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July 9, 2004

VIA EXPRESS MAIL

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

Sir:

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

INVENTORS: Paniagua, et al.

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

Enclosed are:

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

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

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

Please direct all communications regarding the foregoing to the undersigned.

Respectfully submitted,

GREENBERG TRAURIG, P.A.

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MRV/kfh

Enclosures

Express Mail Mailing Label No. ER940080602US

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Docket No. 51458.010100

CONTINUATION IN PART

NON-PROVISIONAL PATENT APPLICATION

SPECIFICATION

TO WHOM IT MAY CONCERN:

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

CONTINUITY INFORMATION

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

BACKGROUND OF THE INVENTION

[0001] 1. Field of the Invention

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

[0002] 2. Description of Related Art

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

SUMMARY OF THE INVENTION

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

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

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

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

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

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

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

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

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

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

DESCRIPTION OF A PREFERRED EMBODIMENT

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

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

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

Stent Member

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

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

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

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

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

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

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

Valve Means

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

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

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

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

Method of Making Replacement Heart Valve Device

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

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

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

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

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

Attachment of the Valve Means to the Stent Member

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

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

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

Implantation of Replacement Heart Valve Device

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CLAIMS

Having thus described the invention, what is claimed is:

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

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

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

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

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

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

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

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

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

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

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

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

obtaining a sheet of biocompatible tissue material;

drying said biocompatible tissue material;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ABSTRACT

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

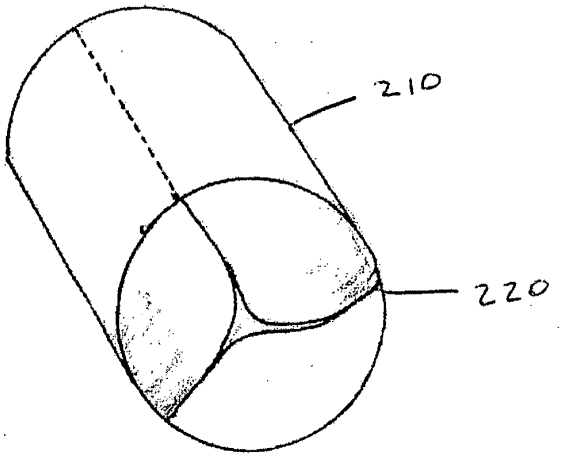

Fig. 1

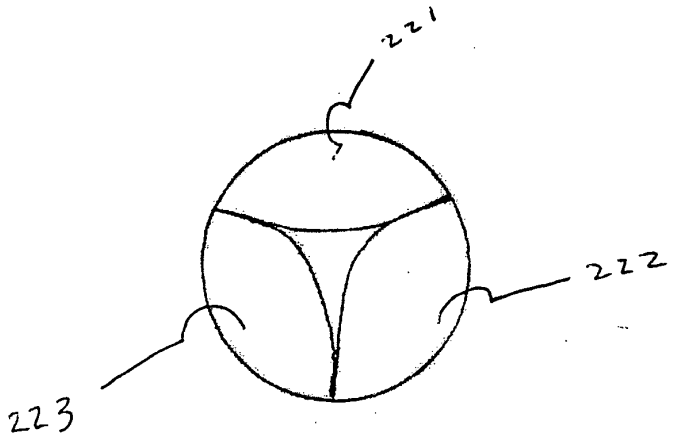

Fig. 2

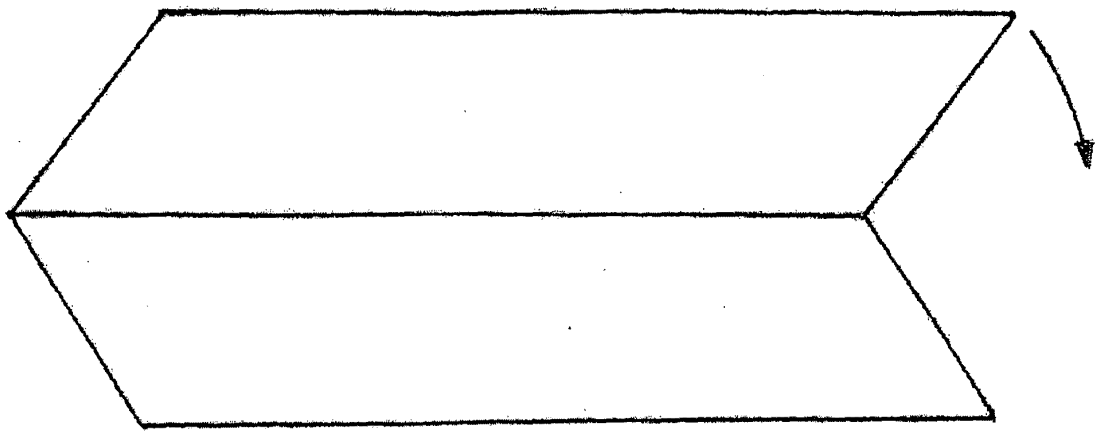

Fig. 3A

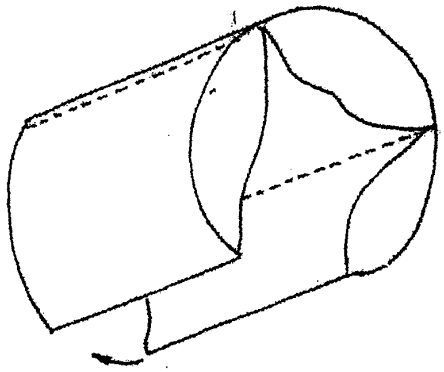

Fig. 3B

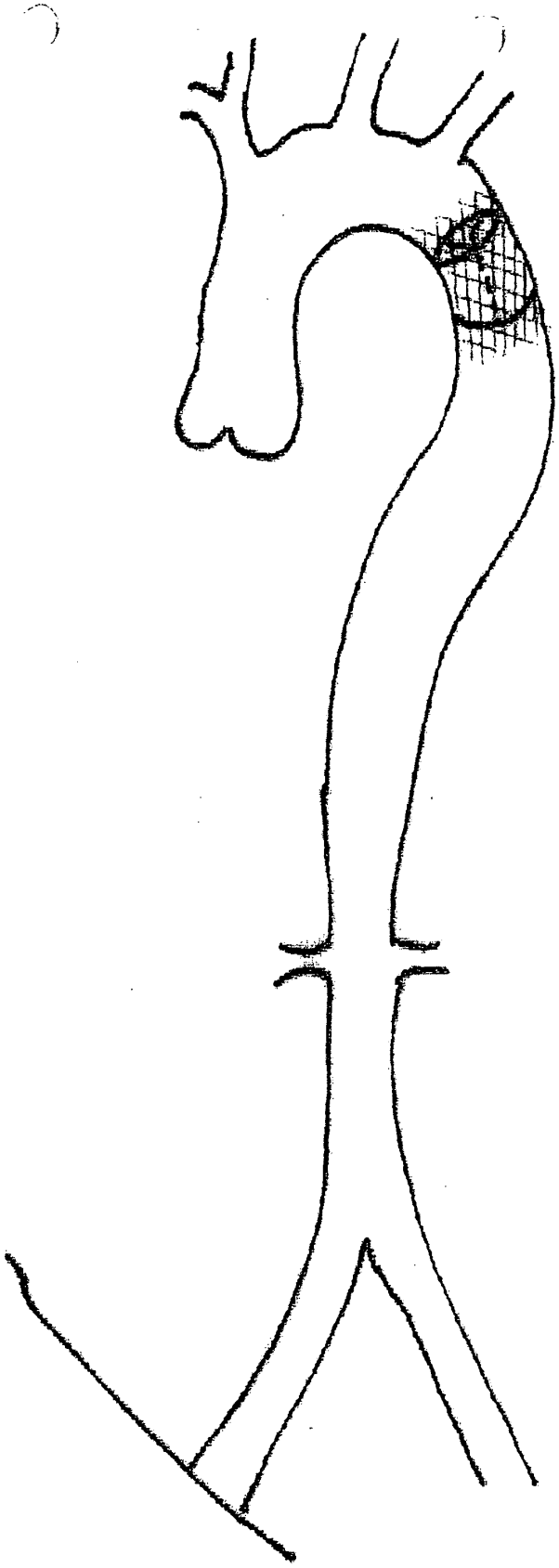

Fig. 4

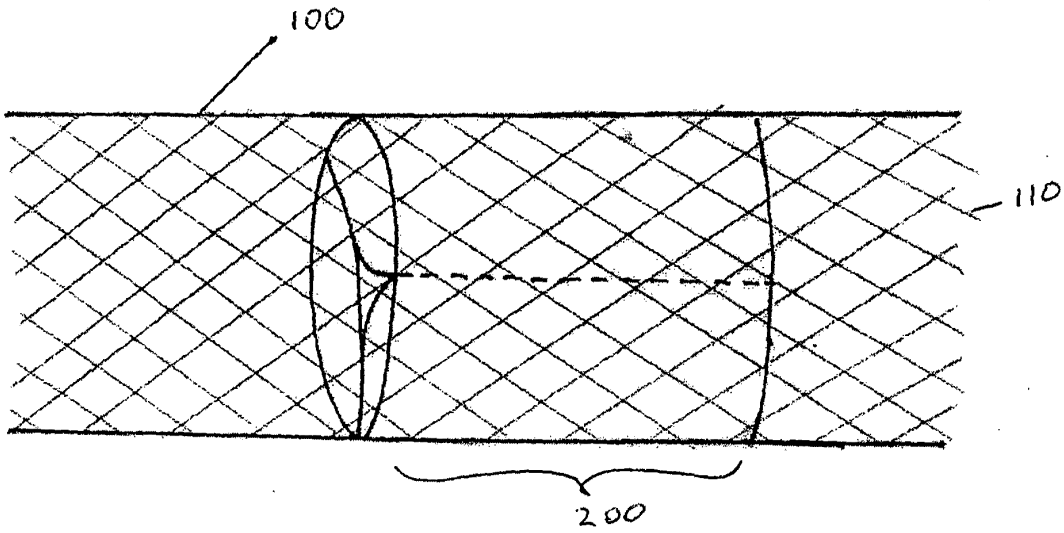

Fig. 5

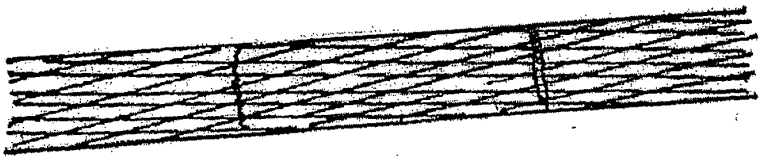

Fig. 6

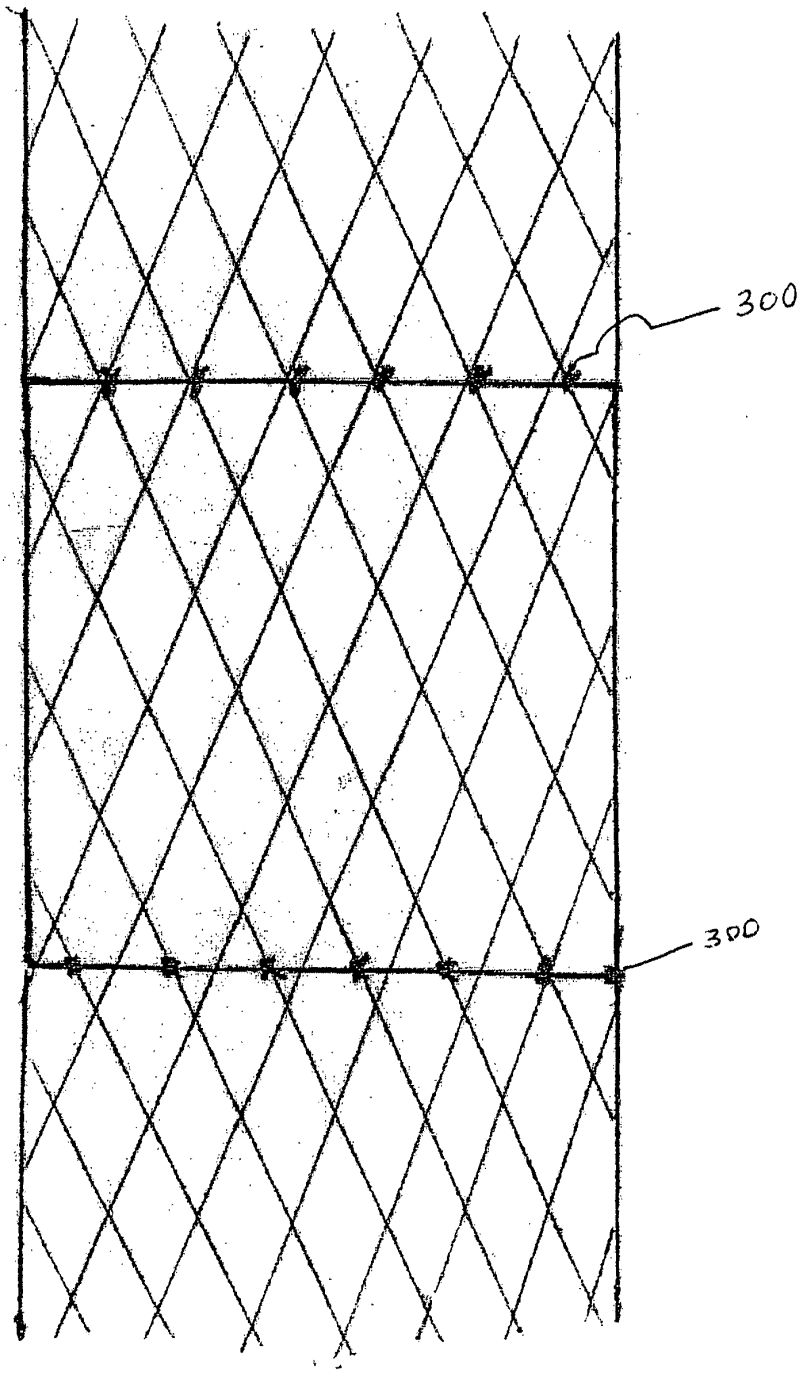

Fig. 7

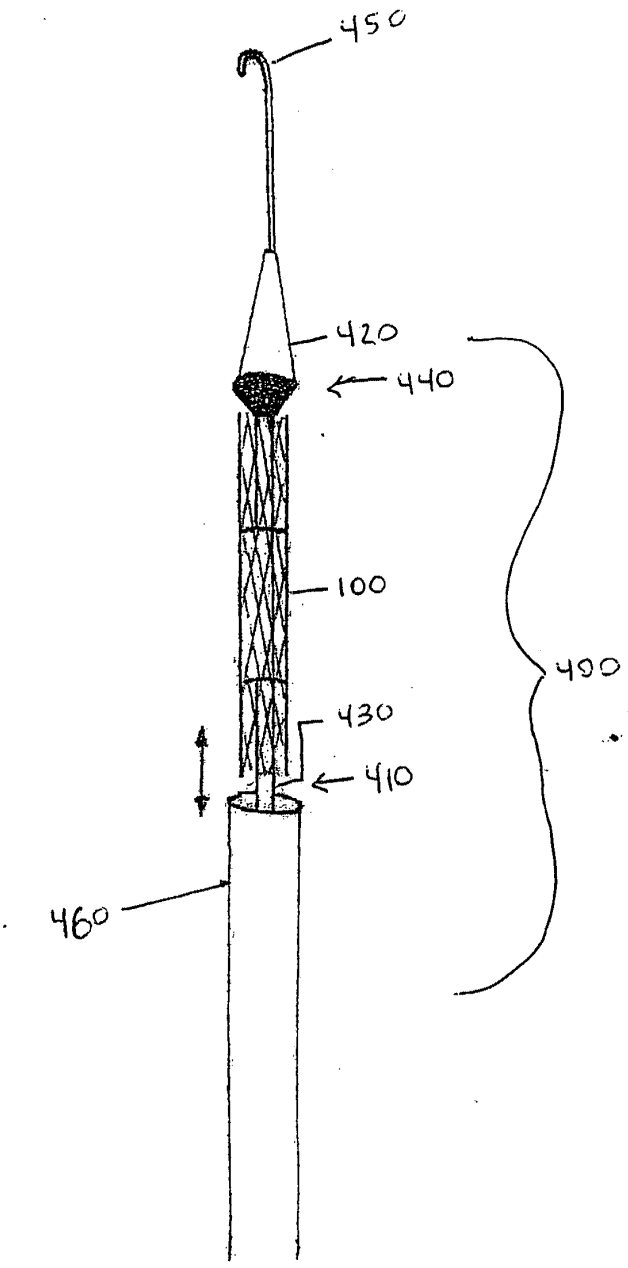

Fig. 8

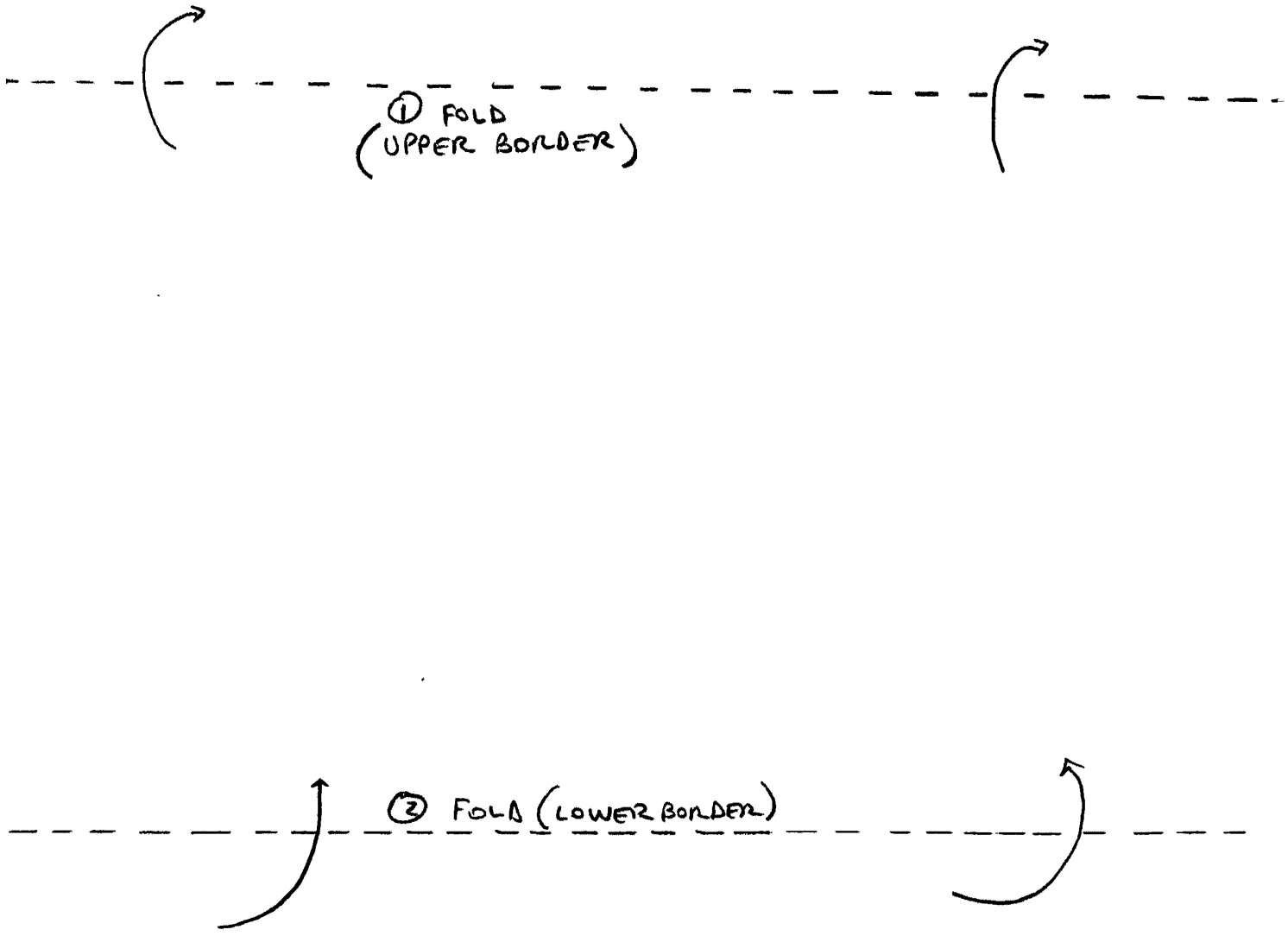

Fig. 9A

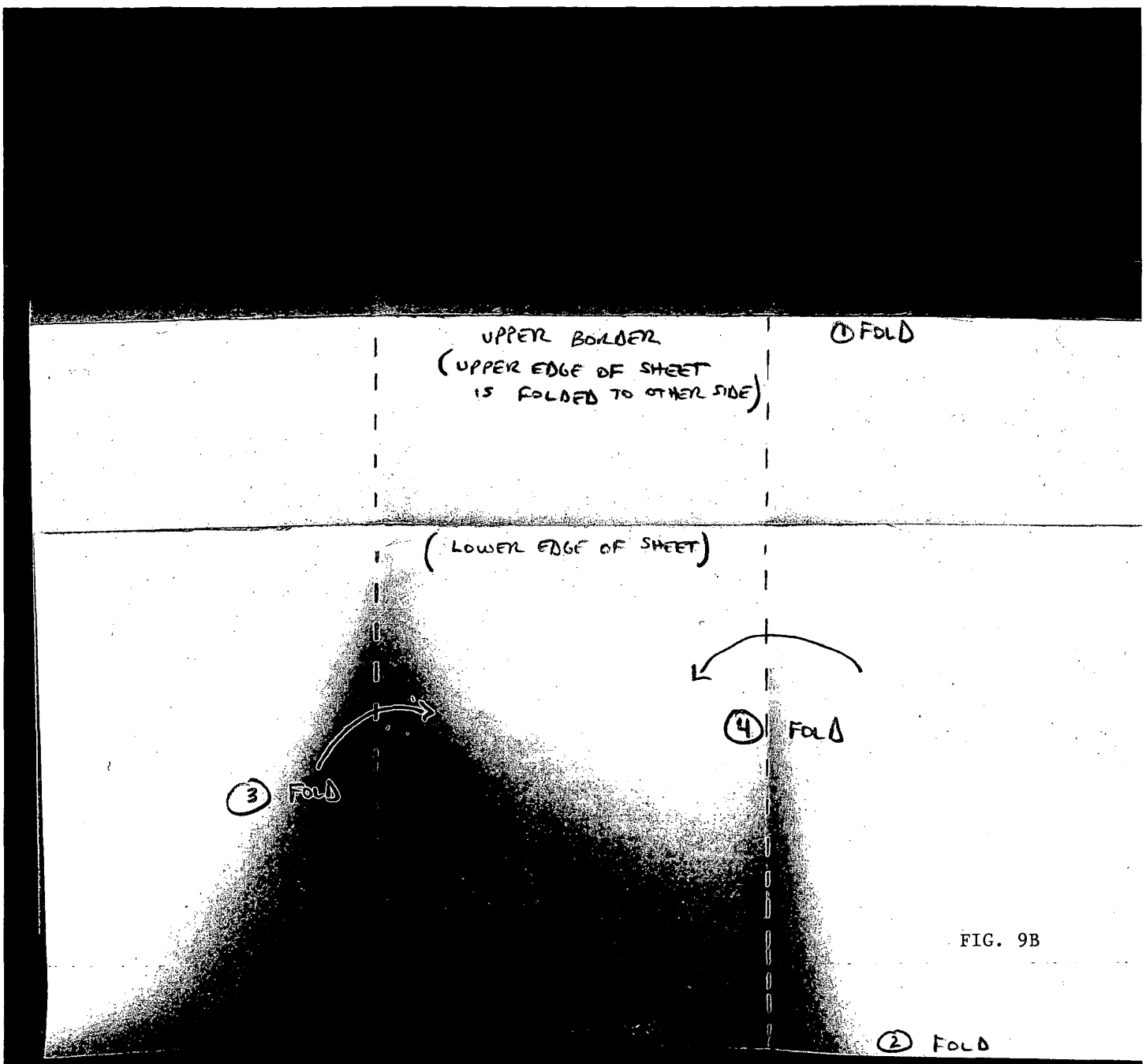
UPPER BORDER
(UPPER EDGE OF SHEET
IS FOLDED TO OTHER SIDE)
(1) FOLD
(LOWER EDGE OF SHEET)
(4) FOLD
(3) FOLD
(2) FOLD

FIG. 9B

Upper Border
(Upper edge of sheet is folded to other side)
① Fold
② Fold
Fold to Leaflet/cusp shape
Fold to Leaflet/cusp shape
Fold to Leaflet/cusp shape
Lower Border
(Lower edge of sheet)

FIG. 9C

Attorney Docket No.: 51458.010100

UTILITY PATENT APPLICATION DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

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

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

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

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

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

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

Prior Foreign Application(s):

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

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

Prior U.S. Application(s):

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

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

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

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

of

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1221 Brickell Avenue
Miami, Florida 33131

with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and all future correspondence should be addressed to him.

****

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Inventor's signature: Date: ____, 2003

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

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Citizenship: Mexico

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Full name of third joint inventor: Carlos Mejia

Inventor's signature: Date: _____ __, 2003

Address: _____

Citizenship: Colombia

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

Docket No. 51458.010100

CONTINUATION IN PART

NON-PROVISIONAL PATENT APPLICATION

SPECIFICATION

TO WHOM IT MAY CONCERN:

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

CONTINUITY INFORMATION

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

BACKGROUND OF THE INVENTION

[0001] 1. Field of the Invention

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

[0002] 2. Description of Related Art

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

SUMMARY OF THE INVENTION

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

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

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

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

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

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

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

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

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

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

DESCRIPTION OF A PREFERRED EMBODIMENT

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

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

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

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

Stent Member

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

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

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

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

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

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

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

Valve Means

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

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

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

Method of Making Replacement Heart Valve Device

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

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

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

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

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

Attachment of the Valve Means to the Stent Member

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

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

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

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

Implantation of Replacement Heart Valve Device

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CLAIMS

Having thus described the invention, what is claimed is:

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

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

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

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

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

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

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

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

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

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

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

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

obtaining a sheet of biocompatible tissue material;

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

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

drying said biocompatible tissue material;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ABSTRACT

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

PATENT APPLICATION SERIAL NO. _____

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

07/14/2004 MBELETE1 00000027 501792 10887688

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

PTO-1556
(5/87)

*U.S. Government Printing Office: 2002 — 489-267/69033

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2003

Application or Docket Number: 10887688

CLAIMS AS FILED - PART I

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

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

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

CLAIMS AS AMENDED - PART II

AMENDMENT A

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

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

AMENDMENT B

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

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

AMENDMENT C

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

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

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** 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."
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APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
10/887,688	07/10/2004	David Paniagua	51458.010100

CONFIRMATION NO. 4909

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

FORMALITIES LETTER

OC000000013837228

Date Mailed: 09/17/2004

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

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

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

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

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

N. Mohammed
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N. Mohammed

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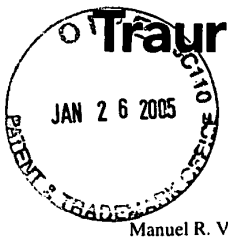
PART 1 - ATTORNEY/APPLICANT COPY

Greenberg Traurig



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

January 26, 2005

VIA EXPRESS MAIL

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

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

Dear Sir:

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

1. Copy of Notice to File Corrected Application Papers.

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

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

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

Respectfully submitted,

GREENBERG TRAURIG, P.A.

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

MRV
Enclosures

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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 51458-010100

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

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

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

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

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

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

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

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

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

I have enclosed a duplicate copy of this sheet.

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

☐ applicant.

☒ attorney or agent of record.

