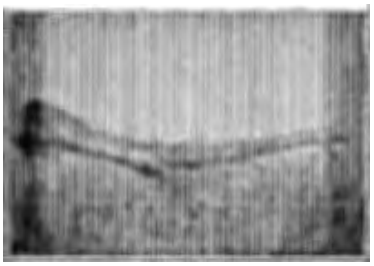


Fig. 13a

Fig. 13b

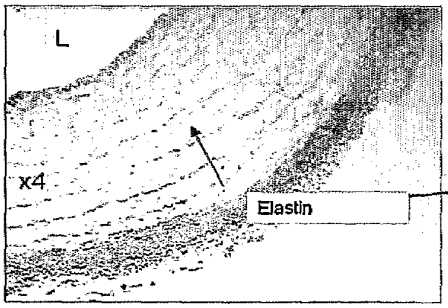


Fig. 14a

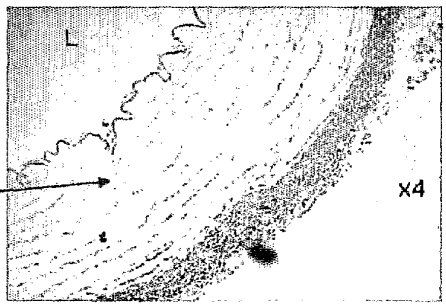


Fig. 14b

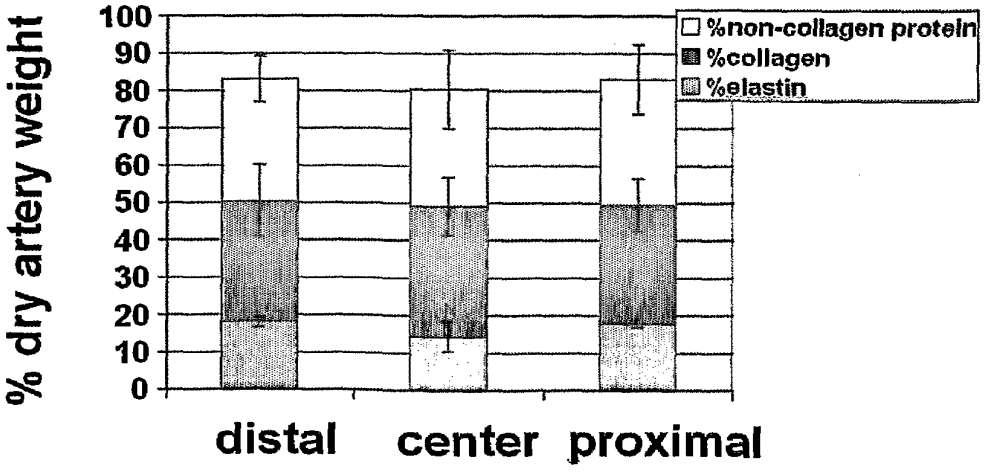
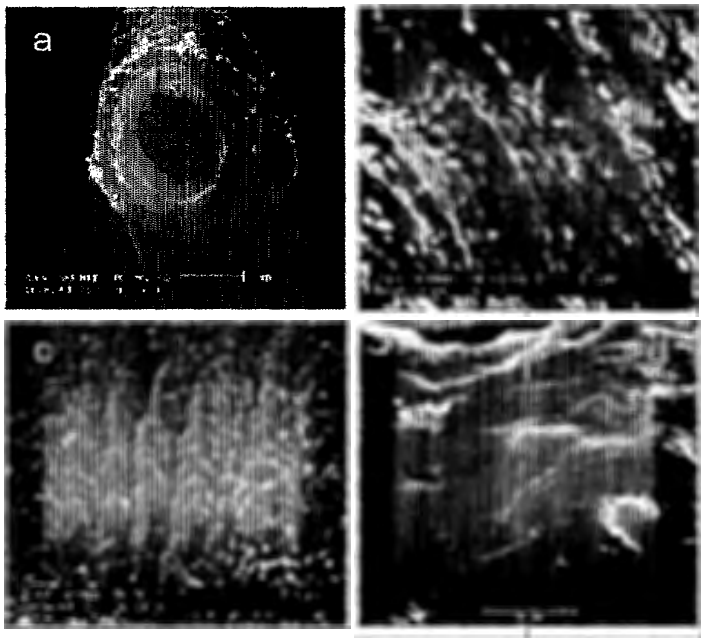


Fig. 15



Figs. 16a-d

Fig. 17

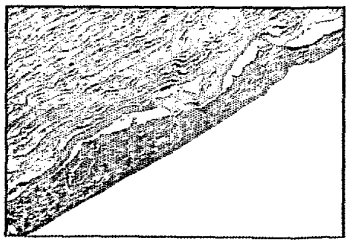


Fig. 18a

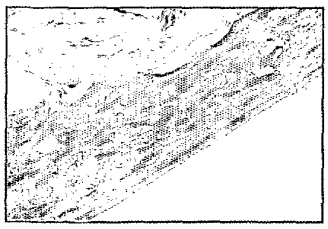


Fig. 18b

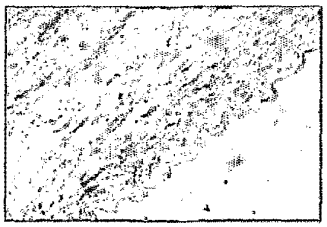
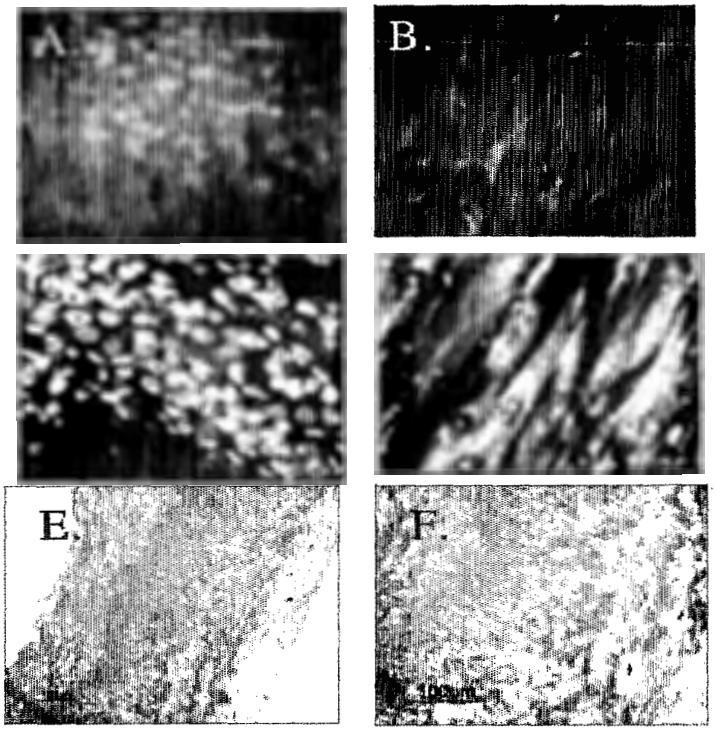
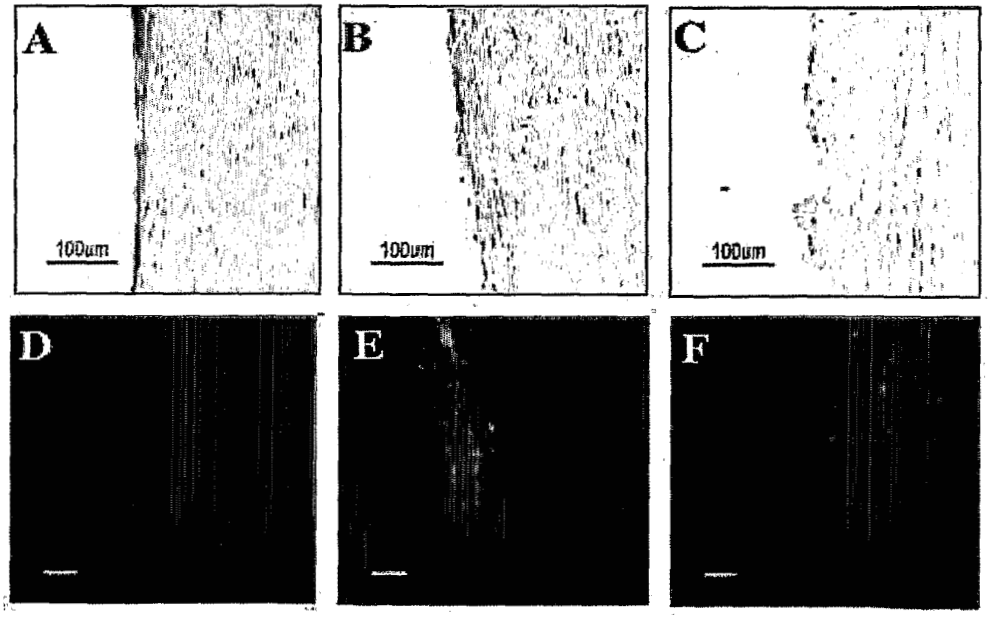


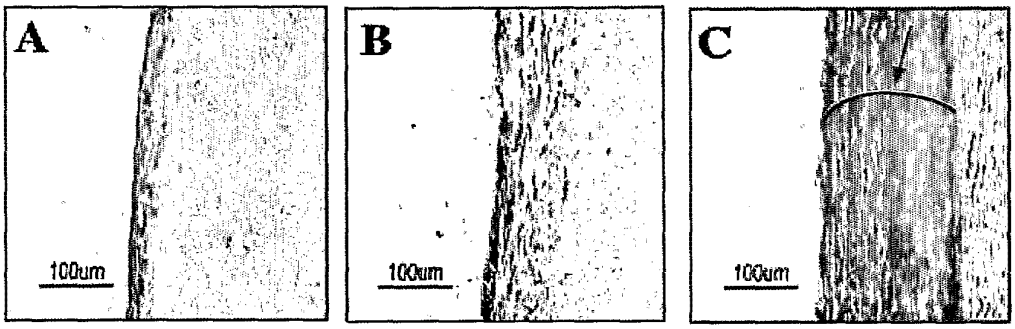
Fig. 18c



Figs. 19a-f



Figs. 20a-f



Figs. 21a-c

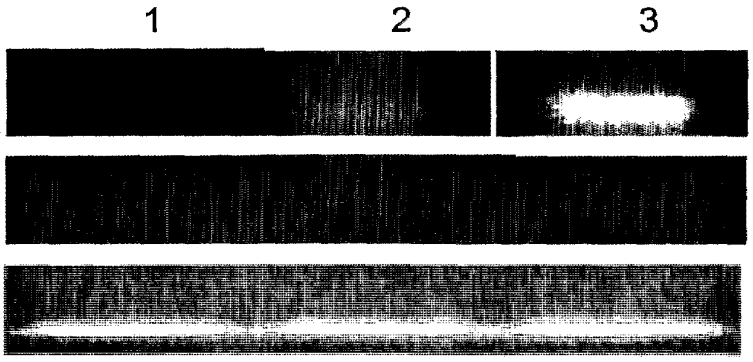
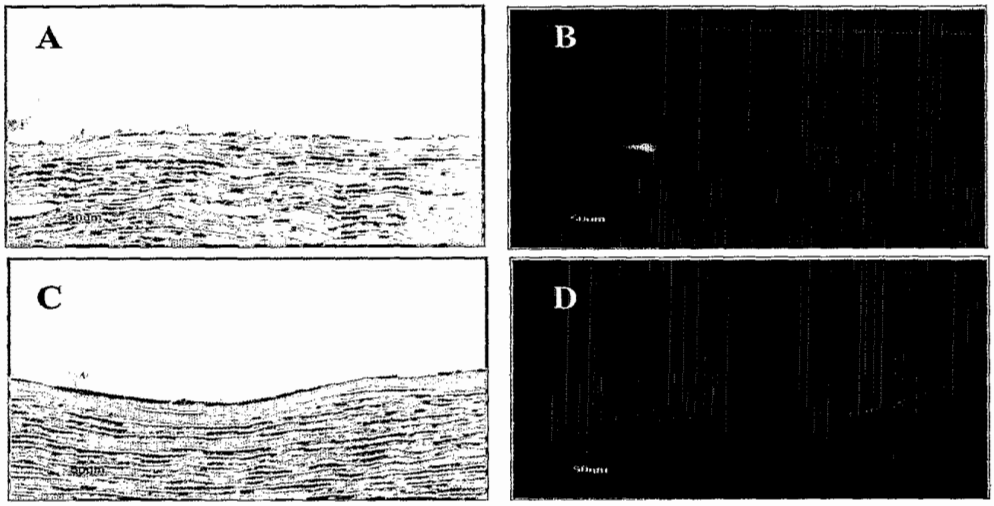


Fig. 22a **Elastin**

Fig. 22b **Collagen III**

Fig. 22c **GAPDH**



Figs. 23a-d

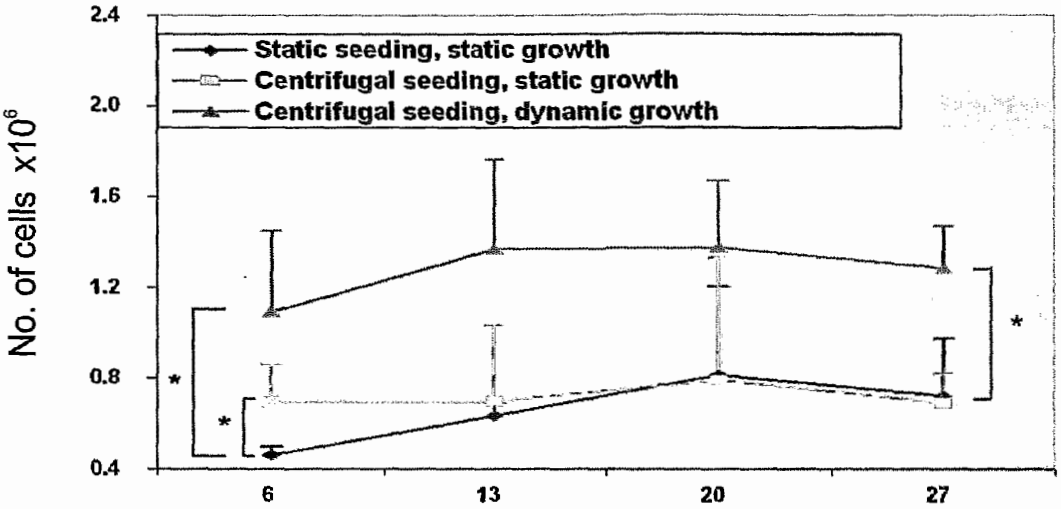
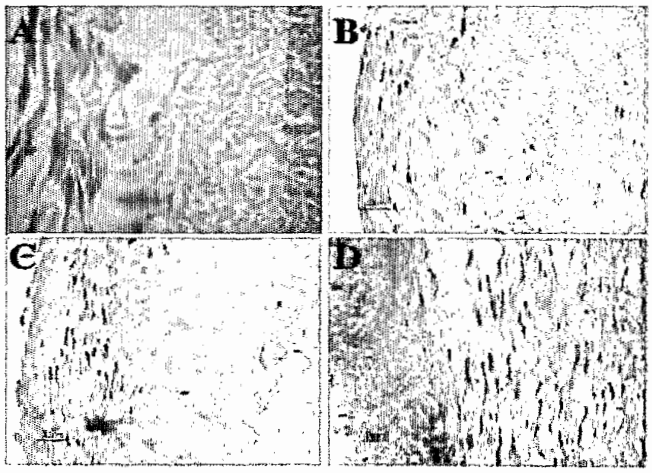
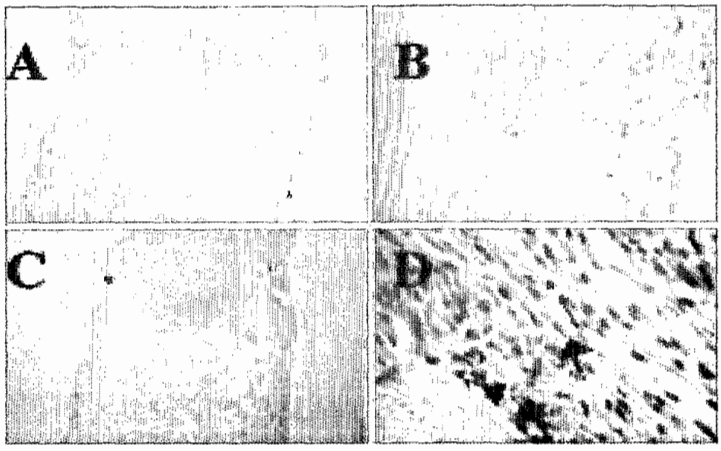


Fig. 24



Figs. 25a-d



Figs. 26a-d

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Marcelle, Machluf
Yuval, Eitan

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

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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	3	6482228		2002-11-19	Norred	
	4	6951571		2005-10-04	Srivastava	
	5	7189259		2007-03-13	Simionescu et al.	
	6	7261732		2007-08-28	Justino	
	7	7318998		2008-01-15	Goldstein et al.	
	8	7329279		2008-02-12	Haug et al.	

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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

	9	7381219		2008-06-03	Salahieh et al.	
	10	7566343		2009-07-28	Jenson et al.	

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	1	HIESTER,E.D. et al., "Optimal bovine pericardial tissue selection sites. I. Fiber architecture and tissue thickness measurements." J. Biomed Mater Res, 1998, Feb, 01; 39(2):207-14	☐
	2	HUFNAGEL, Charles A., M.D., "Basic Concepts in the Development of Cardiovascular Prosthes" The American Journal of Surgery, Vol 137, March 1979	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	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

	3	HUFNAGEL, Charles.A., MD et al., "In the beginning. Surgical Correction of Aortic Insufficiency" 1954; Ann Thorac Surg 1989 May; 47(3), pp. 475-476	☐
	4	HUFNAGEL, Charles.A., MD et al., "Late follow-up of ball-valve prostheses in the descending thoracic aortia", J. Throrac Cardiovasc Surg, December 1976, 72(6), pp. 900-909	☐
	5	HUFNAGEL, Charles.A., MD et al., "Surgical Correction of Aortic Insufficiency" Surgery Vol 35, May, 1954 No. 5	☐
	6	PATHAK, CP et al., "Treatment of bioprosthetic heart valve tissue with long chain alcohol solution to lower calcification potential" J Biomed Mater Res A. 2004 Apr 1;69(1):140-4	☐
	7	SAMOUILLAN, V. et al., " Comparison of chemical treatments on the chain dynamics and thermal stability of bovine pericardium collagen" J Biomed Mater Res A. 2003 Feb 1;64(2):330-8	☐
	8	SHEN, Ming et al., "Effect of ethanol and ether in the prevention of calcification of bioprostheses" Ann Thorac Surg. 2001 May;71(5 Suppl):S413-6	☐
	9	VYAVAHARE, NR et al., "Prevention of Glutaraldehyde-Fixed Bioprosthetic Heart Valve Calcification by Alcohol Pretreatment: Further Mechanistic Studies" J Heart Valve Dis. 2000 Jul;9(4):561-6	☐
	10	HUFNAGEL, Charles A., "Vessels and Valves", Sec. 1: Development of Cardiac Surgery, Chap 7, pp. 43-55	☐

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Examiner Signature		Date Considered	

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(Not for submission under 37 CFR 1.99)

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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Mark L. Yaskanin/	Date (YYYY-MM-DD)	2010-09-08
Name/Print	Mark L. Yaskanin	Registration Number	45246

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 1 hour 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.**

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 record s.

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.

Electronic Patent Application Fee Transmittal

Application Number:	10887688
Filing Date:	10-Jul-2004
Title of Invention:	Percutaneously implantable replacement heart valve device and method of making same
First Named Inventor/Applicant Name:	David Paniagua
Filer:	Mark Lauren Yaskanin/Carol Donahue
Attorney Docket Number:	54813-10100

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	8372004
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:	23337
Filer:	Mark Lauren Yaskanin/Carol Donahue
Filer Authorized By:	Mark Lauren Yaskanin
Attorney Docket Number:	54813-10100
Receipt Date:	08-SEP-2010
Filing Date:	10-JUL-2004
Time Stamp:	14:00:36
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$180
RAM confirmation Number	276
Deposit Account	082665
Authorized User	DONAHUE,CAROL S.

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1	Information Disclosure Statement (IDS) Filed (SB/08)	Supplemental_IDS.pdf	612970 19da546ae03aad7d3b3c0b9aa72ff76eef8ffdf5	no	5
Warnings:					
Information:					
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Warnings:					
Information:					
3	NPL Documents	Hufnagel_Basic_Concepts_ARTICLE.pdf	4573630 e3ca35f5c89cd7c672a4124e96ffb3f6b0ef3f34	no	16
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Warnings:					
Information:					
6	NPL Documents	HUFNAGEL_In_The_Beginning_Surgical_Correction.pdf	2912346 f930646f4f11f982b64d1b7c802bd2fd28c280c5	no	2
Warnings:					
Information:					
7	NPL Documents	Pathak_Treatment_of_Bioprosthetic_Heart.pdf	209469 902ff931f93e7ab58ac7cdc437497d005339e008	no	5
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Warnings:					

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Warnings:					
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10	NPL Documents	Vyavahare_Prevention_of_Glutaraldehyde-Fixed.pdf	1056189 68ce64403862d585c8638804460a3994147fe882	no	6
Warnings:					
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11	NPL Documents	Hufnagel_Vessels_and_Valves.PDF	1988054 ad47ed6f9b9d4b844cd80820b663cdf7b823be74	no	15
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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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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	Examiner Name	Cheryl L. MILLER
	Attorney Docket Number	54813-10100

	1	TOPOL, Eric J., "Textbook of Interventional Cardiology", 1990, Chs. 43-44, pp. 831-867	☐
	2	Office Action issued September 29, 2010, issued in U.S. Application 12/228,192 (54813-10110)	☐
	3	Office Action issued May 8, 2003, issued in U.S. Application 10/037,266	☐
	4	Office Action issued March 9, 2004, issued in U.S. Application 10/037,266	☐
	5	Cross-reference is made to U.S. Application No. 13/038,361, filed on March 1, 2011 (54813-10201)	☐
	6	Cross-reference is made to PCT Application No. PCT/US11/26763, filed on March 1, 2011 (54813-10202)	☐
	7	Cross-reference is made to U.S. Application No. 13/038,260, filed on March 1, 2011 (54813-10250)	☐
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Attorney Docket Number	54813-10100

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☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Mark L.Yaskanin/	Date (YYYY-MM-DD)	2011-04-08
Name/Print	Mark L. Yaskanin	Registration Number	45246

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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.

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Electronic Patent Application Fee Transmittal

Application Number:	10887688
Filing Date:	10-Jul-2004
Title of Invention:	Percutaneously implantable replacement heart valve device and method of making same
First Named Inventor/Applicant Name:	David Paniagua
Filer:	Mark Lauren Yaskanin/Carol Donahue
Attorney Docket Number:	54813-10100

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	9833396
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:	23337
Filer:	Mark Lauren Yaskanin/Carol Donahue
Filer Authorized By:	Mark Lauren Yaskanin
Attorney Docket Number:	54813-10100
Receipt Date:	08-APR-2011
Filing Date:	10-JUL-2004
Time Stamp:	18:47:14
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$180
RAM confirmation Number	5578
Deposit Account	082665
Authorized User	DONAHUE,CAROL S.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	NPL Documents	Topol_Textbook_of_Interventional_Cardiology.pdf	4225303 511d60021cec8bae1413a3eaca66792d91c043bc	no	40
Warnings:					
Information:					
2	NPL Documents	US_10-037266_Final_Office_Action_2004-03-09.pdf	249887 3b61cf802da3c247d0aabdb2afe1ae201b5b1ac5	no	7
Warnings:					
Information:					
3	NPL Documents	US_10-037266_Office_Action_2003-05-08.pdf	259047 914d4eb72f062d336803af5d89d99ff82c7a41b0	no	7
Warnings:					
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4	NPL Documents	12-228192_Office_Action_2010-09-29.pdf	303920 70c49a9433dd0acbff8507779bf833421e8acdb1	no	9
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Information:					
5	Information Disclosure Statement (IDS) Filed (SB/08)	Supp_IDS.pdf	612226 479c27dcc70f75a4bf91a68e624b80b018eef523	no	4
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6	NPL Documents	13-038260_Application_10250.pdf	128680 48b18b0dcd5195a88f964ca5f5afec07d38c26af	no	34
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7	NPL Documents	13-038361_Application_10201.pdf	909891 d0e07523087095220c1ed14ee8e5442266 31a907	no	83
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8	NPL Documents	PCT-US11-26741_Application_10251.pdf	121313 1d14e824416c46ab1bbd543631ed5272225baa56	no	24
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9	NPL Documents	PCT-US11-26763_Application_10202.pdf	897191 291bf2f0e6408aa466439ed990b9218de1f339c2	no	60
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10	Fee Worksheet (PTO-875)	fee-info.pdf	29909 ab0ab77f5bd42e05d50be90cdb2df4b1c47cdeee	no	2
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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/887,688	07/10/2004	David Paniagua	54813-10100	4909

23337 7590 02/16/2012

Bryan Cave LLP (Denver)
1700 LINCOLN STREET, SUITE 4100
DENVER, CO 80203

EXAMINER	
MILLER, CHERYL L	
ART UNIT	PAPER NUMBER
3738	

NOTIFICATION DATE	DELIVERY MODE
02/16/2012	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

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 *02 August 2010*.

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

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *57-65* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *57-65* is/are rejected.

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

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

Application Papers

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

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ 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

13)☐ 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 *4/8/2011, 9/8/2010, 8/13/2010, 8/2/2010 (qt.5)*.
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 August 2, 2010 has been entered.

Response to Arguments

Applicant's arguments with respect to claims 1-56 have been considered but are moot in view of the new ground(s) of rejection.

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 57-65 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.

Claim 57 line 11 (and at other locations within the claim) recites, "at least one". No support was found in the specification for the "at least one" language. At least one encompasses a range of one to infinity and the specification does not appear to support this full range. It is

suggested to change "at least one additional linear crease" to recite --an additional linear crease--. Claims 58-65 depend upon claim 57 and inherit all problems associated with the claim.

Claim 57 line 12 and 13 each recite "two or more". No support was found in the specification for the "two or more" language. Two or more encompasses two to infinity and the specification does not appear to support this full range. The specification instead appears to support two to four leaflets, preferably three leaflets. It is suggested to change "two or more" to recite --two--.

Claim 57 line 16 recites, "at least one point". No support was found in the specification for this language and range. It is suggested to delete this language. It is noted that this language also appears in claim 64.

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 57-65 rejected under 35 U.S.C. 103(a) as being unpatentable over Bailey et al. (US 6,458,153 B1, cited previously) in view of Bessler (US 5,855,601, cited previously). Referring to claims 57 and 58, Bailey discloses a heart valve device (fig.1-5 for example) comprising a collapsible and expandable stent member (12) with inner channel (lumen, see arrow in fig.4); and a single sheet of biological tissue material (11b+26; graft 11 may be attached to either or both the luminal and abluminal surfaces of the stent, thus may be attached to only the luminal; col.5, lines 43-49) attached to the stent member by a plurality of sutures (suturing, col.5,

lines 45-48), the sheet partitioned by a transverse linear crease (at 27) forming an outer cuff layer (11b) and inner leaflet layer (26), the transverse crease (27) oriented parallel to a first edge (free edge of 26) and a second edge (free edge of 11b) of the sheet, the first edge is a free edge of the inner leaflet layer and portions of the inner leaflet layer reside radially adjacent and in contact with the outer cuff layer within the stent member to form a contiguous double-layer folded construct (seen in fig.2, 4), the inner leaflet layer (26) partitioned by one additional linear crease (29) oriented perpendicular to the transverse crease (27) to form valve leaflets, a first lateral edge of the sheet adjoins a second lateral edge of the sheet (any edge, for example any seam 29 or crease along strut 24 may be considered two lateral edges), wherein the single sheet (26+11b) resides entirely within the inner channel of the stent member (this is seen in fig.2, 4), and wherein after deployment in the patient, the contiguous double-layer construct resides as a single element within the inner channel of the stent member (26+11b is a continuous sheet and is a single sheet, col.9, lines 12-20; that is, it is only one sheet, not more than one sheet; noting that the claims do not require the sheet to be the *only* element within the stent, but instead to be present as a single sheet, which it is-it is not multiple sheets; the sheet itself is considered a single sheet and thus meets the claim). Bailey discloses the heart valve substantially as claimed. Bailey discloses the sheet to be made of synthetic or biologically derived materials (col.8, lines 37-40), however is silent to any specific types of biological materials. Bessler teaches in the same field of heart valve devices, the use of porcine pericardium as a specific type of biological material among other materials (col.4, lines 9-11; col.6, lines 19-31) for use as the leaflet material (22) in a valve replacement device (fig.1). It would have been obvious to one having ordinary skill in the art at the time the invention was made to combine Bailey's heart valve

device having a biological material for the sheet with Bessler's material teaching of a using porcine pericardium as a biological material in valves, in order to provide a heart valve device with optimal material properties such as biocompatibility. Such would have been an obvious choice of material known in the art. *In re Leshin*, 227 F.2d 197, 125 USPQ 416 (CCPA 1960).

Referring to claims 59-62, Bailey discloses the claimed stent materials (col.8, lines 4-8, 33-37). Referring to claim 64, the additional linear creases (29) are shown at commissures in the figures. Referring to claim 65, Bailey discloses the folded construct (26+11b) to be continuous from the first edge to the second edge (see figures; col.9, lines 11-20).

Referring to claim 63, Bailey discloses attaching the valve (11b+26) to the stent (12) by suturing or encapsulation, however does not show if the proximal and distal ends are sutured (specific locations of the sutures). It would have been obvious to one having ordinary skill in the art the time the invention to suture both ends of the valve (portion 11b) to the stent (12), since the although the sutures are not shown, the purpose of the sutures is for securement and the suturing at each end would by common sense, provide the most secure connection. If the valve was attached at only one end or any other location therebetween instead, it would not be held together properly and would not provide its intended function of blood regulation.

Claims 57-62 and 64-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garrison (US 6,425,916 B1, cited previously) in view of Bessler et al. (US 5,855,601, cited previously). Referring to claims 57 and 58, Garrison discloses a heart valve device (figs.34-38) comprising a collapsible and expandable stent member (26D+111+8D) with inner channel (lumen); and a single sheet of biological tissue material (membrane part of 6d) attached to the

stent member (see fig.35, 36), the sheet partitioned by a transverse linear crease (crease is at top border to 111; seen in fig.34 and 35) forming an outer cuff layer (bottom portion of membrane 6d, lying inside of 111) and inner leaflet layer (portion of membrane 6d above 111 in fig.34 and inverted in fig.35), the transverse crease (at top edge of 111) oriented parallel to a first edge (free edge leaflets) and a second edge of the sheet, the first edge is a free edge of the inner leaflet layer and portions of the inner leaflet layer reside radially adjacent and in contact with the outer cuff layer within the stent member to form a contiguous double-layer folded construct (this configuration is present during delivery, seen in fig.35), the inner leaflet layer partitioned by one additional linear crease (creases in separating leaflets, three shown in fig.34, 38) oriented perpendicular to the transverse crease to form valve leaflets, a first lateral edge of the sheet adjoins a second lateral edge of the sheet (any edge, for example any seam or crease may be considered two lateral edges meeting), wherein the single sheet (membrane of 6d) resides entirely within the inner channel of the stent member (is entirely within channel at least at some portions in time, for example, fig.38 meets the claim language), and wherein after deployment in the patient, the contiguous double-layer construct resides as a single element within the inner channel of the stent member (Garrison discloses expansion and thus deployment prior to evertion, thus just after expansion/deployment, the leaflet layer is still inverted and in the form of a double layer construct; col.11, lines 26-36). Garrison discloses the heart valve substantially as claimed. Garrison discloses the sheet (membrane of 6d) to be made of any suitable valve material (col.10, lines 55-57), however is silent to any specific materials that are claimed. Garrison also shows the valve attached to the stent member (fig.38), however is silent to mention the means for attachment. Bessler teaches in the same field of heart valve devices, the use of

porcine pericardium as a specific type of biological material among other materials (col.4, lines 9-11; col.6, lines 19-31) for use as the leaflet material (22) in a valve replacement device (fig.1) and also teaching suturing (26) as a means to attach a stent to a valve membrane. It would have been obvious to one having ordinary skill in the art at the time the invention was made to combine Garrison's heart valve device having a biological material for the sheet with Bessler's material teaching of a using porcine pericardium as a biological material in valves, in order to provide a heart valve device with optimal material properties such as biocompatibility and Garrison's attached valve and stent with Bessler's teaching of using sutures as a means to attach the two. Such would have been an obvious choice of material known in the art, *In re Leshin*, 227 F.2d 197, 125 USPQ 416 (CCPA 1960) and obvious mean for attachment.

Referring to claims 59-62, Garrison discloses the claimed stent materials (col.10, lines 59-62, 42-44; col.5, lines 4-7). Referring to claim 64, the additional linear creases are shown at commissures in the figures. Referring to claim 65, Garrison shows the folded construct (membrane of 6d; shown folded in fig.35) to be continuous from the first edge to the second edge.

One suggestion by the examiner that would seemingly overcome the Garrison and Bailey rejections above is as follows: (claim 57 line 18)

~~wherein the single sheet of biocompatible pericardium tissue resides entirely within the inner channel of the stent member,~~ and wherein after deployment in the patient, the contiguous double-layer folded construct with the inner leaflet layer located radially within the outer cuff

layer resides as a single element entirely within the inner channel of the stent member, and wherein only the inner leaflet layer resides radially inward from the outer cuff layer.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Cheryl Miller whose telephone number is 571-272-4755. The examiner can normally be reached on M- F (8am-5:30pm).

If attempts to reach the examiner by telephone are unsuccessful, please contact the examiner's supervisor, Thomas Sweet at 571-272-4761. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

If there are any inquiries that are not being addressed by first contacting the Examiner or the Supervisor, you may send an email inquiry to TC3700_Workgroup_D_Inquiries@uspto.gov.

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
/THOMAS J SWEET/
Supervisory Patent Examiner, Art Unit 3738

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

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

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4035849		1977-07-19	Angell et al.	
	2	6409755		2002-06-25	Vrba	
	3	6482228		2002-11-19	Norred	
	4	6951571		2005-10-04	Srivastava	
	5	7189259		2007-03-13	Simionescu et al.	
	6	7261732		2007-08-28	Justino	
	7	7318998		2008-01-15	Goldstein et al.	
	8	7329279		2008-02-12	Haug et al.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CM/

Receipt date: 09/08/2010	Application Number	10887688	10887688 - GAU: 3738
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2004-07-10	
	First Named Inventor	David PANIAGUA	
	Art Unit	3738	
	Examiner Name	Cheryl L. MILLER	
	Attorney Docket Number	54813-10100	

	9	7381219		2008-06-03	Salahieh et al.	
	10	7566343		2009-07-28	Jenson et al.	

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	1	20050159811		2005-07-21	Lane	

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	1	HIESTER,E.D. et al., "Optimal bovine pericardial tissue selection sites. I. Fiber architecture and tissue thickness measurements." J. Biomed Mater Res, 1998, Feb, 01; 39(2):207-14	☐
	2	HUFNAGEL, Charles A., M.D., "Basic Concepts in the Development of Cardiovascular Prosthes" The American Journal of Surgery, Vol 137, March 1979	☐

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(Not for submission under 37 CFR 1.99)	First Named Inventor	David PANIAGUA	
	Art Unit	3738	
	Examiner Name	Cheryl L. MILLER	
	Attorney Docket Number	54813-10100	

	3	HUFNAGEL, Charles.A., MD et al., "In the beginning. Surgical Correction of Aortic Insufficiency" 1954; Ann Thorac Surg 1989 May; 47(3), pp. 475-476	☐
	4	HUFNAGEL, Charles.A., MD et al., "Late follow-up of ball-valve prostheses in the descending thoracic aortia", J. Throrac Cardiovasc Surg, December 1976, 72(6), pp. 900-909	☐
	5	HUFNAGEL, Charles.A., MD et al., "Surgical Correction of Aortic Insufficiency" Surgery Vol 35, May, 1954 No. 5	☐
	6	PATHAK, CP et al., "Treatment of bioprosthetic heart valve tissue with long chain alcohol solution to lower calcification potential" J Biomed Mater Res A. 2004 Apr 1;69(1):140-4	☐
	7	SAMOUILLAN, V. et al., " Comparison of chemical treatments on the chain dynamics and thermal stability of bovine pericardium collagen" J Biomed Mater Res A. 2003 Feb 1;64(2):330-8	☐
	8	SHEN, Ming et al., "Effect of ethanol and ether in the prevention of calcification of bioprostheses" Ann Thorac Surg. 2001 May;71(5 Suppl):S413-6	☐
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	10	HUFNAGEL, Charles A., "Vessels and Valves", Sec. 1: Development of Cardiac Surgery, Chap 7, pp. 43-55 copyright 1977	☐

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EXAMINER SIGNATURE

Examiner Signature	/Cheryl Miller/	Date Considered	02/08/2012

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	RE40404		2008-06-24	Schmitt et al.	
	2	3014024		1961-12-19	Lieberman et al.	
	3	3029819		1962-04-17	Edward	
	4	3105492		1963-10-01	Jeckel	
	5	3320972		1967-05-23	High et al.	
	6	3409914		1968-11-12	Jones	
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	8	3562820		1971-02-16	Braun	

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Receipt date: 08/02/2010	Application Number	10887688	10887688 - GAU: 3738
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2004-07-10	
	First Named Inventor	David PANIAGUA	
	Art Unit	3738	
	Examiner Name	Cheryl L. MILLER	
	Attorney Docket Number	54813-10100	

	9	3588920		1971-06-29	Wesolowski	
	10	3878565		1975-04-22	Sauvage	
	11	3966401		1976-06-29	Hancock et al.	
	12	3945052		1976-03-23	Liebig	
	13	3986828		1976-10-19	Hoffman, Jr. et al.	
	14	4082507		1978-04-04	Sawyer	
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	16	4164045		1979-08-14	Bokros et al.	
	17	4172295		1979-10-30	Batten	
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	19	4291420		1981-09-29	Reul	

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	First Named Inventor	David PANIAGUA	
	Art Unit	3738	
	Examiner Name	Cheryl L. MILLER	
	Attorney Docket Number	54813-10100	

	20	4350492		1982-09-21	Wright et al.	
	21	4364127		1982-12-21	Pierce et al.	
	22	4388735		1983-06-21	Ionescu et al.	
	23	4441216		1984-04-10	Ionescu et al.	
	24	4456589		1984-06-26	Holman et al.	
	25	4473423		1984-09-25	Kolff	
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	Art Unit	3738	
	Examiner Name	Cheryl L. MILLER	
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	First Named Inventor	David PANIAGUA	
	Art Unit	3738	
	Examiner Name	Cheryl L. MILLER	
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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CM/

Receipt date: 08/02/2010	Application Number	10887688	10887688 - GAU: 3738
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	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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Receipt date: 08/02/2010	Application Number	10887688	10887688 - GAU: 3738
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	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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Receipt date: 08/02/2010	Application Number	10887688	10887688 - GAU: 3738
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	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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Examiner Signature	/Cheryl Miller/	Date Considered	02/08/2012

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Receipt date: 08/02/2010	Application Number	10887688 10887688 - GAU: 3738
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	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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/Cheryl Miller/ 02/08/2012

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re the Application of:	Group Art Unit: 3738
PANIAGUA et al.	Confirmation No. 4909
Application No.: 10/887,688	Examiner: Cheryl L. MILLER
Filed: July 10, 2004	AMENDMENT AND RESPONSE
Atty. File No.: 54813-10100	**Filed Electronically**
Entitled: PERCUTANEOUSLY IMPLANTABLE REPLACEMENT HEART VALVE DEVICE AND METHOD OF MAKING SAME	

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

Dear Sir:

In response to the February 16, 2012 Office Action (the "Office Action"), please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 8 of this paper.

Applicants believe no fees are due for this submission. However, please credit any over payment or debit any under payment to Deposit Account No. 08-2665.

AMENDMENTS TO THE CLAIMS

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

Listing of Claims:

1.-56. **(Cancelled)**

57. **(Currently Amended)** A percutaneously implantable replacement heart valve device for deployment in a patient, comprising:

a collapsible and expandable stent member including an inner channel; and

a single sheet of biocompatible pericardium tissue attached to the stent member by a plurality of sutures, the single sheet of biocompatible pericardium tissue partitioned by a transverse linear crease to form an outer cuff layer and an inner leaflet layer, the transverse linear crease oriented substantially parallel to a first edge and a second edge of the single sheet of biocompatible pericardium tissue, wherein the first edge includes a free edge of the inner leaflet layer, wherein at least portions of the inner leaflet layer reside substantially radially adjacent and in contact with the outer cuff layer within the stent member to form a contiguous double-layer folded construct, the inner leaflet layer partitioned by ~~at least one~~ an additional linear crease oriented substantially perpendicular to the transverse linear crease to form two ~~or more~~ individual valve leaflets wherein the two ~~or more~~ individual valve leaflets are bordered in part by the ~~at least one~~ additional linear crease, the ~~at least one~~ additional linear crease located from the transverse linear crease to the free edge of the inner leaflet layer, wherein the inner leaflet layer resides in contact with the outer cuff layer ~~at at least one point~~ along ~~each~~ the additional linear crease, wherein a first lateral edge of the single sheet of biocompatible pericardium tissue adjoins

a second lateral edge of the single sheet of biocompatible pericardium tissue, ~~wherein the single sheet of biocompatible pericardium tissue resides entirely within the inner channel of the stent member,~~ and wherein after deployment in the patient, the contiguous double-layer folded construct with the inner leaflet layer located radially within the outer cuff layer resides as a single element entirely within the inner channel of the stent member, and wherein only the inner leaflet layer resides radially inward from the outer cuff layer.

58. **(Previously Presented)** The percutaneously implantable replacement heart valve device of Claim 57, wherein the single sheet of biocompatible pericardium tissue comprises one of treated bovine pericardium tissue or treated porcine pericardium tissue.

59. **(Previously Presented)** The percutaneously implantable replacement heart valve device of Claim 57, wherein the stent member comprises a metal alloy.

60. **(Previously Presented)** The percutaneously implantable replacement heart valve device of Claim 57, wherein the stent member comprises stainless steel.

61. **(Previously Presented)** The percutaneously implantable replacement heart valve device of Claim 57, wherein the stent member comprises a shape memory alloy.

62. **(Previously Presented)** The percutaneously implantable replacement heart valve device of Claim 61, wherein the shape memory alloy comprises nitinol.

63. **(Previously Presented)** The percutaneously implantable replacement heart valve device of Claim 57, wherein the plurality of sutures includes sutures at axially distal and proximal ends of the contiguous double-layer folded construct.

64. **(Cancelled)**

65. **(Previously Presented)** The percutaneously implantable replacement heart valve device of Claim 57, wherein the single sheet of biocompatible pericardium tissue forming the contiguous double-layer folded construct is continuous between the first edge to the transverse linear crease and back to the second edge.

66. **(New)** The percutaneously implantable replacement heart valve device of Claim 57, further comprising a second additional linear crease oriented substantially perpendicular to the transverse linear crease, wherein the additional linear crease and the second additional linear crease collectively form three individual valve leaflets.

67. **(New)** The percutaneously implantable replacement heart valve device of Claim 57, wherein the single sheet of biocompatible pericardium tissue comprises first and second pieces of biocompatible pericardium tissue.

68. **(New)** The percutaneously implantable replacement heart valve device of Claim 57, wherein the outer cuff layer comprises one or more separate pieces of biocompatible pericardium tissue.

69. **(New)** A percutaneously implantable replacement heart valve device for deployment in a patient, comprising:

a collapsible and expandable stent member including an inner channel; and

a single sheet of biocompatible pericardium tissue attached to the stent member by a plurality of sutures, the single sheet of biocompatible pericardium tissue partitioned by a transverse linear crease to form an outer cuff layer and an inner leaflet layer, the transverse linear crease oriented substantially parallel to a first edge and a second edge of the single sheet of biocompatible pericardium tissue, wherein the first edge includes a free edge of the inner leaflet layer, wherein at least portions of the inner leaflet layer reside substantially radially adjacent and in contact with the outer cuff layer within the stent member to form a contiguous double-layer folded construct, the inner leaflet layer partitioned by two additional linear creases oriented substantially perpendicular to the transverse linear crease to form three individual valve leaflets wherein the three individual valve leaflets are bordered in part by the two additional linear creases, the two additional linear creases located from the transverse linear crease to the free edge of the inner leaflet layer, wherein the inner leaflet layer resides in contact with the outer cuff layer along the two additional linear creases, wherein a first lateral edge of the single sheet of biocompatible pericardium tissue adjoins a second lateral edge of the single sheet of biocompatible pericardium tissue, and wherein after deployment in the patient, the contiguous double-layer folded construct with the inner leaflet layer located radially within the outer cuff layer resides as a single element entirely within the inner channel of the stent member, and wherein only the inner leaflet layer resides radially inward from the outer cuff layer.

70. **(New)** The percutaneously implantable replacement heart valve device of Claim 69, wherein the single sheet of biocompatible pericardium tissue comprises one of treated bovine pericardium tissue or treated porcine pericardium tissue.

71. **(New)** The percutaneously implantable replacement heart valve device of Claim 69, wherein the stent member comprises a metal alloy.

72. **(New)** The percutaneously implantable replacement heart valve device of Claim 69, wherein the stent member comprises stainless steel.

73. **(New)** The percutaneously implantable replacement heart valve device of Claim 69, wherein the stent member comprises a shape memory alloy.

74. **(New)** The percutaneously implantable replacement heart valve device of Claim 73, wherein the shape memory alloy comprises nitinol.

75. **(New)** The percutaneously implantable replacement heart valve device of Claim 69, wherein the plurality of sutures includes sutures at axially distal and proximal ends of the contiguous double-layer folded construct.

76. **(New)** The percutaneously implantable replacement heart valve device of Claim 69, wherein the single sheet of biocompatible pericardium tissue forming the contiguous double-layer folded construct is continuous between the first edge to the transverse linear crease and back to the second edge.

77. **(New)** The percutaneously implantable replacement heart valve device of Claim 69, wherein the single sheet of biocompatible pericardium tissue comprises first and second pieces of biocompatible pericardium tissue.

78. **(New)** The percutaneously implantable replacement heart valve device of Claim 69, wherein the outer cuff layer comprises one or more separate pieces of biocompatible pericardium tissue.

REMARKS/ARGUMENTS

The present Amendment and Response comprises Applicant's reply to the Examiner's February 16, 2012 Office Action. With the amendments made herein, Claims 1-56 and 64 stand cancelled. Claim 57 is amended. Claims 66-78 have been added. Accordingly, Claims 56-63 and 65-78 are now pending in view of the above amendments. Applicants note that there are now 21 total claims pending in this application. Applicants previously submitted the requite fees for additional claims and believe that no additional claims fees are currently due.

Applicants believe that no new matter has been added with regard to the claim amendments provided herein. Applicants do not donate or disclaim any claims or subject matter with the claim amendments made herein, and the Applicants expressly reserve the right to prosecute the original claims or any unclaimed subject matter in one or more future filed continuing applications.

Reconsideration of the application is respectfully requested in view of the above amendments to the claims and the following remarks. Please note that the following remarks are not intended to be an exhaustive enumeration of the distinctions between any cited reference and the claimed invention. Rather, the distinctions identified and discussed below are presented solely by way of example to illustrate some of the differences between the claimed invention and the cited references. In addition, the Applicants request that the Examiner carefully review any references discussed below to ensure that Applicants' understanding and discussion of the references, if any, is consistent with the Examiner's understanding. Also, Applicants' arguments related to each cited reference are not an admission that the cited references are, in fact, prior art.

I. Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected Claims 57-65 under 35 U.S.C. § 112, First Paragraph, as failing to comply with the written description requirement. The suggestions set forth by the Examiner in the recent Office Action have been adopted by the Applicant. Accordingly, the Applicants respectfully request withdrawal of the 35 U.S.C. § 112, First Paragraph rejections.

II. Prior Art Rejections

Rejections Under 35 U.S.C. § 103(a)

The Examiner rejected Claims 57-65 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,458,153 to Bailey et al. ("Bailey") in view of U.S. Patent No. 5,855,601 to Bessler ("Bessler"). The Examiner also rejected Claims 57-62 and 64-65 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,425,916 to Garrison ("Garrison") in view of Bessler.

The Applicants reiterate the enablement problems with Bailey, Bessler and Garrison, and incorporate herein their previous remarks and arguments, in their entirety, from the Applicants' reply of August 2, 2010.

Applicants wish to express their appreciation for the helpful comments provided by the Examiner regarding claim wording for Claim 57. The Applicants have adopted such claim wording, and the Applicants believe that Bailey, Bessler and Garrison, either alone or in combination, fail to disclose the limitations recited in Claim 57 as amended, including that "after deployment in the patient, the contiguous double-layer folded construct with the inner leaflet layer located radially within the outer cuff layer resides as a single element entirely within the

inner channel of the stent member, and wherein only the inner leaflet layer resides radially inward from the outer cuff layer." More particularly, Bailey includes at least one biasing arm within the inner channel of the valve. Accordingly, at least the limitation given above distinguishes the claimed structure over that of Bailey and/or Bailey in combination with Bessler. The Applicants further believe that amended Claim 57 distinguishes over Garrison and/or Garrison in combination with Bessler because Garrison fails to disclose at least that "only the inner leaflet layer resides radially inward from the outer cuff layer." Accordingly, the Applicants believe that the claims as amended herein are now allowable, and respectfully request withdrawal of the 35 U.S.C. § 103 rejections.

New Claims

The Applicants have added new dependent Claim 66 reciting "a second additional linear crease oriented substantially perpendicular to the transverse linear crease, wherein the additional linear crease and the second additional linear crease collectively form three individual valve leaflets." Support for this claim can be found in Figs. 1-3B.

In addition, the Applicants have added new dependent Claim 67 reciting that "the single sheet of biocompatible pericardium tissue comprises first and second pieces of biocompatible pericardium tissue." Support for this claim can be found in originally filed Claim 26 of the Applicants' CIP patent application that published as U.S. Patent Application Publication No. 2005/0113910.

The Applicants have also added new dependent Claim 68 reciting that "the outer cuff layer comprises one or more separate pieces of biocompatible pericardium tissue." Support for this claim can be found in Paragraph [0047] of the Applicants' CIP patent application that published as U.S. Patent Application Publication No. 2005/0113910, wherein the specification

states "...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."

In addition, the Applicants have also added new independent Claim 69 which recites "two additional linear creases oriented substantially perpendicular to the transverse linear crease to form three individual valve leaflets." Support for this language is provided in Figs. 1-3B. The additional dependent Claims 70-75 are similar to previously presented Claims 58-63, respectively. New Claim 76 is similar to previously presented Claim 65. New Claim 77 is similar to new Claim 67 mentioned above. New Claim 78 is similar to new Claim 68 mentioned in the paragraph above.

Claim 69 is believed to be patentable over the cited references because Claim 68 includes the limitations noted above in the discussion concerning amended Claim 57. Accordingly, the Applicants respectfully request allowance of independent Claim 68, together with its dependent Claims 69-76.

CONCLUSION

In view of the foregoing, Applicants believe the claims as amended are in allowable form. In the event that the Examiner finds a remaining impediment to a prompt allowance of this application that may be clarified through a telephone interview, or which may be overcome by an Examiner's Amendment, the Examiner is requested to contact the undersigned attorney.

Applicants believe no fees are due for this submission. However, please credit any over payment or debit any under payment to Deposit Account No. 08-2665.

Respectfully submitted,

BRYAN CAVE LLP

/ Mark L. Yaskanin /

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Facsimile: (303) 866-0200

Dated: 16 May 2012

Electronic Patent Application Fee Transmittal

Application Number:	10887688
Filing Date:	10-Jul-2004
Title of Invention:	Percutaneously implantable replacement heart valve device and method of making same
First Named Inventor/Applicant Name:	David Paniagua
Filer:	Mark Lauren Yaskanin/Carol Donahue
Attorney Docket Number:	54813-10100

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
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Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	12788654
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:	23337
Filer:	Mark Lauren Yaskanin/Carol Donahue
Filer Authorized By:	Mark Lauren Yaskanin
Attorney Docket Number:	54813-10100
Receipt Date:	16-MAY-2012
Filing Date:	10-JUL-2004
Time Stamp:	17:30:20
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	4741
Deposit Account	082665
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Warnings:					
Information:					
2	Foreign Reference	WO-2011-109450.pdf	3458144 49cb567520f19f7be95fe5acd0e8ad531490 0200	no	61
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3	Foreign Reference	WO-2012-006124.pdf	2412038 222cb6e8e002d8b972225721f752482b6d 4a883	no	40
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5	Foreign Reference	WO-2009-156471.pdf	1102714 34029217aa67c5b5a444eccd48a981219de 58ab4	no	29
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6	Non Patent Literature	US_12-228192_Examiner_Interview_Summary_2011-04-05.pdf	161803 8cd2ca6493510b177d8cfa48b7db348f7fb1 ef65	no	3
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7	Non Patent Literature	US_12-228192_Final_Office_Action_2011-07-14.pdf	12085622 48467f8222486a3724a21d8328047ae8fd6 3e4b7	no	14
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11	Non Patent Literature	PCT-US11-42252_Written_Opinion_Search_Report_10502.PDF	478447 b0c07dc7fdfc4b09ba134c96cc425b9e7d8ecfaa	no	12
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12	Non Patent Literature	US_13-367252_Application_10111.pdf	3242188 d38ad7c4da5aceb6f3f9554f9953cb60c2b5c7d5	no	43
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13	Non Patent Literature	US_13-243980_Application_10222.pdf	686357 08eb8614d73cfb7c67a231d57a4939e8e237d7f6	no	55
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19	Non Patent Literature	Angelini_Affidavit.pdf	89997 1882a66e67c83bdbeaf11b57b173118d0d549524	no	3
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24	Non Patent Literature	Grube_Progress_and_Current_status_Percutaneous_Aortic_Valve_Replacement_ABSTRACT.pdf	90858 217a8fdb260fb0b95019ae4179bd5a0e6023239b	no	2
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33	Non Patent Literature	PCT-US11-53120_Search_Report_and_Written_Opinion_10223.pdf	603193 0827ae040ca9db8890932a29956d0d0fae0b7ff7	no	13
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35		Amendment_Response.pdf	120153 dd539491a8fa9dbb125bae91bd383bbe1d5e352e	yes	12

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	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	7
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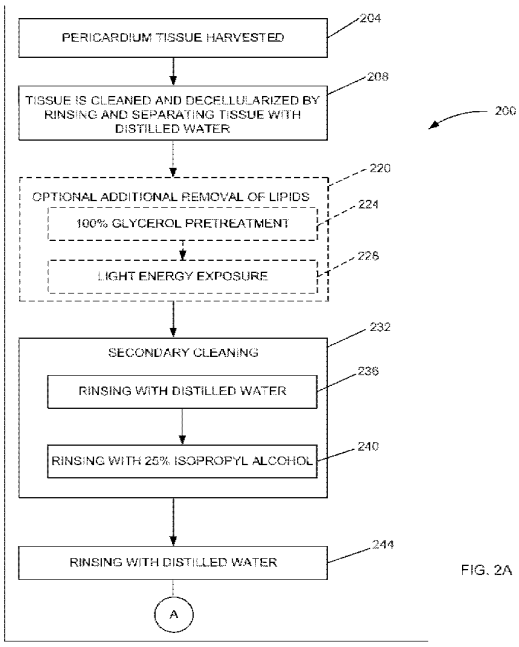

FIG. 2A

(57) **Abstract**: A prepared tissue for medical use with a patient is provided. Methods for preparing such tissue are also provided. Implantable tissue is provided by harvesting a tissue, such as but not limited to a pericardium tissue, and exposing the tissue to various cleaning, rinsing, treatment, separating, and fixation steps. The tissue of at least one embodiment is cleaned with distilled water, rinsed with isopropyl alcohol, and treated with a glutaraldehyde solution. The prepared tissue may be allowed to dry or partially hydrated prior to packaging and shipment. As such, the tissue can be implanted into the receiving patient in either a dry or wet state. The relatively thin yet strong tissue material is adapted for implanting within or grafting to human tissue. By way of example, the tissue may be used in a shunt, a valve, as graft material, as a patch, as a prosthetic tissue in a tendon and/or ligament, and a tissue product for wound management.

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TISSUE FOR PROSTHETIC IMPLANTS AND GRAFTS, AND METHODS ASSOCIATED THEREWITH

FIELD

The present invention relates to the field of tissue engineering, and more particularly, to tissue for prosthetic implants and grafts.

BACKGROUND

Preparing tissue for medical use to treat a patient is common. These tissues are typically used for implanting with or grafting to a human tissue. Prepared tissue is often used in shunts, tissue grafts and patches, as a prosthetic tissue in valves, tendon and/or ligament, and as tissue product for wound management. Many of these medical applications typically employ tissues obtained from mammalian animals and are thus termed xenografts. As with allografts (from human sources), xenograft tissue in the raw state contains immunologically "foreign" proteins and antigenic chemistry provocative of patient host immune responses that would cause destruction of implanted tissue as well as potentially harmful immune-mediated reactions. Thus, tissue for implantation in patients requires a number of preparatory chemical treatments to become biocompatible enough for implantation. For the preparation of xenograft tissue for structural applications, these treatments are typically directed to specific goals to isolate and preserve the structural proteins such as collagen: 1) remove cells within the tissue matrix, 2) remove unwanted chemical constituents, especially lipid components, and 3) chemically fix (i.e., cause thorough cross-linking of) structural proteins. Numerous manipulations of these and other steps in tissue processing have been employed with varying success in the art to achieve durable and biocompatible xenograft tissues for human implant. Nevertheless, conventional tissue materials are plagued by a variety of problems. For example, often in such applications, long-term function and survival of the tissue implants have been compromised by destructive inflammation, loss of structural integrity, and reactive calcification.

When using xenograft tissue membrane for use as formed sheet material, the tissue is usually cleaned and sterilized *ex vivo*, as outlined above. The preparation process itself can deteriorate the strength and biocompatibility characteristics of the tissue, or be the cause of latent host reactions that ultimately cause failure within the body. Often, the prepared tissue must maintain a certain thickness in order to have the desired strength traits. As such, the tissue material may be produced to be relatively thick, which may limit the manner of its application, and may also limit its biocompatibility.

Furthermore, in certain functional forms, such as for prosthetic heart valves, the prepared tissue must be stored in a liquid (usually a preservative) solution, otherwise the tissue will dry out and become brittle and prone to damage. Maintaining the tissue in a "wet" state adds mass and bulk to the tissue product since the moisture content of the tissue is higher and the volume

of the tissue is greater when hydrated. Because the tissue must be stored "wet," packaging must be robust to prevent leaks, the transportation environment must be carefully monitored and controlled, and once at the hospital or medical facility, significant efforts to rinse and prepare the tissue prior to use are needed.

By way of example and not limitation, when a surgeon is ready to use a bioprosthetic tissue heart valve, the valve and attached tissue must be rinsed, and in the case of transcatheter tissue heart valve devices, mounted onto a delivery system. In this example, if the tissue is associated with a percutaneously deliverable heart valve, the prosthetic heart valve is typically mounted to a balloon catheter in a catheterization lab. These steps extend procedure time, require manual manipulation of the tissue, and expose the tissue to harmful contaminants. Moreover, for the example of a percutaneously deliverable heart valve, human errors can be made in mounting and orienting catheters and sheaths.

Because the tissue has a relatively large profile, mass and volume, a surgeon's delivery options are often limited. For example, only patients having large enough vascular systems can use catheter-delivery procedures. Moreover, there is a need for tissue that can be used in a variety of medical indications unrelated to a percutaneously deliverable heart valves.

Accordingly, there is a need to address the shortcomings addressed above.

SUMMARY

It is to be understood that the present invention includes a variety of different versions or embodiments, and this Summary is not meant to be limiting or all-inclusive. This Summary provides some general descriptions of some of the embodiments, but may also include some more specific descriptions of other embodiments.

Embodiments of the one or more present inventions include methods of preparing or treating tissue for medical use, as well as the actual tissue itself. Accordingly, in at least one embodiment, implantable tissue is provided by first harvesting a tissue, and thereafter treating the tissue by: (a) cleaning and decellularizing the tissue by rinsing and separating the tissue with distilled water; (b) optionally treating the tissue to additionally remove lipids by a glycerol pretreatment and exposure to light energy; (c) a secondary cleaning that includes a distilled water rinse, and rinsing with isopropyl alcohol; (d) final rinsing with distilled water; (e) fixation treating for collagen cross-linking by at least one of (I) immersion in formalin, (II) immersion in glycerol, (III) immersion in glutaraldehyde, (IV) immersion in glutaraldehyde filtered to limit oligomeric content, or (V) any of I - IV above with addition to the fixative solution of free amino acids lysine and/or histidine; (f) post-fixation treating by distilled water rinsing then isopropyl alcohol; and (g) final rinsing in distilled water. In at least one embodiment, the implantable tissue is then allowed to dry and thereafter is associated with a package for

shipment. Alternatively, in at least one embodiment, the implantable tissue is then at least partially hydrated and associated with a package for shipment.

As noted above, one or more embodiments described herein are directed to one or more methods of preparing a section of tissue for medical use. By way of example and not limitation, the tissue may be used in a shunt, in a valve, as graft material, as a patch for repair of congenital heart defects, as a prosthetic tissue in tendon and/or ligament replacement, and a tissue product for wound management. Accordingly, a method of preparing a section of tissue for medical use is provided, the method comprising:

(a) cleaning and decellularizing the section of tissue by performing multiple rinses of the section of tissue with distilled water;

(b) rinsing the section of tissue with isopropyl alcohol for a first period of time of not less than about 7 days; and

(c) contacting the section of tissue with one of

(i) a formalin solution, or

(ii) a glutaraldehyde solution

for a second period of time of not less than about 6 days;

wherein step (b) occurs sometime after step (a), and wherein step (c) occurs sometime after step (b).

For the method directly above, in at least one embodiment, for step (c): if the formalin solution is used, then the formalin solution comprises a concentration of about 1-37.5% formalin, and more preferably, about 10% formalin; and if the glutaraldehyde solution is used, then the glutaraldehyde solution comprises a concentration of about 0.1-25% glutaraldehyde, and more preferably, about 0.25% glutaraldehyde.

In at least one embodiment, the method further comprises exposing the section of tissue to light energy for an exposure duration, the exposure duration extending until there is no further visible separation of lipid droplets from an exposed surface of the section of tissue. In at least one embodiment, the light energy is at least equivalent to exposing the section of tissue to a 25-100 watt light source, and more preferably, a 50 watt incandescent light source with a flat radiant face situated at a distance of about 10 centimeters from the exposed surface for about 15 minutes. In at least one embodiment, the method further comprises: (d) rinsing the section of tissue with distilled water and isopropyl alcohol for a post-fixation period of time of not less than about 7 days; wherein step (d) occurs after step (c). In at least one embodiment, the section of tissue comprises an ultimate tensile strength of greater than about 25 MegaPascals. In at least one embodiment, the section of tissue comprises a treated pericardium tissue.

In another embodiment, a method of preparing a tissue for medical use is provided, the method comprising: providing a section of tissue harvested from a mammalian organism; and causing osmotic shocking of the section of tissue by performing multiple rinses of the section of tissue with distilled water. In at least one embodiment, the method further comprises hydrating the section of tissue during a plurality of time intervals using distilled water. In at least one embodiment, the method further comprises not using saline for causing at least one of the osmotic shocking and the hydrating of the tissue. In at least one embodiment, the method further comprises pretreating the section of tissue with glycerol before contacting the section of tissue with one or more of isopropyl alcohol, glutaraldehyde and formalin. In at least one embodiment, the method further comprises contacting the section of tissue with a solution containing formalin after pretreating the section of tissue with glycerol. In at least one embodiment, the method further comprises contacting the section of tissue with a solution containing glutaraldehyde after pretreating the section of tissue with glycerol. In at least one embodiment, the method further comprises pretreating the section of tissue with isopropyl alcohol before contacting the section of tissue with either glutaraldehyde or formalin. In at least one embodiment, the method further comprises contacting the section of tissue with a solution containing formalin after pretreating the section of tissue with isopropyl alcohol. In at least one embodiment, the method further comprises contacting the section of tissue with a solution containing glutaraldehyde after pretreating the section of tissue with isopropyl alcohol. In at least one embodiment, the method further comprises exposing the section of tissue to light energy for a period of time, the period of time extending until there is no further visible separation of lipid droplets from an exposed surface of the section of tissue. In at least one embodiment, the light energy is at least equivalent to exposing the section of tissue to a 50 watt incandescent light source with a flat radiant face situated at a distance of about 10 centimeters from the exposed surface for about 15 minutes. In at least one embodiment, the section of tissue comprises a treated pericardium tissue.

Another embodiment of the one or more present inventions pertains to a method of preparing a section of tissue for medical use, comprising:

(a) contacting the section of tissue with distilled water;

(b) contacting the section of tissue with isopropyl alcohol for a pre-fixation period of time of not less than about 3 days; and

(c) contacting the section of tissue with one of

(i) a formalin solution, or

(ii) a glutaraldehyde solution

for a fixation period of time of not less than about 3 days; and

(d) contacting the section of tissue with isopropyl alcohol for a post-fixation period of time of not less than about 3 days;

wherein step (b) occurs sometime after step (a), wherein step (c) occurs sometime after step (b), and wherein step (d) occurs sometime after step (c).

In at least one embodiment, for step (c): if the formalin solution is used, then the formalin solution comprises a concentration of about 1 - 37.5% formalin; and if the glutaraldehyde solution is used, then the glutaraldehyde solution comprises a concentration of about 0.1 - 25% glutaraldehyde. In at least one embodiment, for step (c): if the formalin solution is used, then the formalin solution comprises a concentration of about 8-12% formalin; and if the glutaraldehyde solution is used, then the glutaraldehyde solution comprises a concentration of about 0.1 - 0.5% glutaraldehyde. In at least one embodiment, the section of tissue comprises a treated pericardium tissue.

As mentioned above, one or more embodiments are directed to a tissue for medical use. Accordingly, a prepared tissue for medical use is provided, comprising: a section of treated tissue harvested from a mammalian organism, the section of tissue including an ultimate tensile strength of greater than about 15 MegaPascals. In at least one embodiment, the section of treated tissue has a thickness of between about 50 to 500 micrometers. In at least one embodiment, the section of treated tissue comprises a water content of less than about 60% by weight of the section of tissue. In at least one embodiment, the section of treated tissue comprises a water content of less than about 50% by weight of the section of treated tissue. In at least one embodiment, the section of treated tissue comprises a water content of less than about 40% by weight of the section of treated tissue. In at least one embodiment, the section of treated tissue is attached to a frame *ex vivo* for at least one of: (a) surgical use; or (b) percutaneous implantation. In at least one embodiment, the section of treated tissue does not include a matrix that has been exposed to a polymer infiltrate. In at least one embodiment, the section of treated tissue is unbraided and uncompounded (as used herein, "unbraided an uncompounded" means the tissue comprises a single layer and is not overlapped or otherwise intertwined). In at least one embodiment, the section of treated tissue comprises an ultimate tensile strength of greater than about 25 MegaPascals. In at least one embodiment, the section of treated tissue has been exposed to isopropyl alcohol before contacting the section of tissue with either glutaraldehyde and formalin. In at least one embodiment, the section of treated tissue has been exposed to a solution containing formalin after pretreatment with isopropyl alcohol. In at least one embodiment, the section of treated tissue has been exposed to a solution containing glutaraldehyde after pretreatment with isopropyl alcohol. In at least one embodiment, the section of treated tissue comprises a pericardium tissue.