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

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

January 25, 2005
Date

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Manuel Valcarcel, Esq.
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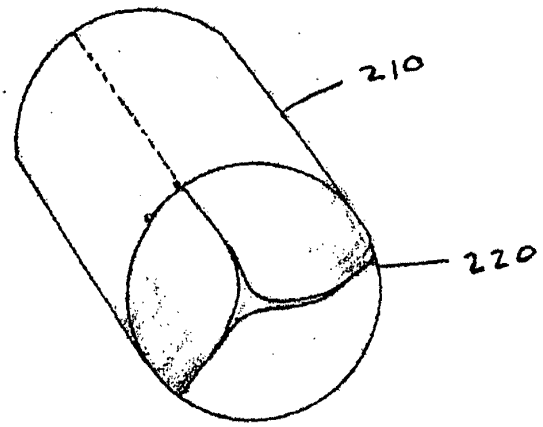

Fig. 1

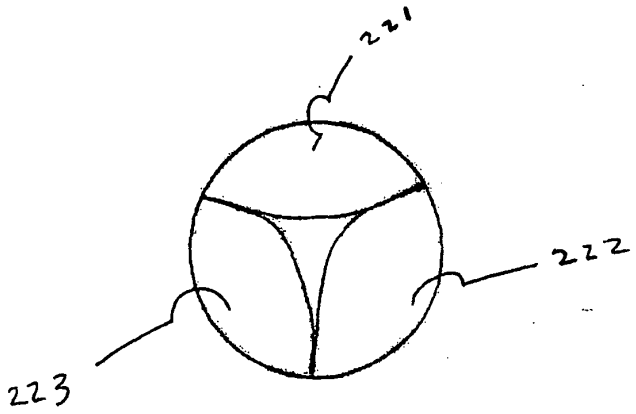

Fig. 2

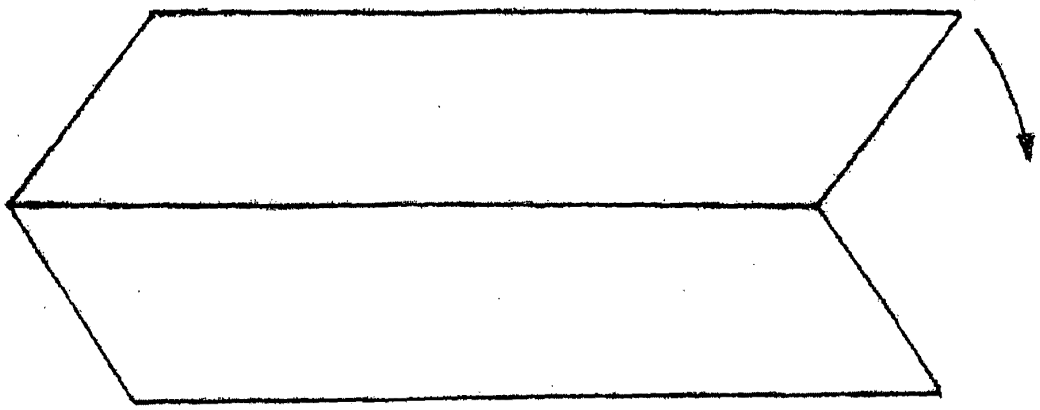

Fig. 3A

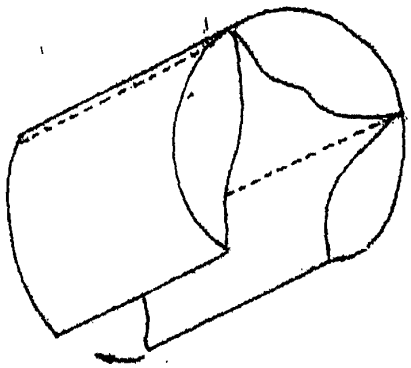

Fig. 3B

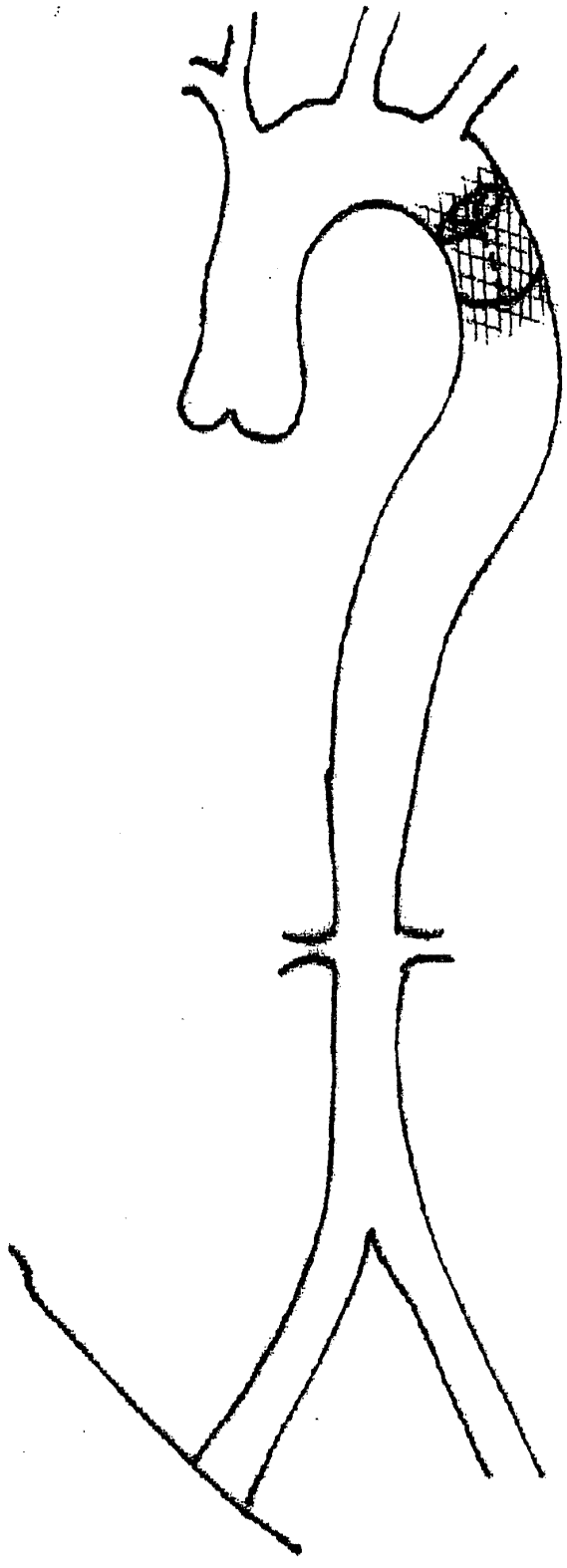

Fig. 4

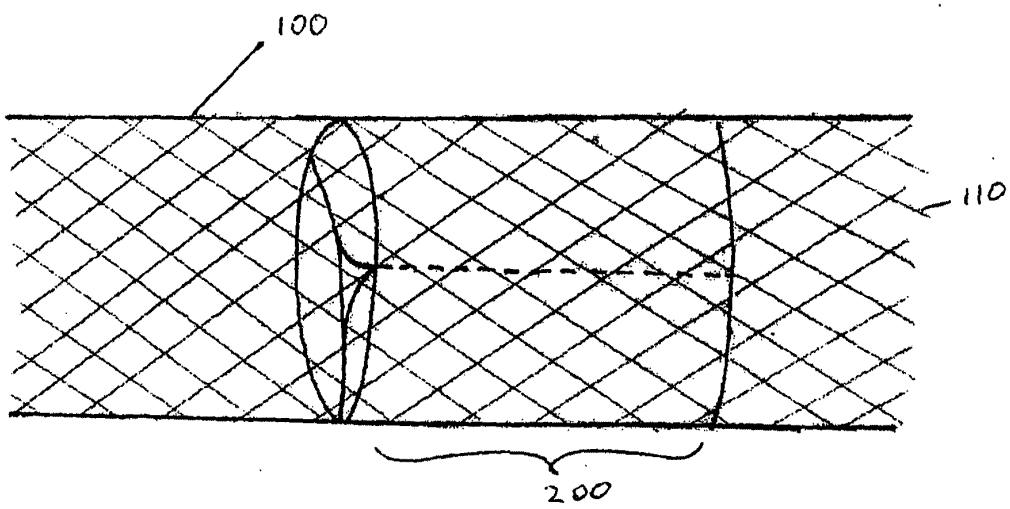

Fig. 5

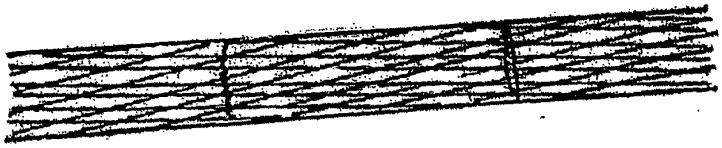

Fig. 6

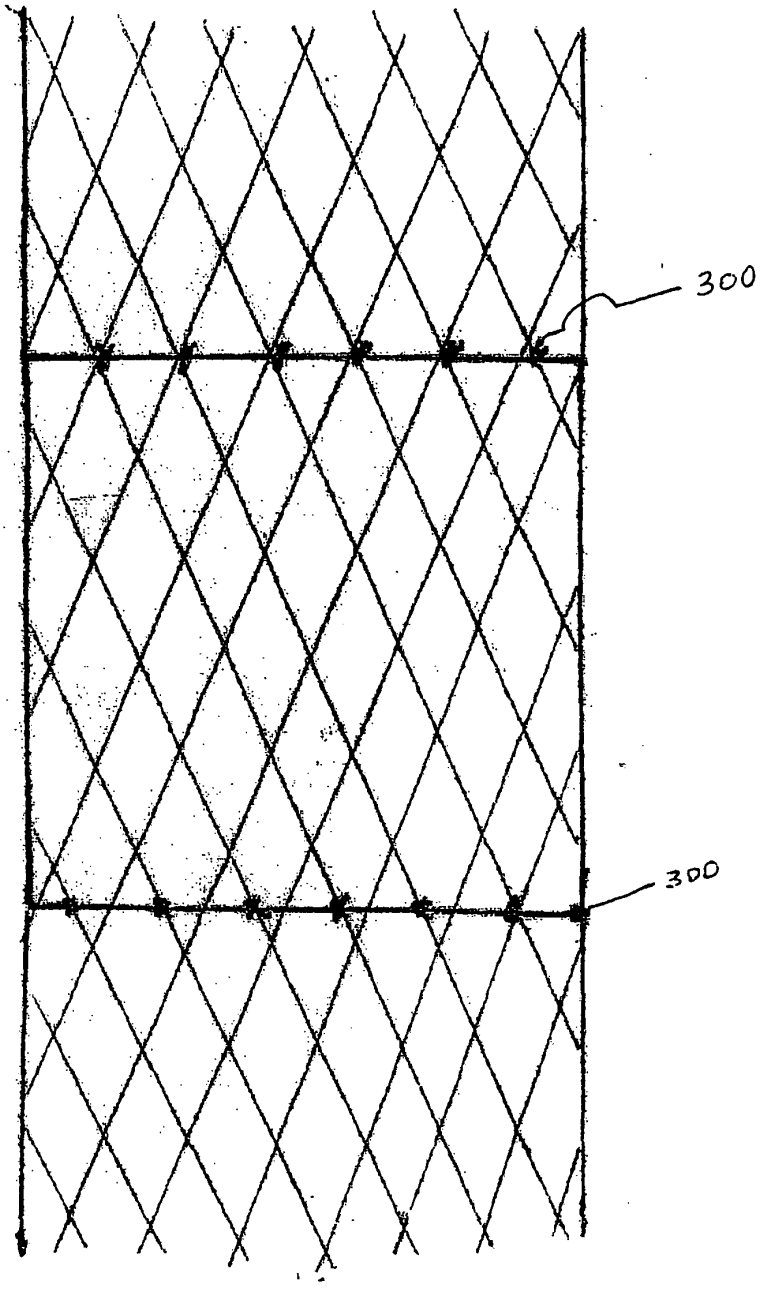

Fig. 7

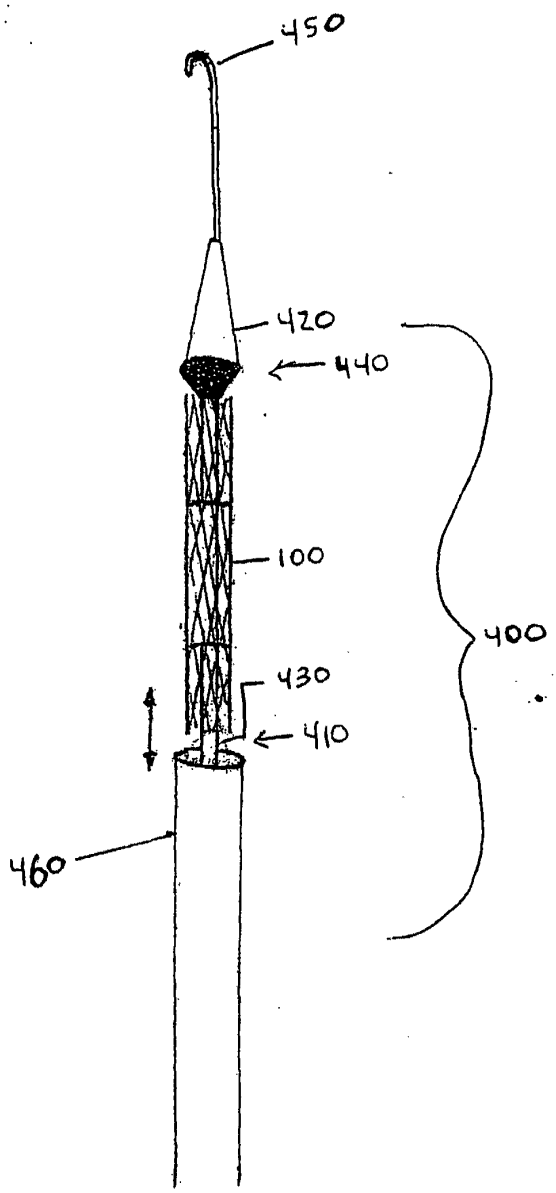

Fig. 8

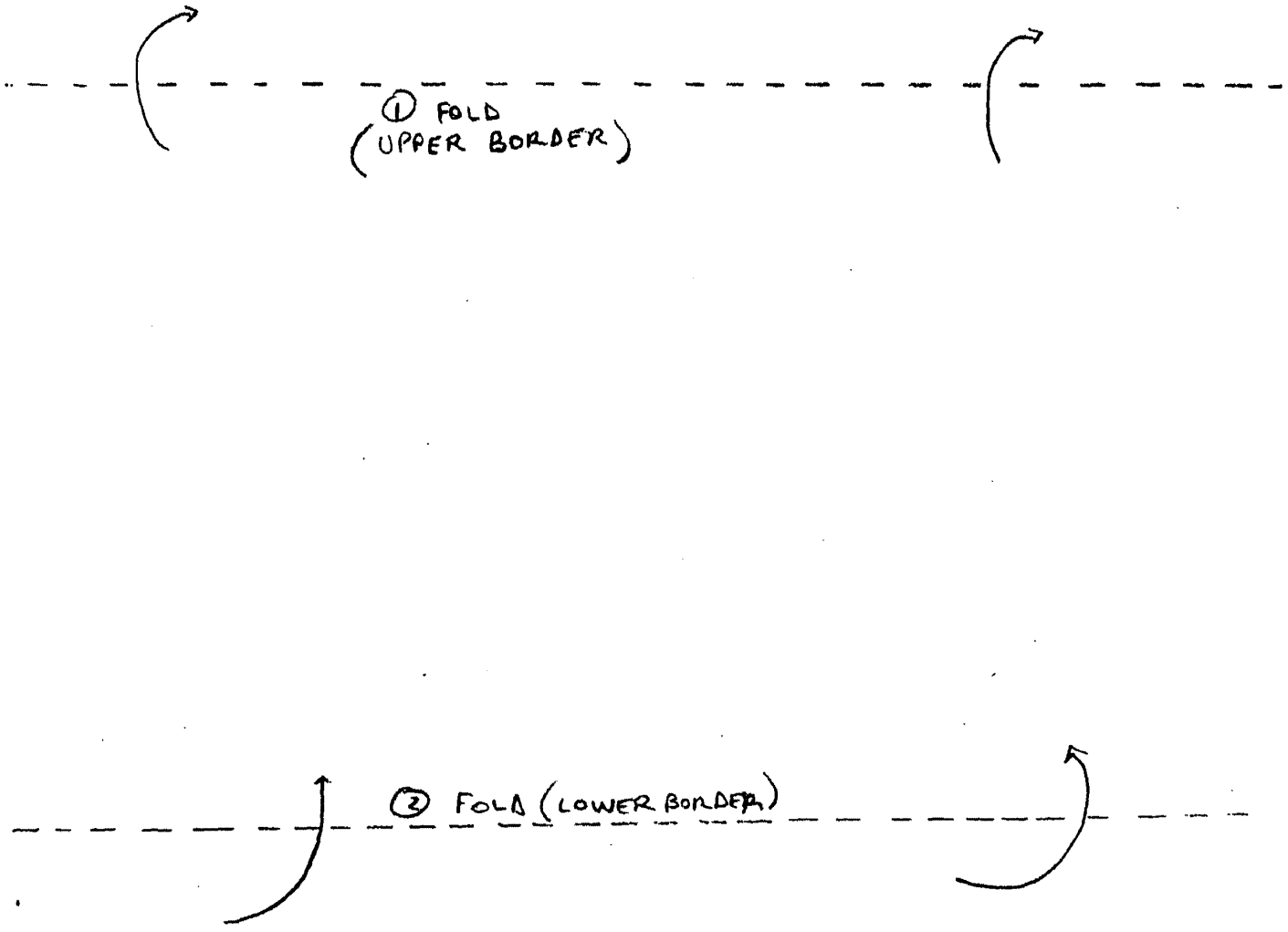

Fig. 9A

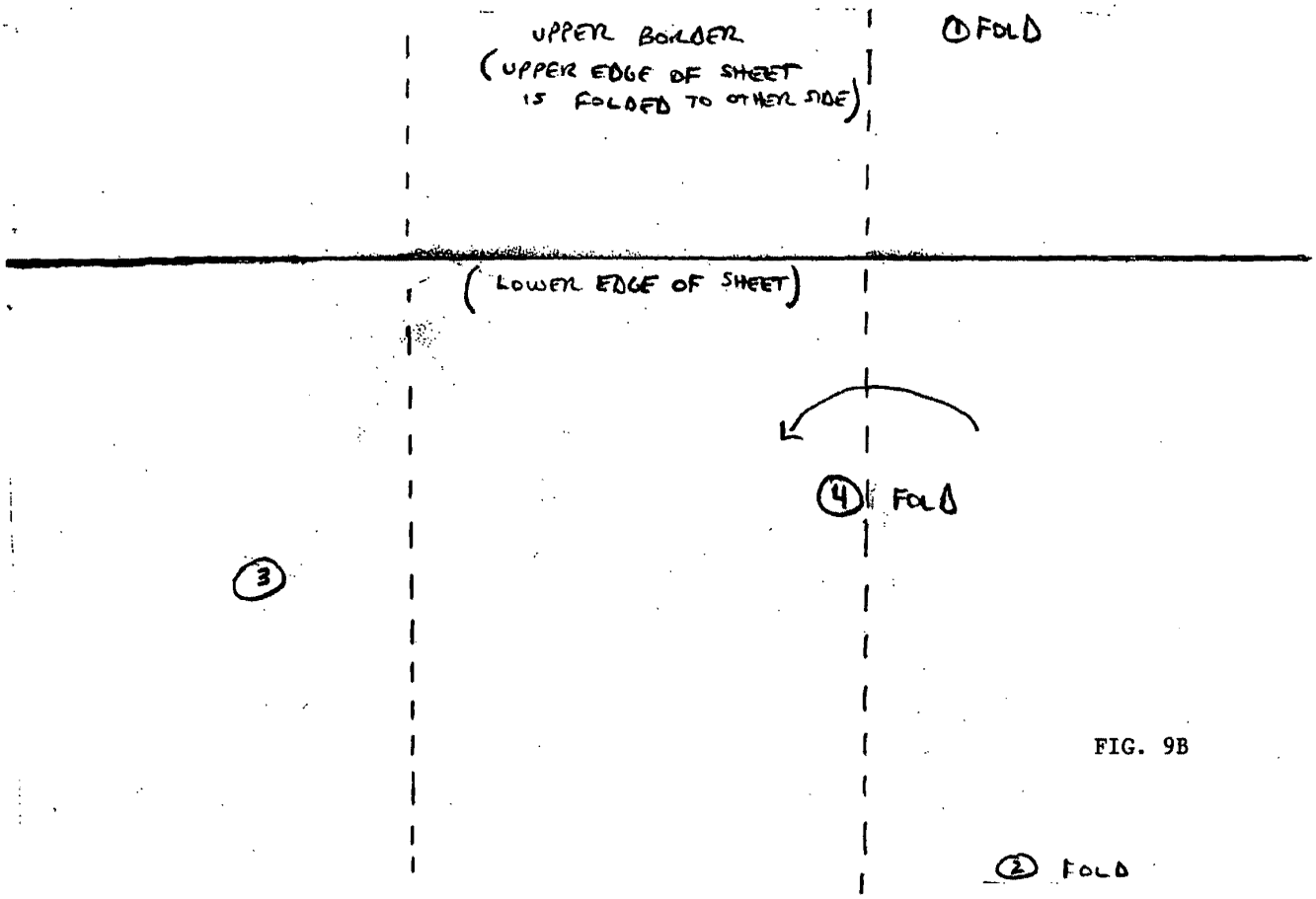
UPPER BORDER
(UPPER EDGE OF SHEET IS FOLDED TO OTHER SIDE)
① FOLD
(LOWER EDGE OF SHEET)
④ FOLD
③
② FOLD

FIG. 9B

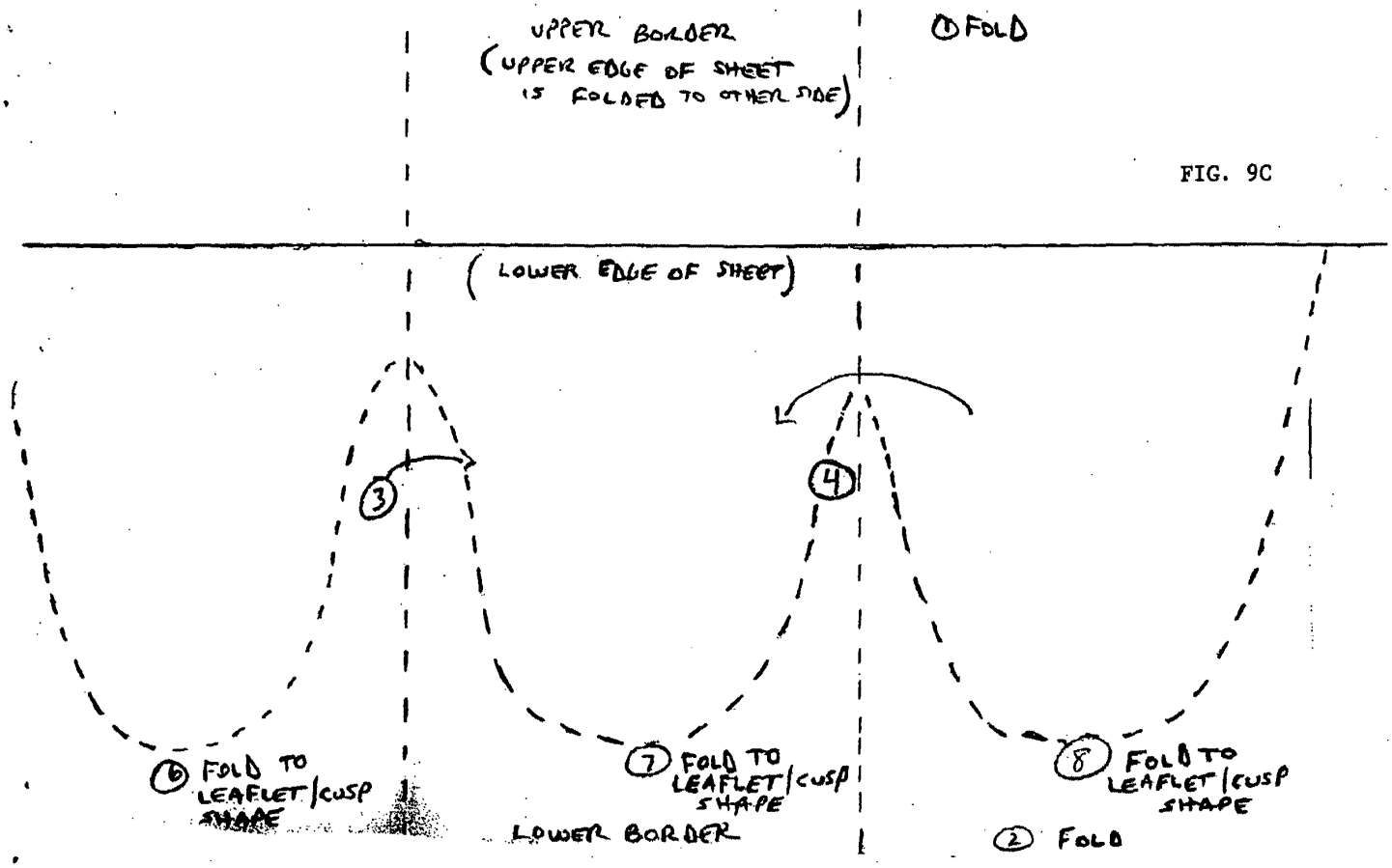
UPPER BORDER
(UPPER EDGE OF SHEET IS FOLDED TO OTHER SIDE)
① FOLD
(LOWER EDGE OF SHEET)
③
④
⑥ FOLD TO LEAFLET/CUSP SHAPE
⑦ FOLD TO LEAFLET/CUSP SHAPE
⑧ FOLD TO LEAFLET/CUSP SHAPE
LOWER BORDER
② FOLD

FIG. 9C

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

Correspondence Address / Fee Address Change

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

- Correspondence Address
- Maintenance Fee Address

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

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

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

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

54353 7590 09/14/2007

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

EXAMINER	
MILLER, CHERYL L	
ART UNIT	PAPER NUMBER
3738	

MAIL DATE	DELIVERY MODE
09/14/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2007*.

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

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

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

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

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

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

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

Application Papers

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

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

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

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Corrine McDermott can be reached on (571) 272-4755. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Cheryl Miller

BRUCE SNOW
PRIMARY EXAMINER

Greenberg Traurig

10-11-07

IFW

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

October 10, 2007

VIA EXPRESS MAIL

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

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

Dear Sir:

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

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

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

Respectfully submitted,

GREENBERG TRAURIG, P.A.

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

EXPRESS MAIL MAILING LABEL NO. EB 580600101 US

MRV/mam
Enclosures

cc: David Paniagua, M.D.

MIA 179764891v1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Examiner: Cheryl Miller
Group Art Unit 3738

RESPONSE TO OFFICE ACTION No. 1

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

Sir:

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

ELECTION OF CLAIMS

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

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AMENDMENTS TO THE CLAIMS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Remarks

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

Respectfully submitted,

Date: October 10, 2007

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

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

MIA 179765011v1

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PTO/SB/06 (07-06)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 10/887,688	Filing Date 07/10/2004	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☒		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

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

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
Linda Wise

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

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

54353 7590 11/28/2007

MANUEL VALCACEL
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MIAMI, FL 33131

EXAMINER	
MILLER, CHERYL L	
ART UNIT	PAPER NUMBER
3738	

MAIL DATE	DELIVERY MODE
11/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2007*.

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

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

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

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

5)☐ Claim(s) _____ is/are allowed.

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

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

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

Application Papers

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

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

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

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

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

Claim Rejections - 35 USC § 112

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

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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

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

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

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

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

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

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

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

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

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

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

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

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

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

Conclusion

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

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

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Corrine McDermott can be reached on (571) 272-4755. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cheryl Miller/

BRUCE SNOW
PRIMARY EXAMINER

Notice of References Cited	Application/Control No. 10/887,688	Applicant(s)/Patent Under Reexamination PANIAGUA ET AL.	
	Examiner Cheryl Miller	Art Unit 3738	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2003/0153974 A1	08-2003	Spenser et al.	623/2.11
*	B	US-6,652,578 B2	11-2003	Bailey et al.	623/1.24
*	C	US-2001/0010017 A1	07-2001	Letac et al.	623/2.11
*	D	US-6,491,719 B1	12-2002	Fogarty et al.	623/1.37
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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

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

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR

Greenberg Traurig

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02-29-08

IFW

February 27, 2008

VIA EXPRESS MAIL

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

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

Dear Sir:

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

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

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

Respectfully submitted,

GREENBERG TRAURIG, P.A.

by /MValcarcel/

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

EXPRESS MAIL MAILING LABEL NO. EH 041385288 US

MRV/mam
Enclosures

cc: David Paniagua, M.D.

MIA 179,967,083v1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Examiner: Cheryl Miller
Group Art Unit 3738

RESPONSE TO OFFICE ACTION No. 2

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

Sir:

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

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AMENDMENTS TO THE CLAIMS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

an expandable stent member having an inner space, and

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

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

Remarks

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

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

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

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

Respectfully submitted,

Date: February 27, 2008

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| MIA 179,917,332v1

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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

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

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

DECLARATION UNDER 37 CFR 1.131

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

Sir:

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

The undersigned co-inventors each hereby declare as follows:

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

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

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

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

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

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

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

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

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

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

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

DAVID PANIAGUA

Signature: _____

Date: January 18, 2008

ACKNOWLEDGEMENT

COUNTY OF Brazoria)
) SS:
STATE OF Texas)

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

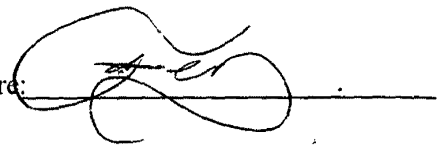
Notary: Janice D Kelley
Print Name: Janice D Kelley

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

My commission expires:

JANICE D. KELLEY
MY COMMISSION EXPIRES
JULY 21, 2009

FRANCISCO LOPEZ-JIMENEZ

Signature: 

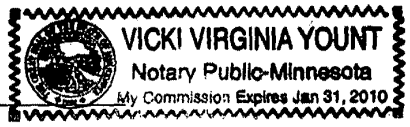
Date: January 18, 2008

ACKNOWLEDGEMENT

COUNTY OF Olmsted)
) SS:
STATE OF Minnesota)

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

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



My commission expires: January 31, 2010

CARLOS MEJIA

Signature: Carlos Mejia

Date: January 21st, 2008

ACKNOWLEDGEMENT

COUNTY OF Brazoria)
) SS:
STATE OF Texas)

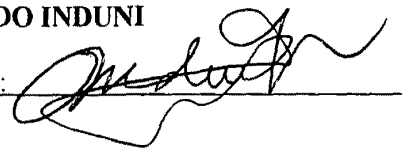
The foregoing Declaration was signed before me this 21st day of January, 2008 by Carlos Mejia. He is personally known to me or has produced Drivers License as identification.

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

My commission expires: 7/21/09

JANICE D. KELLEY
MY COMMISSION EXPIRES
JULY 21, 2009

EDUARDO INDUNI

Signature: 

Date: January 18, 2008

ACKNOWLEDGEMENT

COUNTY OF _____)
) SS:
STATE OF _____)

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

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

My commission expires:

R. DAVID FISH

Signature: RDFish

Date: January 18, 2008

ACKNOWLEDGEMENT

COUNTY OF Brazoria)
) SS:
STATE OF Texas)

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

Notary: Janice D Kelley
Print Name: Janice D Kelley

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

My commission expires:

MIA 179,917,544v1

JANICE D. KELLEY
MY COMMISSION EXPIRES
JULY 21, 2009

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

[redacted]

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

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

[redacted]

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

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

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

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

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

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

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

[redacted]

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

Porcine pulmonary valve

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

Limitations Still bulky

Porcine aortic valve

Limitations Still bulky and the ostium of both coronaries

Bovine pericardium

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

<u>The bovine pericardium</u>

Design

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

The process of management of the pericardium

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

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

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

Dry process

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

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

Then we try ironing and it shrinks to much and corrugate

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

We also tried to photo drying machine

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

Hydrating process

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

Converting the pericardium into a valve

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

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

See diagrams

Types of sutures

Sutures planes

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

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

6-point fixation at each border of the stent

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

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

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

Hooks to the arterial wall Like the Ancure

Double stents

Acute Doppler studies in vitro

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

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

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

See video

October 5th to 11th 2000

We studied different ways to fix the pericardium.