In at least one embodiment, a prepared tissue for medical use with a patient is provided, comprising: a section of tissue harvested from a mammalian organism, wherein the section of tissue is prepared *ex vivo* for future grafting or implantation in the patient, the section of tissue including a thickness of about 50 to 500 micrometers and an ultimate tensile strength of greater than about 25 MegaPascals. In at least one embodiment, the section of tissue is unbraided and uncompounded. In at least one embodiment, the section of tissue comprises a water content of less than about 40% by weight of the section of tissue. In at least one embodiment, the section of tissue is attached to a frame *ex vivo* for at least one of: (a) surgical use; or (b) percutaneous implantation in the patient. In at least one embodiment, the section of tissue does not include a matrix that has been exposed to a polymer infiltrate. In at least one embodiment, the section of tissue comprises a treated pericardium tissue.

One or more embodiments described herein are directed to one or more articles comprising a treated tissue. Accordingly, an article is provided, comprising: a section of tissue harvested from an organism, the section of tissue residing within packaging, wherein the section of tissue is adapted for at least one of implanting within or grafting to a human tissue, and wherein the section of tissue comprises a water content of less than about 40% by weight of the section of tissue.

As used herein, the term "dry" (or "substantially dry") when referring to the state of the tissue means a moisture content less than the water moisture content of the tissue when the tissue is allowed to fully rehydrate in the body of a patient. Typically, 70% by weight of the fully hydrated tissue membrane is water. Drying to a constitution of less than 40% by weight of water usefully alters the handling properties for purposes of folding, sewing or otherwise manipulating the tissue. As those skilled in the art will appreciate, the moisture content of the tissue may vary when dry. For example, the moisture content of the tissue when being folded and dry may be different than the moisture content of the tissue when dry and being shipped, for example, in a premounted state within a catheter delivery system.

With regard to delivery characteristics, another significant advantage of a prosthetic implant using a relatively thin tissue component described herein is that the prosthetic implant offers a relatively low packing volume as compared to commercially available prosthetic implants. In accordance with one or more embodiments, a dry tissue membrane has substantially less mass than a wet membrane. By way of example, a substantially dry pericardium tissue prepared by one or more of the present embodiments has approximately 30% of the mass of a wet pericardium tissue, and a marked reduction in profile and packing volume, thereby achieving a relatively low profile and making it suitable for implantation in greater number of patients.

Various components are referred to herein as "operably associated." As used herein, "operably associated" refers to components that are linked together in operable fashion, and encompasses embodiments in which components are linked directly, as well as embodiments in which additional components are placed between the two linked components.

As used herein, "at least one," "one or more," and "and/or" are open-ended expressions that are both conjunctive and disjunctive in operation. For example, each of the expressions "at least one of A, B and C," "at least one of A, B, or C," "one or more of A, B, and C," "one or more of A, B, or C" and "A, B, and/or C" means A alone, B alone, C alone, A and B together, A and C together, B and C together, or A, B and C together.

As used herein, "sometime" means at some indefinite or indeterminate point of time. So for example, as used herein, "sometime after" means following, whether immediately following or at some indefinite or indeterminate point of time following the prior act.

Various embodiments of the present inventions are set forth in the attached figures and in the Detailed Description as provided herein and as embodied by the claims. It should be understood, however, that this Summary does not contain all of the aspects and embodiments of the one or more present inventions, is not meant to be limiting or restrictive in any manner, and that the invention(s) as disclosed herein is/are understood by those of ordinary skill in the art to encompass obvious improvements and modifications thereto.

Additional advantages of the present invention will become readily apparent from the following discussion, particularly when taken together with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

To further clarify the above and other advantages and features of the one or more present inventions, a more particular description of the one or more present inventions is rendered by reference to specific embodiments thereof which are illustrated in the appended drawings. It is appreciated that these drawings depict only typical embodiments of the one or more present inventions and are therefore not to be considered limiting of its scope. The one or more present inventions is described and explained with additional specificity and detail through the use of the accompanying drawings in which:

Fig. 1 is a generalized flow chart illustrating preparation of tissue for use in an implantable construct or for use as a graft material;

Figs. 2A-2B are flow charts illustrating elements of the tissue preparation;

Fig. 3 is a flow chart illustrating elements of the drying and sizing;

Fig. 4 is an elevation view of a piece of tissue; and

Fig. 5 is a graph that shows actual stress-strain test results for five tissue samples prepared in accordance with at least one embodiment.

The drawings are not necessarily to scale.

DETAILED DESCRIPTION

Embodiments of the one or more inventions described herein include tissue for prosthetic implants and/or methods relating to preparation of tissue for prosthetic implants. A prosthetic implant made at least partially from tissue in accordance with at least one embodiment described herein can be surgically implanted or otherwise grafted to a patient. One or more embodiments of the prosthetic implant described herein have application for at least aortic and pulmonary valves, as well as in forming prosthetic ligaments and tendons.

Referring now to Fig. 1, preparation of tissue for use in an implantable construct or as a graft is generally shown in method 100. Method 100 generally includes preparing the tissue at 200 and then, optionally, drying the tissue at 300 in preparation of manipulating the tissue for forming an implantable construct, such as a braided or folded structure. Further detail of the tissue preparation is provided below.

At least one or more embodiments described herein include a relatively thin tissue component. By way of example and not limitation, in at least one embodiment the tissue has a thickness of approximately 50 - 150 μm, and further possesses characteristics of pliability and resistance to calcification after implantation. The relatively thin nature of the tissue used in the implantable prosthetic implant assists with biocompatibility. In addition, the relatively thin tissue component thereby provides for a relatively low mass.

With reference now to Fig. 2A, the process associated with preparation of a biocompatible tissue consistent with the above-noted characteristics is described. In at least one embodiment, pericardium tissue, such as porcine or bovine pericardium tissue, is harvested at 204 and then processed to serve as biocompatible tissue. Accordingly, subsequent to the harvesting at 204, the pericardium tissue is cleaned and decellularized at 208. More particularly, in at least one embodiment the tissue is initially cleaned with distilled water using gentle rubbing and hydrodynamic pressure at 208 in order to remove adherent non-pericardial and non-collagenous tissue. In at least one embodiment, the hydrodynamic pressure at 208 is provided by spraying the tissue with a relatively weak stream of liquid to remove at least some of the non-collagenous material associated with the tissue. The rinsing at 208 is to achieve effective decellularization of the pericardium tissue through osmotic shock. Typically, the thickness of the tissue in the cleaned condition varies from about 50 to 500 micrometers, depending on the source of raw tissue. Cleaning preferably continues until there is no visible adherent non-pericardial or non-collagenous tissue.

With continued reference to Fig. 2A, after the tissue has been cleaned and decellularized at 208, the tissue then undergoes optional additional removal of lipids at 220 to further treat the

tissue for preventing immunologic response and calcification. More particularly, the tissue first optionally undergoes a 100% glycerol pretreatment at 224 while being positioned on a flat surface (e.g., an acrylic plate), after which the tissue becomes nearly transparent.

At 228, the tissue optionally undergoes a "thermophotonic" process. In at least one embodiment, the tissue is optionally exposed to light energy for additional removal of lipids and for initial cross-linking of the collagen. By way of example and not limitation, in at least one embodiment a 25-100 watt incandescent light source, and more preferably, a 50 watt incandescent light source with a flat radiant face is employed at a distance of about 10 centimeters from the tissue surface, typically requiring 15 minutes of exposure before further visible separation of lipid droplets from the tissue stops.

Still referring to Fig. 2A, the tissue is then cleaned again in secondary cleaning at 232. More particularly, at 236 the tissue is again rinsed with distilled water. Thereafter, at 240 the tissue is rinsed with 25% isopropyl alcohol for periods of several hours to several days and weeks, depending on the desired tissue properties of pliability and tensile strength. By way of example, tissue prepared by the methods described herein has been successfully prepared by rinsing with 25% isopropyl alcohol for a period of 7 days, and after the further treatment steps described herein, provided an ultimate tensile strength of greater than 25 MegaPascals. In at least one embodiment where isopropyl alcohol is described as a rinsing agent, ethanol may be used in its place as an alternative, although resulting tissue properties may vary. Referring back to Fig. 2A, after the tissue is rinsed with isopropyl alcohol at 240, the tissue is then rinsed with distilled water at 244 as a final cleaning step and for rehydration.

Referring now to Fig. 2B, following the rinse with distilled water at 244, treatment of the tissue continues. More particularly, fixation for collagen cross-linking at 248 is achieved by performing at least one of the following:

a. At 248a, immersion of the tissue in 1-37.5% formalin, ideally a buffered solution, for between about 3 days to 5 weeks, and more preferably, for between about 3 days to 4 weeks, and more preferably yet, for between about 3 weeks to 4 weeks, at a temperature of between about 4 to 37°C, and more preferably, 10% formalin for 6 days at 20°C; or

b. At 248b, immersion of the tissue in 100% glycerol for up to 6 weeks at between 4 to 37°C, and more preferably, immersion of the tissue in 100% glycerol for about 3 weeks at 20°C; or

c. At 248c, immersion of the tissue in 0.1 - 25% glutaraldehyde for between about 3 days to 5 weeks, and more preferably, for between about 3 days to 4 weeks, and more preferably yet, for between about 3 weeks to 4 weeks, at 0 to 37°C, and more preferably, immersion of the tissue in 0.25% glutaraldehyde for 7 days at 4°C; or

d. At 248d, immersion of the tissue in 0.1 - 25% glutaraldehyde (filtered to limit oligomeric content) for between about 3 days to 5 weeks, and more preferably, for between about 3 days to 4 weeks, and more preferably yet, for between about 3 weeks to 4 weeks, at 0 to 37°C, and more preferably, 0.25% glutaraldehyde for 7 days at 4°C; or

e. At 248e, immersion in the tissue in one of the above formalin, glutaraldehyde, or oligomeric filtered glutaraldehyde solutions together with added amino acids, lysine and/or histidine, wherein the concentration of the amino acids, L-lysine or histidine, used as an additive to the fixative is in the range of about 100 - 1000 milliMolar, with a preferred value of about 684 mM.

In addition to the foregoing, combinations of the processes listed above may be performed, including: step a followed by step b; step a followed by step c; and step a followed by step d.

As those skilled in the art will appreciate, heat-shrink testing may be conducted on tissue samples to correlate the effectiveness of protein cross-linking. Here, results of heat-shrink testing performed on one or more samples of tissue prepared in accordance with at least one embodiment using formalin showed that the tissue had a shrink temperature of 90°C. This compares favorably with samples prepared using glutaraldehyde, wherein the shrink temperature was 80°C. Accordingly, formalin is a suitable variant of fixation. It is noted that formalin was generally abandoned by the field, largely because of material properties that were unfavorable and because of inadequate or unstable protein cross-linking. Such problems have been overcome through the pretreatments described herein, allowing production of tissue with strength, pliability, and durability in a relatively thin membrane. When used in a prosthetic implant, such as a heart valve, the tissue characteristics imparted by the tissue preparation process facilitate formation of a construct having a relatively low-profile, which also thereby facilitates dry packaging of the prosthetic implant. The same advantages are also achieved using the pretreatments when using a glutaraldehyde process.

Referring still to Fig. 2B, after fixation for collagen cross-linking at 248, an alcohol post-fixation treatment at 252 is preferably performed by rinsing the tissue in distilled water at 256, and then at 260 rinsing the tissue in 25% isopropyl alcohol for between about 30 minutes to 14 days or more at between about 0 to 37°C, and more preferably, for at least about 7 days at 20°C. At 264, the tissue undergoes a rinsing with distilled water.

In accordance with at least one embodiment, treatment of the tissue, including from the time of harvest to the time of implantation or grafting, does not include contact and/or exposure to a polymer to infiltrate and/or encapsulate tissue fibers of the tissue.

Referring now to Fig. 3, the drying process at 300 is performed after the tissue preparation at 200. Thus, in accordance with at least one embodiment, the tissue is dried under a load. More particularly, for the tissue drying at 304, the tissue is placed minimally stretched flat (that is, stretched just enough to eliminate visible wrinkles and bubbles) on a flat surface (e.g., a polymer or acrylic sheet) at 308, and held fixed at its edges at 312. Optionally, the joined tissue and underlying sheet are then set in a slight curve. The tension maintains the substantially flat structure of the tissue as it dries, thereby mitigating or preventing excessive shrinkage, wrinkling, and/or curling at the edges, and also making the rate of drying more uniform across the surface of the tissue because of the surface tension between the plate and the tissue. Alternatively, the tissue is dried while compressed between acrylic plates. When drying the tissue, the temperature is held at between about 4 to 37°C, and more preferably, between about 20 to 37°C (i.e., approximately room temperature to normal human body temperature), and more preferably, at about 20°C. At 314, the drying process is performed in substantially dark conditions (i.e., substantially no visible light) for between about 6 hours to 5 days, and more preferably, for about 72 hours. By way of example, the tissue is dried in dark conditions at a temperature of about 20°C for between about 6 hours to 5 days, and more preferably, for about 72 hours. As those skilled in the art will appreciate, drying the tissue while the tissue is compressed between plates requires a longer period of time.

In at least one embodiment, after drying, the tissue lots are inspected at 316, such as by stereomicroscopy, to identify and discard those with defects or discontinuities of the fiber matrix. If desired, the preferential fiber direction for each piece may be identified to determine a particular orientation, for example, to determine the free edge of the pieces that will form valve leaflets for a heart valve. Depending upon the size (i.e., the area) of the tissue being prepared and the size of tissue needed for a given implant, the tissue may be trimmed or otherwise sized in optional sizing at 320, such as by cutting the tissue into an appropriately sized and shaped sheet for implant formation and/or manipulation. Preferably, cutting of the tissue membrane is oriented so that the resulting free edge is parallel to the preferential fiber direction of the tissue membrane. Optionally, the free edge may also be cut with a parabolic or other curved profile to compensate for any attachment angles in order to increase the total contact surface between the tissue membrane and any associated frame or other structure. This approach minimizes weaknesses in the operating margins of the tissue assembly and advantageously distributes the principal loading forces of the operating implant along the long axis of the collagen fibers. As a result, the tissue is resistant to surface fracture and fraying.

As shown in Fig. 3, optional sizing at 320 is performed after the drying at 304 and inspection at 316. A rectangular shaped piece of tissue 400 is shown in Fig. 4. The tissue 400

may be manipulated for use in a variety of prosthetic implants and grafts.

As mentioned above, tissue prepared by the methods described herein has been successfully prepared by rinsing with 25% isopropyl alcohol for a period of 7 days, and after the further treatment steps described herein, provided an ultimate tensile strength of greater than 25 MegaPascals. Here, the combination of tissue pliability and tensile strength is sought for purposes of producing a material having property characteristics suitable for being physically manipulated to form prosthetic implants, such as a tissue leaflet assembly for a heart valve or a ligament, while providing a tissue material that will operate properly once implanted. These techniques are intended to conserve and preserve collagen fibers, minimize damage to the tissue and improve tissue characteristics. The preparation and fixation techniques produce tissue membrane material that may be rendered and used at lesser thicknesses than typically rendered in the prior art. Thinner membranes are more pliable, but with conventional tissue preparation techniques the tensile strength of the tissue is sacrificed. Advantageously, the preparation techniques described herein have produced membranes that have as much as three times the tensile strength of a commercial product of the prior art. This achieved strength is thus desirable for providing a tissue assembly having a low profile with appropriate durability, even in a substantially dry state. More particularly, the tissue possesses a relatively high tensile strength. By way of example and not limitation, testing has shown that embodiments of tissue prepared as described herein provide a tissue having a tensile strength of approximately three times the tensile strength of current pericardial valve tissue, such as on the order of approximately 25 MegaPascals, thereby providing about 2,000 times the physiologic load strength for valve tissue. Moreover, testing of an embodiment of an implantable prosthetic heart valve made with tissue prepared as described herein and under a static load of greater than approximately 250 mmHg showed less than approximately 14% leakage, wherein such results are generally considered superior to surgical tissue valve prostheses.

With reference to Fig. 5, stress-strain curve results for five different tissue samples prepared in accordance with an embodiment are shown. For the testing results shown, the yield stress or ultimate tensile strength was obtained by attaching strips of tissue fixed at the ends in a linear force tester and increasing the length by 0.3 mm/sec while recording resultant force (tension) until the material ruptured or separated entirely; these measurements were then used to calculate the stress-strain curves depicted in Fig. 5. As illustrated in the graph, the yield stress or ultimate tensile strength of the various tissue samples varied from about 30 to about 50 MegaPascals. More particularly, for each curve shown in Fig. 5, the testing procedures were the same. That is, each of the curves shown pertain to separate pieces of tissue that were subjected to the same test. The results show a minimum ultimate tensile strength of 30 MegaPascals, with

a range up to 50 MegaPascals. Accordingly, the illustrated test results demonstrate consistency of the ultimate tensile strength results for the tissue treatment process.

It is to be understood that the tissue generated from one or more of the tissue preparation procedures described herein may be used for a variety of devices or uses, and that use in a prosthetic heart valve is but one possible application for utilizing the tissue. For example, the tissue may be used in a shunt, or as graft material for repair or modification of one or more human organs, including the heart and its blood vessels. By way of further example, the tissue may be used as a pericardial membrane patch for repair of congenital heart defects. The tissue also has application as a prosthetic tissue in tendon and ligament replacement, and as a tissue product for wound management. Moreover, for use in a prosthetic heart valve, the tissue may be configured in a variety of ways and attached to a frame in a variety of ways. In addition, a plurality of separate tissue pieces may each be connected together, such as by suturing, to form a larger composite of treated tissue material. Thereafter, whether the prosthetic implant or graft is made of a folded tissue assembly or a plurality of separate tissue pieces, the resulting prosthetic implant or graft may then be further manipulated for treatment of a patient.

In at least one embodiment, tissue generated from one or more of the tissue preparation procedures described herein may be used to form a prosthetic implant that includes a stent, frame, bone screw or other fastening or anchoring mechanism. In yet other embodiments, tissue generated from one or more of the tissue preparation procedures described herein may be used to form a prosthetic implant or graph that does not include a stent, frame, bone screw or other fastening or anchoring mechanism. Tissue generated from one or more of the tissue preparation procedures described herein may be may be packaged for delivery in a substantially dry, partially hydrated or hydrated ("wet") state. For example, a prosthetic implant utilizing a prepared tissue described herein may be packaged for delivery as a hydrated prosthetic implant. Accordingly, while a portion of the tissue preparation process may include drying the tissue so that it may be manipulated more easily, the tissue may then be hydrated at a later point in time prior to implantation, and it may be maintained in a hydrated condition up to and including packaging, delivery and implantation into a patient. Hydration of the tissue membrane portion occurs rapidly and begins with simple preparatory flushing of the tissue. Those skilled in the art will appreciate that one or more embodiments described herein provide a tissue 400 suitable for implanting in a human, wherein the implantable tissue may be allowed to dry prior to implanting and effectively rehydrated at the time of implanting, such as by flushing of the tissue at the time of implanting using saline or water.

All embodiments described herein are described for use in human patients. However, all embodiments described herein have application for use in veterinary medicine, such as equine

medicine.

The present invention may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

The one or more present inventions, in various embodiments, include components, methods, processes, systems and/or apparatuses substantially as depicted and described herein, including various embodiments, subcombinations, and subsets thereof. Those of skill in the art will understand how to make and use the present invention after understanding the present disclosure.

The present invention, in various embodiments, includes providing devices and processes in the absence of items not depicted and/or described herein or in various embodiments hereof, including in the absence of such items as may have been used in previous devices or processes (e.g., for improving performance, achieving ease and/or reducing cost of implementation).

The foregoing discussion of the invention has been presented for purposes of illustration and description. The foregoing is not intended to limit the invention to the form or forms disclosed herein. In the foregoing Detailed Description for example, various features of the invention are grouped together in one or more embodiments for the purpose of streamlining the disclosure. This method of disclosure is not to be interpreted as reflecting an intention that the claimed invention requires more features than are expressly recited in each claim. Rather, as the following claims reflect, inventive aspects lie in less than all features of a single foregoing disclosed embodiment. Thus, the following claims are hereby incorporated into this Detailed Description, with each claim standing on its own as a separate preferred embodiment of the invention.

Moreover, though the description of the invention has included descriptions of one or more embodiments and certain variations and modifications, other variations and modifications are within the scope of the invention (e.g., as may be within the skill and knowledge of those in the art, after understanding the present disclosure). It is intended to obtain rights which include alternative embodiments to the extent permitted, including alternate, interchangeable and/or equivalent structures, functions, ranges or acts to those claimed, whether or not such alternate, interchangeable and/or equivalent structures, functions, ranges or acts are disclosed herein, and without intending to publicly dedicate any patentable subject matter.

CLAIMS

What is claimed is:

1. A prepared tissue for medical use, comprising:

a section of treated tissue harvested from a mammalian organism, the section of treated tissue including an ultimate tensile strength of greater than about 15 MegaPascals.

2. The prepared tissue of Claim 1, wherein the section of treated tissue has a thickness of between about 50 to 500 micrometers.

3. The prepared tissue of Claim 1, wherein the section of treated tissue comprises a water content of less than about 60% by weight of the section of treated tissue.

4. The prepared tissue of Claim 1, wherein the section of treated tissue comprises a water content of less than about 50% by weight of the section of treated tissue.

5. The prepared tissue of Claim 1, wherein the section of treated tissue comprises a water content of less than about 40% by weight of the section of treated tissue.

6. The prepared tissue of Claim 1, wherein the section of treated tissue is attached to a frame ex vivo for at least one of: (a) surgical use; or (b) percutaneous implantation.

7. The prepared tissue of Claim 1, wherein the section of treated tissue does not include a matrix that has been exposed to a polymer infiltrate.

8. The prepared tissue of Claim 1, wherein the section of treated tissue is unbraided and uncompounded.

9. The prepared tissue of Claim 1, wherein the section of treated tissue comprises an ultimate tensile strength of greater than about 25 MegaPascals.

10. The prepared tissue of Claim 9, wherein the section of treated tissue is unbraided and uncompounded.

11. The prepared tissue of Claim 1, wherein the section of treated tissue has been exposed to isopropyl alcohol before contacting the section of treated tissue with either glutaraldehyde or formalin.

12. The prepared tissue of Claim 1, wherein the section of treated tissue has been exposed to a solution containing formalin after pretreatment with isopropyl alcohol.

13. The prepared tissue of Claim 1, wherein the section of treated tissue has been exposed to a solution containing glutaraldehyde after pretreatment with isopropyl alcohol.

14. The prepared tissue of Claim 1, wherein the section of treated tissue comprises a pericardium tissue.

15. A prepared tissue for medical use with a patient, comprising:

a section of tissue harvested from a mammalian organism, wherein the section of tissue is prepared ex vivo for future grafting or implantation in the patient, the section of tissue

including a thickness of about 50 to 500 micrometers and an ultimate tensile strength of greater than about 25 MegaPascals.

16. The prepared tissue of Claim 15, wherein the section of tissue is unbraided and uncompounded.

17. The prepared tissue of Claim 15, wherein the section of tissue comprises a water content of less than about 40% by weight of the section of tissue.

18. The prepared tissue of Claim 15, wherein the section of tissue is attached to a frame ex vivo for at least one of: (a) surgical use; or (b) percutaneous implantation in the patient.

19. The prepared tissue of Claim 15, wherein the section of tissue does not include a matrix that has been exposed to a polymer infiltrate.

20. The prepared tissue of Claim 15, wherein the section of tissue comprises a treated pericardium tissue.

21. A method of preparing a tissue for medical use, comprising:

providing a section of tissue harvested from a mammalian organism; and

causing osmotic shocking of the section of tissue by performing multiple rinses of the section of tissue with distilled water.

22. The method of Claim 21, further comprising hydrating the section of tissue during a plurality of time intervals using distilled water.

23. The method of Claim 22, further comprising not using saline for causing at least one of the osmotic shocking and the hydrating of the section of tissue.

24. The method of Claim 21, further comprising pretreating the section of tissue with glycerol before contacting the section of tissue with one or more of isopropyl alcohol, glutaraldehyde and formalin.

25. The method of Claim 24, further comprising contacting the section of tissue with a solution containing formalin after pretreating the section of tissue with glycerol.

26. The method of Claim 24, further comprising contacting the section of tissue with a solution containing glutaraldehyde after pretreating the section of tissue with glycerol.

27. The method of Claim 21, further comprising pretreating the section of tissue with isopropyl alcohol before contacting the section of tissue with either glutaraldehyde or formalin.

28. The method of Claim 27, further comprising contacting the section of tissue with a solution containing formalin after pretreating the section of tissue with isopropyl alcohol.

29. The method of Claim 27, further comprising contacting the section of tissue with a solution containing glutaraldehyde after pretreating the section of tissue with isopropyl alcohol.

30. The method of Claim 21, further comprising exposing the section of tissue to light energy for a period of time, the period of time extending until there is no further visible separation of lipid droplets from an exposed surface of the section of tissue.

31. The method of Claim 30, wherein the light energy is at least equivalent to exposing the section of tissue to a 50 watt incandescent light source with a flat radiant face situated at a distance of about 10 centimeters from the exposed surface for about 15 minutes.

32. The method of Claim 21, wherein the section of tissue comprises a treated pericardium tissue.

33. A method of preparing a section of tissue for medical use, comprising:

(a) cleaning and decellularizing the section of tissue by performing multiple rinses of the section of tissue with distilled water;

(b) rinsing the section of tissue with isopropyl alcohol for a first period of time of not less than about 7 days; and

(c) contacting the section of tissue with one of

(i) a formalin solution, or

(ii) a glutaraldehyde solution

for a second period of time of not less than about 6 days;

wherein step (b) occurs sometime after step (a), and wherein step (c) occurs sometime after step (b).

34. The method of Claim 33, wherein for step (c):

if the formalin solution is used, then the formalin solution comprises a concentration of about 1 - 37.5% formalin; and

if the glutaraldehyde solution is used, then the glutaraldehyde solution comprises a concentration of about 0.1 - 25% glutaraldehyde.

35. The method of Claim 33, further comprising exposing the section of tissue to light energy for an exposure duration, the exposure duration extending until there is no further visible separation of lipid droplets from an exposed surface of the section of tissue.

36. The method of Claim 35, wherein the light energy is at least equivalent to exposing the section of tissue to a 50 watt incandescent light source with a flat radiant face situated at a distance of about 10 centimeters from the exposed surface for about 15 minutes.

37. The method of Claim 33, further comprising:

(d) rinsing the section of tissue with distilled water and isopropyl alcohol for a post-fixation period of time of not less than about 7 days;

wherein step (d) occurs sometime after step (c).

38. The method of Claim 33, wherein the section of tissue comprises an ultimate tensile strength of greater than about 25 MegaPascals.

39. The method of Claim 33, wherein the section of tissue comprises a treated pericardium tissue.

40. A method of preparing a section of tissue for medical use, comprising:

(a) contacting the section of tissue with distilled water;

(b) contacting the section of tissue with isopropyl alcohol for a pre-fixation period of time of not less than about 3 days; and

(c) contacting the section of tissue with one of

(i) a formalin solution, or

(ii) a glutaraldehyde solution

for a fixation period of time of not less than about 3 days; and

(d) contacting the section of tissue with isopropyl alcohol for a post-fixation period of time of not less than about 3 days;

wherein step (b) occurs sometime after step (a), wherein step (c) occurs sometime after step (b), and wherein step (d) occurs sometime after step (c).

41. The method of Claim 40, wherein for step (c):

if the formalin solution is used, then the formalin solution comprises a concentration of about 1 - 37.5% formalin; and

if the glutaraldehyde solution is used, then the glutaraldehyde solution comprises a concentration of about 0.1 - 25% glutaraldehyde.

42. The method of Claim 40, wherein for step (c):

if the formalin solution is used, then the formalin solution comprises a concentration of about 8-12% formalin; and

if the glutaraldehyde solution is used, then the glutaraldehyde solution comprises a concentration of about 0.1-0.5% glutaraldehyde.

43. The method of Claim 40, wherein the section of tissue comprises a treated pericardium tissue.

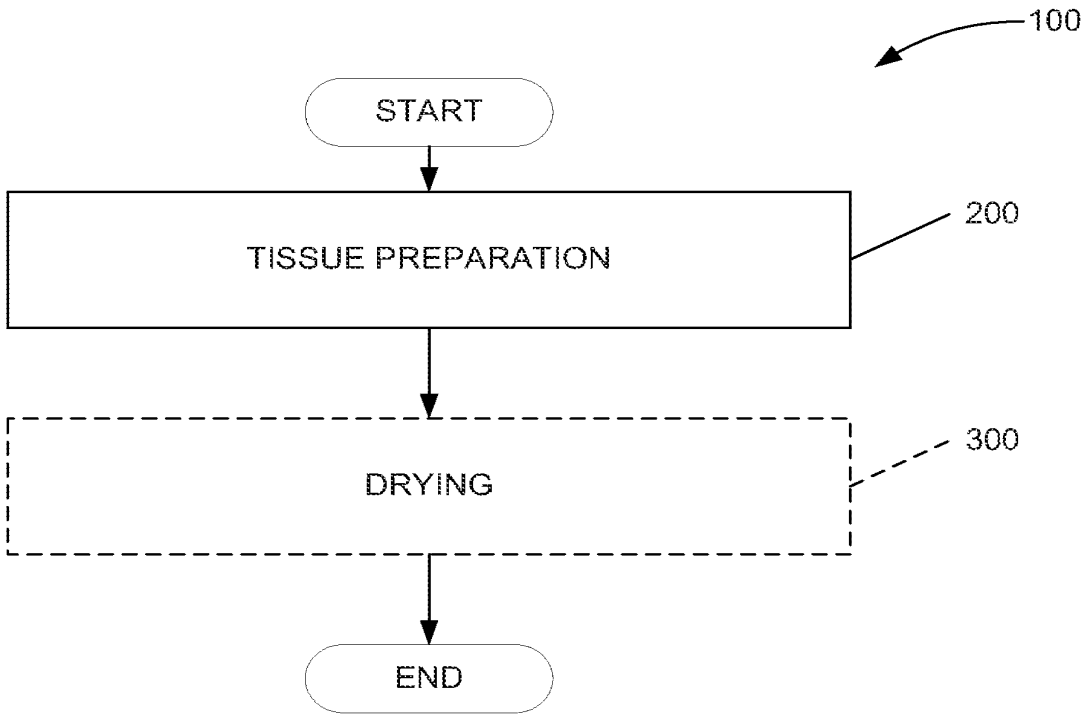


FIG. 1

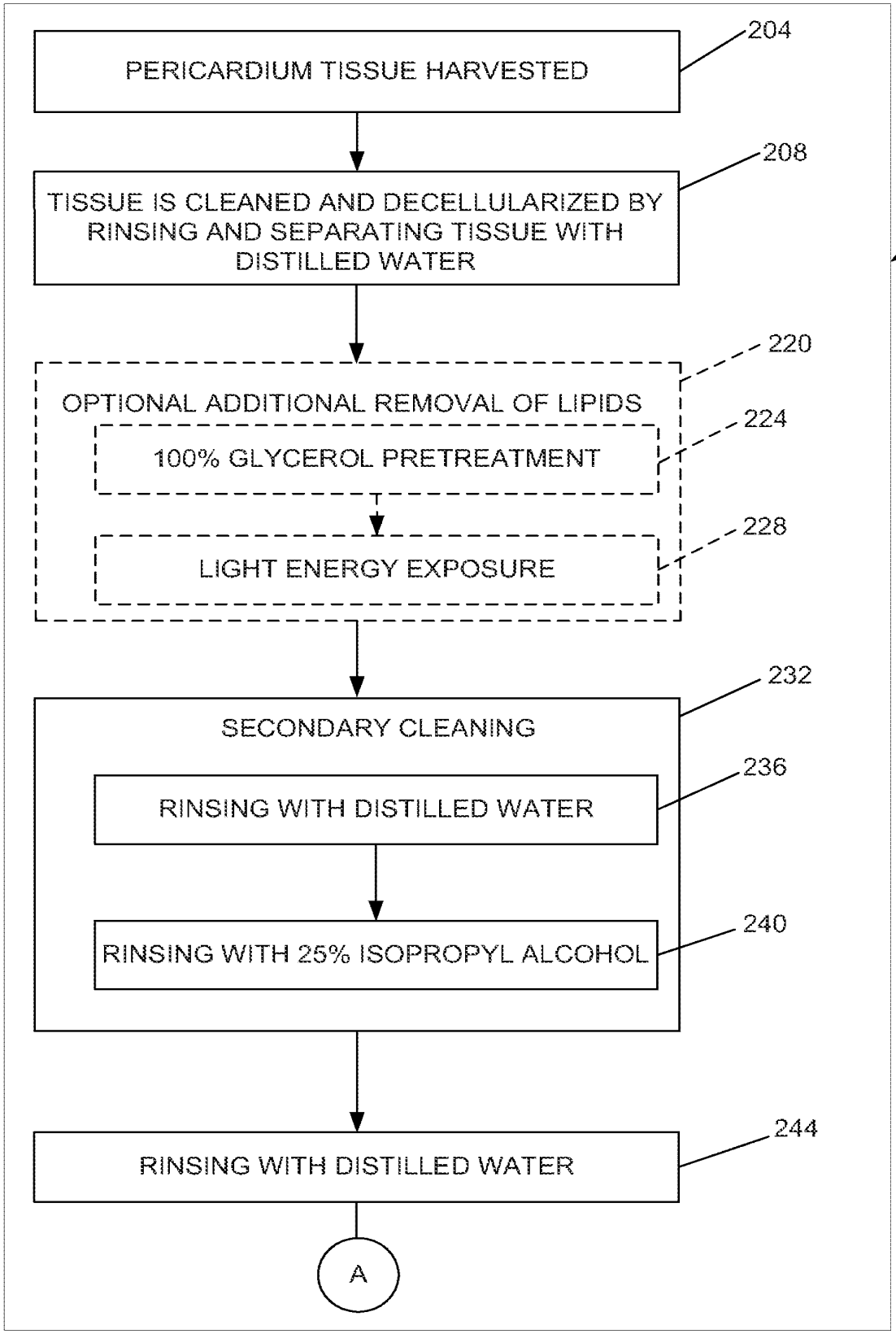

PERICARDIUM TISSUE HARVESTED
204
TISSUE IS CLEANED AND DECELLULARIZED BY RINSING AND SEPARATING TISSUE WITH DISTILLED WATER
208
200
OPTIONAL ADDITIONAL REMOVAL OF LIPIDS
220
100% GLYCEROL PRETREATMENT
224
LIGHT ENERGY EXPOSURE
228
SECONDARY CLEANING
232
RINSING WITH DISTILLED WATER
236
RINSING WITH 25% ISOPROPYL ALCOHOL
240
RINSING WITH DISTILLED WATER
244
A

FIG. 2A

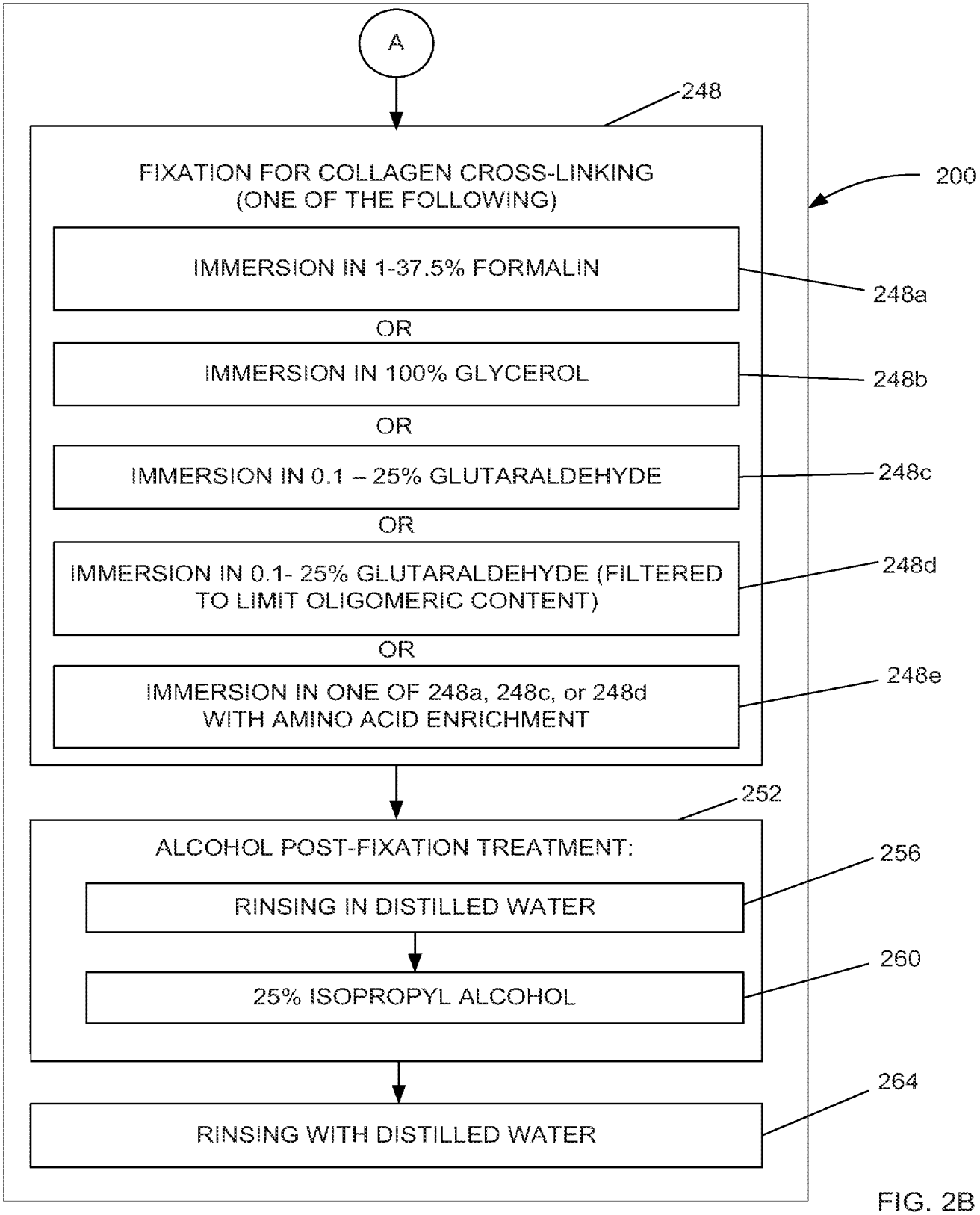

A
248
FIXATION FOR COLLAGEN CROSS-LINKING
(ONE OF THE FOLLOWING)
200
IMMERSION IN 1-37.5% FORMALIN
248a
OR
IMMERSION IN 100% GLYCEROL
248b
OR
IMMERSION IN 0.1 – 25% GLUTARALDEHYDE
248c
OR
IMMERSION IN 0.1- 25% GLUTARALDEHYDE (FILTERED TO LIMIT OLIGOMERIC CONTENT)
248d
OR
IMMERSION IN ONE OF 248a, 248c, or 248d WITH AMINO ACID ENRICHMENT
248e
252
ALCOHOL POST-FIXATION TREATMENT:
256
RINSING IN DISTILLED WATER
260
25% ISOPROPYL ALCOHOL
264
RINSING WITH DISTILLED WATER

FIG. 2B

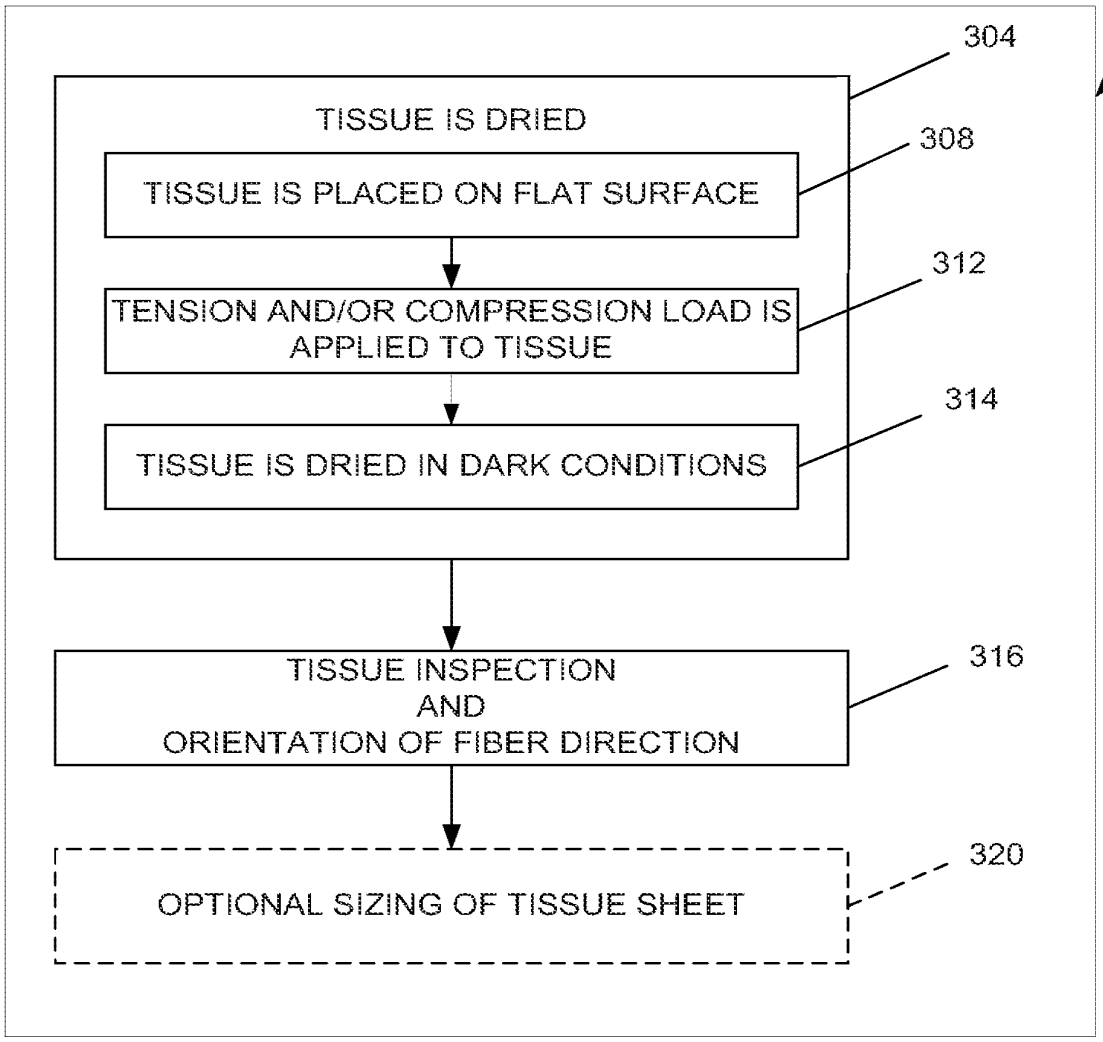

300
304
TISSUE IS DRIED
308
TISSUE IS PLACED ON FLAT SURFACE
312
TENSION AND/OR COMPRESSION LOAD IS APPLIED TO TISSUE
314
TISSUE IS DRIED IN DARK CONDITIONS
316
TISSUE INSPECTION AND ORIENTATION OF FIBER DIRECTION
320
OPTIONAL SIZING OF TISSUE SHEET

FIG. 3

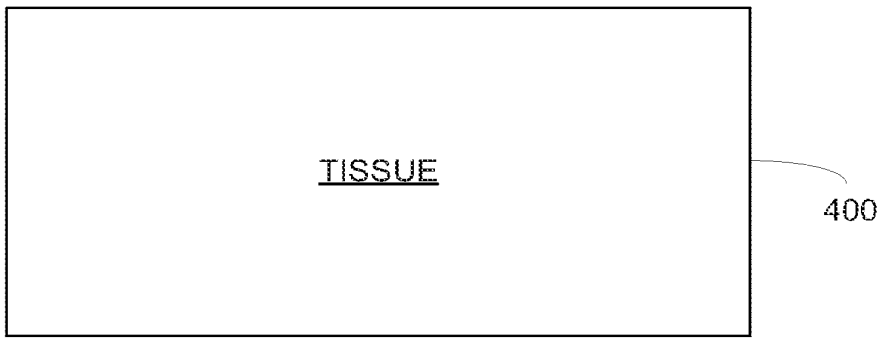
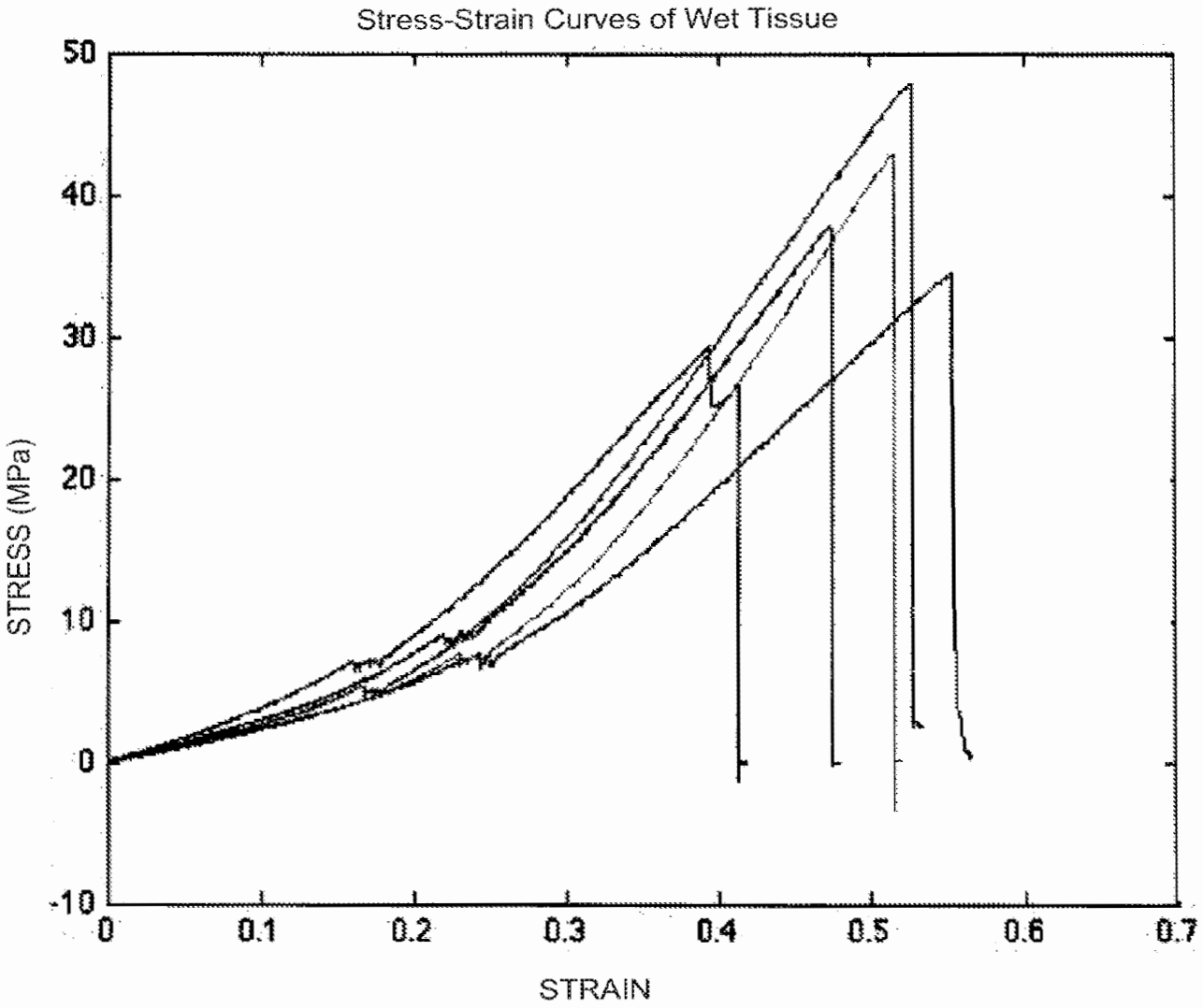

TISSUE
400

FIG.4



Stress-strain curves in wet or hydrated state of five samples. Each curve corresponds to a separate sample.

FIG. 5

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[Continued on next page]

(54) Title: PERCUTANEOUSLY DELIVERABLE HEART VALVE AND METHODS ASSOCIATED THEREWITH

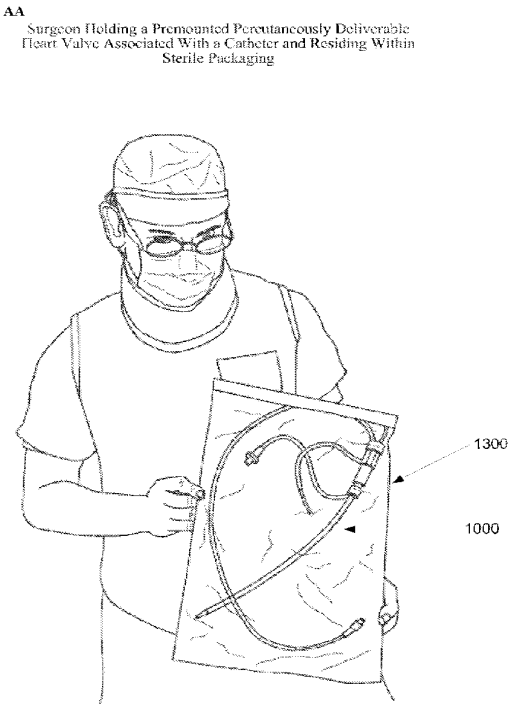

FIG.13

(57) Abstract: A prosthetic heart valve implantable by catheter without surgery includes a substantially "dry" membrane or tissue material. In at least one embodiment, the tissue is folded in a dry state to form a tissue leaflet assembly that is then attached to a frame to form an implantable prosthetic heart valve. Alternatively, one or more tissue leaflets are operatively associated with a frame to form an implantable prosthetic heart valve. The implantable prosthetic heart valve is subsequently pre-mounted on an integrated catheter delivery system. The catheter delivery system that includes the implantable prosthetic heart valve is then packaged and transported while the tissue remains dry. The implantable prosthetic heart valve, while remaining substantially dry, can then be implanted into the receiving patient.

WO 2011/109450 A2

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PERCUTANEOUSLY DELIVERABLE HEART VALVE AND METHODS ASSOCIATED THEREWITH

FIELD

The present invention relates to the field of medical devices, and more particularly, to a percutaneously deliverable heart valve and a method of making a percutaneously deliverable heart valve.

BACKGROUND

Heart valve disease is a common degenerative condition that compromises physiologic function and causes limiting symptoms and threat to life in millions of patients all over the world. There are various underlying causes, but malfunction of heart valves is ultimately expressed as insufficient conduction of blood through the plane of the valve due to narrowing of the anatomic pathway (stenosis), or as incompetent closure that allows blood to return back through the valve again, thereby reducing the effective forward conduction of blood through the valve (insufficiency or regurgitation). These hemodynamic states lead to 1) deficiency of cardiac output and 2) adverse loads on the pumping chambers of the heart, both of which in turn lead to functional compromise of the patient and often premature death unless effectively corrected.

Definitive corrective treatment of heart valve disease is conventionally performed by open-chest surgical techniques, wherein the valve is manipulated, repaired, or replaced with a prosthetic valve under direct vision. Heart valve surgery is performed in hundreds of thousands of cases yearly world-wide, but carries a high burden of cost, morbidity, and mortality, especially in susceptible patients who may be elderly or otherwise physiologically compromised by collateral disease. Further, the costs and resource requirements of the surgical enterprise restrict the availability of heart valve replacement to many more patients all over the world.

In pursuit of alternatives to heart valve surgery, over the last ten years a number of development programs have brought percutaneous, trans-catheter implantation of prosthetic heart valves into commercial use in the European Union (EU) and into pivotal clinical trials in the United States of America. Initial clinical experience in the EU was directed toward patients who had critical aortic valve stenosis, but were deemed to be at unacceptably high risk for open-heart surgical valve replacement. In several thousand such cases, utilizing both balloon-expandable and self-expanding designs in two separate programs, percutaneous heart valve replacement (PHVR) was shown to be feasible and possibly competitive with surgery in selected patients with 12-18 month mortality rates of about 25%. Grube E., et al., *Progress and Current Status of Percutaneous Aortic Valve Replacement: Results of Three Device Generations of the CoreValve Revalving System*, Circ. Cardiovasc Intervent. 2008;1:167-175.

The application of PHVR thus far has been challenged by the technical difficulties of the implantation sequence—especially in the aortic valve position. The technique for available devices is limited by the large caliber of the devices and their delivery catheters; often, if it can be done at all in some smaller arteries, open surgical exposure and management of the femoral artery is required to insert the 18 – 24 French (6 – 8 mm diameter) systems, and their bulkiness inside the central arteries can threaten the safety of the delivery sequence. Further, access site bleeding complications form a significant part of the adverse events of the procedures.

Typically, the current PHV designs comprise a biological membrane forming the operating leaflets of the valve, attached within a metal frame, that is then collapsed onto a delivery catheter or balloon, and then constrained within an outer sheath. After an initial dilation of the diseased valve with a large balloon, this assembly is then advanced to the plane of the valve and deployed by self-expansion or by balloon expansion.

The effective caliber of the valve delivery system is determined by the total bulk of each coaxially mounted component. The bulk of the PHV itself is determined by the diameter of the frame and by the thickness, stiffness, and particular arrangement of the inner membrane forming the operating leaflets of the valve. The characteristic thickness of current PHV membranes is thus a limiting factor in the ultimate delivery profile of the PHV. Such characteristic membrane thickness is, in turn, a result of the methods by which it is processed and ultimately delivered for use. Typically, glutaraldehyde fixation (for protein cross-linking) of animal tissue is employed to produce suitable biological membranes for incorporation. Requirements for strength and durability have determined the most useful ranges for tissue thickness and cross-linking while typically imposing countervailing stiffness and brittleness. Subsequent hydration in suitable solutions improves these characteristics, but the hydrated membrane by this means also gains thickness.

One of the evident requirements for a PHV design is that the valve functions with a high degree of competence immediately on deployment, since the patient's hemodynamic survival depends on it. To this end, in part, like surgical valve prostheses, current PHV designs are completed, transported, and delivered for use in a hydrated state in a jar of solution. In use, commercially available surgical and percutaneously implanted bioprosthetic heart valves are rinsed and prepared before use in a "wet" state. More particularly, commercially available prosthetic heart valves are rinsed, crimped, and mounted in the catheterization lab. Accordingly, problems with current commercially available prosthetic heart valves include the time, cost and variability associated with the necessity to rinse, crimp, and mount the valve in the catheterization lab. That is, current mounting of prosthetic heart valves in the catheterization lab imposes one or more of delay, cost, technical burdens and possible errors. Avoiding one or

more of these problems would be advantageous. In addition, current "wet" valve designs impose additional profile on the collapsed valve. The hydrated membrane, while having desirable and necessary flexibility for reliable operation immediately on deployment, also imposes a large part of the thickness of the assembled and mounted valve that compromises its deliverability.

Expanding on some of the problems described above, the use of current PHVs in the catheter lab requires a number of preparatory acts that are potentially troublesome and can prolong the delivery sequence during a critical phase of the procedure. Since PHVs are delivered for use "wet" in a preservative solution, they have to be treated prior to insertion with a series of cleansing and hydrating solutions. Once this is completed, the PHVs have to be mounted on their delivery catheters. Special crimping and mounting tools are needed in the case of the balloon-expandable Edwards Sapien valve, for example. Accordingly, there is a need to address the shortcomings discussed above.

SUMMARY

It is to be understood that the present invention includes a variety of different versions or embodiments, and this Summary is not meant to be limiting or all-inclusive. This Summary provides some general descriptions of some of the embodiments, but may also include some more specific descriptions of other embodiments.

In at least one embodiment, a substantially "dry" membrane PHV system is provided wherein a tissue material is prepared and folded in a dry state to form a tissue leaflet assembly. Thereafter, the tissue leaflet assembly is attached to a frame to form an implantable prosthetic heart valve that is subsequently pre-mounted in an integrated catheter delivery system. The catheter delivery system that includes the prosthetic heart valve is then packaged and transported while the tissue leaflet assembly remains substantially dry. The prosthetic heart valve is available for use directly out of its package envelope. Accordingly, it can be inserted into the body without need of hydration, crimping or mounting tools, or other preparatory acts. That is, the tissue forming the tissue leaflet assembly of the prosthetic heart valve can be treated and dried, then while remaining dry, folded into a tissue leaflet assembly. Thereafter, the tissue leaflet assembly is at least partially rehydrated and then attached within a frame, such as a stent, to form an implantable prosthetic heart valve. The tissue leaflet assembly of the prosthetic heart valve is then allowed to dry. The prosthetic heart valve can thereafter be subsequently packaged, delivered, and shipped while the tissue leaflet assembly of the prosthetic heart valve remains in a dry condition. The prosthetic heart valve can then be implanted into the receiving patient. Accordingly, the PHV system simplifies arterial insertion, and, as the dry condition also confers lower bulk and profile, procedural manipulation and associated complications may be

reduced if not eliminated. In addition, one or more embodiments of the present invention widen the candidacy of patients with smaller arteries for the PHV procedure. As an added advantage, at least one embodiment of the present invention allows the implantation to take place under shorten elapsed times at the most critical phase of the procedure.

In at least one embodiment, a membrane PHV system is provided wherein a tissue material is prepared and folded in a dry state to form a tissue leaflet assembly, and further wherein the tissue leaflet assembly is thereafter at least partially hydrated and attached to a frame that is subsequently pre-mounted in an integrated catheter delivery system.

In at least one embodiment, a membrane PHV system is provided wherein a tissue material is prepared and folded in a dry state to form a tissue leaflet assembly, and further wherein the tissue leaflet assembly is at least partially hydrated and attached to a frame to form the prosthetic heart valve. Thereafter, the prosthetic heart valve is allowed to dry and subsequently pre-mounted in an integrated catheter delivery system after which the tissue leaflet assembly of the prosthetic heart valve remains dry, and wherein the system is then associated with a package for shipment while the tissue leaflet assembly remains dry.

In at least one embodiment, a membrane PHV system is provided wherein a tissue material is prepared and then folded in a dry state to form a tissue leaflet assembly, and further wherein the tissue leaflet assembly is at least partially hydrated and attached to a frame to form the prosthetic heart valve. Thereafter, the prosthetic heart valve is allowed to dry and subsequently pre-mounted in an integrated catheter delivery system after which the tissue leaflet assembly of the prosthetic heart valve is then at least partially hydrated and associated with a package for shipment.

In at least one embodiment, an article adapted for trans-catheter delivery into a patient is provided, comprising: a prosthetic heart valve further comprising a treated tissue attached to a frame, wherein the treated tissue comprises a thickness of about 50 to 500 micrometers and an ultimate tensile strength of greater than about 15 MegaPascals when at a water content of less than about 50% by weight of the section of treated tissue. Here it is noted that the tensile strength of the treated tissue described herein is higher than the tensile strength of other known prepared tissues, whether hydrated or dry. In at least one embodiment, the water content of the treated tissue is less than about 40% by weight of the treated tissue. In at least one embodiment, the ultimate tensile strength is greater than about 20 MegaPascals. In at least one embodiment, the treated tissue does not include a matrix that has been exposed to a polymer infiltrate. In at least one embodiment the treated tissue comprises a treated pericardium tissue.

In at least one embodiment, the method further comprises exposing the section of tissue to light energy for an exposure duration, the exposure duration extending until there is no further

visible separation of lipid droplets from an exposed surface of the section of tissue. In at least one embodiment, the light energy is at least equivalent to exposing the section of tissue to a 25-100 watt light source, and more preferably, a 50 watt incandescent light source with a flat radiant face situated at a distance of about 10 centimeters from the exposed surface for about 15 minutes. In at least one embodiment, the method further comprises: (d) rinsing the section of tissue with distilled water and isopropyl alcohol for a post-fixation period of time of not less than about 7 days; wherein step (d) occurs after step (c).

In at least one embodiment, an article adapted for implantation in a patient is provided, comprising: a prosthetic heart valve further comprising a treated tissue attached to a frame, wherein the treated tissue comprises a water content of less than about 60% by weight of the treated tissue. In at least one embodiment, the treated tissue comprises a section of pericardium tissue having an ultimate tensile strength of greater than about 12 MegaPascals. In at least one embodiment, the section of treated tissue comprises a thickness of between about 50 to 300 micrometers. In at least one embodiment, the water content of the treated tissue is less than about 40% by weight of the treated tissue.

As used herein, the term "dry" (or "substantially dry") when referring to the state of the tissue that forms the heart valve of the percutaneous heart valve means a moisture content less than the water moisture content of the tissue when the tissue is allowed to fully rehydrate in the body of a patient. Typically, pericardium tissue treated in accordance with one or more embodiments described herein is about 70% by weight water when fully hydrated. Drying to a constitution of less than 40% by weight of water usefully alters the handling properties for purposes of folding and sewing the tissue. As those skilled in the art will appreciate, the moisture content of the tissue may vary when dry. For example, the moisture content of the tissue when being folded and dry may be different than the moisture content of the tissue when dry and being shipped in a premounted state within a catheter delivery system.

Advantageously, at least one embodiment of the one or more present inventions is directed to a prosthetic heart valve that is mounted onto a valve delivery system and stored in a sterile package. Accordingly, in at least one embodiment, an assembly is provided, comprising:

a prosthetic heart valve including:

a frame; and

a tissue leaflet assembly attached to the frame;

a percutaneously insertable valve delivery mechanism, wherein the prosthetic heart valve is releasably mounted onto the percutaneously insertable valve delivery mechanism; and

sterile packaging containing the prosthetic heart valve releasably mounted onto the percutaneously insertable valve delivery mechanism.

In at least one embodiment, the percutaneously insertable valve delivery mechanism comprises a balloon catheter. In at least one embodiment, the balloon catheter is a 12 to 14 French balloon catheter. In at least one embodiment, the balloon catheter is less than about 12 French. In at least one embodiment, the balloon catheter is between about 5 to 12 French. In at least one embodiment, the percutaneously insertable valve delivery mechanism comprises a mandrel. In at least one embodiment, tissue forming the tissue leaflet assembly within the sterile packaging is at least one of hydrated and not substantially dry. In at least one embodiment, tissue forming the tissue leaflet assembly within the sterile packaging is substantially dry. In at least one embodiment, the frame comprises a stent. In at least one embodiment, tissue forming the tissue leaflet assembly comprises treated pericardium tissue.

At least one embodiment of the one or more present inventions includes a prosthetic heart valve for implantation in a patient. Accordingly, a pre-packaged percutaneous, trans-catheter deliverable prosthetic heart valve ready for implantation in a patient is provided, comprising:

a frame; and,

a tissue leaflet assembly attached to the frame, the tissue leaflet assembly comprising a substantially dry tissue.

In at least one embodiment, the substantially dry tissue comprises treated pericardium tissue. In at least one embodiment, the frame and tissue leaflet assembly attached thereto are operably associated with a 12 to 14 French balloon catheter. In at least one embodiment, the frame and tissue leaflet assembly attached thereto are operably associated with a balloon catheter having a size of less than about 12 French. In at least one embodiment, the frame and tissue leaflet assembly attached thereto are operably associated with a balloon catheter having a size of between about 5 to 12 French. In at least one embodiment, the substantially dry tissue comprises a water moisture content of less than about 40% by weight of the substantially dry tissue.

In at least another embodiment, an assembly for use with a patient is provided, comprising:

a sealed sterile package containing a delivery system for percutaneously deploying a heart valve in the patient, the heart valve including:

a frame releasably mounted on the delivery system within the sealed sterile package; and

a tissue leaflet assembly attached to the frame.

In at least one embodiment, the tissue leaflet assembly comprises pericardium tissue.

In at least one embodiment, a method is provided, comprising:

partially compressing and mounting a prosthetic heart valve upon a delivery catheter, the

prosthetic heart valve comprising a tissue;

allowing the tissue to at least partially dry;

further compressing and mounting the prosthetic heart valve upon the delivery catheter; and

sterilizing and packaging the prosthetic heart valve and delivery catheter.

In at least one embodiment, the method further comprises transporting the sterilized and packaged prosthetic heart valve and delivery catheter. In at least one embodiment, the tissue comprises treated pericardium tissue. In at least one embodiment, prior to partially compressing and mounting the prosthetic heart valve upon the delivery catheter, the tissue is at least one of (a) not substantially dry, and (b) at least partially hydrated.

For the various embodiments described herein, the prosthetic heart valve, including the tissue leaflet assembly, comprises membrane tissue other than pericardium tissue.

In at least one embodiment, a method is provided, comprising:

attaching pericardium tissue to a frame;

partially compressing and mounting the frame, with the tissue attached thereto, upon a delivery catheter;

allowing the tissue to at least partially dry;

further compressing and mounting the frame, with the tissue attached thereto, upon the delivery catheter; and

sterilizing and packaging the frame and delivery catheter, with the tissue attached thereto.

In at least one embodiment, prior to partially compressing and mounting the frame, the tissue is at least one of (a) not substantially dry, and (b) at least partially hydrated. In at least one embodiment, the method further comprises transporting the sterilized and packaged frame, with the tissue attached thereto, mounted upon the delivery catheter, to a surgical or medical procedure facility. In at least one embodiment, prior to attaching the tissue to the frame the tissue is folded to form a tissue leaflet assembly. In at least one embodiment, the tissue leaflet assembly comprises at least one cuff and at least one pleat.

In at least one embodiment, a method of preparing a percutaneous, trans-catheter prosthetic heart valve is provided, the method comprising:

providing a membrane tissue from an organism;

treating the membrane tissue with at least one chemical to produce a treated membrane tissue;

drying the treated membrane tissue until it is a substantially dry tissue;

attaching the substantially dry tissue in a frame;

rehydrating the substantially dry tissue that is attached within the frame to form a rehydrated tissue;

collapsing the frame with the rehydrated tissue attached thereto; and

drying the rehydrated tissue within the collapsed frame until it is a substantially dry tissue.