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

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

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

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

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

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

Delivery device

Chronic studies in vitro

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

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

Histological studies

Preservation of the pericardium several month in ETOH

Glutaraldehido

[redacted]

E-mails

[redacted]

Materials

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

Heparin Plavix for the animal

Surgical equipment

Echo Doppler

OR equipment cri solution

Injector X ray tech
Person in charge of anesthesia, monitoring

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

Ventilators Lamps

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

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

[redacted]

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

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

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

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

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

We are going to make two valves

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

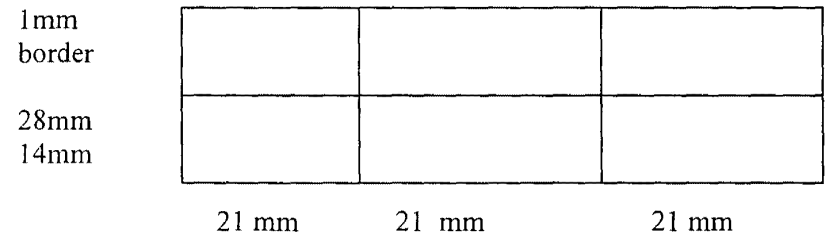
December 2 2000

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

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

January 2001

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



1 mm at each end to suture the valve.

February 2001

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

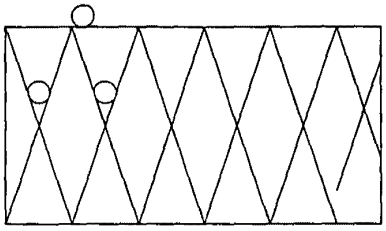
[redacted]

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

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

We eliminate the folds at each end of the valve.

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



○ Fixation points

18 fixation points at each plane

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

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

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

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

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

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

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

March 24, 2001

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

We will perform collapsibility test of the valve.

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

April 21, 2001

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

June 9, 2001

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

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

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

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

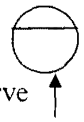
We tried the aortic valvuloplasty balloon to test if it can be used to expand the distal end of the stented valve in the case this extreme does not open.

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

June 12, 2001

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

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



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

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

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

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

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

June 13 2001

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

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

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

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

June 16 2001

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

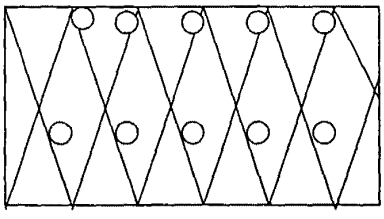
We developed a temporary delivery system that consisted of a central catheter big enough to let a 0.38 wire pass through its lumen, a cover sheath made of plastic material with a sliding device that allows to expose the stented valve.

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

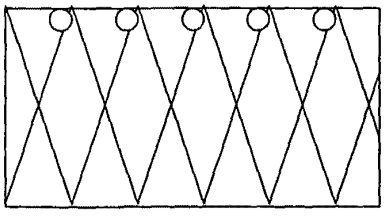
The other observation is that two planes of fixation point at the distal attachment of the valve to the stent causes a lot of tension to the valve when we are collapsing it.

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

Proximal fixation points / expanded



Proximal fixation points sliding down



when stent collapses

○ ○ ○ ○ ○

○ Fixation points

18 fixation points at each plane

June 29, 2001

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

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

September 8

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

September 22

The valve is mounted in the chronic testing model

Description of the model

United States Patent

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

PERCUTANEOUS VALVE REPLACEMENT

Abstract

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

The valve replacement system includes the following components:

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

Inventors:

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

Exhibit B

U.S. Patent Documents

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

Foreign Patent Documents

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

Claims

What is claimed is:

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

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

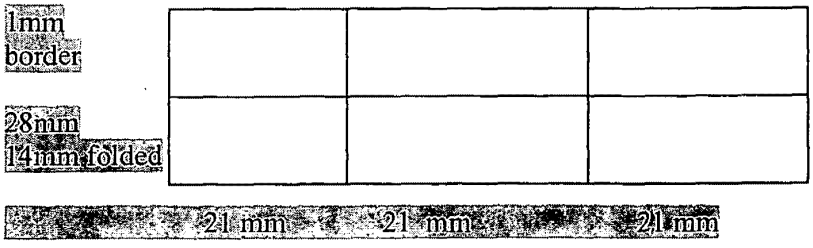
a - The delivery system has a central part which consist of a hollow tube that allows a metallic wire to be advanced inside it. The stented valve is collapsed over this central metallic tubing and it is covered by a movable sheath. The sheath keeps the stented valve in the collapsed position. Once the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

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

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

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

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



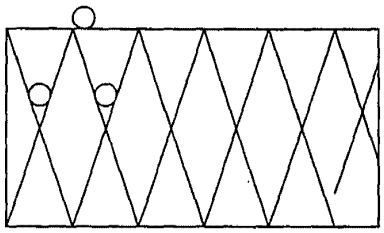
1 mm at each end to suture the valve.

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

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

We eliminate the folds at each end of the valve.

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



○ Fixation points

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

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

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

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

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

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

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

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

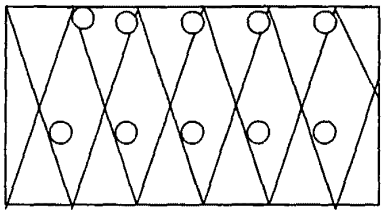
The new valve design includes the creation of a curve in each cusp of the valve

Curve

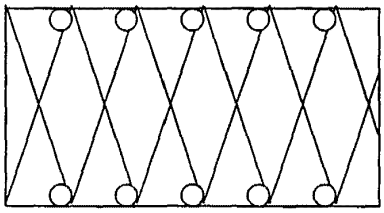
We also used straight suture lines of the cusp.
The other observation is that two planes of fixation point at the distal attachment of the the valve to the stent causes a lot of tension to the valve when we are collapsing it.

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

Proximal fixation points / expanded



Proximal fixation points sliding down when stent collapses



○ Fixation points

18 fixation points at each plane

NEEDS DETAIL DESCRIPTION OF WHAT IS CLAIM

DESCRIPTION

FIELD OF THE INVENTION

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

BACKGROUND

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

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

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

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

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

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

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

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

RELEVANT LITERATURE

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

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

SUMMARY OF THE INVENTION

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

The valve replacement system includes the following components:

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

DESCRIPTION OF THE DRAWINGS

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

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

FIG. 3 illustrates a bottom view of stented valve.

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

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

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

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

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

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

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

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

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

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

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

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

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

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

GENERAL DESCRIPTION OF THE PROCEDURE

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

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

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

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

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

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

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

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

* * * * *

GREENBERG
ATTORNEYS AT LAW
TRAURIG

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

ATTORNEY-CLIENT PRIVILEGED
CONFIDENTIAL INFORMATION

August 29, 2001

VIA FACSIMILE (703) 413-4150
AND FED EX

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

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

Dear Mr. Miller:

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

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

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

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

Exhibit C

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

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

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

B. Implantation Method.

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

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

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

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

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

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

Sincerely,

GREENBERG TRAURIG, P.A.

Manuel R. Valcarcel, Esq.

MRV/ps

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

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

ATTORNEY-CLIENT PRIVILEGED
CONFIDENTIAL INFORMATION

August 29, 2001

VIA FACSIMILE (703) 413-4150
AND FED EX

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

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

Dear Mr. Miller:

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

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

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

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ATTORNEYS AT LAW
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Manuel R. Valcarcel
(305) 579-0812

November 27, 2001

ATTORNEY-CLIENT PRIVILEGED
CONFIDENTIAL COMMUNICATION

VIA HAND DELIVERY

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

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

Dear Dr. Paniagua:

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

Best regards,

GREENBERG TRAURIG, P.A.

Manuel R. Valcarcel, Esq.

MRV/ps
Enclosures

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

Exhibit D

Docket No. 51458.010100

NON-PROVISIONAL PATENT APPLICATION

SPECIFICATION

TO WHOM IT MAY CONCERN:

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

BACKGROUND OF THE INVENTION

1. Field of the Invention

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

2. Description of Related Art

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

SUMMARY OF THE INVENTION

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

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

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

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

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

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

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

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

DESCRIPTION OF A PREFERRED EMBODIMENT

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

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

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

Stent Member

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

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

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

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

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

Valve Means

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

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

Method of Making Replacement Heart Valve Device

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

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

Attachment of the Valve Means to the Stent Member

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

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

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

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

Implantation of Replacement Heart Valve Device

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CLAIMS

Having thus described the invention, what is claimed is:

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

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

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

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

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

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

obtaining a substantially rectangular segment of biocompatible tissue material;

soaking said biocompatible tissue material in a gluteraldehyde solution;

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

drying said biocompatible tissue material;

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

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

ABSTRACT

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

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December 28, 2001

ATTORNEY-CLIENT PRIVILEGED
CONFIDENTIAL COMMUNICATION

VIA HAND DELIVERY

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

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

Dear Dr. Paniagua:

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

Best regards,

GREENBERG TRAURIG, P.A.

Manuel R. Valcarcel, Esq.

MRV/mp

Enclosure

\\MIA-SRV01\VALCARCELM\1359513v01\12/28/01\51458.010100

Docket No. 51458.010100

NON-PROVISIONAL PATENT APPLICATION

SPECIFICATION

TO WHOM IT MAY CONCERN:

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

BACKGROUND OF THE INVENTION

1. Field of the Invention

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

2. Description of Related Art

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

SUMMARY OF THE INVENTION

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

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

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

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

Fig. ~~4~~**5** depicts a side ~~perspective~~-view of **one embodiment of** the replacement heart valve **device** of the present invention ~~in one embodiment~~-mounted within a **self-expanding** stent**, with the stent in the expanded position**.

Fig. ~~5~~**6** depicts a ~~cross-sectional~~**side perspective** view of one embodiment of the replacement heart valve **device** of the present invention mounted within a self-expanding stent~~, with the stent~~ in the ~~expanded~~**collapsed** position.

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

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

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

DESCRIPTION OF A PREFERRED EMBODIMENT

The present invention comprises a percutaneously implantable replacement heart valve and a method for making same. The artificial heart valve device of the present invention is capable of exhibiting a variable diameter between a compressed or collapsed position and an expanded position. A preferred embodiment of the replacement heart valve device according to the present invention is set forth in ~~FIGS~~FIG. ~~1 and 2.~~5. The replacement heart valve device comprises a stent member ~~—~~100 and a flexible valve means ~~—~~200. The stent member 100 is preferably self-expanding although balloon-expandable stents can be used as well, and has a first cylindrical shape in its compressed or collapsed configuration and a second, larger cylindrical shape in its expanded configuration. ~~The~~Referring to FIG. 1, the valve means 200 comprises a generally tubular ~~center~~ portion 210 and, preferably, a peripheral upstanding cusp or leaflet portion~~.~~ 220. The valve means 200 is disposed within the cylindrical stent member 100 with the tubular portion 210 transverse of and at some acute angle relative to the stent walls. The diameter of the tubular portion 210 is substantially the same as the inside diameter of the stent member in its initial expanded configuration. The peripheral upstanding cusp or leaflet portion 220 is disposed substantially parallel to the walls of the stent member similar to a cuff on a shirt. The ~~center~~cusp or leaflet portion ~~—~~220 of the valve means ~~—~~200

is generally tubular in shape and comprises three leaflets —221, 222 and 223 as shown, although it is understood that there could be from two to four leaflets. The tubular portion of the valve means 200 is attached to the stent member —100 by a plurality of sutures —300, as depicted in FIG. 7.

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

Stent Member

The stent member —100 preferably comprises a self-expanding nickel-titanium alloy stent, also called "nitinol," in a sine wave-like configuration as shown in FIG. ~~1.~~5. An enlarged view of a preferred embodiment of the stent member for use in the replacement heart valve of the invention is depicted in FIG. 5. The stent member —100 includes a length of wire —110 formed in a closed zigzag configuration. The wire can be a single piece, stamped or extruded, or it could be formed by welding the free ends together ~~as at~~—. The straight sections —of the stent member 100 are joined by bends—. The stent is readily compressible to a small cylindrical shape as depicted in FIGS. 6 and 8, and resiliently self-expandable to the shape shown in FIG. 5.

The stent ~~members~~member 100 of the artificial heart ~~valves~~valve device of the present invention may be made from various metal alloys, titanium, titanium alloy, nitinol,

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

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

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

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

Valve Means

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

The cusp or leaflet portion 220 of the valve means 200 is formed by folding of the pericardium material used to create the valve. FIGS. 3A and 3B depict the way the sheet of heart valve starting material is folded. The cusps/leaflets 221, 222 and 223 open in

response to blood flow in one direction and close in response to blood flow in the opposite direction. Preferably the ~~tubular~~cusp or leaflet portion 220 of the valve means 200 contains the same number of cusps as the native valve being replaced, in substantially the same size and configuration.

Method of Making Replacement Heart Valve Device

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

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

Attachment of the Valve Means to the Stent Member

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

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

Different suture materials can be used, including, in a preferred embodiment, prolene 6-0 and Mersilene 6-0 which is a braided suture.

Implantation of Replacement Heart Valve Device

The replacement heart valve device of the present invention is preferably used in surgical procedures involving the percutaneous and transluminal removal of the diseased or defective heart valve and the percutaneous and transluminal implantation of the new heart

valve described above. The defective heart valve is removed by a suitable modality, such as, for example, laser, ultrasound, mechanical, or other suitable forms of delivery of energy, or phacoemulsion, including, but not limited to, laser lithotripsy, mechanical lithotripsy, electrohydraulic lithotripsy, and laser or mechanical ablation. To remove the native heart valve that is being replaced, a guidewire is inserted percutaneously and transluminally using standard vascular or angiography techniques. The distal end of the guidewire is manipulated to extend through and across the defective heart valve. Then a catheter is advanced distally through the femoral artery to a point proximal to the defective heart valve, between the origin of the coronary artery and the origin of the right subclavian artery. The position of the distal end of catheter can be monitored by observation of radiopaque markers. Collector member is preferably inflated and occludes the aorta at a point between the origin of the coronary artery and the right subclavian artery. Next, a balloon and cutting tool are advanced through the catheter so that the cutting tool and uninflated balloon are distal to the defective heart valve. Optionally an additional step, such as balloon dilatation or atherectomy, may be required to provide a passageway through the heart valve. A catheter is also placed into the coronary sinus via a transjugular puncture. This catheter is used for infusion of blood or cardioplegia solution during the portion of the procedure when the aorta is occluded. The absence of valves in the cardiac venous system allows retrograde flow so that there will be an effluence of fluid from the coronary arteries. This flow of fluid is desired to prevent embolization of material into the coronary arteries during the procedure. Once the cutting tool is in place, the balloon is inflated and flexible shaft is rotated. Once the cutting tool has reached the appropriate rotation speed, the cutting tool is pulled proximally to remove the defective heart valve. The balloon and the cutting tool are spaced apart so that the inflated balloon will be stopped by the perimeter, unremoved portion of the defective heart valve, which will signal the physician that the valve has been removed, as well as protect the heart and aorta from damage from the valve removal

device. Once it is determined that the defective heart valve has been removed, the cutting tool is slowed or stopped altogether and the balloon is deflated. The cutting tool and the deflated balloon are pulled proximally through catheter. Then, a catheter containing an artificial heart valve is inserted and the artificial heart valve is placed as described above.

The delivery and implantation system of the replacement artificial heart valve of the present invention percutaneously and transluminally includes a flexible catheter **400** which may be inserted into a vessel of the patient and moved within that vessel **as depicted in FIG. 8.** The distal end **410** of the catheter~~, 400,~~ which is hollow and carries the replacement heart valve **device** of the present invention in its collapsed configuration, is guided to a site where it is desired to implant the replacement heart valve. The catheter has a pusher member **420** disposed within the catheter lumen **430** and extending from the proximal end **440** of the catheter to the hollow section at the distal end **410** of the catheter. Once the distal end **410** of the catheter is positioned as desired, the pusher mechanism **420** is activated and the distal portion of the replacement heart valve **device** is pushed out of the catheter and the stent member **100** partially expands. In this position the stent member **100** is restrained so that it doesn't pop out and is held for controlled release, with the potential that the replacement heart valve **device** can be recovered if there is a problem with the positioning. The catheter **400** is ~~them~~**then** retracted slightly and the replacement heart valve **device** is completely pushed out of the catheter **400** and released from the catheter to allow the stent member **100** to fully expand. If the stent member **100 preferably** includes two circles of barbs on its outer surface as previously described, the first push and retraction will set one circle of barbs in adjacent tissue and the second push and release of the replacement heart valve **device** will set the other circle of barbs in adjacent tissue and securely fix the replacement heart valve **device** in place when the ~~valve~~**device** is released from the catheter.

Alternatively, or in combination with the above, the replacement heart valve **device** could be positioned over a metallic guidewire that is advanced through the catheter. The replacement heart valve device of the present invention is preferably implanted percutaneously through an aortic passageway to, or near to, the location from which the natural heart valve has been removed. Referring to ~~Fig~~**FIG**. 8, the implantation system comprises a flexible hollow tube catheter **410** with a metallic guide wire **450** disposed within it. The stented valve **device** is collapsed over the tube and is covered by a moveable sheath **460**. The moveable sheath **460** maintains the stented valve **device** in the collapsed position. **The implantation method** comprises the following steps: inserting the replacement heart valve device in the lumen of a central blood vessel via entry through the brachial or femoral artery using a needle or exposing the artery surgically; placing a guide wire **450** through the entry vessel and advancing it to the desired position; advancing dilators over the wire to increase the lumen of the entry site, thereby preparing the artery to receive the heart-valve; and advancing the heart-valve **device** to the desired place. The stented-valve **device** is released by pulling the cover sheath **460** of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advanced over the wire and an aortogram is performed to assess the competency of the valve.

Before creation of the valve means and implantation, the patient is studied to determine the architecture of the patient's heart. Useful techniques include fluoroscopy, transesophageal echocardiography, MRI, and angiography. The results of this study will enable the physician to determine the appropriate size for the replacement heart valve.

In one procedure for implantation of the replacement heart valve device of the present invention, the femoral artery of the patient is canulated using a Cook needle and a standard J wire is advanced into the artery either percutaneously or after surgical exposure of the artery. An 8 F introducer is advanced into the femoral artery over the wire. The J wire is then

withdrawn and anticoagulation is started using heparin 60 U/Kg intravenously. Once vascular access is obtained an aortogram is performed for anatomical evaluation. A special wire (Lunderquist or Amplatz superstiff) is advanced into the aortic arch and dilators progressively larger are advanced over the wire, starting with 12 F all the way to 18 F. After this the valve introducer device containing the prosthetic valve device is then inserted and used to transport the replacement valve over a guidewire to the desired position. The stented-valve is released by pulling the cover sheath of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advanced over the wire and repeat aortogram is performed to assess the competency of the valve.

When the device is used to treat severe leakage of the aortic valve, the native valve is left in place and the prosthetic stented valve is deployed below the subclavian artery. When the device is used to treat aortic stenosis, first the stenotic valve needs to be opened using either aortic valvuloplasty or cutting and if this procedure induces aortic insufficiency the stented valve is placed to prevent the regurgitation.

Intravascular ultrasound or an angioscope passed intravascularly via either the venous system through the intra-atrial septum across the mitral valve and into the left ventricle or retrograde via the femoral artery would provide the added benefit of allowing constant high definition imaging of the entire procedure and high flow irrigation.

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The prosthetic valve device can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and

patients unable to tolerate open heart procedures or life-long anticoagulation. In addition, with the development of longer-life, flexible, non-thrombogenic synthetic valve alternatives to bioprosthesis, the prosthetic valve device will be indicated in all patients where the relative advantages of the life-span, the non-thrombogenic quality, and the ease of insertion of prosthetic valve devices outweigh the disadvantages of mechanical valves. Anticoagulation may be beneficial in certain clinical situations for either short or long term use.

This method of percutaneous endovascular heart-valve replacement, in contrast to open heart surgical procedures, requires only local anesthesia, partial or no cardiac bypass, one to two days hospitalization, and should result in a reduced mortality rate as compared to open heart procedures.

While the present invention has been shown and described herein in what is considered to be a preferred embodiment thereof, illustrating the results and advantages over the prior art obtained through the present invention, the invention is not limited to the specific embodiments described above. Thus, the forms of the invention shown and described herein are to be taken as illustrative and other embodiments may be selected without departing from the spirit and scope of the present invention.

CLAIMS

Having thus described the invention, what is claimed is:

1. A percutaneously implantable replacement heart valve device comprising a ~~self-expanding~~-stent member and an artificial valve means made of biocompatible tissue material and disposed within the inner cavity of said stent member affixed at one or more points to said stent member, said valve means having cusps or leaflets formed by folding of **a substantially rectangular sheet of** said biocompatible tissue material.

2. The percutaneously implantable replacement heart valve **device** of claim 1, wherein said stent member is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium, stainless steel **[add others]**.

3. The percutaneously implantable replacement heart valve **device** of claim 1, wherein said biocompatible tissue material of said valve means comprises bovine pericardium tissue.

4. The percutaneously implantable replacement heart valve **device** of claim 1, wherein said biocompatible tissue material of said valve means comprises porcine pericardium tissue.

5. The percutaneously implantable replacement heart valve **device** of claim 1, wherein said biocompatible tissue material of said valve means comprises autologous tissue obtained from the patient into whom said replacement heart valve **device** will be implanted.

6. The percutaneously implantable heart valve device of claim 1, wherein said stent member is self-expanding when implanted.

7. The percutaneously implantable heart valve device of claim 1, wherein said stent member is balloon catheter expandable when implanted.

~~6.~~8. A method of making a percutaneously implantable replacement heart valve device comprising the following steps:

obtaining a substantially rectangular ~~segment~~sheet of biocompatible tissue material;

soaking said biocompatible tissue material in a gluteraldehyde solution;

transferring said biocompatible tissue material from said gluteraldehyde solution to an ethanol solution;

drying said biocompatible tissue material;

folding said dried biocompatible tissue material to create cusps or leaflets and a cuffed tubular valve structure;

affixing said folded biocompatible tissue material to the inner cavity of a stent.

9. The method of making a percutaneously implantable replacement heart valve device claim 8, wherein said biocompatible tissue material comprises bovine pericardium tissue.

10. The method of making a percutaneously implantable replacement heart valve device claim 8, wherein said biocompatible tissue material comprises porcine pericardium tissue.

11. The method of making a percutaneously implantable replacement heart valve device claim 8, wherein said biocompatible tissue material comprises autologous tissue obtained from the patient into whom said replacement heart valve device will be implanted.

12. The method of making a percutaneously implantable replacement heart valve device of claim 8, wherein said stent is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium, stainless steel, [add others].

13. The method of making a percutaneously implantable replacement heart valve device of claim 8, wherein said stent is self-expanding when implanted.

14. The method of making a percutaneously implantable replacement heart valve device of claim 8, wherein said stent is balloon catheter expandable when implanted.

ABSTRACT

The present invention comprises a percutaneously implantable replacement heart valve device and a method of making same. The replacement heart valve device comprises a stent member made of stainless steel or self-expanding nitinol, a biological tissue artificial valve means disposed within the inner space of the stent member. An implantation and delivery system having a central part which consists of a flexible hollow tube catheter that allows a metallic wire guide to be advanced inside it. The endovascular stented-valve is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow. The present invention also comprises a novel method of making a replacement heart valve by taking a rectangular fragment of bovine pericardium treating, drying, folding and rehydrating it in such a way that forms a two- or three-leaflet/cusp valve with the leaflets/cusps formed by folding, thereby eliminating the extent of suturing required, providing improved durability and function.

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 10/887,688	Filing Date 07/10/2004	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☒		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
	02/28/2008	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	* 36	Minus	** 33	= 3	X $25 =	75	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 8	Minus	***5	= 3	X $105 =	315	OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE	390	OR	TOTAL ADD'L FEE	

		(Column 1)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/JOY DOBBS/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/887,688	07/10/2004	David Paniagua	51458.010100	4909

54353 7590 07/15/2008

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EXAMINER	
MILLER, CHERYL L	
ART UNIT	PAPER NUMBER
3738	

MAIL DATE	DELIVERY MODE
07/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/887,688	PANIAGUA ET AL.	
	Examiner	Art Unit	
	CHERYL MILLER	3738	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *11-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 27-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

This application repeats a substantial portion of prior Application No. 10/037,266, filed January 4, 2002, and adds and claims additional disclosure not presented in the prior application. Since this application names an inventor or inventors named in the prior application, it may constitute a continuation-in-part of the prior application. Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78. Added subject new to the current application includes: the sheet material being *unslit* and *without affixing separate cusps* (claims 1, 33, and 36), the material to be made of *metals* (claim 8), a *second sheet* forming a *cuff* (claim 27), and the configuration and formation of multiple folds (claims 34, 35). All this subject matter has been given the priority date of July 10, 2004 as it was not found in the parent application.

Response to Amendment

The declaration filed on February 28, 2008 under 37 CFR 1.131 has been considered but is ineffective to overcome the Spenser (US 2003/0153974 A1) and Bailey (US 6,652,578 B2) references.

Although all inventors signatures are present in the declaration, the signature of Eduardo Induni was not singed before a notary public, thus the declaration is insufficient for this reason. See MPEP 715.04 [R-6], I, II.

The evidence submitted is additionally insufficient to establish a conception of the invention prior to the effective date of the Bailey reference. While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a

complete disclosure to another. Conception is more than a vague idea of how to solve a problem. The requisite means themselves and their interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897). Although the exhibits disclose general recitation of a "new valve" and details of the material used and how it is chemically treated, there is no evidence of the actual structure of the valve (location of the fold, how it is shaped or what it looks like). There is reference to diagrams or figures in Exhibit A, however no figures were found attached. It is not clear that applicants had support for the fold and location of the fold, non-slit and not separate attached leaflets that are claimed, at the time prior to December 31, 1999. The declaration is therefore insufficient to overcome the Bailey reference.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7 and 8 are indefinite since the independent claims require the valve to be a *tissue* material (natural) and claims 7 and 8 are attempting to alter the claim to make the material synthetic (non tissue). It is unclear how the material may be tissue and also synthetic at the same time.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 7-10, 27, 30, and 33-36 are rejected under 35 U.S.C. 102(e) as being anticipated by Bailey et al. (US 6,652,578, cited previously). Bailey discloses an implantable heart valve (fig.2, 8, 14) comprising an expandable stent (12) and an inner flexible compressible valve (26) made of biocompatible tissue (col.8, lines 47-49) disposed within the stent (12) and affixed to the stent (col.9, lines 55-59) the valve having leaflets without slits (see fig.2; valve body disclosed as a tubular graft extension, col.9, lines 7-26). Bailey discloses the stent (12) to be made of the materials claimed (nitinol; col.8, lines 13-18). Bailey discloses the valve to be formed of biological or synthetic materials (col.8, lines 46-49). Bailey's valve is capable of self-expansion or balloon expansion (col.8, lines 13-18). Bailey discloses an outer cuff portion (considered 11a). Bailey discloses the sheet of tissue (11b) having an upper border (top of device in fig.4) with an outward fold (material 11b is folded outwardly at 11a) and a lower border (bottom of 11b in fig.4) having an inward fold (inward fold considered 26). See col.9, lines 27-32.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-6, 28-29 and 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bailey et al. (US 6,652,578 B2, cited previously). Referring to claims 3-6, Bailey discloses an implantable valve, the valve being formed of either biological tissue or biocompatible synthetic polymer (col.8, lines 46-49). Bailey does not however, disclose a specific type of biological material (such as claimed, mammal, porcine, or juvenile pericardium or PTFE or polyester biopolymers). It would have been obvious to one having ordinary skill in the art at the time the invention was made to have the specific biological materials claimed, since it has been held to be within the general skill of a worker in the art to select a known material (mammal, porcine, juvenile pericardium) on the basis of its suitability for the intended use (valve replacement) as a matter of obvious design choice. *In re Leshin*, 125 USPQ 416.

Referring to claims 28-29 and 31-32, Bailey discloses attachment of the cuff (11a) to the valve (11b extension 26; col.9, lines 10-19), however is silent to mention how the members are coupled. It would have been obvious to one having ordinary skill in the art at the time the invention was made to use sutures, double sutures to attach the two membranes (cuff and valve) since suturing is a common means of attachment in the vascular art and would be applicable to Bailey's invention. See Fogarty et al, US 6,491,719 B1; col.10, lines 5-8 as evidence of common means of attaching layers of material (31, 32) in the vascular art which include stitching, welding, adhering.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHERYL MILLER whose telephone number is (571)272-4755. The examiner can normally be reached on Monday-Friday 7:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Corrine McDermott can be reached on (571) 272-4755. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cheryl Miller/
Examiner, Art Unit 3738

/Corrine M McDermott/
Supervisory Patent Examiner, Art Unit 3738

Notice of References Cited	Application/Control No. 10/887,688	Applicant(s)/Patent Under Reexamination PANIAGUA ET AL.	
	Examiner CHERYL MILLER	Art Unit 3738	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-5,855,601	01-1999	Bessler et al.	623/2.38
*	B	US-5,840,081	11-1998	Andersen et al.	623/1.11
*	C	US-6,425,916 B1	07-2002	Garrison et al.	623/2.11
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L2	76	garrison.in. and valve and frame	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 17:51
L3	10	garrison.in. and (623/1.24.ccls. or 623/1.26.ccls.)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 17:53
L4	31	(US-20060167543-$ or US-20060142846-$ or US-20050096736-$ or US-20040106976-$ or US-20040098098-$ or US-20040039436-$ or US-20030114913-$ or US-20030023300-$ or US-20020107565-$ or US-20010021872-$ or US-20010010017-$ or US-20050075725-$ or US-20030153974-$ or US-20030120330-$ or US-20010041928-$ or US-20080154356-$).did. or (US-7195641-$ or US-6979350-$ or US-6730118-$ or US-6652578-$ or US-6458153-$ or US-5957949-$ or US-5855601-$ or US-6491719-$ or US-6168614-$ or US-6027525-$ or US-5840081-$ or US-5713953-$ or US-5607465-$ or US-4655771-$ or US-4275469-$).did.	US-PGPUB; USPAT	OR	ON	2008/07/13 17:56
S1	367	623/1.24.ccls. or 623/1.26.ccls.	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/25 15:58
S2	1	"10/037,266"	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/25 16:12
S3	1	"10/887,688"	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/25 16:13
S4	123	S1 and @rlad<"20020104"	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/25 16:13
S5	119	S1 and @ad<"20020104"	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/25 16:14

S6	188	S4 S5	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/25 16:14
S7	17	(US-20060167543-$ or US-20060142846-$ or US-20050096736-$ or US-20040106976-$ or US-20040098098-$ or US-20040039436-$ or US-20030114913-$ or US-20030023300-$ or US-20020107565-$ or US-20010021872-$ or US-20010010017-$).did. or (US-7195641-$ or US-6979350-$ or US-6730118-$ or US-6652578-$ or US-6458153-$ or US-5957949-$).did.	US-PGPUB; USPAT	OR	ON	2007/11/25 16:49
S8	9	"09/975,750"	US-PGPUB; USPAT	OR	ON	2007/11/25 16:51
S9	1	623/900.ccls. and bessler.in.	US-PGPUB; USPAT	OR	ON	2007/11/25 16:52
S10	1	"5824063".pn.	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/26 08:14
S11	1	"5480424".pn.	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/26 08:17
S12	9	"09/975,750"	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/26 08:30
S13	24	((inner with (graft or liner)) with (stitched or suture$2) with (outer with (graft or liner))) and (623/1.$2.ccls. or 623/2.$2.ccls.)	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/26 08:32
S14	9	S13 and @rlad<"20020104"	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/26 08:32
S15	12	S13 and @ad<"20020104"	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/26 08:32
S16	14	S14 S15	US-PGPUB; USPAT; EPO; JPO	OR	ON	2007/11/26 08:32
S17	1	"6458153".pn.	US-PGPUB; USPAT; EPO; JPO	OR	ON	2008/07/11 19:49
S18	2	"6458153".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/11 19:50

S19	1448	623/1.24.ccls. or 623/1.26.ccls. or 623/2.1$.ccls.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 12:25
S20	906	S19 not 623/2.11.ccls.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 12:26
S21	278	S20 and @rlad<"20020104"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 12:26
S22	377	S20 and @ad<"20020104"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 12:26
S23	518	S21 S22	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 12:26
S24	194	S23 and @pd<"20010104"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 12:29
S25	93	jayaraman.in. and stent	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 15:42
S26	13	jayaraman.in. and stent and valve	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 15:42
S27	308	garrison.in. and valve	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 16:02
S28	27	garrison.in. and valve and stent	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/07/13 16:03

7/13/08 6:13:44 PM
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Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/887,688	PANIAGUA ET AL.	
	Examiner	Art Unit	
	CHERYL MILLER	3738	

SEARCHED			
Class	Subclass	Date	Examiner
623	1.24, 1.26, 2.11-2.19	7/13/2008	CM

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
East text search	7/13/2008	CM

12-16-08

1st RCE

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PTO/SB/30 (11-08)
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Request for Continued Examination (RCE) Transmittal

Address to:
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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	10/887,688
Filing Date	July 10, 2004
First Named Inventor	Paniagua
Art Unit	3738
Examiner Name	Miller, Cheryl
Attorney Docket Number	051458.010100

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☑ Enclosed

      i. ☑ Amendment/Reply

      ii. ☑ Affidavit(s)/ Declaration(s)

      iii. ☐ Information Disclosure Statement (IDS)

      iv. ☐ Other _____

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. ☑ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 50-1792.

      i. ☑ RCE fee required under 37 CFR 1.17(e)

      ii. ☑ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☐ Other _____

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Manuel Valcarcel/	Date	November 26, 2008
Name (Print/Type)	Manuel Valcarcel, Esq.	Registration No.	41,360

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Signature			
Name (Print/Type)		Date	

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 051458.010100

In re Application of Paniagua, et al.	
Application Number 10/887,688	Filed July 10, 2004
Group Art Unit 3738	Examiner: Miller, Cheryl L.

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows: (check time period desired):

____	One month (37 CFR 1.17(a)(1))	$ ____
☒	Two months (37 CFR 1.17(a)(2))	$ 490.00
☐	Three months (37 CFR 1.17(a)(3))	$ ____
☐	Four months (37 CFR 1.17(a)(4))	$ ____
☐	Five months (37 CFR 1.17(a)(5))	$ ____

☒ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: $245.00

A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Commissioner has already been authorized to charge fees in this application to a Deposit Account.

☒ The Commissioner is hereby authorized to charge the fee and any additional fees which may be required, or credit any overpayment, to Deposit Account Number 50-1792.

I have enclosed a duplicate copy of this sheet.

I am the ☐ assignee of record of the entire interest.

☐ applicant.

☒ attorney or agent of record.

☐ attorney or agent under 37 CFR 1.34(a).
Registration number if acting under 37 CFR 1.34(a) _____.

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November 26, 2008
Date

Signature

Manuel Valcarcel, Esq.
Typed or printed name (Reg. 41,360)

Burden Hour Statement: This form is estimated to take 0.1 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

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02 FC:2252 245.00 DA

Greenberg Traurig

Manuel R. Valcarcel, Esq.
305-579-0812 Tel.
305-961-5812 Fax
mrv@gtlaw.com

December 15, 2008

VIA EXPRESS MAIL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Re: U.S. Patent Application No. 10/887,688
Invention: Percutaneously implantable replacement heart valve device and method of making same
Request for Continued Examination, Petition for Extension of Time and Response to Office Action No. 3
Our Ref. No. 051458.010100

Dear Sir:

Enclosed under cover of this transmittal letter is a Request for Continued Examination together with a Petition for Extension of Time (two months) and response to office action no. 3 in the above-referenced application.

Please charge the RCE Fee ($405) and Extension Petition Fee ($245), the fee for one additional independent claim ($110.00), and any other required fees for the enclosed submission to Deposit Account No. 50-1792.

Please confirm receipt of the enclosed documents by date-stamping and returning the enclosed postage paid return postcard. Please direct all communications regarding the foregoing to the undersigned.

Respectfully submitted,

GREENBERG TRAURIG, P.A.

By /Valcarcel/
Manuel R. Valcarcel, Esq.
Reg. No. 41,360

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MRV/mam
Enclosures
cc: David Paniagua, M.D.
MIA 180,227,872v1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of
Paniagua, et al.
Serial No. 10/887,688
Filed: July 10, 2004
Invention: Percutaneously Implantable Replacement Heart Valve Device and Method of Making Same

Examiner: Cheryl Miller
Group Art Unit 3738

RESPONSE TO OFFICE ACTION No. 3

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

In response to Office Action No. 3 dated July 15, 2008 in the above-referenced application, the Applicants respectfully submit this response. Claim amendments begin on page 2. Remarks begin on page 11. A new Declaration under 37 C.F.R. § 1.131 together with Exhibits A-H of evidence is enclosed antedating the Bailey et al. reference (6,652,578B2) cited as the basis for the claim rejections. The remarks also discuss differences between the Applicants' invention and the device taught by Bailey. Please charge the fee for new independent claim 37 to deposit account no. 50-1792.

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AMENDMENTS TO THE CLAIMS

The following listing will replace all prior versions of the claims in the application:

1. (currently amended) A percutaneously implantable replacement heart valve device comprising an expandable stent member having an inner space and a flexible, compressible artificial valve disposed within said inner space of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising ~~having a cusp or leaflet portion comprising~~ a ~~folded unslit~~ sheet of biocompatible ~~tissue~~ material having one or more folds defining one or more cusps or leaflets without slits cut into said material or separate cusps or leaflets ~~separate cusps or leaflets~~ affixed thereto.

2. (original) The percutaneously implantable replacement heart valve device of claim 1, wherein said expandable stent member is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium and stainless steel.

3. (currently amended) The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible ~~tissue~~ material of said artificial valve comprises mammal pericardium tissue.

4. (currently amended) The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible ~~tissue~~ material of said artificial valve comprises porcine pericardium tissue.

5. (currently amended) The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible ~~tissue~~ material of said artificial valve is obtained from a juvenile animal pericardium.

6. (currently amended) The percutaneously implantable replacement heart valve device of claim 1, wherein said biocompatible ~~tissue~~ material of said artificial valve comprises autologous tissue obtained from the patient into whom said replacement heart valve device will be implanted.

7. (currently amended) The percutaneously implantable heart valve device of claim 1, wherein said biocompatible ~~tissue~~ material of said artificial valve comprises a synthetic biocompatible material.

8. (original) The percutaneously implantable heart valve device of claim 7, wherein said synthetic biocompatible material is selected from the group consisting of polytetrafluoroethylene, polyester, metal, metal alloy including combinations thereof.

9. (original) The percutaneously implantable heart valve device of claim 1, wherein said stent member is self-expanding when implanted.

10. (original) The percutaneously implantable heart valve device of claim 1, wherein said stent member is balloon catheter expandable when implanted.

11. (previously withdrawn) A method of making a percutaneously implantable replacement heart valve device comprising the following steps: obtaining a sheet of biocompatible tissue material; drying said biocompatible tissue material; folding said dried biocompatible tissue material to create inner cusps or leaflets and an outer tubular cuff structure without affixing of separate cusps or leaflets or cutting slits into said material to form said cusps or leaflets; affixing said folded biocompatible tissue material at one or more points on its outer surface to the inner cavity of a stent; and soaking said biocompatible tissue material in one or more alcohol solutions and a solution of gluteraldehyde.

12. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said soaking step comprises soaking said biocompatible tissue material in a solution of isopropyl alcohol, a solution of ethanol, a solution of glycerol and a solution of gluteraldehyde.

13. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material comprises bovine pericardium tissue.

14. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material comprises porcine pericardium tissue.

15. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material is obtained from a juvenile animal pericardium.

16. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said biocompatible tissue material comprises autologous tissue obtained from the patient into whom said replacement heart valve device will be implanted.

17. (previously withdrawn) The percutaneously implantable heart valve device of claim 11, wherein said biocompatible tissue material of said artificial valve comprises a synthetic biocompatible material.

18. (previously withdrawn) The percutaneously implantable heart valve device of claim 17, wherein said synthetic biocompatible material is selected from the group consisting of polytetrafluoroethylene, polyester, metal, metal alloy including combinations thereof.

19. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said stent is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium and stainless steel.

20. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said stent is self-expanding when implanted.

21. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, wherein said stent is balloon catheter expandable when implanted.

22. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve device of claim 11, further comprising the step of cleaning said biocompatible tissue material using hydromechanical force means.

23. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve of claim 11, further comprising the step of compressing said biocompatible tissue material.

24. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve of claim 11, further comprising the step of gas sterilization of said biocompatible tissue material.

25. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve of claim 11, wherein said drying step comprises photomechanical compression of said biocompatible tissue material.

26. (previously withdrawn) The method of making a percutaneously implantable replacement heart valve of claim 11, wherein said folding step comprises folding of a first piece of said biocompatible tissue material to create an outer tubular cuff structure, folding of a second separate piece of biocompatible tissue material to create inner cusps or leaflets without affixing of separate cusps or cutting slits into said second separate piece of biocompatible tissue material, and affixing said second separate piece to said first piece.

27. (currently amended) A percutaneously implantable replacement heart valve device comprising an expandable stent member having an inner space and a flexible, compressible artificial valve made of biocompatible ~~tissue~~ material and disposed within said inner space of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising a leaflet or cusp portion formed by folding of a first sheet portion of said biocompatible tissue material without ~~affixing of separate cusps or leaflets or~~ cutting slits into said first sheet portion to form said cusps or leaflets, and an outer tubular cuff structure formed by folding a second sheet portion of biocompatible tissue material, said first sheet portion and second sheet portion being affixed together.

28. (original) The device of claim 27, wherein said first sheet portion and said second sheet portions are affixed together by suturing.

29. (original) The device of claim 28, wherein said suturing is in the form of double continuous sutures.

30. (currently amended) A percutaneously implantable replacement heart valve device comprising a sheet of flexible, compressible biocompatible material folded to form ~~an outer~~ tubular~~cylindrical~~ cuff portion having an inner tubular space and folded further to form an inner peripheral upstanding~~uncut/unslit~~ cusp or leaflet portion~~layer~~ disposed~~attached~~ within said inner tubular space of said tubular ~~outer~~ cuff portion, said cusps/leaflets opening in response to blood flow through said tubular inner space of said tubular cuff portion in one direction and closing in response to blood flow in the opposite direction.

31. (currently amended) The device of claim 30, wherein said leaflet portion~~layer~~ comprises a separate sheet of said compressible biocompatible material including one or more additional lengthwise pleats through which said leaflet portion is attached to said tubular cuff portion~~is attached within said outer cuff portion by suturing~~.

32. (currently amended) The device of claim 3~~1~~0, wherein said biocompatible material further includes a folded edge through which said material is attached to an expandable stent having an inner channel, said attachment being made to said inner channel of said expandable stent member ~~wherein said suturing is in the form of double continuous sutures~~ by suturing.

33. (currently amended) A percutaneously implantable replacement heart valve device comprising an expandable stent member having an inner space and a flexible, compressible artificial valve made of biocompatible ~~tissue~~ material and disposed within said inner space of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising a sheet of biocompatible material having a first inward fold disposed parallel to an edge of said sheet and one or more inward folds spaced along said sheet perpendicular to said first inward fold, the free edge of said first inward fold defining a

peripheral upstanding leaflet or cusp portion without cutting of slits to form said cusps or leaflets said sheet having two opposite ends perpendicular to said first inward fold, said opposite ends being joined to define a tubular portion within which said cusp or leaflet portion is disposed, said folded cusps or leaflets causing said valve to open in response to blood flow in one direction and close in response to blood flow in the opposite direction.

~~leaflet or cusp portion formed by folding of a first sheet portion of said biocompatible tissue material without affixing of separate cusps or leaflets or cutting slits into said sheet to form said cusps or leaflets.~~

34. (currently amended) A percutaneously implantable replacement heart valve device comprising an expandable stent member having an inner space and a flexible, compressible artificial valve having a generally tubular portion and a peripheral upstanding cusp or leaflet portion disposed within said inner space of said stent member and affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising a continuous uncut, unslit sheet of biocompatible tissue material having an upper border with an outward fold, a lower border with an inward fold, a first edge and a second edge, said first edge and second edge being disposed perpendicular to said upper border and said lower border, said first edge and said second edge being folded inwardly in relation to eachother and said inward folds of said first edge and said second edge being joined ~~to said second edge~~ to form said generally tubular portion having an inner space, with said inward~~ner~~ folds being disposed within said inner space of said generally tubular portion to form said peripheral upstanding cusp or leaflet portion.

35. (currently amended) A percutaneously implantable replacement heart valve device comprising:

an expandable stent member having an inner space, and

a flexible, compressible artificial valve disposed within said inner space of said stent member, affixed at one or more points on said artificial valve's outer surface to said stent member, comprising a first single continuous uncut, unslit sheet of biocompatible tissue material having an upper border, a lower border opposite and parallel to said upper border, an inner fold disposed at said lower border, and two opposite edges perpendicular to said upper border and said lower border and folded inwardly in relation to eachother with the edge of said inward folds of said two opposite edges ~~–~~joined to eachother, and a second sheet of biocompatible tissue material having an upper border with an outward fold and a lower border opposite and parallel to said upper border, and having two opposite edges perpendicular to said upper border and said lower border and joined to eachother, said upper border of said first sheet joined to said lower border of said second sheet.

36. (currently amended) A percutaneously implantable replacement heart valve device comprising an expandable stent member having an inner space and a flexible, compressible artificial valve disposed within said inner space of said stent member affixed at one or more points on said artificial valve's outer surface to said stent member, said artificial valve comprising a generally tubular portion and a cusp or leaflet portion, said generally tubular portion and said cusp or leaflet portion comprising a single folded unslit sheet of biocompatible tissue material ~~without separate cusps or leaflets affixed thereto~~.

37. (New) A percutaneously implantable replacement heart valve device comprising an expandable stent member having an inner space and a flexible, compressible artificial valve disposed within said inner space of said stent member affixed at one or more points on said

artificial valve's outer surface to said stent member, said artificial valve comprising a single sheet of biocompatible material having one or more folds defining one or more cusps or leaflets without slits cut into said material.

Remarks

Claims 1-10 and 27-36 remain in the application. A new claim 37 has been added, and claims 1, 3-7, 27 and 30-36 have been amended. The Applicants have noted the examiner's Section 112, 102(e) and 103 rejections of the claims and respectfully request reconsideration and withdrawal of said rejections based on the claim amendments and remarks contained in this response as well as the Applicants' new Declaration under 37 CFR §1.131 antedating U.S. Patent No. 6,652,578B2 to Bailey. Claims 1-10 and 27-36, as amended, remain in the application. The Applicants note the examiner's comments regarding priority at page 2 of the office action. The present application is a continuation in part application and the benefit of the filing date of the earlier application, which was application serial no. 10/037,266 filed on January 4, 2002, was requested on initial filing of the present application as noted in the first page of the application, as well as in the transmittal, and confirmation of present application's continuation in part status is indicated in the filing receipt.

Additionally, the Applicants respectfully note that the examiner's assertion that the subject matter consisting of the sheet material being unslit and without affixing separate cusps, and the configuration and formation of multiple folds is new to the current application and was not part of the parent application is incorrect. The parent application discusses the valve material being unslit and without affixing of cusps at the end of paragraphs [0027] and [0049] of the parent application ("the folding of the pericardium material to create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of valve leaflets. . . present invention also greatly reduces the risk of tearing of the cusps or leaflets, since they are integral to the valve rather than being attached by suturing.") Figures 3A and 3B of the

parent application also show the folding of the material, the material being unslit and without affixing of separate cusps or leaflets.

Regarding the prior Declaration under 37 C.F.R. 1.131 that was submitted, the undersigned respectfully submits that the prior Declaration was not insufficient for lack of notarization of one signature, because it was a Declaration including the required acknowledgment by the declarants that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. Section 1001) and may jeopardize the validity of the application or any patent issuing thereon, and set forth in the body of the declaration that all statements made of the declarants' own knowledge are true and that all statements made on information and belief are believed to be true. A Declaration in such form, unlike an Affidavit, does not require an oath or notarization. Notarization of a Declaration is beneficial in order to have a witness in the event that a witness to the signature is needed later, but is not required.

Claim 7 has been amended to eliminate the basis for examiner's Section 112 second paragraph rejection as to Claims 7 and 8. Said claims have been revised to refer to the biocompatible material instead of the biocompatible *tissue* material of said valve comprising a synthetic biocompatible material. The Applicants respectfully request that the examiner withdraw the Section 112 rejections.

With respect to the examiner's Section 102(e) and 103(a) rejections, the Applicants respectfully submit the enclosed new Declaration under 37 CFR §1.131 antedating U.S. Patent No. 6,652,578B2 to Bailey. Additional evidence has been provided showing that the inventors had conceived of and had begun taking steps to reduce to practice their invention as of a date prior to December 31, 1999, the priority date for Bailey. Such additional evidence includes a replica of a prototype of the folded valve of the present invention formed using a paper sheet as

well as a replica of a prototype of the folded stent mounted valve in addition to copies of sketches and other materials prior to December 31, 1999, as well as inventors' notes describing their conception and preliminary efforts to reduce to practice the folding of a sheet of valve material to form the valve and the leaflets rather than cutting slits into the material to create leaflets or affixing of separate leaflets. The Applicants respectfully submit that the enclosed new Declaration under 37 C.F.R. Section 1.131 is sufficient to antedate and Bailey.

In addition, while the cited reference is overcome by the enclosed Declaration, the Applicants note further that the Applicants' invention as claimed in the claims as amended, is not anticipated or rendered obvious by Bailey for the following reasons: Nowhere does Bailey teach a valve comprising a sheet of biocompatible material having one or more folds defining cusps or leaflets. In fact, the word "fold" is never even used in description of the invention disclosed in Bailey. The device disclosed in Bailey has a graft member 11 *consisting* of two parts, one which is affixed to the *inner surface* of the stent and the other affixed to the *outer surface* of the stent. It is not a folded sheet of material. The inner and outer graft members are coupled to each other through the stent. See Column 9, lines 12-19: "the graft member 11 consists of an outer or ablumenal graft member 11a and an inner or lumenal graft member 11b. The outer graft member 11a *encloses at least a portion of the ablumenal surface of the intermediate annular section of the stent body member, while the inner graft member 11b is coupled, on the lumenal surface of the intermediate annular section of the stent body member 12, to the outer graft member 11a through the interstices 14 of the stent body member.*" (emphasis added)).

The Applicants' valve, by contrast, is disposed entirely within the inner space of the stent. The valve material in the Applicants' invention is disposed entirely within the inner space of the stent-there is no encapsulation of the stent between inner and outer graft members as in

Bailey. By having the valve material the inner surface and outer surface of the stent, the device disclosed in Bailey is more complicated in design and manufacture, since the stent and the valve must be connected to eachother during creation of the valve portion (the valve material being partially inside and partially outside the stent and connected through the stent), whereas the Applicants' device allows for the valve to be created at one point in time and be coupled to the stent at a later point in time.

Additionally, Bailey includes as an essential element a stent that has "valve arms" or "regulator struts" that support the valve material and which control the opening and closing of the valve in Bailey, forcing separate valve flaps closed by applying a biasing force. (See Column 5, lines 61-63: "The stent body member is shaped to include the following stent sections: proximal and distal anchors, a [sic] intermediate annular section *and at least one valve arm or blood flow regulator struts*." (emphasis added)). Column 9, lines 7-10, referring to Figure 2 of Bailey, discloses a "valve body 26 and valve arms or flow regulator struts 24 coupled to the stent body member 12." The "*valve arms or regulator struts are coupled or formed integral with the stent body member* and are positioned adjacent the junction point between intermediate annular section and the proximal anchor flange 22 of the stent body member 12. The valve arms 24 are oriented radially inward toward the central longitudinal axis of stent body member 12 when in their zero strain state. The valve arms 24 are *attached or coupled* to *the valve flap portions 28 of the inner graft member leaflets* to bias the valve flap portions 28 to the closed position when under zero pressure differential across the stent valve 10." Bailey, Column 9 at lines 32-42 (emphasis added). Column 5, lines 58-60 in Bailey note that "the valve leaflets are preferably *formed* by sections of the graft material attached to the stent body member." The reference to "formed" does not teach or suggest "folding." Column 6 lines 20-39 of Bailey further state that

"[f]low regulation in the inventive stent valve prosthesis is provided by the combination of the prosthetic valve leaflets *and the valve arms and is biased closed in a manner to that described for a surgically implanted replacement heart valve by Boretos, U.S. Pat No. 4,222,126.* The valve regulator-struts are preferably configured to be positioned to radiate inward from the stent body member toward the central longitudinal axis of the prosthesis . . . *The struts of the stent are encapsulated by the outer graft membrane. The valve regulator struts are encapsulated by the inner leaflet membrane and serve to bias the valve to the closed position*. The regulator struts also prevent inversion or prolapse *of the otherwise unsupported leaflet membrane* during increased supra-valvular pressure." (emphasis added). If reference is made to Boretos U.S. Patent No. 4,222,126, it is made further clear that in Bailey the regulator struts support the valve material which is attached to the stent body member and is supported by the struts (see column 5 lines 55-60: "[the graft] is attached to the stent body member on at least portions of either or both of the lumenal and ablumenal surfaces of the stent body member by suturing to or encapsulating stent struts. The valve leaflets are preferably formed by sections of the graft material attached to the stent body member." As shown in Figure 4 in Bailey, the valve arms 24 force the valve leaflets 28 to collapse into the center of the lumen of the stent valve 10, thus biasing the valve to its closed position. The flow regulator struts in Bailey are thus connected to or are part of the stent itself at one end, and are encapsulated by the valve outer membrane and inner leaflet membrane and are responsible for providing support to the valve leaflets and opening and closing of the valve leaflets.

The Applicants' invention does not include such "valve arms" or "regulator struts" whether as part of the stent or as part of the valve. The Applicants' valve with folded cusps and leaflets provides more natural functioning, less susceptability to tearing and allow for effective

opening and closing of the valve without the regulator struts required in Bailey to support and bias the flaps. The folded design invented by the Applicants does not require struts that are part of the stent and are affixed to the valve by suturing or encapsulation in the valve material for valve leaflet material support or valve opening and closing. It is precisely such suturing or encapsulation that the Applicants' folded design is intended to eliminate, resulting in less susceptibility to suture failure and/or tearing of the valve material. In the Applicants' invention opening and closing of the valve is based on the natural blood flow pressure differential. The valve in Bailey does not function to control blood flow without the valve regulator struts. The Applicants have therefore eliminated at least one critical element of the Bailey valve while retaining valve functionality.

The Applicants further reiterate that the product by process limitations in the claims must be given weight because they impart structural limitations, namely, folds, rather than slits or sutures connecting separate leaflet pieces, and thereby impart a number of advantages over prior devices, including reducing susceptibility to failure by improving resistance to tearing of leaflets, and providing a more closely resembling the form and function of a native heart valve. "The structure implied by the process steps should be considered when assessing the patentability of product by process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process would be expected to impart distinctive structural characteristics to the final product." MPEP Section 2113 (citing *In re Garnero*, 412 F.2d 276, 279 (CCPA 1979)). Such is the case with the Applicants' invention. The Applicants therefore respectfully request withdrawal of the examiner's Section 102(e) and Section 103(a) rejections and allow the present case. Nonetheless,

should the examiner have any comments, questions or suggestions, the examiner is respectfully requested to telephone the undersigned at the telephone number listed below.

Respectfully submitted,

Date: December 15, 2008

GREENBERG TRAURIG, P.A.
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MIA 180,225,752v2

EXPRESS MAIL MAILING LABEL NO. EM 248929807 US

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

In re the application of:	)	
	)	
Paniagua, et al.	)	Group Art Unit 3738
Serial No. 10/887,688	)	
Filed: 7/10/2004	)	Examiner: Miller, Cheryl L.
	)	

For: Percutaneously Implantable Replacement Heart Valve Device and Method of Making Same

DECLARATION UNDER 37 CFR 1.131

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia

Sir:

The undersigned co-inventors each hereby declare as follows:

1. I am a co-inventor of the invention claimed in the patent application identified above.

2. I was directly and personally involved in the conception and reduction to practice of the invention throughout the period from prior to December 31, 1999 until the filing date of U.S. Patent Application Serial No. 10/037,266 on January 4, 2002, of which the present application is a continuation in part.

3. Prior to December 31, 1999, the percutaneously implantable replacement heart valve device and method of making same described and claimed in the above-referenced application had been conceived by co-inventors David Paniagua and Francisco-Lopez Jimenez who were at the time cardiology fellows at Mount Sinai Medical Center in Miami Beach, Florida. Attached as Exhibit A is a copy of an electronic diary that was kept with respect to development of the invention by co-inventor Paniagua, with entries dating back to prior to December 31, 1999 indicating that the Applicants had by then already conceived of the invention. The dates for certain of the entries are blacked out but predate December 31, 1999.

4. Prior to December 31, 1999, co-inventors Eduardo Induni and David Paniagua conceived of the folded design of the valve means and the method of folding an unslit sheet of valve material to create a valve with cusps that are created by the folds without suturing separate leaflets or cutting of slits to create leaflets. Enclosed as Exhibit B is a replica of one of the co-inventors' initial paper models of the valve means created prior to December 31, 1999, showing a single piece folded design. Additionally, enclosed as Exhibit C is replica of one of the co-inventors' initial prototypes which was created prior to December 31, 1999, which includes the valve means with the folded design mounted in a stent. The original prototypes and related notes

from dating back prior to December 31, 1999 were lost when co-inventor Paniagua relocated from Miami to Houston and/or during Hurricane Ike. However, attached as Exhibit D are copies of sketches that were created prior to December 31, 1999 which show the co-inventors had already conceived of their folded sheet valve design, including valve cusps and leaflets formed by folding rather than by slitting material or affixing separate cusps or leaflets.

5. During the time period from prior to December 31, 1999 through January 4, 2002, the first prototypes and the method of making same of the invention were created and tested. As indicated in Exhibit A, during the time period from September 1999 through December 1999, anatomical studies were done with respect to porcine aortic and pulmonary valves as well as the aortic arch, including measurements of valve length, cusp length, vertical diameters, attachment points, interaction with other cusps, interaction with the Sino tubular junction and coronary ostium and observation of characteristics of the opening and closing, redundancy of tissue and sinus of Valsalva measurements and the initial prototypes were studied and tested. Durability and fatigue studies were conducted with regard to the valve material and folded design during the months prior to December 31, 1999. A protocol for in-vitro testing was written by Co-Inventor Paniagua in the early months of 2000. The in-vitro model consisted of a plastic hose tubing filled with a 30% solution of glycerol to resemble blood viscosity, a continuous pump, pressure recording instruments and pressure generating clamps. The study indicated excellent opening and closing profiles of the valve with no evidence of regurgitation even at pressures of 200 mmHg.