In at least one embodiment the method further comprises compressing and mounting the frame, with the substantially dry tissue attached thereto, upon a delivery catheter. In at least one embodiment the method further comprises sterilizing and packaging the frame, with the substantially dry tissue attached thereto, mounted upon the delivery catheter. In at least one embodiment, the treating comprises sterilizing the frame with the substantially dry tissue attached thereto with exposure to at least one of ethylene oxide, a proton beam, and gamma radiation. In at least one embodiment, the method further comprises shipping the sterilized and packaged frame with the substantially dry tissue attached thereto, mounted upon the delivery catheter, to a surgery or medical procedure facility. In at least one embodiment, prior to the attaching step the dry tissue is not folded to provide a cuff and/or a pleat. In at least one embodiment, prior to the attaching step the dry tissue is folded to form a tissue leaflet assembly. In at least one embodiment, the tissue leaflet assembly comprises at least one cuff and at least one pleat.

In at least one embodiment, the method of preparing a percutaneous, trans-catheter prosthetic heart valve further comprises implanting the frame with the substantially dry tissue attached thereto into a patient. In at least one embodiment, the frame comprises a stent. In at least one embodiment, the method further comprises mounting the frame and the tissue leaflet assembly attached thereto upon a 12 to 14 French balloon catheter. In at least one embodiment, the method further comprises mounting the frame and the tissue leaflet assembly attached thereto upon a balloon catheter having a size of less than about 12 French. In at least one embodiment, the method further comprises mounting the frame and the tissue leaflet assembly attached thereto upon a balloon catheter having a size of between about 5 to 12 French. In at least one embodiment, the method further comprises mounting the frame and the tissue leaflet assembly attached thereto on a mandrel. In at least one embodiment, the method of preparing a percutaneous, trans-catheter prosthetic heart valve further comprises immersion of the membrane tissue in buffered or unbuffered 1-37.5% formalin for between about 3 days to 3 weeks. In at least one embodiment, the method of preparing a percutaneous, trans-catheter prosthetic heart valve further comprises immersion of the membrane tissue in buffered or unbuffered 1-37.5% formalin for between about 3 days to 5 weeks. In at least one embodiment the treating comprises immersion of the membrane tissue in 100% glycerol for greater than 3

weeks. In at least one embodiment the treating comprises immersion of the membrane tissue in 0.1 - 25% glutaraldehyde for between about 3 days to 3 weeks. In at least one embodiment the treating comprises immersion of the membrane tissue in 0.1 - 25% glutaraldehyde for between about 3 days to 5 weeks. In at least one embodiment the treating comprises immersion of the membrane tissue in oligomeric filtered 0.1 - 25% glutaraldehyde for between about 3 days to 3 weeks. In at least one embodiment the treating comprises immersion of the membrane tissue in oligomeric filtered 0.1 - 25% glutaraldehyde for between about 3 days to 5 weeks. In at least one embodiment the treating comprises immersion of the membrane tissue in the aforementioned formalin, glutaraldehyde, or oligomeric filtered glutaraldehyde solutions with the added free amino acids lysine and/or histidine. In at least one embodiment the treating does not include contact and/or exposure to a polymer to infiltrate and/or encapsulate tissue fibers of the tissue.

In at least one embodiment, a method of preparing a percutaneous, trans-catheter prosthetic heart valve is provided, the method comprising:

providing a section of tissue harvested from a mammalian organism; and

causing osmotic shocking of the section of tissue by performing multiple rinses of the section of tissue with distilled water. In at least one embodiment, the method further comprises hydrating the section of tissue during a plurality of time intervals using distilled water. In at least one embodiment the section tissue comprises pericardium tissue. In at least one embodiment, the method further comprises not using saline for causing at least one of the osmotic shocking and the hydrating of the tissue. In at least one embodiment, the method further comprises pretreating the section of tissue with glycerol before contacting the section of tissue with one or more of isopropyl alcohol, glutaraldehyde and formalin. In at least one embodiment, the method further comprises contacting the section of tissue with a solution containing formalin after pretreating the section of tissue with glycerol. In at least one embodiment, the method further comprises contacting the section of tissue with a solution containing glutaraldehyde after pretreating the section of tissue with glycerol. In at least one embodiment, the method further comprises pretreating the section of tissue with isopropyl alcohol before contacting the section of tissue with either glutaraldehyde and formalin. In at least one embodiment, the method further comprises contacting the section of tissue with a solution containing formalin after pretreating the section of tissue with isopropyl alcohol. In at least one embodiment, the method further comprises contacting the section of tissue with a solution containing glutaraldehyde after pretreating the section of tissue with isopropyl alcohol. In at least one embodiment, the method further comprises exposing the section of tissue to light energy for a period time, the period of time extending until there is no further visible separation

of lipid droplets from an exposed surface of the section of tissue. In at least one embodiment, the light energy is at least equivalent to exposing the section of tissue to a 50 watt incandescent light source with a flat radiant face situated at a distance of about 10 centimeters from the exposed surface for about 15 minutes.

With regard to delivery characteristics, another significant advantage of an implantable prosthetic heart valve using a relatively thin tissue component described herein is that the implantable prosthetic heart valve offers a relatively low packing volume as compared to commercially available prosthetic heart valves. As a result, the implantable prosthetic heart valve provides a relatively low catheter delivery profile, thereby enabling implantation in patients possessing relatively small diameter vascular systems.

In accordance with one or more embodiments, a dry tissue membrane has substantially less mass than a wet membrane. By way of example, a substantially dry pericardium tissue prepared by one or more of the present embodiments has approximately 30% of the mass of a wet pericardium tissue, and marked reduction in profile and packing volume, thereby achieving a relatively low profile and making it suitable for implantation in greater number of patients, especially those having small diameter vascular systems. In addition, a dry prosthetic heart valve does not require storage and transport in preservative. A dry prosthetic heart valve can be mounted on a delivery catheter at its location of manufacture, which allows for pre-packaging of an integrated delivery system. Together with a relatively low profile, embodiments of the prosthetic heart valves thereby offer reliability and convenience because the implantable prosthetic heart valve is pre-mounted upon a delivery catheter and forms part of a pre-packaged delivery system. In addition, a dry prosthetic heart valve does not require rinsing, rehydration, or mounting upon a delivery catheter in a catheterization lab. Therefore, a dry prosthetic heart valve can be inserted directly from package into the body at a critical time during the procedure. Advantageously, this avoids procedure time, manipulation, and errors of mounting, crimping, and orienting catheters and sheaths. Once at the surgical facility/location, the dry prosthetic heart valve is inserted and delivered by balloon catheter expansion in the plane of the diseased valve in the standard way and the dry prosthetic heart valve begins to function immediately, even in its dry state or not fully rehydrated state (because some rehydration will occur upon flushing of the catheter with the prosthetic heart valve residing therein), with rehydration of the tissue membrane subsequently completing naturally in the body.

Various components are referred to herein as "operably associated." As used herein, "operably associated" refers to components that are linked together in operable fashion, and encompasses embodiments in which components are linked directly, as well as embodiments in which additional components are placed between the two linked components.

As used herein, "at least one," "one or more," and "and/or" are open-ended expressions that are both conjunctive and disjunctive in operation. For example, each of the expressions "at least one of A, B and C," "at least one of A, B, or C," "one or more of A, B, and C," "one or more of A, B, or C" and "A, B, and/or C" means A alone, B alone, C alone, A and B together, A and C together, B and C together, or A, B and C together.

As used herein, "sometime" means at some indefinite or indeterminate point of time. So for example, as used herein, "sometime after" means following, whether immediately following or at some indefinite or indeterminate point of time following the prior act.

Various embodiments of the present inventions are set forth in the attached figures and in the Detailed Description as provided herein and as embodied by the claims. It should be understood, however, that this Summary does not contain all of the aspects and embodiments of the one or more present inventions, is not meant to be limiting or restrictive in any manner, and that the invention(s) as disclosed herein is/are understood by those of ordinary skill in the art to encompass obvious improvements and modifications thereto.

Additional advantages of the present invention will become readily apparent from the following discussion, particularly when taken together with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

To further clarify the above and other advantages and features of the one or more present inventions, a more particular description of the one or more present inventions is rendered by reference to specific embodiments thereof which are illustrated in the appended drawings. It is appreciated that these drawings depict only typical embodiments of the one or more present inventions and are therefore not to be considered limiting of its scope. The one or more present inventions is described and explained with additional specificity and detail through the use of the accompanying drawings in which:

Fig. 1 is a flow chart of a method associated with at least of one embodiment of the present invention;

Figs. 2A-2B are a flow chart illustrating elements of the tissue preparation;

Fig. 3 is a flow chart illustrating elements of the drying and sizing;

Fig. 4 is a flow chart illustrating elements of the valve construction with attachment of tissue membrane leaflets to a frame;

Fig. 5 is a flow chart illustrating elements of the mounting of the valve into a delivery system;

Fig. 6 is a flow chart illustrating elements of the ensheathing, sterilization, and packaging;

Fig. 7 is a flow chart illustrating elements of the delivery of the valve into a patient;

Fig. 8A is a view of a one-piece section of tissue prior to being folded;

Fig. 8B is a view of two (of three) separate pieces of tissue after folding (detailed below);

Fig. 8C is a view of the two pieces of tissue shown in Fig. 8B after being sutured together at the pleat formed after folding (detailed below);

Fig. 8D is a view of a tissue blank with the line of primary fold shown using a dashed line;

Fig. 8E is a perspective view of the tissue blank being folded along the primary fold line;

Fig. 8F is a 2-part figure showing the pleats fold lines and pleats after folding;

Fig. 8G is a detail perspective view of a single pleat shown in Fig. 8F;

Fig. 8H is a perspective schematic view of a folded and seamed tissue leaflet assembly;

Fig. 8I is a perspective schematic view of a frame;

Fig. 8J is a perspective schematic view of the frame of Fig. 8I with the tissue leaflet assembly of Fig. 8H attached thereto;

Fig. 8K is side elevation schematic view of the device shown in Fig. 8J;

Fig. 8L is an end schematic view of the frame and tissue leaflet assembly attached thereto;

Fig. 9 is a graph that shows actual stress-strain test results for five tissue samples prepared in accordance with at least one embodiment;

Fig. 10 is a schematic of a portion of a catheter with a percutaneously deliverable heart valve mounted thereto;

Fig. 11A is a photo of an implantable prosthetic heart valve, including a tissue leaflet assembly attached within a frame, wherein the tissue is situated in a partially open orientation;

Fig. 11B is a drawing of an implantable prosthetic heart valve, including a tissue leaflet assembly attached within a frame, wherein the tissue is situated in a closed orientation;

Fig. 11C is a side cutaway view of an implantable prosthetic heart valve, including a tissue leaflet assembly attached within a frame, wherein the tissue is situated in a closed orientation;

Fig. 11D is another side cutaway view of an implantable prosthetic heart valve, including a tissue leaflet assembly attached within a frame, wherein the tissue is situated in a closed orientation;

Fig. 12 is a photo of valve tissue after testing through 30,000,000 cycles of pumping used to model human heart conditions, wherein the photo shows a smooth uniform surface;

Fig. 13 is a drawing of a surgeon holding a premounted percutaneously deliverable heart valve associated with a catheter and residing within sterile packaging;

Fig. 14 is a schematic of a simplified cutaway view of a human heart, including heart valves that may be targeted for receiving an embodiment of an implantable prosthetic heart valve;

Fig. 15 is a schematic of a human aorta receiving a catheter with an implantable prosthetic heart valve mounted thereto; and

Fig. 16 is a schematic of a human aorta with the implanted prosthetic heart valve implanted at the site of the original diseased aortic valve.

The drawings are not necessarily to scale.

DETAILED DESCRIPTION

Embodiments of the one or more inventions described herein include one or more devices, assemblies and/or methods related to a prosthetic heart valve. A prosthetic heart valve in accordance with at least one embodiment described herein can be surgically implanted, such as by percutaneous, trans-catheter delivery, to the implantation site within the patient. One or more embodiments of the prosthetic heart valves described herein have application for at least aortic and pulmonary valve positions, including for structural defects and diseased valves.

In at least one embodiment, biocompatible material is attached within a frame to form an implantable prosthetic heart valve, and then at a later time, the implantable prosthetic heart valve is implanted within a patient, such as by way of a percutaneous, trans-catheter delivery mechanism. Once implanted, the prosthetic heart valve serves to regulate the flow of blood associated with the patient's heart by allowing forward blood flow and substantially preventing backflow or valvular regurgitation.

Referring now to Fig. 1, a flow chart illustrates at least one embodiment of a prosthetic heart valve preparation and delivery method 100. The prosthetic heart valve preparation and delivery method 100 generally includes a plurality of procedures to include tissue preparation at 200, drying at 300, tissue leaflet assembly construction and attachment to frame at 400 to form an implantable prosthetic heart valve, mounting of the prosthetic heart valve (that is, the frame with the tissue leaflet assembly) into a delivery system at 500, ensheathing, sterilizing and packaging the delivery system including the prosthetic heart valve at 600, and finally, delivering the prosthetic heart valve into the patient at 700. Further detail of the prosthetic heart valve preparation and delivery method 100 is provided below.

At least one or more embodiments described herein include a relatively thin tissue component. By way of example and not limitation, in at least one embodiment the tissue has a thickness of approximately 50 - 150 μm, and further possesses characteristics of pliability and resistance to calcification after implantation. The relatively thin nature of the tissue used in the implantable prosthetic heart valve assists with biocompatibility. In addition, the relatively thin

tissue component thereby provides for a relatively low mass. As a result, an implantable prosthetic heart valve using the tissue can accelerate to a relatively high heart rate in beats per minute with competent function.

Tissue suitable for use in the one or more prosthetic heart valves and/or one or more assemblies described herein is relatively thin and can generally be considered to be a membrane. Those skilled in the art will appreciate that both natural and synthetic types of materials may be used to form a leaflet assembly of a prosthetic heart valves. Accordingly, it is to be understood that although treated pericardium tissue is described as a suitable material for use in the leaflet assembly of a prosthetic heart valve of one or more embodiments described herein, material other than xenograft tissue membrane can be used, and indeed, xenograft tissue membrane other than pericardium tissue can be used. More specifically, synthetic materials may include, but are not limited to, PTFE, PET, Dacron, and nylon. In addition, other than pericardium tissue, xenograft tissue membrane may include, but is not limited to, membrane material from the intestine, lung and brain. Suitable material may also comprise allograft material, that is, material from human sources. The listing of possible materials is for exemplary purposes and shall not be considered limiting.

With reference now to Fig. 2A, the process associated with preparation of a biocompatible tissue consistent with the above-noted characteristics is described. In at least one embodiment, pericardium tissue, such as porcine or bovine pericardium tissue, is harvested at 204 and then processed to serve as the biocompatible tissue for association with a frame, such as by attaching within a frame. Accordingly, subsequent to the harvesting at 204, the pericardium tissue is cleaned and decellularized at 208. More particularly, in at least one embodiment the tissue is initially cleaned with distilled water using gentle rubbing and hydrodynamic pressure at 208 in order to remove adherent non-pericardial and non-collagenous tissue. In at least one embodiment, the hydrodynamic pressure at 208 is provided by spraying the tissue with a relatively weak stream of liquid to remove at least some of the non-collagenous material associated with the tissue. The rinsing at 208 is to achieve effective decellularization of the pericardium tissue through osmotic shock. Typically, the thickness of the tissue in the cleaned condition varies from about 50 to 500 micrometers, depending on the source of raw tissue. Cleaning preferably continues until there is no visible adherent non-pericardial or non-collagenous tissue.

With continued reference to Fig. 2A, after the tissue has been cleaned and decellularized at 208, the tissue then undergoes optional additional removal of lipids at 220 to further treat the tissue for preventing immunologic response and calcification. More particularly, the tissue first optionally undergoes a 100% glycerol pretreatment at 224 while being positioned on a flat

surface (e.g., an acrylic plate), after which the tissue becomes nearly transparent.

At 228, the tissue optionally undergoes a "thermophotonic" process. In at least one embodiment, the tissue is optionally exposed to light energy for additional removal of lipids and for initial cross-linking of the collagen. By way of example and not limitation, in at least one embodiment a 25-100 watt incandescent light source, and more preferably, a 50 watt incandescent light source with a flat radiant face is employed at a distance of about 10 centimeters from the tissue surface, typically requiring 15 minutes of exposure before further visible separation of lipid droplets from the tissue stops.

Still referring to Fig. 2A, the tissue is then cleaned again in secondary cleaning at 232. More particularly, at 236 the tissue is again rinsed with distilled water. Thereafter, at 240 the tissue is rinsed with 25% isopropyl alcohol for periods of several hours to several days and weeks, depending on the desired tissue properties of pliability and tensile strength. By way of example and not limitation, tissue has been successfully prepared by rinsing with 25% isopropyl alcohol for a period of 7 days, and after further treatment steps described herein, provided an ultimate tensile strength of greater than 25 MegaPascals. Here, the combination of tissue pliability and tensile strength is sought for purposes of producing a material having property characteristics suitable for being physically manipulated to form a tissue leaflet assembly or other configuration appropriate for attaching with a frame, while providing a tissue material that will operate properly once implanted. These techniques are intended to conserve and preserve collagen fibers, minimizing damage to the tissue and improving tissue characteristics. The preparation and fixation techniques produce tissue membrane material that may be rendered and used at lesser thickness than typically rendered in the prior art. Thinner membranes are more pliable, but with conventional preparation techniques the tensile strength of the tissue is sacrificed. Advantageously, the preparation techniques described herein have produced membranes that have as much as three times the tensile strength of a commercial product of the prior art. This achieved strength is thus enabling for providing a tissue leaflet assembly having a low profile with appropriate durability, even in a substantially dry state. More particularly, the tissue possesses a relatively high tensile strength. By way of example and not limitation, testing has shown that embodiments of tissue prepared as described herein provide a tissue with a tensile strength of approximately three times the tensile strength of current pericardial valve tissue, such as on the order of approximately 25 MegaPascals, thereby providing about 2000 times the physiologic load strength for valve tissue. Moreover, testing of an embodiment of an implantable prosthetic heart valve made with tissue prepared as described herein and under a static load of greater than approximately 250 mmHg showed less than approximately 14% leakage, wherein such results are generally considered superior to surgical tissue valve

prostheses.

In at least one embodiment where isopropyl alcohol is described as a rinsing agent, ethanol may be used in its place as an alternative, although resulting tissue properties may vary.

With reference to Fig. 9, stress-strain curve results for five different tissue samples prepared in accordance with an embodiment are shown. For the testing results shown, the yield stress or ultimate tensile strength was obtained by mounting strips of tissue fixed at the ends in a linear force tester and increasing the length by 0.3 mm/sec while recording resultant force (tension) until the material ruptured or separated entirely; these measurements were then used to calculate the stress-strain curves depicted in Fig. 9. As illustrated in the graph, the yield stress or ultimate tensile strength of the various tissue samples varied from about 30 to about 50 MegaPascals. More particularly, for each curve shown in Fig. 9, the testing procedures were the same. That is, each of the curves shown pertain to separate pieces of tissue that were subjected to the same test. The results show a minimum ultimate tensile strength of 30 MegaPascals, with a range up to 50 MegaPascals. Accordingly, the illustrated test results demonstrate consistency of the ultimate tensile strength results for the tissue treatment process.

With reference back to Fig. 2A, the tissue is rinsed with distilled water at 244 as a final cleaning step and for rehydration.

Referring now to Fig. 2B, following the rinse with distilled water at 244, treatment of the tissue continues. More particularly, fixation for collagen cross-linking at 248 is achieved by performing at least one of the following:

a. At 248a, immersion of the tissue in 1-37.5% formalin, ideally a buffered solution, for between about 3 days to 5 weeks, and more preferably, for between about 3 days to 4 weeks, and more preferably yet, for between about 3 weeks to 4 weeks, at a temperature of between about 4 to 37°C, and more preferably, 10% formalin for 6 days at 20°C; or

b. At 248b, immersion of the tissue in 100% glycerol for up to 6 weeks at between 4 to 37°C, and more preferably, immersion of the tissue in 100% glycerol for about 3 weeks at 20°C; or

c. At 248c, immersion of the tissue in 0.1 - 25% glutaraldehyde for between about 3 days to 5 weeks, and more preferably, for between about 3 days to 4 weeks, and more preferably yet, for between about 3 weeks to 4 weeks, at 0 to 37°C, and more preferably, immersion of the tissue in 0.25% glutaraldehyde for 7 days at 4°C; or

d. At 248d, immersion of the tissue in 0.1 - 25% glutaraldehyde (filtered to limit oligomeric content) for between about 3 days to 5 weeks, and more preferably, for between about 3 days to 4 weeks, and more preferably yet, for between about 3 weeks to 4 weeks, at 0 to 37°C, and more preferably, 0.25% glutaraldehyde for 7 days at 4°C; or

e. At 248e, immersion in the tissue in one of the above formalin, glutaraldehyde, or oligomeric filtered glutaraldehyde solutions together with added amino acids, lysine and/or histidine, wherein the concentration of the amino acids, L-lysine or histidine, used as an additive to the fixative is in the range of about 100 - 1000 milliMolar, with a preferred value of about 684 mM.

In addition to the foregoing, combinations of the processes listed above may be performed, including: step a followed by step b; step a followed by step c; and step a followed by step d.

As those skilled in the art will appreciate, heat-shrink testing may be conducted on tissue samples to correlate the effectiveness of protein cross-linking. Here, results of heat-shrink testing performed on one or more samples of tissue prepared in accordance with at least one embodiment using formalin showed that the tissue had a shrink temperature of 90°C. This compares favorably with samples prepared using glutaraldehyde, wherein the shrink temperature was 80°C. Accordingly, formalin is a suitable variant of fixation. It is noted that formalin was generally abandoned by the field, largely because of material properties that were unfavorable and because of inadequate or unstable protein cross-linking. Such problems have been overcome through the pretreatments described herein, allowing production of tissue with strength, pliability, and durability in a relatively thin membrane. When used in a percutaneous deliverable heart valve (also referred to herein as "prosthetic heart valve"), the tissue characteristics imparted by the tissue preparation process facilitate formation of a construct having a relatively low-profile, which also thereby facilitates dry packaging of the prosthetic heart valve. The same advantages are also achieved using the pretreatments when using a glutaraldehyde process.

Referring still to Fig. 2B, after fixation for collagen cross-linking at 248, an alcohol post-fixation treatment at 252 is preferably performed by rinsing the tissue in distilled water at 256, and then at 260 rinsing the tissue in 25% isopropyl alcohol for between about 30 minutes to 14 days or more at between about 0 to 37°C, and more preferably, for at least about 7 days at 20°C. At 264, the tissue undergoes a rinsing with distilled water.

In accordance with at least one embodiment, treatment of the tissue, including from the time of harvest to the time of implantation or grafting, does not include contact and/or exposure to a polymer to infiltrate and/or encapsulate tissue fibers of the tissue.

Referring now to Figs. 1 and 3, the drying process at 300 is performed after the tissue preparation at 200. Thus, in accordance with at least one embodiment, the tissue is dried under a load. More particularly, for the tissue drying at 304, the tissue is placed minimally stretched flat (that is, stretched just enough to eliminate visible wrinkles and bubbles) on a flat surface (e.g., a polymer or acrylic sheet) at 308, and held fixed at its edges at 312. Optionally, the joined tissue

and underlying sheet are then set in a slight curve. The tension maintains the substantially flat structure of the tissue as it dries, thereby mitigating or preventing excessive shrinkage, wrinkling, and/or curling at the edges, and also making the rate of drying more uniform across the surface of the tissue because of the surface tension between the plate and the tissue. Alternatively, the tissue is dried while compressed between acrylic plates. When drying the tissue, the temperature is held at between about 4 to 37°C, and more preferably, between about 20 to 37°C (i.e., approximately room temperature to normal human body temperature), and more preferably, at about 20°C. At 314, the drying process is performed in substantially dark conditions (i.e., substantially no visible light) for between about 6 hours to 5 days, and more preferably, for about 72 hours. By way of example, the tissue is dried in dark conditions at a temperature of about 20°C for between about 6 hours to 5 days, and more preferably, for about 72 hours. As those skilled in the art will appreciate, drying the tissue while the tissue is compressed between plates requires a longer period of time.

In at least one embodiment, after drying, the tissue lots are inspected at 316, such as by stereomicroscopy, to identify and discard those with defects or discontinuities of the fiber matrix. In addition, the preferential fiber direction for each piece is identified to determine the necessary orientation of the free edge of the pieces that will form the valve leaflets. Depending upon the size (i.e., the area) of the tissue being prepared and the size of tissue needed for a given valve, the tissue may be trimmed or otherwise sized in optional sizing at 320, such as by cutting the tissue into an appropriately sized and shaped sheet for valve formation. Preferably, cutting of the tissue membrane is oriented so that the resulting free edge of the leaflet is parallel to the preferential fiber direction of the tissue membrane. Optionally, the free edge of the leaflets may also be cut with a parabolic or other curved profile to compensate for the downward angle from the commissural leaflet attachment point to the central coaptation point and to increase the total contact surface between the coapting leaflets. This approach minimizes focal weaknesses in the operating margins of the leaflet assembly and advantageously distributes the principal loading forces of the operating valve along the long axis of the collagen fibers. As a result, the tissue is resistant to surface fracture and fraying. As shown in Fig. 3, optional sizing at 320 is performed after the drying at 304 and inspection at 316.

With reference now to Fig. 4, an embodiment associated with forming a tissue leaflet assembly and attachment to a frame to form a prosthetic heart valve at 400 is further described. It is to be understood that the tissue generated from one or more of the tissue preparation procedures described herein may be used for a variety of devices or uses, and that use in a prosthetic heart valve is but one possible application for utilizing the tissue. For example, the tissue may be used in a shunt, or as graft material for repair or modification of one or more

human organs, including the heart and its blood vessels. By way of further example, the tissue may be used as a pericardial membrane patch for repair of congenital heart defects. The tissue also has application as a prosthetic tissue in tendon and ligament replacement, and as a tissue product for wound management. Moreover, for use in a prosthetic heart valve, the tissue may be configured in a variety of ways and attached to a frame in a variety of ways. By way of example and not limitation, in at least one embodiment, the prepared tissue is formed into a tissue leaflet assembly at 404 by folding the tissue at 408, preferably while the tissue is in a dry state, to form at least a portion of the tissue leaflet assembly. Here, those skilled in the art will appreciate that a completed tissue leaflet assembly may be formed of a single monolithic piece of tissue 800, such as that shown in Fig. 8A, or alternatively, as shown in Figs. 8B and 8C, it may be formed of a plurality of tissue pieces 802 that are operatively connected, such as by gluing or sewing the tissue pieces together along seams 804. As seen in Fig. 8C, the seams 804 are preferably situated at overlapping portions of pleats 832 of the plurality of tissue pieces 802.

As those skilled in the art will further appreciate, a single monolithic piece of tissue 800 or a plurality of tissue pieces 802 may be used to form a prosthetic heart valve, wherein the tissue leaflet assembly is not a folded construct. By way of example and not limitation, a plurality of separate tissue pieces may each be attached to a frame (such as by suturing) to form a prosthetic heart valve. Thereafter, whether the prosthetic heart valve is made of a folded tissue leaflet assembly or a plurality of separate tissue pieces attached to a frame, the resulting prosthetic heart valve may then be further manipulated for delivery as a dry prosthetic heart valve.

In an alternative embodiment, tissue generated from one or more of the tissue preparation procedures described herein may be used to form a prosthetic heart valve that includes a frame, and that may be implanted by a "trans-apical" approach in which the prosthetic heart valve is surgically inserted through the chest wall and the apex of the heart.

In yet another alternative embodiment, tissue generated from one or more of the tissue preparation procedures described herein may be used to form a prosthetic heart valve that does not include a frame, and is not delivered via a catheter, but rather, is implanted via a surgical opening through the patient's chest. In such a case, the prosthetic heart valve may be packaged for delivery as a dry prosthetic heart valve.

In still yet another alternative embodiment, tissue generated from one or more of the tissue preparation procedures described herein may be used to form a prosthetic heart valve that includes a frame, but that is not delivered via a catheter, but rather, is implanted via a surgical opening through the patient's chest. In such a case, the prosthetic heart valve may be packaged for delivery as a dry prosthetic heart valve.

As a further alternative to the embodiments described herein, tissue may be implanted in a "wet" or hydrated state. For example, a prosthetic heart valve utilizing a prepared tissue described herein may be packaged for delivery as a hydrated prosthetic heart valve. Accordingly, while a portion of the tissue preparation process may include drying the tissue so that it may be manipulated more easily, the tissue may then be hydrated at a later point in time prior to implantation, and it may be maintained in a hydrated condition up to and including packaging, delivery and implantation into a patient. Advantages associated with using a folded tissue leaflet assembly include that a folded structure allows a relatively thin membrane to be used by avoiding suture lines in loaded, dynamically active surfaces. Accordingly, a sutureless leaflet assembly preserves long-term integrity. However, it is to be understood that a prosthetic heart valve that does not include a folded tissue leaflet assembly is encompassed by one or more embodiments described herein.

With reference now to Figs. 8D-8L, and in accordance with at least one embodiment, for a prosthetic heart valve that includes a tissue leaflet assembly formed of a folded tissue membrane, the folding sequence for the tissue is shown for configuring the tissue into a completed tissue leaflet assembly. More particularly, a tissue blank 808 is shown in Fig. 8D, wherein the tissue blank 808 is a single monolithic piece of tissue 800. Depending upon the size requirements for a given tissue leaflet assembly, a line of primary fold or fold line 812 (shown as a dashed line) is visualized for the tissue blank 808. As shown in Fig. 8D, the primary fold 814 is achieved along the fold line 812 by folding the bottom edge 816 of the tissue blank 808 toward the top edge 820, but leaving a cuff portion 824 along the upper portion 828 of the tissue blank 808. Here, it is noted that the direction of top and bottom are relative to each other and are used as a convenience for describing the folding sequence, wherein such directions correspond to the orientation of the page illustrating the drawings. Advantageously, the folding geometry of Figs. 8D-8L forms cuffs 824 that are continuous with the leaflets, thereby reducing the risk of aortic insufficiency or leakage.

With reference now to Fig. 8F, after folding the tissue blank 808 along fold line 812 to form primary fold 814, pleats are formed by folding the tissue along its length. For the embodiment shown in Fig. 8F, three pleats 832a, 832b, and 832c are shown. Fig 8G illustrates a detail drawing of a single pleat 832 representative of one of pleats 832a-c. In Fig. 8G, the inner leaflet layer free edge 836 is shown, as is the valve sinus 840 and the commissure folds 844.

Referring again to Fig. 4 as well as Fig. 8H, at 412 the folded tissue is seamed to form a folded tissue leaflet assembly. More particularly, Fig. 8H shows a schematic perspective drawing of tissue leaflet assembly 848, wherein the pleated tissue construct shown in the bottom half of Fig. 8F is seamed, such as along seam 850, to form a substantially tubular construct. At

416, the folded tissue leaflet assembly 848 is maintained dry or is partially hydrated prior to mounting the tissue leaflet assembly in a frame. At 420, the tissue leaflet assembly 848 is then attached within a frame, such as frame 852 shown in Fig. 8I. The tissue leaflet assembly 848 attached within a frame 852 forms an implantable prosthetic heart valve 860, such as that shown in the schematic perspective drawing of Fig. 8J, side elevation view Fig. 8K, as well as that shown in the photo of Fig. 11A, and drawing of Fig. 11B. Fig. 8K illustrates possible suture points 864 where the tissue leaflet assembly 848 can be sutured to the frame 852. That is, the tissue leaflet assembly 848 may be attached within the frame 852, such as by suturing the outer layer of the tissue leaflet assembly 848 to the frame. In the foregoing sentence, and as used herein, it is noted that the term "attached" means that the tissue leaflet assembly 848 is secured to the frame 852, although the inner leaflet layer free edges 836 are able to readily move during operation of the prosthetic heart valve 860.

Referring now to Fig. 11C, a cutaway side elevation view of a prosthetic heart valve 860 that includes a frame 852 with a tissue leaflet assembly 848 attached therein is shown. The tissue membrane leaflet assembly 848 is disposed coaxially within the frame 852. As shown in Fig. 11C, the valve 860 is illustrated in the closed position with the leaflet free edges 836 in at least partial contact with each other. An arc 1112 of the leaflet free edges 836 (out of plane of the cutaway view) is continuous with pleats 832 at the radial edge of the tissue leaflet assembly 848, and may be seen in the alternate view shown in Fig. 8L. The tissue membrane leaflet assembly 848 is attached to the frame 852 along the axially oriented membrane pleats 832, as illustrated again in Fig. 8L. The extended cuff layer is attached circumferentially at the distal edge 1104 of the frame 852. By way of example and not limitation, continuous suture attachment 1108 may be used to attach the extended cuff layer to the distal edge 1104.

Referring now to Fig. 11D, an embodiment is shown wherein the cuff layer is not extended distally to the distal edge 1104 of the frame 852. As shown in Fig. 11D, the distal edge of the cuff layer is attached circumferentially to an inner aspect of the frame 852, such as along those possible suture points 864 illustrated in Fig. 8K. As a result, a distal portion 1116 of the frame 852 does not include any portion of the tissue leaflet assembly 848, such as the cuff layer. However, with the valve 860 in the closed position the leaflet free edges 836 still at least partially contact each other.

With reference now to Fig. 8L, an end view of the prosthetic heart valve is shown. As depicted in Fig. 8L, the pleats 832 are used as the portion of the tissue leaflet assembly 848 to attach to the frame 852. As can be seen in Fig. 8L, the outer cuff layer is attached to the frame members of frame 852. When the prosthetic heart valve 860 is closed, the cusps 868 formed by the inner leaflet layer are generally situated as depicted in Fig. 8L. Fig. 12 is a photo of the

tissue leaflets of a prosthetic heart valve after 30,000,000 cycles of testing to model performance if associated with a human heart. In testing, the prosthetic heart valve 860 has demonstrated a natural opening gradient of approximately 5 mmHg.

It will be appreciated by one of ordinary skill in the art that the tissue leaflet assembly 848 described and shown herein is but one possible construct for forming a flow control mechanism that can be attached to a frame to regulate the flow of blood in a patient's vascular system upon deployment. That is, the illustrated tissue leaflet assembly 848 is provided by way of example and not limitation, and in no way should be interpreted to limit the geometries of membrane leaflet assemblies that can be used to regulate fluid flow. Accordingly, other leaflet configurations and constructs are considered encompassed by claims directed to or otherwise including premounted percutaneously deliverable valves.

As those skilled in the art will appreciate, the frame 852 may be a stent or a structure having similarities to a stent. The frame 852 essentially serves as a holding mechanism for the tissue leaflet assembly 848 that can then be inserted percutaneously into a patient, wherein the frame 852 serves as a way to anchor the folded tissue leaflet assembly 848 to a vascular portion (e.g., *in situ* arterial tissue) of the patient. Thus, at 424 the tissue leaflet assembly 848 is inserted into a frame 852. More particularly, at 424a the frame 852 may comprise a balloon-expandable frame, or alternatively, at 424b a self-expanding frame may be used. After the tissue leaflet assembly is inserted into the frame, at 428 the folded tissue leaflet assembly 848 is attached to the frame 852, such as by suturing the tissue leaflet assembly 848 to the frame 852 to form an implantable prosthetic heart valve 860, such as that shown in Fig. 8L. In at least one embodiment, after attaching the tissue leaflet assembly 848 within the frame 852 and connecting the tissue leaflet assembly 848 to the frame 852 to form an implantable prosthetic heart valve 860, at 432 the prosthetic heart valve 860 is fully hydrated for inspection and testing. Thereafter, the fully constructed implantable prosthetic heart valve 860 may be dried and maintained in a substantially dry condition. Accordingly, as those skilled in the art will appreciate, one or more embodiments described herein provide a tissue 800 suitable for implanting in a human, wherein the implantable tissue may be allowed to dry prior to implanting, or it may be hydrated prior to implanting. In addition, the tissue 800 is suitable for use in forming a tissue leaflet assembly 848 for use in a prosthetic heart valve, including an implantable prosthetic heart valve 860 that can be implanted with its tissue leaflet assembly in a dry state, or with its tissue leaflet assembly in a partially or fully hydrated state.

One or more of the embodiments of the tissue leaflet assemblies described herein may be implanted into the patient using a balloon-expandable frame or a self-expanding frame. Expandable frames are generally conveyed to the site of the target valve on balloon catheters.

For insertion, the expandable frame is positioned in a compressed configuration along the delivery device, for example crimped onto the balloon of a balloon catheter that is part of the delivery device intended for coaxial mounting on a guidewire. After the expandable frame is positioned across the plane of the valve, the expandable frame is expanded by the delivery device. For a self-expanding frame, commonly a sheath is retracted, allowing expansion of the self-expanding frame.

In at least one embodiment, the frame comprises a metal alloy frame possessing a high strain design tolerance that is compressible to a relatively small diameter. By providing a device with a low profile, the implantable prosthetic heart valve 860 allows standard retrograde arterial aortic delivery via femoral artery insertion, without surgical cutdown or general anesthesia. This is achieved by providing the prosthetic heart valve on a premounted delivery system with the tissue leaflet assembly or tissue membrane construct in a substantially dry condition.

In accordance with one or more embodiments, a dry tissue membrane has substantially less mass than a wet membrane. By way of example, a substantially dry pericardium tissue prepared by one or more of the present embodiments has approximately 30% of the mass of a wet pericardium tissue, and marked reduction in profile and packing volume, thereby achieving a relatively low profile and making it suitable for implantation in greater number of patients, especially those having small diameter vascular systems. In addition, a dry prosthetic heart valve does not require storage and transport in preservative. A dry prosthetic heart valve can be mounted on a delivery catheter at its location of manufacture, which allows for pre-packaging of an integrated delivery system. In the foregoing sentence, it is noted that the term "mounted" means that the prosthetic heart valve 860 is temporarily associated with the delivery catheter. Together with a relatively low profile, embodiments of the prosthetic heart valve thereby offer reliability and convenience because the implantable prosthetic heart valve 860 is pre-mounted upon its delivery catheter and forms part of a pre-packaged delivery system. In addition, a dry prosthetic heart valve does not require rinsing, rehydration, or mounting in a catheterization lab. Therefore, a dry prosthetic heart valve can be inserted directly from package into the patient's body at a critical time during the procedure. Advantageously, this avoids procedure time, manipulation, and errors of mounting, crimping, and orienting catheters and sheaths. Once at the surgical facility/location, the dry prosthetic heart valve is inserted and delivered by balloon catheter expansion in the plane of the target valve in the standard way and the dry prosthetic heart valve begins to function immediately, even without specific steps to rehydrate the tissue membrane portion of the heart valve from its dry state, with hydration of the tissue membrane subsequently occurring rapidly and naturally in the body. More particularly, hydration of the tissue membrane portion occurs rapidly and begins with simple preparatory flushing of catheter

lumens with saline. Thereafter, hydration continues with device insertion and dwelling into the central blood vessels, and completes naturally after deployment in the patient's body.

The low profile of the implantable prosthetic valve is particularly advantageous for patient's having relatively small diameter vascular systems. Table 1 provides aortic and pulmonary valve prosthesis sizing.

Table 1: Aortic and Pulmonary Valve Prosthesis Sizing

Aorta/Pulmonary Valve Diameter	**Collapsed Implantable Prosthetic Heart Valve Size (French)**	**Collapsed Implantable Prosthetic Heart Valve Diameter**
19 - 21 mm	12 French	4.0 mm
22 - 26 mm	14 French	4.7 mm
27 - 30 mm	16 French	5.3 mm

For most human patients, the femoral artery has a diameter of between about 5-8 mm. Accordingly, it is apparent that embodiments of the collapsed implantable prosthetic heart valves 860 described herein offer a low profile that enables a larger group of patients to qualify for receiving an implantable prosthetic heart valve 860. As a result of the sizing advantages offered by one or more embodiments of implantable prosthetic heart valves 860 described herein, virtually no candidate patients would be excluded from treatment with an implantable prosthetic heart valve 860 without open heart surgery and without general anesthesia on the basis of inadequate femoral blood vessel access caliber. In addition, one or more embodiments of the implantable prosthetic heart valve 860 described herein feature a scalable construct, wherein the implantable prosthetic heart valves 860 can be produced to accommodate target valve diameters ranging between 6 - 35 mm, and wherein the implantable prosthetic heart valves 860 offer consistent function using fundamentally a single design.

Referring now to Fig. 5, the mounting of the implantable prosthetic heart valve 860 into a delivery system at 500 is further described. More particularly, at 504 an implantable prosthetic heart valve 860 (also referred to herein as a percutaneously deliverable heart valve) is collapsed. The initial phase of collapsing the percutaneously deliverable heart valve is executed with the tissue membrane in a hydrated condition. That is, since the percutaneously deliverable heart valve 860 includes the frame 852 with the tissue leaflet assembly 848 attached within the frame 852, the percutaneously deliverable heart valve 860 is collapsed down as an integral unit. If a balloon-expandable frame is used, then an axial puller may be utilized to collapse down the frame 852 of the percutaneously deliverable heart valve 860 without the application of force directly to the sides of the frame 852. This procedure offers the advantage of preserving the cell structure of the frame 852 while also maintaining the orientation of the leaflets of the tissue leaflet assembly 848 as the percutaneously deliverable heart valve 860 is compressed. The

proper orientation and disposition of the leaflets is facilitated by the hydrated state of the leaflets. This assists in preventing tissue prolapse or bulging of the tissue 800 or 802 through the frame 852. In addition, this technique reduces recompression strain on the metal frame 852 (e.g., a stent) that can tend to compromise fatigue life of the frame 852. This technique also tends to promote the circumferentially uniform collapsing of cells in the frame 852, thereby mitigating bunching of the tissue that forms the tissue leaflet assembly 848 of the percutaneously deliverable heart valve 860. For a self-expanding frame, the sides are forced to collapse by providing a radial compression force to the frame and may be assisted by axial traction force.

With further reference to Fig. 5, the percutaneously deliverable heart valve 860 (i.e., the frame 852 with the tissue leaflet assembly 848 attached thereto) is collapsed in an initially hydrated state. At 508 the delivery mandrel or balloon is inserted into a delivery sheath, and the mounting segment is then extended out the end of the sheath. Thereafter, at 512 the sheath and frame are coaxially mounted and then compressed with initial crimping onto the mounting segment with the tissue leaflet assembly 848 still in a hydrated state. At 516, the tissue leaflet assembly 848 of the percutaneously deliverable heart valve 860 is then allowed to dry, which further reduces the volume and profile of the tissue membrane leaflets, permitting further compression by radial force. Accordingly, in the final compression step, the percutaneously deliverable heart valve 860 is then further crimped with a circumferential crimping tool at 520 to finally mount the compressed valve/frame onto the delivery mandrel or balloon catheter.

Referring now to Fig. 6, the ensheathing, sterilization and packaging at 600 is described. More particularly, once the percutaneously deliverable heart valve 860 is coaxially mounted and crimped on a delivery mandrel or balloon catheter as described above and shown in Fig. 5, the assembly is then inserted at 604 into a distal end of a delivery sheath, such as by "backloading" the assembly into position with a distal end of the percutaneously deliverable heart valve 860 contained within the delivery sheath proximate the end of the sheath. Reference here is made to Fig. 10 that schematically illustrates catheter 1000 with an implantable prosthetic heart valve 860 mounted thereto.

With further reference to Fig. 6, at 608 the percutaneously deliverable heart valve 860 and delivery catheters are sterilized, such as by using by one or more of ethylene oxide, proton beam, or gamma radiation. At 612, the assembly is then optionally packaged in a sterile package. Additional elements are optionally shipped with the assembly, wherein, by way of example, such elements may include any necessary delivery tools and documentation. In at least one embodiment, the package may optionally contain a device to control the water vapor content

within the sealed volume of the package. Fig. 13 depicts a surgeon holding a sterile package 1300 containing a premounted percutaneously implantable prosthetic heart valve.

Referring now to Fig. 7, a flow chart illustrating the general procedure associated with implantation of the percutaneously deliverable heart valve 860 is provided. More particularly, at 704, catheter access is gained to the patient's femoral artery and a guidewire is placed through the plane of the diseased valve that is targeted to receive the implant. Fig. 14 is a schematic of a simplified cutaway view of a human heart, including heart valves that may be targeted for receiving an embodiment of an implantable prosthetic heart valve. Fig. 15 illustrates the aorta with the guidewire placed through the diseased aortic valve. At 708, the percutaneously deliverable heart valve 860 in the form of a prepackaged assembled dry prosthetic heart valve is removed from the sterile packaging. The dry prosthetic heart valve assembly, including its lumens, are preferably flushed and prepared in the usual fashion for standard balloons and catheters that do not contain a biocompatible tissue. Advantageously, implantation of the dry prosthetic heart valve assembly can be conducted without specific maneuvers for rehydration of the tissue leaflet assembly 848 of the percutaneously deliverable heart valve 860. Some rehydration of the tissue leaflets may occur as a consequence of the routine flushing of the catheter lumens in preparation for use as with any other catheters. Additionally, implantation of the dry prosthetic heart valve assembly can proceed without additional cleaning steps, such as by having to use alcohol or water rinsing solutions. In addition, further mounting of the dry tissue leaflet assembly 848 that resides in the frame 852 of the percutaneously deliverable heart valve 860 is not needed, thereby obviating the need for another mounting step. Accordingly, the percutaneously deliverable heart valve 860 can essentially be implanted percutaneously in its dry state. At 712, the carrier catheter or balloon catheter is then coaxially mounted and advanced over the guidewire, such as under fluoroscopic vision initially to the level of the great vessel where it can be inspected under fluoroscopy. At 716, and after the nominal position and configuration is confirmed, the delivery system is advanced through the plane of the diseased valve under fluoroscopy, and the covering sheath is withdrawn, either at this point or during the advance prior to it, thus exposing the mounted implantable prosthetic heart valve 860 in place. At 720, in the case of a balloon expandable frame, and assuming the delivery approach involving the pre-mounting of the percutaneously deliverable heart valve 860 on the expansion balloon, the balloon is then inflated, deploying the percutaneously deliverable heart valve 860 in the plane of the valve. At 724, the leaflets of the percutaneously deliverable heart valve 860 operate immediately. The deployed prosthetic heart valve 860 is shown in Fig. 16, wherein the tissue leaflet assembly 848 serves to properly control the flow blood.

The present invention may be embodied in other specific forms without departing from

its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

The one or more present inventions, in various embodiments, include components, methods, processes, systems and/or apparatus substantially as depicted and described herein, including various embodiments, subcombinations, and subsets thereof. Those of skill in the art will understand how to make and use the present invention after understanding the present disclosure.

The present invention, in various embodiments, includes providing devices and processes in the absence of items not depicted and/or described herein or in various embodiments hereof, including in the absence of such items as may have been used in previous devices or processes (e.g., for improving performance, achieving ease and/or reducing cost of implementation).

The foregoing discussion of the invention has been presented for purposes of illustration and description. The foregoing is not intended to limit the invention to the form or forms disclosed herein. In the foregoing Detailed Description for example, various features of the invention are grouped together in one or more embodiments for the purpose of streamlining the disclosure. This method of disclosure is not to be interpreted as reflecting an intention that the claimed invention requires more features than are expressly recited in each claim. Rather, as the following claims reflect, inventive aspects lie in less than all features of a single foregoing disclosed embodiment. Thus, the following claims are hereby incorporated into this Detailed Description, with each claim standing on its own as a separate preferred embodiment of the invention.

Moreover, though the description of the invention has included description of one or more embodiments and certain variations and modifications, other variations and modifications are within the scope of the invention (e.g., as may be within the skill and knowledge of those in the art, after understanding the present disclosure). It is intended to obtain rights which include alternative embodiments to the extent permitted, including alternate, interchangeable and/or equivalent structures, functions, ranges or acts to those claimed, whether or not such alternate, interchangeable and/or equivalent structures, functions, ranges or acts are disclosed herein, and without intending to publicly dedicate any patentable subject matter.

CLAIMS

What is claimed is:

1. An assembly, comprising:

a prosthetic heart valve including:

a frame; and

a tissue leaflet assembly attached to the frame;

a percutaneously insertable valve delivery mechanism, wherein the prosthetic heart valve is releasably mounted onto the percutaneously insertable valve delivery mechanism; and

sterile packaging containing the prosthetic heart valve releasably mounted onto the percutaneously insertable valve delivery mechanism.

2. The assembly of Claim 1, wherein the percutaneously insertable valve delivery mechanism comprises a balloon catheter.

3. The assembly of Claim 2, wherein the balloon catheter is a 12 to 14 French balloon catheter.

4. The assembly of Claim 2, wherein the balloon catheter is less than about 12 French.

5. The assembly of Claim 2, wherein the balloon catheter is between about 5 to 12 French.

6. The assembly of Claim 1, wherein the percutaneously insertable valve delivery mechanism comprises a mandrel.

7. The assembly of Claim 1, wherein tissue forming the tissue leaflet assembly within the sterile packaging is at least one of hydrated and not substantially dry.

8. The assembly of Claim 1, wherein tissue forming the tissue leaflet assembly within the sterile packaging is substantially dry.

9. The assembly of Claim 1, wherein the frame comprises a stent.

10. The assembly of Claim 1, wherein tissue forming the tissue leaflet assembly comprises treated pericardium tissue.

11. A pre-packaged percutaneous, trans-catheter deliverable prosthetic heart valve ready for implantation in a patient, comprising:

a frame; and

a tissue leaflet assembly attached to the frame, the tissue leaflet assembly comprising a substantially dry tissue.

12. The pre-packaged percutaneous, trans-catheter deliverable prosthetic heart valve of Claim 11, wherein the substantially dry tissue comprises treated pericardium tissue.

13. The pre-packaged percutaneous, trans-catheter deliverable prosthetic heart valve of Claim 11, wherein the substantially dry tissue comprises a water moisture content of less than about 40% by weight of the substantially dry tissue.

14. The pre-packaged percutaneous, trans-catheter deliverable prosthetic heart valve of Claim 11, wherein the frame and the tissue leaflet assembly attached thereto are operably associated with a 12 to 14 French balloon catheter.

15. The pre-packaged percutaneous, trans-catheter deliverable prosthetic heart valve of Claim 11, wherein the frame and the tissue leaflet assembly attached thereto are operably associated with a balloon catheter having a size of less than about 12 French.

16. The pre-packaged percutaneous, trans-catheter deliverable prosthetic heart valve of Claim 11, wherein the frame and the tissue leaflet assembly attached thereto are operably associated with a balloon catheter having a size of between about 5 to 12 French.

17. An assembly for use with a patient, comprising:

a sealed sterile package containing a delivery system for percutaneously deploying a heart valve in the patient, the heart valve including:

a frame releasably mounted on the delivery system within the sealed sterile package; and

a tissue leaflet assembly attached to the frame.

18. The assembly of Claim 17, wherein the tissue leaflet assembly comprises a treated pericardium tissue.

19. The assembly of Claim 17, wherein the delivery system includes a percutaneously insertable balloon catheter.

20. The assembly of Claim 19, wherein the balloon catheter is a 12 to 14 French balloon catheter.

21. The assembly of Claim 19, wherein the balloon catheter is less than about 12 French.

22. The assembly of Claim 19, wherein the balloon catheter is between about 5 to 12 French.

23. The assembly of Claim 17, wherein the delivery system includes a percutaneously insertable mandrel.

24. The assembly of Claim 17, wherein the tissue leaflet assembly within the sealed sterile package is at least one of partially hydrated and not substantially dry.

25. The assembly of Claim 17, wherein the tissue leaflet assembly within the sealed sterile package is substantially dry.

26. The assembly of Claim 17, wherein the frame comprises a stent.

27. An article adapted for implantation in a patient, comprising:

a prosthetic heart valve further comprising a treated tissue attached to a frame, wherein the treated tissue comprises a water content of less than about 60% by weight of the treated tissue.

28. The article of Claim 27, wherein the treated tissue comprises a section of treated pericardium tissue having an ultimate tensile strength of greater than about 12 MegaPascals.

29. The article of Claim 28, wherein the section of pericardium tissue comprises a thickness of between about 50 to 300 micrometers.

30. The article of Claim 27, wherein the water content of the treated tissue is less than about 40% by weight of the treated tissue.

31. An article adapted for trans-catheter delivery into a patient, comprising:

a prosthetic heart valve further comprising a treated tissue attached to a frame, wherein the treated tissue comprises a thickness of about 50 to 500 micrometers and an ultimate tensile strength of greater than about 15 MegaPascals when at a water content of less than about 50% by weight of the treated tissue.

32. The article of Claim 31, wherein the treated tissue comprises a treated pericardium tissue.

33. The article of Claim 31, wherein the water content of the treated tissue is less than about 40% by weight of the treated tissue.

34. The article of Claim 31, wherein the ultimate tensile strength is greater than about 20 MegaPascals.

35. The article of Claim 31, wherein the treated tissue does not include a matrix that has been exposed to a polymer infiltrate.

36. A method, comprising:

partially compressing and mounting a prosthetic heart valve upon a delivery catheter, the prosthetic heart valve comprising a tissue;

allowing the tissue to at least partially dry;

further compressing and mounting the prosthetic heart valve upon the delivery catheter; and

sterilizing and packaging the prosthetic heart valve and delivery catheter.

37. The method of Claim 36, further comprising transporting the sterilized and packaged prosthetic heart valve and delivery catheter.

38. The method of Claim 36, wherein the tissue comprises a treated pericardium tissue.

39. The method of Claim 36, wherein prior to partially compressing and mounting the prosthetic heart valve upon the delivery catheter, the tissue is at least one of (a) not substantially dry, and (b) at least partially hydrated.

40. A method, comprising:

attaching a tissue to a frame;

partially compressing and mounting the frame, with the tissue attached thereto, upon a delivery catheter;

allowing the tissue to at least partially dry;

further compressing and mounting the frame, with the tissue attached thereto, upon the delivery catheter; and

sterilizing and packaging the frame and delivery catheter, with the tissue attached thereto.

41. The method of Claim 40, wherein prior to partially compressing and mounting the frame, the tissue is at least one of (a) not substantially dry, and (b) at least partially hydrated.

42. The method of Claim 40, further comprising transporting the sterilized and packaged frame, with the tissue attached thereto, mounted upon the delivery catheter, to a surgical or medical procedure facility.

43. The method of Claim 40, wherein prior to attaching the tissue to the frame the tissue is folded to form a tissue leaflet assembly.

44. The method of Claim 43, wherein the tissue leaflet assembly comprises at least one cuff and at least one pleat.

45. The method of Claim 40, wherein the tissue comprises a treated pericardium tissue.

46. A method of preparing a percutaneous, trans-catheter prosthetic heart valve, comprising:

providing a membrane tissue from an organism;

treating the membrane tissue with at least one chemical to produce a treated membrane tissue;

drying the treated membrane tissue until it is a substantially dry tissue;

attaching the substantially dry tissue to a frame;

rehydrating the substantially dry tissue that is attached to the frame to form a rehydrated tissue;

collapsing the frame with the rehydrated tissue attached thereto; and

drying the rehydrated tissue attached to the collapsed frame until it is a substantially dry tissue.

47. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, further comprising compressing and mounting the frame, with the tissue attached thereto, upon a delivery catheter.

48. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 47, further comprising sterilizing and packaging the frame, with the substantially dry tissue attached thereto, mounted upon the delivery catheter.

49. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 48, further comprising at least one of transporting and shipping the sterilized and packaged frame with the substantially dry tissue attached thereto, mounted upon the delivery catheter, to a surgical or medical procedure facility.

50. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 49, further comprising implanting the frame with the substantially dry tissue attached thereto into a patient.

51. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein the frame comprises a stent.

52. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein prior to the attaching step the dry tissue is not folded with a cuff and a pleat.

53. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein prior to the attaching step the dry tissue is folded to form a tissue leaflet assembly.

54. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 53, wherein the tissue leaflet assembly comprises at least one cuff and at least one pleat.

55. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 53, further comprising mounting the frame and the tissue leaflet assembly attached thereto upon a 12 to 14 French balloon catheter.

56. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 53, further comprising mounting the frame and the tissue leaflet assembly attached thereto upon a balloon catheter having a size of less than about 12 French.

57. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 53, further comprising mounting the frame and the tissue leaflet assembly attached thereto upon a balloon catheter having a size of between about 5 to 12 French.

58. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 53, further comprising mounting the frame and the tissue leaflet assembly attached thereto on a mandrel.

59. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, further comprising sterilizing the frame with the substantially dry tissue attached thereto with exposure to at least one of ethylene oxide, a proton beam, and gamma radiation.

60. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in a buffered or unbuffered 1 – 37.5% formalin solution for between about 3 days to 3 weeks.

61. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in a buffered or unbuffered 1 – 37.5% formalin solution for between about 3 days to 5 weeks.

62. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in a buffered or unbuffered 1 - 37.5% formalin solution containing at least one of free amino acids (a) lysine and (b) histidine, for between about 3 days to 3 weeks.

63. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in a buffered or unbuffered 1 - 37.5% formalin solution containing at least one of free amino acids (a) lysine and (b) histidine, for between about 3 days to 5 weeks.

64. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in 100% glycerol for greater than about 3 weeks.

65. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in a 0.1 - 25% glutaraldehyde solution for between about 3 days to 3 weeks.

66. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in a 0.1 - 25% glutaraldehyde solution for between about 3 days to 5 weeks.

67. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in a 0.1 - 25% glutaraldehyde solution containing at least one of free amino acids (a) lysine and (b) histidine, for between about 3 days to 3 weeks.

68. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in a 0.1 - 25% glutaraldehyde solution containing at least one of free amino acids (a) lysine and (b) histidine, for between about 3 days to 5 weeks.

69. The met ous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in an oligomeric filtered 0.1 - 25% glutaraldehyde solution for between about 3 days to 3 weeks.

70. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in an oligomeric filtered 0.1 - 25% glutaraldehyde solution for between about 3 days to 5 weeks.

71. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in an oligomeric filtered 0.1 - 25% glutaraldehyde solution containing at least one of free amino acids (a) lysine and (b) histidine, for between about 3 days to 3 weeks.

72. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein said treating comprises immersion of the membrane tissue in an oligomeric filtered 0.1 - 25% glutaraldehyde solution containing at least one of free amino acids (a) lysine and (b) histidine, for between about 3 days to 5 weeks.

73. The method of preparing a percutaneous, trans-catheter prosthetic heart valve of Claim 46, wherein the membrane tissue comprises a treated pericardium tissue.

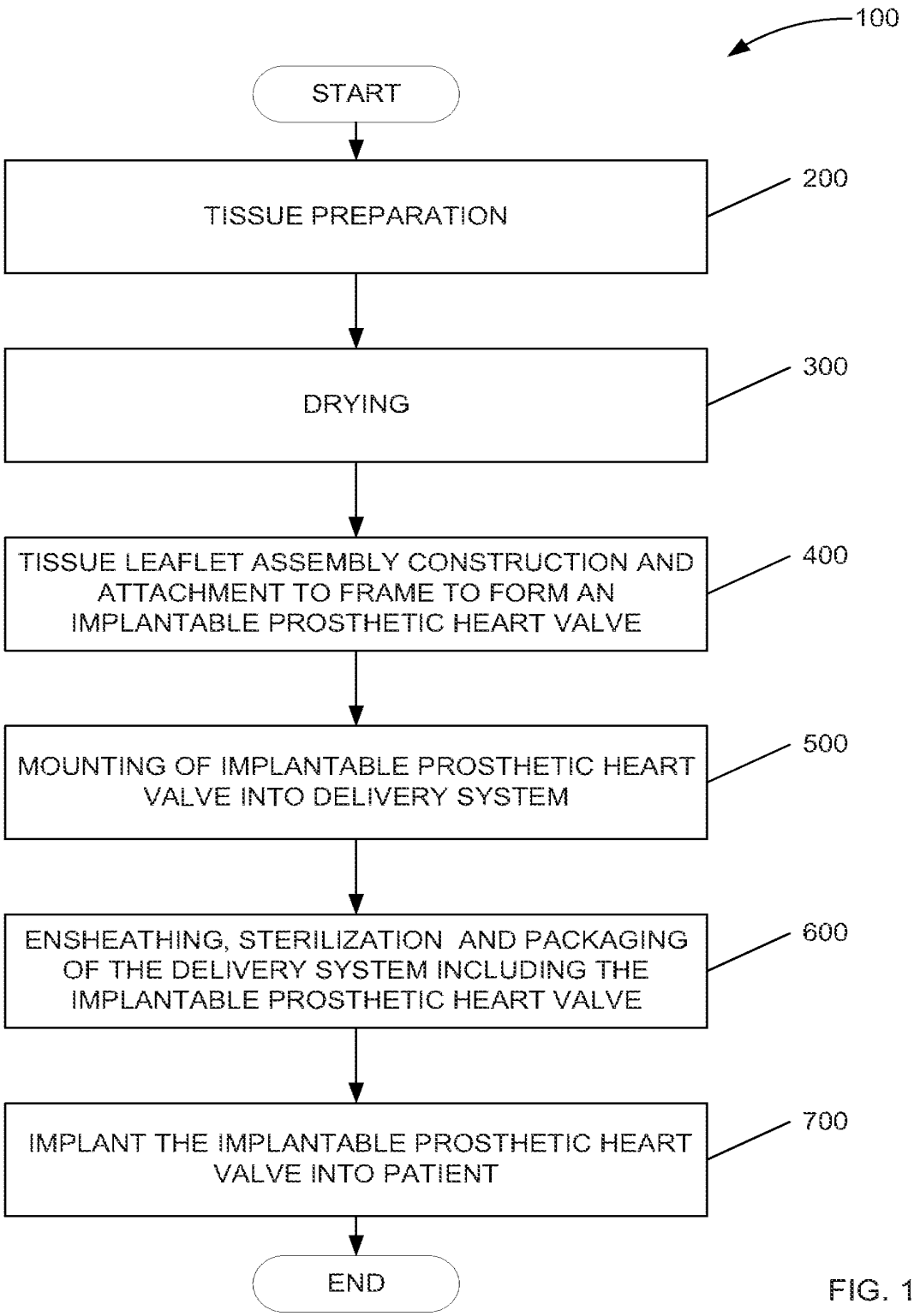

100
START
TISSUE PREPARATION
200
DRYING
300
TISSUE LEAFLET ASSEMBLY CONSTRUCTION AND ATTACHMENT TO FRAME TO FORM AN IMPLANTABLE PROSTHETIC HEART VALVE
400
MOUNTING OF IMPLANTABLE PROSTHETIC HEART VALVE INTO DELIVERY SYSTEM
500
ENSHEATHING, STERILIZATION AND PACKAGING OF THE DELIVERY SYSTEM INCLUDING THE IMPLANTABLE PROSTHETIC HEART VALVE
600
IMPLANT THE IMPLANTABLE PROSTHETIC HEART VALVE INTO PATIENT
700
END

FIG. 1

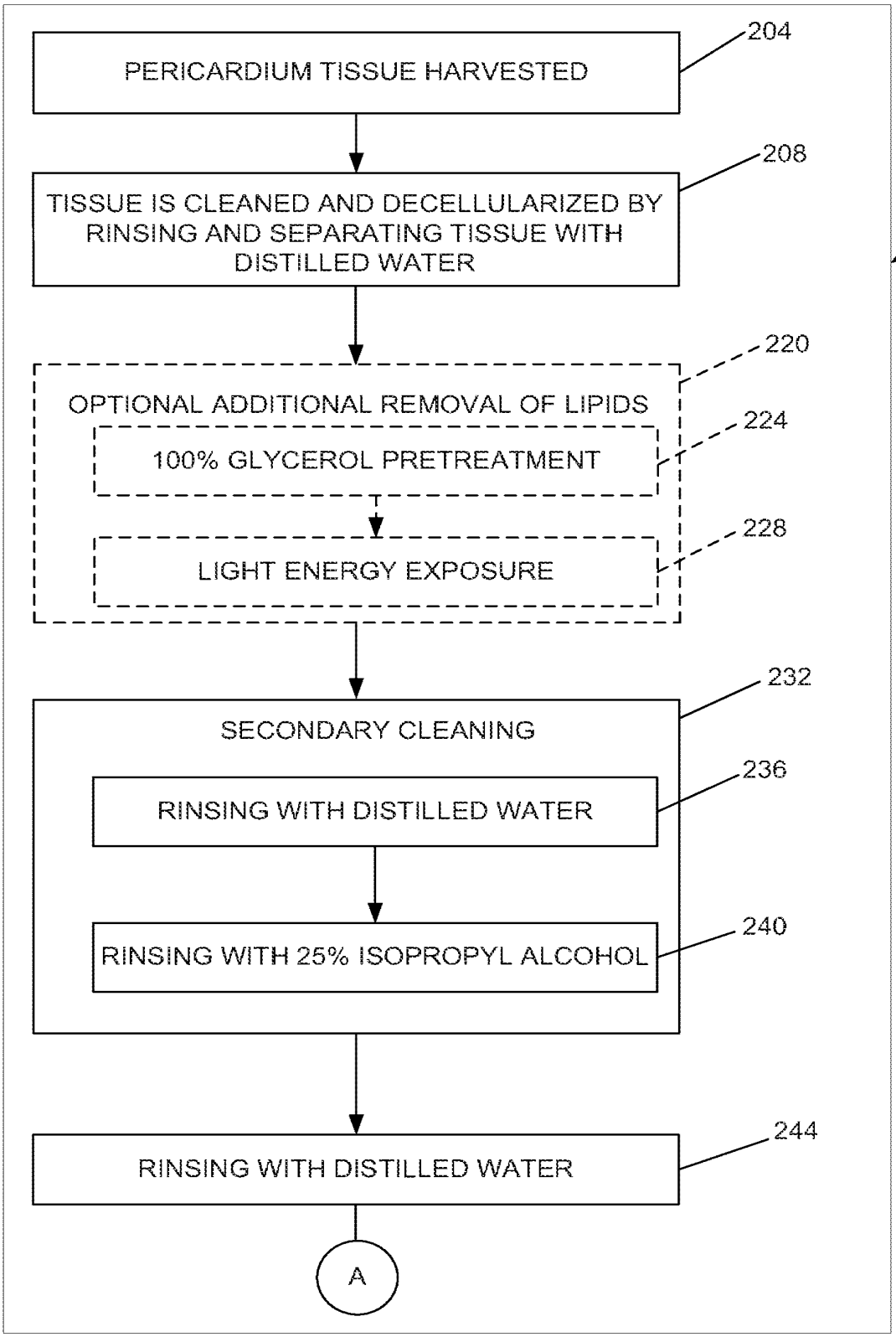

PERICARDIUM TISSUE HARVESTED
204
TISSUE IS CLEANED AND DECELLULARIZED BY RINSING AND SEPARATING TISSUE WITH DISTILLED WATER
208
200
OPTIONAL ADDITIONAL REMOVAL OF LIPIDS
220
100% GLYCEROL PRETREATMENT
224
LIGHT ENERGY EXPOSURE
228
SECONDARY CLEANING
232
RINSING WITH DISTILLED WATER
236
RINSING WITH 25% ISOPROPYL ALCOHOL
240
RINSING WITH DISTILLED WATER
244
A

FIG. 2A

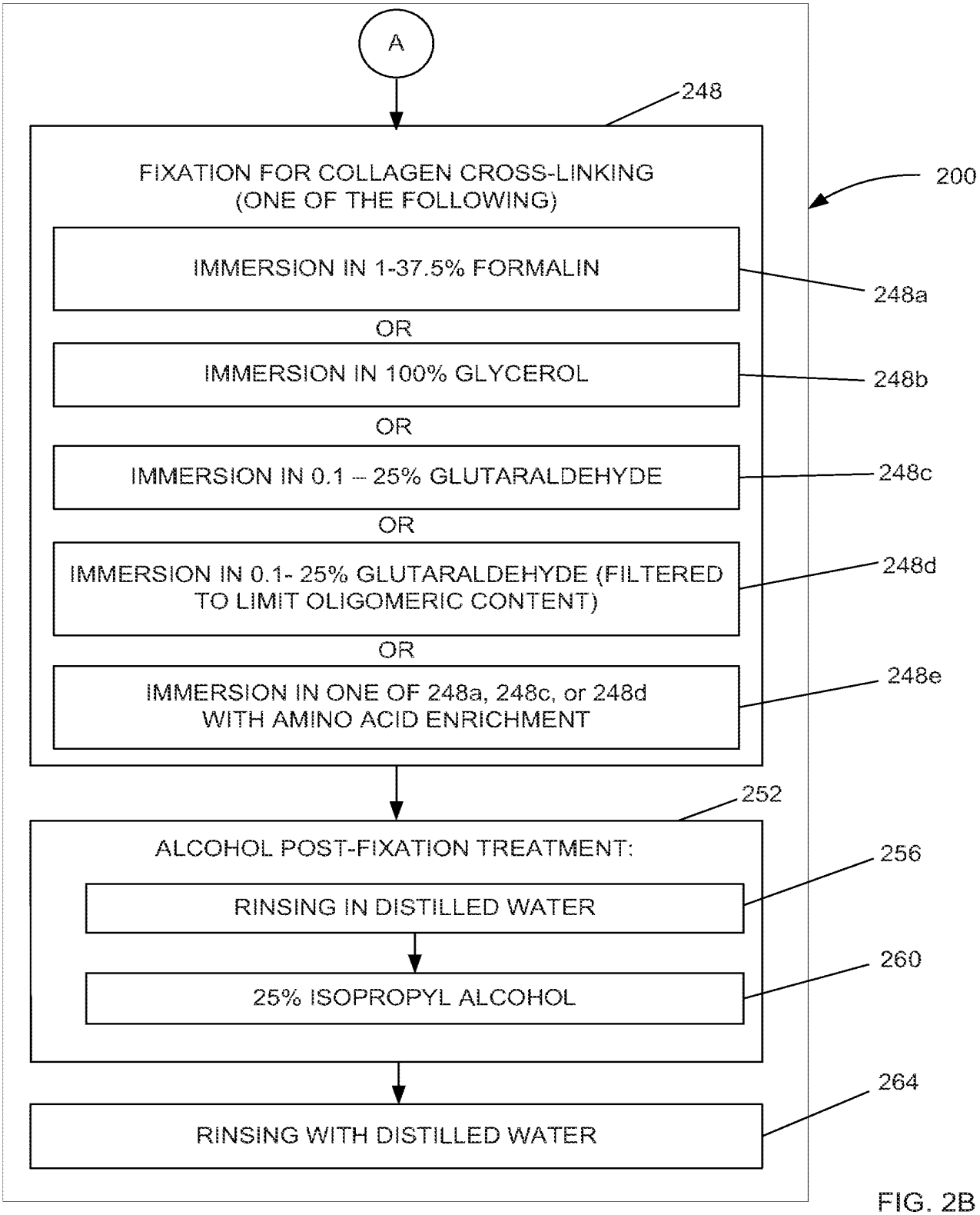

A
248
FIXATION FOR COLLAGEN CROSS-LINKING
(ONE OF THE FOLLOWING)
200
IMMERSION IN 1-37.5% FORMALIN
248a
OR
IMMERSION IN 100% GLYCEROL
248b
OR
IMMERSION IN 0.1 – 25% GLUTARALDEHYDE
248c
OR
IMMERSION IN 0.1- 25% GLUTARALDEHYDE (FILTERED TO LIMIT OLIGOMERIC CONTENT)
248d
OR
IMMERSION IN ONE OF 248a, 248c, or 248d WITH AMINO ACID ENRICHMENT
248e
252
ALCOHOL POST-FIXATION TREATMENT:
256
RINSING IN DISTILLED WATER
260
25% ISOPROPYL ALCOHOL
264
RINSING WITH DISTILLED WATER

FIG. 2B

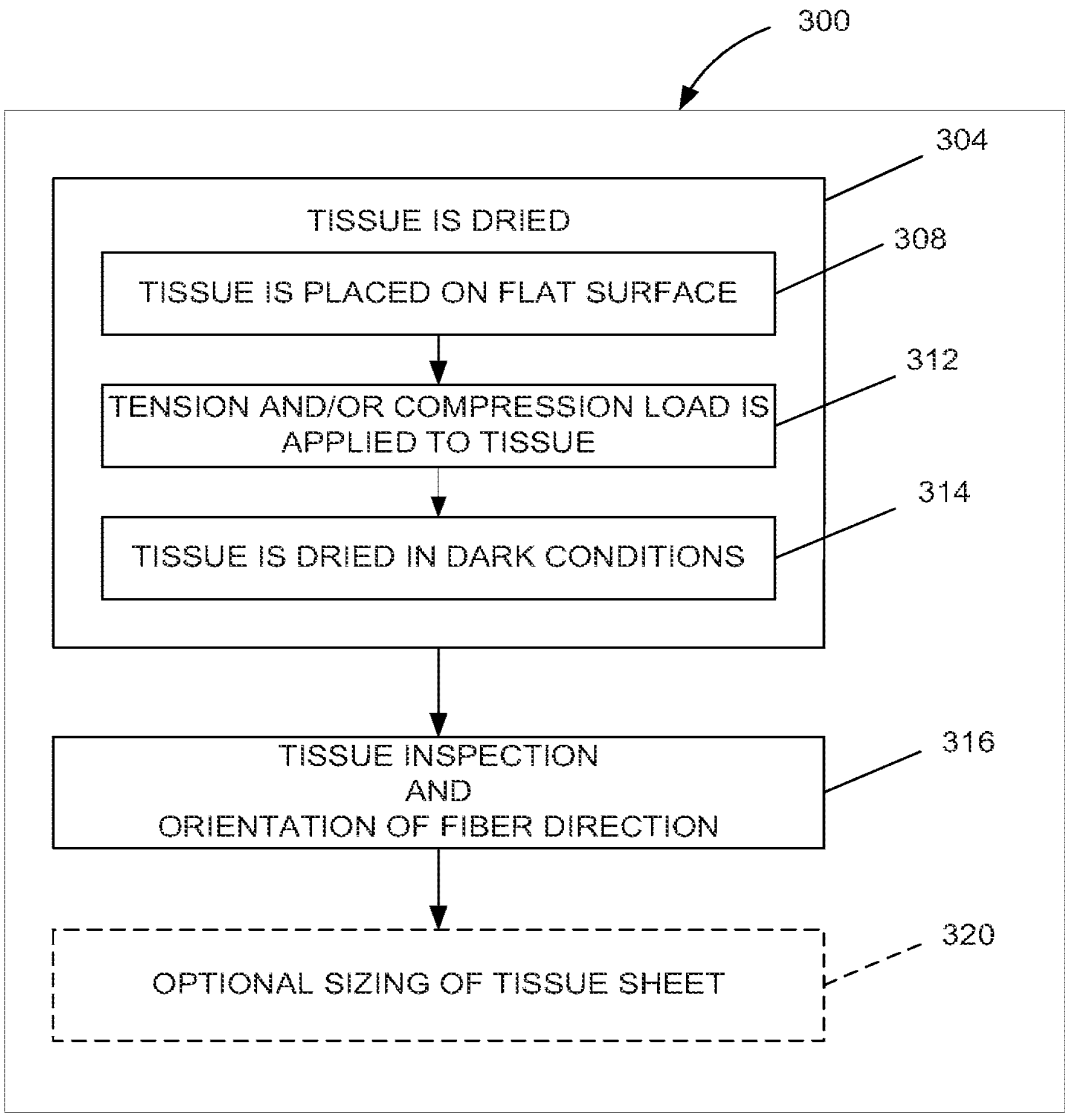

300
304
TISSUE IS DRIED
308
TISSUE IS PLACED ON FLAT SURFACE
312
TENSION AND/OR COMPRESSION LOAD IS APPLIED TO TISSUE
314
TISSUE IS DRIED IN DARK CONDITIONS
316
TISSUE INSPECTION AND ORIENTATION OF FIBER DIRECTION
320
OPTIONAL SIZING OF TISSUE SHEET

FIG. 3

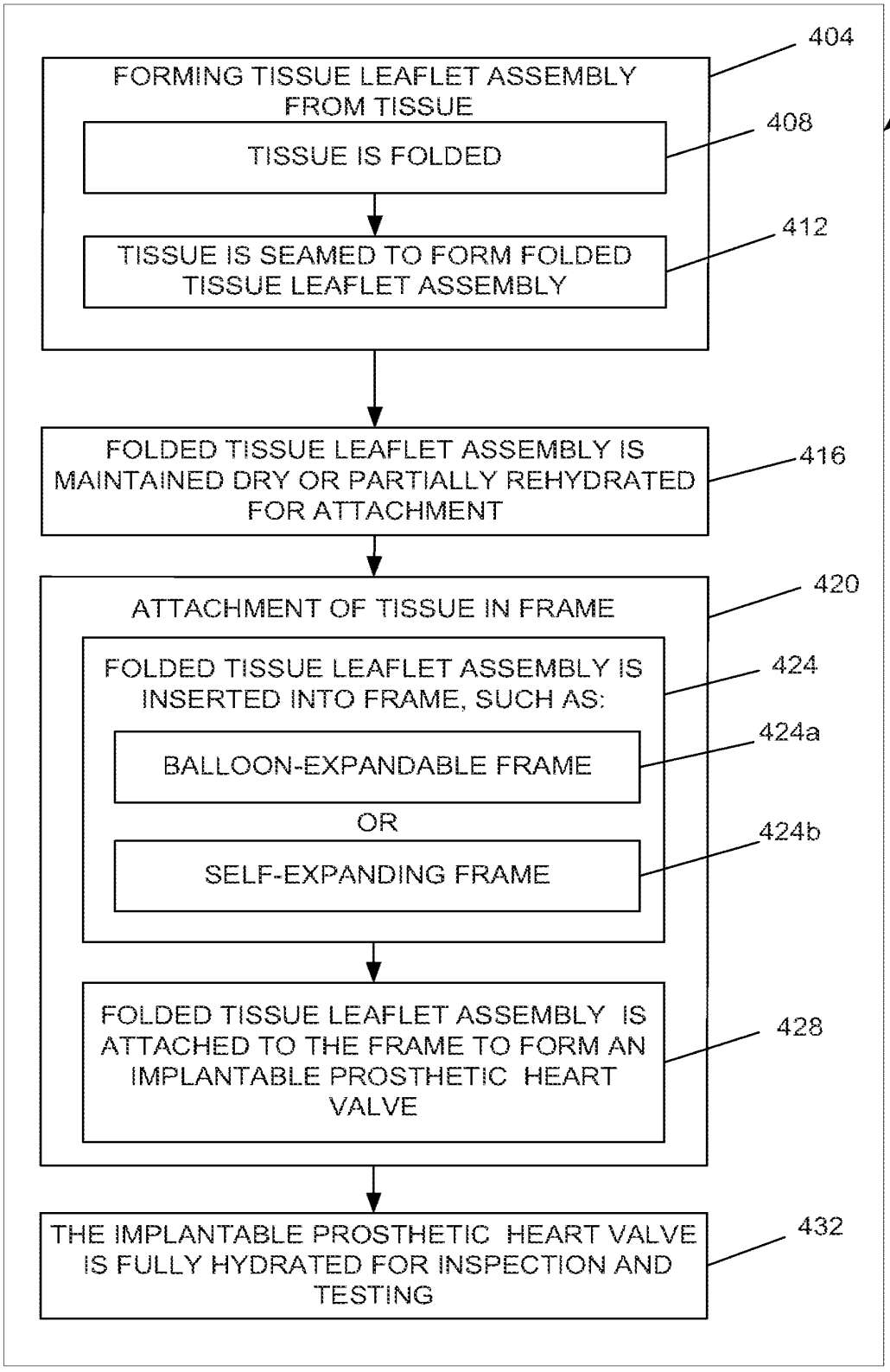

400
404
FORMING TISSUE LEAFLET ASSEMBLY FROM TISSUE
408
TISSUE IS FOLDED
412
TISSUE IS SEAMED TO FORM FOLDED TISSUE LEAFLET ASSEMBLY
416
FOLDED TISSUE LEAFLET ASSEMBLY IS MAINTAINED DRY OR PARTIALLY REHYDRATED FOR ATTACHMENT
420
ATTACHMENT OF TISSUE IN FRAME
424
FOLDED TISSUE LEAFLET ASSEMBLY IS INSERTED INTO FRAME, SUCH AS:
424a
BALLOON-EXPANDABLE FRAME
OR
424b
SELF-EXPANDING FRAME
428
FOLDED TISSUE LEAFLET ASSEMBLY IS ATTACHED TO THE FRAME TO FORM AN IMPLANTABLE PROSTHETIC HEART VALVE
432
THE IMPLANTABLE PROSTHETIC HEART VALVE IS FULLY HYDRATED FOR INSPECTION AND TESTING

FIG. 4

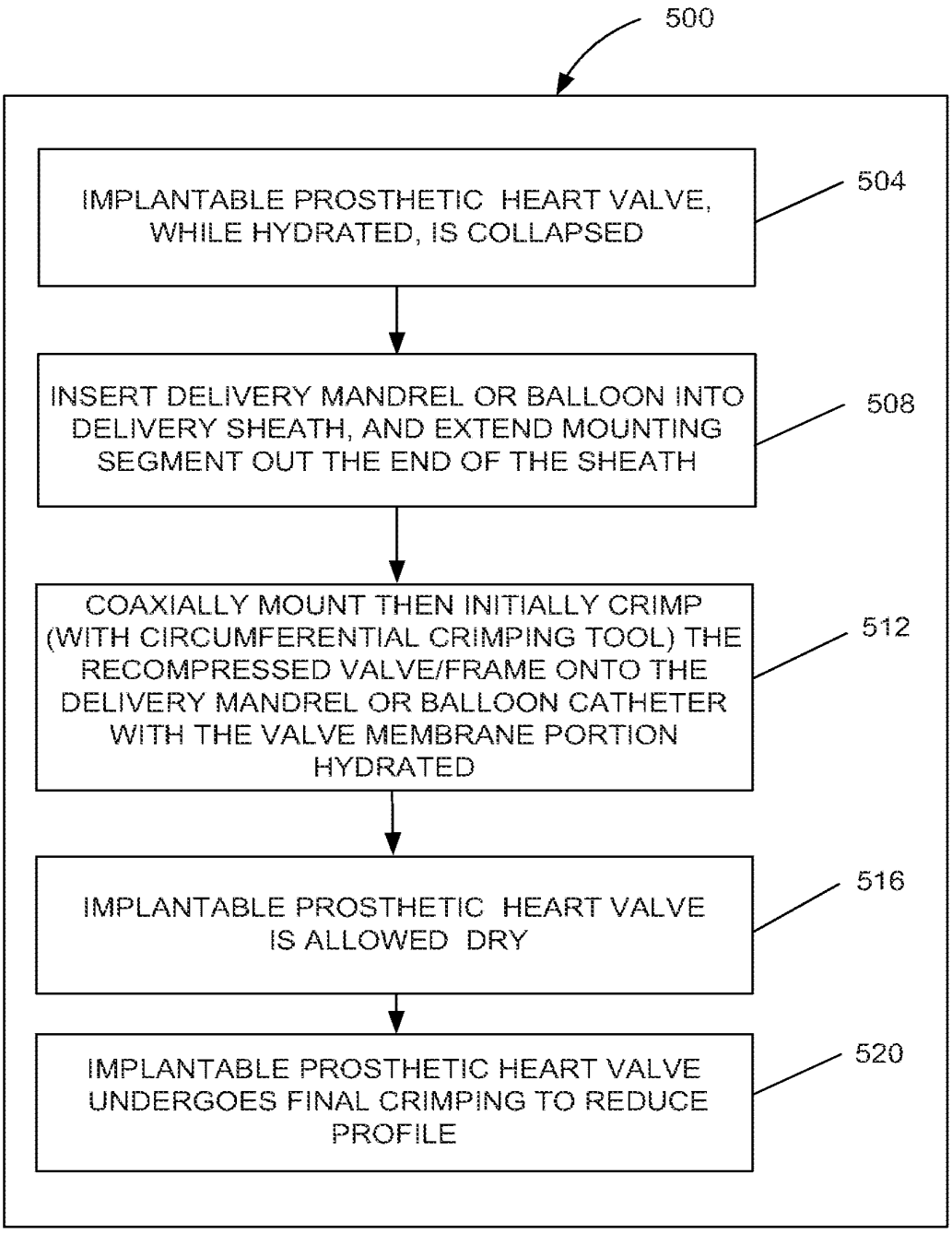

500
IMPLANTABLE PROSTHETIC HEART VALVE, WHILE HYDRATED, IS COLLAPSED
504
INSERT DELIVERY MANDREL OR BALLOON INTO DELIVERY SHEATH, AND EXTEND MOUNTING SEGMENT OUT THE END OF THE SHEATH
508
COAXIALLY MOUNT THEN INITIALLY CRIMP (WITH CIRCUMFERENTIAL CRIMPING TOOL) THE RECOMPRESSED VALVE/FRAME ONTO THE DELIVERY MANDREL OR BALLOON CATHETER WITH THE VALVE MEMBRANE PORTION HYDRATED
512
IMPLANTABLE PROSTHETIC HEART VALVE IS ALLOWED DRY
516
IMPLANTABLE PROSTHETIC HEART VALVE UNDERGOES FINAL CRIMPING TO REDUCE PROFILE
520

FIG. 5

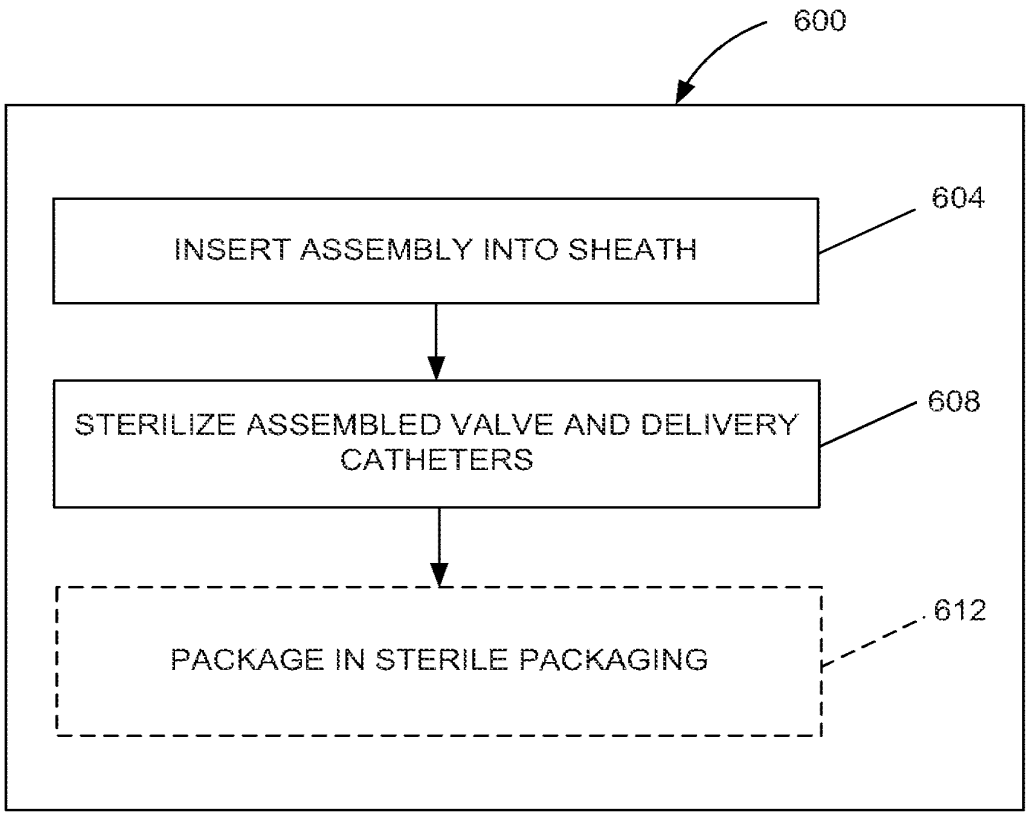


FIG. 6

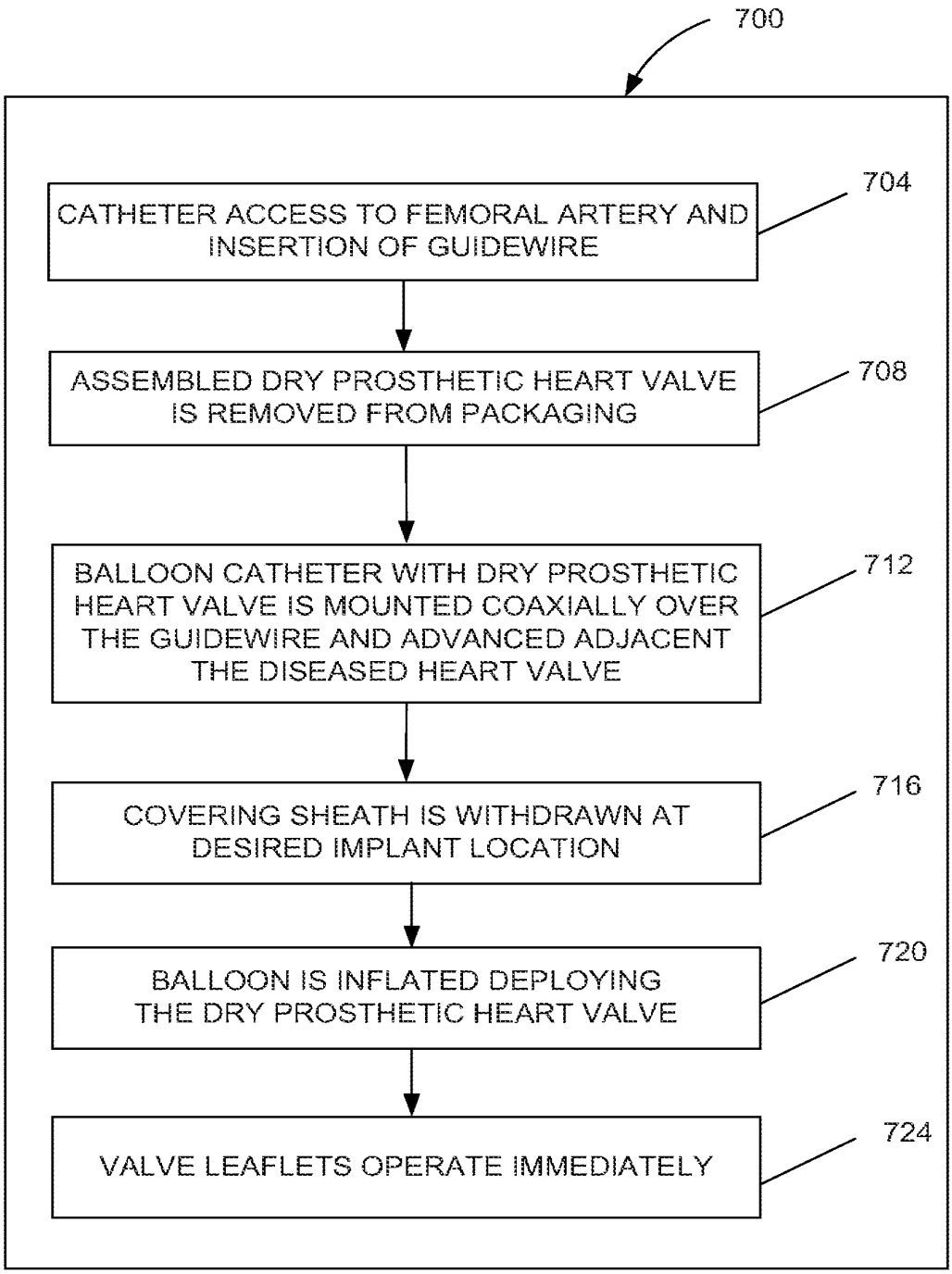

700
CATHETER ACCESS TO FEMORAL ARTERY AND INSERTION OF GUIDEWIRE
704
ASSEMBLED DRY PROSTHETIC HEART VALVE IS REMOVED FROM PACKAGING
708
BALLOON CATHETER WITH DRY PROSTHETIC HEART VALVE IS MOUNTED COAXIALLY OVER THE GUIDEWIRE AND ADVANCED ADJACENT THE DISEASED HEART VALVE
712
COVERING SHEATH IS WITHDRAWN AT DESIRED IMPLANT LOCATION
716
BALLOON IS INFLATED DEPLOYING THE DRY PROSTHETIC HEART VALVE
720
VALVE LEAFLETS OPERATE IMMEDIATELY
724

FIG.7

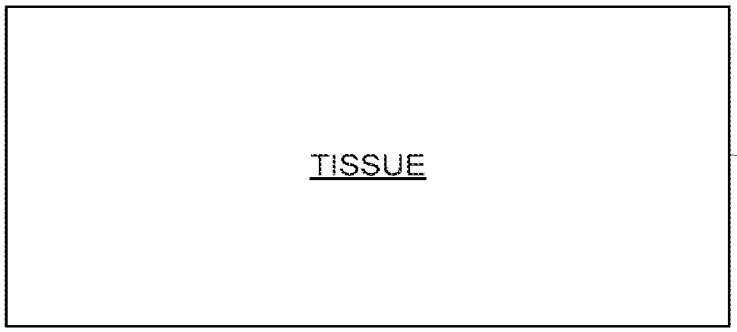


FIG.8A

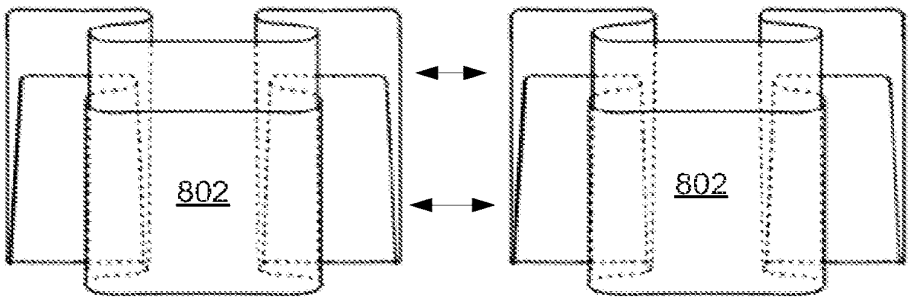


FIG.8B

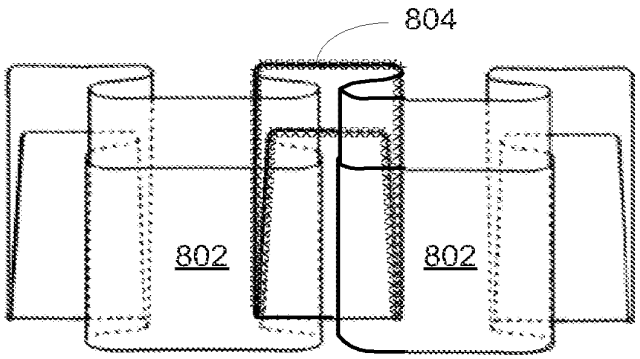


FIG.8C

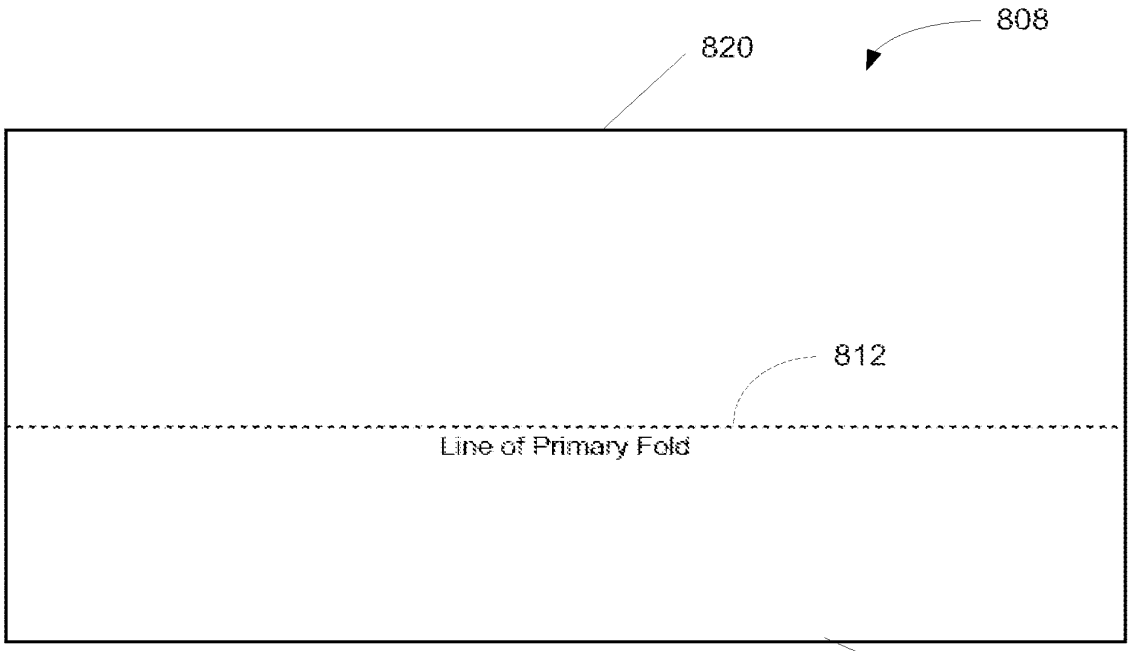

808
820
812
Line of Primary Fold
816

FIG.8D

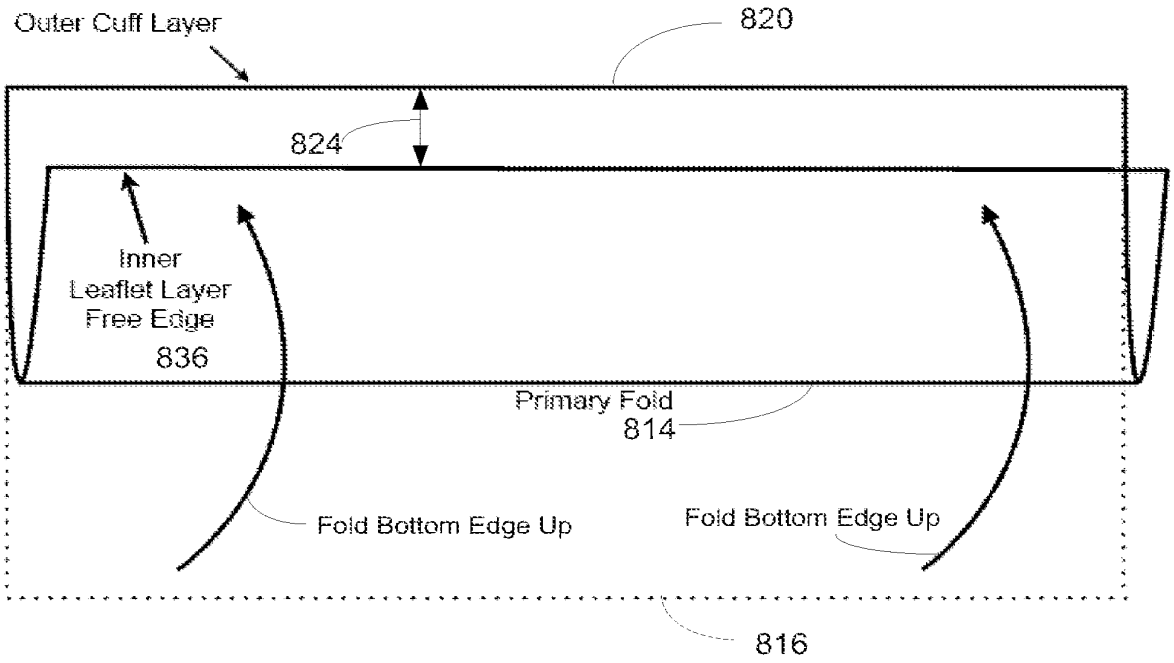

Outer Cuff Layer
820
824
Inner
Leaflet Layer
Free Edge
836
Primary Fold
814
Fold Bottom Edge Up
Fold Bottom Edge Up
816

FIG.8E

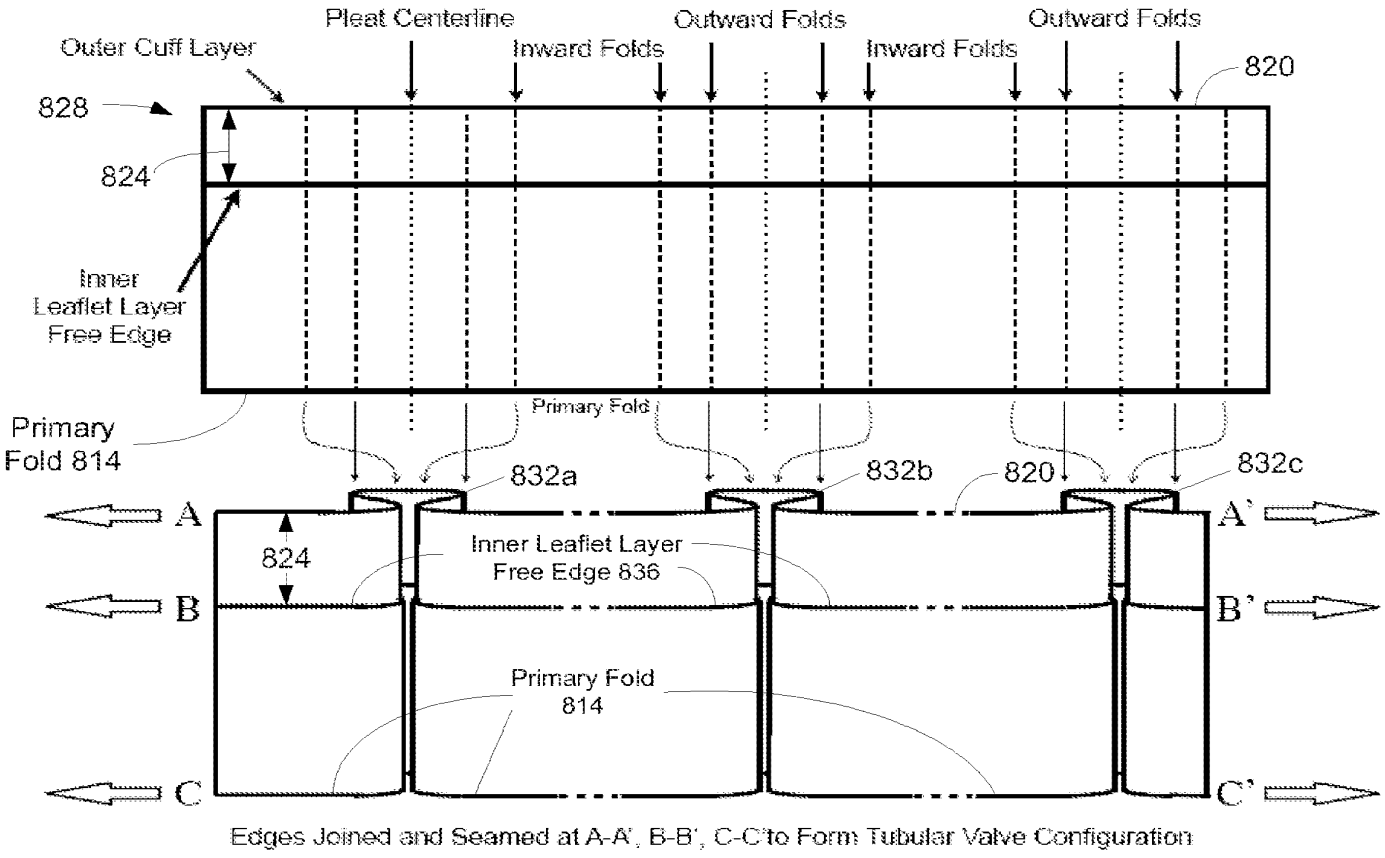

Pleat Centerline
Outward Folds
Outward Folds
Outer Cuff Layer
Inward Folds
Inward Folds
820
828
824
Inner
Leaflet Layer
Free Edge
Primary Fold
Primary
Fold 814
832a
832b
820
832c
A
A'
824
Inner Leaflet Layer
Free Edge 836
B
B'
Primary Fold
814
C
C'
Edges Joined and Seamed at A-A', B-B', C-C'to Form Tubular Valve Configuration

FIG.8F

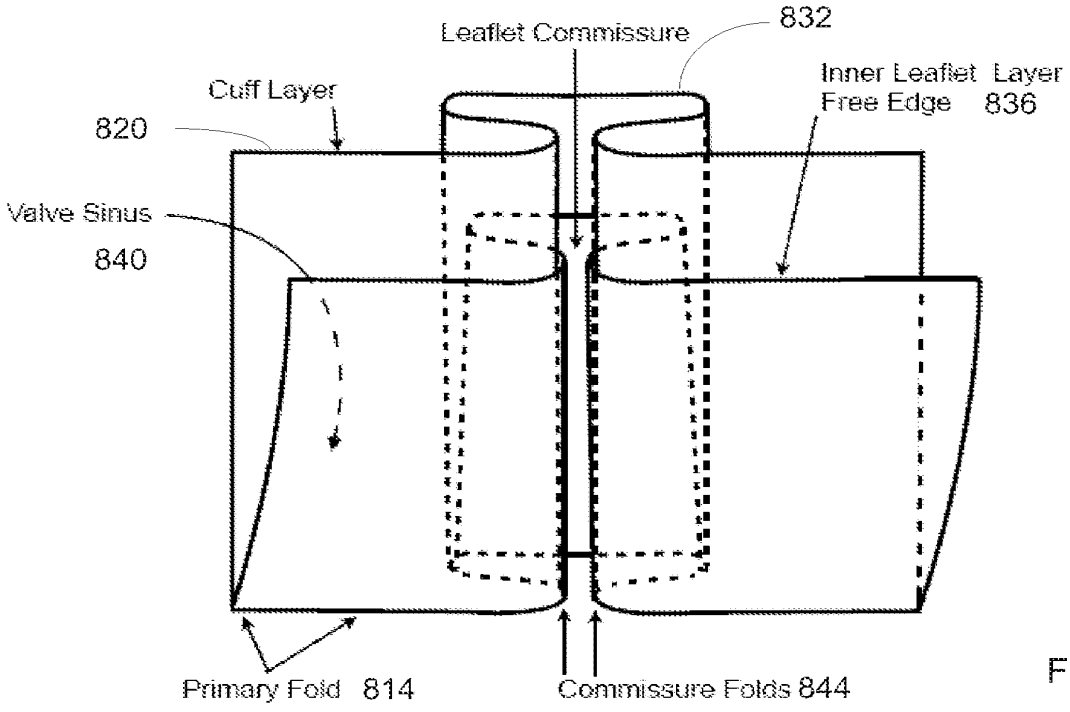


FIG.8G

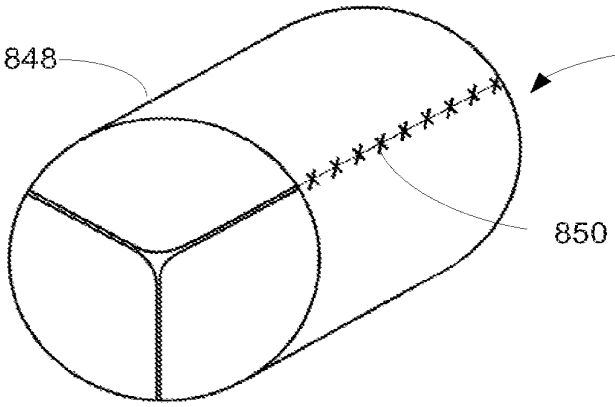


FIG.8H

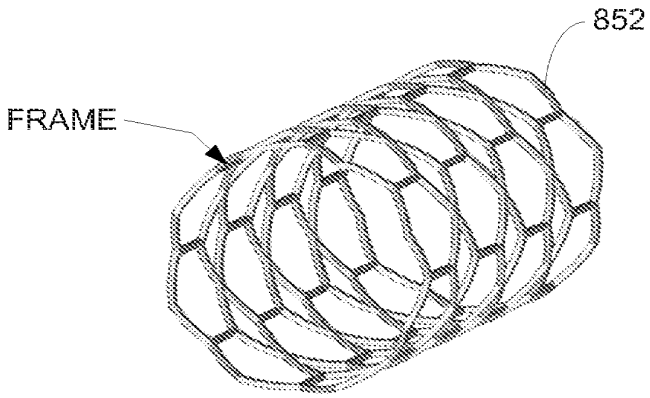


FIG.8I

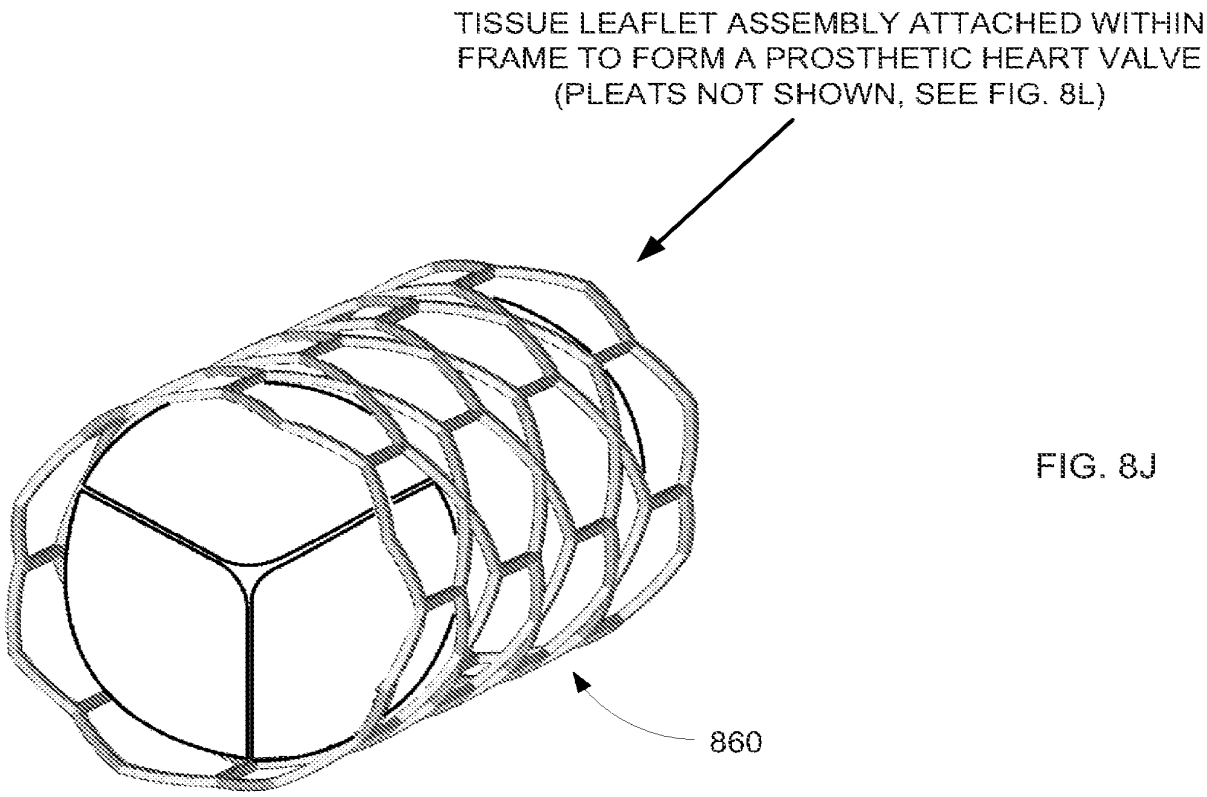

TISSUE LEAFLET ASSEMBLY ATTACHED WITHIN
FRAME TO FORM A PROSTHETIC HEART VALVE
(PLEATS NOT SHOWN, SEE FIG. 8L)
860

FIG. 8J

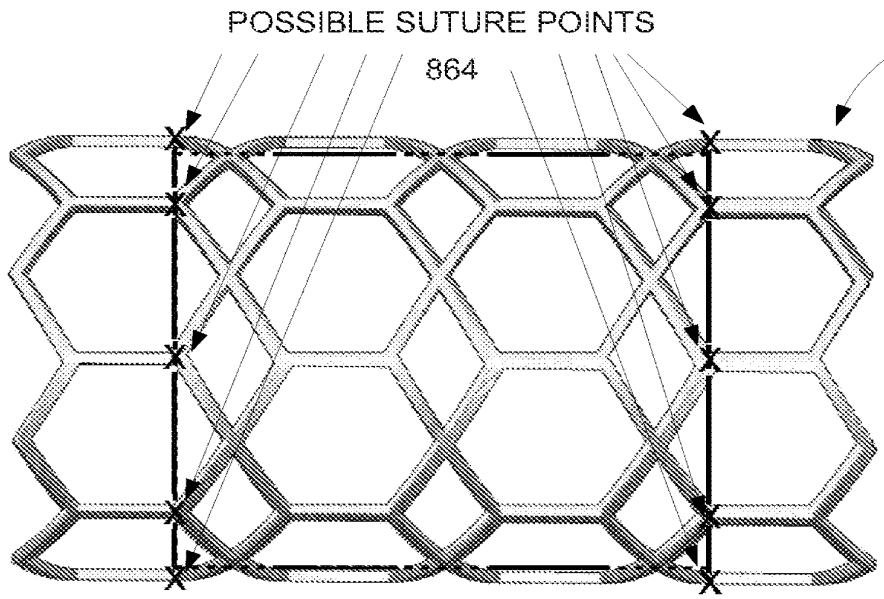

POSSIBLE SUTURE POINTS
864
860

FIG. 8K

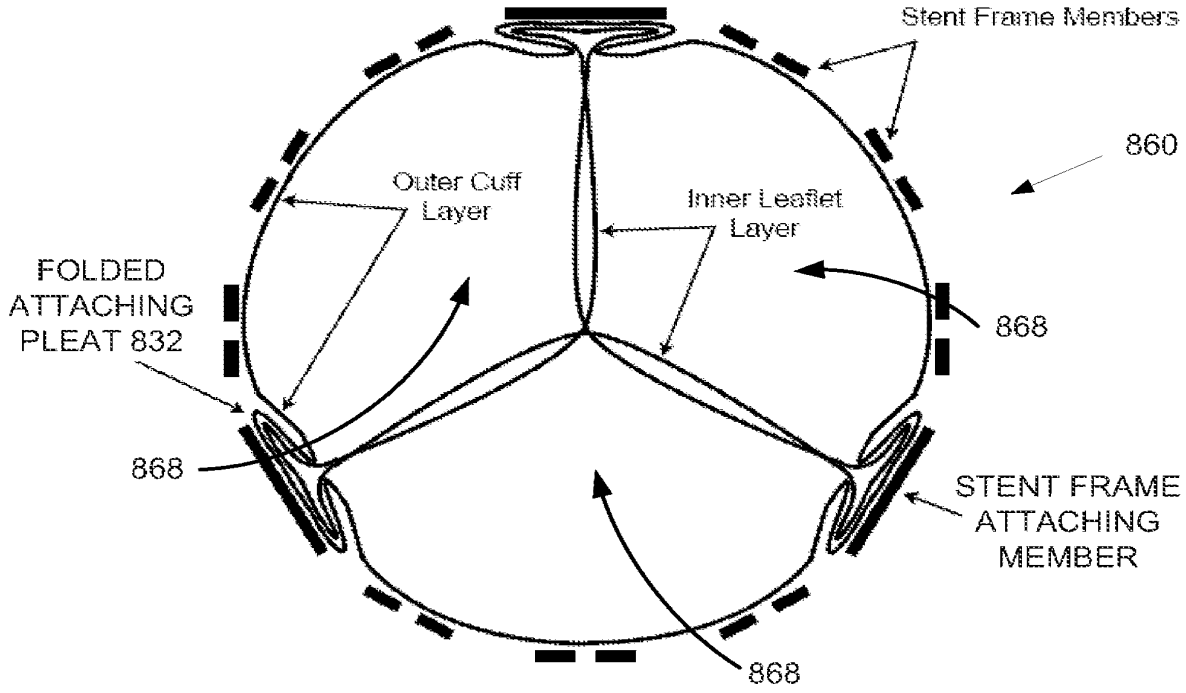
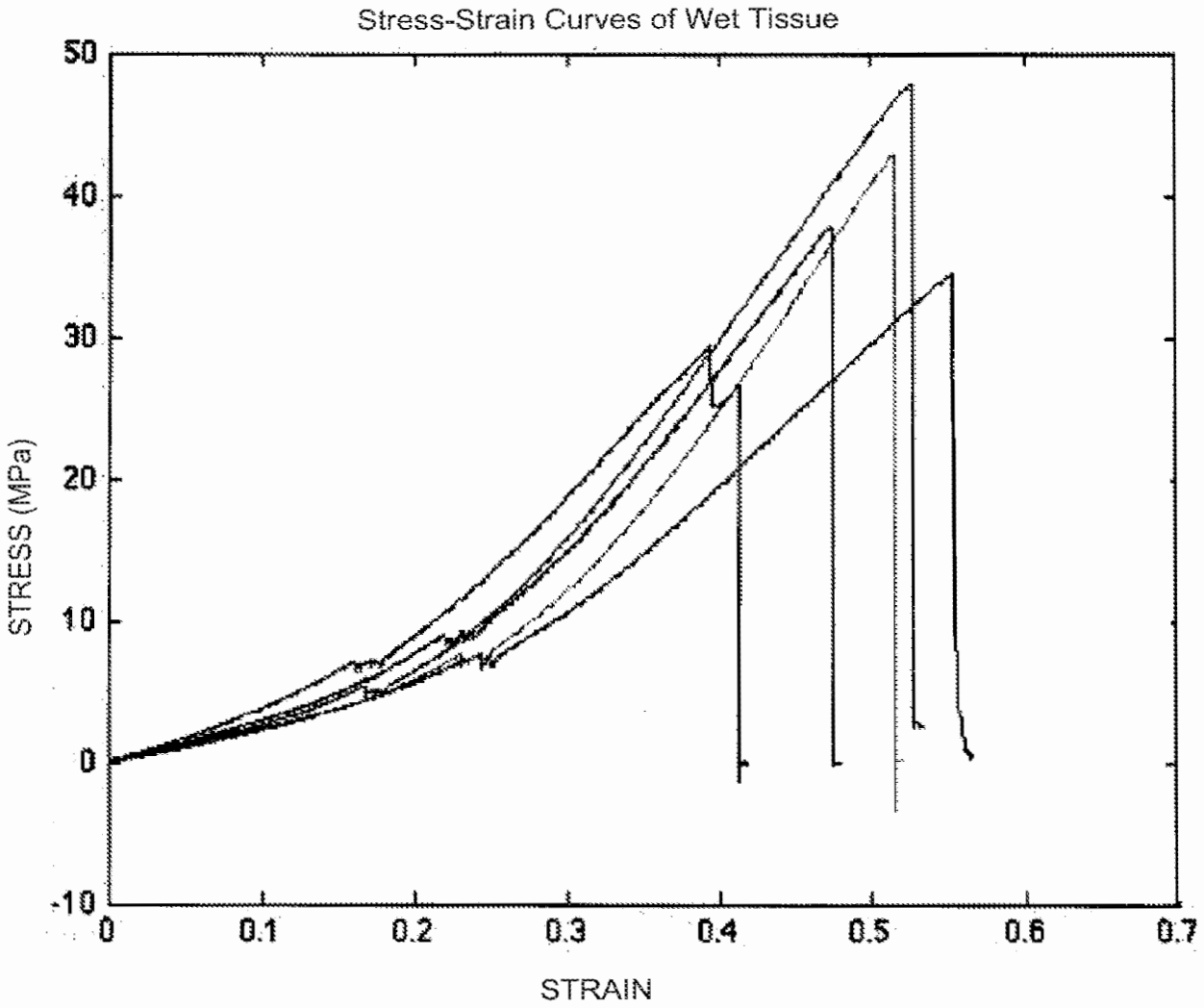


FIG.8L



Stress-strain curves in wet or hydrated state of five samples. Each curve corresponds to a separate sample.

FIG. 9

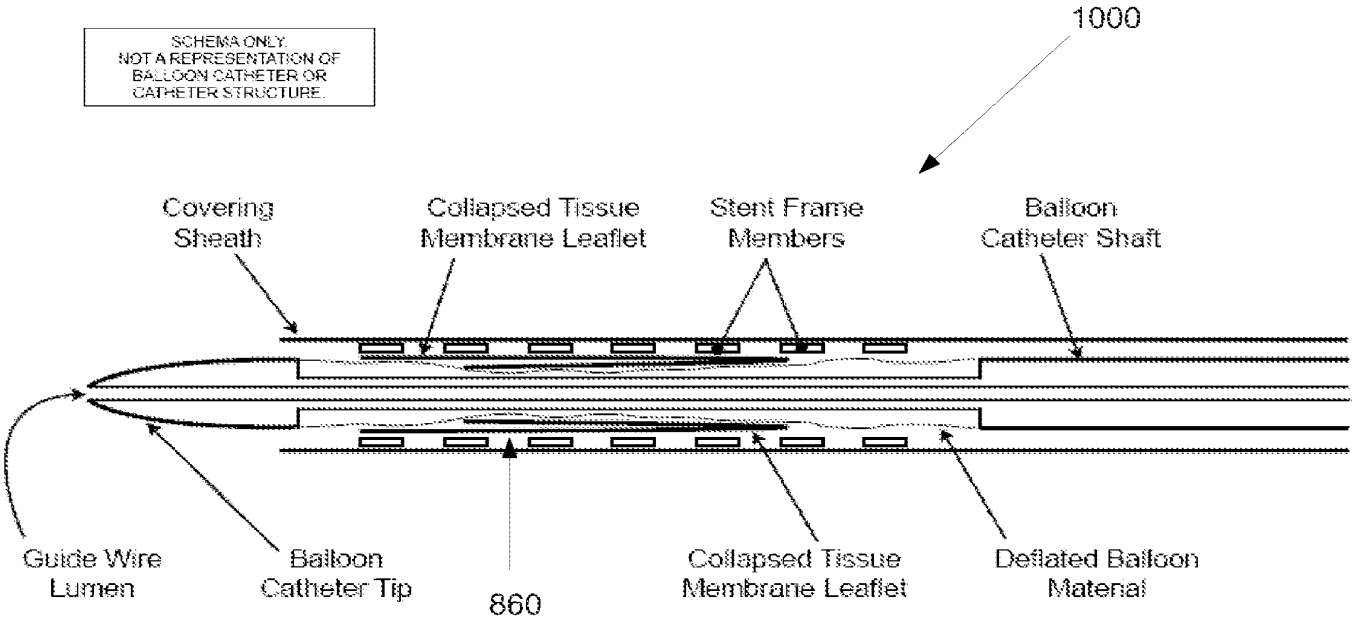

SCHEMA ONLY.
NOT A REPRESENTATION OF
BALLOON CATHETER OR
CATHETER STRUCTURE.
1000
Covering Sheath
Collapsed Tissue Membrane Leaflet
Stent Frame Members
Balloon Catheter Shaft
Guide Wire Lumen
Balloon Catheter Tip
860
Collapsed Tissue Membrane Leaflet
Deflated Balloon Material

FIG.10

Photo of Tissue Leaflet Assembly Attached in Frame to Form Implantable Prosthetic Heart Valve

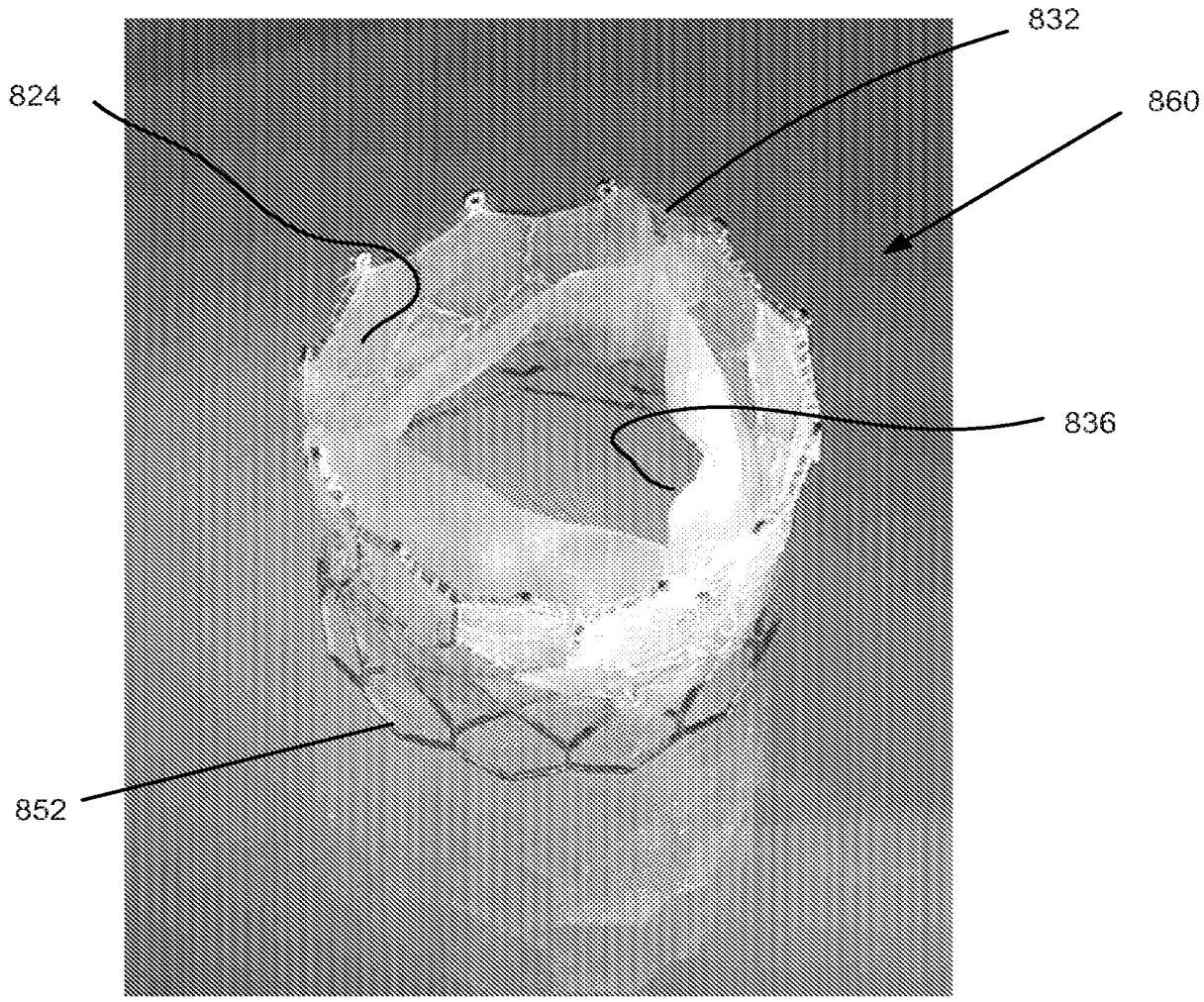


FIG.11A

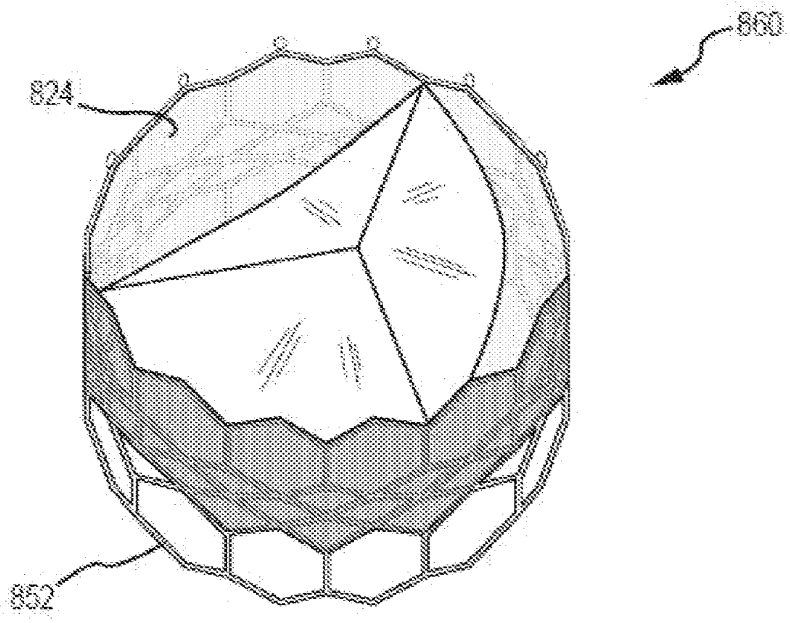


FIG. 11B

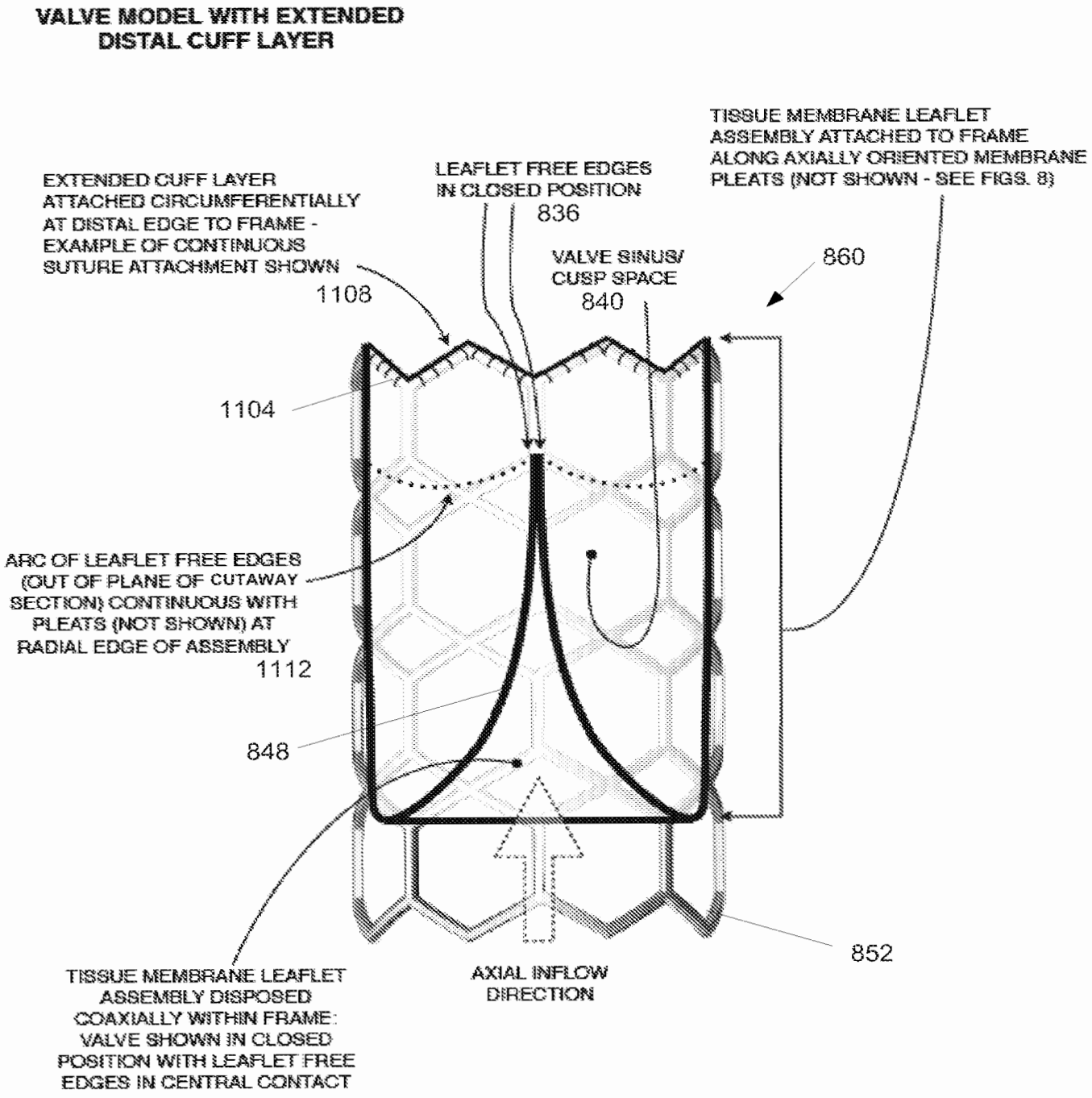

VALVE MODEL WITH EXTENDED DISTAL CUFF LAYER
TISSUE MEMBRANE LEAFLET ASSEMBLY ATTACHED TO FRAME ALONG AXIALLY ORIENTED MEMBRANE PLEATS (NOT SHOWN - SEE FIGS. 8)
LEAFLET FREE EDGES IN CLOSED POSITION
836
EXTENDED CUFF LAYER ATTACHED CIRCUMFERENTIALLY AT DISTAL EDGE TO FRAME - EXAMPLE OF CONTINUOUS SUTURE ATTACHMENT SHOWN
1108
VALVE SINUS/ CUSP SPACE
840
860
1104
ARC OF LEAFLET FREE EDGES (OUT OF PLANE OF CUTAWAY SECTION) CONTINUOUS WITH PLEATS (NOT SHOWN) AT RADIAL EDGE OF ASSEMBLY
1112
848
852
TISSUE MEMBRANE LEAFLET ASSEMBLY DISPOSED COAXIALLY WITHIN FRAME: VALVE SHOWN IN CLOSED POSITION WITH LEAFLET FREE EDGES IN CENTRAL CONTACT
AXIAL INFLOW DIRECTION