6. During the time period from prior to December 31, 1999 through January 4, 2002, which is the filing date of Patent Application Serial No. 10/037,266, to which the above-referenced application is a continuation in part and claims priority, we also worked with diligence toward reduction to practice of the invention by preparing a written description of the invention (see copy of a later draft dated April 22, 2001, attached hereto as Exhibit E).

7. During the time period from prior to December 31, 1999 through January 4, 2002, we also worked with diligence toward reduction to practice of the invention by conducting various tests and trials relating to preparation of the valve starting material, formation of the valve, optimal stent composition and configuration, attachment of the valve to the stent and attachment of the stented valve to an artery. See the attached entries from the electronic diary attached hereto as Exhibit A, which include entries relating to tests regarding preparation of the valve starting materials and formation of the valve in October, November and December 2000 and January, February, March, and June 2001. See also the attached entries from the electronic diary attached hereto as Exhibit A, which include entries pertaining to animal studies in June, September and November 2000 and April, 2001.

8. In August 2001, patent counsel was engaged to conduct a patent search directed to the invention and prepare and file a patent application for same. Enclosed as Exhibit F are copies of a search patent request letter dated August 29, 2001 which was sent to order a patent search for the invention, the invention being described in the letter. Said request letter was received by the patent search provider on August 30, 2001 as evidenced by the stamped confirmation of receipt attached to Exhibit G.

9. The patent search results were received on or about mid-September, 2001 and were reviewed by patent counsel, as well as by the undersigned, in the weeks that followed (bearing in mind that during such time period there were various office closures and disruptions due to the September 11, 2001 terrorist attacks and their immediate aftermath).

10. After the patent search results were reviewed and discussed with patent counsel, the patent application was prepared, reviewed, revised, figures for the application were prepared, and the application and figures were submitted on January 4, 2002. Attached as Exhibit H are copies of correspondence from patent counsel enclosing drafts of the patent application for the invention dated November 27, 2001 and December 28, 2001.

The undersigned co-inventors each hereby declare that all statements made herein of his own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

[THIS SPACE LEFT BLANK INTENTIONALLY]

DAVID PANIAGUA

Signature: _____

Date: October 11, 2008

ACKNOWLEDGEMENT

COUNTY OF Harris)
) SS:
STATE OF Texas)

The foregoing Declaration was signed before me this 11 day of October, 2008 by David Paniagua. He is personally known to me or has produced _____ as identification.

Notary: _____
Print Name: ROSIE HIDALGO

[NOTARIAL SEAL]
Notary Public, _____

ROSIE HIDALGO
MY COMMISSION EXPIRES
AUGUST 18, 2009

My commission expires: 8/18/09

FRANCISCO LOPEZ-JIMENEZ

Signature: _____

Date: October 10, 2008

ACKNOWLEDGEMENT

COUNTY OF Olmsted)
) SS: 016 78 3147
STATE OF MN)

The foregoing Declaration was signed before me this 10th day of October, 2008 by Francisco Lopez-Jimenez. He is personally known to me or has produced _____ as identification.

Notary: Vicki Virginia Yount
Print Name: Vicki Virginia Yount

[NOTARIAL SEAL]

VICKI VIRGINIA YOUNT
Notary Public-Minnesota
My Commission Expires Jan 31, 2010

Notary Public, _____

My commission expires: January 31, 2010

R. DAVID FISH

Signature: _____

Date: October 13, 2008

ACKNOWLEDGEMENT

COUNTY OF Harris)
) SS:
STATE OF Texas)

The foregoing Declaration was signed before me this 13th day of October, 2008 by R. David Fish. He is personally known to me or has produced _____ as identification.

Notary: _____ [NOTARIAL SEAL]
Print Name: Mary R. Jones Notary Public, 10-13-08

My commission expires: 8-27-10

MIA 180,228,061v1

MARY R. JONES
NOTARY PUBLIC
STATE OF TEXAS
MY COMM. EXP. 8-27-10

CARLOS MEJIA

Signature: Carlos Mejia A.

Date: October 10, 2008

ACKNOWLEDGEMENT

COUNTY OF HARRIS)
) SS:
STATE OF TEXAS)

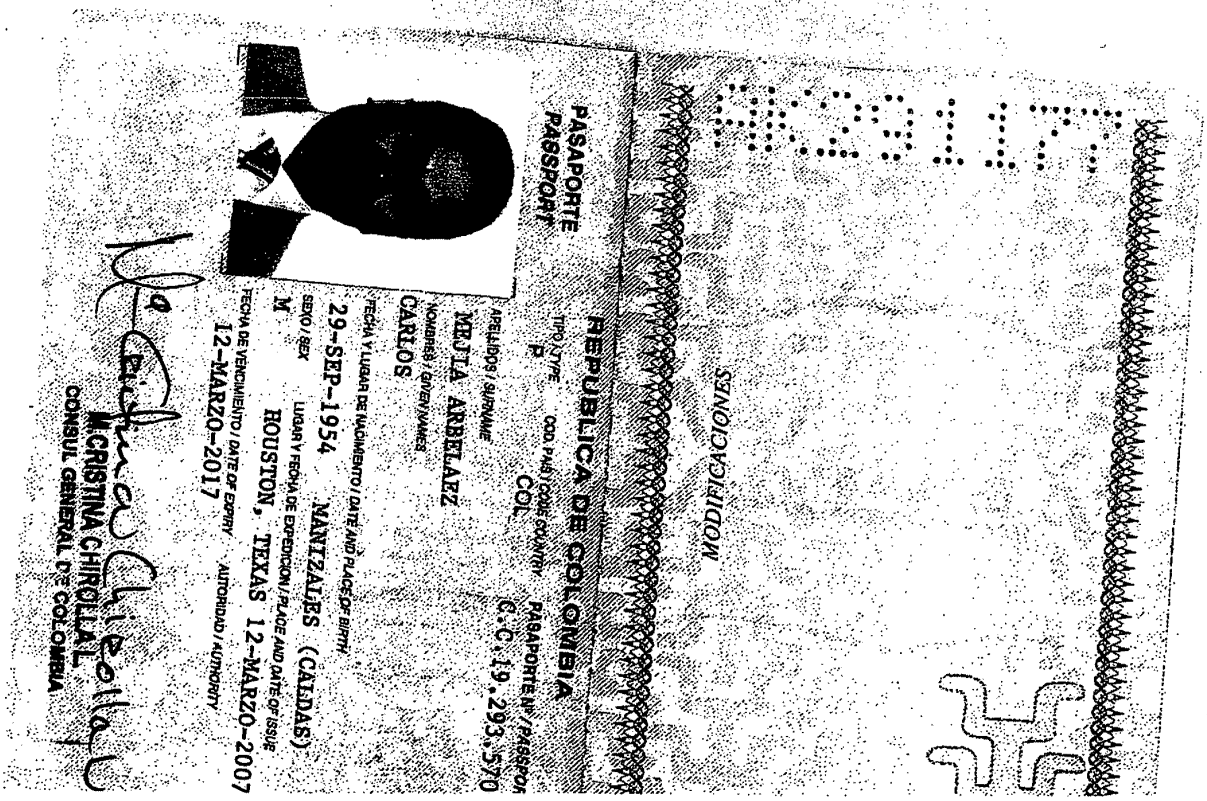
The foregoing Declaration was signed before me this 10th day of October, 2008 by Carlos Mejia. He is personally known to me or has produced COLOMBIAN PASSPORT as identification.

Notary: R Hidalgo
Print Name: ROSIE HIDALGO

[NOTARIAL SEAL]
Notary Public,

ROSIE HIDALGO
MY COMMISSION EXPIRES
AUGUST 18, 2009

My commission expires: 8-18-09



EDUARDO INDUNI

Signature: _____

Date: October 10, 2008

ACKNOWLEDGEMENT

COUNTY OF HARRIS)
) SS:
STATE OF TEXAS)

The foregoing Declaration was signed before me this 11th day of October, 2008 by Eduardo Induni. He is personally known to me or has produced REPUBLICA OF COSTARICA as identification.

Notary: _____ [NOTARIAL SEAL]
Print Name: ROSIE HIDALGO Notary Public, _____

ROSIE HIDALGO
MY COMMISSION EXPIRES
AUGUST 18, 2009

My commission expires: 8/18/09

EXHIBIT A

St Lizy Project: A new percutaneous device to decrease Valvular insufficiency

[redacted]

David Paniagua and **Francisco Lopez-Jimenez** (cardiology fellows at that time) discussed the need to develop a percutaneous valve. This discussion took place in the cardiology fellow's room at Mount Sinai Medical Center in Miami Beach Florida.

After this initial discussion a careful and extensive literature search was started. All articles in the field were reviewed as well as all information regarding patents filed.

[redacted]

The candidate stents that we thought of using in our project were: balloon expandable and self-expandable stents. The balloon expandable stents have been used in the past in two animal experiments reported in the literature. One of them was in Denmark and the other in New York. No other study has been reported after these two original reports. No one has implanted a percutaneous valve in a human being. We believe that the main limitation of the balloon expandable stents is its bulky design.

Among the self-expandable stents, we decided to start using in the first phase the Wallstent and we were planning to use the Smart stent in the second phase. These self-expandable stents has never been used for percutaneous implantation of a valve.

The **Wallstent** is a stainless steel self-expandable stent (Boston Scientific, Boston, MA) that has been used in human since 1987. The main advantage of this stent is its protruding metal wires suitable for fixation in the arterial wall. The main limitation is that the length of the stent changes significant from the collapsed state to the expanded state.

The SMART is a stent made of smart material nitinol an alloy of [redacted] It has the particularity that the stent changes form with temperature. The Smart stent expands when it is in contact with body temperature. The main advantages on the other hand that its length in the collapse and expanded state is quite similar.

The valves that we thought of placing in the stent: porcine pulmonary valve, porcine aortic valve, a new special valve made of bovine pericardium or a valve made of smart materials.

David Fish suggested the utility of using Smart materials in the development of the valve.

Exhibit A

September to December 1999
Anatomical studies in animals
David Paniagua and his wife Elizabeth while in Houston, Texas studied more than 100 porcine aortic and pulmonary valves as well as the aortic arch. Carefull measurement of the valve length, cusp length, vertical diameters, attachment points, interaction with the other cusps, interaction with the Sino tubular junction, coronary ostium. Characteristics of the opening and closing, redundancy of the tissue, sinus of Valsalva measurements

[redacted]

On a trip to Vienna, Austria; Francisco Lopez-Jimenez and David Paniagua discussed all the research synthesis. The pros and cons of different options were discussed and finally a strategy to develop our new percutaneous valve took place.

Porcine pulmonary valve

The main advantage of this valve is the thickness of the arterial wall is significantly less than the aortic wall.

Limitations Still bulky

Porcine aortic valve

Limitations Still bulky and the ostium of both coronaries

Bovine pericardium

We designed a new model of valve with special features to be suitable to use in the stent.

<u>The bovine pericardium</u>

Design

The horizontal length of the stent is equal to diameter x π.
The vertical length suffer a lot of modifications in the last 18 months

The process of management of the pericardium

The pericardium is membrane that surrounds the heart and isolates it from the rest of the chest wall structures.

The pericardium is a thin and very slippery, what makes it difficult for suturing in a millimetric precise way that is required for the valve that we were planning to develop.

Carlos Mejia is a high fashion tailor with experience in tissue management: leather, wool, cotton, etc. developed a process to dry the pericardium in such a way that makes it possible to handle the way we needed.

Dry process

Since the pericardium is such a slippery material we started looking the way to make it easier to manipulate.

We try to dry it at room temperature, but se hacia muy duro y corrugado tieso

Then we try ironing and it shrinks to much and corrugate

We try with artificial light usmg a 60 watt lamp reflecting its light to the pericardium that was placed in a flat aluminium surface to dry it homogeneously

We also tried to photo drying machine

When we dry it this way, the final result was an homogeneous tissue that looked like a plastic paper and makes it easy to manipulate to suture the valve.

Hydrating process

Once the valve was done we hydrated the valve back again by placing it in a solution of water and 70% alcohol. In approximately 3 days the valve hydrate back again.

Converting the pericardium into a valve

David Paniagua and **Eduardo Induni** (a cardiovascular surgeon) discussed the best way to suture a flat pericardium and converted into a complete valve.

Many designs were made in paper until we developed a working model in that resembles the human valve.

See diagrams

Types of sutures

Sutures planes

Francisco Lopez-Jimenez introduced the trapezoid modification
We tested the trapezoid modification but it did not work. It introduces too much redundant tissue.

Attachment of the valve to the stent
3-point fixation on border of the stent

6-point fixation at each border of the stent

Fixation on both borders 18 points at each end following a single plane
36 fixation points following to adjacent vertical planes.

Fixation without any fold in the border resulted in tears, so we made a fold that resolved the problem.

Attachment of the valve to the aorta
R. David Fish suggested the possibility of attaching the mother stent to the subclavian artery using a daughter stent deployed first in the subclavian artery and attached to the mother stent that will be deployed in the descending aorta.

Hooks to the arterial wall Like the Ancure

Double stents

Acute Doppler studies in vitro

Francisco Lopez-Jimenez and David Paniagua performed the first Doppler studies in an in-vitro model.

The model consisted of a plastic hose tubing filled with a 30% solution of glycerol to resemble the blood viscosity, a continuous pump, pressure recording instruments and pressure generating clamps.

In this acute in vitro study we document excellent opening and closing profile of the valve. There was no evidence of regurgitation even at pressures of 200 mmHg.

See video

October 5th to 11th 2000

We studied different ways to fix the pericardium.

1- Piece of pericardium-- dried with light in our standard procedure then placed in glutaraldehyde for 36 hours and hydrate back in alcohol 70%. It looses resistant and it breaks easily.

2- Natural pericardium that was in alcohol solution for 2 months at least and we fix it with gluteraldehyde for 36 hours and then place in the alcohol solution with excellent results in terms of tissue resistance. We were not able to break it.

3 We fix a piece of diaphragm after drying it with light and then gluteraldehyde and we obtained the same result than with the pericardium.. The tissue resistance significant decreased and we were able to tear the tissue.

4 We placed a previously done valve in the stent in the gluteraldehyde solution for 36 hours to fix it and later put it back in the alcohol solution

5 Pericardium dried with light then hydrate with alcohol until it is completely hydrated and then fix it with gluteraldehyde for 36 hours and then re hydrate it back again

6 Pericardium fix with gluteraldehyde for 36 hours and then dry it with light

Delivery device

Chronic studies in vitro

On Sep 17 2001, we created a chronic model to test the valve. The model consisted of a pump attached to an 18 mm tubing system that is also attached to a 3 liters container that is placed 180 cms above the pump.

The stented valve was placed at the bottom of a 180 cm water column to mimic the diastolic pressure.

Histological studies

Preservation of the pericardium several month in ETOH

Glutaraldehido

[redacted]

E-mails

[redacted]

Materials

Calf
The device Delivery system
Cook needle Wires
Pigtails Dilators 11 F, 14F, 16F, 18F, 20F
Contrast media
Balloons PTA of the aorta.

Heparin Plavix for the animal

Surgical equipment

Echo Doppler

[redacted]

Injector X ray tech
Person in charge of anesthesia, monitoring

Circulating person	Endotracheal tube	IV fluids
IV connections	angiocaths	4 liter of IV fluids

Ventilators Lamps

KYJELLY
ET TUBE
ANTIBIOTICS
HEPARIN
XYLOCAINE
BETADINE
KETAMINE
EMERGENCY DRUGS
PROPOFOL XYLAZINE
INJECTION T SPRAY
ALCOHOL

STERILE TOWELS T DRAPES
STERILE SURGICAL TRAY
RECTAL TEMP PROBE
STERILE BOWL FOR SALINE
NS SALINE D5RL
COLLOID
SYRINGES-DIFFERENT SIZES
NEEDLES- DIFFERENT SIZES
HEATING PAD
IV CATLETERS, TOURNIGUETS
VASCULAR CLAMPS
SUCTION CATLETERS
SCISSORS
SECADORA PELO

[redacted]

Carlos Mejia and David Paniagua meet to discuss and design the next experiment.

We reviewed the previous information in video tapes, all films were discussed with emphasis in how we can decrease the size of the valve to try to identify the optimal Dimension of the valves.

We are going to try a valve 10mm deep and the circumference of the valve is going to be 71 mm for a 24mm diameter stent. The width of each pocket is going to be 22 mm

We did the valve in a rubber model with 10 mm deep and it was competent, for this reason we decided to try it in the pericardium.

The change in dimension of the valve with hydration after it is place in alcohol is unpredictable at the present time.

We are going to make two valves

1- Following our previous method of drying the valve with light and sewing to the stent when it its dried and then hydrating it with alcohol. Same design than previously, with folds.
2- A valve with pericardium fixed with gluteraldehyde. No folds in the upper part.

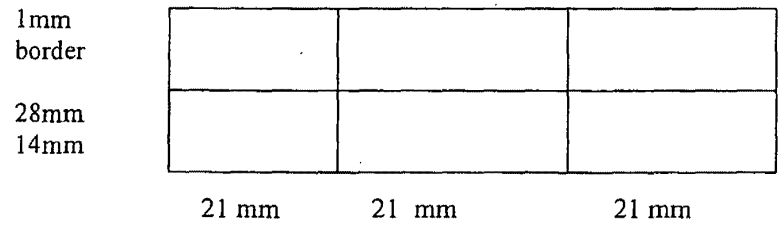
December 2 2000

Eduardo Induni, Carlos Mejia, David Paniagua review all the data collected so far in all the previous experiments and plan a strategy.
We found out that the material needs to be fix with gluteraldehyde before we implant the device. We study different concentrations of gluteraldehyde to fix the valve.

Finally we conclude that we the best is to fix the valve with 0.7% gluteraldehyde and keep it in this solution until the time to use it. At this moment we need to put the valve in normal saline before we implant it

January 2001

We designed a new valve with modification of its length. The pericardium was fixed with gluteraldehyde at 0.7% and later we did the valve and kept it in the same solution until the time to implant it.
During the creation of the valve constant hydration was maintain with frequent immersion of the pericardium in gluteraldehyde.



1 mm at each end to suture the valve.

February 2001

David Fish, Eduardo Induni and David Paniagua review the new stent-pericardium-valve and discussed the design improvement and decided to implant it in a new animal experiment.

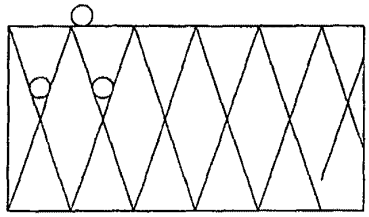
[redacted]

The valve required 7-0 prolene, 24-inch long 10 packs
3 to suture the valve and 7 to attach the valve to the stent.

The valve was attached to a 24 mm maximal diameter Wallstent.

We eliminate the folds at each end of the valve.

The valve was fixed in its **superior border** using two fixation planes with 18 fixation points at each plane.



○ Fixation points

18 fixation points at each plane

There are two rows of fixation point at the upper or proximal end of the stent and one row of fixation point at the lower or distal end of the stent.

Each fixation point was knotted 5 times in the upper plane and 7 knots in the lower plane.

The fixation of the **inferior border** of the valve to the stent was done with a single plane with 18 fixation points. Each fixation point was knotted 7 times using prolene 7-0.

The vertical fixation of the valve to the stent was done along the suture line of each cusp of the valve. We used 3 fixation points at each vertical suture line. Each fixation point was knotted 7 times.

The vertical fixation was mildly loose to allow easy collapsibility of the valve.

The approximate time to suture and attach the valve was 10 hours.

The stent-valve is maintained in 0.7% gluteraldehyde solution.

March 24, 2001

We plan to place the valve in a chronic in vitro model to evaluate its chronic function.

We will perform collapsibility test of the valve.

The delivery system that we plan to use is the AneuRx deployment device.

April 21, 2001

We did an animal experiment in Costa Rica, see description in animal studies.

June 9, 2001

Carlos Mejia and David Paniagua in Miami got together to discuss about the evolution of the valve.

We were discussing how to reduce the dimension to the optimal size of the valve and prevent valvular folds.

The last valve length was 65 mm after fixation, but if you pull it to its maximum length it grows 10 mm more up to 75 mm. Carlos decreased the length of the valve to 55 mm and 57 mm. We were concerned about the elastic recoil of the pericardium once implanted in the valve, because if it is not tense the pericardium makes folds, we want to achieve the optimal length that does not produce folds and that it is not so tight that causes so much elastic recoil that does not allow the stent to expand.

We had the idea of fixing the valve in the closing position using tiny metallic clips to keep the cusps close to each other.

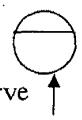
We tried the aortic valvuloplasty balloon to test if it can be used to expand the distal end of the stented valve in the case this extreme does not open.

We tried the consistency of different suture materials: Ticro 4-0, braided nylon and prolene. We discussed pros and cons of monofilament versus braided suture material.

June 12, 2001

At Carlos Mejia's' house we evaluated the design of the valve.

The new valve design includes the creation of a curve in each cusp of the valve



The other modification that we are doing in the handling process is to fix the pericardium in gluteraldehyde and transfer it to a solution of alcohol while making the valve and attaching it to the stent.

We changed the attachment position of the valve to be closer to the proximal and wider part of the Walstent, based on the previous experience during the animal study Alba.

We discussed the use of a pericardium piece fix in glutaraldehyde in a flat glass and the possibility of doing the valve with the natural pericardium and then fixing it with gluteraldehyde after mounting it in the stent.

One observation that we noted is that the material becomes whiter and apparently increases its elasticity

We obtained 1mm vascular clips to keep the cusps coapted while fixing them in gluteraldehyde.

June 13 2001

We evaluated the results of the use of metallic clips to keep both cusps adjacent to each other after 24 hours of fixation in gluteraldehyde. The results were very satisfactory to educate the material and make the primary position of the valve cusps adjacent to each other. After we removed the clips, there were no lesions to the valve. After doing this test, we use the metallic clips to keep both cusps together and immersed it in gluteraldehyde for 24 hours.

We evaluated different suture material that included praline 6-0 and Madrilène 6- 0 which is a braided suture.

We make more fixing fluid using gluteraldehyde 25% in a concentration of 3ml per 97 ml of fluid.

The pericardium of the first valve was in gluteraldehyde for 6 months approximately, then we put it in alcohol 60 during 2 to 3 days and after making the valve and placing in the transport fluid which consist of 60% alcohol.

June 16 2001

We were ready to perform another animal experiment in Costa Rica, but unfortunately all our equipment of dilator and the temporary delivery system was lost.

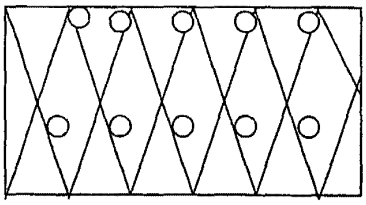
We developed a temporary delivery system that consisted of a central catheter big enough to let a 0.38 wire pass through its lumen, a cover sheath made of plastic material with a sliding device that allows to expose the stented valve.

Dr Eduardo Induni and David Paniagua discussed different ways to improve the collapsibility of the valve
The new observation was that the fixation points at the proximal part should be placed at the midpoint of the rhomboid structure to allow some mobility of the valve when we collapse it. This is true when using Walstent material not smart material

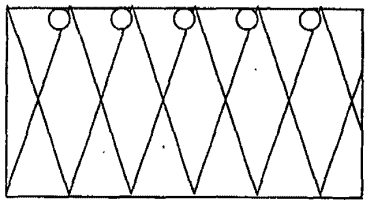
The other observation is that two planes of fixation point at the distal attachment of the valve to the stent causes a lot of tension to the valve when we are collapsing it.

One plane of fixation points will probably be enough to prevent systolic collapsed of the proximal edge of the valve

Proximal fixation points / expanded



Proximal fixation points sliding down



when stent collapses

○ ○ ○ ○ ○

○ Fixation points

18 fixation points at each plane

June 29, 2001

We discussed again the fixation points of the valve to the stent in such a way that they allow mobility of the stent over the valve without exerting too much tension. We believe this will allow better profile to the valve.

We also discussed the different suture materials and call Eduardo Induni and we make the decision that a braided suture is better than a monofilament, for this reason we are going to use mersilene which is a polyester braided suture.

[redacted]

September 8

Carlos Mejia and David Paniagua designed the in vitro model to test chronically the valve and list all the required material

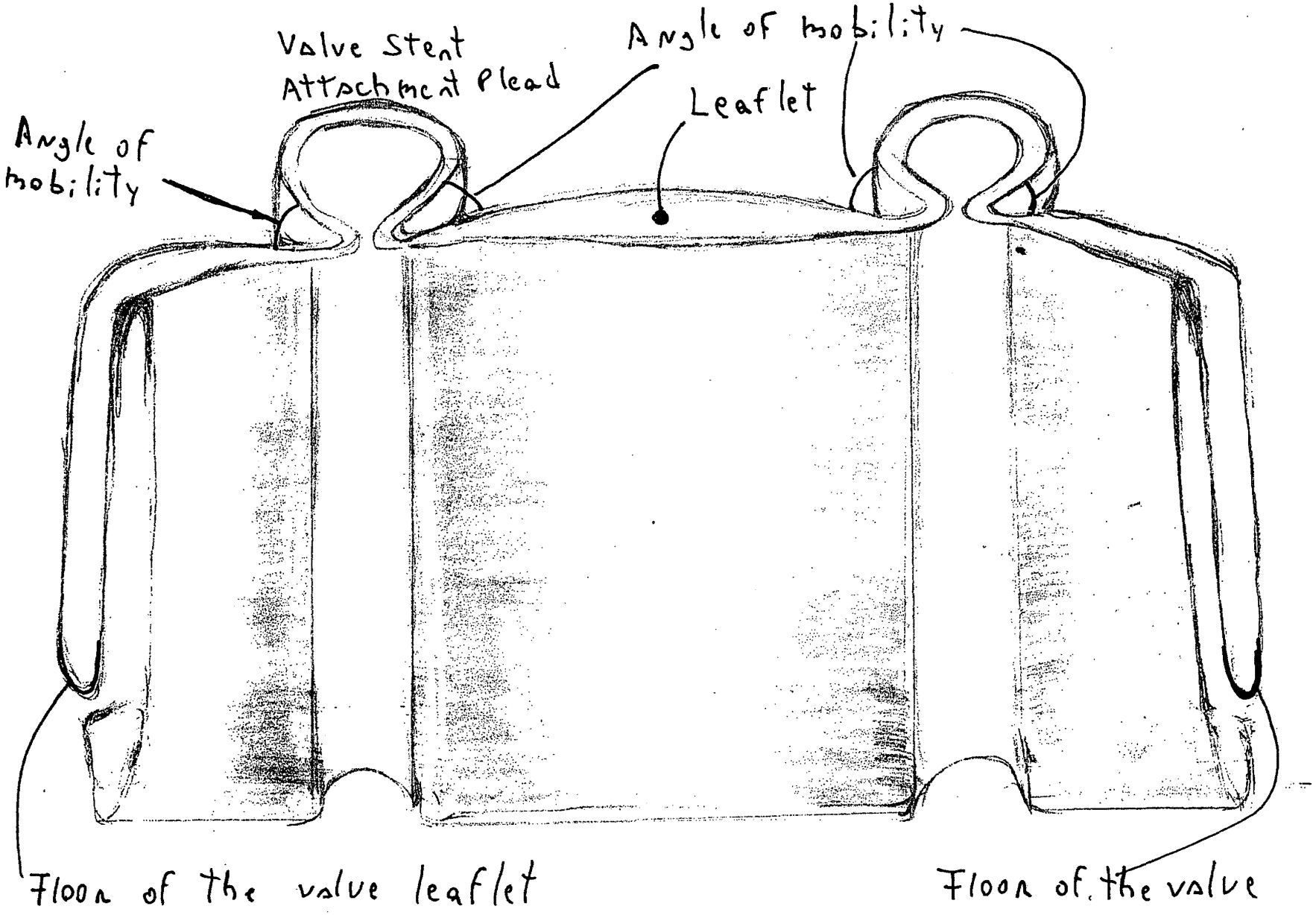
September 22

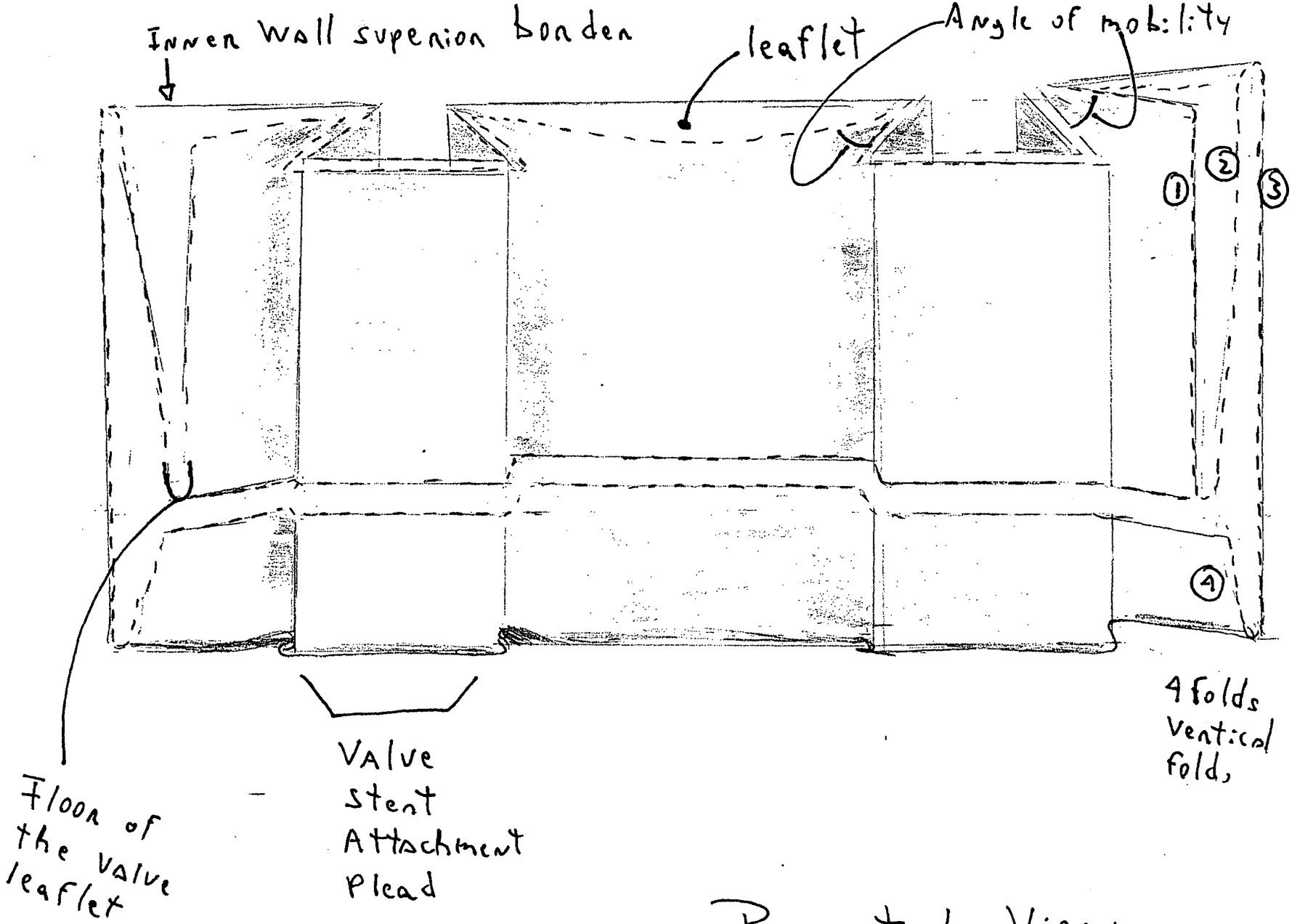
The valve is mounted in the chronic testing model

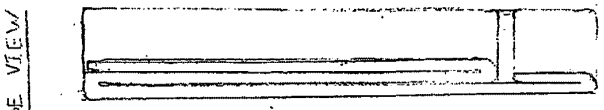
[redacted]

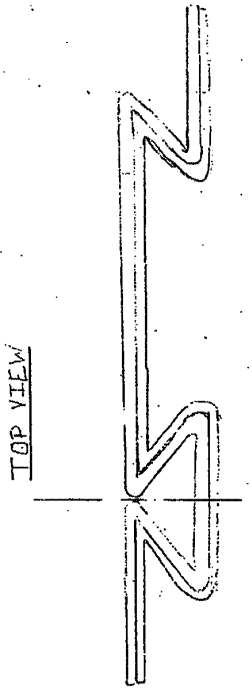
EXHIBIT D

Internal View






SIDE VIEW


TOP VIEW

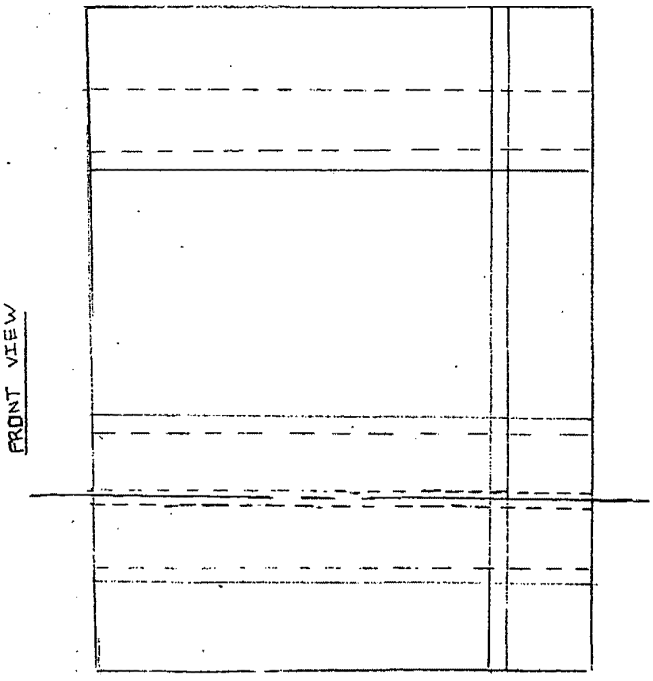

FRONT VIEW

EXHIBIT E

United States Patent

Paniagua, Induni, Mejia, Lopez, Fish, April 22, 2001

PERCUTANEOUS VALVE REPLACEMENT

Abstract

The invention relates to a new technique and a special type of device that allows percutaneous heart-valve replacement without the need for open-heart surgery.