FIG. 11C

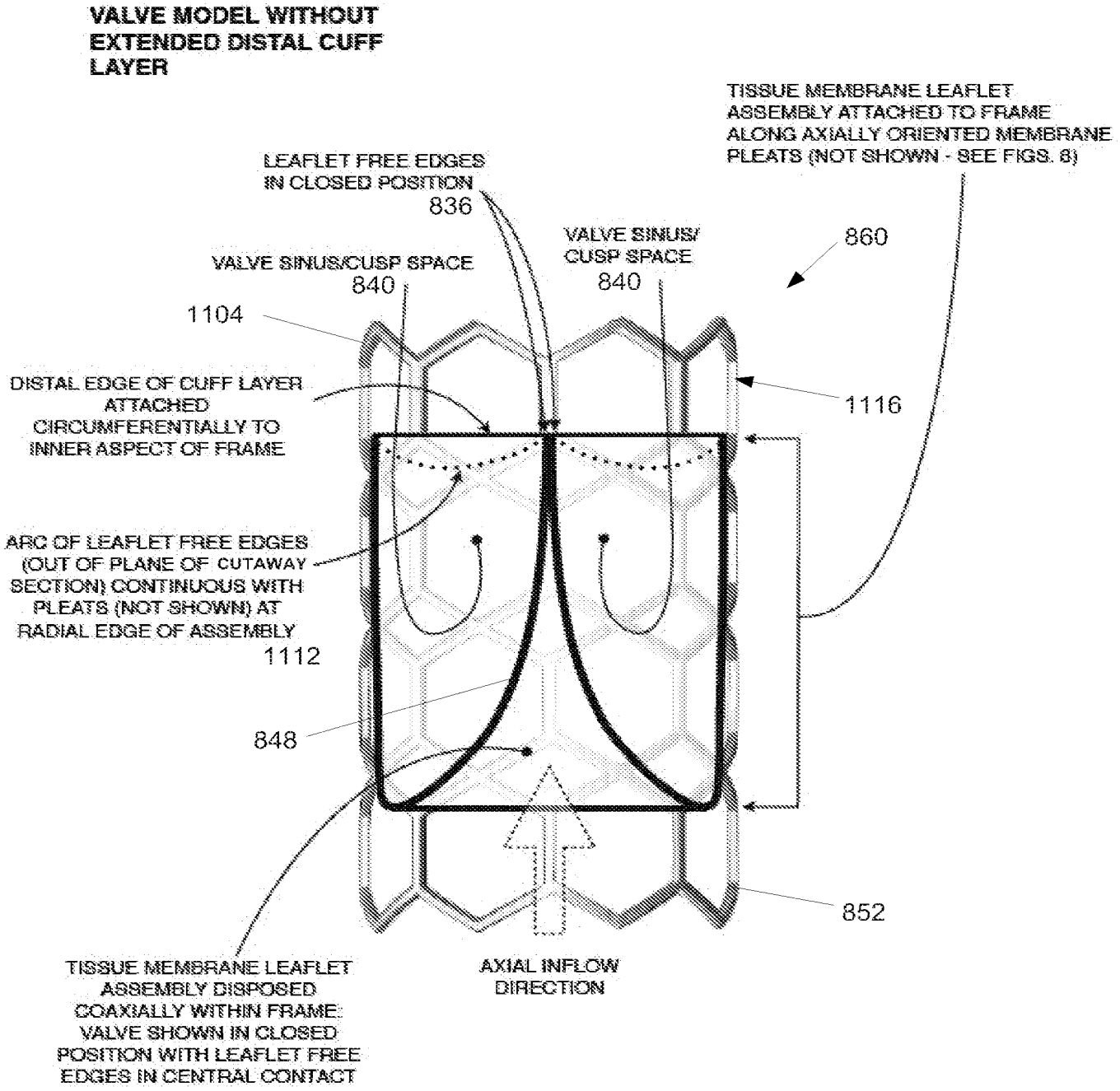

VALVE MODEL WITHOUT EXTENDED DISTAL CUFF LAYER
TISSUE MEMBRANE LEAFLET ASSEMBLY ATTACHED TO FRAME ALONG AXIALLY ORIENTED MEMBRANE PLEATS (NOT SHOWN - SEE FIGS. 8)
LEAFLET FREE EDGES IN CLOSED POSITION
836
VALVE SINUS/CUSP SPACE
840
VALVE SINUS/ CUSP SPACE
840
860
1104
DISTAL EDGE OF CUFF LAYER ATTACHED CIRCUMFERENTIALLY TO INNER ASPECT OF FRAME
1116
ARC OF LEAFLET FREE EDGES (OUT OF PLANE OF CUTAWAY SECTION) CONTINUOUS WITH PLEATS (NOT SHOWN) AT RADIAL EDGE OF ASSEMBLY
1112
848
852
TISSUE MEMBRANE LEAFLET ASSEMBLY DISPOSED COAXIALLY WITHIN FRAME: VALVE SHOWN IN CLOSED POSITION WITH LEAFLET FREE EDGES IN CENTRAL CONTACT
AXIAL INFLOW DIRECTION

FIG. 11D

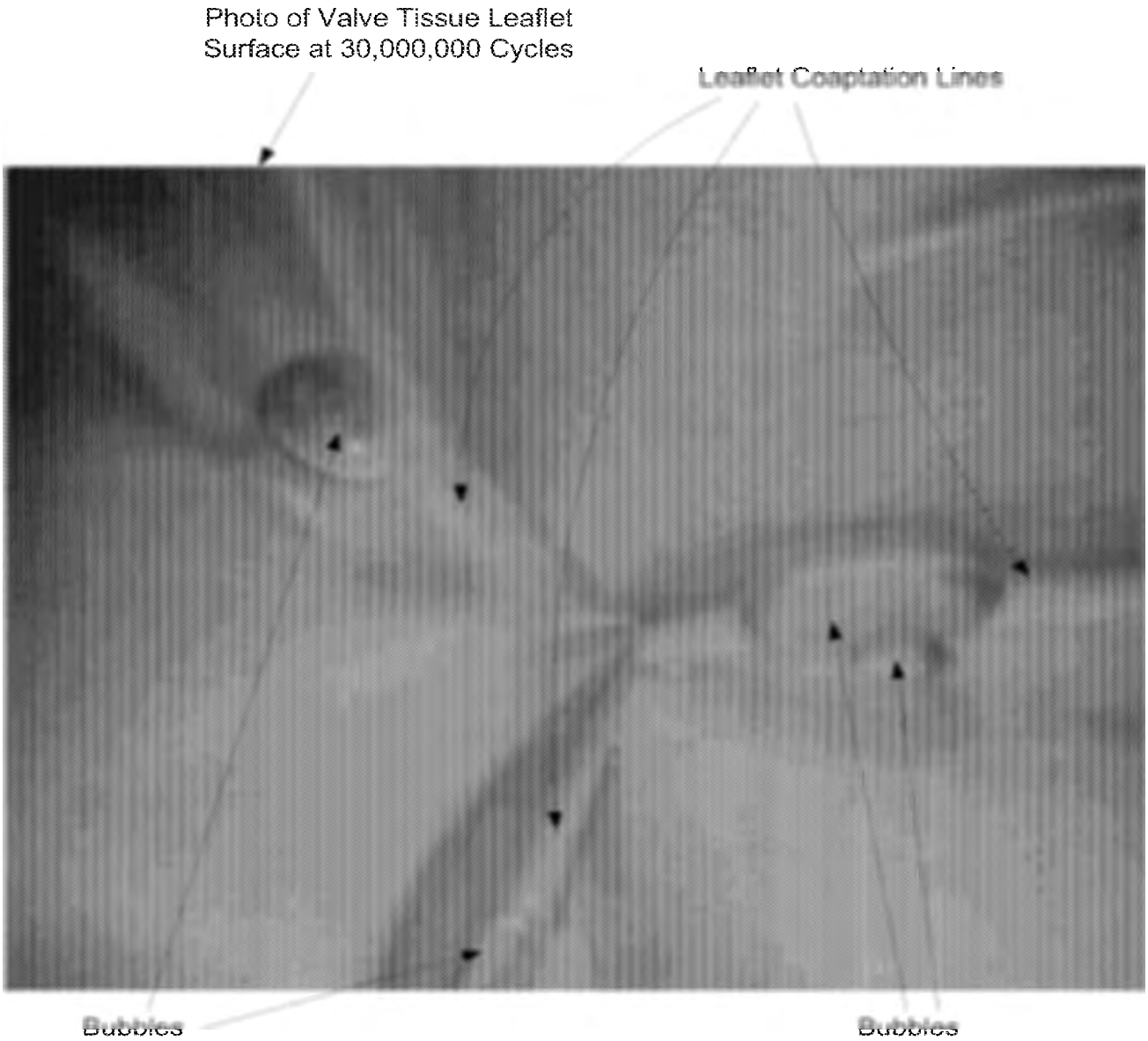


FIG.12

Surgeon Holding a Premounted Percutaneously Deliverable Heart Valve Associated With a Catheter and Residing Within Sterile Packaging

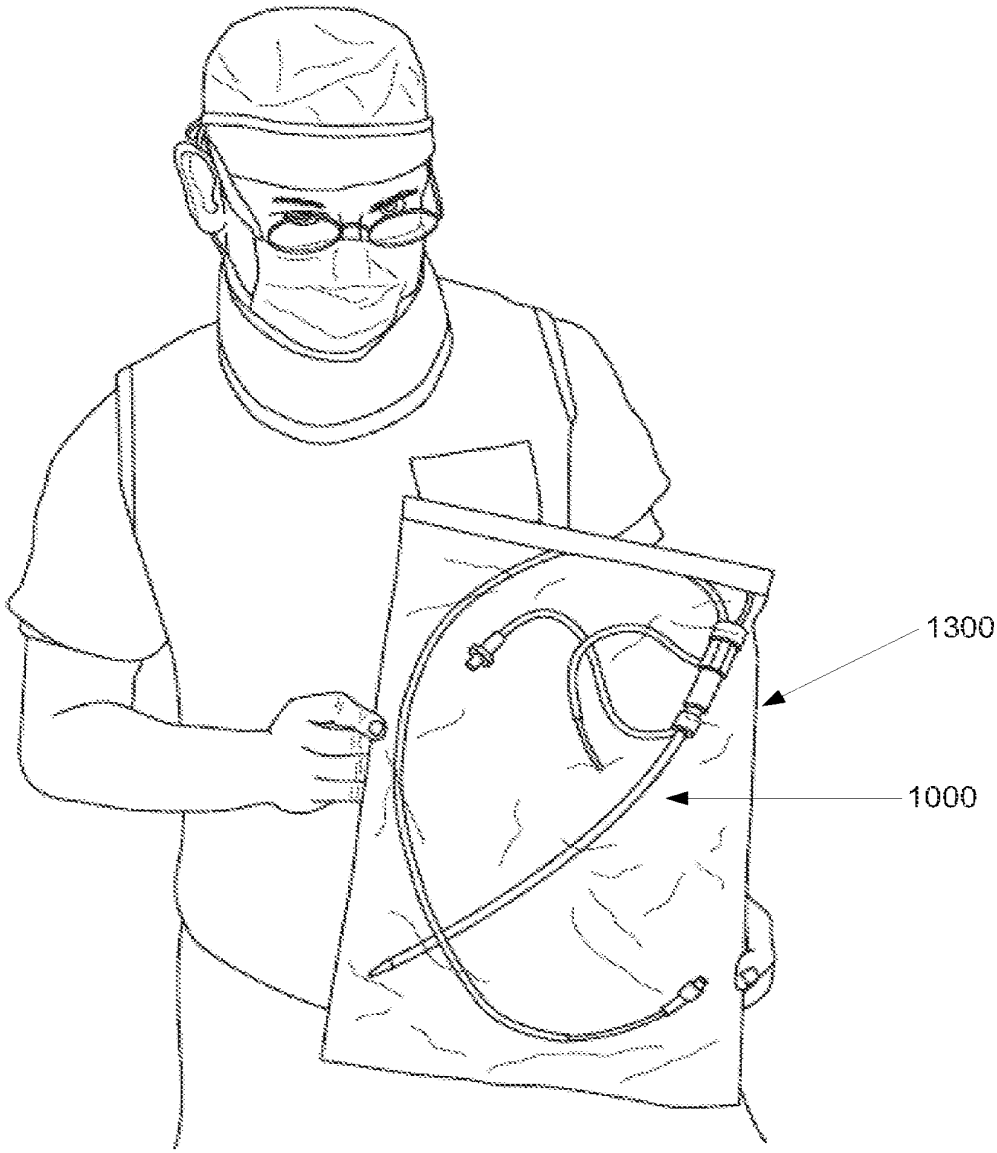


FIG.13

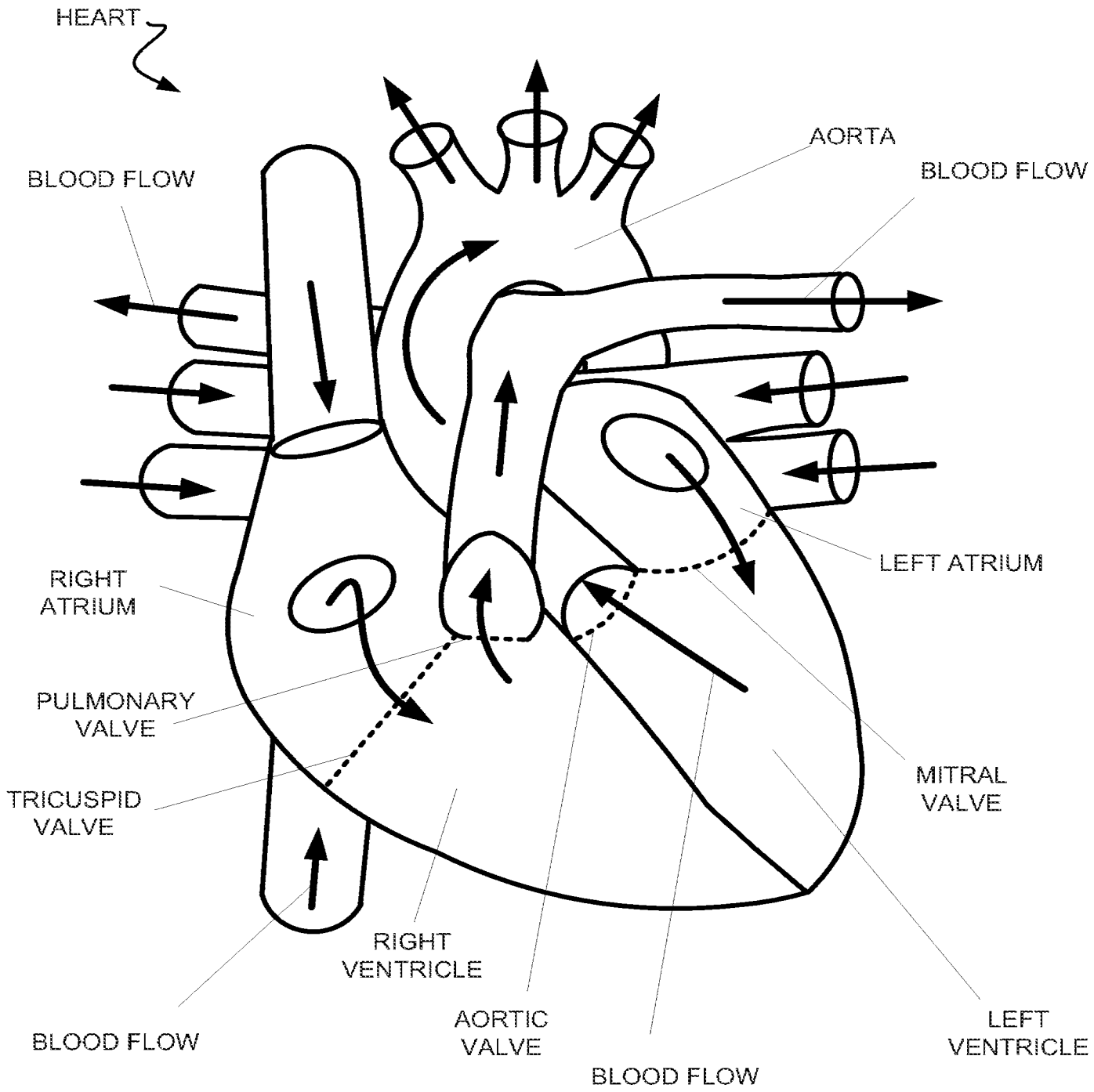

HEART
BLOOD FLOW
AORTA
BLOOD FLOW
LEFT ATRIUM
RIGHT ATRIUM
PULMONARY VALVE
TRICUSPID VALVE
MITRAL VALVE
RIGHT VENTRICLE
BLOOD FLOW
AORTIC VALVE
BLOOD FLOW
LEFT VENTRICLE

FIG.14

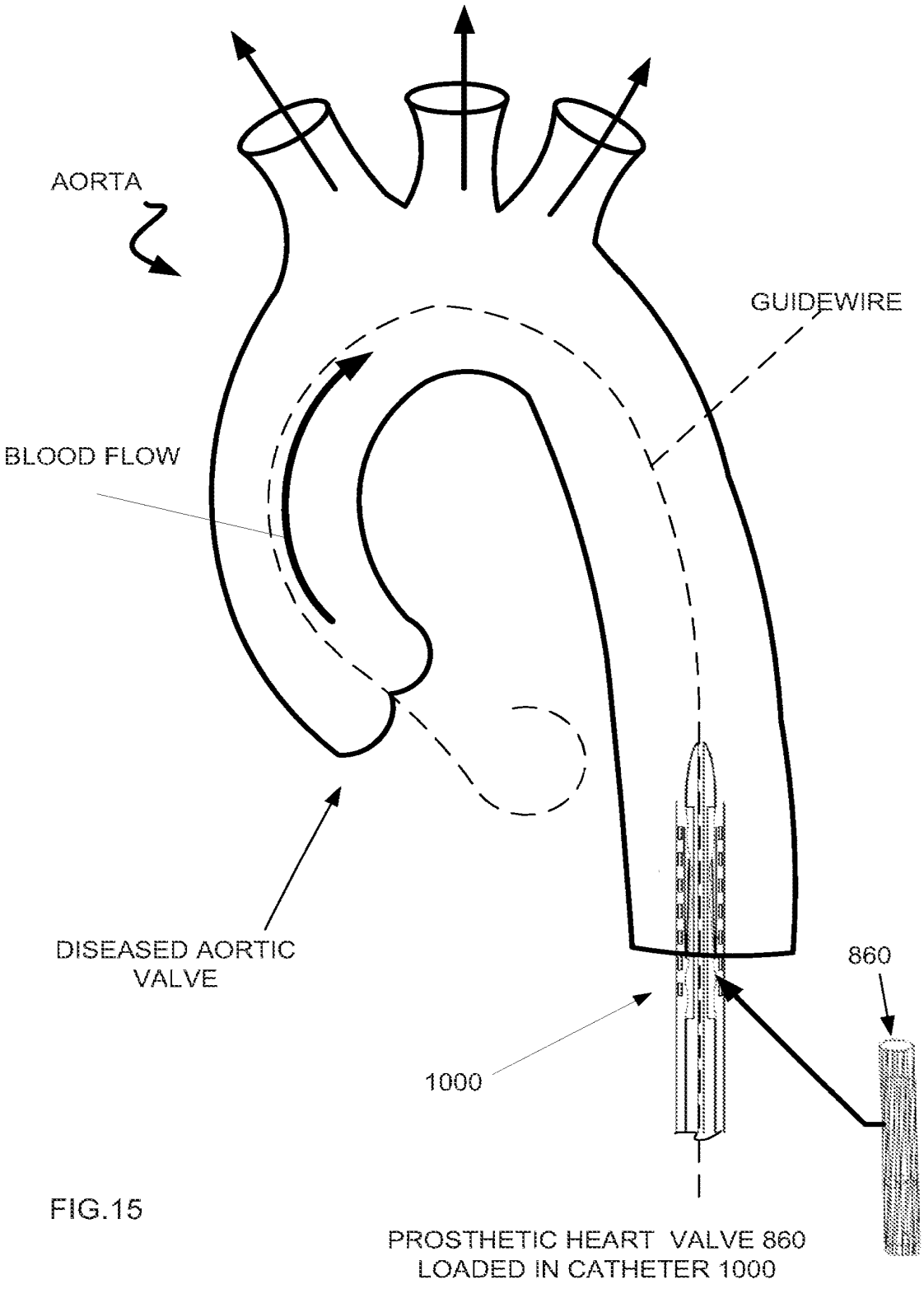

AORTA
GUIDEWIRE
BLOOD FLOW
DISEASED AORTIC VALVE
860
1000
PROSTHETIC HEART VALVE 860 LOADED IN CATHETER 1000

FIG.15

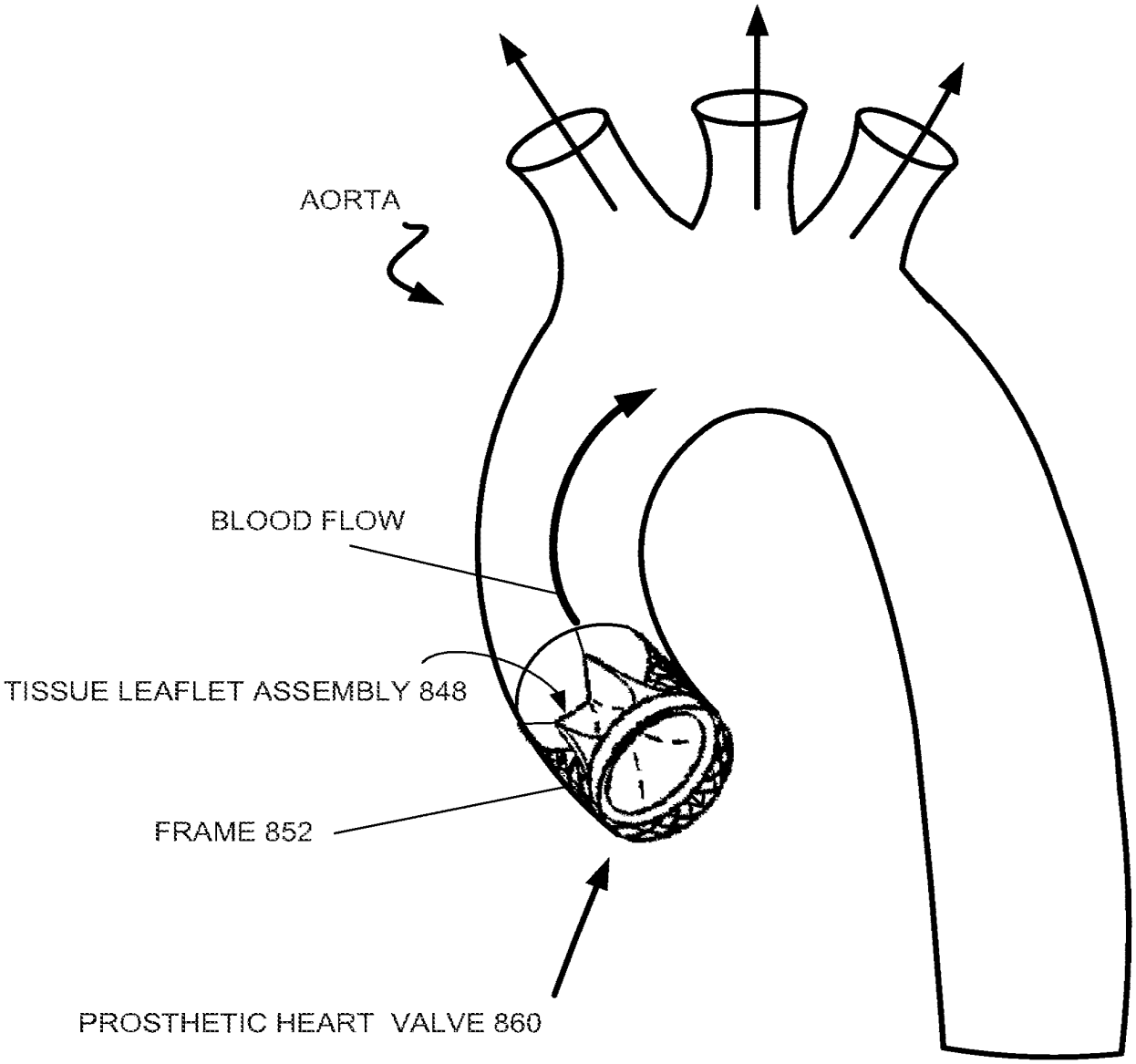


FIG. 16

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(54) **Title**: METHOD AND APPARATUS FOR THE ENDOLUMINAL DELIVERY OF INTRAVASCULAR DEVICES

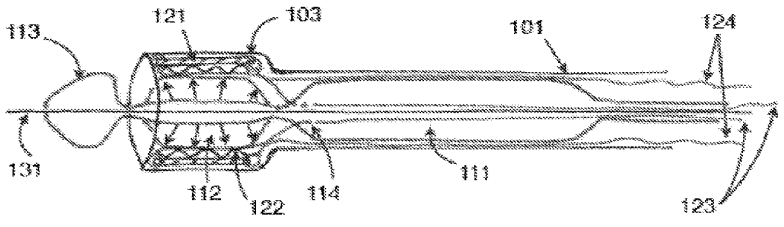


FIG. 4B

(57) **Abstract**: A dual-balloon delivery catheter system includes a carrier segment that is a lead/carrier balloon or mandrel at a distal portion of a catheter. The carrier segment is sequentially arrayed with a more proximally positioned delivery segment, wherein the delivery segment is a delivery balloon or mandrel. The first carrier segment expands the stent-valve a sufficient amount to receive the delivery segment after the carrier segment is moved away from the sent-valve. The delivery segment is then positioned at the target site and the stent-valve is then deployed.

WO 2012/006124 A2

METHOD AND APPARATUS FOR THE ENDOLUMINAL DELIVERY OF INTRAVASCULAR DEVICES

FIELD

Embodiments of the one or more present inventions relate to surgical methods and apparatus in general, and more particularly to surgical methods and apparatus for the endoluminal delivery of intravascular devices to a site within the body.

For the purposes of illustration but not limitation, embodiments of the one or more present inventions will hereinafter be discussed in the context of delivering a percutaneous heart valve to a valve seat located within the heart; however, it should be appreciated that at least one embodiment of the one or more present inventions is also applicable to other endoluminal delivery applications.

BACKGROUND

Percutaneous aortic valves, such as those available from Edwards Lifesciences LLC (Irvine, CA) under the tradename SAPIEN® typically utilize an expandable frame having valve leaflets attached thereto. This expandable frame essentially comprises a stent, with the valve leaflets (preferably in the form of tissue membrane) attached to a portion thereof. For this reason, these percutaneous aortic valves are commonly referred to as "stent-valves". Typically, the percutaneous aortic stent-valve is compressed down upon a deflated balloon catheter, the combined assembly is then inserted into the femoral artery through a covering sheath, and then the combined assembly is delivered endoluminally through the iliac artery and aorta to the valve seat. At the valve seat, the balloon is used to expand the stent so that the stent-valve is set at the valve seat, then the balloon is deflated, and finally the balloon catheter is withdrawn, whereupon the leaflets of the stent-valve act in place of the natural leaflets of the diseased aortic valve.

Percutaneous heart valves of the sort described above currently show great promise, particularly for elderly and/or otherwise infirm patients who cannot tolerate the trauma of conventional open heart valve replacement procedures.

Unfortunately, current percutaneous heart valve systems require the use of relatively large delivery/deployment apparatus. More particularly, since the internal balloon must be capable of expanding the stent portion of the stent-valve to the full size of the natural valve seat, and since the deflated size of a balloon having this full-expansion capability is relatively large, and since the stent-valve must be disposed circumferentially outboard of the balloon, the overall size of the delivery/deployment apparatus is necessarily large. By way of example but not limitation, the Edwards SAPIEN® delivery/deployment apparatus is typically approximately 7 to 8 mm in diameter.

Clinically, this can present a significant problem for the surgeon, since the preferred access to the vascular system of the patient is via the femoral artery, with subsequent delivery to the aortic valve seat via the iliac artery and aorta. However, the femoral artery is typically only about 5 to 8 mm in diameter, and this 5-8 mm range is for the general population as a whole - elderly female patients, who are expected to make up a substantial percentage of the candidate population for percutaneous aortic valve replacement, are on the smaller end of this range (e.g., perhaps 5-6 mm in diameter). Thus, it can be difficult or even impossible to pass the 7-8 mm (diameter) SAPIEN® device through the 5-6 mm (diameter) femoral artery of an elderly female patient, particularly where the femoral artery is tortuous, stenotic and/or occluded. Surgical incision has sometimes been required in order to gain access to a higher level of the ilio-femoral artery (e.g., within the pelvis) that is large enough to accommodate the stent-valve assembly. However, this approach is generally more invasive, and often leads to complications such as substantial bleeding and artery obstruction.

Referring now to Fig. 1, a schematic side view of a catheter-deliverable device, or stent-valve, known in the prior art is shown. The stent-valve may have an expanded diameter of approximately 25 mm. However, the stent-valve can be compressed to approximately 4 mm in diameter. As shown in Fig. 2, to achieve expansion of the stent-valve, it may be mounted on a typical prior art large-diameter delivery balloon catheter that is inflatable to a diameter of 25 mm. However, the combined diameter of the stent-valve mounted on to the large-diameter delivery balloon catheter is perhaps 18 Fr or 6 mm, which is too large to insert into some patient's femoral artery.

For the foregoing reasons, there is a substantial need for a new and improved method and apparatus for the endoluminal delivery of intravascular devices to a site within the body.

SUMMARY

It is to be understood that embodiments of the one or more present inventions include a variety of different versions or embodiments, and this Summary is not meant to be limiting or all-inclusive. This Summary provides some general descriptions of some of the embodiments, but may also include some more specific descriptions of other embodiments.

When first considered, a solution associated with the difficulty of placing a stent-valve in a relatively small femoral artery appears to be use of a small delivery device. Accordingly, a small-diameter delivery balloon initially appears to address the problem. However, and with reference now to Fig. 3, if a small diameter delivery balloon catheter is used, then while the stent-valve can be compressed to a relatively small diameter, the small-diameter delivery balloon is incapable of fully expanding the stent-valve to 25 mm; that is, a small diameter

delivery balloon may only be capable of expanding the stent-valve to approximately 10 mm in diameter, for example.

At least one embodiment of the one or more present inventions addresses the aforementioned problems associated with the prior art by providing a novel method and apparatus for the endoluminal delivery of intravascular devices to a site within the body, at least one embodiment of the one or more present inventions takes advantage of the principle of dividing the volume of the stent-valve delivery apparatus into smaller diameter parts for separate insertion into the vascular system of a patient (e.g., into a relatively small diameter access vessel such as the femoral artery) and then re-assembling those parts within another portion of the vascular system of the patient (e.g., in a larger diameter vessel such as the aorta) which can accommodate the full size of the assembled components. By dividing the balloon expansion task into two serially-deployed balloons, activated in a staged fashion, the stent-valve can be delivered with a smaller profile, yet full stent-valve expansion at the valve seat can be ensured. Accordingly, novel devices and methods are proposed that involve transfer of a deliverable device, such as a stent-valve, after insertion into the body from its "carrier segment" to another "delivery segment" which may reside on the same or separate catheters, and deployment of the stent-valve from that "delivery segment" that is capable of expansion to suitable diameter for the stent-valve.

In at least one embodiment of the one or more present inventions, the stent-valve can be pre-mounted within a packaged pre-assembled delivery system for ready transport and clinical use.

In a first preferred form of the one or more present inventions, the first "carrier" balloon and second "delivery" balloon are mounted on separate inserter elements for independent delivery to the larger blood vessel, such as the aorta, where the second "delivery" balloon is united with the then-partially-expanded stent-valve – in this form, each balloon is independently advanced to the aorta via its own inserter element.

In a second preferred form of the one or more present inventions, the first and second balloons are serially disposed on a single inserter element, with the first "carrier" balloon being mounted to the inserter element distal to (or, optionally, more proximal to) the second "delivery" balloon – in this form, a single inserter element is used to sequentially position the first "carrier" balloon and second "delivery" balloon relative to the stent-valve.

In a third preferred form of the one or more present inventions, the first "carrier" balloon and second "delivery" balloon are mounted on separate inserter elements, but these inserter elements are arranged in a co-axial fashion so as to permit a telescoping action between the two inserter elements (and hence a telescoping action between the first "carrier" balloon and the

second "delivery" balloon). In this form, the first "carrier" balloon shaft, being coaxially mounted upon a leading guide wire, can act as something of a firmer guidewire for the second "delivery" balloon.

In addition to the foregoing, after initial expansion of the stent-valve via the first "carrier" balloon, the first "carrier" balloon catheter can be removed and replaced by a shaped catheter element in order to provide guidance and assistance in traversing the central arteries and crossing the plane of (and, optionally, preparing) the native valve seat. This shaped catheter element can be disposed on an inserter element distal to the second "delivery" balloon or to the first carrier balloon, if desired.

If desired, the first "carrier" balloon can alternatively be another expandable device, e.g., the first "carrier" balloon (which constitutes the mounting segment for the stent-valve) can be an expandable mandrel. Alternatively, the stent-valve may be initially mounted on a non-expanding element, that is, simply a low-profile mandrel or other segment of the delivery catheter.

It should be appreciated that while at least one embodiment of the one or more present inventions has sometimes been discussed in the context of delivering a stent-valve to the aortic valve seat, it may also be used to deliver other valves to other valve seats, and/or for delivering other intravascular devices to other sites within the body.

It should also be appreciated that while at least one embodiment of the one or more present inventions is sometimes discussed in the context of advancing the stent-valve through the arterial system of the body, it may also be used to advance the stent-valve through the venous system of the body, or to endoluminally advance a device through some other luminal system of the body.

In at least one embodiment of the one or more present inventions, the covering sheath (through which the various components are advanced into the blood vessel) can be flexible and expandable so as to allow initial expansion of the stent-valve, and the exchange of the first "carrier" balloon and the second "delivery" balloon within the covering sheath, so that the apparatus is continuously protected.

It will be seen that at least one embodiment of the one or more present inventions provides a novel method and apparatus for the endoluminal delivery of an intravascular device to a site within the body.

Accordingly, at least one embodiment described herein is directed to a stent-valve and delivery system that is inserted separately into the femoral artery, then assembled inside the aorta, and thereafter advanced for deployment at the valve plane. This means that the limiting size of the artery (or vein, for the pulmonary valve) access diameter is determined by the largest

single piece of the system - effectively the stent/valve itself. When the stent/valve is compressed without the balloon catheter, it is possible to deliver a valve into the circulation in as small as 14 French sheath rather than an 18 to 24 French, as has previously been achieved.

In at least one embodiment, an in-line dual-balloon delivery catheter system includes a carrier segment that is a lead/carrier balloon or mandrel at the distal portion of a catheter with the carrier segment arrayed in-line on a catheter shaft with a more proximally positioned delivery segment together at the distal portion of the catheter shaft. In essence, since the first "carrier" balloon only needs to expand the stent-valve a sufficient amount to receive the deflated second "delivery" balloon, the first "carrier" balloon can be quite small in its deflated condition. Moreover, the stent-valve, unrestricted by the traditional need for mounting on a single, relatively large deployment balloon, can be compressed to its minimum structural diameter for mounting on the relatively small first "carrier" balloon. As a result, the combined assembly (i.e., of carrier balloon catheter and stent-valve) can be much smaller in diameter than previous delivery devices at the time of accessing the vascular system of the patient. At the same time, by thereafter uniting the stent-valve with the second, larger "delivery" balloon, sufficient stent expansion can be provided to ensure secure valve seating.

In at least one embodiment, a woven wire "stent" with or without sheath investment is provided wherein its length is coupled to diameter. Nitinol or another alloy wire is formed in an expanded sheath shape and compressed by traction on trailing wire ends. At the point of the procedure requiring distal sheath expansion, the traction is released to allow expansion to a mechanically biased open position. Alternatively, traction wires may be attached to a distal end of the wire weave within the sheath and a traction force, there applied, causes simultaneous expansion and shortening of the distal end of the sheath, thereby advantageously releasing the underlying mounted stent-valve and exposing it for deployment.

In at least one embodiment a mechanism is provided for retaining a stent-valve frame on a delivery balloon by magnetic or electromagnetic means. The frame is preferably constituted of or contains ferrous metal elements. By such means, a stent-valve can be securely advanced through the vascular system without need for a covering sheath, thereby simplifying the delivery procedure and the system. The stent-valve is retained on the balloon segment by magnetic force.

In at least one embodiment, a device that utilizes magnetic force to deploy and, if desired, later retrieve a stent-valve is provided, the device using a magnetic force set at a level to permit ready balloon expansion of a stent-valve at a plane of the diseased native valve. As the frame of the stent-valve is pushed away from the magnet, retention force weakens, thereby allowing unimpeded final device expansion. A stronger magnet/electromagnet mounted on a separate catheter can be used to retrieve or reposition the stent-valve. In addition, a strong

magnet mounted on a retrieval catheter can be used to retract the stent-valve frame from the native valve seat.

For the purposes of illustration but not limitation, embodiments of the one or more present inventions are hereinafter discussed in the context of delivering a prosthetic stent-valve to the aortic valve seat; however, it should be appreciated that at least one embodiment of the one or more present inventions is also applicable to other endoluminal delivery applications.

Accordingly, in at least one embodiment, a system for providing endoluminal delivery of a deliverable device through vasculature of a patient to a delivery site within the patient is provided, the system comprising:

an outer delivery sheath including a distal section, wherein at least a portion of the outer delivery sheath is sized for insertion into the vasculature of the patient;

a carrier segment located at a distal portion of a catheter shaft, the carrier segment having an outer surface sized to temporarily hold the deliverable device in the distal section of the outer delivery sheath, wherein at least a portion of the catheter shaft is located within and coaxial to the outer delivery sheath; and

a delivery segment located coaxial to the outer delivery sheath, the delivery segment having an outer surface sized to radially fit within the deliverable device after detaching the deliverable device from the carrier segment when the deliverable device resides within the distal section of the outer delivery sheath, wherein the delivery segment is configured to deploy the deliverable device at the delivery site.

In addition to the foregoing, in at least one embodiment at least a portion of the distal section of the outer delivery sheath is expandable. In at least one embodiment, the at least a portion of the distal section of the outer delivery sheath comprises one or more electrically activated elements. In at least one embodiment, the at least a portion of the distal section of the outer delivery sheath comprises one or more piezo-ceramic elements. In at least one embodiment, the at least a portion of the distal section of the outer delivery sheath comprises a passively expandable material that is expandable upon application of an outward radial force applied by at least one of the carrier segment and the delivery segment. In at least one embodiment, the at least a portion of the distal section of the outer delivery sheath expands upon application of a tensile force to the at least a portion of the distal section.

In at least one embodiment, the distal section includes at least one of an internal projection and a narrowed area extending radially inward from an interior surface of the distal section.

In at least one embodiment, a portion of an internal surface of the outer delivery sheath further comprises a guide for retaining at least a portion of a longitudinally extending element

configured to selectively manipulate at least a part of the outer delivery sheath or a structure coaxial to the outer delivery sheath. In at least one embodiment, a portion of an internal surface of the outer delivery sheath further comprises a guide, the guide comprising at least one of:

(a) a lumen; and

(b) a grommet;

wherein the guide retains at least one control line for selective retention of the deliverable device.

In at least one embodiment, the carrier segment and the delivery segment are both situated upon the catheter shaft. In at least one embodiment, the carrier segment is situated upon the catheter shaft, and wherein the delivery segment is associated with a delivery segment shaft that is coaxial to the catheter shaft and axially moveable relative to the catheter shaft. In at least one embodiment, the carrier segment is an expandable balloon having an expanded diameter smaller than an expanded diameter for the delivery segment. In at least one embodiment, the delivery segment is an expandable balloon having an expanded diameter larger than an expanded diameter for the carrier segment. In at least one embodiment, at least one of the carrier segment and the delivery segment is a mandrel. In at least one embodiment, the mandrel is expandable by mechanical or electromechanical means. In at least one embodiment, the mandrel is not expandable.

In at least one embodiment, the delivery segment is located axially proximal to the carrier segment. In at least one embodiment, the delivery segment is located axially distal to the carrier segment.

In at least one embodiment, one or both of the carrier segment and the delivery segment include at least one magnet or electromagnet to aid manipulation of the deliverable device.

In at least one embodiment an assembly for intravascular delivery of a deliverable device to a delivery site within a patient is provided, comprising:

a first catheter including a first catheter shaft;

a carrier segment situated along the first catheter shaft, the carrier segment configured to receive the deliverable device prior to inserting the first catheter within the patient; and

a delivery segment sequentially positioned in an axial orientation relative to the carrier segment, wherein the delivery segment is configured to engage the deliverable device within the patient while the deliverable device is coaxial to at least a portion of the first catheter, and wherein the delivery segment is configured to thereafter deploy the deliverable device at the delivery site.

[0037] In at least one embodiment, the delivery segment is also situated along the first catheter. In at least one embodiment, the delivery segment is situated along a second catheter, the second catheter comprising a coaxial lumen through which passes the first catheter. In at least one embodiment, at least one of the first catheter and the second catheter comprise a curved distal portion.

One or more embodiments of the one or more present inventions also pertain to methods of delivering a device, such as a stent-valve, within a patient. Accordingly, in at least one embodiment, a method of delivering a deliverable device through vasculature of a patient to a target site within the patient is provided, comprising:

mounting the deliverable device on a selectively expandable carrier segment located along a catheter shaft, wherein at least a portion of the catheter shaft is located within and coaxial to an outer delivery sheath;

inserting the outer delivery sheath and catheter shaft into the patient;

moving the outer delivery sheath within the patient to position the selectively expandable carrier segment and the deliverable device near the target site;

partially expanding the deliverable device using the selectively expandable carrier segment while the deliverable device remains at least partially within the outer delivery sheath;

positioning a delivery segment radially within the deliverable device and partially expanding the delivery segment to facilitate engagement of the delivery segment with the deliverable device;

moving the delivery segment and deliverable device to the target site; and

deploying the deliverable device at the target site by further expanding the delivery segment.

Various components are referred to herein as "operably associated." As used herein, "operably associated" refers to components that are linked together in operable fashion, and encompasses embodiments in which components are linked directly, as well as embodiments in which additional components are placed between the two linked components.

As used herein, "at least one," "one or more," and "and/or" are open-ended expressions that are both conjunctive and disjunctive in operation. For example, each of the expressions "at least one of A, B and C," "at least one of A, B, or C," "one or more of A, B, and C," "one or more of A, B, or C" and "A, B, and/or C" means A alone, B alone, C alone, A and B together, A and C together, B and C together, or A, B and C together.

Various embodiments of the present inventions are set forth in the attached figures and in the Detailed Description as provided herein and as embodied by the claims. It should be

understood, however, that this Summary does not contain all of the aspects and embodiments of the one or more present inventions, is not meant to be limiting or restrictive in any manner, and that the invention(s) as disclosed herein is/are understood by those of ordinary skill in the art to encompass obvious improvements and modifications thereto.

Additional advantages of at least one embodiment of the one or more present inventions will become readily apparent from the following discussion, particularly when taken together with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

To further clarify the above and other advantages and features of the one or more present inventions, a more particular description of the one or more present inventions is rendered by reference to specific embodiments thereof which are illustrated in the appended drawings. It should be appreciated that these drawings depict only typical embodiments of the one or more present inventions and are therefore not to be considered limiting of its scope. The one or more present inventions are described and explained with additional specificity and detail through the use of the accompanying drawings in which:

Fig. 1 is a schematic side view of a catheter-deliverable device frame (or stent-valve) known in the prior art;

Fig. 2 is a schematic side view of a typical prior art large-diameter delivery balloon catheter in a deflated state;

Fig. 3 is a schematic side view of a small-diameter delivery balloon catheter in a deflated state;

Fig. 4A is a side view of an in-line dual balloon delivery system in accordance with at least one embodiment of the one or more present inventions;

Fig. 4B is a side view of the system shown in Fig. 4A, wherein the carrier balloon is dilated to partially expand a stent-valve to accommodate the larger delivery balloon (catheter inflation ports, lumens, wire lumens not shown for clarity);

Fig. 4C is a side view of the system shown in Fig. 4B, wherein the deflated carrier balloon is advanced out of the partially expanded valve device as the delivery balloon is advanced into the stent-valve to "capture" or "dock" with the stent-valve;

Fig. 4D is a side view of the system shown in Fig. 4C, wherein the carrier balloon is optionally inflated to facilitate crossing the plane of the diseased heart valve with the delivery system, and wherein the delivery balloon is positioned astride the stent-valve to capture and subsequently deploy the stent-valve;

Fig. 4E is a side view of the system shown in Fig. 4D, wherein after the stent-valve is positioned in the plane of the heart valve, the sheath is withdrawn to expose the stent-valve in place at the heart valve seat and to allow for deployment if the stent-valve by expansion;

Fig. 4F is a side view of the system shown in Fig. 4E, wherein with the stent-valve is positioned at the valve seat and the sheath withdrawn, and wherein the delivery balloon then expanded to deploy the stent-valve;

Fig. 5A is a side view of a catheter delivery system in accordance with another embodiment of the one or more present inventions, wherein a carrier balloon shaft passes through a central coaxial lumen of a delivery balloon (wherein the wall of central lumen is omitted for clarity);

Fig. 5B is a side view of the system shown in Fig. 5A, wherein partial inflation of the leading carrier balloon may be used as a "nose cone" to facilitate insertion of the delivery catheter into a patient's artery;

Fig. 5C is a side view of the system shown in Fig. 5B, wherein full inflation of the leading carrier balloon partially expands the stent-valve within an expandable sheath segment;

Fig. 5D is a side view of the system shown in Fig. 5C, wherein at "(1)" the leading carrier balloon is deflated and advanced out of the stent-valve, and wherein at "(2)" the delivery balloon is advanced into position within stent-valve to "dock" with or "capture" the stent-valve;

Fig. 5E is a side view of the system shown in Fig. 5D, wherein the leading carrier balloon and guidewire are first advanced into the left ventricle (in the case of implantation in the native aortic valve seat), and wherein the leading carrier balloon shaft then acts as a guide rail for delivery of the balloon catheter;

Fig. 6A is a side view of an embodiment of a sheath, wherein traction elongates the sheath weave and reduces its diameter, and wherein release of the traction shortens/retracts the sheath weave and expands its diameter;

Fig. 6B is a side view of an embodiment of a cut shape memory alloy stent (nitinol) within a sheath wall investment that expands as a contained balloon and/or stent-valve (omitted for clarity) is expanded therein and self-contracts as the balloon is deflated;

Fig. 6C is a side view of an embodiment of a plastic material sheath that passively expands;

Fig. 6D is a side view of an embodiment of electrically actuated piezo-ceramic (p-c) elements sealed within an elastic sheath wall, wherein each p-c element is connected by a conductor pair to a voltage controlled power source, wherein a switch engages a power source, and wherein p-c elements expand the sheath when electrically energized;

Fig. 6E is a perspective view of an embodiment of actuator elements that utilize differential alloy laminates, wherein an application of current induces bend in the actuator;

Fig. 7 is a side view of an embodiment of a device for retaining a stent-valve on a delivery balloon by magnetic or electromagnetic means (for Figs. 7-8B, conductors and a power source for electromagnet are not shown; the valve membrane or other valve mechanism is not shown; the balloon inflation lumen and optional control lines/harness are omitted for clarity);

Fig. 8A is a side view of an embodiment of a retrieval catheter device that utilizes magnetic force to retrieve a stent-valve;

Fig. 8B is a side view of a stent-valve wherein the stent-valve is contracted by magnetic force and thereafter can be retracted from the native valve seat by optional control lines or a harness;

Fig. 8C is a side perspective view of an embodiment of a multipolar magnetic retrieval catheter system; and

Fig. 8D is an end view of the system shown in Fig. 8C positioned radially within a stent-valve.

For the figures presented herein, balloons in a collapsed state are depicted as partially expanded to emphasize the difference in sizes. In addition, balloon catheter wire lumen and inflation lumens are omitted for clarity.

The drawings are not necessarily to scale.

DETAILED DESCRIPTION

Overview

In general, at least one embodiment of the one or more present inventions uses a serial approach for delivering and deploying the percutaneous aortic valve at the valve seat. This serial approach allows various components of the combined assembly (i.e., the various components of the balloon catheter and the stent-valve) to be separately introduced into the vascular system of the patient, each with its own minimized profile, so as to facilitate a low-profile endoluminal delivery of the system components into the large central blood vessels (e.g. the aorta) where, in a preferred sequence, these components are co-axially re-assembled prior to advancement to the target valve seat. As a result, at least one embodiment of the one or more present inventions facilitates femoral artery access to the aortic valve seat, even with patients having small femoral artery diameters (e.g., elderly female patients). In other words, since the various components of the system are not fully assembled at the time of insertion into the vascular system of the patient, and are only fully assembled at some point subsequent to insertion (e.g., within a larger diameter blood vessel upstream (farther inward) of the insertion site), a relatively large access vessel is no longer necessary - thereby making percutaneous heart

valve therapy available for a larger patient population and with a lower risk of access site and blood vessel complications. By way of example but not limitation, where the intravascular device comprises an aortic stent-valve, the various components of the system can be easily introduced into a relatively narrow femoral artery and thereafter assembled in a larger upstream (farther inward) vessel (e.g., in the relatively wide aorta) before being advanced to and seated at the native aortic valve seat.

More particularly, at least one embodiment of the one or more present inventions preferably utilizes two separate balloons for a staged deployment of the stent-valve: a first, smaller-diameter "carrier" balloon for initial stent expansion (e.g., for preliminarily expanding the stent while the stent-valve is disposed in the descending aorta), and a second, larger-diameter "delivery" balloon for ultimate stent seating at the native valve seat. In one preferred form of at least one embodiment of the one or more present inventions, the stent-valve is mounted on the deflated first, smaller-diameter "carrier" balloon, then this relatively small assembly is introduced (within a covering sheath) into the relatively small femoral artery, advanced through the femoral artery, up through the iliac artery, and then into the relatively large descending aorta. The first, smaller-diameter "carrier" balloon is then inflated so as to expand the stent-valve to an intermediate diameter configuration that is large enough in diameter to receive the deflated second, larger-diameter "delivery" balloon. The first "carrier" balloon is then deflated, the first "carrier" balloon is withdrawn and replaced by the deflated second "delivery" balloon which, by partial inflation or other means, captures the stent-valve, and the assembly is then advanced up the descending aorta, ascending aorta, etc. to the native valve seat. The second "delivery" balloon is then inflated so as to set the stent-valve at the valve seat. Finally, the second "delivery" balloon is deflated and withdrawn from the surgical site.

In-line Dual-Balloon Catheter Delivery System

With reference now to Figs. 4A-4F, a stent-valve 120 may be advanced upon a first, smaller-diameter "carrier" balloon to the aorta and initially deployed (using the first, smaller-diameter "carrier" balloon) to an intermediate size, followed by co-axial exchange for the second, larger-diameter "delivery" balloon for advancement to the valve seat, and then further expansion of the stent-valve 120 at the valve seat. Alternatively, the stent-valve 120 may be advanced upon the carrier balloon all the way to the target valve seat and initially deployed before coaxial exchange for the delivery balloon and subsequent final expansion.

Referring now to Fig. 4A, an integrated system is shown in the form of an in-line dual-balloon delivery catheter system 100 that features an in-line dual-balloon catheter configuration. The configuration shown in Fig. 4A illustrates the in-line dual-balloon delivery catheter system 100 as it is being translated through the patient's body toward the target valve seat, such as the

aortic valve. For the in-line dual-balloon delivery catheter system 100 described herein, the carrier segment 112 is a lead/carrier balloon or mandrel at the distal portion of a catheter with the carrier segment 112 arrayed in-line on a catheter shaft with a more proximally positioned delivery segment 111 together at the distal portion of the catheter shaft. Alternatively, the delivery segment may be positioned distal to the carrier segment. The carrier segment 112 and delivery segment 111 are, for the case of the balloon-expandable stent-valve 120 example in this discussion, expandable balloons, for example, but may also be mandrels or expandable mandrels.

Here, it is noted that, in at least one embodiment (including both the in-line dual-balloon delivery catheter system 100 and the telescoping delivery system 200), a delivery segment comprising a delivery mandrel can be non-expanding. By way of example and not limitation, the means by which the delivery segment retains the stent-valve may vary. For example, in addition to friction, the delivery segment may retain the stent-valve by use of magnetic force. For such an assembly, if the stent-valve (or other deliverable device) is self-expanding or actuated to expansion and retained on the delivery segment for release by some other means (electronic, heat, e.g.), then the delivery mandrel can be non-expanding.

For the configuration shown in Fig. 4A, an outer delivery sheath 101 having, for example, a lengthwise body 104 that is 14 French inside diameter, is coaxially situated over a guidewire 131, for example, a 0.035 inch diameter wire, whereupon the integrated pair of expandable balloons reside. It is noted that all sizes and material types presented herein are exemplary and are not intended to be limiting, nor should they be interpreted as limiting, unless otherwise claimed. Although not required, an optional nose cone 113 may be positioned distally of the carrier segment 112 to assist with insertion of the catheter into the artery and subsequent traverse through it. In the embodiment wherein the delivery segment is disposed distal to the carrier segment, said nose cone is positioned immediately distal to the delivery segment and approximated to the tip of the sheath. The carrier segment 112 is used to hold the stent-valve 120 in place within the outer delivery sheath 101 and provide initial expansion of the stent-valve 120. Thereafter, the delivery segment 111 is used to provide final expansion of the stent-valve 120 for deployment of the stent-valve 120 at the valve seat.

The in-line dual-balloon delivery catheter system 100 is assembled external to the body by passing the delivery catheter with its linearly arrayed carrier segment 112 and delivery segment 111 within the central coaxial lumen of the delivery sheath 101 such that the carrier segment 112 of the catheter extends and is fully exposed beyond the distal terminal opening of the delivery sheath 101. The catheter-deliverable device, such as the stent-valve 120 in this example, is then coaxially mounted upon the carrier segment 112 by collapsing and compressing

it onto the carrier segment 112 such that friction between the two retains the device 120 upon the carrier segment 112. The carrier segment 112 with the catheter-deliverable device (stent-valve 120) mounted upon it is then retracted back (proximally) into the distal portion of the delivery sheath 101 so that the device is completely covered within the sheath 101. In some cases the tip of the carrier segment 112 may be extended beyond the end of the sheath. In such a case, partial expansion of the leading tip 113 of the carrier segment 112 (balloon or expandable mandrel) may be used to form the tapered "nose cone" as noted above, to facilitate advancement or insertion of the delivery system into the blood vessel. Alternatively, the carrier segment may be fabricated with a soft plastic tapered tip for this purpose.

In the example of retrograde (in relation to blood flow) passage of the delivery system carrying the catheter-deliverable device, initial guidance for passage of the delivery system is established by advancement of the guidewire 131 across the heart valve seat 141 into the upstream anatomic chamber, such as the left ventricle, there acting as a guiding rail for the coaxial advancement of the delivery system catheters. Then, at a point external to the body, by inserting the guide wire 131 into the distal tip of the carrier segment 112 of the delivery catheter, the assembled in-line dual-balloon delivery catheter system 100 with sheath 101 is then advanced into the body coaxially over the guidewire 131 to a position proximate to but short of the target anatomic site--in this case, the diseased heart valve seat 141.

Referring now to Fig. 4B, when in the aorta, the leading carrier segment 112 is expanded as by balloon inflation, thus partially expanding the catheter-deliverable device (stent-valve 120) within the expandable distal segment 103 of the delivery sheath 101. That is, the carrier segment 112 is used to pre-dilate the stent-valve 120 so that the diameter of the stent-valve 120 is sufficient to accept the delivery segment 111 when the delivery segment 111 is at least partially deflated or not fully expanded. The outer delivery sheath may include an expandable and flexible distal segment to accommodate the partially expanded stent-valve 120 and hold the partially expanded stent-valve 120 in place. The carrier segment 112 is then contracted as by balloon deflation and advanced by advancing the delivery catheter out of the catheter-deliverable device (stent-valve 120) that is retained within the expanded distal segment 103 of the sheath 101. Optional shallow flanges 102 on the internal surface of the sheath 101 immediately proximal and/or distal to the mounted position of the device 120 can be used to assist in retention of the device during movement relating to the exchange of the carrier segment 112 for the delivery segment 111 with the advance of the delivery catheter. Alternatively, retention or control lines 123, 124 of wire or suture material may be attached to the device 120, as on the frame 121 of the stent-valve 120. Other forms of retaining force may be advantageously

applied, such as by incorporating magnetic or electromagnetic elements within the delivery catheter shaft or within the sheath wall.

Referring now to Fig. 4C, as the delivery catheter 110 is thus advanced, the delivery segment 111 integrated thereupon thus is also advanced within the sheath 101 to a position astride the catheter-deliverable device (stent-valve 120) within the delivery sheath 101, with the tip of the delivery catheter extended beyond the tip of the delivery sheath 101. More particularly, the delivery segment 111 is advanced axially to a position radially interior to the stent-valve 120. The delivery segment 111 is then partially expanded to contact the stent-valve 120.

Referring to Fig. 4D, with the delivery segment 111 positioned within the stent-valve 120, in at least one embodiment the carrier segment 112 is positioned at the valve seat and may be further expanded to facilitate advancement of the stent-valve 120 within the plane of the aortic valve. That is, if deemed desirable by the surgeon, the carrier segment 112 is temporarily expanded and then contracted or deflated within the plane of the valve seat to facilitate subsequent axial advancement of the delivery segment 111 that carries the stent-valve 120.

With the projected tip of the delivery segment, and beyond that the carrier segment leading, the delivery catheter, catheter-deliverable device (stent-valve 120), and delivery sheath 101 are advanced together as a unit across the target anatomic plane (native heart valve seat 141, for example) to a position astride the target plane deemed suitable for deployment of the catheter-deliverable device (stent-valve 120). In the embodiment wherein the carrier segment is disposed proximal to the delivery segment this advancement occurs with the tip of the delivery segment leading the catheter assembly, and the carrier segment further proximal within the sheath. Referring now to Fig. 4E, after the delivery segment 111 is positioned in the plane of the target valve seat, the outer delivery sheath of the delivery system is withdrawn (as shown by the arrows in Fig. 4E) to expose the stent-valve 120; however, the stent-valve 120 remains undeployed because it continues to remain attached to the delivery segment 111. That is, the delivery sheath 101 is coaxially retracted with the delivery catheter held in place so as to expose the catheter-deliverable device (stent-valve 120) retained upon the delivery segment 111 at the site of deployment. The catheter-deliverable device (stent-valve 120) is then deployed by expansion of the delivery segment 111, such as by balloon inflation. Accordingly, and referring now to Fig. 4F, after the stent-valve 120 is exposed at the plane of the aortic valve, the delivery segment 111 is expanded to deploy the stent-valve 120. With full expansion and deployment of the catheter-deliverable device (stent-valve 120) the device is retained within the target anatomic plane (native heart valve seat 141). The delivery segment 111 is then contracted as by balloon deflation, function of the deployed device is confirmed, and the delivery catheter, delivery

sheath 101, and guidewire 131 are retracted from the anatomic target area and removed from the body to complete the procedure.

In at least one embodiment, optional retention/control lines 123, 124 are released from valve frame 121 after successful deployment of stent-valve 120 is confirmed. Then balloon catheter 110 and guidewire 131 are removed from the valve seat 141 and withdrawn into sheath 101 for removal from the body.

In at least one embodiment, the carrier segment 112 is located axially proximal to the delivery segment 111. For such a configuration, the delivery segment 111 is advanced outside the sheath 101 and leads the assembly until the point the exchange is made. Then after the stent-valve 120 is partially expanded by the carrier segment 112, the delivery segment 111 is pulled back into the sheath 101 where the stent-valve 120 is retained, and the delivery segment 111 then captures the stent-valve 120. In this case, the tip of the delivery segment 111 at the tip of the sheath 101 will lead the further advance while the carrier segment 112 is sequestered more proximally in the sheath 101.

Telescoping Catheter Delivery System

Referring now to Figs. 5A-5E, in an alternative embodiment, a telescoping delivery system 200 for a stent-valve 120 is provided wherein a delivery balloon catheter 210 is co-axially situated or "threaded" over a carrier balloon catheter shaft 224 associated with a carrier segment 221. Accordingly, the carrier segment 221 can be advanced axially independent of the axial position of the delivery balloon 211. As a result, the carrier segment shaft 224 acts as a guide rail for the delivery balloon catheter 210 and the stent-valve 120 that is then radially positioned exterior to the delivery balloon 211. Step-by-step illustrations are provided in the drawings and are described in the following paragraphs.

Referring now to Fig. 5A, an outer delivery sheath 101 having, for example, a proximal shaft body with a 14 French inside diameter, is coaxially situated over a guidewire 131, whereupon a carrier segment shaft 224 and a delivery balloon shaft 214 are also co-axially situated. For the embodiment of the telescoping delivery system 200 described, the carrier segment 221 is a carrier balloon or mandrel at a distal portion of a carrier catheter 220 that is passed within the central lumen of a larger delivery catheter 210 that has a delivery segment 211 at its distal portion. By way of example and not limitation, the carrier segment shaft has a 0.035 inch outer diameter and is connected to the carrier segment 221 that is expandable to between 5-10 mm in diameter. The delivery segment 211 is, for the case of the balloon-expandable stent-valve 120 example, an expandable delivery balloon, for example. Accordingly, the delivery balloon may have an outside diameter of, for example, approximately 12-14 French when

uninflated, and, in separate embodiments, is located axially either proximal or distal to the carrier segment 221.

The system is assembled external to the body by passing the carrier catheter 220 within the central coaxial lumen of the larger delivery catheter 210 such that the carrier segment 221 extends and is fully exposed beyond the tip 212 of the delivery catheter. These two catheters thus joined are then passed together through the delivery sheath 101 such that the carrier segment 221 of the carrier catheter 220 again extends and is fully exposed beyond the tip of the delivery sheath 101. The catheter-deliverable device, such as the stent-valve 120 in this example, is then coaxially mounted upon the carrier segment 221 by collapsing and compressing it onto the carrier segment 221 such that friction between the two retains the device 120 upon the carrier segment 221. The carrier segment 221 with the catheter-deliverable device (stent-valve 120) mounted upon it is then retracted back (proximally) into the delivery sheath 101 so that the device is completely covered within the sheath 101.

Referring now to Fig. 5B, the lead carrier segment balloon 221 optionally may be partially expanded to hold the stent-valve 120 within the outer delivery sheath 101. In addition, in some cases the tip 222 of the carrier catheter and carrier segment 221 may be extended beyond the end of the sheath 101. In such a case, partial expansion of the leading tip 223 of the carrier segment 221 (balloon or expandable mandrel) may be used to form a tapered "nose cone" to facilitate advancement or insertion of the delivery system into the blood vessel. Alternatively, and as previously noted for the in-line dual-balloon delivery catheter system 100, the carrier catheter 220 for the telescoping delivery system 200 may be fabricated with a soft plastic tapered tip for this purpose.

In the example of retrograde (in relation to blood flow) passage of the delivery system carrying the catheter-deliverable device, initial guidance for passage of the delivery system is established by advancement of the guidewire 131 across the heart valve seat 141 into the upstream anatomic chamber, such as the left ventricle, there acting as a guiding rail for the coaxial advancement of the delivery system catheters. Then, at a point external to the body, by inserting the guide wire 131 into the distal tip of the carrier catheter 220, the assembled delivery catheter system 200 with carrier catheter 220, delivery catheter 210 and sheath 101 is then advanced into the body coaxially over the guidewire 131 to a position proximate to but short of the target anatomic site--in this case, the diseased heart valve seat 141.

Referring now to Fig. 5C, in at least one embodiment, when in the aorta the carrier segment 221 is further expanded to effect expansion of the stent-valve 120 within the outer delivery sheath so that the delivery balloon can be advanced axially and positioned radially to the interior of the stent-valve 120. That is, when in the aorta, the leading carrier segment 221 is

expanded, such as by balloon inflation, thus partially expanding the catheter-deliverable device (stent-valve 120) within the expandable distal segment 103 of the delivery sheath 101. In at least one embodiment, the outer delivery sheath 101 includes an expandable, flexible distal segment 103 that allows partial expansion of the stent-valve 120 within the outer delivery sheath, such as to a sufficient diameter to receive the unexpanded delivery balloon 211. Although the distal segment of the outer delivery sheath may be expandable, the outer delivery sheath shaft 104 located axially proximal to the carrier segment 221 preferably remains relatively small in diameter, that is, at its original unexpanded diameter, such as having a 14 French inside diameter at the entry point of the body and blood vessel.

With reference now to Fig. 5D, after partial expansion of the stent-valve 120 within the distal portion 103 of the outer delivery sheath 101, the carrier segment 221 is contracted as by balloon deflation and is then advanced axially beyond the outer delivery sheath 101 and out of the catheter-deliverable device (stent-valve 120) leaving it retained within the expanded distal segment 103 of the sheath 101.

The delivery segment balloon 211 is then axially advanced to a position radially to the interior of the stent-valve 120. With the delivery segment 211 of the delivery catheter 210 then coaxially advanced over the shaft 224 of the carrier catheter to a position astride the catheter-deliverable device (stent-valve 120) within the delivery sheath 101, the delivery segment balloon 211 is then partially expanded to dock or capture the stent-valve 120.

Referring now to Fig. 5E, the leading carrier segment balloon 221 of the carrier catheter 220 is then advanced across the target anatomic plane (native heart valve seat 141) coaxially following the guide wire 131 there in place, where it then provides additional mechanical guidance and support for the further coaxial advancement of the larger delivery catheter 210 upon the shaft 224 of the carrier catheter 220. Alternatively, the carrier catheter 220 may be coaxially withdrawn from the system and the body leaving the guide wire in place , then a shaped catheter (one with specifically designed terminal curves, such as "pig tail" or Amplatz type curves commonly found on angiographic catheters, to facilitate its being properly situated relative to the anatomy) may then be advanced over the guide wire to the upstream anatomic chamber, its shaft then substituting for the shaft 224 of the carrier catheter. Accordingly, Fig. 5E illustrates the guidewire 131 and carrier segment 221 as having passed the aortic valve such that the guidewire and carrier segment reside within the patient's left ventricle. Axial advancement of the carrier segment 221 and the carrier catheter shaft 224 can be done independent of the location of the delivery balloon 211. Thereafter, the delivery segment balloon 211 and the delivery catheter shaft 214 are axially advanced co-axially over the carrier catheter shaft 224 that acts as a guide rail for the delivery segment balloon 211. More

particularly, with the projected tip 212 of the delivery catheter 211 leading beyond the tip of the sheath, the delivery segment 211, catheter-deliverable device (stent-valve 120), and delivery sheath 101 are advanced together as a unit across the target anatomic plane (native heart valve seat 141, for example) to a position astride the target plane deemed suitable for deployment of the catheter-deliverable device (stent-valve 120).

Once positioned at the plane of the valve seat of the patient's aortic valve, the delivery sheath 101 is coaxially retracted with the delivery catheter held in place so as to expose the catheter-deliverable device (stent-valve 120) retained upon the delivery segment 211 at the site of deployment. Thereafter, the final delivery balloon is expanded to deploy the stent-valve 120.

With full expansion and deployment of the catheter-deliverable device (stent-valve 120) the device is retained within the target anatomic plane (native heart valve seat 141). The delivery segment 211 is then contracted as by balloon deflation, function of the deployed device is confirmed, and the delivery catheter, carrier catheter, delivery sheath 101, and guide wire 131 are retracted from the anatomic target area and removed from the body to complete the procedure.

Expandable Outer Delivery Sheath

As described herein, at least one embodiment of the endoluminal delivery system includes an outer delivery sheath that further comprises a distal segment that is expandable. Several different ways of providing an expandable distal segment are described in the following paragraphs.

Referring now to Fig. 6A, the distal segment of the outer delivery sheath 310 may comprise a woven alloy wire portion 311. By way of example and not limitation, the distal segment may be similar in design to the IDEV TECHNOLOGIES SUPERA® stent that includes woven nitinol wire. Alternatively, in at least one embodiment, the woven wire portion 311 may further comprise a flexible plastic investment; that is, a configuration wherein the woven wire portion resides within a flexible plastic matrix forming a tubular portion of the outer delivery sheath. In typical operation, the wire weave is formed in expanded configuration and elongated by longitudinal traction force on the wire elements with resulting contraction of the tubular form to a decreased diameter. Thereafter, the release of traction force effects self-expansion of the weave. In at least one embodiment, a distal portion of the distal segment of the outer delivery sheath 310 may be widened by using control lines to pull on control ends of the woven wire portion of the distal segment.

Referring now to Fig. 6B, in an alternative embodiment, the distal segment of the outer delivery sheath 320 includes a cut nitinol stent 321 residing within the sheath investment. More particularly, the distal segment of the outer delivery sheath includes a nitinol stent 321

embedded within the distal segment, wherein the nitinol stent 321 provides shape-memory functionality for the distal segment. As a result, when the balloon catheter is inflated within the distal segment with the stent-valve 120 mounted on it, the distal segment expands to accommodate the inflated balloon catheter and stent-valve. Thereafter, when the balloon catheter is pushed out of the outer delivery sheath 320, the distal segment then retracts because of the shape-memory functionality associated with the nitinol stent 321 residing with the distal segment.

Referring now to Fig. 6C, in at least one embodiment the distal segment of the outer delivery sheath 330 comprises an elastic material that can passively expand and optionally retract. That is, when a balloon catheter is expanded within the distal segment, the elastic material accommodates the expansion. Thereafter, with deflation of the balloon catheter the elastic material forming the distal segment retracts. Alternatively, the sheath material, such as PTFE (polytetrafluoroethylene) may expand but not contract. In such case, the thin-walled sheath material folds inward along longitudinal lines when retracted through a proximally disposed entry sheath or the vascular entry point itself, permitting ready removal from the body, even in a persistently expanded condition.

Referring now to Fig. 6D, in an alternative embodiment, the distal segment of the outer delivery sheath 340 includes a plurality of electrically actuated piezo-ceramic elements 341. Electrical wiring or conductors 342 extend to the proximal end of the outer delivery sheath 340 to facilitate application of an electrical current to the piezo-ceramic elements 341. When desired, the surgeon closes a circuit to engage a power source 343 and apply the electrical current to the piezo-ceramic elements 341 via the electrical wiring or conductors 342. Upon being energized, the piezo-ceramic elements 341 expand the distal segment of the outer delivery sheath 340. Contraction of the distal segment is achieved by terminating the electrical current to the piezo-ceramic elements 341. Further reference here is made to U.S. Patent No. 5,415,633, the content of which is incorporated by reference in its entirety.

Referring now to Fig. 6E, a variation of the use of electrically charged elements comprises the use of active elements featuring differential alloy sandwiches or laminates 344 that bend when a current is applied. The bending of the active elements causes the distal segment to expand. As with the piezo-ceramic elements 341 described above, contraction of the distal segment is achieved by terminating the application of electrical current to the differential alloy sandwiches or laminates 344.

In another alternative embodiment, a magnetic or electromagnetic force is used to retain a stent-valve 120 on a delivery segment balloon for advancement to the target valve plane and subsequent deployment. More particularly, and with reference now to Fig. 7, an alternative

endoluminal magnetic delivery system 400 is shown that utilizes a magnetic or electromagnetic force to maintain the position of the stent-valve 120 on the delivery segment balloon 411, wherein the delivery segment balloon 411 is located at or near the distal portion of a delivery catheter shaft 414. The magnet or electromagnet 416 are preferably incorporated into the balloon catheter shaft 414 co-axial to and axially centered along the delivery segment balloon 411 so as to align with the axial position of the mounted stent-valve. As one of skill in the art will appreciate, the stent-valve 120 must incorporate a material susceptible to magnetism in a sufficient quantity and distribution to facilitate attraction of the stent-valve 120 to the magnet or electromagnet 416 incorporated into the balloon catheter shaft 414. A guidewire 131 serves to guide the co-axially situated delivery balloon catheter 410. The delivery balloon may be partially expanded to: (a) provide a nose cone for facilitating insertion of the delivery system into, and traverse through the patient's blood vessel; and/or (b) to provide further frictional force for securing the stent-valve 120. Since the stent-valve 120 is held in place by a magnetic or electromagnetic force as well as any further frictional force due to partial expansion of the delivery balloon, the stent-valve 120 can be securely advanced through the patient's vascular system without need of an outer delivery sheath, thereby simplifying and reducing the profile of the delivery system. Once the target valve plane is reached, the delivery balloon 411 is expanded, thereby overcoming the magnetic or electromagnetic force (of course, an electromagnetic force may be terminated by stopping current to the electromagnet), to deploy the stent-valve 120 at the plane of the diseased native valve. Similarly, the magnet of the magnetic delivery catheter 410 may be incorporated into the delivery segment balloons of the in-line dual balloon system 100 and/or the telescoping catheter delivery system 200 in a similar manner to facilitate capture and retention of the stent-valve upon the delivery segment balloon in its traverse through the anatomic structures.

In addition to endoluminal delivery of a stent-valve 120, at least one embodiment of the one or more present inventions is directed to a retrieval and/or repositioning system 500 that can be used to remove a deployed stent-valve 120 from a patient, or otherwise reposition the stent-valve 120 within the patient. With reference now to Figs. 8A and 8B, an embodiment of a retrieval and/or repositioning system 500 is shown. The retrieval and/or repositioning system comprises a retrieval catheter 510 on a distal portion of which is integrated a magnet 511, and more preferably, an electromagnet of sufficient strength to at least partially collapse and secure a previously deployed stent-valve 120. With reference to Fig. 8B, the partially collapsed valve is then either withdrawn (that is, retrieved from the patient), for example as by traction on optional control lines 124 as shown, or repositioned and then redeployed.

Referring now to Figs. 8C and 8D, in a separate embodiment, a multipolar magnetic retrieval catheter system 520 is provided in which multiple magnetic elements 522 are circumferentially arrayed and disposed at a distal portion of a retrieval catheter 521 in a manner that allows the radially outward movement of the magnets 522, and the portions of the underlying catheter elements 523 to which they are attached, into contact with the radially interior surface of the deployed stent-valve 120. In at least one embodiment, the underlying portions 523 of the catheter to which the magnets 522 are attached are longitudinally separate from each other so that they are free to move independently from each other as the attached magnets 522 move radially outward. In at least one embodiment, the magnets 522 are of like polarity and are initially restrained into proximity with each other by an overlying sheath mechanism. When said sheath 524 is retracted the distal catheter portions 523 with their attached magnets 522 move radially outward under repulsive magnetic force into contact with the stent-valve 120. The close proximity if not complete contact of the magnets 522 to the stent-valve frame 121 advantageously maximizes the retention force facilitating the traction force applied in the removal of the device from the valve plane. The sheath 524 may be re-advanced over the magnetic distal portions 523 of the catheter, thus applying radially inward force on the device frame that serves to contract it and facilitate its removal under axial traction.

Shaped Catheter

The various sheath and catheter shafts described herein for the various embodiments may include a "shaped" distal portion. More particularly, a "shaped" catheter may be used to assist in crossing anatomic resistance or provide guidance for recrossing the valve plane in the event the guide wire is displaced from the ventricle. This problem occurs when the stent-valve and the delivery system are advanced around the aorta. In such a situation, the traction forces, not uncommonly, will pull the guide wire out of the ventricle. If this happens—with the delivery system already in the aorta—it requires the delivery system be removed from the patient's body and the sequence started over from the beginning. Advantageously, one or more embodiments described herein can assist with avoiding this problem. That is, a catheter can be used that includes a distal portion with one or more curved shapes, such as "pig tail" or Amplatz type curves commonly found on angiographic catheters, and including a central coaxial lumen through which is passed the guidewire. The shaped catheter is used to "steer" the guide wire across the very narrowed valve orifice. Thus, in one embodiment, a "shaped" catheter is passed within the central lumen of the delivery catheter. In such a configuration, the guide wire can be re-crossed through the valve plane more readily, and the shaped catheter—advantageously, a relatively firm catheter—can be advanced to the ventricle and left to act as an enhanced support rail for the delivery catheter.

To assist in the understanding of the present invention the following list of components and associated numbering found in the drawings is provided herein:

Number	Component
100	In-Line Dual Balloon Catheter Delivery System
101	Delivery Sheath
102	Optional Flange Of Internal Sheath
103	Expandable, Flexible Sheath Segment
104	Sheath Body
110	Dual In-Line Balloon Catheter Assembly
111	Delivery Segment Is Delivery Balloon
112	Carrier Segment Is In-Line Leading Carrier Balloon
113	Optional Nose Cone
114	Exit Of Distal Control Lines From Catheter Shaft
120	Stent-Valve Assembly
121	Valve Frame
122	Collapsed Valve Membrane
123	Optional Control Lines Attached To Distal End Of Valve Frame (Passed Within Catheter Shaft)
124	Optional Control Lines Attached To Proximal End Of Valve Frame
130	Guide Wire Assembly
131	Guide Wire
140	Native Heart Valve
141	Native Heart Valve Seat
200	Telescoping Balloon Catheter Delivery System
210	Delivery Balloon Catheter Assembly
211	Delivery Segment Is Delivery Balloon
212	Tip Of Delivery Segment Balloon
213	Partially Inflated Leading Tip Of Delivery Segment Balloon
214	Delivery Balloon Catheter Shaft
220	Carrier Balloon Catheter Assembly
221	Carrier Segment Is Leading Balloon That Coaxially Telescopes Within Central Lumen Of Delivery Segment Balloon
222	Tip Of Carrier Segment Balloon
223	Inflated Leading Tip Of Carrier Segment Balloon
224	Shaft Of Carrier Catheter

300 Expandable Sheath System
310 Woven Wire Sheath
320 Sheath With Embedded Nitinol Stent
321 Nitinol Stent
330 Flexible Plastic Sheath
340 Electronically Actuated Sheath
341 Piezo-Ceramic Elements
342 Conductors
343 Power Source
344 Alloy Laminates
400 Magnetic Balloon Catheter Delivery System
410 Magnetic Balloon Delivery Catheter
411 Delivery Balloon
412 Tip Of Magnetic Balloon Delivery Catheter
413 Partially Inflated Tip Of Delivery Balloon
414 Shaft Of Magnetic Balloon Delivery Catheter
415 Guide Wire Lumen Of Magnetic Balloon Delivery Catheter
416 Magnet Or Electromagnet
500 Magnetic Retrieval Catheter System
510 Magnetic Retrieval Catheter Assembly
511 Magnet Or Electromagnet
520 Multipolar Magnetic Retrieval Catheter Assembly
521 Multipolar Magnetic Retrieval Catheter
522 Magnets – Circumferentially Arrayed
523 Distal Mobile Catheter Elements Attaching To Magnets
524 Sheath

The one or more present inventions may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the one or more present inventions is, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

The one or more present inventions, in various embodiments, includes components, methods, processes, systems and apparatus substantially as depicted and described herein, including various embodiments, subcombinations, and subsets thereof. Those of skill in the art

will understand how to make and use the one or more present inventions after understanding the present disclosure.

The one or more present inventions, in various embodiments, includes providing devices and processes in the absence of items not depicted and/or described herein or in various embodiments hereof, including in the absence of such items as may have been used in previous devices or processes (e.g., for improving performance, achieving ease and/or reducing cost of implementation).

The foregoing discussion of the one or more present inventions has been presented for purposes of illustration and description. The foregoing is not intended to limit the one or more present inventions to the form or forms disclosed herein. In the foregoing Detailed Description for example, various features of the one or more present inventions are grouped together in one or more embodiments for the purpose of streamlining the disclosure. This method of disclosure is not to be interpreted as reflecting an intention that the claimed one or more present inventions requires more features than are expressly recited in each claim. Rather, as the following claims reflect, inventive aspects lie in less than all features of a single foregoing disclosed embodiment. Thus, the following claims are hereby incorporated into this Detailed Description, with each claim standing on its own as a separate preferred embodiment of the one or more present inventions.

Moreover, though the description of the one or more present inventions has included description of one or more embodiments and certain variations and modifications, other variations and modifications are within the scope of the one or more present inventions (e.g., as may be within the skill and knowledge of those in the art, after understanding the present disclosure). It will be understood that many changes in the details, materials, steps and arrangements of elements, which have been herein described and illustrated in order to explain the nature of the invention, may be made by those skilled in the art without departing from the scope of embodiments of the one or more present inventions. It is intended to obtain rights which include alternative embodiments to the extent permitted, including alternate, interchangeable and/or equivalent structures, functions, ranges or steps to those claimed, whether or not such alternate, interchangeable and/or equivalent structures, functions, ranges or steps are disclosed herein, and without intending to publicly dedicate any patentable subject matter.

CLAIMS

What Is Claimed Is:

1. A system for providing endoluminal delivery of a deliverable device through vasculature of a patient to a delivery site within the patient, comprising:

an outer delivery sheath including a distal section, wherein at least a portion of the outer delivery sheath is sized for insertion into the vasculature of the patient;

a carrier segment located at a distal portion of a catheter shaft, the carrier segment having an outer surface sized to temporarily hold the deliverable device in the distal section of the outer delivery sheath, wherein at least a portion of the catheter shaft is located within and coaxial to the outer delivery sheath; and

a delivery segment located coaxial to the outer delivery sheath, the delivery segment having an outer surface sized to radially fit within the deliverable device after detaching the deliverable device from the carrier segment when the deliverable device resides within the distal section of the outer delivery sheath, wherein the delivery segment is configured to deploy the deliverable device at the delivery site.

2. The system of Claim 1, wherein at least a portion of the distal section of the outer delivery sheath is expandable.

3. The system of Claim 2, wherein the at least a portion of the distal section of the outer delivery sheath comprises one or more electrically activated elements.

4. The system of Claim 2, wherein the at least a portion of the distal section of the outer delivery sheath comprises one or more piezo-ceramic elements.

5. The system of Claim 2, wherein the at least a portion of the distal section of the outer delivery sheath comprises a passively expandable material that is expandable upon application of an outward radial force applied by at least one of the carrier segment and the delivery segment.

6. The system of Claim 2, wherein the at least a portion of the distal section of the outer delivery sheath expands upon application of a tensile force to the at least a portion of the distal section.

7. The system of Claim 1, wherein the distal section includes at least one of an internal projection and a narrowed area extending radially inward from an interior surface of the distal section.

8. The system of Claim 1, wherein a portion of an internal surface of the outer delivery sheath further comprises a guide for retaining at least a portion of a longitudinally extending element configured to selectively manipulate at least a part of the outer delivery sheath or a structure coaxial to the outer delivery sheath.

9. The system of Claim 1, wherein a portion of an internal surface of the outer delivery sheath further comprises a guide, the guide comprising at least one of:

(a) a lumen; and

(b) a grommet;

wherein the guide retains at least one control line for selective retention of the deliverable device.

10. The system of Claim 1, wherein the carrier segment and the delivery segment are both situated upon the catheter shaft.

11. The system of Claim 1, wherein the carrier segment is situated upon the catheter shaft, and wherein the delivery segment is associated with a delivery segment shaft that is coaxial to the catheter shaft and axially moveable relative to the catheter shaft.

12. The system of Claim 1, wherein the carrier segment is an expandable balloon having an expanded diameter smaller than an expanded diameter for the delivery segment.

13. The system of Claim 1, wherein the delivery segment is an expandable balloon having an expanded diameter larger than an expanded diameter for the carrier segment.

14. The system of Claim 1, wherein at least one of the carrier segment and the delivery segment is a mandrel.

15. The system of Claim 14, wherein the mandrel is expandable by mechanical or electromechanical means.

16. The system of Claim 14, wherein the mandrel is not expandable.

17. The system of Claim 1, wherein the delivery segment is located axially proximal to the carrier segment.

18. The system of Claim 1, wherein the delivery segment is located axially distal to the carrier segment.

19. The system of Claim 1, wherein the delivery segment includes a magnet to aid in capture and retention of the deliverable device on the delivery segment.

20. An assembly for intravascular delivery of a deliverable device to a delivery site within a patient, comprising:

a first catheter including a first catheter shaft;

a carrier segment situated along the first catheter shaft, the carrier segment configured to receive the deliverable device prior to inserting the first catheter within the patient; and

a delivery segment sequentially positioned in an axial orientation relative to the carrier segment, wherein the delivery segment is configured to engage the deliverable device within the patient while the deliverable device is coaxial to at least a portion of

the first catheter, and wherein the delivery segment is configured to thereafter deploy the deliverable device at the delivery site.

21. The assembly of Claim 20, wherein the delivery segment is also situated along the first catheter.

22. The assembly of Claim 20, wherein the delivery segment is situated along a second catheter, the second catheter comprising a coaxial lumen through which passes the first catheter.

23. The assembly of Claim 22, wherein at least one of the first catheter and the second catheter comprise a curved distal portion.

24. The assembly of Claim 20, wherein the carrier segment is an expandable balloon.

25. The assembly of Claim 20, wherein the carrier segment is a mandrel.

26. The assembly of Claim 25, wherein the mandrel is expandable by mechanical or electromechanical means.

27. The assembly of Claim 25, wherein the mandrel is non-expandable.

28. The assembly of Claim 20, wherein the delivery segment is an expandable balloon.

29. The assembly of Claim 20, wherein the delivery segment is a mandrel.

30. The assembly of Claim 29, wherein the mandrel is expandable by mechanical or electromechanical means.

31. The assembly of Claim 29, wherein the mandrel is non-expandable.

32. The assembly of Claim 20, wherein the delivery segment includes a magnet to aid in capture and retention of the deliverable device on the delivery segment.

33. The assembly of Claim 20, wherein the delivery segment includes an electromagnet to aid in capture and retention of the deliverable device on the delivery segment.

34. A method of delivering a deliverable device through vasculature of a patient to a target site within the patient, comprising:

mounting the deliverable device on a selectively expandable carrier segment located along a catheter shaft, wherein at least a portion of the catheter shaft is located within and coaxial to an outer delivery sheath;

inserting the outer delivery sheath and catheter shaft into the patient;

moving the outer delivery sheath within the patient to position the selectively expandable carrier segment and the deliverable device near the target site;

partially expanding the deliverable device using the selectively expandable carrier segment while the deliverable device remains at least partially within the outer delivery sheath;

positioning a delivery segment radially within the deliverable device and partially expanding the delivery segment to facilitate engagement of the delivery segment with the deliverable device;

moving the delivery segment and deliverable device to the target site; and

deploying the deliverable device at the target site by further expanding the delivery segment.

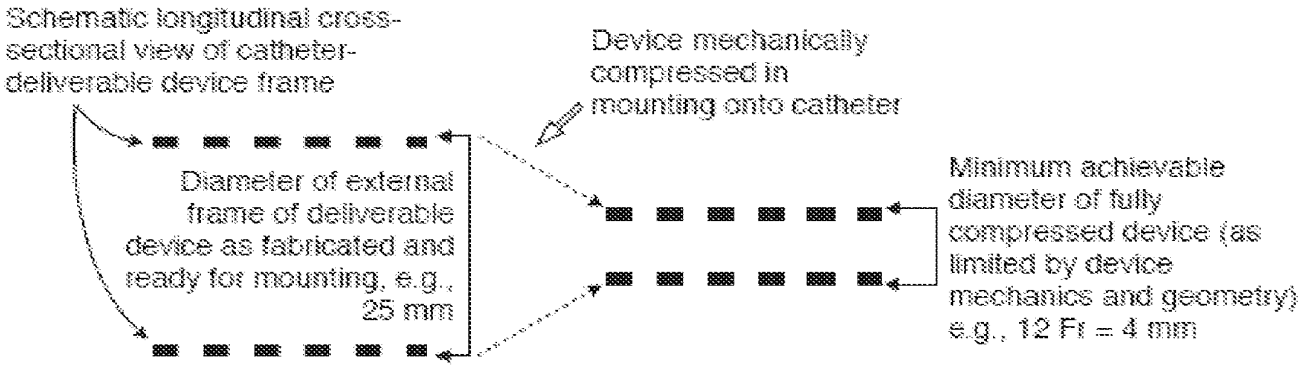


FIG. 1
(PRIOR ART)

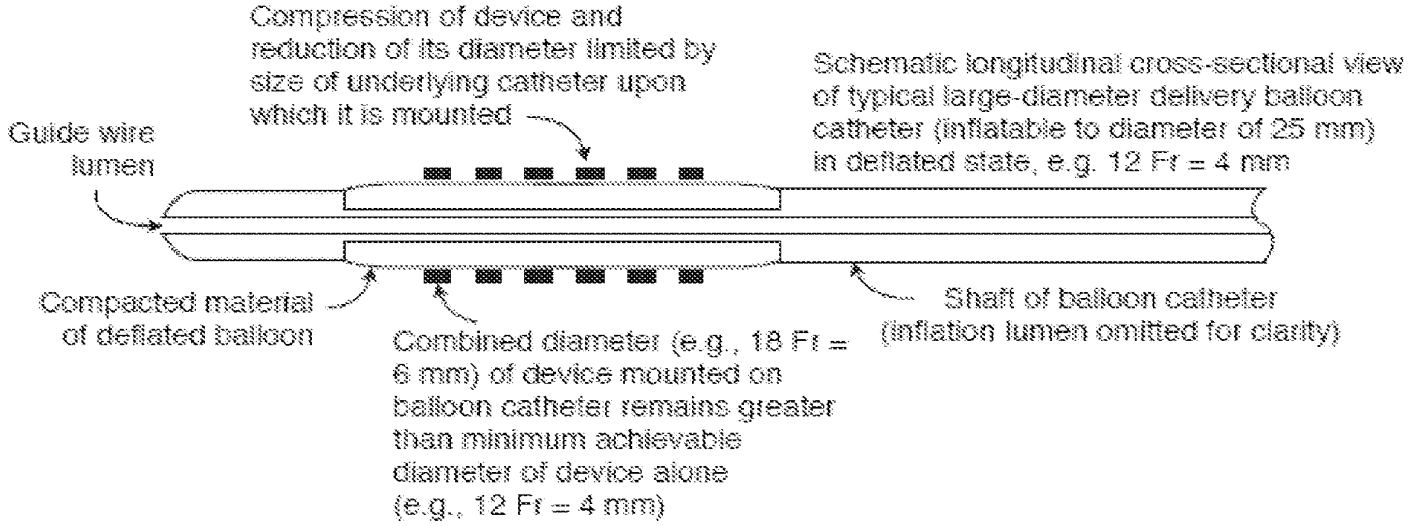


FIG. 2
(PRIOR ART)

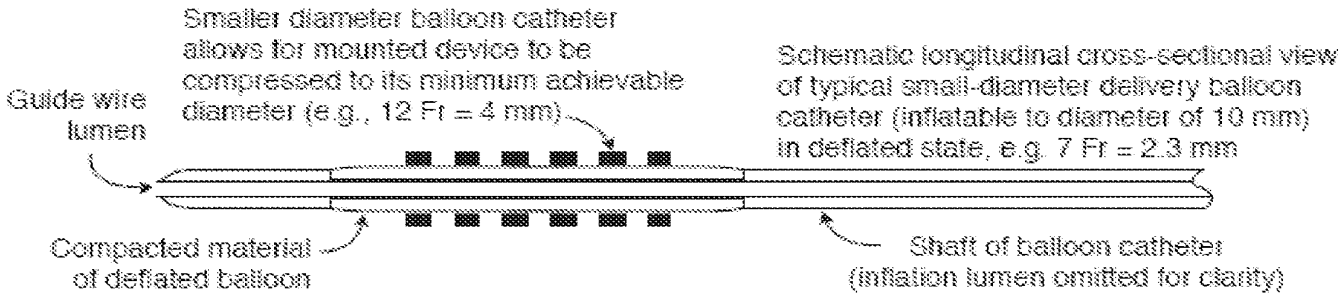
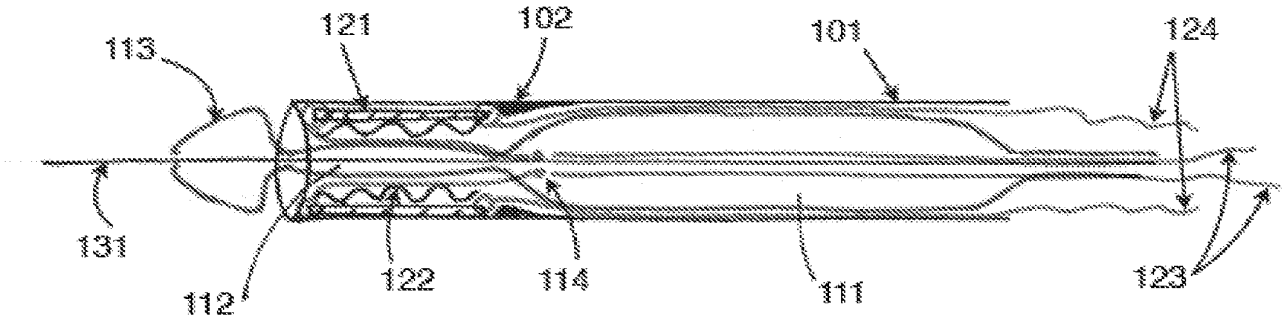

Smaller diameter balloon catheter allows for mounted device to be compressed to its minimum achievable diameter (e.g., 12 Fr = 4 mm)
Guide wire lumen
Schematic longitudinal cross-sectional view of typical small-diameter delivery balloon catheter (inflatable to diameter of 10 mm) in deflated state, e.g. 7 Fr = 2.3 mm
Compacted material of deflated balloon
Shaft of balloon catheter (inflation lumen omitted for clarity)

FIG. 3

FIG. 4A



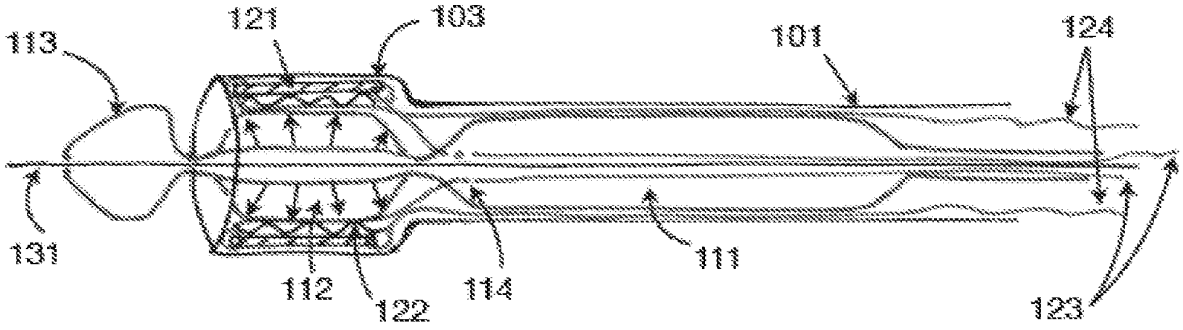


FIG. 4B

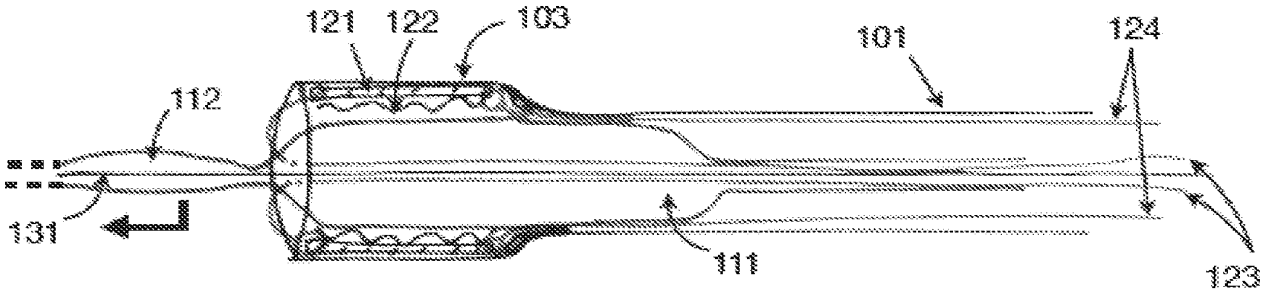
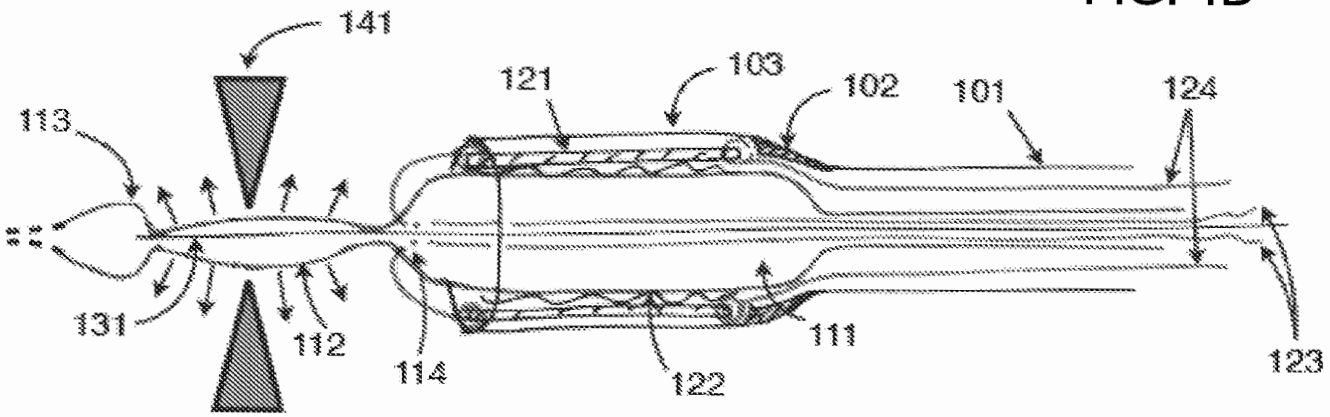


FIG. 4C

FIG. 4D



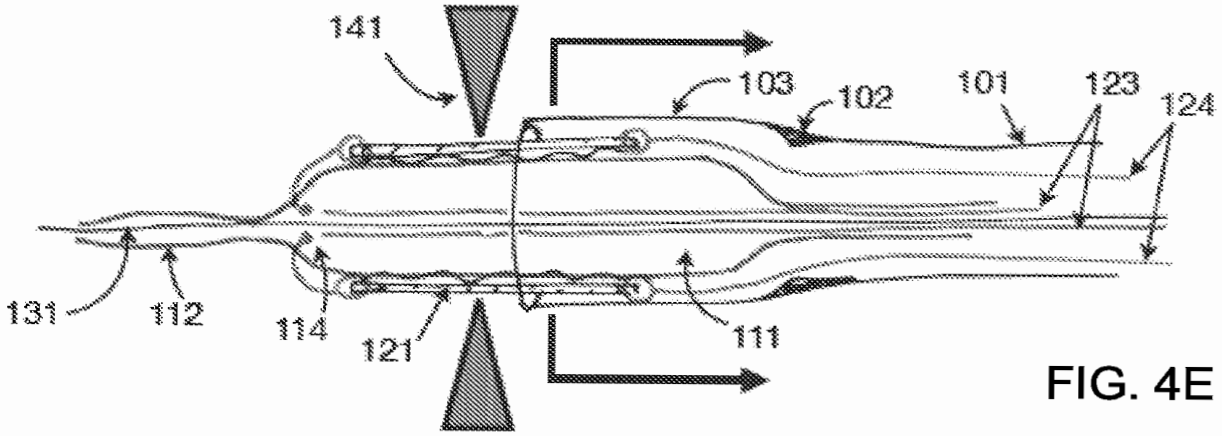


FIG. 4E

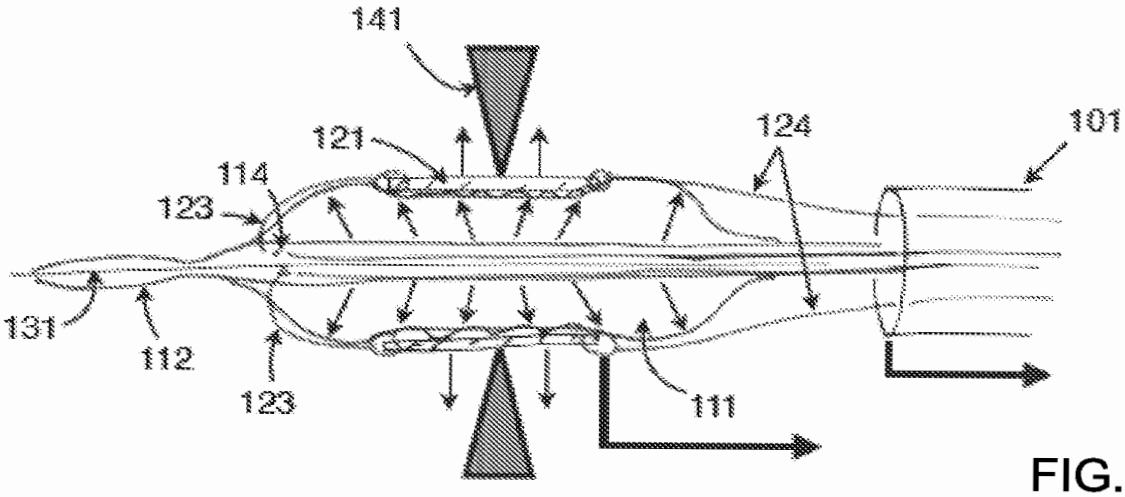


FIG. 4F

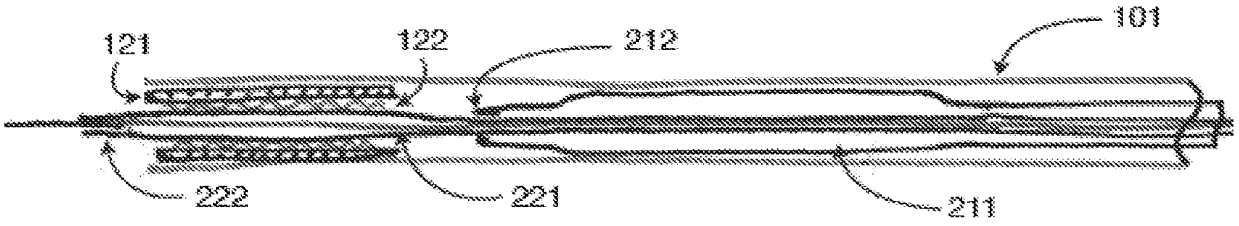


FIG. 5A

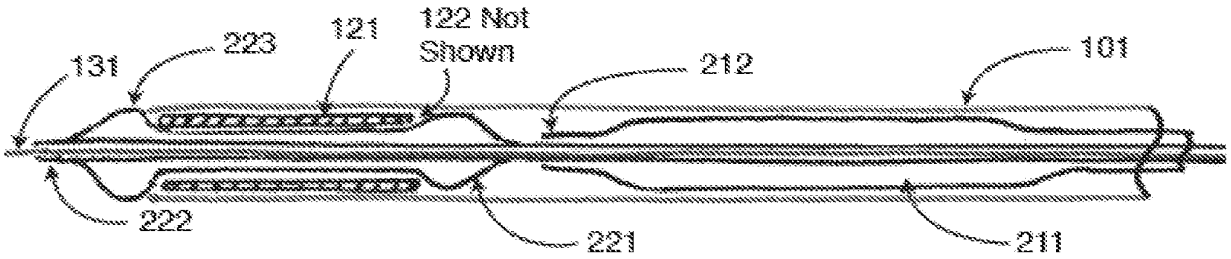


FIG. 5B

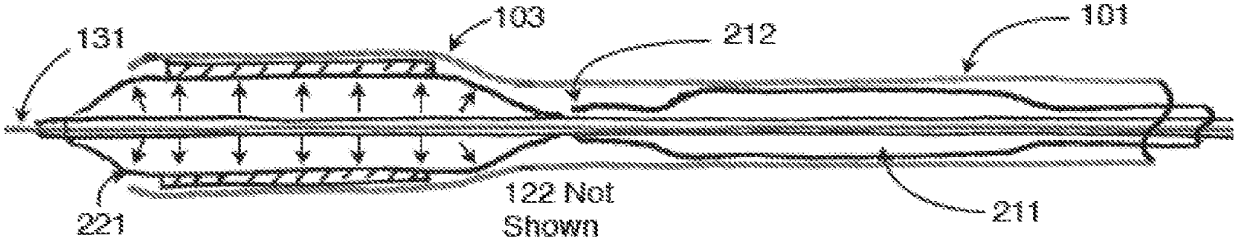


FIG. 5C

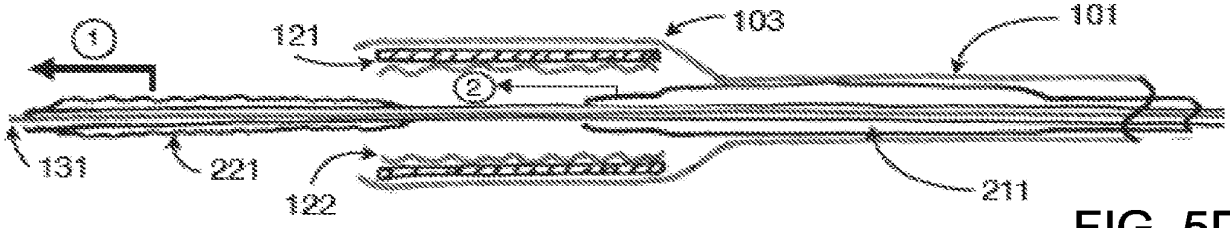


FIG. 5D

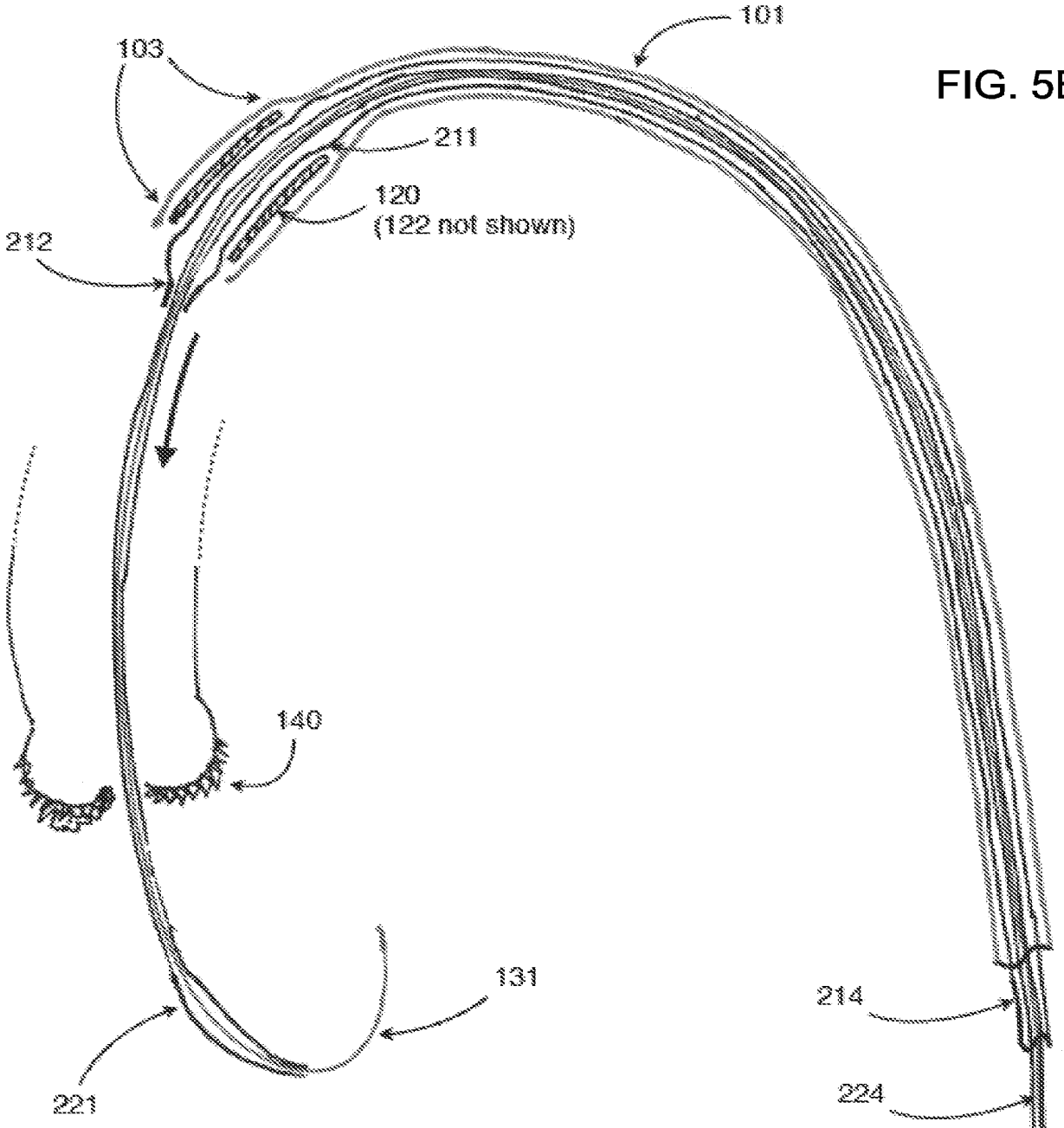
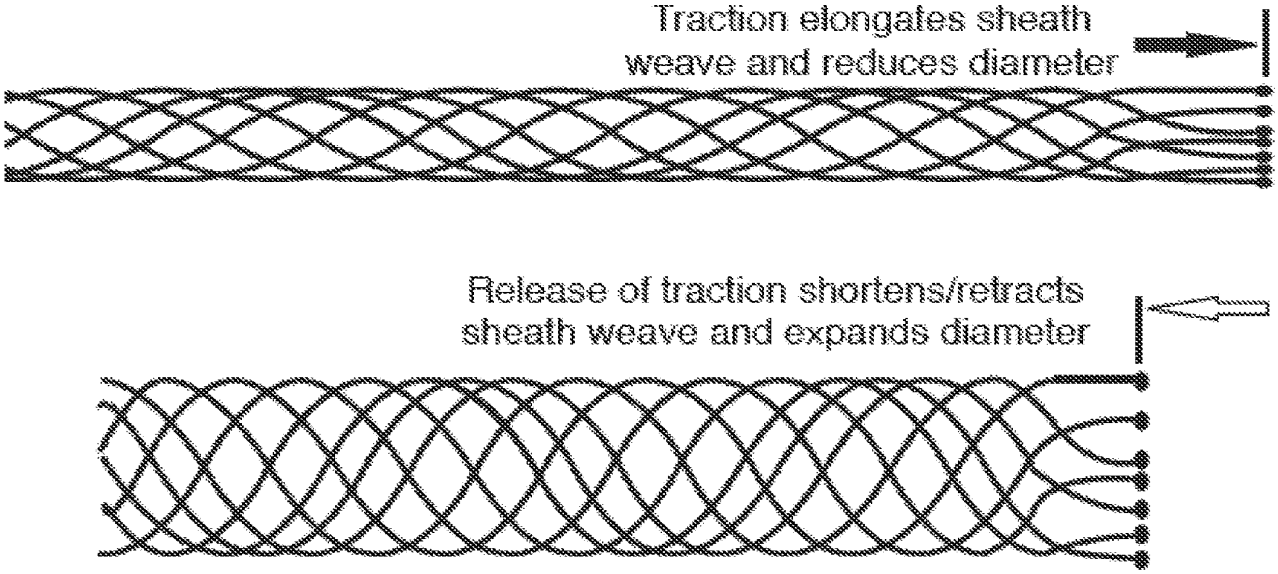

101
103
211
120
(122 not shown)
212
140
131
214
221
224
Proximal catheter ports and hubs not shown

FIG. 5E

FIG. 6A



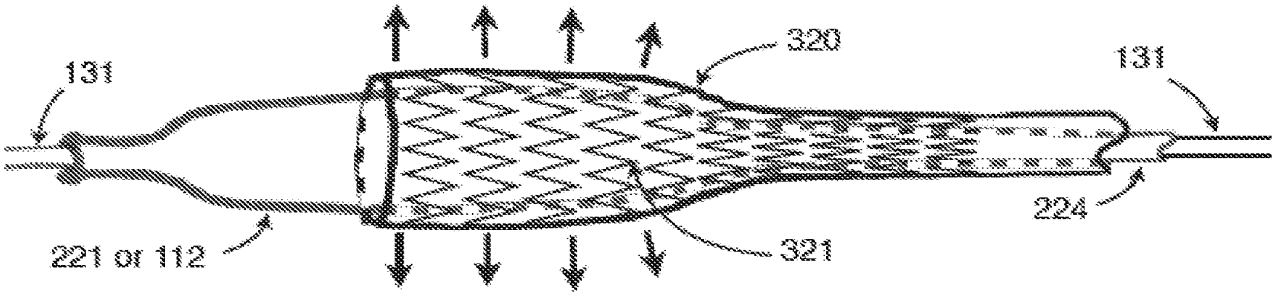


FIG. 6B

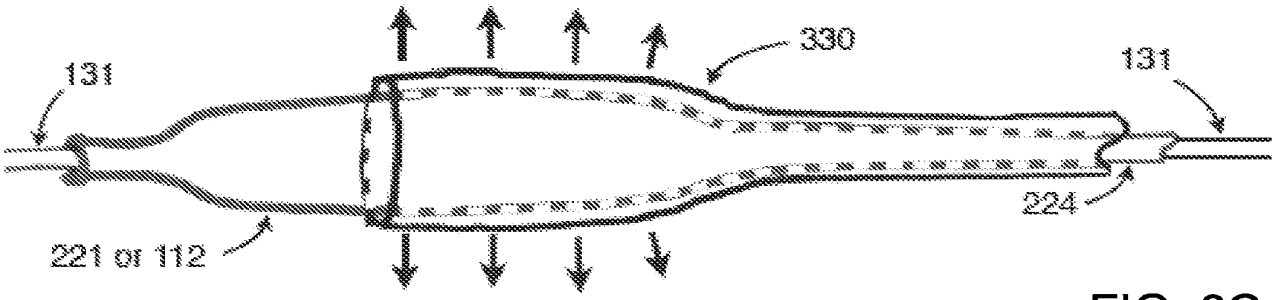
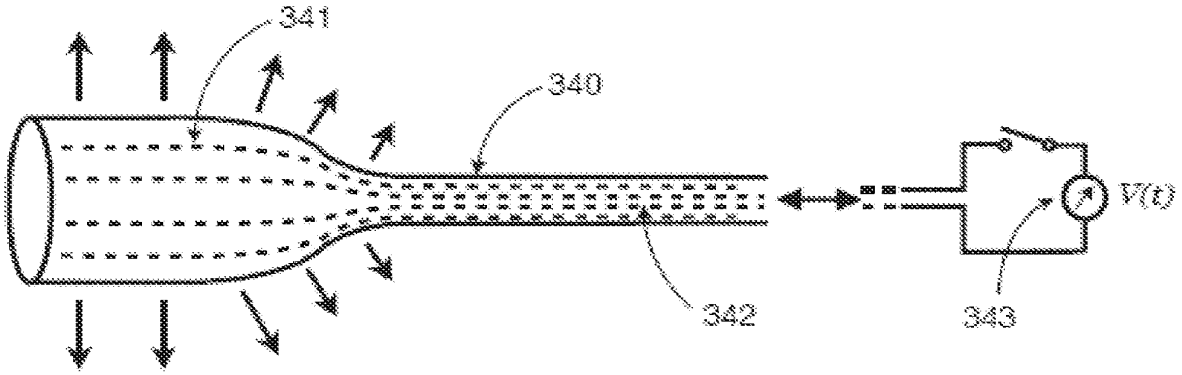


FIG. 6C

FIG. 6D



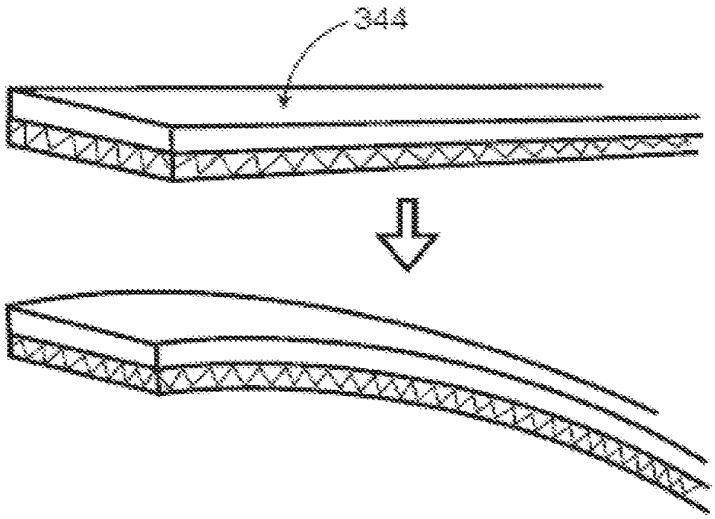


FIG. 6E

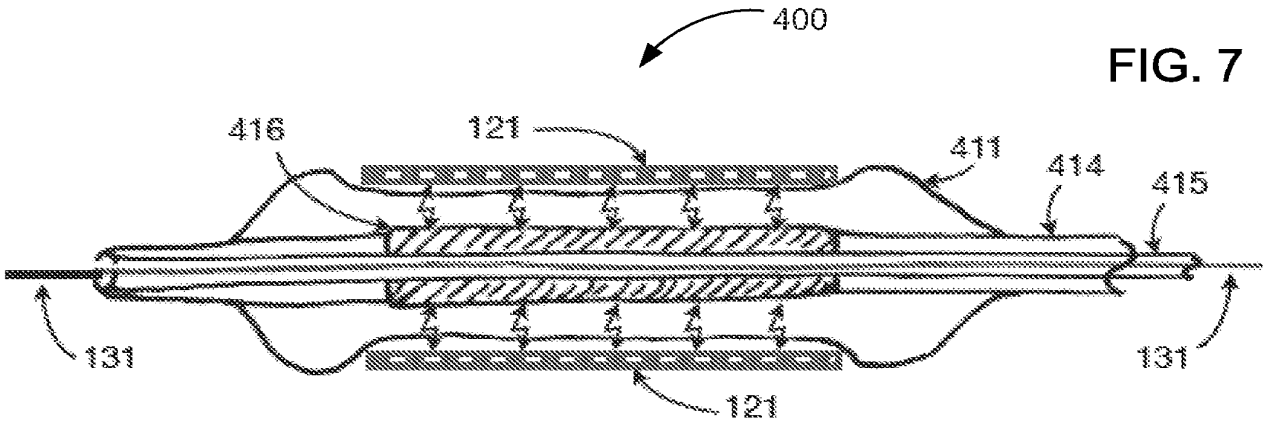


FIG. 7

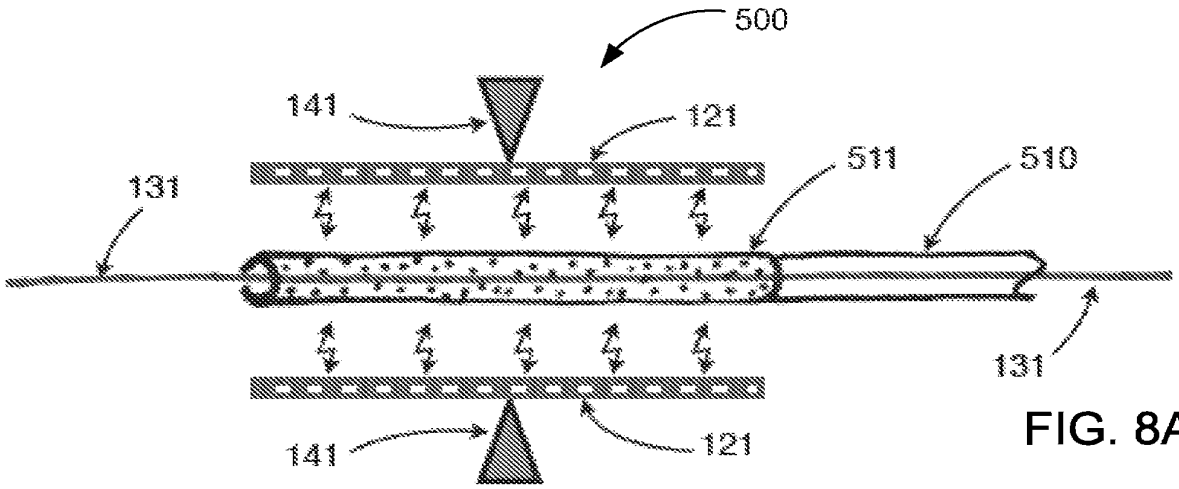


FIG. 8A

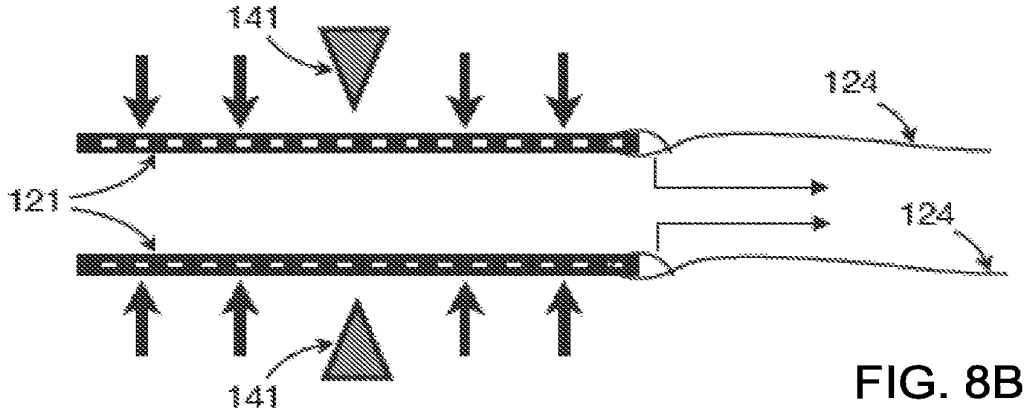


FIG. 8B

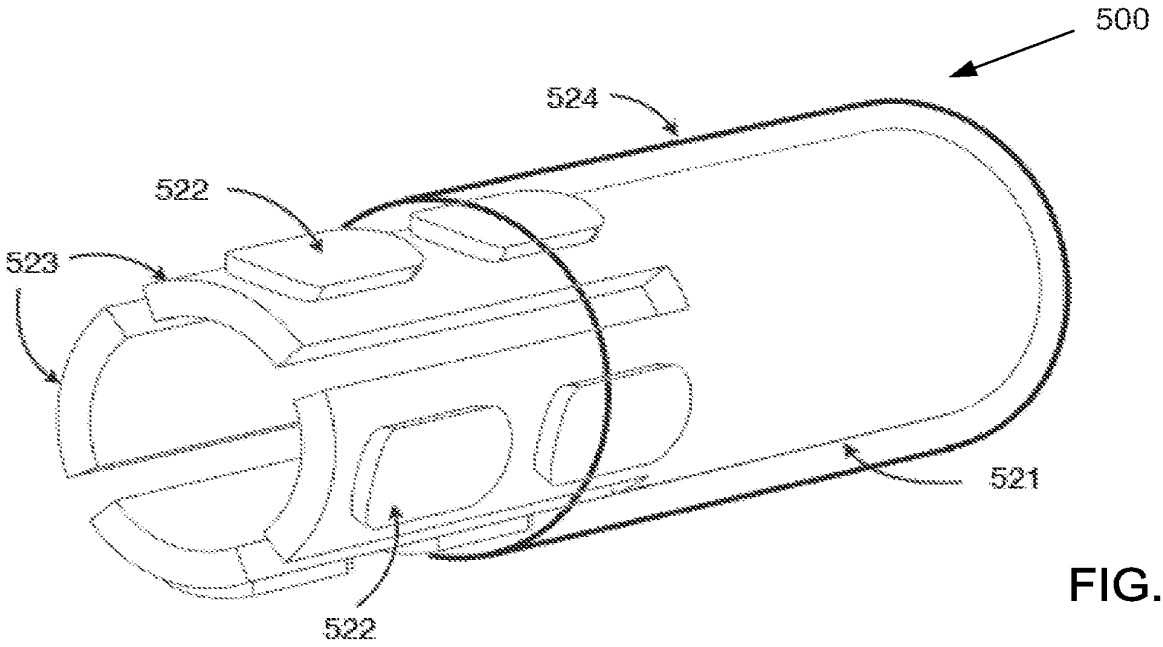

500
524
522
523
521
522

FIG. 8C

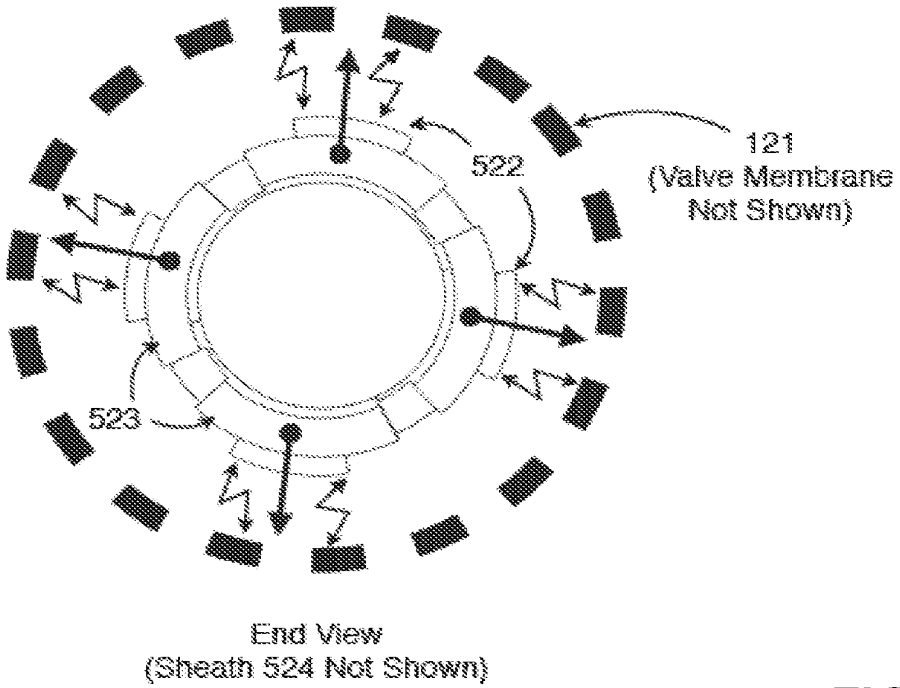

121
(Valve Membrane
Not Shown)
522
523
End View
(Sheath 524 Not Shown)

FIG. 8D

CORRECTED VERSION*

PCT

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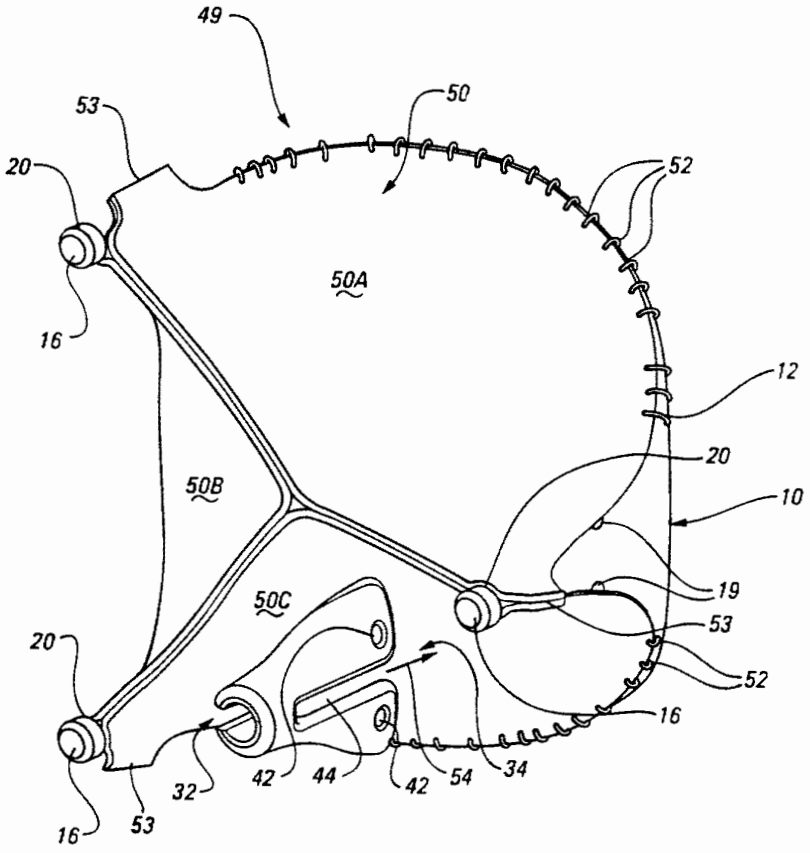
(54) Title: PROSTHETIC HEART VALVE STENT UTILIZING MOUNTING CLIPS

(57) Abstract

A prosthetic heart valve is provided having a stent (10) and a piece of biocompatible material (50). The stent (10) includes an inflow ring (12) and a plurality of posts (14), each post (14) extending from the ring (12) to a post tip (16). The piece of material (50) extends over the stent (10) and substantially conforms to a profile of the stent (10). The piece of material (50) includes a portion which extends adjacent a post tip (16). A clip (30) is provided which has a shape generally conforming to the post tip (16) to thereby clamp the portion of the piece of material (50) to the post tip (16).



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PROSTHETIC HEART VALVE STENT UTILIZING MOUNTING CLIPS

FIELD OF THE INVENTION

The present invention relates to prosthetic heart valves. More specifically, the present invention relates to attaching a biocompatible material to a stent for a prosthetic heart valve.

BACKGROUND OF THE INVENTION

Prosthetic heart valves have been used for replacing damaged heart valves in patients. Various types of prosthetic heart valves are known, including mechanical heart valves and bioprosthetic heart valves. One group of prosthetic heart valves may include a material such as tissue or synthetic polymers carried on a stent. The material typically comprises animal tissue such as porcine aortic valve material or bovine pericardium.

Various techniques are known for coupling the material to the stent. For example, suturing the valve material to the stent is one common technique used to couple the material to the stent. However, such suturing has been found to place stress on the material as the valve opens and closes, thus leading to a shorter useful life for the prosthetic heart valve. In fact, any attachment technique which creates a hole in the tissue near the post tips will concentrate destructive stresses in those areas.

Other types of attachment techniques are also shown in the prior art. For example, U.S. Patent No. 4,501,030, issued February 26, 1985, entitled "METHOD OF LEAFLET ATTACHMENT FOR PROSTHETIC HEART VALVES" describes the use of a clamping force to hold the material to the

stent. However, the design uses sutures which are positioned near the top of each of the stent posts. Further, U.S. Patent No. 4,501,030 focuses the clamping force in a small region of the material between the thin wire stent and a polymer clamping piece. By further concentrating the clamping force, the valve may be more likely to require early replacement. It may be possible to improve the performance of this device by increasing the area over which the clamping force is applied. In addition, this device applies stress to the leaflet material in direct relation to the closing load of the valve. U.S. Patent No. 4,441,216 issued April 10, 1984, entitled "TISSUE HEART VALVE AND STENT" describes the use of sutures along the top of each of the stent posts in order to attach the material to the stent. U.S. Patent Nos. 5,163,955, 5,423,887 and 5,489,298 to Love all describe the use of alignment members at the tops of the posts. These alignment members put holes into the material. Further, the designs of Love are relatively complicated in that they require several pieces and use an inner and an outer stent which adds considerable thickness to the device. Similar problems are encountered in U.S. Patent No. 4,725,274, to Lane which issued February 16, 1988. The Lane patent requires four separate stent components which, when assembled, create a relatively thick stent.

SUMMARY OF THE INVENTION

The present invention includes a prosthetic heart valve having a stent and one or more pieces of biocompatible material which generally comprises leaflets or cusps. The stent includes an inflow ring and a plurality of posts. Each post extends from the ring to a post tip. The leaflets extend over the stent and

substantially conform to a profile of the stent. The material includes a portion which extends adjacent a post tip. A clip is provided which has a shape generally conforming to the post to thereby clamp the portion of the material to the post tip. The clips reduce the stress applied to the leaflets during opening and closing of the valve. One aspect of the invention includes providing knobs at the ends of the post tips to maintain the clip in position.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a perspective view of a stent in accordance with the present invention.

Figure 2 is a perspective view of a commissure post clip for use with the stent of Figure 1 in accordance with the present invention.

Figure 3 is a perspective view showing three commissure post clips of the type shown in Figure 2 coupled to posts of the stent shown in Figure 1.

Figure 4 is a perspective view of a prosthetic valve including a commissure post clip of Figure 2.

Figure 5 is a side plan view showing commissure post clips securing material to the stent of Figure 1.

Figure 6A is a top plan view of a commissure post clip coupling material to a stent in which the material is in an open position.

Figure 6B is a top plan view of a commissure post clip coupling material to a stent in which the material is in a closed position.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Figure 1 is a perspective view of a stent 10 in accordance with the present invention. Stent 10 includes an inflow ring 12 which may be scalloped and

commissure posts 14 extending therefrom to individual post tips 16. As shown in Figure 1, stent 10 provides a relatively smooth profile for carrying cusps or leaflets made of biocompatible material (not shown in Figure 1) which will hereinafter be referred to as leaflets. Stent 10 includes openings 18 and retaining holes 19 formed therein which are used to couple material (not shown in Figure 1) to the stent. Post tip knobs 20 are carried at tips 16 of each of the commissure posts 14. Preferably, stent 10 is formed of a biocompatible material such as polyetheretherketone (PEEK).

Figure 2 is a perspective view of a commissure post clamp or clip 30 in accordance with one embodiment of the present invention. Commissure post clip 30 includes tip region 32, base region 34, inner side wall 36 and outer side wall 38. Inner wall 36 of clip 30 is generally formed in the shape of a C-shape and is configured to fit over posts 14 of stent 10 shown in Figure 1 adjacent tips 16. The general C-shape of clip 30 is formed by end walls 40 which extend from tip region 32 to base region 34. Additionally, retaining holes 42 are formed in clip 30 near base region 34. Retaining holes 42 are located such that they are generally in alignment with retaining holes 19 of stent 10 when clip 30 is positioned over post 14. Clip 30 includes segmented region 44 to allow spreading between clip portions 46 and 48.

Figure 3 is a perspective view of stent 10 including three commissure post clips 30 coupled to each post 14. For simplicity, the leaflets are not shown in Figure 3. As shown in Figure 3, clips 30 have a shape which is configured to generally conform to the profile of posts 14. Further, post tip knobs 20 positioned at

tips 16 of posts 14 secure clips 30 on posts 14. Retaining holes 42 are substantially aligned with retaining holes 19 whereby an attachment mechanism, such as a suture (not shown in Figure 3) can be secured proximate the base region 34 of clip 30 to couple clip 30 to a post 14. Relative pre-assembly spacing and alignment of retaining holes 19 on stent 10 and retaining holes 42 on clip 30 can be varied to adjust clamping force.