The valve replacement system includes the following components:

(1) A system for removing a damaged heart valve
(2) a delivery system of the prosthetic valve device
(3) a prosthetic valve device
(4) an implantation technique

Inventors:

David Paniagua
Eduardo Induni
Carlos Mejia
Francisco Lopez
R. David Fish

U.S. Patent Documents

4056854	Nov.1977	Boretos et al.	623/2.
4631052	Dec., 1986	Kensey	606/159.
4883458	Nov., 1989	Shiber	606/159.
4966604	Oct., 1990	Reiss	606/159.
4979939	Dec., 1990	Shiber	606/159.
5007896	Apr., 1991	Shiber	606/159.
5011488	Apr., 1991	Ginsburg	606/159.
5026366	Jun., 1991	Leckrone	606/7.
5032128	Jul., 1991	Alonso	623/2.
5047041	Sep., 1991	Samuels	606/159.
5080660	Jan., 1992	Buelna	606/49.
5152771	Oct., 1992	Sabbaghian	606/159.

Foreign Patent Documents

WO91/17720	Nov., 1991	WO.
WO91/17118	Oct., 1992	WO.

Claims

What is claimed is:

1- An endovasculat system for delivering a heart valve.
2- An artificially percutaneous heart valve
3- An implantation technique

1. An endovascular system for delivering a replacement heart valve through an aortic passageway to or near to the location from which the natural heart valve has been removed, comprising:

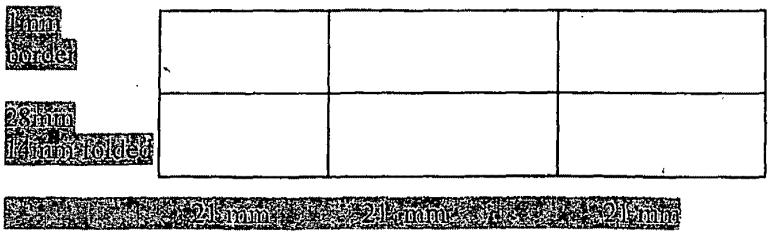
a- The delivery system has a central part which consist of a hollow tube that allows a metallic wire to be advanced inside it. The stented valve is collapsed over this central metallic tubing and it is covered by a movable sheath. The sheath keeps the stented valve in the collapsed position. Once the cover sheath is move backwards this will allow the stented valve to be deployed.

b The stented valve consist of a stainless steel or nitinol self expanding stent in which a completely newly designed biological valve is attached.
One of the novelties of our invention is the use of self-expanding stents instead of balloon expandable stents.

c- The valve is made of bovine pericardium. Initially the pericardium is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean it is fixed using a solution of glutaraldehyde at a concentration of 0.07% during 36 hours, then the pericardium is transfered to a solution of ethanol at 60% before making the valve.

d- The designed of the valve consist of a rectangular fragment of pericardium that is folded in such a way that forms a three leaflet valve.

The horizontal length of the pericardium piece is equal to the desired diameter x π.
The vertical length suffer a lot of modifications in the last 18 months



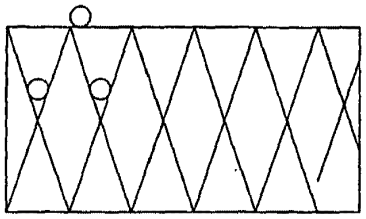
1 mm at each end to suture the valve.

The valve required 7-0 prolene, 24 inch long, 10 packs
3 to suture the valve and 7 to attach the valve to the stent.

The valve was attached to a 24 mm maximal diameter Wall stent.

We eliminate the folds at each end of the valve.

The valve was fixed in its **superior border** using one or two fixation planes with multiple fixation points at each plane.



○ Fixation points

There are one or two rows of fixation points at the upper or proximal end of the stent and one row of fixation point at the lower or distal end of the stent.

Each fixation point was knotted 5 times in the upper plane and 7 knots in the lower plane.

The fixation of the **inferior border** of the valve to the stent was done with a single plane with 18 fixation points. Each fixation point was knotted 7 times using prolene 7-0.

The vertical fixation of the valve to the stent was done along the suture line of each cusp of the valve. We used 3 fixation points at each vertical sutured line. Each fixation point was knotted 7 times.

The vertical fixation was mildly loose to allow easy collapsibility of the valve.

The approximate time to suture and attach the valve was 10 hours.

The stent valve is maintained in 0.7% gluteraldehyde solution.

We had the idea of fixing the valve in the closing position using tiny metallic clips to keep the cusps close to each other and help the material maintain closing memory.

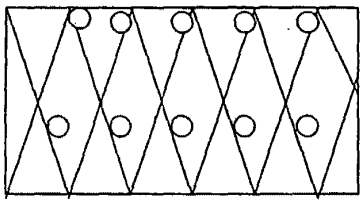
The new valve design includes the creation of a curve in each cusp of the valve

Curve

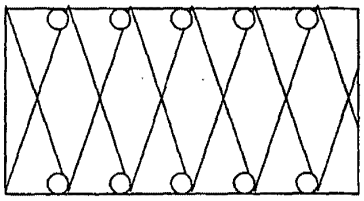
We also used straight suture lines of the cusp

The other observation is that two planes of fixation point at the distal attachment of the the valve to the stent causes a lot of tension to the valve when we are collapsing it.

One plane of fixation points will probably be enough to prevent systolic collapsed of the proximal edge of the valve



Proximal fixation points, expanded



Proximal fixation points sliding down when stent collapses

○ Fixation points

18 fixation points at each plane

NEEDS DETAIL DESCRIPTION OF WHAT IS CLAIM

DESCRIPTION

FIELD OF THE INVENTION

This invention relates to devices and methods for percutaneous endovascular replacement of heart valves.

BACKGROUND

When a heart valve is malfunctioning in such a degree that interferes with normal cardiac function it may be necessary to replace it. Currently this requires a surgical procedure that involves open-heart surgery requiring general anesthesia, full cardiopulmonary bypass with complete cessation of cardiopulmonary activity. Usually after the surgical procedure seven to ten days of hospitalization and months of recuperation time are required. This valve replacement surgery is not free of complication and it is associated with a mortality rate in the best hands and circumstances of about five to six percent.

Endovascular procedures for valve replacement provide an alternative to open heart surgery and this is the goal of our new invention.

Previous endovascular treatments of disease heart-valves have focus in opening stenotic lesions in the mitral and aortic valve using specially designs balloons to dilate or split commissures in diseased aortic or mitral valves with commissural fusion and to crack calcific plaques in calcified stenotic aortic valves.

The success for the mitral valve has been rewarding but the aortic valve results have been discouraging This method provides only partial and temporary relief for a patient with a stenotic aortic valve and this method cannot be used to treat valves with leakage. Moreover, aortic valvuloplasty in a few cases may induce severe aortic leakage that is not compatible with life.

The method that we describe is to use a percutaneously endovascular valve replacement. supplantation. In this procedure, a delivery system is used to insert a biological or mechanical valve in the lumen of a central blood vessel via entry through the brachial or femoral artery. Vascular access is obtained using a needle or exposing the artery surgically and a guide wire is placed through the entry vessel and it is advanced to the desired placed under fluoroscopically guidance. Dilators are advanced over the wire to increase the lumen of the entry site preparing the artery to receive the delivery system of our heart-valve. The heart-valve is then advanced to the desired place and deployed under X-ray guidance.

This new technique of percutaneous endovascular heart-valve replacement, in contrast to open heart surgical procedures, would require only local anesthesia, partial or no cardiac bypass, one to two days hospitalization, and should have a reduced mortality rate as compared to open heart procedures.

The endovascular stented valve is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow. Bioprosteic valves are presently a mainstay in aortic valve replacement and they are preferable in patients who cannot tolerate long-term anticoagulant therapy or are otherwise potentially noncompliant with a long-term medical regimen.

The endovascular valve can also be fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts or synthetic non-biological, non-thrombogenic material.

RELEVANT LITERATURE

U.S. Pat. No. 3,671,979 to Moulopoulos, issued Jun. 27, 1972, describes a endovascularly inserted conical shaped umbrella-like valve positioned and held in place by an elongated mounting catheter at a supra-annular site to the aortic valve in a nearby arterial vessel. The conical end points toward the malfunctioning aortic valve and the umbrella's distal ends open up against the aorta wall with reverse blood flow, thereby preventing regurgitation.

U.S. Pat. No. 4,056,854 to Boretos, issued Nov. 8, 1977, describes a endovascularly inserted, catheter mounted, supra-annular valve in which the circular frame abuts the wall of the artery and attached flaps of flexible membrane extend distally in the vasculature. The flaps lie against the artery wall during forward flow, and close inward towards the central catheter to prevent regurgitation during reverse blood flow. The Boretos valve was designed to be positioned against the artery wall during forward flow, as compared to the mid-center position of the Moulopoulos valve, to reduce the stagnation of blood flow and consequent thrombus and embolic formation expected from a valve at mid-center position.

SUMMARY OF THE INVENTION

The invention relates to a new technique and a special type of device that allows percutaneous heart-valve replacement without the need for open-heart surgery.

The valve replacement system includes the following components:

1- A delivery system of the prosthetic valve device.
2- A prosthetic valve device.
3- An implantation technique

DESCRIPTION OF THE DRAWINGS

FIG. 1 Delivery system of the self-expanded stented valve.

FIG. 2 Initial deployment of the self-expanded stented valve.

FIG. 3 illustrates a bottom view of stented valve.

FIG. 4 illustrates a top view of the stented valve.

FIG. 5 illustrates a tissue laser wire used to cut the commisures of stenotic valve.

FIG. 6 illustrates a diagram of the relationships, dimensions and folds used to create the valve.

FIG. 7 illustrates a side view of a valve introducer.

FIG. 9 illustrates a side view of the attachment point of the valve to the stent.

FIG. 10 illustrates a top view showing the attachment points of the cusp of the valve.

FIG. 11 illustrates an aortic valve in the side position.

FIG. 12 illustrates an aortic valve from the top view.

FIG. 13 is a side cross-sectional view of the valve mounted in the self-expanded stent.

FIG. 14 illustrates a front view of the valve mounted in the stent in the open position.

FIG. 15A is a close-up side cross-sectional view of the mounting stent and FIG. 15B in the closed position.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

The present invention relates to the supplantation or replacement of a cardiac valve in a host through percutaneous endovascular means.

The valve replacement system includes
(1) a delivery device
(2) a prosthetic valve device
(3) an implantation technique.

GENERAL DESCRIPTION OF THE PROCEDURE

The Femoral artery is canulated using a Cook needle and a standard J wire is advance into the artery either perutaneously or after surgical exposure of the artery. An 8 F introducer is advanced into the femoral artery over the wire. The J wire is then withdraw and anticoagulation is started using heparin 60 U/Kg intravenously. Once vascular access is obtained an aortogram is performed for anatomical evaluation.

A special wire (Lunderquist or Amplatz superstiff) is advanced into the aortic arch and dilators progressively larger are advance over the wire, starting with 12 F all the way to 18 F after this the valve introducer device containing the prosthetic valve device is then inserted and used to transport the replacement valve over a guidewire to the desired position.

The stented-valve is released by pulling the cover sheath of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advance over the wire and repeat aortogram is performed to assess the competency of the valve.

When the device is used to treat severe leakage of the aortic valve, the native valve is left in placed and the prostetic stented valve is deployed below the subclavian artery. When the device is used to treat aortic stenosis, first the stenotic valve needs to be opened using either aortic valvuloplasty or the new laser wire cutters and if this procedure induces aortic insufficiency the stented valve is placed to prevent the regurgitation.

[redacted]

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The prosthetic valve device can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation. In addition, with the development of longer-life, flexible, non thrombogenic synthetic valve alternatives to bioprosthesis', the prosthetic valve device will be indicated in all patients where the relative advantages of the life-span, the non-thrombogenic quality, and the ease of insertion of prosthetic valve devices outweigh the disadvantages of mechanical valves. Anticoagulation may be beneficial in certain clinical situations for either short or long term use.

All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

* * * * *

EXHIBIT F

GREENBERG
ATTORNEYS AT LAW
TRAURIG

Manuel R. Valcarcel
305-579-0812
valcarcelm@gtlaw.com

ATTORNEY-CLIENT PRIVILEGED
CONFIDENTIAL INFORMATION

August 29, 2001

VIA FACSIMILE (703) 413-4150
AND FED EX

Mr. Mark Miller
Just Files
2001 Jefferson Davis Highway
Suite 506
Arlington, VA 22202

Re: Novelty Search for Percutaneous heart valve replacement device and method
Our Reference No. 51458.010100

Dear Mr. Miller:

Please conduct a novelty search for the above-identified invention which is described below.

A. Replacement Heart Valve Device. The replacement heart valve device comprises a stent made of stainless steel or self-expanding nitinol, a completely newly designed biological valve disposed within the inner space of the stent, and a delivery system having a central part which consists of a hollow tube that allows a metallic wire to be advanced inside it. The stented valve is collapsed over this central metallic tubing and it is covered by a movable sheath. The sheath keeps the stented valve in the collapsed position. Once the cover sheath is moved backwards, the stented valve can be deployed.

The endovascular stented-valve is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow. Bioprostetic valves are presently a mainstay in aortic valve replacement and they are preferable in patients who cannot tolerate long-term anticoagulant therapy or are otherwise potentially noncompliant with a long term medical regimen.

In making of the valve initially, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a

solution of gluteraldehyde at a concentration of 0.07% during 36 hours, then the pericardium is transferred to a solution of ethanol at 60% before making the valve.

The valve is formed by taking a rectangular fragment of bovine pericardium and folding it in such a way that forms a three-leaflet valve.

The endovascular valve can also be fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts or synthetic non-biological, non-thrombogenic material.

B. Implantation Method.

The method for implanting said replacement heart valve device through an aortic passageway to, or near to, the location from which the natural heart valve has been removed comprises the following steps:

inserting the replacement heart valve device in the lumen of a central blood vessel via entry through the brachial or femoral artery using a needle or exposing the artery surgically; placing a guide wire through the entry vessel and advancing it to the desired position; advancing dilators over the wire to increase the lumen of the entry site, thereby preparing the artery to receive the heart-valve; and advancing the heart-valve to the desired place.

This new technique of percutaneous endovascular heart-valve replacement, in contrast to open heart surgical procedures, would require only local anesthesia, partial or no cardiac bypass, one to two days hospitalization, and should have a reduced mortality rate as compared to open heart procedures.

When the device is used to treat severe leakage of the aortic valve, the native valve is left in placed and the prosthetic stented valve is deployed below the subclavian artery. When the device is used to treat aortic stenosis, first the stenotic valve is opened using either aortic valvuloplasty or laser wire cutters and if this procedure induces aortic insufficiency the stented valve is placed to prevent the regurgitation.

The stented-valve is released by pulling the cover sheath of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advanced over he wire and an aortogram is performed to assess the competency of the valve.

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The prosthetic valve device can be used in any patient where

bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation.

Please do not hesitate to contact me at 305-579-0812 if you have any questions or need additional information to complete the search. Please let me know beforehand if the search will cost more than $400.00.

Sincerely,

GREENBERG TRAURIG, P.A.

Manuel R. Valcarcel, Esq.

MRV/ps

\\MIA-SRV01\VALCARCELM\1333881v01\8/29/01\51458.010100

EXHIBIT G

GREENBERG
ATTORNEYS AT LAW
TRAURIG

Manuel R. Valcarcel
305-579-0817
valcarcelm@gtlaw.com

ATTORNEY-CLIENT PRIVILEGED
CONFIDENTIAL INFORMATION

August 29, 2001

VIA FACSIMILE (703) 413-4150
AND FED EX

Mr. Mark Miller
Just Files
2001 Jefferson Davis Highway
Suite 506
Arlington, VA 22202

Re: Novelty Search for Percutaneous heart valve replacement device and method
Our Reference No. 51458.010100

Dear Mr. Miller:

Please conduct a novelty search for the above-identified invention which is described below.

A. Replacement Heart Valve Device. The replacement heart valve device comprises a stent made of stainless steel or self-expanding nitinol, a completely newly designed biological valve disposed within the inner space of the stent, and a delivery system having a central part which consists of a hollow tube that allows a metallic wire to be advanced inside it. The stented valve is collapsed over this central metallic tubing and it is covered by a movable sheath. The sheath keeps the stented valve in the collapsed position. Once the cover sheath is moved backwards, the stented valve can be deployed.

The endovascular stented-valve is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow. Bioprostetic valves are presently a mainstay in aortic valve replacement and they are preferable in patients who cannot tolerate long-term anticoagulant therapy or are otherwise potentially noncompliant with a long term medical regimen.

In making of the valve initially, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a

EXHIBIT H

GREENBERG
ATTORNEYS AT LAW
TRAURIG

Manuel R. Valcarcel
(305) 579-0812

November 27, 2001

ATTORNEY-CLIENT PRIVILEGED
CONFIDENTIAL COMMUNICATION

VIA HAND DELIVERY

David Paniagua, M.D.
1865 – 79th Street Causeway
Apartment 7-H
Miami Beach, Florida 33141

Re: Draft of patent application specification for percutaneously implantable heart valve replacement device and method of making same

Dear Dr. Paniagua:

Enclosed for your review and revision as appropriate is the draft of the nonprovisional patent application specification for your above-referenced invention. Please review the draft at your earliest convenience (please also review the draft with the other co-inventors) and provide your comments, revisions and additional text. Please note the descriptions of the figures in the draft and if you have drawings or clear digital photographs that provide the views described in the description of the drawings, please provide them. The photographs provided previously are not clear enough for use in the application. If you do not have such photographs, please let me know if you can provide an actual sample of the device so that a draftsman can prepare the figures.

Best regards,

GREENBERG TRAURIG, P.A.

Manuel R. Valcarcel, Esq.

MRV/ps
Enclosures

\\MIA-SRV01\VALCARCELM\1353475v01\11/27/01\51458.010100

Docket No. 51458.010100

NON-PROVISIONAL PATENT APPLICATION

SPECIFICATION

TO WHOM IT MAY CONCERN:

BE IT KNOWN THAT WE, David Paniagua, Eduardo Induni, Carlos Mejia, Francisco Lopez and R. David Fish, each citizens of the United States of America, have invented a new and useful percutaneously implantable replacement heart valve and method of making same, of which the following is the Specification.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is in the field of heart valve replacement. More specifically, the present invention is directed to a percutaneously implantable replacement heart valve and method of making same.

2. Description of Related Art

There have been numerous efforts in the field of heart valve replacement to improve both the durability and effectiveness of replacement heart valves as well as the ease of implantation. A brief description of heart valves and heart function follows to provide relevant background for the present invention.

There are four valves in the heart that serve to direct the flow of blood through the two sides of the heart in a forward direction. On the left (systemic) side of the heart are: 1) the mitral valve, located between the left atrium and the left ventricle, and 2) the aortic valve, located between the left ventricle and the aorta. These two valves direct oxygenated blood coming from the lungs through the left side of the heart into the aorta for distribution to the body. On the right (pulmonary) side of the heart are: 1) the tricuspid valve, located between the right atrium and the right ventricle, and 2) the pulmonary valve, located between the right ventricle and the pulmonary artery. These two valves direct de-oxygenated blood coming from the body through the right side of the heart into the pulmonary artery for distribution to the lungs, where it again becomes re-oxygenated to begin the circuit anew.

Heart valves are passive structures that simply open and close in response to differential pressures on either side of the particular valve. They consist of moveable "leaflets" that are designed simply to open and close in response to differential pressures on either side of the valve's leaflets. The mitral valve has two leaflets and the tricuspid valve has three. The aortic and pulmonary valves are referred to as "semilunar valves" because of the unique appearance

of their leaflets, which are more aptly termed "cusps" and are shaped somewhat like a half-moon. The aortic and pulmonary valves each have three cusps.

In general, the components of heart valves include the valve annulus, which will remain as a roughly circular open ring after the leaflets of a diseased or damaged valve have been removed; leaflets or cusps; papillary muscles which are attached at their bases to the interior surface of the left or right ventricular wall; and multiple chordae tendineae, which couple the valve leaflets or cusps to the papillary muscles. There is no one-to-one chordal connection between the leaflets and the papillary muscles; instead, numerous chordae are present, and chordae from each papillary muscle attach to both of the valve leaflets.

When the left ventricular wall relaxes so that the ventricular chamber enlarges and draws in blood, the leaflets of the mitral valve separate and the valve opens. Oxygenated blood flows in a downward direction through the valve, to fill the expanding ventricular cavity. Once the left ventricular cavity has filled, the left ventricle contracts, causing a rapid rise in the left ventricular cavitary pressure. This causes the mitral valve to close while the aortic valve opens, allowing the oxygenated blood to be ejected from the left ventricle into the aorta. The chordae tendineae of the mitral valve prevent the mitral leaflets from prolapsing back into the left atrium when the left ventricular chamber contracts.

The three leaflets, chordae tendineae, and papillary muscles of the tricuspid valve function in a similar manner, in response to the filling of the right ventricle and its subsequent contraction. The cusps of the aortic valve also respond passively to pressure differentials between the left ventricle and the aorta. When the left ventricle contracts, the aortic valve cusps open to allow the flow of oxygenated blood from the left ventricle into the aorta. When the left ventricle relaxes, the aortic valve cusps reapproximate to prevent the blood which has entered the aorta from leaking (regurgitating) back into the left ventricle. The pulmonary valve cusps respond passively in the same manner in response to relaxation and contraction of the right ventricle in moving de-oxygenated blood into the pulmonary artery and thence to the lungs for

re-oxygenation. Neither of these semilunar valves has associated chordae tendineae or papillary muscles.

Problems that can develop with heart valves consist of stenosis, in which a valve does not open properly, and/or insufficiency, also called regurgitation, in which a valve does not close properly. In addition to stenosis and insufficiency of heart valves, heart valves may need to be surgically repaired or replaced due to certain types of bacterial or fungal infections in which the valve may continue to function normally, but nevertheless harbors an overgrowth of bacteria (vegetation) on the leaflets of the valve that may embolize and lodge downstream in a vital artery. If such vegetations are on the valves of the left side (i.e., the systemic circulation side) of the heart, embolization may occur, resulting in sudden loss of the blood supply to the affected body organ and immediate malfunction of that organ. The organ most commonly affected by such embolization is the brain, in which case the patient suffers a stroke. Thus, surgical replacement of either the mitral or aortic valve (left-sided heart valves) may be necessary for this problem even though neither stenosis nor insufficiency of either valve is present. Likewise, bacterial or fungal vegetations on the tricuspid valve may embolize to the lungs resulting in a lung abscess and therefore, may require replacement of the tricuspid valve even though no tricuspid valve stenosis or insufficiency is present.

These problems are treated by surgical repair of valves, although often the valves are too diseased to repair and must be replaced. If a heart valve must be replaced, there are currently several options available, and the choice of a particular type of artificial valve depends on factors such as the location of the valve, the age and other specifics of the patient, and the surgeon's experiences and preferences. Currently in the United States over 100,000 defective heart valves are replaced annually, at an approximate cost of $30-50,000 per procedure, and thus it would be desirable if heart valves could be replaced using minimally invasive techniques and without having to repeat the procedure within a matter of years due to the lack of durability of the replacement heart valve. It would be especially advantageous if a defective heart valve

could be removed via an endovascular procedure, that is, a procedure where the invasion into the body is through a blood vessel such as the femoral artery. The procedure is then carried out percutaneously and transluminally using the vascular system to convey appropriate devices to the position in the body wherein it is desired to carry out the desired procedure. An example of such a procedure would be angioplasty, wherein a catheter carrying a small balloon at its distal end is manipulated through the body's vessels to a point where there is a blockage in a vessel. The balloon is expanded to create an opening in the blockage, and then the balloon is deflated and the catheter and balloon are removed from the vessel.

Endovascular procedures have substantial benefits both from the standpoint of health and safety as well as cost. Such procedures require minimal invasion of the human body, and there is consequently considerable reduction and in some instances even elimination, of the use of a general anesthesia and much shorter hospital stays.

Replacement heart valves can be categorized as either artificial mechanical valves, transplanted valves and tissue valves. Replacement heart valves are designed to optimize hemodynamic performance, thrombogenicity and durability. Another factor taken into consideration is the relative ease of surgical implantation.

Mechanical valves are typically constructed from nonbiological materials such as plastics, metals and other artificial materials which, while durable, are expensive and prone to blood clotting which increases the risk of an embolism. Anticoagulants taken to help against blood clotting can further complicate the patient's health due to increased risks for hemorrhages.

Transplanted valves are natural valves taken from cadavers. These valves are typically removed and frozen in liquid nitrogen, and are stored for later use. They are typically fixed in glutaraldehyde to eliminate antigenicity and are sutured in place, typically with a stent.

Artificial tissue valves are valves constructed from animal tissue, such as bovine or porcine tissue. Efforts have also been made at using tissue from the patient for which the valve will be constructed.

Most tissue valves are constructed by sewing the leaflets of pig aortic valves to a stent to hold the leaflets in proper position, or by constructing valve leaflets from the pericardial sac of cows or pigs and sewing them to a stent. The porcine or bovine tissue is chemically treated to alleviate any antigenicity. The pericardium is a membrane that surrounds the heart and isolates it from the rest of the chest wall structures. The pericardium is a thin and very slippery, which makes it difficult for suturing in a millimetricly precise way. The method of making the replacement heart valve of the present invention solves this problem through a process to dry the pericardium in such a way that makes it possible to handle and fold more easily.