Figure 4 is an exploded view of a heart valve prosthesis 49 having stent 10 and clip 30 including leaflets 50 carried thereon. Leaflets may be a single piece or multiple pieces. In one embodiment, leaflets 50 are formed of three separate material pieces, 50A, 50B and 50C which are sewn to ring 12 using suture 52. Leaflets 50 extend over post 14 and form leaflet tabs 53 which are located generally at the tip 16 of post 14. As shown in Figure 4, commissure post clip 30 is aligned generally coaxially with post 14 and moved in a direction shown by arrow 54. As clip 30 is moved over post 14, segmented region 44 allows clip 30 to spread such that it will securely fit over post 14 and post tip knob 20.

Figure 5 is a side plan view of prosthetic heart valve 49 in accordance with the present invention including clips 30 coupled to posts 14 of stent 10. As shown in Figure 5, clips 30 are secured to posts 14 using suture 60 which extends through retaining holes 42 and retaining holes 19 (not shown in Figure 5). Leaflet tabs 53 fit in segmented region 44. As exemplified in Figure 5, clips 30 secure leaflets 50 to posts 14 of stent 10. Further, the securing of material 50 to post 14 places only limited stress on the leaflets. Such stress is spread out over a relatively large area and requires no

sutures near post tip 16.

Figures 6A and 6B are top plan views of prosthetic valve 49 showing material 50 in an open and closed position, respectively. As illustrated in Figure 6A, in the open position leaflet pieces 50A and 50C form against the smooth contour side wall 40 of clip 30. This reduces the stress on material 50 during operation of prosthetic valve 49 over the lifetime of the device.

A prosthetic valve in accordance with the present invention may be made with other types of stents than that shown specifically herein. For example, the stent may be formed of various materials and have any desired flexibility for a particular application. The posts, or commissure supports may be formed as desired having other characteristics, tapering or configurations. The locations and the number of the posts may also be varied. A prosthetic heart valve in accordance with the invention may include a fabric covering or wrap, and/or a sewing ring or cuff. The construction, design and placement of these features are well known in the art. While a stent and the clip in accordance with the invention may be produced of any biocompatible material, e.g., material compatible with blood and/or tissue, practical considerations suggest the use of commercially, medically available materials. For example, these parts may be formed or preformed from any metal, synthetic polymer, biopolymer, etc. which is capable of functioning as required, or may be composite materials. It may also be desirable to sterilize the material by exposure to gas plasma, steam, gamma or electron beam irradiation, or chemical sterilization such as ethylene oxide, formaldehyde, glutaraldehyde, peroxides, and propylene oxide, and preferably any such material is capable of

withstanding such exposure. The invention is not limited to the material used to construct the stent and includes other materials, their mixtures, etc.

Suitable synthetic polymers for use as a stent or clip include, but are not limited to, thermoplastics, such as polyolefins, polyesters, polyamides, polysulfones, acrylics, polyacrylonitriles, and polyaramides. Examples, include, but are not limited to polyetheretherketone (PEEK).

Suitable biopolymers for the stent or clip are biomolecules that have a repeating or polymer-like structure, including but not limited to, natural polymers such as collagen or elastin, or synthetic biopolymers, such as polyaminoacids or synthetic proteins, polysaccharides and mixtures or composites thereof.

Suitable metals for the stent or clip include, but are not limited to, cobalt, titanium, and alloys thereof. For example, an alloy sold under the trademark Eligiloy® is a cobalt-chromium-nickel-molybdenum-iron alloy (ASTM F1058).

Suitable ceramics for use as a stent or clip include, but are not limited to, alumina, zirconia, carbides, nitrides, and cermets. Closely related carbons could also be used. For example, pyrolytic carbon has desirable properties and is widely used in various heart valves.

Preferred materials are synthetic, polymeric materials, and most preferred are materials that can be injection molded. The selected material needs to have both the required stress and strain characteristics as well as good long term mechanical stability. Certain metals, such as Eligiloy®, may be advantageously used, as well as various polymers or biopolymers. PEEK is

known to have mechanical properties in the desirable range, including a tensile strength of 14.5; a flexural modulus of 594.0; and a flexural strength of 24.65 (all in ksi at 73°F). PEEK is also advantageous in that it has a high fatigue endurance limit, a low rate of creep, a low rate of water absorption at equilibrium, and significant radiation resiliency for the purposes of sterilization. At present, the most desirable starting material for use in forming a stent according to the present invention is PEEK.

The biocompatible material for the leaflets preferably includes both biological or synthetic polymers which could be either naturally occurring or artificially produced.

Biological material for use in this invention includes relatively intact tissue as well as decellularized or otherwise modified tissue. These tissues may be obtained from, for example, heart valves, pericardial tissue, dura mater, fascia, skin or any other membranous tissue. Generally, the tissue is composed of collagen-containing structures derived from different animal species such as human, bovine, porcine, equine, seal, or kangaroo, as well as engineered tissues. Engineered tissue typically involves repopulated matrices which can be derived from the tissues mentioned above or synthetically fabricated. The biological tissue may be fixed to cross-link the tissue and provide mechanical stabilization by preventing enzymatic degradation of the tissue, although the matrices do not necessarily need to be fixed. Glutaraldehyde is typically used to fix the material, but other fixation methods, such as epoxides, other difunctional aldehydes, or photooxidation can be used.

Synthetic, biocompatible materials for use in the prosthesis of the present invention include synthetic polymers as well as biological polymers. Synthetic polymers include polyamides (nylon), polyesters, polystyrene, polyacrylates, vinyl polymers (e.g. polyethylene, polytetraflouroethylene, polypropylene and polyvinylchoride), polycarbonate, polyurethane, polydimethyl siloxane, cellulose acetate, polymethyl, methacrylate, ethylene vinyl acetate, polysulfone, and similar copolymers. Biological polymers include natural forms such as collagen, elastin and cellulose or purified biopolymers such as polyaminoacids or polysaccharides. All of these materials can be used singularly or in a combination thereof and can be molded or cast into the selected forms or can be knit or woven into a mesh to form a matrix.

Materials which comprise either the stent, clips or leaflets can remain untreated or can be treated to effect a desired result, for example, to make the part(s) more effective within the environment of the heart. The modification could be in the form of surface finish alterations or in chemical modifications applied to the stent, clip or leaflet material. Surface finish alterations could include adding texture to the inside of the clip and/or the outside of the commissure post to increase the friction force imparted on the leaflet material by the clip, effectively increasing the clamping force. Surface texture could also be added to the external surfaces of the stent, clip or leaflet to optimize cell adhesion and growth. The degree of texturing must be controlled such that cell adhesion is encouraged without introducing the possibility of increased thrombolytic problems. To achieve this end,

the surface finish of some portions of the stent and clip may require a reduction in roughness. Ideally, the surface finish of different surface locations on the stent and clip may be tuned independently to optimize the characteristics of the entire prosthesis. Other surface finish modifications may be implemented to increase the wetting surface tension, to decrease the harmful effects of some sterilization protocols, or to ease production.

Appropriate chemical modifications to these materials can include any or all of the following. Thrombogenicity of the surface can be modified, for example with heparin. Other modifiers such as fibronectin or other arginine-glycine-aspartic acid (RGD) sequence containing peptides can be used to modify the healing response of the part(s). Additionally, growth factors such as fibroblast or endothelial cell growth factors or other chemotactants can be applied to improve biocompatability.

Problems associated with calcification can be mitigated by the application of anticalcifics such as multivalent ions and diphosphonates. The part(s) can also be modified to reduce the potential of microbial colonization by treating them with antimicrobial compounds such as silver or gold or with any of a host of commonly available antibiotics.

The present invention is particularly advantageous because it provides a simple and secure technique for coupling a biocompatible material to a stent. Further, the clips set forth herein distribute stresses over a relatively large area of the material to thereby reduce localized stress which can lead to damage to the valve material. The present invention utilizes a permanent clamping force between the clip and the stent

which is independent of the closing load of the valve. The edges of the clips are preferably rounded to provide a smooth bending radius for the leaflets when they are in the open position, thereby reducing flexural stresses. The radius of the clip can be optimized to reduce leaflet stresses and strains based on the thickness of the leaflet material. For example, calculations for bending indicate that the leaflet strain is equivalent to the leaflet thickness divided by twice the bending radius. The configuration of the stent and clip also allows the open leaflets to wrap around the outside surface of the clip, increasing the valve's orifice size. The increased orifice results in improved hemodynamics. Assembly of the device is quick and simple and the clip is self aligning with the post and material tab. The clip opens slightly to allow the material tab to fit in the segmented region of the clip. Further, the configuration of the clip and the post ensure that the clip is securely fit against and aligned with the post and the tissue tabs aid in alignment of leaflets to ensure coaptation. The clip is easily sutured to the stent. However, other attachment techniques may be used including wire ties, staples, rivets, etc. Alternatively, the clip could be welded or glued to the commissure post following assembly. The design of the present invention minimizes the amount of hand labor required, facilitating the use of automated equipment to increase valve to valve consistency.

WHAT IS CLAIMED IS:

1. A prosthetic heart valve, comprising:

a stent having an inflow ring and a plurality of posts, each post extending from the ring to a post tip;

biocompatible leaflet material extending over the stent and substantially conforming to a profile of the stent, the material including a plurality of portions each of which extends adjacent a post tip; and

a clip having a shape generally conforming around one of the plurality of posts to clamp one of the portions of the material to the one of the plurality of posts.

2. The prosthetic heart valve of claim 1 including a post tip knob located at the post tip to maintain the clip on the one of the plurality of posts.

3. The prosthetic heart valve of claim 1 wherein the clip has an elongated generally 'C' shape.

4. The prosthetic heart valve of claim 1 wherein the clip comprises a polymer.

5. The prosthetic heart valve of claim 1 wherein the stent comprises a polymer.

6. The prosthetic heart valve of claim 1 wherein the clip comprises a metal.

7. The prosthetic heart valve of claim 1 including a means for coupling the clip to the stent proximate the ring.

8. The prosthetic heart valve of claim 1 including a plurality of clips to clamp respective, adjacent portions of material to each of the plurality of posts.

9. The prosthetic heart valve of claim 1 wherein the clip includes a segmented region formed therein and the material includes a tab which fits in the segmented region to aid alignment and ensure leaflet coaptation.

10. The prosthetic heart valve of claim 1 wherein the material moves between an open position and a closed position and the clip includes a curved side wall, the material pressing against the curved side wall when in the open position.

11. The prosthetic heart valve of claim 1 wherein each of the plurality of posts taper in a direction toward the post tip and the clip has a shape generally conforming to the taper.

Fig. 1

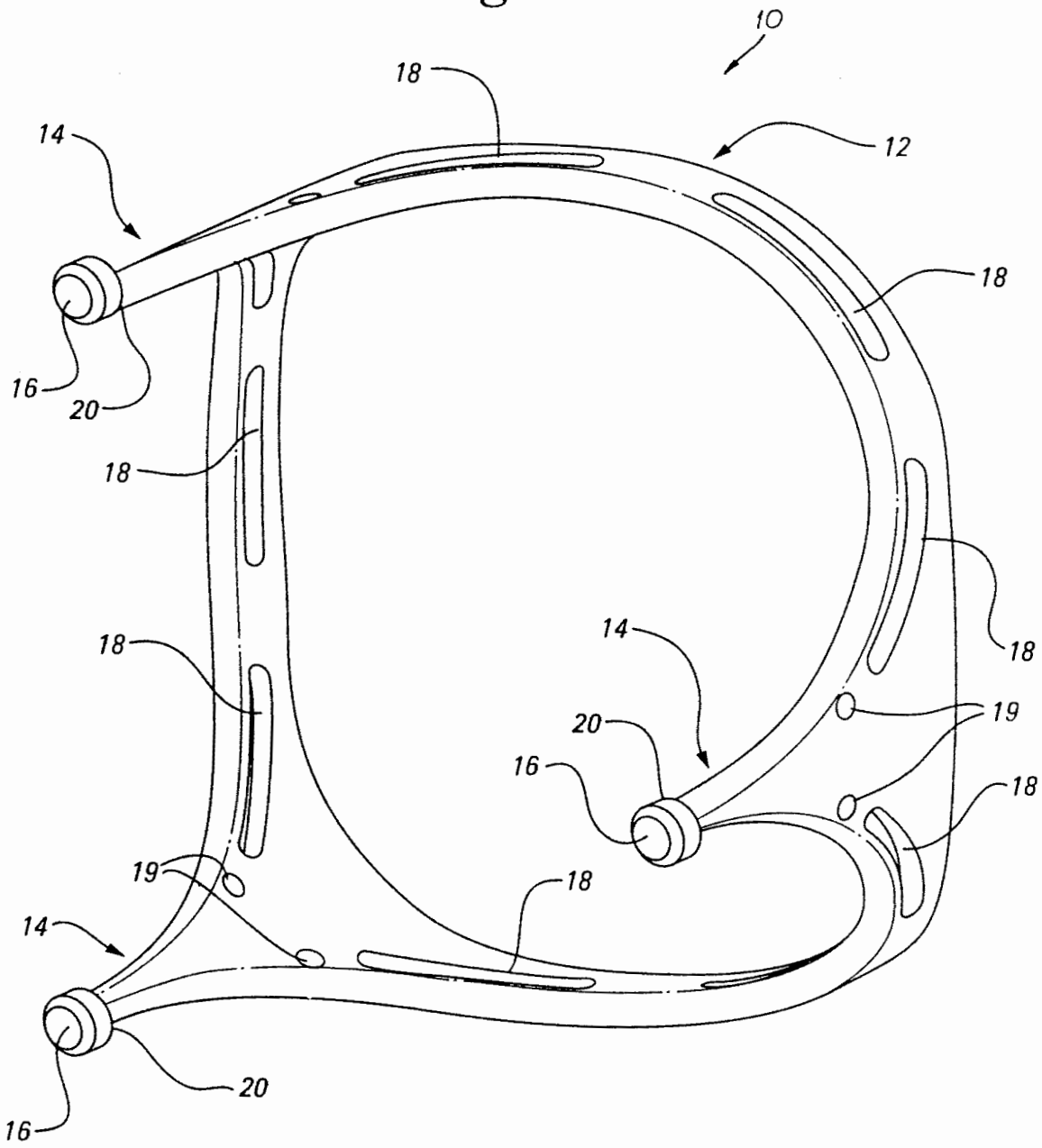


Fig. 2

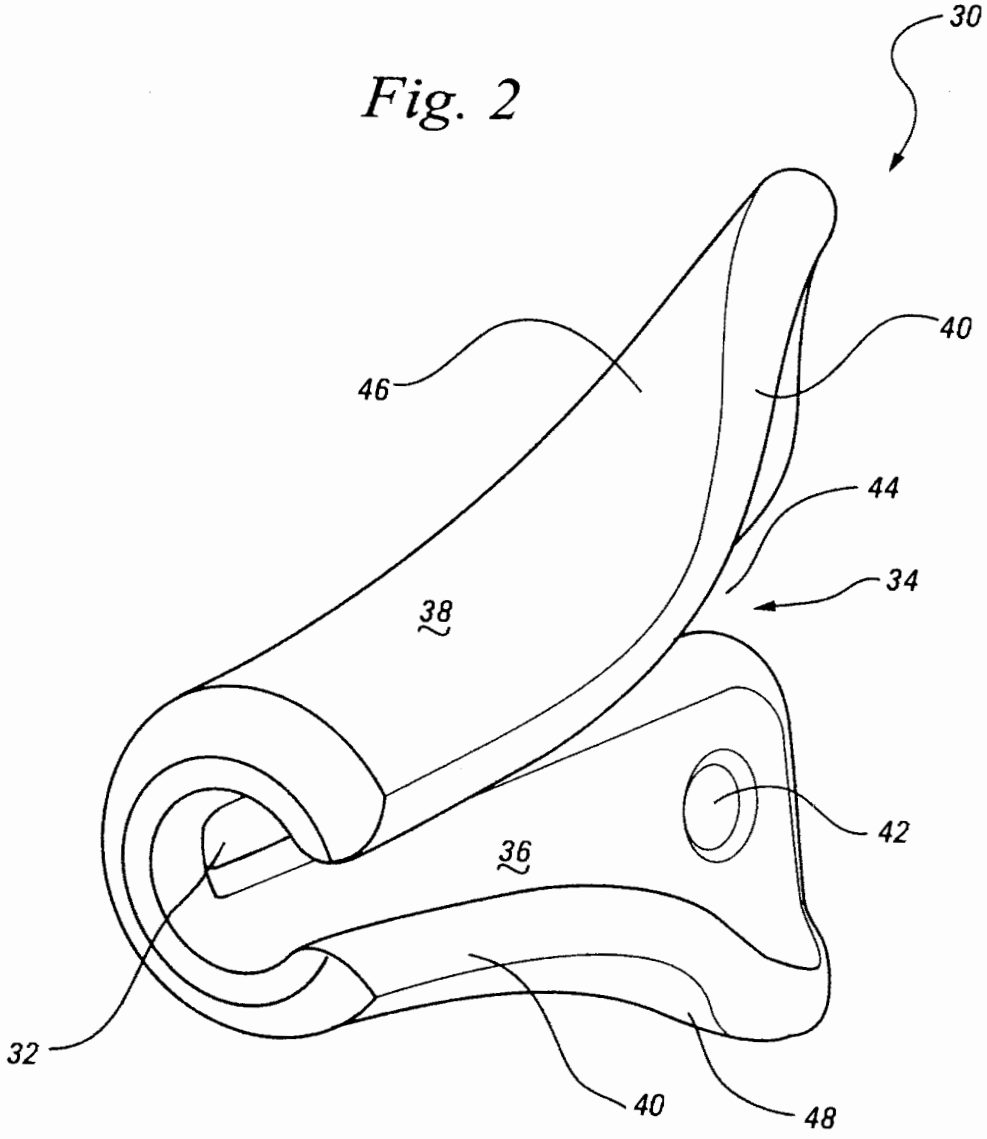


Fig.3

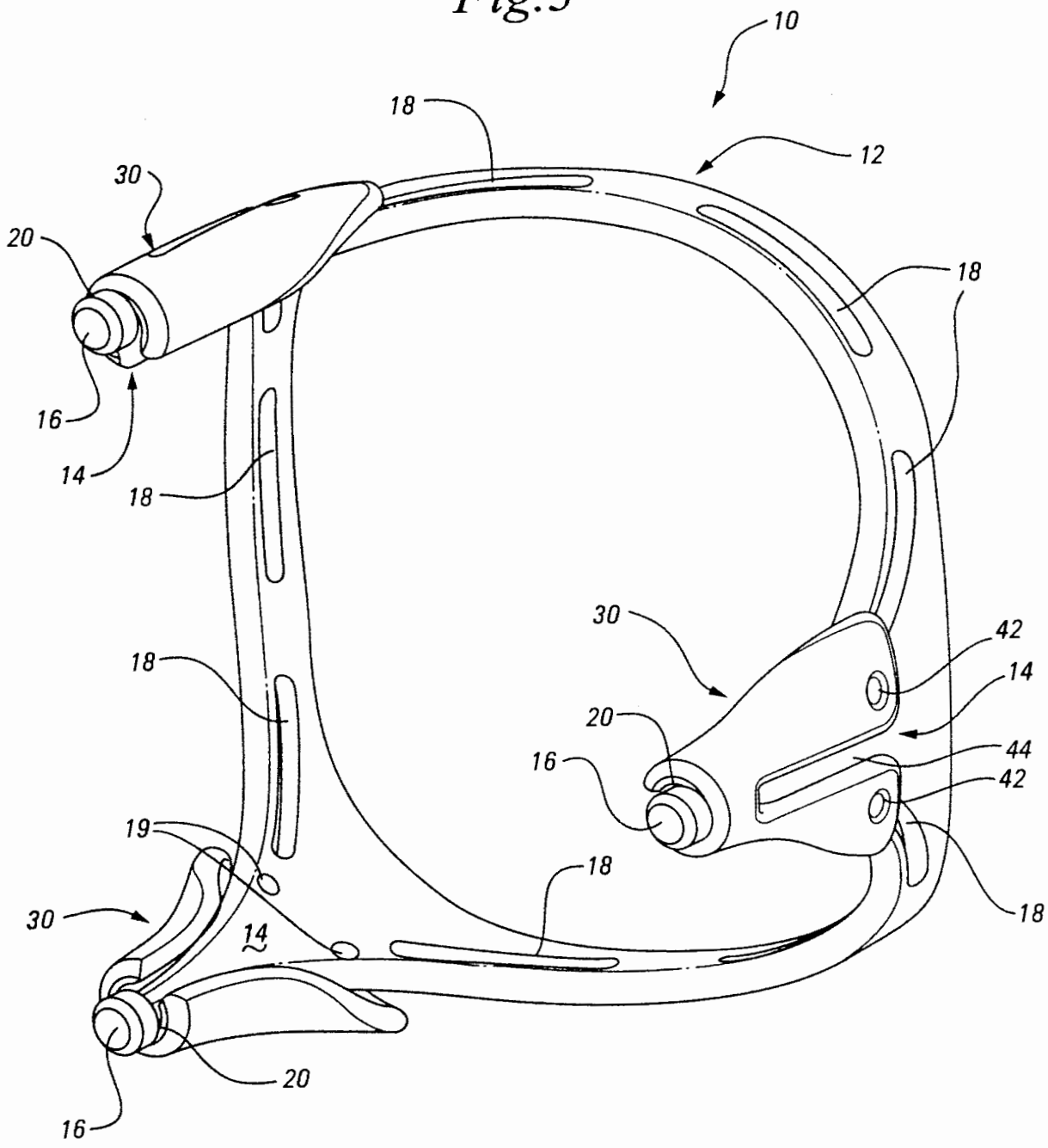
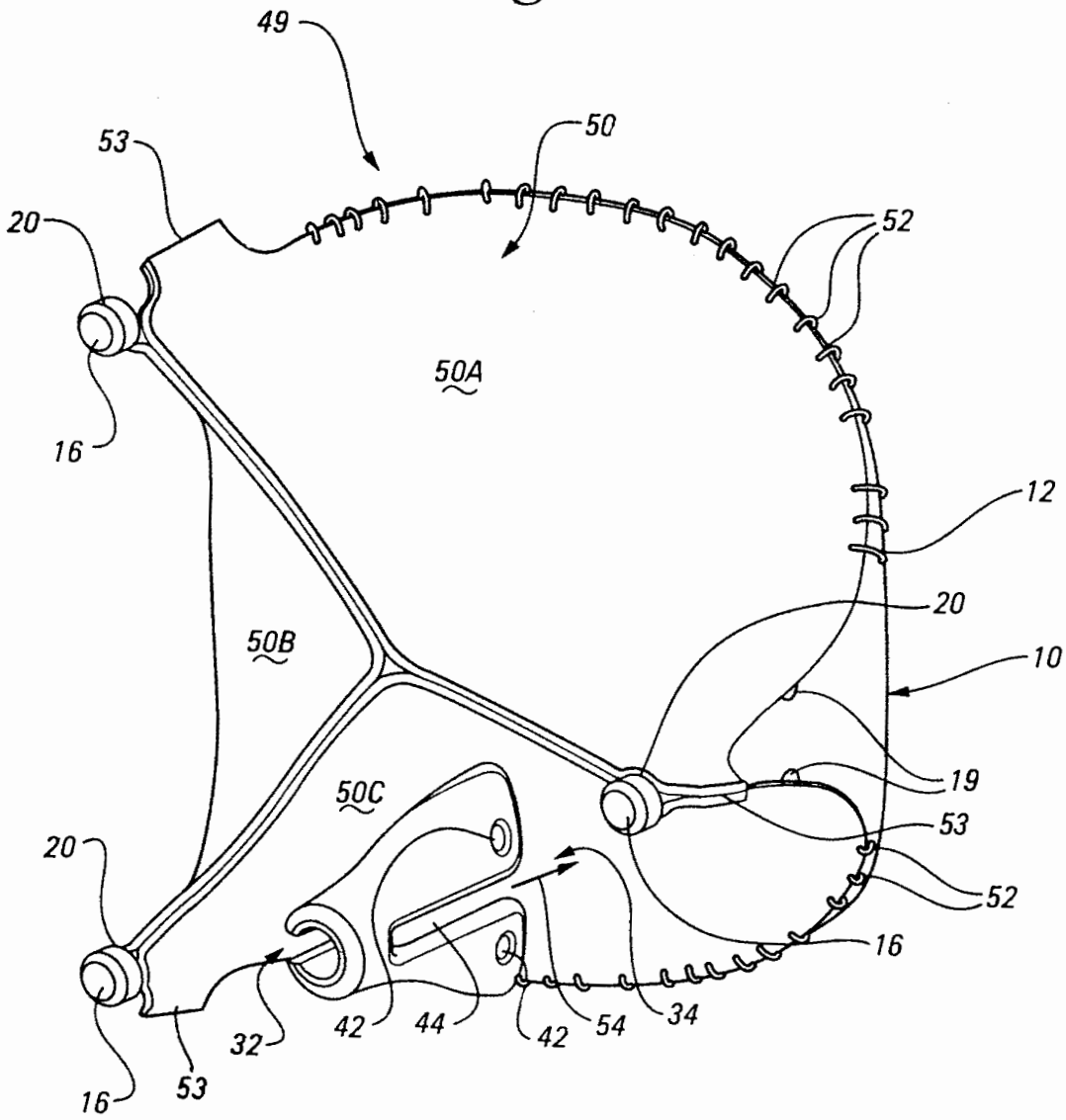


Fig. 4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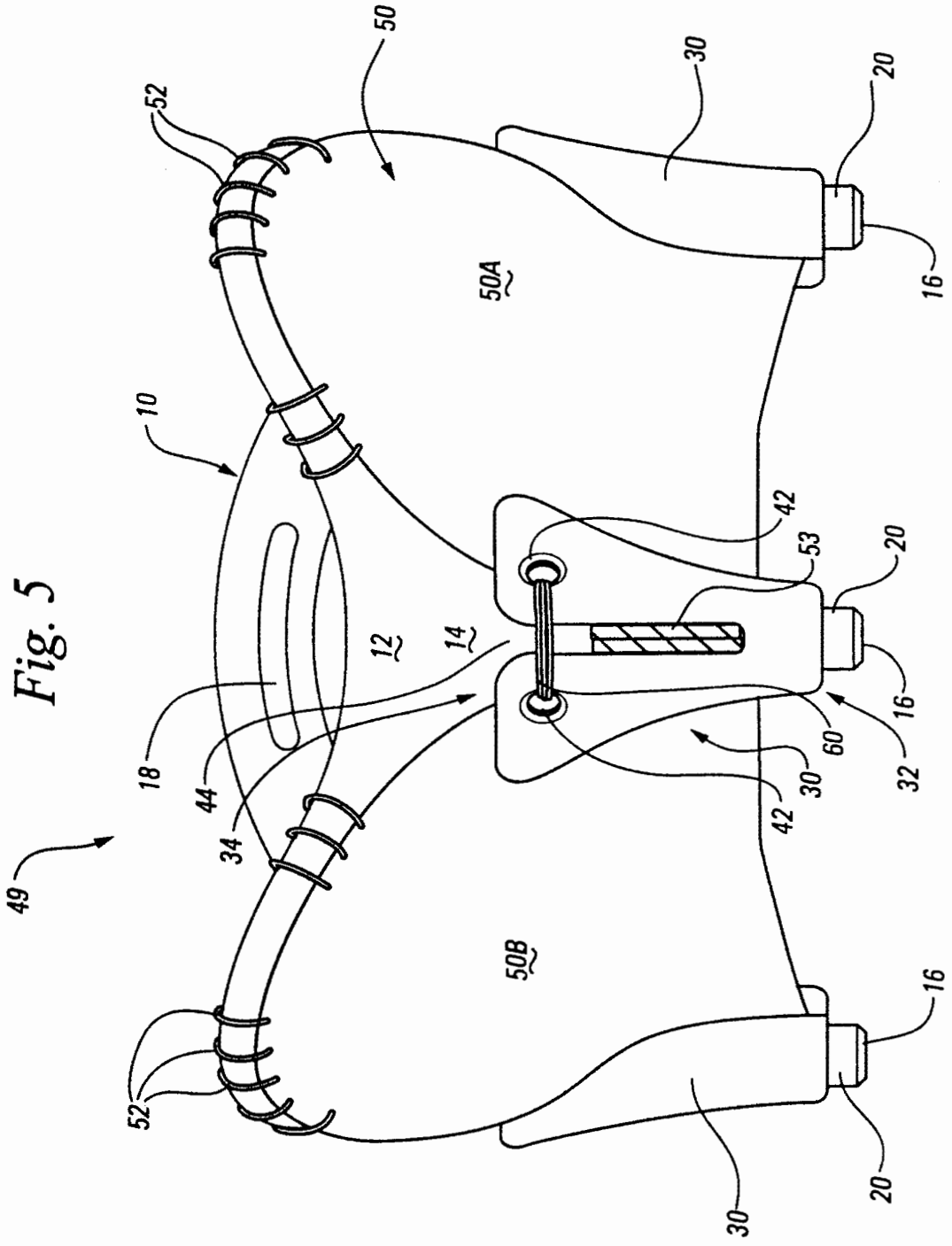


Fig. 5

Fig. 6b

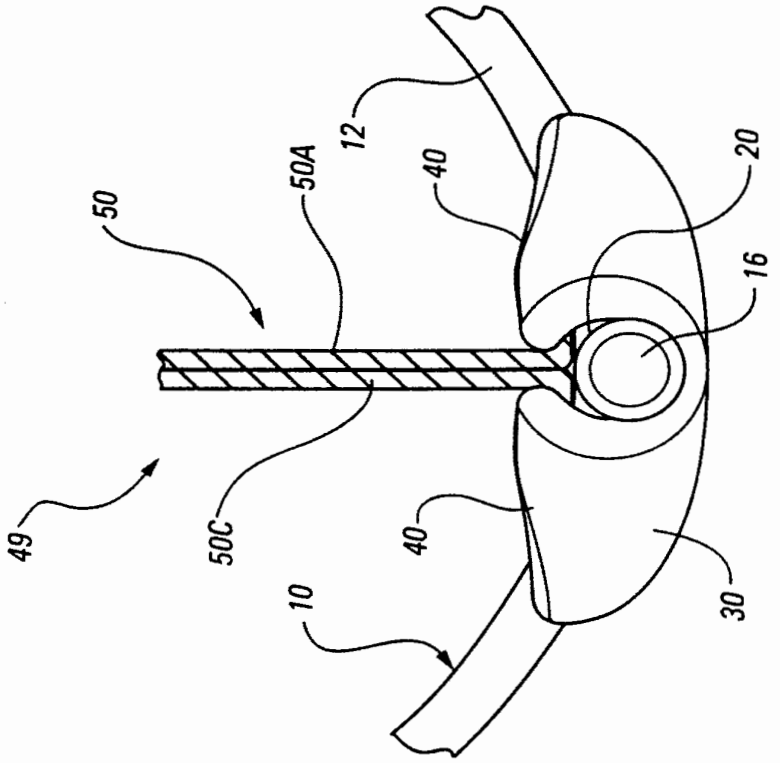
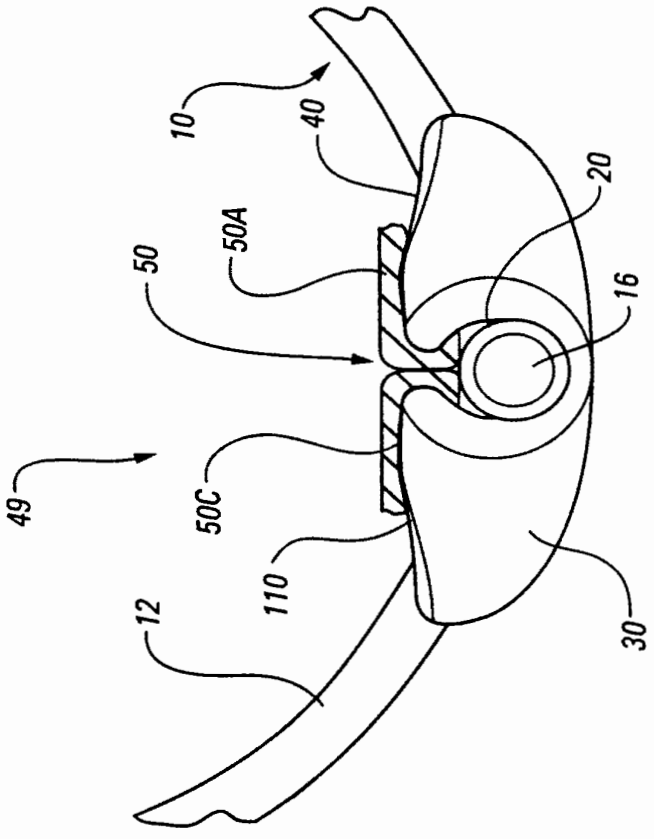


Fig. 6a



INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/US 98/26173

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 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 6 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 470 157 A (LOVE JACK W) 11 September 1984 see column 5, line 56 - line 68; claims 17,27; figure 16	1
A	US 5 562 729 A (PURDY DAVID L ET AL) 8 October 1996 see column 4, line 45 - line 57; figures 1,2	1
A	US 4 687 483 A (FISHER JOHN ET AL) 18 August 1987 see column 4, line 10 - line 36; claim 1; figures 1,6	1

☐ Further documents are listed in the continuation of box C.

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Information on patent family members

In ıtional Application No
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(54) **Title**: PROSTHETIC HEART VALVE AND METHOD FOR MAKING SUCH A VALVE

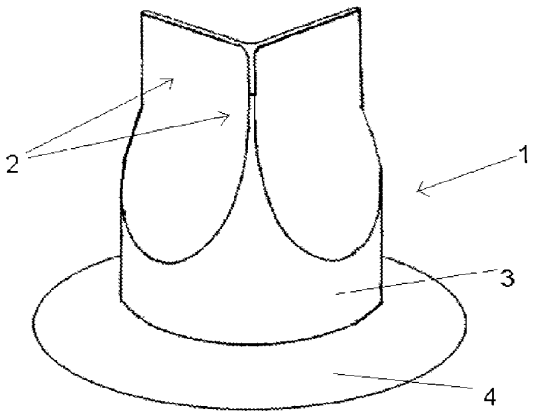

Figure 3(a)

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

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Prosthetic heart valve and method for making such a valve

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

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

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

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

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

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

US 2003/0130729 describes a percutaneously implantable

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

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

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

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

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

positive and a negative shape is advantageous in the process of shaping the heart valve.

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

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

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

Preferably, the tanning step occurs by subjecting the biological tissue to a glutaraldehyde solution. The tanning step occurs simultaneously with the shaping of the heart valve, with the biological tissue placed in or over

a mould. The goal of the tanning step is to make the tissue biocompatible. Other aldehydes are known in the art and may be used. The best results have been obtained with glutaraldehyde solutions with concentrations between 0.1 and 1%, preferably around 0.65%.

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

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

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

According to another aspect of the invention, a prosthetic heart valve of a single piece of biological tissue is provided, said valve comprising a

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

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

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

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

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

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

support perforating the tissue of the heart valve, and as such securing the valve in place. Other mechanical means, such as clamps or clips could also be used for fixing the leaflets along the support structure.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

transportation. During the cleansing, the distilled water may be refreshed a number of times. The tissue is then transported to the laboratory where the heart valve is going to be made.

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

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

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

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

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

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

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

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

in figure 2(g). Negative mould (15') has the negative shape of positive mould (10').

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

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

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

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

of a meshed material, such that it is permeable to a certain extent.

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

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

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

Another possible support structure is shown in figure 4(b), which shows a schematic view of a balloon expandable stent. A self-expandable

stent may also be used, such as shown in figure 4(c). Such alternative structures are well known in the art. The invention is not limited to any particular support structure. Instead the heart valve according to the present invention may be used with any suitable support structure.

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

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

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

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

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

Claims

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

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

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

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

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

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

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

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

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

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

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

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

13. A prosthetic heart valve according to any of claims 10-12, characterised in that the heart valve is made by a method according to any of the claims 1-6.

14. A prosthetic heart valve device comprising a prosthetic heart valve according to any of claims 10-13 and a support structure (20; 20'; 20'') for supporting said valve.

15. A prosthetic heart valve device according to claim 14, characterised in that the support structure (20) comprises three legs (24) and the leaflets (2) of the valve are each connected to one of said legs.

16. A prosthetic heart valve device according to claim 14 or 15, characterised in that the support structure comprises two annular discs (21,23) for positioning the prosthetic heart valve in place, said two rings interconnected

by a cylindrical structure (22).

17. A prosthetic heart valve device according to claim 14, characterised in that the support structure is a balloon expandable or a self-expandable stent.

18. A prosthetic heart valve device according to any of claims 14-16, characterised in that the support structure is collapsible.

19. A prosthetic heart valve device according to claim 18, characterised in that, said support structure is made from nitinol.

20. A prosthetic heart valve device according to claim 18, characterised in that, said support structure is made from stainless steel or a cobalt chromium alloy.

21. A prosthetic heart valve device according to any of claims 14-20, characterised in that it is a prosthetic aortic or pulmonary heart valve device.

22. A prosthetic heart valve device according to any of claims 14-21, characterised in that is a percutaneous heart valve device.

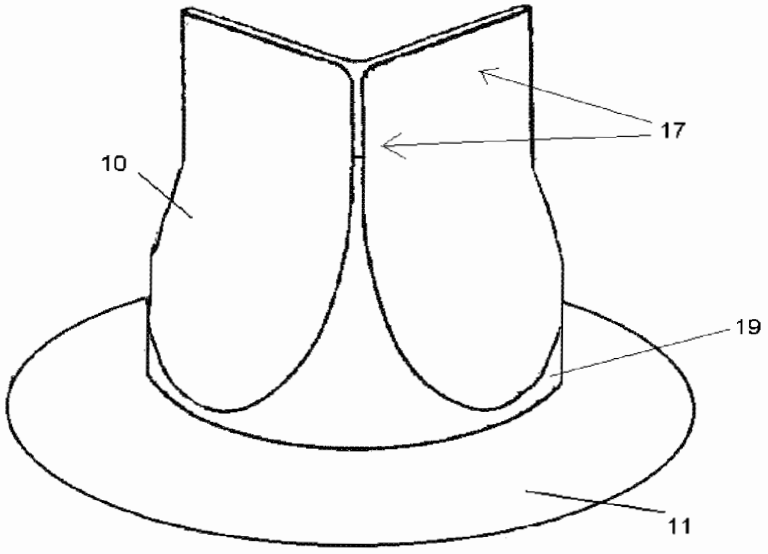

Figure 1(a)

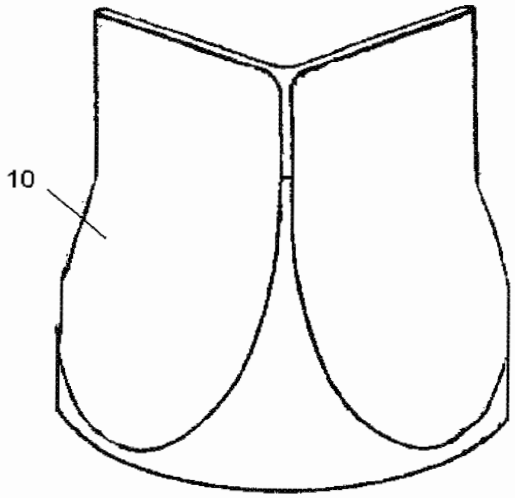

Figure 1(b)

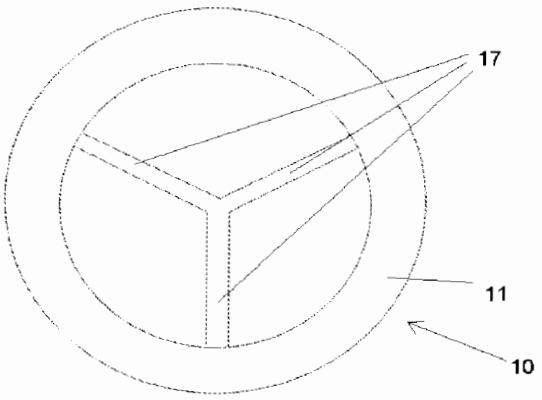

Figure 1(c)

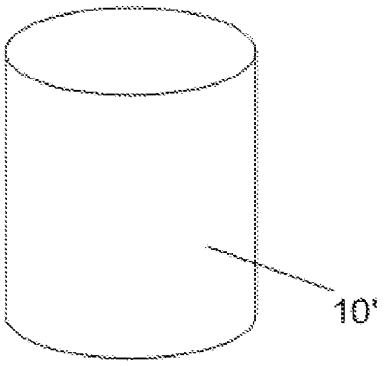

Figure 1 (d)

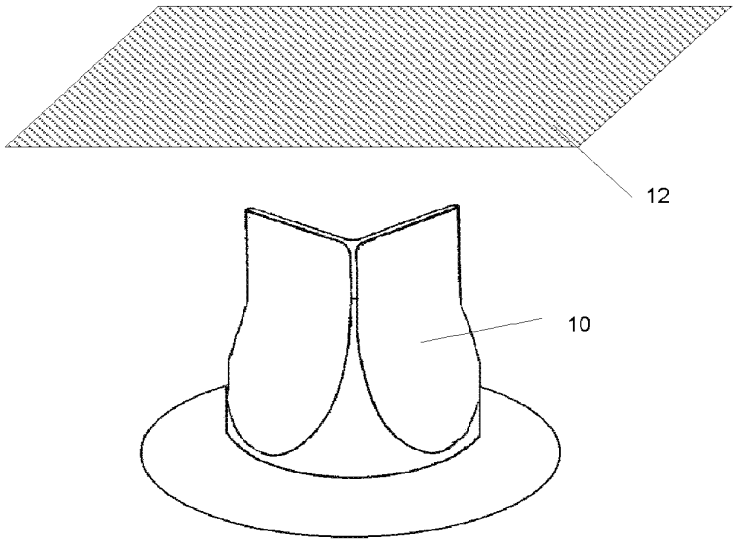

Figure 2(a)

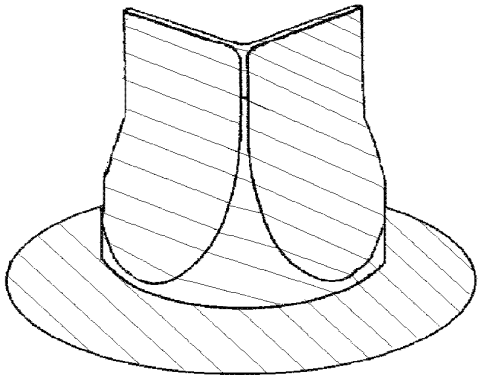

Figure 2(b)

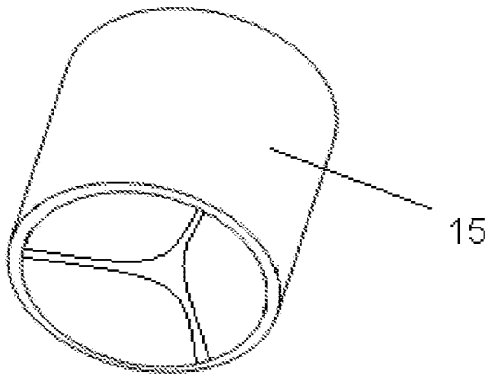

Figure 2(c)

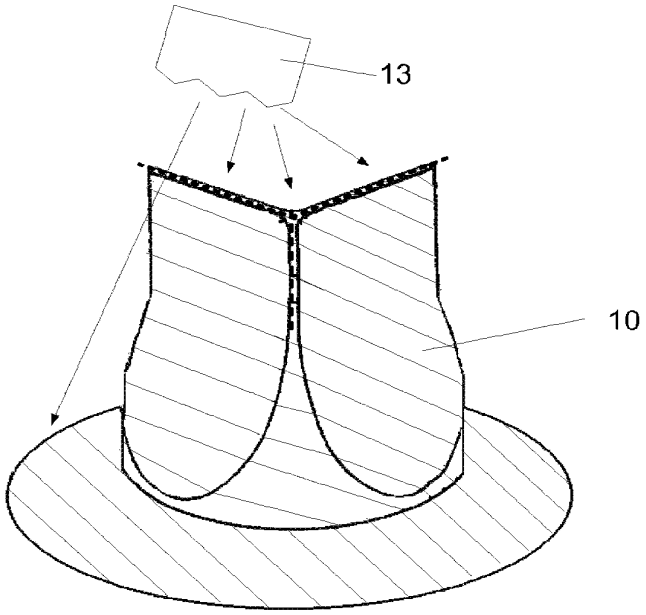

Figure 2(d)

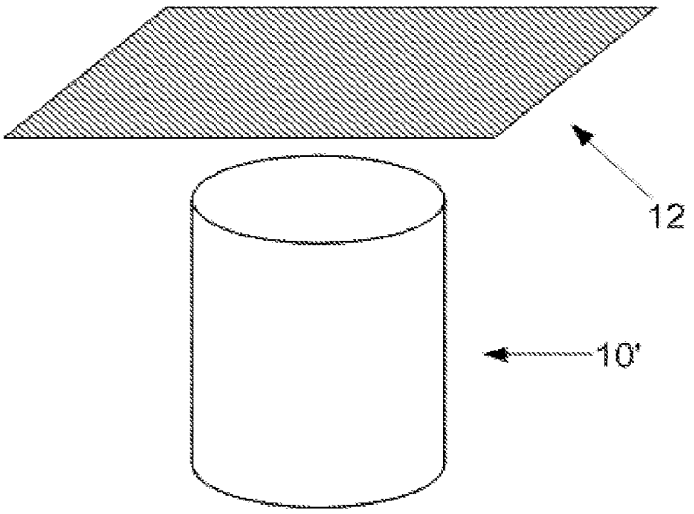

Figure 2(e)

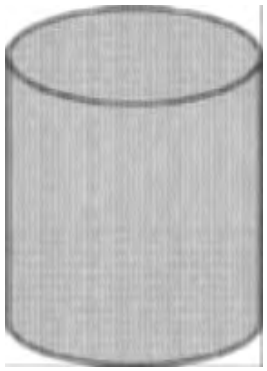

Figure 2(f)

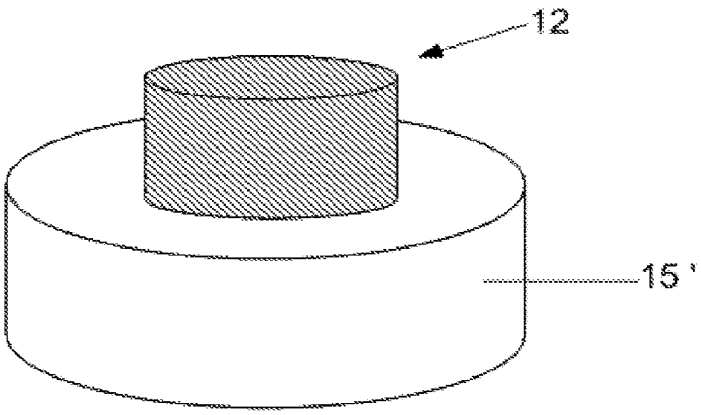

Figure 2(g)

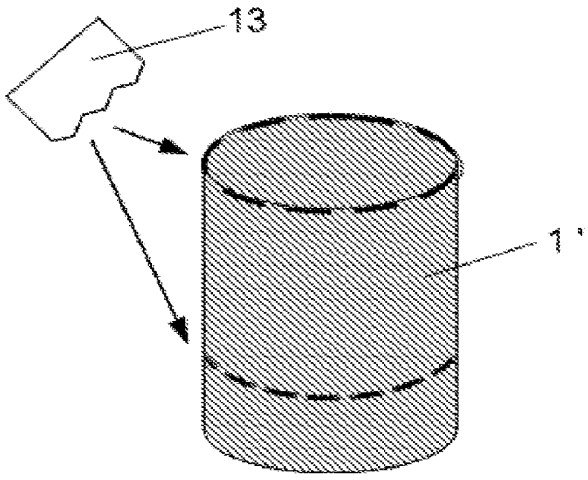

Figure 2(h)

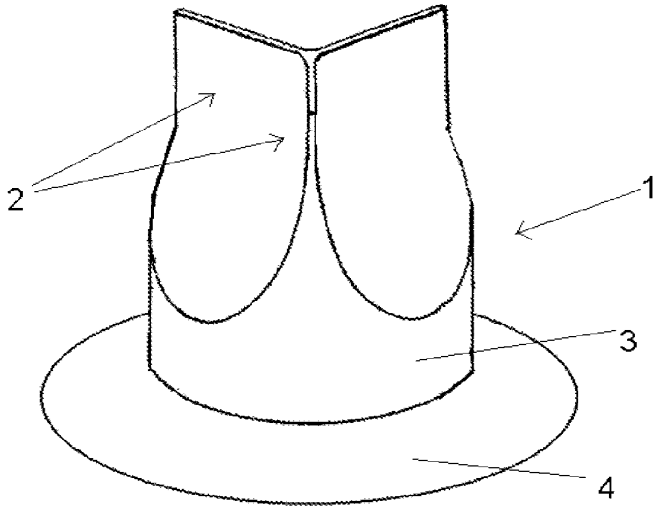

Figure 3(a)

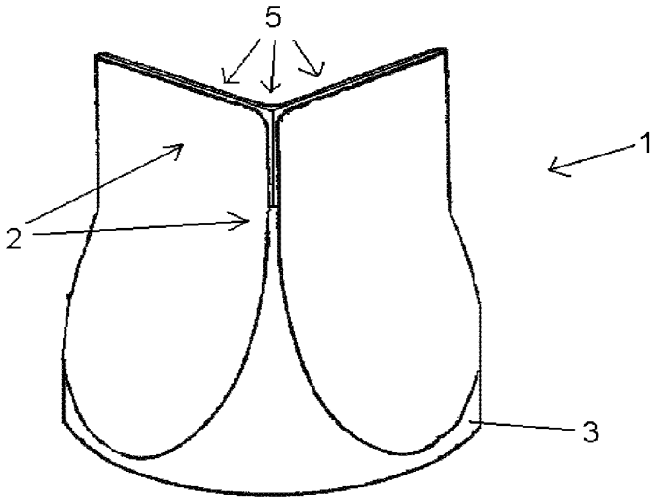

Figure 3(b)

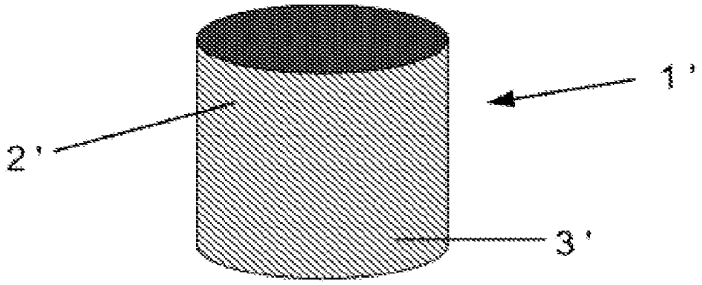

Figure 3(c)

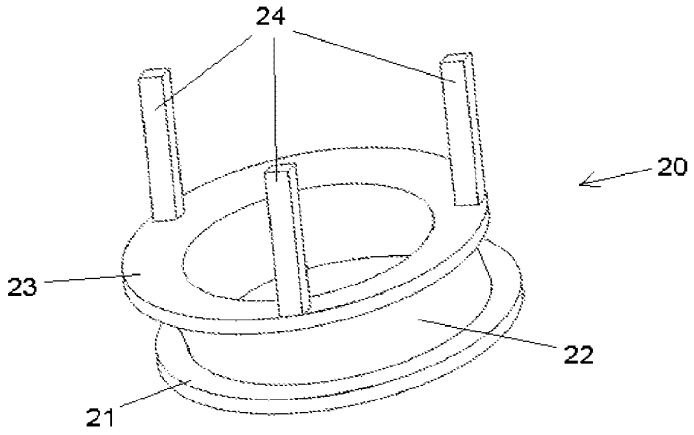

Figure 4 (a)

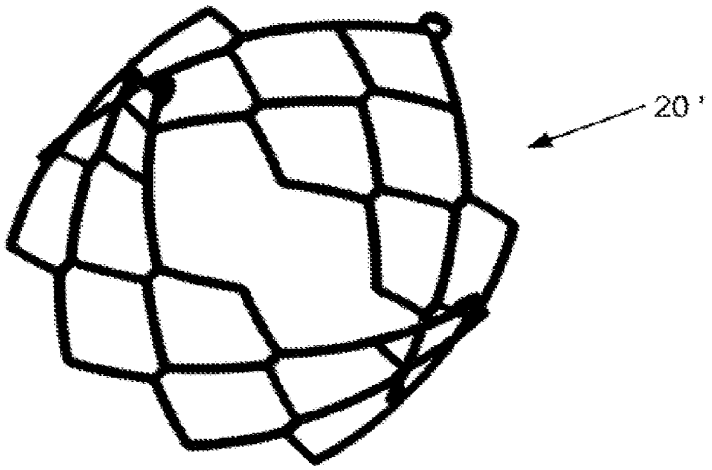

Figure 4 (b)

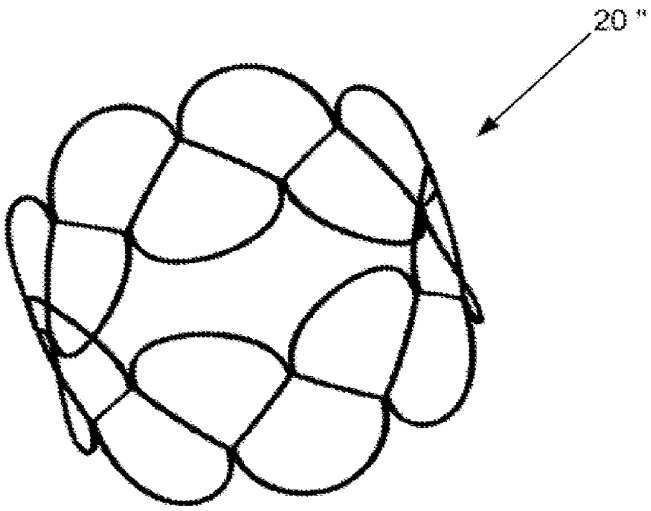

Figure 4(c)

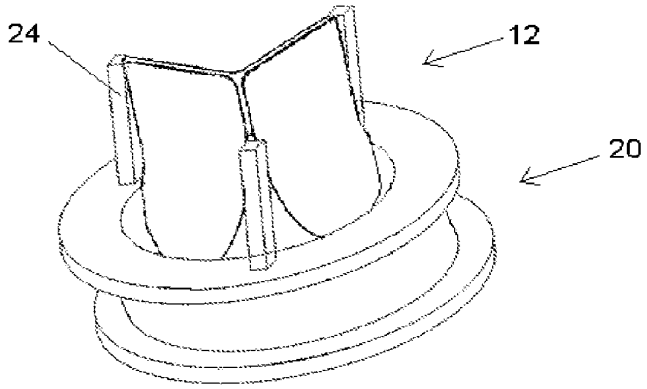

Figure 5(a)

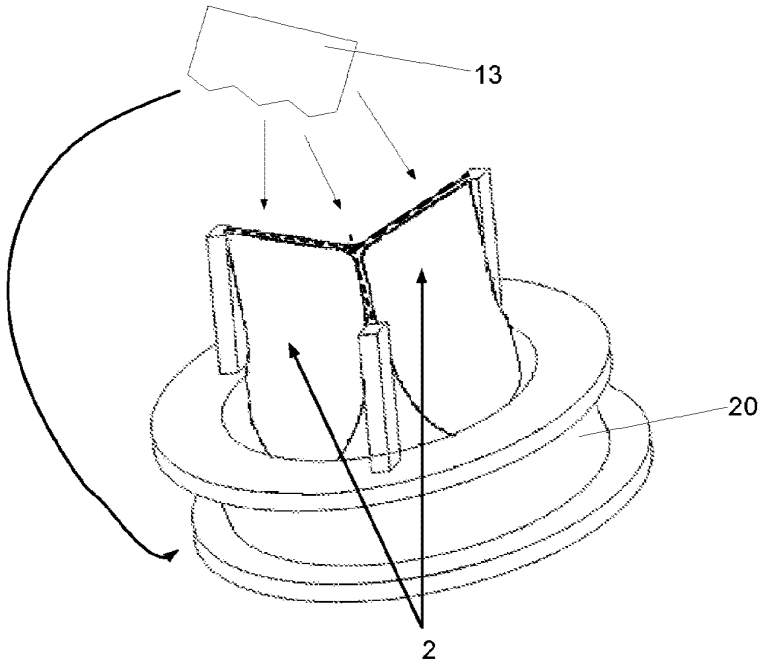

Figure 5(b)

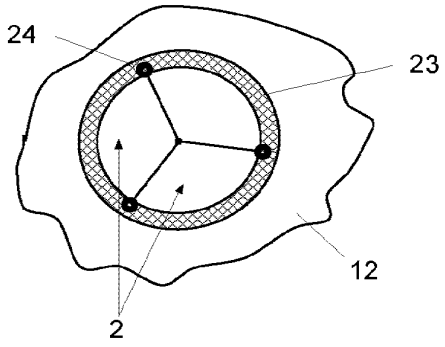

Figure 5(c)

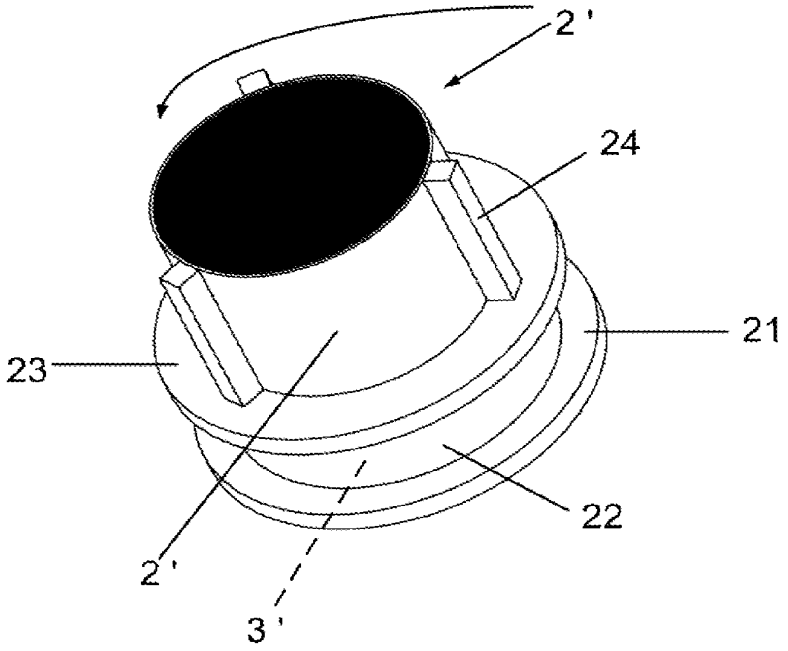

Figure 5(d)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/057970

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61F2/24

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 046 165 A (ROSS D N; BODNAR E) 12 November 1980 (1980-11-12) page 2, line 99 - page 3, line 31 figures 1-3	1-3, 5-15, 17-22
X	US 6 129 758 A (LOVE JACK W [US]) 10 October 2000 (2000-10-10) column 12, lines 55-64 figure 5b	1-3,5-9
X	WO 2007/046000 A (UNIV NANYANG [SG]; YEO JOON HOCK [SG]; LIM KHEE HIANG [SG]; GOETZ WOLF) 26 April 2007 (2007-04-26) paragraph [0040] figures 2,4a,4b	1-3, 5-14, 17-22

-/--

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

[X] See patent family annex.

* 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
11 August 2009	19/08/2009

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

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/057970

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/26587 A (INTERNAT HEART INST OF MONTANA [US]) 19 April 2001 (2001-04-19) page 12, lines 26-28 page 14, lines 18-28 figures 17,18	1-3, 5-14,21, 22
X	EP 1 671 604 A (PURDUE RESEARCH FOUNDATION [US]) 21 June 2006 (2006-06-21) paragraph [0038] figures 6a,6b	10-12, 14-22
A		4

1

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/057970

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
GB 2046165	A	12-11-1980	NONE		
US 6129758	A	10-10-2000	AT	295134 T	15-05-2005
			AU	7388296 A	28-04-1997
			CA	2231563 A1	10-04-1997
			DE	69634736 D1	16-06-2005
			DE	69634736 T2	19-01-2006
			EP	0862394 A1	09-09-1998
			WO	9712565 A1	10-04-1997
			US	5716399 A	10-02-1998
WO 2007046000	A	26-04-2007	EP	1933769 A1	25-06-2008
			JP	2009506853 T	19-02-2009
WO 0126587	A	19-04-2001	AU	1820601 A	23-04-2001
			US	6491511 B1	10-12-2002
EP 1671604	A	21-06-2006	NONE		

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

YASKANIN MARK L.

HOLME ROBERTS & OWEN LLP 1700 LINCOLN STREET, SUITE 4100 DENVER CO 80203 USA

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 54813-10202	Date of mailing *(day/month/year)* 14 NOVEMBER 2011 (14.11.2011) **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. **PCT/US2011/026763**	International filing date *(day/month/year)* **01 MARCH 2011 (01.03.2011)**
Applicant **COLIBRI HEART VALVE LLC et al**	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 . 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90bis.1 and 90bis.3).

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19months.

For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the PCT Applicant's Guide, National Chapters.

Name and mailing address of the ISA/KR Korean Intellectual Property Office Government Complex-Daejeon, 189 Cheongsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer COMMISSIONER Telephone No. 82-42-481-8755

Form PCT/ISA/220 (July 2010)

* Attention

Copies of the documents cited in the international search report can be searched in the following Korean Intellectual Property Office English website for three months from the date of mailing of the international search report.

http://www.kipo.go.kr/en/ => PCT Services => PCT Services

ID : PCT international application number
PW : **JWL3BKD2**

Inquiries related to PCT International Search Report or Written Opinion prepared by KIPO as an International Searching Authority can be answered not only by KIPO but also through IPKC (Intellectual Property Korea Center), located in Vienna, VA, which functions as a PCT Help Desk for PCT applicants.

Homepage: http://www.ipkcenter.com
Email: ipkc@ipkcenter.com
Phone: +1 703 388 1066
Fax: +1 703 388 1084

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
54813-10202		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2011/026763	**01 MARCH 2011 (01.03.2011)**	01 MARCH 2010 (01.03.2010)

Applicant

COLIBRI HEART VALVE LLC et al

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      ☒ the international application in the language in which it was filed
      ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. ☐ **Certain claims were found unsearchable** (See Box No. II)
3. ☐ **Unity of invention is lacking** (See Box No. III)
4. With regard to the **title,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. With regard to the drawings,
   a. the figure of the **drawings** to be published with the abstract is Figure No. 13
      ☒ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☐ none of the figure is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/026763

A. CLASSIFICATION OF SUBJECT MATTER

A61F 2/24(2006.01)i, A61M 25/01(2006.01)i, A61B 19/02(2006.01)i, A61M 29/02(2006.01)i, A61F 2/82(2006.01)i, C12N 5/071(2010.01)i, A61M 5/00(2006.01)i, A61L 2/08(2006.01)i, A61L 2/16(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61F 2/24; A61F 2/06; A61F 2/82; A61B 19/02

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

Korean utility models and applications for utility models
Japanese utility models and applications for utility models

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

eKOMPASS (KIPO internal) "prosthetic heart valve" , "tissue leaflet" , "sterile packaging" , and similar terms,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages		Relevant to claim No.
X A	US 2008-0200977 A1 (PAUL, R. H. et al.) See abstract, paragraphs (54,96,100,103), and claims (1,2,12,19)	21 Aug. 2008	1,3-5,10,11,14-18 ,20-22,36,38,40 2,6-9,12,13,19 ,23-35,37,39,41-73
X A	US 2007-0050014 A1 (JOHNSON, C. E.) See abstract, paragraphs (25,29,45,66), and claims (1,7,21,43,46)	01 Mar. 2007	1,11,17,36,40 2-10,12-16,18-38 ,37-39,41-73
A	US 2009-0030511 A1 (PANIAGUA, D. et al.) See abstract, paragraphs (45,50,54), and claims (1,3,4,5,11)	29 Jan. 2009	1-73
A	US 2007-0213813 A1 (VON SEGESSER, L. K. et al.) See abstract, paragraphs (66,97), and claims (1,4,32,33,73)	13 Sep. 2007	1-73

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of 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
14 NOVEMBER 2011 (14.11.2011)	**14 NOVEMBER 2011 (14.11.2011)**

Name and mailing address of the ISA/KR	Authorized officer
Korean Intellectual Property Office Government Complex-Daejeon, 189 Cheongsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	HYUN, SEUNG HOON Telephone No. 82-42-481-8401

Form PCT/ISA/210 (second sheet) (July 2009)

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages		Relevant to claim No.
PX	US 2010-0161036 A1 (PINTOR, R. et al.) See abstract, paragraphs (78,88,92), and claims (1,14,15)	24 Jun. 2010	1,2,9,11,17,19,36 ,40
PX	US 2010-0256749 A1 (TRAN, D. et al.) See abstract, paragraphs (26,36,46), and claims (1,6)	07 Oct. 2010	1,10,11,17,18,36 ,38,40

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2011/026763

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2008-0200977 A1	21.08.2008	AT 515244 T	15.07.2011
		EP 2120795 A2	25.11.2009
		EP 2120795 B1	06.07.2011
		WO 2008-101083 A2	21.08.2008
		WO 2008-101083 A3	27.11.2008
US 2007-0050014 A1	01.03.2007	None	
US 2009-0030511 A1	29.01.2009	US 2003-130729 A1	10.07.2003
		US 2005-113910 A1	26.05.2005
US 2007-0213813 A1	13.09.2007	AU 2006-328896 A1	28.06.2007
		AU 2007-294199 A1	13.03.2008
		AU 2007-294199 B2	18.11.2010
		AU 2009-200985 A1	02.04.2009
		AU 2011-200683 A1	10.03.2011
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		BR PI0716544A2	03.05.2011
		CA 2634358 A1	28.06.2007
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		CN 101374477 A	25.02.2009
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		CN 101636128 A	27.01.2010
		DE 202007018551 U1	11.12.2008
		EP 1968491 A2	17.09.2008
		EP 1968491 B1	07.07.2010
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		EP 2248486 A2	10.11.2010
		EP 2248486 A3	09.03.2011
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		JP 2009-195712 A	03.09.2009
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		JP 2010-502320 T	28.01.2010
		KR 10-2008-0103510 A	27.11.2008
		KR 10-2009-0078327 A	17.07.2009
		KR 10-2009-0082181 A	29.07.2009
		KR 10-2011-0089190 A	04.08.2011
		KR20090078327A	17.07.2009
		KR20090082181A	29.07.2009
		MX 2009002556 A	13.05.2009
		US 2009-0171432 A1	02.07.2009
		US 2009-0171447 A1	02.07.2009
		WO 2007-071436 A2	28.06.2007

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		WO 2007-071436 A3	28.06.2007
		WO 2008-028569 A1	13.03.2008
US 2010-0161036 A1	24.06.2010	AU 2009-335700 A1	15.07.2010
		CA 2744395 A1	15.07.2010
		WO 2010-080594 A2	15.07.2010
		WO 2010-080594 A3	14.10.2010
		WO 2010-080594 A3	15.07.2010
		WO 2010-080594 A8	15.07.2010
US 2010-0256749 A1	07.10.2010	US 2010-252470 A1	07.10.2010
		US 7967138 B2	28.06.2011
		WO 2010-117541 A1	14.10.2010
		WO 2010-117543 A1	14.10.2010

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
YASKANIN MARK L.