For example, one prior replacement heart valve requires each sculpted leaflet to be trimmed in a way that forms an extended flap, which becomes a relatively narrow strand of tissue near its tip. The tip of each pericardial tissue strand is sutured directly to a papillary muscle, causing the strand to mimic a chordae tendineae. Each strand extends from the center of a leaflet in the valve, and each strand is sutured directly to either an anterior and posterior papillary muscle. This requires each leaflet to be positioned directly over a papillary muscle. This effectively rotates the leaflets of the valve about 90 degrees as compared to the leaflets of a native valve. The line of commissure between the leaflets, when they are pressed together during systole, will bisect (at a perpendicular angle) an imaginary line that crosses the peaks of the two papillary muscles, instead of lying roughly along that line as occurs in a native valve.

A different approach to creating artificial tissue valves is described in U.S. Patent Nos. 5,163,955 to Calvin, et al. and 5,571,174 and 5,653,749 to Love. Using a cutting die, the pericardial tissue is cut into a carefully defined geometric shape, treated with glutaraldehyde, then clamped in a sandwich-fashion between two stent components. This creates a tri-leaflet

valve that resembles an aortic or pulmonary valve, having semilunar-type cusps rather than atrioventricular-type leaflets.

U.S. Patent No. 3,671,979 to Moulopoulos describes an endovascularly inserted conical shaped umbrella-like valve positioned and held in place by an elongated mounting catheter at a supra-annular site to the aortic valve in a nearby arterial vessel. The conical end points toward the malfunctioning aortic valve and the umbrella's distal ends open up against the aorta wall with reverse blood flow, thereby preventing regurgitation.

U.S. Patent No. 4,056,854 to Boretos describes an endovascularly inserted, catheter mounted, supra-annular valve in which the circular frame abuts the wall of the artery and attached flaps of flexible membrane extend distally in the vasculature. The flaps lie against the artery wall during forward flow, and close inward towards the central catheter to prevent regurgitation during reverse blood flow. The Boretos valve was designed to be positioned against the artery wall during forward flow, as compared to the mid-center position of the Moulopoulos valve, to reduce the stagnation of blood flow and consequent thrombus and embolic formation expected from a valve at mid-center position.

The main advantage of tissue valves is that they do not cause blood clots to form as readily as do the mechanical valves, and therefore, they do not absolutely require systemic anticoagulation. The major disadvantage of tissue valves is that they lack the long-term durability of mechanical valves. Tissue valves have a significant failure rate, usually within ten years following implantation. One cause of these failures is believed to be the chemical treatment of the animal tissue that prevents it from being antigenic to the patient. In addition, the presence of extensive suturing prevents the artificial tissue valve from being anatomically accurate in comparison to a normal heart valve, even in the aortic valve position.

A shortcoming of prior artificial tissue valves has been the inability to effectively simulate the exact anatomy of a native heart valve. Although transplanted human or porcine aortic valves have the gross appearance of native aortic valves, the fixation process (freezing with

liquid nitrogen, and chemical treatment, respectively) alters the histologic characteristics of the valve tissue. Porcine and bovine pericardial valves not only require chemical preparation (usually involving fixation with glutaraldehyde), but the leaflets must be sutured to cloth-covered stents in order to hold the leaflets in position for proper opening and closing of the valve. Additionally, the leaflets of most such tissue valves are constructed by cutting or suturing the tissue material, resulting in leaflets that do not duplicate the form and function of a real valve.

SUMMARY OF THE INVENTION

The present invention is a replacement heart valve device and method of making same. The replacement heart valve device, in a preferred embodiment, comprises a stent made of stainless steel or self-expanding nitinol and a completely newly designed artificial biological tissue valve disposed within the inner space of the stent. The cusp or leaflet portion of the valve means is formed by folding of the pericardium material used to create the valve. The cusps/leaflets open in response to blood flow in one direction and close in response to blood flow in the opposite direction. Preferably the tubular portion of the valve means contains the same number of cusps as the native valve being replaced, in substantially the same size and configuration. The outer surface of the valve means is attached to the stent member.

The replacement heart valve device is preferably implanted using a delivery system having a central part which consists of a flexible hollow tube catheter that allows a metallic guide wire to be advanced inside it. The stented valve is collapsed over the central tube and it is covered by a movable sheath. The sheath keeps the stented valve in the collapsed position. Once the cover sheath is moved backwards, the stented valve can be deployed. The endovascular stented-valve, in a preferred embodiment, is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow.

The present invention also comprises a method of making a replacement heart valve device. In order to make the valve, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a

solution of gluteraldehyde, preferably at a concentration of about 0.07% during 36 hours, then the pericardium is transferred to a solution of ethanol, preferably at a concentration of about 60% before making the valve. The material is dried in order to make it easier to handle and fold. The valve is formed by taking a rectangular fragment of bovine pericardium and folding it in such a way that forms a three-leaflet valve. The valve can also be made from fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts or synthetic non-biological, non-thrombogenic material. The folding of the pericardium material to create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of the valve leaflets. The valve is rehydrated after being formed. The method of the present invention also greatly reduces the risk of tearing of the cusps or leaflets, since they are integral to the valve rather than being attached by suturing.

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The replacement heart valve device of the present invention can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation medication and treatment. The present invention can be practiced in applications with respect to each of the heart's valves.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 depicts a side perspective view of the replacement heart valve of the present invention in one embodiment without the stent.

Fig. 2 depicts the folds which form the leaflets or cusps of the replacement heart valve of the present invention in one embodiment.

Fig. 3 depicts the procedure for folding the pericardium tissue starting material to create the replacement heart valve of the present invention.

Fig. 4 depicts a side perspective view of the replacement heart valve of the present invention in one embodiment mounted within a stent.

Fig. 5 depicts a cross-sectional view of one embodiment of the replacement heart valve of the present invention mounted within a self-expanding stent, with the stent in the expanded position.

Fig. 6 depicts a side perspective view of one embodiment of the replacement heart valve of the present invention mounted within a self-expanding stent in the collapsed position.

Fig. 7 depicts the suture points of one embodiment of the replacement heart valve of the present invention.

Fig. 8 depicts the implantation/delivery system used with the present invention in a preferred embodiment.

DESCRIPTION OF A PREFERRED EMBODIMENT

The present invention comprises a percutaneously implantable replacement heart valve and a method for making same. The artificial heart valve device of the present invention is capable of exhibiting a variable diameter between a compressed or collapsed position and an expanded position. A preferred embodiment of the replacement heart valve according to the present invention is set forth in FIGS. 1 and 2. The replacement heart valve comprises a stent member __ and a flexible valve means __. The stent member is self-expanding and has a first cylindrical shape in its compressed or collapsed configuration and a second, larger cylindrical shape in its expanded configuration. The valve means comprises a generally tubular center portion and, preferably, a peripheral upstanding cusp or leaflet portion. The valve means is

disposed within the cylindrical stent member with the tubular portion transverse of and at some acute angle relative to the stent walls. The diameter of the tubular portion is substantially the same as the inside diameter of the stent member in its initial expanded configuration. The peripheral upstanding cusp or leaflet portion is disposed substantially parallel to the walls of the stent member similar to a cuff on a shirt. The center portion __ of the valve means __ is generally tubular in shape and comprises three leaflets __ as shown, although it is understood that there could be from two to four leaflets. The tubular portion of the valve means is attached to the stent member __ by a plurality of sutures __.

The leaflet portion of the valve means __ extends across or transverse of the cylindrical stent. The leaflets __ are the actual valve and allow for one-way flow of blood. The leaflet portion as connected to the rest of the valve resembles the cuff of a shirt. The configuration of the stent member __ and the flexible, resilient material of construction allows the valve to collapse into a relatively small cylinder __ as seen in FIG. 6. The replacement heart valve will not stay in its collapsed configuration without being restrained. Once the restraint is removed, the self-expanding stent member __ will cause the artificial heart valve to take its expanded configuration, as seen in FIG. __.

Stent Member

The stent member __ comprises self-expanding nickel-titanium alloy, also called "nitinol," in a sine wave-like configuration as shown in FIG. 1. An enlarged view of a preferred embodiment of the stent member for use in the replacement heart valve of the invention is depicted in FIG. 5. The stent member __ includes a length of wire __ formed in a closed zigzag configuration. The wire can be a single piece, stamped or extruded, or it could be formed by welding the free ends together as at __. The straight sections __ of the stent are joined by bends __. The stent is readily compressible to a small cylindrical shape and resiliently self-expandable to the shape shown in FIG. 5.

The stent members of the artificial heart valves of the present invention may be made from various metal alloys, titanium, titanium alloy, nitinol, stainless steel, or other resilient, flexible non-toxic, non-thrombogenic, physiologically acceptable and biocompatible materials. The configuration may be the zigzag configuration shown or a sine wave configuration, mesh configuration or a similar configuration which will allow the stent to be readily collapsible and self-expandable. When a zigzag or sine wave configured stent member is used, the diameter of the wire from which the stent is made should be from about [0.010 to 0.035] inches, preferably from about [0.012 to 0.025] inches. The diameter of the stent member will be from about [1.5 to 3.5 cm], preferably from about [1.75 to 3.00 cm], and the length of the stent member will be from about [1.0 to 10 cm], preferably from about [1.1 to 5 cm.]

The stent used in a preferred embodiment of the present invention is fabricated from a "shaped memory" alloy, nitinol, which is composed of nickel and titanium. Nitinol wire is first fashioned into the desired shape for the device and then the device is heat annealed. A meshwork of nitinol wire of approximately 0.008 inch gauge is formed into a tubular structure with a minimum central diameter of 20 min to make the stent. Away from its central portion, the tubular structure flares markedly at both ends in a trumpet-like configuration. The maximum diameter of the flared ends of the stent is approximately 30 mm. The purpose of the stent is to maintain a semi-rigid patent channel through the diseased cardiac valve following its implantation.

When the components of the replacement heart valve device are exposed to cold temperatures, they become very flexible and supple, allowing them to be compressed down and pass easily through the delivery sheath. A cold temperature is maintained within the sheath during delivery to the deployment site by constantly infusing the sheath with an iced saline solution. Once the valve components are exposed to body temperature at the end of the sheath, they instantaneously reassume their predetermined shapes, thus allowing them to function as designed.

Preferably the stent member carries a plurality of barbs extending outwardly from the outside surface of the stent member for fixing the heart valve in a desired position. More preferably the barbs are disposed in two spaced-apart, circular configurations with the barbs in one circle extending in an upstream direction and the barbs in the other circle extending in a downstream direction. It is especially preferable that the barbs on the inflow side of the valve point in the direction of flow and the barbs on the outflow side point in the direction opposite to flow. It is preferred that the stent be formed of titanium alloy wire or other flexible, relatively rigid, physiologically acceptable material arranged in a closed zigzag configuration so that the stent member will readily collapse and expand as pressure is applied and released, respectively.

Valve Means

The valve means is flexible, compressible, host-compatible, and non-thrombogenic. The valve can be, for example, fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts. Synthetic biocompatible materials such as polytetrafluoroethylene, polyester and the like may be used. The preferred material for the valve means is bovine pericardium tissue. The valve means is disposed within the cylindrical stent member with the tubular portion transverse of and at some acute angle relative to the stent walls. The diameter of the tubular portion is substantially the same as the inside diameter of the stent member in its initial expanded configuration. The peripheral upstanding cusp or leaflet portion is disposed substantially parallel to the walls of the stent member similar to a cuff on a shirt.

The cusp or leaflet portion of the valve means is formed by folding of the pericardium material used to create the valve. The cusps/leaflets open in response to blood flow in one direction and close in response to blood flow in the opposite direction. Preferably the tubular portion of the valve means contains the same number of cusps as the native valve being replaced, in substantially the same size and configuration.

Method of Making Replacement Heart Valve Device

The present invention also comprises a method of making a replacement heart valve device. In order to make the valve, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a solution of gluteraldehyde, preferably at a concentration of about 0.07% during 36 hours, then the pericardium is transferred to a solution of ethanol, preferably at a concentration of about 60% before making the valve. The valve is formed by taking a rectangular fragment of bovine pericardium and folding it in such a way that forms a three-leaflet or desired number of leaflet valve. FIG. 2 depicts the folds which form the cusps or leaflets, and FIG. 3 depicts the folding procedure. The folding of the pericardium material to create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of the valve leaflets. It also greatly reduces the risk of tearing of the cusps or leaflets, since they are integral to the valve rather than being attached by suturing.

In order to make the pericardium material less slippery and easier to fold, the pericardium is dried, preferably with artificial light using a 60-watt lamp with the pericardium material placed in a flat aluminum surface to dry it homogeneously. A photo drying machine can also be used. The final result is a homogeneous tissue that looks like plastic paper and makes it easy to manipulate to fold and suture the valve. Once the valve is formed it is re-hydrated by placing it in a solution of water and 70% alcohol. In approximately 3 days the valve is fully rehydrated.

Attachment of the Valve Means to the Stent Member

The valve means is then attached to the inner channel of the stent member by suturing the outer surface of the valve means' pericardium material to the stent member. Fig. 7 depicts preferred suture points of one embodiment of the present invention: 3-point fixation or 6-point fixation at each border of the stent. Other fixation schemes can be utilized, such as, by way of

non-limiting example, fixation on both borders 18 points at each end following a single plane and 36 fixation points following to adjacent vertical planes. The use of only one plane of fixation points helps prevent systolic collapse of the proximal edge of the valve means. A fold on the border of the pericardium material prevents tearing. The attachment position of the valve is preferably closer to the proximal and wider part of the stent.

The sequence of steps can vary. The pericardium material can be fixed in glutaraldehyde before attachment to the stent or the valve can be formed and then fixed with gluteraldehyde after mounting it in the stent. One observation noted is that the material becomes whiter and apparently increases its elasticity. 1mm vascular clips keep the cusps coapted while fixing them in gluteraldehyde. The use of metallic clips to keep both cusps adjacent to each other after 24 hours of fixation in gluteraldehyde helps to educate the material and make the primary position of the valve cusps adjacent to each other. After the clips are removed, there are no lesions to the valve.

Different suture materials can be used, including, in a preferred embodiment, prolene 6-0 and Mersilene 6-0 which is a braided suture.

Implantation of Replacement Heart Valve Device

The replacement heart valve device of the present invention is preferably used in surgical procedures involving the percutaneous and transluminal removal of the diseased or defective heart valve and the percutaneous and transluminal implantation of the new heart valve described above. The defective heart valve is removed by a suitable modality, such as, for example, laser, ultrasound, mechanical, or other suitable forms of delivery of energy, or phacoemulsion, including, but not limited to, laser lithotripsy, mechanical lithotripsy, electrohydraulic lithotripsy, and laser or mechanical ablation. To remove the native heart valve that is being replaced, a guidewire is inserted percutaneously and transluminally using standard vascular or angiography techniques. The distal end of the guidewire is manipulated to extend

through and across the defective heart valve. Then a catheter is advanced distally through the femoral artery to a point proximal to the defective heart valve, between the origin of the coronary artery and the origin of the right subclavian artery. The position of the distal end of catheter can be monitored by observation of radiopaque markers. Collector member is preferably inflated and occludes the aorta at a point between the origin of the coronary artery and the right subclavian artery. Next, a balloon and cutting tool are advanced through the catheter so that the cutting tool and uninflated balloon are distal to the defective heart valve. Optionally an additional step, such as balloon dilatation or atherectomy, may be required to provide a passageway through the heart valve. A catheter is also placed into the coronary sinus via a transjugular puncture. This catheter is used for infusion of blood or cardioplegia solution during the portion of the procedure when the aorta is occluded. The absence of valves in the cardiac venous system allows retrograde flow so that there will be an effluence of fluid from the coronary arteries. This flow of fluid is desired to prevent embolization of material into the coronary arteries during the procedure. Once the cutting tool is in place, the balloon is inflated and flexible shaft is rotated. Once the cutting tool has reached the appropriate rotation speed, the cutting tool is pulled proximally to remove the defective heart valve. The balloon and the cutting tool are spaced apart so that the inflated balloon will be stopped by the perimeter, unremoved portion of the defective heart valve, which will signal the physician that the valve has been removed, as well as protect the heart and aorta from damage from the valve removal device. Once it is determined that the defective heart valve has been removed, the cutting tool is slowed or stopped altogether and the balloon is deflated. The cutting tool and the deflated balloon are pulled proximally through catheter. Then, a catheter containing an artificial heart valve is inserted and the artificial heart valve is placed as described above.

The delivery and implantation system of the replacement artificial heart valve of the present invention percutaneously and transluminally includes a flexible catheter which may be inserted into a vessel of the patient and moved within that vessel. The distal end of the catheter,

which is hollow and carries the replacement heart valve of the present invention in its collapsed configuration, is guided to a site where it is desired to implant the replacement heart valve. The catheter has a pusher member disposed within the catheter lumen and extending from the proximal end of the catheter to the hollow section at the distal end of the catheter. Once the distal end of the catheter is positioned as desired, the pusher mechanism is activated and the distal portion of the replacement heart valve is pushed out of the catheter and the stent member partially expands. In this position the stent member is restrained so that it doesn't pop out and is held for controlled release, with the potential that the replacement heart valve can be recovered if there is a problem with the positioning. The catheter is them retracted slightly and the replacement heart valve is completely pushed out of the catheter and released from the catheter to allow the stent member to fully expand. If the stent member includes two circles of barbs on its outer surface as previously described, the first push and retraction will set one circle of barbs in adjacent tissue and the second push and release of the replacement heart valve will set the other circle of barbs in adjacent tissue and securely fix the replacement heart valve in place when the valve is released from the catheter.

Alternatively, or in combination with the above, the replacement heart valve could be positioned over a metallic guidewire that is advanced through the catheter. The replacement heart valve device of the present invention is preferably implanted percutaneously through an aortic passageway to, or near to, the location from which the natural heart valve has been removed. Referring to Fig. 8, the implantation system comprises a flexible hollow tube catheter with a metallic guide wire disposed within it. The stented valve is collapsed over the tube and is covered by a moveable sheath. The moveable sheath maintains the stented valve in the collapsed position. comprises the following steps: inserting the replacement heart valve device in the lumen of a central blood vessel via entry through the brachial or femoral artery using a needle or exposing the artery surgically; placing a guide wire through the entry vessel and advancing it to the desired position; advancing dilators over the wire to increase the lumen of

the entry site, thereby preparing the artery to receive the heart-valve; and advancing the heart-valve to the desired place. The stented-valve is released by pulling the cover sheath of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advanced over the wire and an aortogram is performed to assess the competency of the valve.

Before creation of the valve means and implantation, the patient is studied to determine the architecture of the patient's heart. Useful techniques include fluoroscopy, transesophageal echocardiography, MRI, and angiography. The results of this study will enable the physician to determine the appropriate size for the replacement heart valve.

In one procedure for implantation of the replacement heart valve device of the present invention, the femoral artery of the patient is canulated using a Cook needle and a standard J wire is advanced into the artery either percutaneously or after surgical exposure of the artery. An 8 F introducer is advanced into the femoral artery over the wire. The J wire is then withdrawn and anticoagulation is started using heparin 60 U/Kg intravenously. Once vascular access is obtained an aortogram is performed for anatomical evaluation. A special wire (Lunderquist or Amplatz superstiff) is advanced into the aortic arch and dilators progressively larger are advanced over the wire, starting with 12 F all the way to 18 F. After this the valve introducer device containing the prosthetic valve device is then inserted and used to transport the replacement valve over a guidewire to the desired position. The stented-valve is released by pulling the cover sheath of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advanced over the wire and repeat aortogram is performed to assess the competency of the valve.

When the device is used to treat severe leakage of the aortic valve, the native valve is left in place and the prosthetic stented valve is deployed below the subclavian artery. When the device is used to treat aortic stenosis, first the stenotic valve needs to be opened using either

aortic valvuloplasty or cutting and if this procedure induces aortic insufficiency the stented valve is placed to prevent the regurgitation.

Intravascular ultrasound or an angioscope passed intravascularly via either the venous system through the intra-atrial septum across the mitral valve and into the left ventricle or retrograde via the femoral artery would provide the added benefit of allowing constant high definition imaging of the entire procedure and high flow irrigation.

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The prosthetic valve device can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation. In addition, with the development of longer-life, flexible, non-thrombogenic synthetic valve alternatives to bioprosthesis, the prosthetic valve device will be indicated in all patients where the relative advantages of the life-span, the non-thrombogenic quality, and the ease of insertion of prosthetic valve devices outweigh the disadvantages of mechanical valves. Anticoagulation may be beneficial in certain clinical situations for either short or long term use.

This method of percutaneous endovascular heart-valve replacement, in contrast to open heart surgical procedures, requires only local anesthesia, partial or no cardiac bypass, one to two days hospitalization, and should result in a reduced mortality rate as compared to open heart procedures.

While the present invention has been shown and described herein in what is considered to be a preferred embodiment thereof, illustrating the results and advantages over the prior art obtained through the present invention, the invention is not limited to the specific embodiments

described above. Thus, the forms of the invention shown and described herein are to be taken as illustrative and other embodiments may be selected without departing from the spirit and scope of the present invention.

CLAIMS

Having thus described the invention, what is claimed is:

1. A percutaneously implantable replacement heart valve device comprising a self-expanding stent member and an artificial valve means made of biocompatible tissue material and disposed within the inner cavity of said stent member affixed at one or more points to said stent member, said valve means having cusps or leaflets formed by folding of said biocompatible tissue material.

2. The percutaneously implantable replacement heart valve of claim 1, wherein said stent member is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium, stainless steel [add others].

3. The percutaneously implantable replacement heart valve of claim 1, wherein said biocompatible tissue material of said valve means comprises bovine pericardium tissue.

4. The percutaneously implantable replacement heart valve of claim 1, wherein said biocompatible tissue material of said valve means comprises porcine pericardium tissue.

5. The percutaneously implantable replacement heart valve of claim 1, wherein said biocompatible tissue material of said valve means comprises autologous tissue obtained from the patient into whom said replacement heart valve will be implanted.

6. A method of making a percutaneously implantable replacement heart valve comprising the following steps:

obtaining a substantially rectangular segment of biocompatible tissue material;

soaking said biocompatible tissue material in a gluteraldehyde solution;

transferring said biocompatible tissue material from said gluteraldehyde solution to an ethanol solution;

drying said biocompatible tissue material;

folding said dried biocompatible tissue material to create cusps or leaflets and a cuffed tubular valve structure;

affixing said folded biocompatible tissue material to the inner cavity of a stent.

ABSTRACT

The present invention comprises a percutaneously implantable replacement heart valve device and a method of making same. The replacement heart valve device comprises a stent member made of stainless steel or self-expanding nitinol, a biological tissue artificial valve means disposed within the inner space of the stent member. An implantation and delivery system having a central part which consists of a flexible hollow tube catheter that allows a metallic wire guide to be advanced inside it. The endovascular stented-valve is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow. The present invention also comprises a novel method of making a replacement heart valve by taking a rectangular fragment of bovine pericardium treating, drying, folding and rehydrating it in such a way that forms a two- or three-leaflet/cusp valve with the leaflets/cusps formed by folding, thereby eliminating the extent of suturing required, providing improved durability and function.

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TRAURIG

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December 28, 2001

ATTORNEY-CLIENT PRIVILEGED
CONFIDENTIAL COMMUNICATION

VIA HAND DELIVERY

David Paniagua, M.D.
1865 – 79th Street Causeway
Apartment 7-H
Miami Beach, Florida 33141

Re: Revised draft of patent application specification for percutaneously implantable heart valve replacement device and method of making same

Dear Dr. Paniagua:

Enclosed for your review and revision is a revised draft of the nonprovisional patent application specification for your above-referenced invention. Please review the draft at your earliest convenience (please also review the draft with the other co-inventors) and provide your comments, revisions and additional text.

Best regards,

GREENBERG TRAURIG, P.A.

Manuel R. Valcarcel, Esq.

MRV/mp

Enclosure

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Docket No. 51458.010100

NON-PROVISIONAL PATENT APPLICATION

SPECIFICATION

TO WHOM IT MAY CONCERN:

BE IT KNOWN THAT WE, David Paniagua, Eduardo Induni, Carlos Mejia, Francisco Lopez and R. David Fish, ~~each citizens of the United States of America,~~ have invented a new and useful percutaneously implantable replacement heart valve **device** and method of making same, of which the following is the Specification.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is in the field of heart valve replacement. More specifically, the present invention is directed to a percutaneously implantable replacement heart valve and method of making same.

2. Description of Related Art

There have been numerous efforts in the field of heart valve replacement to improve both the durability and effectiveness of replacement heart valves as well as the ease of implantation. A brief description of heart valves and heart function follows to provide relevant background for the present invention.

There are four valves in the heart that serve to direct the flow of blood through the two sides of the heart in a forward direction. On the left (systemic) side of the heart are: 1) the mitral valve, located between the left atrium and the left ventricle, and 2) the aortic valve, located between the left ventricle and the aorta. These two valves direct oxygenated blood coming from the lungs through the left side of the heart into the aorta for distribution to the body. On the right (pulmonary) side of the heart are: 1) the tricuspid valve, located between the right atrium and the right ventricle, and 2) the pulmonary valve, located between the right ventricle and the pulmonary artery. These two valves direct de-oxygenated blood coming from the body through the right side of the heart into the pulmonary artery for distribution to the lungs, where it again becomes re-oxygenated to begin the circuit anew.

Heart valves are passive structures that simply open and close in response to differential pressures on either side of the particular valve. They consist of moveable "leaflets" that are designed simply to open and close in response to differential pressures on either side of the valve's leaflets. The mitral valve has two leaflets and the tricuspid valve has three. The

aortic and pulmonary valves are referred to as "semilunar valves" because of the unique appearance of their leaflets, which are more aptly termed "cusps" and are shaped somewhat like a half-moon. The aortic and pulmonary valves each have three cusps.

In general, the components of heart valves include the valve annulus, which will remain as a roughly circular open ring after the leaflets of a diseased or damaged valve have been removed; leaflets or cusps; papillary muscles which are attached at their bases to the interior surface of the left or right ventricular wall; and multiple chordae tendineae, which couple the valve leaflets or cusps to the papillary muscles. There is no one-to-one chordal connection between the leaflets and the papillary muscles; instead, numerous chordae are present, and chordae from each papillary muscle attach to both of the valve leaflets.

When the left ventricular wall relaxes so that the ventricular chamber enlarges and draws in blood, the leaflets of the mitral valve separate and the valve opens. Oxygenated blood flows in a downward direction through the valve, to fill the expanding ventricular cavity. Once the left ventricular cavity has filled, the left ventricle contracts, causing a rapid rise in the left ventricular cavitary pressure. This causes the mitral valve to close while the aortic valve opens, allowing the oxygenated blood to be ejected from the left ventricle into the aorta. The chordae tendineae of the mitral valve prevent the mitral leaflets from prolapsing back into the left atrium when the left ventricular chamber contracts.

The three leaflets, chordae tendineae, and papillary muscles of the tricuspid valve function in a similar manner, in response to the filling of the right ventricle and its subsequent contraction. The cusps of the aortic valve also respond passively to pressure differentials between the left ventricle and the aorta. When the left ventricle contracts, the aortic valve cusps open to allow the flow of oxygenated blood from the left ventricle into the aorta. When the left ventricle relaxes, the aortic valve cusps reapproximate to prevent the blood which has entered the aorta from leaking (regurgitating) back into the left ventricle. The pulmonary valve cusps

respond passively in the same manner in response to relaxation and contraction of the right ventricle in moving de-oxygenated blood into the pulmonary artery and thence to the lungs for re-oxygenation. Neither of these semilunar valves has associated chordae tendineae or papillary muscles.

Problems that can develop with heart valves consist of stenosis, in which a valve does not open properly, and/or insufficiency, also called regurgitation, in which a valve does not close properly. In addition to stenosis and insufficiency of heart valves, heart valves may need to be surgically repaired or replaced due to certain types of bacterial or fungal infections in which the valve may continue to function normally, but nevertheless harbors an overgrowth of bacteria (vegetation) on the leaflets of the valve that may embolize and lodge downstream in a vital artery. If such vegetations are on the valves of the left side (i.e., the systemic circulation side) of the heart, embolization may occur, resulting in sudden loss of the blood supply to the affected body organ and immediate malfunction of that organ. The organ most commonly affected by such embolization is the brain, in which case the patient suffers a stroke. Thus, surgical replacement of either the mitral or aortic valve (left-sided heart valves) may be necessary for this problem even though neither stenosis nor insufficiency of either valve is present. Likewise, bacterial or fungal vegetations on the tricuspid valve may embolize to the lungs resulting in a lung abscess and therefore, may require replacement of the tricuspid valve even though no tricuspid valve stenosis or insufficiency is present.

These problems are treated by surgical repair of valves, although often the valves are too diseased to repair and must be replaced. If a heart valve must be replaced, there are currently several options available, and the choice of a particular type of artificial valve depends on factors such as the location of the valve, the age and other specifics of the patient, and the surgeon's experiences and preferences. Currently in the United States over 100,000 defective heart valves are replaced annually, at an approximate cost of $30-50,000 per procedure, and

thus it would be desirable if heart valves could be replaced using minimally invasive techniques and without having to repeat the procedure within a matter of years due to the lack of durability of the replacement heart valve. It would be especially advantageous if a defective heart valve could be removed via an endovascular procedure, that is, a procedure where the invasion into the body is through a blood vessel such as the femoral artery. The procedure is then carried out percutaneously and transluminally using the vascular system to convey appropriate devices to the position in the body wherein it is desired to carry out the desired procedure. An example of such a procedure would be angioplasty, wherein a catheter carrying a small balloon at its distal end is manipulated through the body's vessels to a point where there is a blockage in a vessel. The balloon is expanded to create an opening in the blockage, and then the balloon is deflated and the catheter and balloon are removed from the vessel.

Endovascular procedures have substantial benefits both from the standpoint of health and safety as well as cost. Such procedures require minimal invasion of the human body, and there is consequently considerable reduction and in some instances even elimination, of the use of a general anesthesia and much shorter hospital stays.