HOLME ROBERTS & OWEN LLP 1700 LINCOLN STREET, SUITE 4100 DENVER CO 80203 USA

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing *(day/month/year)*	**14 NOVEMBER 2011 (14.11.2011)**
Applicant's or agent's file reference 54813-10202	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2011/026763	**01 MARCH 2011 (01.03.2011)**	01 MARCH 2010 (01.03.2010)

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

A61F 2/24(2006.01)i, A61M 25/01(2006.01)i, A61B 19/02(2006.01)i, A61M 29/02(2006.01)i, A61F 2/82(2006.01)i, C12N 5/071(2010.01)i, A61M 5/00(2006.01)i, A61L 2/08(2006.01)i, A61L 2/16(2006.01)i

Applicant

COLIBRI HEART VALVE LLC et al

1. This opinion contains indications relating to the following items:

- [x] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [x] Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [x] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/KR	Date of completion of this opinion	Authorized officer
Korean Intellectual Property Office Government Complex-Daejeon, 189 Cheongsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	14 NOVEMBER 2011 (14.11.2011)	HYUN, SEUNG HOON Telephone No.82-42-481-8401

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2011/026763

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. a sequence listing filed or furnished
      ☐ on paper
      ☐ in electronic form

   b. time of filing or furnishing
      ☐ contained in the international application as filed.
      ☐ filed together with the international application in electronic form.
      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additioanl copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2011/026763

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	2,6-9,12,13,19,23-35,37,39,41-73	YES
	Claims	1,3-5,10,11,14-18,20-22,36,38,40	NO
Inventive step (IS)	Claims	2,6-9,12,13,19,23-35,37,39,41-73	YES
	Claims	1,3-5,10,11,14-18,20-22,36,38,40	NO
Industrial applicability (IA)	Claims	1-73	YES
	Claims	NONE	NO

2. Citations and explanations :

Reference is made to the following documents:

D1: US 2008-0200977 A1 (21 Aug. 2008)
D2: US 2007-0050014 A1 (01 Mar. 2007)
D3: US 2009-0030511 A1 (29 Jan. 2009)
D4: US 2007-0213813 A1 (13 Sep. 2007)

The present invention relates to the field of medical devices, and more particularly, to a percutaneously deliverable heart valve and a method of making a percutaneously deliverable heart valve.

Document D1 relates to medical devices, more particularly to artificial valve prostheses and the like.

Document D2 relates generally medical devices and methods and in particular aspects to implantable valve devices comprising isolated granulation tissue.

Document D3 relates to the field of heart valve replacement, more particularly to a method of making a percutaneously implantable replacement heart valve.

Document D4 relates to stent-valves, associated methods and systems for their delivery via minimally-invasive surgery, and guide-wire compatible closure devices for sealing access orifices.

D1 is the closest prior art. Consequently, the present invention is compared with D1 as follows:

1. Novelty and Inventive Step
1) Claims 1, 3-5, 10, 11, 14-18, 20-22, 36, 38, and 40
D1, which is considered to represent the most relevant state of the art, discloses a percutaneously deliverable heart valve and a method of making a percutaneously deliverable heart valve.
The compositions of claims 1, 3-5, 10, 11, 14-18, 20-22, 36, 38, and 40 are disclosed in D1 [a frame(claim 1,2,9); a valve leaflet(claims 1,2,12,19, paragraph 54); a catheter(claim 20, paragraph 96); a kit, sterile packaging(paragraph 103); various sizes of delivery catheter(paragraph 100); pericardium(claim 12, paragraph 54); and so on.]

As all of the features of claims 1, 3-5, 10, 11, 14-18, 20-22, 36, 38, and 40are disclosed in D1, these claims are anticipated by D1.

(Continued on Supplemental Sheet.)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US2011/026763

Box No. VI Certain documents cited

1. Certain published documents (Rule 43bis.1 and 70.10)

	Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
P,X	US 12-635471	24/06/2010	10/12/2009	None
P,X	US 12-418684	07/10/2010	06/04/2009	None

Application No. US 12-635471 (publication No. US 2010-0161036A1) does not constitute prior art within the meaning of PCT Rule 64.3, but appears to disclose all the features of claims 1, 2, 9, 11, 17, 19, 36, and 40. In case the priority of the present application is not valid, this document is relevant for assessing novelty and inventive step.

Application No. US 12-418684(publication No. US 2010-0256749 A1) does not constitute prior art within the meaning of PCT Rule 64.3, but appears to disclose all the features of claims 1, 10, 11, 17, 18, 36, 38, and 40. In case the priority of the present application is not valid, this document is relevant for assessing novelty and inventive step.

2. Non-written disclosures (Rule 43bis.1 and 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

BOX V.

2) Claims 2, 6-9, 12, 13, 19, 23-35, 37, 39, 41-73
None of the prior art including the documents of D1-D4 teach or fairly suggest the following features described in claims 2, 6-9, 12, 13, 19, 23-35, 37, 39, 41-73: claim 2 [restricting a balloon catheter]; claim 6 [restricting a mandrel]; claims 7 and 8[restricting tissue forming the tissue leaflet assembly within the sterile packaging] claims 9 and 26[restricting a stent]; claims 12 and 13 [restricting the substantially dry tissue]; claim 19 [including a percutaneously insertable balloon catheter]; claim 23 [restricting a percutaneously insertable mandrel]; claims 24 and 25[restricting the tissue leaflet assembly within the sealed sterile package]; claims 27-30 [an article adapted for implantation in a patient]; claims 31-35 [an article adapted for trans-catheter delivery into a patient]; claim 37 [further comprising transporting the sterilized and package prosthetic heart valve and delivery catheter]; claims 39 [restricting prior to partially compressing and mounting the prosthetic heart valve upon the delivery catheter]; claim 41 [restricting prior to partially compressing and mounting the frame]; claim 42 [further comprising transporting the sterilized and package frame]; claim 43 [restricting prior to attaching the tissue to the frame]; claim 44 [restricting the tissue leaflet assembly]; claim 45 [restricting a treated pericardium]; and 46-73 [a method of preparing a percutaneous, trans-catheter prosthetic heart valve].

Therefore, it is considered the subject matters of claims 2, 6-9, 12, 13, 19, 23-35, 37, 39, 41-73 in the present invention involve invention step set forth in the PCT Article 33(3).

2. Industrial Applicability
The subject matters of claims 1-73 seem to be industrially applicable under the PCT Article 33(4).

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

YASKANIN MARK L.

HOLME ROBERTS & OWEN LLP 1700 LINCOLN STREET, SUITE 4100 DENVER CO 80203 USA

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 54813-10251	Date of mailing *(day/month/year)* 28 NOVEMBER 2011 (28.11.2011) **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. **PCT/US2011/026741**	International filing date *(day/month/year)* **01 MARCH 2011 (01.03.2011)**
Applicant **VELA BIOSYSTEMS LLC et al**	

1. ☐ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.
   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):
   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.
   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70
   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 . 9.011.

2. ☒ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90bis.1 and 90bis.3).

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.
In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19months.

For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the PCT Applicant's Guide, National Chapters.

Name and mailing address of the ISA/KR Korean Intellectual Property Office Government Complex-Daejeon, 189 Cheongsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer COMMISSIONER Telephone No. 82-42-481-8755

Form PCT/ISA/220 (July 2010)

PATENT COOPERATION TREATY

PCT

DECLARATION OF NON-ESTABLISHMENT OF INTERNATIONAL SEARCH REPORT

(PCT Article 17(2)(a), Rules 13*ter*.1(c) and (d) and 39)

Applicant's or agent's file reference	IMPORTANT DECLARATION	Date of mailing (*day/month/year*)
54813-10251		28 NOVEMBER 2011 (28.11.2011)
International application No.	International filing date (*day/month/year*)	(Earlist) Priority date (*day/month/year*)
PCT/US2011/026741	**01 MARCH 2011 (01.03.2011)**	01 MARCH 2010 (01.03.2010)

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

C12N 5/071(2010.01)i, A61L 27/38(2006.01)i, A61K 35/12(2006.01)i, A61F 2/02(2006.01)i

Applicant

VELA BIOSYSTEMS LLC et al

This International Searching Authority hereby declares, according to Article 17(2)(a), that **no international search report will be established** on the international application for the reasons indicated below.

1. ☐ The subject matter of the international application relates to:
   - a. ☐ scientific theories.
   - b. ☐ mathematical theories.
   - c. ☐ plant varieties.
   - d. ☐ animal varieties.
   - e. ☐ essentially biological processes for the production of plants and animals, other than microbiological processes and the products of such processes.
   - f. ☐ schemes, rules or methods of doing business.
   - g. ☐ schemes, rules or methods of performing purely mental acts.
   - h. ☐ schemes, rules or methods of playing games.
   - i. ☐ methods for treatment of the human body by surgery or therapy.
   - j. ☐ methods for treatment of the animal body by surgery or therapy.
   - k. ☐ diagnostic methods practised on the human or animal body.
   - l. ☐ mere presentation of information.
   - m. ☐ computer programs for which this International Searching Authority is not equipped to search prior art.
2. ☒ The failure of the following parts of the international application to comply with prescribed requirements prevents a meaningful search from being carried out:

   ☒ the description ☒ the claims ☐ the drawings
3. ☐ A meaningful search could not be carried out without the sequence listing; the applicant did not, within the prescribed time limit:
   - ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
   - ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
   - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b)
4. Further coments:

Name and mailing address of ISA/KR

Korean Intellectual Property Office
Government Complex-Daejeon, 189 Cheongsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea

Facsimile No. 82-42-472-7140

Authorized officer

Lee Hyojin

Telephone No. 82-42-481-8743

Form PCT/ISA/203 (July 2009)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
YASKANIN MARK L.

HOLME ROBERTS & OWEN LLP 1700 LINCOLN STREET, SUITE 4100 DENVER CO 80203 USA

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing *(day/month/year)* **28 NOVEMBER 2011 (28.11.2011)**

Applicant's or agent's file reference
54813-10251

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2011/026741	**01 MARCH 2011 (01.03.2011)**	01 MARCH 2010 (01.03.2010)

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

C12N 5/071(2010.01)i, A61L 27/38(2006.01)i, A61K 35/12(2006.01)i, A61F 2/02(2006.01)i

Applicant

VELA BIOSYSTEMS LLC et al

1. This opinion contains indications relating to the following items:

- [x] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [x] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [ ] Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/KR	Date of completion of this opinion	Authorized officer
Korean Intellectual Property Office Government Complex-Daejeon, 189 Cheongsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	15 NOVEMBER 2011 (15.11.2011)	Lee Hyojin Telephone No.82-42-481-8743

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2011/026741

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of :

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____ , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. a sequence listing filed or furnished
      ☐ on paper
      ☐ in electronic form

   b. time of filing or furnishing
      ☐ contained in the international application as filed.
      ☐ filed together with the international application in electronic form.
      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additioanl copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2011/026741

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☒ the entire international application

☐ claims Nos. _____

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

The present invention is related to a prepared tissue for medical use and methods for preparing such tissue. However, the claimed tissues and methods are considered to be essentially speculative, leaving a person skilled in the art in doubt with respect to the feasibility of the said invention. The description merely describes several methods for preparing tissue for medical use. However, it does not show any concrete proof from which a person skilled in the art could accept that a tissue for medical use is actually made by any of the said methods[Article 34(4)(a)(ii)].

☒ the claims, or said claims Nos. 1-43 are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

Claims 1-43 are not fully supported by the description either, because the description does not show any concrete proof from which a person skilled in the art could accept that any claimed tissue is actually made by any methods described in description or in claims[Article 34(4)(a)(ii)].

☒ no international search report has been established for said claims Nos. 1-43

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Istructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Istructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ See Supplemental Box for further details.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

YASKANIN MARK L.

HOLME ROBERTS & OWEN LLP 1700 LINCOLN STREET, SUITE 4100 DENVER CO 80202 USA

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing *(day/month/year)* 06 APRIL 2012 (06.04.2012)	
Applicant's or agent's file reference 54813-10502	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. **PCT/US2011/042252**	International filing date *(day/month/year)* **28 JUNE 2011 (28.06.2011)**

Applicant

VELA BIOSYSTEMS LLC et al

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:

   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 . 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90bis.1 and 90bis.3).

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19months.

For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the PCT Applicant's Guide, National Chapters.

Name and mailing address of the ISA/KR Korean Intellectual Property Office Government Complex-Daejeon, 189 Cheongsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea	Authorized officer COMMISSIONER
Facsimile No. 82-42-472-7140	Telephone No. 82-42-481-8755

Form PCT/ISA/220 (July 2010)

* Attention

Copies of the documents cited in the international search report can be searched in the following Korean Intellectual Property Office English website for three months from the date of mailing of the international search report.

http://www.kipo.go.kr/en/ => PCT Services => PCT Services

ID : PCT international application number
PW : **66B39QBW**

Inquiries related to PCT International Search Report or Written Opinion prepared by KIPO as an International Searching Authority can be answered not only by KIPO but also through IPKC (Intellectual Property Korea Center), located in Vienna, VA, which functions as a PCT Help Desk for PCT applicants.

Homepage: http://www.ipkcenter.com
Email: ipkc@ipkcenter.com
Phone: +1 703 388 1066
Fax: +1 703 388 1084

Notes to Form PCT/ISA/220 (July 2010)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
54813-10502		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2011/042252	**28 JUNE 2011 (28.06.2011)**	28 JUNE 2010 (28.06.2010)

Applicant

VELA BIOSYSTEMS LLC et al

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of **5** sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      ☒ the international application in the language in which it was filed
      ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. ☒ **Certain claims were fonnd unsearchable** (See Box No. II)
3. ☐ **Unity of invention is lacking** (See Box No. III)
4. With regard to the **title,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. With regard to the drawings,
   a. the figure of the **drawings** to be published with the abstract is Figure No. **4B**
      ☒ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☐ none of the figure is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/042252

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 34
because they relate to subject matter not required to be searched by this Authority, namely:
Claim 34 pertains to methods for treatment of the human body by therapy, and thus relates to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional 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 and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/042252

A. CLASSIFICATION OF SUBJECT MATTER

A61M 25/10(2006.01)i, A61M 25/01(2006.01)i, A61M 25/088(2006.01)i, A61M 25/06(2006.01)i, A61M 29/02(2006.01)i

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)

A61M 25/10; A61F 2/24; A61M 29/00; A61B 17/00

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

Korean utility models and applications for utility models
Japanese utility models and applications for utility models

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

eKOMPASS(KIPO internal) & Keywords: endoluminal, catheter, balloon, stent

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 05733299A (SHEIBAN; IMAD et al.) 31 March 1998 See the whole document.	1-33
A	US 05226889A (SHEIBAN; IMAD) 13 July 1993 See the whole document.	1-33
A	US 05261878A (GALINDO ALVARO) 16 November 1993 See the whole document.	1-33
A	US 2003-0130729 A1 (DAVID PANIAGUA et al.) 10 July 2003 See the whole document.	1-33
A	US 06004328A (SOLAR; RONALD J.) 21 December 1999 See the whole document.	1-33

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of 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
28 MARCH 2012 (28.03.2012)	**06 APRIL 2012 (06.04.2012)**

Name and mailing address of the ISA/KR

Korean Intellectual Property Office
Government Complex-Daejeon, 189 Cheongsa-ro,
Seo-gu, Daejeon 302-701, Republic of Korea

Facsimile No. 82-42-472-7140

Authorized officer

Kang Yeon Mu

Telephone No. 82-42-481-5516

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2011/042252

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 05733299A	31.03.1998	EP 0707837 A1	24.04.1996
		EP 0707837 B1	10.12.2003
		EP 0707864 A1	24.04.1996
		EP 0707864 B1	28.12.2005
		EP 0707865 A1	24.04.1996
		JP 03-750874 B2	01.03.2006
		JP 08-206217 A	13.08.1996
		JP 08-238322 A	17.09.1996
		JP 08-238323 A	17.09.1996
		US 05632760 A	27.05.1997
		US 05846246 A	08.12.1998
US 05226889A	13.07.1993	US 05226889A A	13.07.1993
US 05261878A	16.11.1993	None	
US 2003-0130729 A1	10.07.2003	US 2005-0113910 A1	26.05.2005
		US 2009-030511 A1	29.01.2009
US 06004328A	21.12.1999	AU 1999-49832 A1	01.02.2000
		CA 2290990 A1	23.12.1998
		CA 2293341 A1	30.12.1998
		CA 2294401 A1	30.12.1998
		CA 2294401 C	21.08.2007
		CA 2335473 A1	20.01.2000
		EP 0989877 A1	05.04.2000
		EP 0990119 A1	05.04.2000
		EP 0990119 B1	30.11.2005
		EP 0990119 B8	01.02.2006
		EP 1095361 A1	02.05.2001
		EP 1095361 A4	14.07.2004
		EP 1095361 B1	23.11.2005
		EP 1095361 B8	01.02.2006
		EP 1626382 A1	15.02.2006
		EP 1626382 B1	31.10.2007
		EP 1630523 A1	01.03.2006
		EP 1630523 B1	31.10.2007
		GB 2340499 A	23.02.2000
		GB 2341112 A	08.03.2000
		JP 03-373859 B2	22.11.2002
		JP 2000-516521 A	12.12.2000
		JP 2002-505608 A	19.02.2002
		JP 2002-505782 A	19.02.2002
		JP 2003-526828 A	09.09.2003
		KR 10-0782090 B1	04.12.2007
		KR 10-0782096 B1	04.12.2007
		KR 10-2007-0068444 A	29.06.2007
		KR 10-2008-0026629 A	25.03.2008
		KR 10-2008-0083000 A	12.09.2008

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		US 05806855 A	15.09.1998
		US 05840788 A	24.11.1998
		US 05884336 A	23.03.1999
		US 06133853 A	17.10.2000
		US 06148261 A	14.11.2000
		US 2003-0117297 A1	26.06.2003
		US 2003-0163251 A1	28.08.2003
		US 2005-0128102 A1	16.06.2005
		US 2005-0165545 A1	28.07.2005
		US 2007-0112508 A1	17.05.2007
		US 2008-0068142 A1	20.03.2008
		US 2010-0228475 A1	09.09.2010
		US 6515595 B1	04.02.2003
		US 6529824 B1	04.03.2003
		US 6868335 B2	15.03.2005
		US 6924748 B2	02.08.2005
		US 7236100 B2	26.06.2007
		US 7561065 B2	14.07.2009
		US 7702455 B2	20.04.2010
		WO 00-03364 A1	20.01.2000
		WO 98-57692 A1	23.12.1998
		WO 98-57966 A1	23.12.1998
		WO 98-58702 A1	30.12.1998
		WO 98-58713 A1	30.12.1998
		WO 98-58727 A1	30.12.1998
		WO 98-58827 A1	30.12.1998
		WO 98-58995 A1	30.12.1998
		WO 98-59215 A1	30.12.1998

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
YASKANIN MARK L.

HOLME ROBERTS & OWEN LLP 1700 LINCOLN STREET, SUITE 4100 DENVER CO 80202 USA

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing *(day/month/year)*	**06 APRIL 2012 (06.04.2012)**
Applicant's or agent's file reference 54813-10502	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2011/042252	**28 JUNE 2011 (28.06.2011)**	28 JUNE 2010 (28.06.2010)

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

A61M 25/10(2006.01)i, A61M 25/01(2006.01)i, A61M 25/088(2006.01)i, A61M 25/06(2006.01)i, A61M 29/02(2006.01)i

Applicant

VELA BIOSYSTEMS LLC et al

1. This opinion contains indications relating to the following items:

- [x] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [x] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [x] Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/KR	Date of completion of this opinion	Authorized officer
Korean Intellectual Property Office Government Complex-Daejeon, 189 Cheongsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	28 MARCH 2012 (28.03.2012)	Kang Yeon Mu Telephone No.82-42-481-5516

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2011/042252

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. a sequence listing filed or furnished
      ☐ on paper
      ☐ in electronic form

   b. time of filing or furnishing
      ☐ contained in the international application as filed.
      ☐ filed together with the international application in electronic form.
      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additioanl copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2011/042252

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 34

because:

☒ the said international application, or the said claims Nos. 34 relate to the following subject matter which does not require an international search *(specify)*:

Claim 34 pertains to methods for treatment of the human body by therapy, and thus relates to a subject matter which this International Searching Authority is not required, under Rules 43 bis.1(b), Rule 67.1 (iv)), to search.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 34

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Istructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Istructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2011/042252

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-33	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	1-33	YES
	Claims	NONE	NO
Industrial applicability (IA)	Claims	1-33	YES
	Claims	NONE	NO

2. Citations and explanations :

Reference is made to the following documents:

D1: US 05733299 A (SHEIBAN; IMAD et al.) 31 March 1998
D2: US 05226889 A (SHEIBAN; IMAD) 13 July 1993
D3: US 05261878 A (GALINDO ALVARO) 16 November 1993
D4: US 2003-0130729 A1 (DAVID PANIAGUA et al.) 10 July 2003
D5: US 06004328 A (SOLAR; RONALD J.) 21 December 1999

1. Novelty and Inventive Step

1.1. Independent Claims 1,20

1.1.1. Concerning Claim 1

None of the documents cited in the ISR show a system for providing endoluminal delivery of a deliverable device through vasculature of a patient to a delivery site within the patient comprising an outer delivery sheath; and a carrier segment configured to hold the deliverable device temporarily. Accordingly, claim 1 is not anticipated by any of the documents, nor is it obvious by the documents, taken alone or in combination. Therefore, claim 1 is novel and involves an inventive step under PCT Article 33(2) and (3)

1.1.2. Concerning Claim 20

None of the documents cited in the ISR show a system for providing endoluminal delivery of a deliverable device through vasculature of a patient to a delivery site within the patient comprising a carrier segment configured to receive the deliverable device prior to inserting the first catheter within the patient. Accordingly, claim 20 is not anticipated by any of the documents, nor is it obvious by the documents, taken alone or in combination. Therefore, claim 20 is novel and involves an inventive step under PCT Article 33(2) and (3)

1.2. Dependent claims 2-19,21-33

Claims 2-19,21-33 are dependent on either claim 1 or 20. Consequently, claims 2-19,21-33 are also considered to be novel and to involve an inventive step under PCT Article 33(2) and (3).

Continued on Supplemental Box

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

Box V

2. Industrial Applicability

Claims 1-33 are industrially applicable under PCT Article 33(4).

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

YASKANIN MARK

HOLME ROBERTS & OWEN LLP 1700 LINCOLN STREET, SUITE 4100 DENVER CO 80203 USA

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing *(day/month/year)* 27 APRIL 2012 (27.04.2012)	
Applicant's or agent's file reference 54813-~~10222~~ 10223	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. **PCT/US2011/053120**	International filing date *(day/month/year)* **23 SEPTEMBER 2011 (23.09.2011)**

Applicant

COLIBRI HEART VALVE LLC et al

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 . 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90bis.1 and 90bis.3).

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19months.

For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the PCT Applicant's Guide, National Chapters.

Name and mailing address of the ISA/KR Korean Intellectual Property Office Government Complex-Daejeon, 189 Cheongsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea	Authorized officer COMMISSIONER
Facsimile No. 82-42-472-7140	Telephone No. 82-42-481-8753

Form PCT/ISA/220 (July 2010)

* Attention

Copies of the documents cited in the international search report can be searched in the following Korean Intellectual Property Office English website for three months from the date of mailing of the international search report.

http://www.kipo.go.kr/en/ => PCT Services => PCT Services

ID : PCT international application number
PW : **NMQ7Y68G**

Inquiries related to PCT International Search Report or Written Opinion prepared by KIPO as an International Searching Authority can be answered not only by KIPO but also through IPKC (Intellectual Property Korea Center), located in Vienna, VA, which functions as a PCT Help Desk for PCT applicants.

Homepage: http://www.ipkcenter.com
Email: ipkc@ipkcenter.com
Phone: +1 703 388 1066
Fax: +1 703 388 1084

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
54813-10222		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2011/053120	**23 SEPTEMBER 2011 (23.09.2011)**	23 SEPTEMBER 2010 (23.09.2010)

Applicant

COLIBRI HEART VALVE LLC et al

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of **5** sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of :
      ☒ the international application in the language in which it was filed
      ☐ a translation of the international application into _____ , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. ☒ **Certain claims were found unsearchable** (See Box No. II)
3. ☐ **Unity of invention is lacking** (See Box No. III)
4. With regard to the **title,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. With regard to the drawings,
   a. the figure of the **drawings** to be published with the abstract is Figure No. **1A**
      ☒ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☐ none of the figure is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/053120

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 30
because they relate to subject matter not required to be searched by this Authority, namely:
Judging from the subject matter of claim 30 which includes a method comprising implanting the trans-catheter into a patient, said claim pertains to methods for treatment of the human body by surgery, and thus relates to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional 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 and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/053120

A. CLASSIFICATION OF SUBJECT MATTER

A61F 2/24(2006.01)i, A61F 2/04(2006.01)i, A61L 27/28(2006.01)i, A61F 2/82(2006.01)i, A61L 27/04(2006.01)i, A61M 25/01(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61F 2/24; A61F 2/06; A61F 2/04

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

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

eKOMPASS(KIPO internal) & Keywords: prosthetic heart valve, frame, catheter, biocompatible tissue, biocompatible membrane, metal, alloy, stent, leaflet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	US 7381218 B2 (STEFAN SCHRECK) 03 June 2008 See Figs. 1, 2, and 6; column 1, lines 42-45 - column 8, lines 49-64.	1-3,5,6,11-13,33,35 4,7-10,14-29,31,32,34
A	US 2006-0259137 A1 (JASON ARTOF et al.) 16 November 2006 See the whole document.	1-29,31-35
A	WO 99-30646 A1 (ST. JUDE MEDICAL, INC.) 24 June 1999 See the whole document.	1-29,31-35
A	US 2009-0248149 A1 (SHLOMO GABBAY) 01 October 2009 See the whole document.	1-29,31-35
A	US 2008-0154356 A1 (JOSEPH F. OBERMILLER et al.) 26 June 2008 See the whole document.	1-29,31-35

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of 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
26 APRIL 2012 (26.04.2012)	**27 APRIL 2012 (27.04.2012)**

Name and mailing address of the ISA/KR	Authorized officer
Korean Intellectual Property Office Government Complex-Daejeon, 189 Cheongsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea	Heo, Joo-Hyung
Facsimile No. 82-42-472-7140	Telephone No. 82-42-481-8150

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2011/053120

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 7381218 B2	03.06.2008	AU 2001-256985 B2	31.08.2006
		CA 2407062 A1	18.10.2001
		EP 1267753 B1	19.10.2005
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		JP 04755176 B2	03.06.2011
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		US 2010-0100176 A1	22.04.2010
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		US 7044966 B2	16.05.2006
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		US 7604650 B2	20.10.2009
		US 7842084 B2	30.11.2010
		WO 2005-046528 A1	26.05.2005
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		JP 2002-508211 A	19.03.2002
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US 2008-0154356 A1	26.06.2008	US 2004-0049262 A1	11.03.2004
		US 2005-0096736 A1	05.05.2005

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
YASKANIN MARK

HOLME ROBERTS & OWEN LLP 1700 LINCOLN STREET, SUITE 4100 DENVER CO 80203 USA

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing *(day/month/year)*	**27 APRIL 2012 (27.04.2012)**
Applicant's or agent's file reference 54813-10222	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2011/053120	**23 SEPTEMBER 2011 (23.09.2011)**	23 SEPTEMBER 2010 (23.09.2010)

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

A61F 2/24(2006.01)i, A61F 2/04(2006.01)i, A61L 27/28(2006.01)i, A61F 2/82(2006.01)i, A61L 27/04(2006.01)i, A61M 25/01(2006.01)i

Applicant

COLIBRI HEART VALVE LLC et al

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/KR	Date of completion of this opinion	Authorized officer
Korean Intellectual Property Office Government Complex-Daejeon, 189 Cheongsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	26 APRIL 2012 (26.04.2012)	Heo, Joo-Hyung Telephone No.82-42-481-8150

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2011/053120

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. a sequence listing filed or furnished
      ☐ on paper
      ☐ in electronic form

   b. time of filing or furnishing
      ☐ contained in the international application as filed.
      ☐ filed together with the international application in electronic form.
      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additioanl copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2011/053120

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 30

because:

☒ the said international application, or the said claims Nos. 30 relate to the following subject matter which does not require an international search *(specify)*:

Judging from the subject-matter of claim 30 which comprises a method comprising implanting the trans-catheter into a patient, said claim does not require an opinion, as it is directed to a treatment method of the human body [Rule 43 bis.1(b), Rule 67.1(iv)].

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 30

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Istructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Istructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2011/053120

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	4,7-10,14-29,31,32,34	YES
	Claims	1-3,5,6,11-13,33,35	NO
Inventive step (IS)	Claims	4,7-10,14-29,31,32,34	YES
	Claims	1-3,5,6,11-13,33,35	NO
Industrial applicability (IA)	Claims	1-29,31-35	YES
	Claims	NONE	NO

2. Citations and explanations :

Reference is made to the following document:

D1: US 7381218 B2 (STEFAN SCHRECK) 03 June 2008

(1) Novelty and Inventive Step

(1-1) Regarding claims 1-13

Claims 1-3, 5, 6, and 11-13 lack novelty under PCT Article 33(2) as being anticipated by D1.

D1, which is considered to represent the most relevant state of the art, discloses a percutaneous, trans-catheter prosthetic valve for implantation in a patient, comprising: a frame (See Fig. 1; corresponding to "a stent 24" and "a tubular base 40".) including an abluminal surface extending between a proximal end (corresponding to the lower portion of the tubular base in Fig. 1) of the frame and a distal end of the frame (corresponding to the upper portion of the tubular base in Fig. 1), wherein the frame is collapsible and expandable and adapted for trans-catheter delivery (See claim 1 and column 8, lines 49-64; corresponding to "a delivery catheter" and a "balloon catheter".); and a biocompatible tissue material mounted to the abluminal surface of the frame to form a plurality of valve leaflets (See column 4, lines 31-55; corresponding to "a pericardial tissue" etc.), wherein an entire interior surface of the biocompatible tissue material between the proximal end of the frame and the distal end of the frame resides radially exterior to the abluminal surface of the frame (Fig. 1 shows that a flexible tubular member 22 covers the exterior surface, namely abluminal surface of the tubular base 40.): (a) at all points of attachment (See column 7, lines 42-51; correspondung to "The flexible tubular member 22 attached to the support stent 24 as seen in Fig. 2...the fabric section 34 may be attached to the exterior of the tubular base 40, such as by sutures passed through the fabric and through openings in the tubular base..."); and (b) when the plurality of valve leaflets are in an operationally fully open position (See Figs. 1 and 2).

D1 teaches that the material of the frame comprises metal alloy characterized in claim 2 (See claim 1 and column 7, lines 23-26; corresponding to "a metallic support" and "...stainless-steel, titanium, or Elgiloy..."). D1 describes a ring at the proximal portion of the frame characterized in claim 3 (See column 1, lines 42-45; corresponding to "a sewing ring") and a lattice structure featured in claims 5 and 6 (Figs. 1 and 6 show the circumferentially continuous lattice structure of the tubular base 40.). D1 also discloses the location of the biocompatible tissue material characterized in claims 11-13 (See column 7, lines 45-51; corresponding to "...the fabric section 34 surrounds the tubular base 40...").

Therefore, claims 1-3, 5, 6, and 11-13 are considered to lack novelty under PCT Article 33(2), and do not meet the requirements of inventive step under PCT Article 33(3).

(Continued on Supplemental Box.)

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of :

Box V.

Dependent claims 4 and 7-10 further define a prosthetic valve which comprises a proximal portion of the frame having a circumferential zig-zag of wire, a circumferentially discontinuous lattice, configurations of projections in the frame and a stabilization framework, or regions of circumferentially discontinuity (See Figs. 2 and 6; corresponding to upper parts of the valve).

However, none of the prior art documents cited in the international search report disclose, teach, or suggest said features. Moreover, it is not obvious to a person skilled in the art by the documents, taken alone or in combination. Therefore, dependent claims 4 and 7-10 appear to be novel and inventive under PCT Article 33(2) and 33(3).

(1-2) Regarding claims 14-27

The subject-matter of claim 14 differs from that of D1 in that a valve comprises a frame including an abluminal surface extending between a proximal edge of the frame and a distal edge of the frame, the distal edge undulating axially to define at least two areas of circumferential discontinuity in the frame, wherein the frame is collapsible and expandable and adapted for trans-catheter delivery; and a single layer of a biocompatible membrane material mounted to the abluminal surface of the frame to form leaflet portions, wherein the leaflet portions are collocated with the at least two areas of circumferential discontinuity in the frame. D1 does not show the undulated-distal edge and areas of circumferential discontinuity in the frame and leaflet portions collocated with the at least two areas of circumferential discontinuity in the frame. It is not obvious to a person skilled in the art by the known documents, taken alone or in combination.

Therefore, claim 14 meets the requirements of PCT Article 33(2) and 33(3) with respect to novelty and inventive step. Dependent claims 15-27 are also considered to be novel under PCT Article 33(2) and inventive under PCT Article 33(3).

(1-3) Regarding claims 28-32

The subject-matter of claim 28 differs from that of D1 in that a method of preparing a prosthetic valve comprises mounting a single layer of a biocompatible tissue material to an abluminal surface of a trans-catheter deliverable frame such that an interior surface of the biocompatible tissue material between a proximal end of the frame and a distal end of the frame resides radially exterior to and substantially adjacent the abluminal surface of the frame at all points of attachment and in entirety when a plurality of leaflets of the biocompatible tissue material are in a fully open position. It is not obvious to a person skilled in the art by the known documents, taken alone or in combination.

Therefore, claim 28 meets the requirements of PCT Article 33(2) and 33(3) with respect to novelty and inventive step. Dependent claims 29, 31, and 32 are also considered to be novel under PCT Article 33(2) and inventive under PCT Article 33(3).

(Continued on the Next Supplemental Box.)

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

(The Previous Sheet.)

(1-4) Regarding claims 33-35

Claims 33 and 35 lack novelty under PCT Article 33(2) as being anticipated by D1.

D1 teaches a method (See column 4, lines 32-55) comprising: attaching a biocompatible membrane material (See column 6, lines 36-44; corresponding to "a pericardial tissue" etc.) to a collapsible and expandable frame (See Fig. 1; corresponding to "a stent 24" and "a tubular base 40".) to form a trans-catheter deliverable prosthetic valve (See claim 1 and column 8, lines 49-64; corresponding to "a delivery catheter" and "a balloon catheter".), wherein an entire interior surface of the biocompatible membrane material is located exterior of an abluminal surface of the collapsible and expandable frame when leaflet portions of the biocompatible membrane material are in a fully open position (See column 7, lines 42-55; corresponding to "...the fabric section 34 may be attached to the exterior of the tubular base 40, such as by sutures passed through the fabric and through openings in the tubular base...").

D1 also discloses the method comprising a trans-catheter deliverable prosthetic valve with a catheter (See column 8, lines 49-57; corresponding to "..the valve 20 is loaded about a balloon catheter and within a delivery cannula...").

Therefore, claims 33 and 35 are considered to lack novelty under PCT Article 33(2), and do not meet the requirements of inventive step under PCT Article 33(3).

Dependent claim 34 further defines an attachment by suturing the biocompatible membrane material to a distal edge of the frame undulating in an axial direction around the frame.

However, none of the prior art documents cited in the international search report disclose said feature. Additionally, it is not obvious to a person skilled in the art by the documents, taken alone or in combination. Therefore, dependent claim 34 appears to be novel and inventive under PCT Article 33(2) and 33(3).

(2) Industrial Applicability

The subject-matter of claims 1-29 and 31-35 meets the requirements for industrial applicability under PCT Article 33(4).

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

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

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4801299		1989-01-31	Brendel et al.	
	2	4976733		1990-12-11	Giradot	
	3	5226889		1993-07-13	Sheiban	
	4	5261878		1993-11-16	Galindo	
	5	5634928		1997-06-03	Fischell et al.	
	6	5733299		1998-03-31	Sheiban et al.	
	7	6004328		1999-12-21	Solar	
	8	6174327		2001-01-16	Mertens et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	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

	9	6221091		2001-04-24	Khosravi	
	10	6383171		2002-05-07	Gifford et al.	
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	13	7153324		2006-12-26	Case et al.	
	14	7622276		2009-11-24	Cunanan et al.	

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20010023372		2001-09-20	Chen et al.	
	2	20050043819		2005-02-24	Schmidt et al.	
	3	20060004439		2006-01-05	Spenser et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	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

	4	20060259134		2006-11-16	Schwammenthal et al.	
	5	20070050014		2007-03-01	Johnson	
	6	20070213813		2007-09-13	Von Segessler et al.	
	7	20080147182		2008-06-19	Righini et al.	
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	9	20090030511		2009-01-29	Paniagua et al.	
	10	20100161036		2010-06-24	Pintor et al.	
	11	20100256749		2010-10-07	Tran et al.	
	12	20110300625		2011-12-08	Paniagua et al.	
	13	20110301700		2011-12-08	Fish et al.	
	14	20060259137		2006-11-16	Artof et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	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

	15	20080154356		2008-06-26	Obermiller et al.	
	16	20080102439		2008-05-01	Tian et al.	
	17	20080177381		2008-07-24	Navia et al.	
	18	20090062907		2009-03-05	Quijano et al.	
	19	20090164005		2009-06-25	Dove et al.	
	20	20090187241		2009-07-23	Melsheimer	
	21	20090248149		2009-10-01	Gabbay	
	22	20090254175		2009-10-08	Quijano et al.	
	23	20090030511		2009-01-29	Paniagua et al.	
	24	20100161036		2010-06-24	Pintor et al.	
	25	20100234878		2009-09-16	Hruska	

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	26	20100256749		2010-10-07	Tran et al.	
	27	20110300625		2011-12-08	Paniagua et al.	
	28	20110301700		2011-12-08	Fish et al.	

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	1	2011/109433	WO		2011-03-01	Colibri Heart Valve LLC		☐
	2	2011/109450	WO		2011-09-09	Colibri Heart Valve LLC		☐
	3	2012/006124	WO		2012-01-12	Colibri Heart Valve LLC		☐
	4	1999/030646	WO		1999-06-24	St. Jude Medical, Inc.		☐
	5	2009/156471	WO		2009-12-30	Iberhospitex, S.A.		☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	First Named Inventor	David PANIAGUA
	Art Unit	3738
	Examiner Name	Cheryl L. MILLER
	Attorney Docket Number	54813-10100

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T5
	1	Examiner Interview Summary, dated 04/05/2011 in U.S. Application No. 12/228,192 (54813-10110)	☐
	2	Final Office Action issued July 14, 2011, in U.S. Application No. 12/228,192 (54813-10110)	☐
	3	PCT International Search Report and Written Opinion, in Application PCT/US2011/026763, dated 11/14/2011 (54813-10202)	☐
	4	PCT Written Opinion, in Application PCT/US2011/026741, dated 11/28/2011 (54813-10251)	☐
	5	Applicants' Reply to Written Opinion, filed 2/28/2012, in App. PCT/US2011/026741 (54813-10251)	☐
	6	PCT International Search Report and Written Opinion, in Application PCT/US2011/042252, dated 04/06/2011 (54813-10502)	☐
	7	Cross-reference is made to U.S. Application No. 13/367,252, filed on February 6, 2012 (54813-10111)	☐
	8	Cross-reference is made to U.S. Application No. 13/243,980, filed on September 23, 2011 (54813-10222)	☐
	9	Cross-reference is made to PCT Application No. PCT/US11/53120, filed on September 23, 2011 (54813-10223)	☐
	10	Cross-reference is made to U.S. Application No. 13/326,196, filed on December 14, 2011 (54813-10402)	☐

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	Attorney Docket Number	54813-10100

	11	Cross-reference is made to PCT Application No. PCT/US11/64989, filed on December 14, 2011 (54813-10403)	☐
	12	Cross-reference is made to U.S. Application No. 13/171,400, filed on June 28, 2011 (54813-10501)	☐
	13	Cross-reference is made to PCT Application No. PCT/US11/42252, filed on June 28, 2011 (54813-10502)	☐
	14	Affidavit of Dr. Paolo Angelini, M.D., signed August 25, 2009	☐
	15	Affidavit of Dr. Gervasio A. Lamas, M.D., signed September 3, 2009	☐
	16	"Artificial heart valve" http://en.wikipedia.org/Artificial_heart_valve, printed May 13, 2009	☐
	17	"Collagen" http://en.wikipedia.org/wiki/Collagen, printed May 13, 2009	☐
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	19	Grube E., et al., "Progress and Current Status of Percutaneous Aortic Valve Replacement: Results of Three Device Generations of the CoreValve Revalving System", Circ. Cardiovasc Intervent. 2008;1:167-175 (abstract)	☐
	20	Introduction to Stereomicroscopy, http://www.microscopyu.com/articles/stereomicroscopy/stereointro.html, Copyrigth 2000-2012, printed on March 15, 2012	☐
	21	IOPATCH(R) Tutoplast(R) Processed Pericardium Directions for Use; http://www.iopinc.com/surgeons_and_medical_professionals/iopatch/directions.asp, printed on June 2, 2009	☐

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	Attorney Docket Number	54813-10100

	22	LIAO, Jun et al., "Molecular orientation of collagen in intact planar connective tissues under biaxial stretch" Acta Biomateriala, Vol. 1, Iss. 1, January 2005, pp 45-54	☐
	23	MIRNAJAFI, A. et al. "The effects of collagen fiber orientation of the flexural properties of pericardial heterograft biomaterials" Biomaterials, 2005 Mar; 26(7): 795-804	☐
	24	MIRZAIE, M. et al., "A new storage solution for porcine aortic valves" Ann Thorac Cardiovasc Surg. 2007 Apr;13 (2):102-9	☐
	25	Optical Microscope, Wikipedia, http://en.wikipedia.org/wiki/Stereomiscroscope, May 13, 2009	☐
	26	Orthogonality, http://en.wikipedia.org/wiki/Orthogonal, May 13, 2009	☐
	27	PICK, Adam, "True or False: An Edwards Lifescience' Tissue Valve Replacement Requires 1,800 Hand-Sewn Stitches" http://heart-valve-surgery.com/heart-surgery-blog/2008/02/26. printed August 13, 2010	☐
	28	PCT International Search Report and Written Opinion, in Application PCT/US2011/053120, dated 04/27/2012 (54813-10223)	☐

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Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	10887688
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Art Unit	3738
Examiner Name	Cheryl L. MILLER
Attorney Docket Number	54813-10100

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/ Mark L. Yaskanin /	Date (YYYY-MM-DD)	2012-05-16
Name/Print	Mark L. Yaskanin	Registration Number	45246

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 1 hour 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.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

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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.

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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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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

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ 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 05/16/2012	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 21	Minus	** 20	= 1	X $30 =	30	OR	X $ =	
Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $125 =	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	30	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:
/THERESA OKON/

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NOTICE OF ALLOWANCE AND FEE(S) DUE

23337 7590 08/17/2012

Bryan Cave LLP (Denver)
1700 LINCOLN STREET, SUITE 4100
DENVER, CO 80203

EXAMINER
MILLER, CHERYL L

ART UNIT	PAPER NUMBER
3738	

DATE MAILED: 08/17/2012

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/887,688	07/10/2004	David Paniagua	54813-10100	4909

TITLE OF INVENTION: PERCUTANEOUSLY IMPLANTABLE REPLACEMENT HEART VALVE DEVICE AND METHOD OF MAKING SAME

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$870	$300	$0	$1170	11/19/2012

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

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B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

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A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

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III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

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Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
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Alexandria, Virginia 22313-1450
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23337 7590 08/17/2012

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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

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(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/887,688	07/10/2004	David Paniagua	54813-10100	4909

TITLE OF INVENTION: PERCUTANEOUSLY IMPLANTABLE REPLACEMENT HEART VALVE DEVICE AND METHOD OF MAKING SAME

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$870	$300	$0	$1170	11/19/2012

EXAMINER	ART UNIT	CLASS-SUBCLASS
MILLER, CHERYL L	3738	623-002140

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

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1 _____

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3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

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❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

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

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

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This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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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 08/17/2012

Bryan Cave LLP (Denver)
1700 LINCOLN STREET, SUITE 4100
DENVER, CO 80203

EXAMINER	
MILLER, CHERYL L	

ART UNIT	PAPER NUMBER
3738	

DATE MAILED: 08/17/2012

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 1027 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 1027 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No.	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--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *5/16/2012*.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *57-63,65,66 and 69-76*.
4. ☐ 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 the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 5/16/2012
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Cheryl Miller/
Examiner, Art Unit 3738

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Mark Yaskanin (Registration No.45,246) on August 9, 2012. It is the examiners position that claims 67, 68, 77, and 78 raise 112 2nd issues in that two *separate* pieces directly conflicts with "*single*" required in the independent claim since it is unclear if a sheet is singular, how it may also be two separate pieces. Applicant did not necessarily agree, however claims 67, 68, 77, and 78 were agreed to be cancelled in efforts to advance prosecution.

The application has been amended as follows:

Claims 67, 68, 77, and 78 have been cancelled.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Cheryl Miller whose telephone number is 571-272-4755. The examiner can normally be reached on M- F (8am-5:30pm).

If attempts to reach the examiner by telephone are unsuccessful, please contact the examiner's supervisor, Thomas Sweet at 571-272-4761. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cheryl Miller/
Examiner, Art Unit 3738

/CHRISTOPHER D KOHARSKI/
Primary Examiner, Art Unit 3763

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

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

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4801299		1989-01-31	Brendel et al.	
	2	4976733		1990-12-11	Giradot	
	3	5226889		1993-07-13	Sheiban	
	4	5261878		1993-11-16	Galindo	
	5	5634928		1997-06-03	Fischell et al.	
	6	5733299		1998-03-31	Sheiban et al.	
	7	6004328		1999-12-21	Solar	
	8	6174327		2001-01-16	Mertens et al.	

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Receipt date: 05/16/2012	Application Number	10887688	10887688 - GAU: 3738
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2004-07-10	
	First Named Inventor	David PANIAGUA	
	Art Unit	3738	
	Examiner Name	Cheryl L. MILLER	
	Attorney Docket Number	54813-10100	

	9	6221091		2001-04-24	Khosravi	
	10	6383171		2002-05-07	Gifford et al.	
	11	6696074		2004-02-24	Dia et al.	
	12	6908481		2005-06-21	Cribier	
	13	7153324		2006-12-26	Case et al.	
	14	7622276		2009-11-24	Cunanan et al.	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20010023372		2001-09-20	Chen et al.	
	2	20050043819		2005-02-24	Schmidt et al.	
	3	20060004439		2006-01-05	Spenser et al.	

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	Attorney Docket Number	54813-10100	

	4	20060259134		2006-11-16	Schwammenthal et al.	
	5	20070050014		2007-03-01	Johnson	
	6	20070213813		2007-09-13	Von Segessler et al.	
	7	20080147182		2008-06-19	Righini et al.	
	8	20080200977		2009-08-21	Paul et al.	
	9	20090030511		2009-01-29	Paniagua et al.	
	10	20100161036		2010-06-24	Pintor et al.	
	11	20100256749		2010-10-07	Tran et al.	
	12	20110300625		2011-12-08	Paniagua et al.	
	13	20110301700		2011-12-08	Fish et al.	
	14	20060259137		2006-11-16	Artof et al.	

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	Art Unit	3738	
	Examiner Name	Cheryl L. MILLER	
	Attorney Docket Number	54813-10100	

	15	20080154356		2008-06-26	Obermiller et al.	
	16	20080102439		2008-05-01	Tian et al.	
	17	20080177381		2008-07-24	Navia et al.	
	18	20090062907		2009-03-05	Quijano et al.	
	19	20090164005		2009-06-25	Dove et al.	
	20	20090187241		2009-07-23	Melsheimer	
	21	20090248149		2009-10-01	Gabbay	
	22	20090254175		2009-10-08	Quijano et al.	
	23	20090030511		2009-01-29	Paniagua et al.	
	24	20100161036		2010-06-24	Pintor et al.	
	25	20100234878		2009-09-16	Hruska	

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	26	20100256749		2010-10-07	Tran et al.	
	27	20110300625		2011-12-08	Paniagua et al.	
	28	20110301700		2011-12-08	Fish et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2011/109433	WO		2011-03-01	Colibri Heart Valve LLC		☐
	2	2011/109450	WO		2011-09-09	Colibri Heart Valve LLC		☐
	3	2012/006124	WO		2012-01-12	Colibri Heart Valve LLC		☐
	4	1999/030646	WO		1999-06-24	St. Jude Medical, Inc.		☐
	5	2009/156471	WO		2009-12-30	Iberhospitex, S.A.		☐

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(Not for submission under 37 CFR 1.99)	Art Unit	3738
	Examiner Name	Cheryl L. MILLER
	Attorney Docket Number	54813-10100

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Examiner Interview Summary, dated 04/05/2011 in U.S. Application No. 12/228,192 (54813-10110)	☐
	2	Final Office Action issued July 14, 2011, in U.S. Application No. 12/228,192 (54813-10110)	☐
	3	PCT International Search Report and Written Opinion, in Application PCT/US2011/026763, dated 11/14/2011 (54813-10202)	☐
	4	PCT Written Opinion, in Application PCT/US2011/026741, dated 11/28/2011 (54813-10251)	☐
	5	Applicants' Reply to Written Opinion, filed 2/28/2012, in App. PCT/US2011/026741 (54813-10251)	☐
	6	PCT International Search Report and Written Opinion, in Application PCT/US2011/042252, dated 04/06/2011 (54813-10502)	☐
	7	Cross-reference is made to U.S. Application No. 13/367,252, filed on February 6, 2012 (54813-10111)	☐
	8	Cross-reference is made to U.S. Application No. 13/243,980, filed on September 23, 2011 (54813-10222)	☐
	9	Cross-reference is made to PCT Application No. PCT/US11/53120, filed on September 23, 2011 (54813-10223)	☐
	10	Cross-reference is made to U.S. Application No. 13/326,196, filed on December 14, 2011 (54813-10402)	☐

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	Examiner Name	Cheryl L. MILLER	
	Attorney Docket Number	54813-10100	

	11	Cross-reference is made to PCT Application No. PCT/US11/64989, filed on December 14, 2011 (54813-10403)	☐
	12	Cross-reference is made to U.S. Application No. 13/171,400, filed on June 28, 2011 (54813-10501)	☐
	13	Cross-reference is made to PCT Application No. PCT/US11/42252, filed on June 28, 2011 (54813-10502)	☐
	14	Affidavit of Dr. Paolo Angelini, M.D., signed August 25, 2009	☐
	15	Affidavit of Dr. Gervasio A. Lamas, M.D., signed September 3, 2009	☐
	16	"Artificial heart valve" http://en.wikipedia.org/Artificial_heart_valve, printed May 13, 2009	☐
	17	"Collagen" http://en.wikipedia.org/wiki/Collagen, printed May 13, 2009	☐
	18	Edwards Lifesciences Receives FDA Approval for New Heart Valve, http:www.medicalnewstoday.com/articles/149588.php, May 11, 2009	☐
	19	Grube E., et al., "Progress and Current Status of Percutaneous Aortic Valve Replacement: Results of Three Device Generations of the CoreValve Revalving System", Circ. Cardiovasc Intervent. 2008;1:167-175 (abstract)	☐
	20	Introduction to Stereomicroscopy, http://www.microscopyu.com/articles/stereomicroscopy/stereointro.html, Copyrigth 2000-2012, printed on March 15, 2012	☐
	21	IOPATCH(R) Tutoplast(R) Processed Pericardium Directions for Use; http://www.iopinc.com/surgeons_and_medical_professionals/iopatch/directions.asp, printed on June 2, 2009	☐

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	First Named Inventor	David PANIAGUA	
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	Examiner Name	Cheryl L. MILLER	
	Attorney Docket Number	54813-10100	

	22	LIAO, Jun et al., "Molecular orientation of collagen in intact planar connective tissues under biaxial stretch" Acta Biomateriala, Vol. 1, Iss. 1, January 2005, pp 45-54	☐
	23	MIRNAJAFI, A. et al. "The effects of collagen fiber orientation of the flexural properties of pericardial heterograft biomaterials" Biomaterials, 2005 Mar; 26(7): 795-804	☐
	24	MIRZAIE, M. et al., "A new storage solution for porcine aortic valves" Ann Thorac Cardiovasc Surg. 2007 Apr;13 (2):102-9	☐
	25	Optical Microscope, Wikipedia, http://en.wikipedia.org/wiki/Stereomiscroscope, May 13, 2009	☐
	26	Orthogonality, http://en.wikipedia.org/wiki/Orthogonal, May 13, 2009	☐
	27	PICK, Adam, "True or False: An Edwards Lifescience' Tissue Valve Replacement Requires 1,800 Hand-Sewn Stitches" http://heart-valve-surgery.com/heart-surgery-blog/2008/02/26. printed August 13, 2010	☐
	28	PCT International Search Report and Written Opinion, in Application PCT/US2011/053120, dated 04/27/2012 (54813-10223)	☐

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EXAMINER SIGNATURE

Examiner Signature	/Cheryl Miller/	Date Considered	08/02/2012

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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CONFIRMATION NO. 4909

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/887,688	07/10/2004	623	3738	54813-10100

APPLICANTS
David Paniagua, North Bay Village, FL;
Eduardo Induni, Alajvela, COSTA RICA;
Carlos Mejia, Miami Beach, FL;
Francisco Lopez-Jimenez, Rochester, MN;
R. David Fish, Houston, TX;

**** CONTINUING DATA **************************
This application is a CIP of 10/037,266 01/04/2002 ABN

**** FOREIGN APPLICATIONS **************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
09/17/2004

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /CHERYL L MILLER/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		FL	12	~~33~~ 17	~~5~~ 2

ADDRESS
Bryan Cave LLP (Denver)
1700 LINCOLN STREET, SUITE 4100
DENVER, CO 80203
UNITED STATES

TITLE
Percutaneously implantable replacement heart valve device and method of making same

FILING FEE RECEIVED		
4721	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Issue Classification	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/887,688	PANIAGUA ET AL.	
	Examiner	Art Unit	
	CHERYL MILLER	3738	

ISSUE CLASSIFICATION

ORIGINAL			CROSS REFERENCE(S)						
CLASS	SUBCLASS	CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)						
623	2.14								
INTERNATIONAL CLASSIFICATION									
A 6 1 F	2/24								
	/								
	/								
	/								
	/								

/Cheryl Miller/ 8/9/2012 (Assistant Examiner) (Date)	/Christopher Koharski/ 8/12/12 (Primary Examiner) (Date)	Total Claims Allowed: 17
(Legal Instruments Examiner) (Date)		O.G. Print Claim(s): 1 / O.G. Print Fig.: 5

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		31	5	61		91		121		151		181
	2		32	6	62		92		122		152		182
	3		33	7	63		93		123		153		183
	4		34		64		94		124		154		184
	5		35	8	65		95		125		155		185
	6		36	9	66		96		126		156		186
	7		37		67		97		127		157		187
	8		38		68		98		128		158		188
	9		39	10	69		99		129		159		189
	10		40	11	70		100		130		160		190
	11		41	12	71		101		131		161		191
	12		42	13	72		102		132		162		192
	13		43	14	73		103		133		163		193
	14		44	15	74		104		134		164		194
	15		45	16	75		105		135		165		195
	16		46	17	76		106		136		166		196
	17		47		77		107		137		167		197
	18		48		78		108		138		168		198
	19		49		79		109		139		169		199
	20		50		80		110		140		170		200
	21		51		81		111		141		171		201
	22		52		82		112		142		172		202
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	24		54		84		114		144		174		204
	25		55		85		115		145		175		205
	26		56		86		116		146		176		206
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	28	2	58		88		118		148		178		208
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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
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			USPAT; USOCR			
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L27	2632	623/1.24.ccls. or 623/1.26.ccls. or 623/2.1$.ccls. or 623/900.ccls.	US-PGPUB; USPAT; USOCR	OR	ON	2012/08/02 15:46
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L34	36	stent and leaflets and biological and fold$3 and crease and layer	US-PGPUB; USPAT; USOCR	OR	ON	2012/08/02 17:08
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S7	17	(US-20060167543-$ 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-$).did.	US-PGPUB; USPAT	OR	ON	2007/11/25 16:49
S8	9	"09/975,750"	US-PGPUB; USPAT	OR	ON	2007/11/25 16:51
S9	1	623/900.ccls. and bessler.in.	US-PGPUB; USPAT	OR	ON	2007/11/25 16:52
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S18	2	"6458153".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/11 19:50
S19	1448	623/1.24.ccls. or 623/1.26.ccls. or 623/2.1$.ccls.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 12:25
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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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S34	1	"6425916".pn.	US-PGPUB; USPAT; EPO; JPO	OR	ON	2012/02/08 18:14
S35	1	"8109995".pn.	US-PGPUB; USPAT; EPO; JPO	OR	ON	2012/08/02 12:25
S36	2520	623/1.24.ccls. or 623/1.26.ccls. or 623/2.1$.ccls.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2012/08/02 12:30
S37	2558	623/1.24.ccls. or 623/1.26.ccls. or 623/2.1$.ccls.	US-PGPUB; USPAT; USOCR	OR	ON	2012/08/02 12:30
S38	1558	S37 not 623/2.11.ccls.	US-PGPUB; USPAT; USOCR	OR	ON	2012/08/02 12:30
S39	348	S38 and @rlad<"20020104"	US-PGPUB; USPAT; USOCR	OR	ON	2012/08/02 12:31
S40	381	S38 and @ad<"20020104"	US-PGPUB; USPAT; USOCR	OR	ON	2012/08/02 12:31
S41	590	S39 S40	US-PGPUB; USPAT; USOCR	OR	ON	2012/08/02 12:31
S42	2632	623/1.24.ccls. or 623/1.26.ccls. or 623/2.1$.ccls. or 623/900.ccls.	US-PGPUB; USPAT; USOCR	OR	ON	2012/08/02 12:32
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8/2/2012 5:13:42 PM
C:\Users\cmiller2\Documents\EAST\Workspaces\10887688.wsp

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
update		8/6/2012	cm

SEARCH NOTES		
Search Notes	**Date**	**Examiner**
East text search	8/6/2012	cm

INTERFERENCE SEARCH			
Class	**Subclass**	**Date**	**Examiner**
623	1.24, 1.26, 2.1-2.19	8/6/2012	cm

/CHERYL MILLER/ Examiner.Art Unit 3738	

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23337 7590 08/17/2012

Bryan Cave LLP (Denver)
1700 LINCOLN STREET, SUITE 4100
DENVER, CO 80203

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/887,688	07/10/2004	David Paniagua	54813-10100	4909

TITLE OF INVENTION: PERCUTANEOUSLY IMPLANTABLE REPLACEMENT HEART VALVE DEVICE AND METHOD OF MAKING SAME

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$870	$300	$0	$1170	11/19/2012

EXAMINER	ART UNIT	CLASS-SUBCLASS
MILLER, CHERYL L	3738	623-002140

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Fox Rothschild LLP
2 Mark L. Yaskanin
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Colibri Heart Valve, LLC

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Broomfield, CO

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

☒ Issue Fee

☒ Publication Fee (No small entity discount permitted)

☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

☐ A check is enclosed.

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

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature /Mark L. Yaskanin/ Date October 5, 2012

Typed or printed name Mark L. Yaskanin Registration No. 45,246

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re the Application of:	Group Art Unit: 3738
PANIAGUA et al.	Confirmation No. 4909
Application No.: 10/887,688	Examiner: Cheryl L. MILLER
Filed: July 10, 2004	APPLICANT'S COMMENTS REGARDING EXAMINER'S AMENDMENT
Atty. File No.: 54813-10100	**Filed Electronically**
Entitled: PERCUTANEOUSLY IMPLANTABLE REPLACEMENT HEART VALVE DEVICE AND METHOD OF MAKING SAME	

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Dear Sir:

Applicant is in receipt of a Notice of Allowability and an Examiner's Amendment dated August 17, 2012 in the matter of the above-referenced patent application. As noted by the Examiner in the Examiner's Amendment, the Applicant does not necessarily agree with the Examiner's position that two separate pieces directly conflicts with wording of the independent claims, but agreed to cancel Claims 67, 68, 77 and 78 to advance prosecution of the present application which has been pending for over 8 years. As mentioned in the August 9, 2012 call with the Examiner, the Applicant reserves the right to file one or more continuation and/or divisional patent applications to pursue any unclaimed subject matter, and/or any previously presented, amended or cancelled claims. Finally, the Applicant sincerely appreciates the Examiner contacting Applicant's counsel to facilitate placing the present application in a condition for allowance.

Applicant believes no fees are due for this submission. However, please credit any over payment or debit any under payment to Deposit Account No. 50-1943.

Dated: October 5, 2012

Respectfully submitted,

FOX ROTHSCHILD LLP

/ Mark L. Yaskanin /

Mark L. Yaskanin
Registration No. 45,246
Fox Rothschild LLP
1200 17th Street
Tabor Center Suite 975
Denver, CO 80202
(303) 446-3852
(609) 896-1469 Fax

Electronic Patent Application Fee Transmittal

Application Number:	10887688
Filing Date:	10-Jul-2004
Title of Invention:	PERCUTANEOUSLY IMPLANTABLE REPLACEMENT HEART VALVE DEVICE AND METHOD OF MAKING SAME
First Named Inventor/Applicant Name:	David Paniagua
Filer:	Mark Lauren Yaskanin/olga ayala
Attorney Docket Number:	0535534

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl issue fee	2501	1	885	885
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1185**

Electronic Acknowledgement Receipt

EFS ID:	13922703
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:	23337
Filer:	Mark Lauren Yaskanin/olga ayala
Filer Authorized By:	Mark Lauren Yaskanin
Attorney Docket Number:	0535534
Receipt Date:	05-OCT-2012
Filing Date:	10-JUL-2004
Time Stamp:	16:11:47
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1185
RAM confirmation Number	3243
Deposit Account	501943
Authorized User	AYALA, OLGA

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	ISSUEFEE.pdf	112264 2fab753de35427b75118b8db11a2be7de6cab0a0	no	1
Warnings:					
Information:					
2	Miscellaneous Incoming Letter	COMMENTS.pdf	17839 e908fa3035749645e622f91dc2ae99ca19edeaee	no	2
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32011 973aab88c419468773b7159fb4aec1d5df726db3	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	162114		

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

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

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	7084082		2006-08-01	Shimizu	
	2	7164145		2007-01-16	Shakespeare	
	3	7166570		2007-01-23	Hunter et al.	
Change(s) applied to document, /A.J.P./ 10/16/2012	4	~~7216301~~ 7,213,601		2007-05-08	Stevens et al.	
	5	7214242		2007-05-08	Abraham et al.	
	6	7232461		2007-06-19	Ramer	
	7	7289211		2007-10-30	Walsh Jr. et al.	
	8	7309461		2007-12-18	Kujawski et al.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CM/

PTO/SB/80 (11-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(b).

I hereby appoint:

[X] Practitioners associated with the Customer Number: 29880

OR

[ ] Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(b).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(b) to:

[X] The address associated with Customer Number: 29880

OR

[ ] Firm or Individual Name

Address					
City		State		Zip	
Country		Telephone		Email	

Assignee Name and Address:

Mr. Joseph B. Horn
President and CEO
Colibri Heart Valve LLC
2150 W. 6th Avenue, Suite M
Broomfield, CO 80020

A copy of this form, together with a statement under 37 CFR 3.73(b) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(b) may be completed by one of the practitioners appointed in this form if the appointed practitioner is authorized to act on behalf of the assignee, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature	Joseph B Horn	Date	10/16/12
Name	JOSEPH B. HORN	Telephone	303-460-8667
Title	PRESIDENT & CEO		

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: COLIBRI HEART VALVE 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

COLIBRI HEART VALVE LLC , a LLC

(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 and 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.

/ Mark L. Yaskanin / 24 October 2012

Signature Date

Mark L. Yaskanin Attorney of Record

Printed or Typed Name Title

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: COLIBRI HEART VALVE 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

COLIBRI HEART VALVE LLC , a LLC

(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: Endoluminal Technology LLC To: Vela Biosystems LLC

The document was recorded in the United States Patent and Trademark Office at Reel 027411, Frame 0552, or for which a copy thereof is attached.

2. From: Vela Biosystems LLC To: R. David Fish and David Paniagua

The document was recorded in the United States Patent and Trademark Office at Reel 027411, Frame 0615, or for which a copy thereof is attached.

3. From: R. David Fish and David Paniagua To: Colibri Heart Valve LLC

The document was recorded in the United States Patent and Trademark Office at Reel 027412, Frame 0659, 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 / 24 October 2012

Signature Date

Mark L. Yaskanin Attorney of Record

Printed or Typed Name Title

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

Electronic Acknowledgement Receipt

EFS ID:	14065048
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:	23337
Filer:	Mark Lauren Yaskanin/carol donahue
Filer Authorized By:	Mark Lauren Yaskanin
Attorney Docket Number:	0535534
Receipt Date:	24-OCT-2012
Filing Date:	10-JUL-2004
Time Stamp:	15:11:07
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	Colibri_POA.pdf	53836 085a6a7c9f941afaf8b5276d5426e4c04205c8bf	no	1

Warnings:	
Information:	

2	Assignee showing of ownership per 37 CFR 3.73.	3-73b_Statement.pdf	148881 51fd0c5aaa50582299620 7bf8209a5e8708c5c5a	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	202717

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 NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/887,688	11/13/2012	8308797	0535534	4909

23337 7590 10/24/2012

Bryan Cave LLP (Denver)
One Renaissance Square
Two North Central Ave., Suite 2200
Phoenix, AZ 85004-4406

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 1467 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

David Paniagua, North Bay Village, FL;
Eduardo Induni, Alajvela, COSTA RICA;
Carlos Mejia, Miami Beach, FL;
Francisco Lopez-Jimenez, Rochester, MN;
R. David Fish, Houston, TX;

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	

CONFIRMATION NO. 4909

POA ACCEPTANCE LETTER

29880
FOX ROTHSCHILD LLP
PRINCETON PIKE CORPORATE CENTER
997 LENOX DRIVE
BLDG. #3
LAWRENCEVILLE, NJ 08648

OC000000057351831

Date Mailed: 10/29/2012

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 10/24/2012.

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.

/jtfitzhugh sr/

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 NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/887,688	07/10/2004	David Paniagua	0535534

CONFIRMATION NO. 4909

POWER OF ATTORNEY NOTICE

23337
Bryan Cave LLP (Denver)
One Renaissance Square
Two North Central Ave., Suite 2200
Phoenix, AZ 85004-4406

OC000000057351830

Date Mailed: 10/29/2012

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 10/24/2012.

- 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).

/jtfitzhugh sr/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101