Replacement heart valves can be categorized as either artificial mechanical valves, transplanted valves and tissue valves. Replacement heart valves are designed to optimize hemodynamic performance, thrombogenicity and durability. Another factor taken into consideration is the relative ease of surgical implantation.

Mechanical valves are typically constructed from nonbiological materials such as plastics, metals and other artificial materials which, while durable, are expensive and prone to blood clotting which increases the risk of an embolism. Anticoagulants taken to help against blood clotting can further complicate the patient's health due to increased risks for hemorrhages.

Transplanted valves are natural valves taken from cadavers. These valves are typically removed and frozen in liquid nitrogen, and are stored for later use. They are typically fixed in glutaraldehyde to eliminate antigenicity and are sutured in place, typically with a stent.

Artificial tissue valves are valves constructed from animal tissue, such as bovine or porcine tissue. Efforts have also been made at using tissue from the patient for which the valve will be constructed.

Most tissue valves are constructed by sewing the leaflets of pig aortic valves to a stent to hold the leaflets in proper position, or by constructing valve leaflets from the pericardial sac of cows or pigs and sewing them to a stent. The porcine or bovine tissue is chemically treated to alleviate any antigenicity. The pericardium is a membrane that surrounds the heart and isolates it from the rest of the chest wall structures. The pericardium is a thin and very slippery, which makes it difficult for suturing in a millimetricly precise way. The method of making the replacement heart valve of the present invention solves this problem through a process to dry the pericardium in such a way that makes it possible to handle and fold more easily.

For example, one prior replacement heart valve requires each sculpted leaflet to be trimmed in a way that forms an extended flap, which becomes a relatively narrow strand of tissue near its tip. The tip of each pericardial tissue strand is sutured directly to a papillary muscle, causing the strand to mimic a chordae tendineae. Each strand extends from the center of a leaflet in the valve, and each strand is sutured directly to either an anterior and posterior papillary muscle. This requires each leaflet to be positioned directly over a papillary muscle. This effectively rotates the leaflets of the valve about 90 degrees as compared to the leaflets of a native valve. The line of commissure between the leaflets, when they are pressed together during systole, will bisect (at a perpendicular angle) an imaginary line that crosses the peaks of the two papillary muscles, instead of lying roughly along that line as occurs in a native valve.

A different approach to creating artificial tissue valves is described in U.S. Patent Nos. 5,163,955 to Calvin, et al. and 5,571,174 and 5,653,749 to Love. Using a cutting die, the pericardial tissue is cut into a carefully defined geometric shape, treated with glutaraldehyde, then clamped in a sandwich-fashion between two stent components. This creates a tri-leaflet valve that resembles an aortic or pulmonary valve, having semilunar-type cusps rather than atrioventricular-type leaflets.

U.S. Patent No. 3,671,979 to Moulopoulos describes an endovascularly inserted conical shaped umbrella-like valve positioned and held in place by an elongated mounting catheter at a supra-annular site to the aortic valve in a nearby arterial vessel. The conical end points toward the malfunctioning aortic valve and the umbrella's distal ends open up against the aorta wall with reverse blood flow, thereby preventing regurgitation.

U.S. Patent No. 4,056,854 to Boretos describes an endovascularly inserted, catheter mounted, supra-annular valve in which the circular frame abuts the wall of the artery and attached flaps of flexible membrane extend distally in the vasculature. The flaps lie against the artery wall during forward flow, and close inward towards the central catheter to prevent regurgitation during reverse blood flow. The Boretos valve was designed to be positioned against the artery wall during forward flow, as compared to the mid-center position of the Moulopoulos valve, to reduce the stagnation of blood flow and consequent thrombus and embolic formation expected from a valve at mid-center position.

The main advantage of tissue valves is that they do not cause blood clots to form as readily as do the mechanical valves, and therefore, they do not absolutely require systemic anticoagulation. The major disadvantage of tissue valves is that they lack the long-term durability of mechanical valves. Tissue valves have a significant failure rate, usually within ten years following implantation. One cause of these failures is believed to be the chemical treatment of the animal tissue that prevents it from being antigenic to the patient. In addition,

the presence of extensive suturing prevents the artificial tissue valve from being anatomically accurate in comparison to a normal heart valve, even in the aortic valve position.

A shortcoming of prior artificial tissue valves has been the inability to effectively simulate the exact anatomy of a native heart valve. Although transplanted human or porcine aortic valves have the gross appearance of native aortic valves, the fixation process (freezing with liquid nitrogen, and chemical treatment, respectively) alters the histologic characteristics of the valve tissue. Porcine and bovine pericardial valves not only require chemical preparation (usually involving fixation with glutaraldehyde), but the leaflets must be sutured to cloth-covered stents in order to hold the leaflets in position for proper opening and closing of the valve. Additionally, the leaflets of most such tissue valves are constructed by cutting or suturing the tissue material, resulting in leaflets that do not duplicate the form and function of a real valve.

SUMMARY OF THE INVENTION

The present invention is a replacement heart valve device and method of making same. The replacement heart valve device, in a preferred embodiment, comprises a stent made of stainless steel or self-expanding nitinol and a completely newly designed artificial biological tissue valve disposed within the inner space of the stent. The cusp or leaflet portion of the valve means is formed by folding of the pericardium material used to create the valve. Other forms of tissue and suitable synthetic materials can also be used for the valve, formed in a sheet of starting material. The folded design provides a number of advantages over prior designs, including improved resistance to tearing at suture lines. The cusps/leaflets open in response to blood flow in one direction and close in response to blood flow in the opposite direction. Preferably the tubular portion of the valve means contains the same number of cusps as the native valve being replaced, in substantially the same size and configuration. The outer surface of the valve means is attached to the stent member.

The replacement heart valve device is preferably implanted using a delivery system having a central part which consists of a flexible hollow tube catheter that allows a metallic guide wire to be advanced inside it. The stented valve is collapsed over the central tube and it is covered by a movable sheath. The sheath keeps the stented valve in the collapsed position. Once the cover sheath is moved backwards, the stented valve can be deployed. The endovascular stented-valve, in a preferred embodiment, is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow. The stent can either be self-expanding or the stent can be expandable through use of a balloon catheter.

The present invention also comprises a method of making a replacement heart valve device. In order to make the valve, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a solution of gluteraldehyde, preferably at a concentration of about 0.07% during 36 hours, then the pericardium is transferred to a solution of ethanol, preferably at a concentration of about 60% before making the valve. The material is dried in order to make it easier to handle and fold. The valve is formed by taking a rectangular fragment of bovine pericardium and folding it in such a way that forms a three-leaflet valve. The valve can also be made in the same manner from fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts or synthetic non-biological, non-thrombogenic material. The folding of the pericardium material to create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of the valve leaflets. The valve is rehydrated after being formed. The method of the present invention also greatly reduces the risk of tearing of the cusps or leaflets, since they are integral to the valve rather than being attached by suturing.

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as

used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The replacement heart valve device of the present invention can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and patients unable to tolerate open heart procedures or life-long anticoagulation medication and treatment. The present invention can be practiced in applications with respect to each of the heart's valves.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 depicts a side perspective view of the replacement heart valve device of the present invention in one embodiment ~~without~~with the ~~stent~~valve in the closed position.

Fig. 2 depicts the folds which form the leaflets or cusps of the replacement heart valve of the present invention in one embodiment.

~~Fig.~~Figs. 3 ~~depicts~~A and 3B depict the procedure for folding the pericardium tissue starting material to create the replacement heart valve of the present invention.

Fig. 4 depicts a side perspective view of the replacement heart valve device of the present invention in one embodiment represented as if implanted within an artery.

Fig. 45 depicts a side ~~perspective~~ view of one embodiment of the replacement heart valve device of the present invention ~~in one embodiment~~ mounted within a self-expanding stent, with the stent in the expanded position.

Fig. 56 depicts a ~~cross-sectional~~side perspective view of one embodiment of the replacement heart valve device of the present invention mounted within a self-expanding stent, ~~with the stent~~ in the ~~expanded~~collapsed position.

~~Fig. 6 depicts a side perspective view of one embodiment of the replacement heart valve of the present invention mounted within a self-expanding stent in the collapsed position.~~

~~Fig.~~Fig. 7 ~~depicts~~depicts the suture points of one embodiment of the replacement heart valve device of the present invention.

Fig. 8 depicts the implantation/delivery system used with the present invention in a preferred embodiment.

DESCRIPTION OF A PREFERRED EMBODIMENT

The present invention comprises a percutaneously implantable replacement heart valve and a method for making same. The artificial heart valve device of the present invention is capable of exhibiting a variable diameter between a compressed or collapsed position and an expanded position. A preferred embodiment of the replacement heart valve device according to the present invention is set forth in ~~FIGS~~FIG. ~~1 and 2.5.~~ The replacement heart valve device comprises a stent member ~~—~~100 and a flexible valve means ~~—~~200. The stent member 100 is preferably self-expanding although balloon-expandable stents can be used as well, and has a first cylindrical shape in its compressed or collapsed configuration and a second, larger cylindrical shape in its expanded configuration. ~~The~~Referring to FIG. 1, the valve means 200 comprises a generally tubular ~~center~~ portion 210 and, preferably, a peripheral upstanding cusp or leaflet portion~~,~~ 220. The valve means 200 is disposed within the cylindrical stent member 100 with the tubular portion 210 transverse of and at some acute angle relative to the stent walls. The diameter of the tubular portion 210 is substantially the same as the inside diameter of the stent member in its initial expanded configuration. The peripheral upstanding cusp or leaflet portion 220 is disposed substantially parallel to the walls of the stent member similar to a cuff on a shirt. The ~~center~~cusp or leaflet portion ~~—~~220 of the valve means ~~—~~200

is generally tubular in shape and comprises three leaflets —221, 222 and 223 as shown, although it is understood that there could be from two to four leaflets. The tubular portion of the valve means 200 is attached to the stent member —100 by a plurality of sutures —300, as depicted in FIG. 7.

The leaflet portion 220 of the valve means —200 extends across or transverse of the cylindrical stent, 100. The leaflets —221, 222 and 223 are the actual valve and allow for one-way flow of blood. The leaflet portion 220 as connected to the rest of the valve resembles the cuff of a shirt. The configuration of the stent member —100 and the flexible, resilient material of construction allows the valve to collapse into a relatively small cylinder —as seen in FIG. 6. The replacement heart valve will not stay in its collapsed configuration without being restrained. Once the restraint is removed, the self-expanding stent member —100 will cause the artificial heart valve to take its expanded configuration, as seen in FIG. —5.

Stent Member

The stent member —100 preferably comprises a self-expanding nickel-titanium alloy stent, also called "nitinol," in a sine wave-like configuration as shown in FIG. ~~1~~5. An enlarged view of a preferred embodiment of the stent member for use in the replacement heart valve of the invention is depicted in FIG. 5. The stent member —100 includes a length of wire —110 formed in a closed zigzag configuration. The wire can be a single piece, stamped or extruded, or it could be formed by welding the free ends together ~~as at~~—. The straight sections —of the stent member 100 are joined by bends—. The stent is readily compressible to a small cylindrical shape as depicted in FIGS. 6 and 8, and resiliently self-expandable to the shape shown in FIG. 5.

The stent ~~members~~member 100 of the artificial heart ~~valves~~valve device of the present invention may be made from various metal alloys, titanium, titanium alloy, nitinol,

stainless steel, or other resilient, flexible non-toxic, non-thrombogenic, physiologically acceptable and biocompatible materials. The configuration may be the zigzag configuration shown or a sine wave configuration, mesh configuration or a similar configuration which will allow the stent to be readily collapsible and self-expandable. When a zigzag or sine wave configured stent member is used, the diameter of the wire from which the stent is made ~~should~~is ~~be~~preferably from about [0.010 to 0.035] inches and still, preferably from about [0.012 to 0.025] inches. The diameter of the stent member will be from about [1.5 to 3.5 cm], preferably from about [1.75 to 3.00 cm], and the length of the stent member will be from about [1.0 to 10 cm], preferably from about [1.1 to 5 cm.]

The stent used in a preferred embodiment of the present invention is fabricated from a "shaped memory" alloy, nitinol, which is composed of nickel and titanium. Nitinol wire is first fashioned into the desired shape for the device and then the device is heat annealed. A meshwork of nitinol wire of approximately 0.008 inch gauge is formed into a tubular structure with a minimum central diameter of 20 min to make the stent. Away from its central portion, the tubular structure flares markedly at both ends in a trumpet-like configuration. The maximum diameter of the flared ends of the stent is approximately 30 mm. The purpose of the stent is to maintain a semi-rigid patent channel through the diseased cardiac valve following its implantation.

When the components of the replacement heart valve device are exposed to cold temperatures, they become very flexible and supple, allowing them to be compressed down and pass easily through the delivery sheath. A cold temperature is maintained within the sheath during delivery to the deployment site by constantly infusing the sheath with an iced saline solution. Once the valve components are exposed to body temperature at the end of the sheath, they instantaneously reassume their predetermined shapes, thus allowing them to function as designed.

Preferably the stent member 100 carries a plurality of barbs extending outwardly from the outside surface of the stent member for fixing the heart valve device in a desired position. More preferably the barbs are disposed in two spaced-apart, circular configurations with the barbs in one circle extending in an upstream direction and the barbs in the other circle extending in a downstream direction. It is especially preferable that the barbs on the inflow side of the valve point in the direction of flow and the barbs on the outflow side point in the direction opposite to flow. It is preferred that the stent be formed of titanium alloy wire or other flexible, relatively rigid, physiologically acceptable material arranged in a closed zigzag configuration so that the stent member will readily collapse and expand as pressure is applied and released, respectively.

Valve Means

The valve means 200 is flexible, compressible, host-compatible, and non-thrombogenic. The valve means 200 can be made from various materials, for example, fresh, cryopreserved or glutaraldehyde fixed allografts or xenografts. Synthetic biocompatible materials such as polytetrafluoroethylene, polyester and the like may be used. The preferred material for the valve means 200 is bovine pericardium tissue. The valve means 200 is disposed within the cylindrical stent member 100 with the tubular portion 210 transverse of and at some acute angle relative to the stent walls. The diameter of the tubular portion 210 is substantially the same as the inside diameter of the stent member 100 in its initial expanded configuration. The peripheral upstanding cusp or leaflet portion 220 is disposed substantially parallel to the walls of the stent member 100 similar to a cuff on a shirt.

The cusp or leaflet portion 220 of the valve means 200 is formed by folding of the pericardium material used to create the valve. FIGS. 3A and 3B depict the way the sheet of heart valve starting material is folded. The cusps/leaflets 221, 222 and 223 open in

response to blood flow in one direction and close in response to blood flow in the opposite direction. Preferably the ~~tubular~~cusp or leaflet portion 220 of the valve means 200 contains the same number of cusps as the native valve being replaced, in substantially the same size and configuration.

Method of Making Replacement Heart Valve Device

The present invention also comprises a method of making a replacement heart valve device. In order to make the valve, the bovine pericardium material is isolated and all the fat tissue and extra fibers are removed. Once the pericardium is completely clean, it is placed in a solution of gluteraldehyde, preferably at a concentration of about 0.07% during 36 hours, then the pericardium is transferred to a solution of ethanol, preferably at a concentration of about 60% before making the valve. The valve is formed by taking a rectangular fragment of bovine pericardium and folding it in such a way that forms a three-leaflet or desired number of leaflet valve. ~~FIG. 2 depicts the folds which form the cusps or leaflets, and FIG.~~ as shown in FIGS. 3A and 3 ~~depicts the folding procedure~~B. The folding of the pericardium material to create the cusps or leaflets reduces the extent of suturing otherwise required, and resembles the natural form and function of the valve leaflets. It also greatly reduces the risk of tearing of the cusps or leaflets, since they are integral to the valve rather than being attached by suturing.

In order to make the pericardium material less slippery and easier to fold, the pericardium is dried, preferably with artificial light using a 60-watt lamp with the pericardium material placed in a flat aluminum surface to dry it homogeneously. A photo drying machine can also be used. The final result is a homogeneous tissue that looks like plastic paper and makes it easy to manipulate to fold and suture the valve. Once the valve is formed it is re-hydrated by placing it in a solution of water and 70% alcohol. In approximately 3 days the valve is fully rehydrated.

Attachment of the Valve Means to the Stent Member

The valve means 200 is then attached to the inner channel of the stent member 100 by suturing the outer surface of the valve means' pericardium material to the stent member. ~~Fig~~FIG. 7 depicts preferred suture points of one embodiment of the present invention: 3-point fixation or 6-point fixation at each border of the stent. Other fixation schemes can be utilized, such as, by way of non-limiting example, fixation on both borders 18 points at each end following a single plane and 36 fixation points following to adjacent vertical planes. The use of only one plane of fixation points helps prevent systolic collapse of the proximal edge of the valve means. A fold on the border of the pericardium material prevents tearing. The attachment position of the valve is preferably closer to the proximal and wider part of the stent.

The sequence of steps can vary. The pericardium material can be fixed in glutaraldehyde before attachment to the stent or the valve can be formed and then fixed with gluteraldehyde after mounting it in the stent. One observation noted is that the material becomes whiter and apparently increases its elasticity. 1mm vascular clips keep the cusps coapted while fixing them in gluteraldehyde. The use of metallic clips to keep both cusps adjacent to each other after 24 hours of fixation in gluteraldehyde helps to educate the material and make the primary position of the valve cusps adjacent to each other. After the clips are removed, there are no lesions to the valve.

Different suture materials can be used, including, in a preferred embodiment, prolene 6-0 and Mersilene 6-0 which is a braided suture.

Implantation of Replacement Heart Valve Device

The replacement heart valve device of the present invention is preferably used in surgical procedures involving the percutaneous and transluminal removal of the diseased or defective heart valve and the percutaneous and transluminal implantation of the new heart

valve described above. The defective heart valve is removed by a suitable modality, such as, for example, laser, ultrasound, mechanical, or other suitable forms of delivery of energy, or phacoemulsion, including, but not limited to, laser lithotripsy, mechanical lithotripsy, electrohydraulic lithotripsy, and laser or mechanical ablation. To remove the native heart valve that is being replaced, a guidewire is inserted percutaneously and transluminally using standard vascular or angiography techniques. The distal end of the guidewire is manipulated to extend through and across the defective heart valve. Then a catheter is advanced distally through the femoral artery to a point proximal to the defective heart valve, between the origin of the coronary artery and the origin of the right subclavian artery. The position of the distal end of catheter can be monitored by observation of radiopaque markers. Collector member is preferably inflated and occludes the aorta at a point between the origin of the coronary artery and the right subclavian artery. Next, a balloon and cutting tool are advanced through the catheter so that the cutting tool and uninflated balloon are distal to the defective heart valve. Optionally an additional step, such as balloon dilatation or atherectomy, may be required to provide a passageway through the heart valve. A catheter is also placed into the coronary sinus via a transjugular puncture. This catheter is used for infusion of blood or cardioplegia solution during the portion of the procedure when the aorta is occluded. The absence of valves in the cardiac venous system allows retrograde flow so that there will be an effluence of fluid from the coronary arteries. This flow of fluid is desired to prevent embolization of material into the coronary arteries during the procedure. Once the cutting tool is in place, the balloon is inflated and flexible shaft is rotated. Once the cutting tool has reached the appropriate rotation speed, the cutting tool is pulled proximally to remove the defective heart valve. The balloon and the cutting tool are spaced apart so that the inflated balloon will be stopped by the perimeter, unremoved portion of the defective heart valve, which will signal the physician that the valve has been removed, as well as protect the heart and aorta from damage from the valve removal

device. Once it is determined that the defective heart valve has been removed, the cutting tool is slowed or stopped altogether and the balloon is deflated. The cutting tool and the deflated balloon are pulled proximally through catheter. Then, a catheter containing an artificial heart valve is inserted and the artificial heart valve is placed as described above.

The delivery and implantation system of the replacement artificial heart valve of the present invention percutaneously and transluminally includes a flexible catheter 400 which may be inserted into a vessel of the patient and moved within that vessel as depicted in FIG. 8. The distal end 410 of the catheter, 400, which is hollow and carries the replacement heart valve device of the present invention in its collapsed configuration, is guided to a site where it is desired to implant the replacement heart valve. The catheter has a pusher member 420 disposed within the catheter lumen 430 and extending from the proximal end 440 of the catheter to the hollow section at the distal end 410 of the catheter. Once the distal end 410 of the catheter is positioned as desired, the pusher mechanism 420 is activated and the distal portion of the replacement heart valve device is pushed out of the catheter and the stent member 100 partially expands. In this position the stent member 100 is restrained so that it doesn't pop out and is held for controlled release, with the potential that the replacement heart valve device can be recovered if there is a problem with the positioning. The catheter 400 is ~~them~~then retracted slightly and the replacement heart valve device is completely pushed out of the catheter 400 and released from the catheter to allow the stent member 100 to fully expand. If the stent member 100 preferably includes two circles of barbs on its outer surface as previously described, the first push and retraction will set one circle of barbs in adjacent tissue and the second push and release of the replacement heart valve device will set the other circle of barbs in adjacent tissue and securely fix the replacement heart valve device in place when the ~~valve~~device is released from the catheter.

Alternatively, or in combination with the above, the replacement heart valve device could be positioned over a metallic guidewire that is advanced through the catheter. The replacement heart valve device of the present invention is preferably implanted percutaneously through an aortic passageway to, or near to, the location from which the natural heart valve has been removed. Referring to ~~Fig~~FIG. 8, the implantation system comprises a flexible hollow tube catheter 410 with a metallic guide wire 450 disposed within it. The stented valve device is collapsed over the tube and is covered by a moveable sheath 460. The moveable sheath 460 maintains the stented valve device in the collapsed position. The implantation method comprises the following steps: inserting the replacement heart valve device in the lumen of a central blood vessel via entry through the brachial or femoral artery using a needle or exposing the artery surgically; placing a guide wire 450 through the entry vessel and advancing it to the desired position; advancing dilators over the wire to increase the lumen of the entry site, thereby preparing the artery to receive the heart-valve; and advancing the heart-valve device to the desired place. The stented-valve device is released by pulling the cover sheath 460 of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advanced over the wire and an aortogram is performed to assess the competency of the valve.

Before creation of the valve means and implantation, the patient is studied to determine the architecture of the patient's heart. Useful techniques include fluoroscopy, transesophageal echocardiography, MRI, and angiography. The results of this study will enable the physician to determine the appropriate size for the replacement heart valve.

In one procedure for implantation of the replacement heart valve device of the present invention, the femoral artery of the patient is canulated using a Cook needle and a standard J wire is advanced into the artery either percutaneously or after surgical exposure of the artery. An 8 F introducer is advanced into the femoral artery over the wire. The J wire is then

withdrawn and anticoagulation is started using heparin 60 U/Kg intravenously. Once vascular access is obtained an aortogram is performed for anatomical evaluation. A special wire (Lunderquist or Amplatz superstiff) is advanced into the aortic arch and dilators progressively larger are advanced over the wire, starting with 12 F all the way to 18 F. After this the valve introducer device containing the prosthetic valve device is then inserted and used to transport the replacement valve over a guidewire to the desired position. The stented-valve is released by pulling the cover sheath of the delivery system allowing the self-expanding stent to achieve its full expansion. At this point, a pigtail catheter is advanced over the wire and repeat aortogram is performed to assess the competency of the valve.

When the device is used to treat severe leakage of the aortic valve, the native valve is left in place and the prosthetic stented valve is deployed below the subclavian artery. When the device is used to treat aortic stenosis, first the stenotic valve needs to be opened using either aortic valvuloplasty or cutting and if this procedure induces aortic insufficiency the stented valve is placed to prevent the regurgitation.

Intravascular ultrasound or an angioscope passed intravascularly via either the venous system through the intra-atrial septum across the mitral valve and into the left ventricle or retrograde via the femoral artery would provide the added benefit of allowing constant high definition imaging of the entire procedure and high flow irrigation.

Once the endovascular implantation of the prosthetic valve device is completed in the host, the function of the prosthetic valve device can be monitored by the same methods as used to monitor valve replacements done by open heart surgery. Routine physical examination, periodic echocardiography or angiography can be performed. In contrast to open heart surgery, however, the host requires a short recovery period and can return home within one day of the endovascular procedure. The prosthetic valve device can be used in any patient where bioprosthetic valves are indicated, namely elderly patients with cardiac valve diseases, and

patients unable to tolerate open heart procedures or life-long anticoagulation. In addition, with the development of longer-life, flexible, non-thrombogenic synthetic valve alternatives to bioprosthesis, the prosthetic valve device will be indicated in all patients where the relative advantages of the life-span, the non-thrombogenic quality, and the ease of insertion of prosthetic valve devices outweigh the disadvantages of mechanical valves. Anticoagulation may be beneficial in certain clinical situations for either short or long term use.

This method of percutaneous endovascular heart-valve replacement, in contrast to open heart surgical procedures, requires only local anesthesia, partial or no cardiac bypass, one to two days hospitalization, and should result in a reduced mortality rate as compared to open heart procedures.

While the present invention has been shown and described herein in what is considered to be a preferred embodiment thereof, illustrating the results and advantages over the prior art obtained through the present invention, the invention is not limited to the specific embodiments described above. Thus, the forms of the invention shown and described herein are to be taken as illustrative and other embodiments may be selected without departing from the spirit and scope of the present invention.

CLAIMS

Having thus described the invention, what is claimed is:

1. A percutaneously implantable replacement heart valve device comprising a ~~self-expanding~~-stent member and an artificial valve means made of biocompatible tissue material and disposed within the inner cavity of said stent member affixed at one or more points to said stent member, said valve means having cusps or leaflets formed by folding of **a substantially rectangular sheet of** said biocompatible tissue material.

2. The percutaneously implantable replacement heart valve **device** of claim 1, wherein said stent member is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium, stainless steel **[add others]**.

3. The percutaneously implantable replacement heart valve **device** of claim 1, wherein said biocompatible tissue material of said valve means comprises bovine pericardium tissue.

4. The percutaneously implantable replacement heart valve **device** of claim 1, wherein said biocompatible tissue material of said valve means comprises porcine pericardium tissue.

5. The percutaneously implantable replacement heart valve **device** of claim 1, wherein said biocompatible tissue material of said valve means comprises autologous tissue obtained from the patient into whom said replacement heart valve **device** will be implanted.

6. The percutaneously implantable heart valve device of claim 1, wherein said stent member is self-expanding when implanted.

7. The percutaneously implantable heart valve device of claim 1, wherein said stent member is balloon catheter expandable when implanted.

~~6.~~8. A method of making a percutaneously implantable replacement heart valve device comprising the following steps:

obtaining a substantially rectangular ~~segment~~sheet of biocompatible tissue material;

soaking said biocompatible tissue material in a gluteraldehyde solution;

transferring said biocompatible tissue material from said gluteraldehyde solution to an ethanol solution;

drying said biocompatible tissue material;

folding said dried biocompatible tissue material to create cusps or leaflets and a cuffed tubular valve structure;

affixing said folded biocompatible tissue material to the inner cavity of a stent.

9. The method of making a percutaneously implantable replacement heart valve device claim 8, wherein said biocompatible tissue material comprises bovine pericardium tissue.

10. The method of making a percutaneously implantable replacement heart valve device claim 8, wherein said biocompatible tissue material comprises porcine pericardium tissue.

11. The method of making a percutaneously implantable replacement heart valve device claim 8, wherein said biocompatible tissue material comprises autologous tissue obtained from the patient into whom said replacement heart valve device will be implanted.

12. The method of making a percutaneously implantable replacement heart valve device of claim 8, wherein said stent is made of a metal or alloy of metals selected from the group consisting of nickel-titanium alloy, titanium, stainless steel, [add others].

13. The method of making a percutaneously implantable replacement heart valve device of claim 8, wherein said stent is self-expanding when implanted.

14. The method of making a percutaneously implantable replacement heart valve device of claim 8, wherein said stent is balloon catheter expandable when implanted.

ABSTRACT

The present invention comprises a percutaneously implantable replacement heart valve device and a method of making same. The replacement heart valve device comprises a stent member made of stainless steel or self-expanding nitinol, a biological tissue artificial valve means disposed within the inner space of the stent member. An implantation and delivery system having a central part which consists of a flexible hollow tube catheter that allows a metallic wire guide to be advanced inside it. The endovascular stented-valve is a glutaraldehyde fixed bovine pericardium which has two or three cusps that open distally to permit unidirectional blood flow. The present invention also comprises a novel method of making a replacement heart valve by taking a rectangular fragment of bovine pericardium treating, drying, folding and rehydrating it in such a way that forms a two- or three-leaflet/cusp valve with the leaflets/cusps formed by folding, thereby eliminating the extent of suturing required, providing improved durability and function.

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2 Other, description: **EXHIBITS**
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March 8, 2004

PTO/SB/06 (07-06)
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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

	(Column 1)	(Column 2)	SMALL ENTITY ☒		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 12/15/2008	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 37	Minus	** 36	= 1	X $26 =	26	OR	X $ =	
Independent (37 CFR 1.16(h))	* 9	Minus	***8	= 1	X $110 =	110	OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE	136	OR	TOTAL ADD'L FEE	

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/887,688	07/10/2004	David Paniagua	51458.010100	4909

54353 7590 03/16/2009

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EXAMINER	
MILLER, CHERYL L	
ART UNIT	PAPER NUMBER
3738	

MAIL DATE	DELIVERY MODE
03/16/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/887,688	PANIAGUA ET AL.	
	Examiner	Art Unit	
	CHERYL MILLER	3738	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *11-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 27-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 15, 2008 has been entered.

Response to Arguments

Applicant's arguments with respect to claims 1-10 and 27-36 have been considered but are moot in view of the new ground(s) of rejection.

The Bailey et al. (US 6,652,578 B2) rejection has been maintained for some of the claims and the examiner has responded to applicants arguments. The applicant has argued that Bailey does not disclose a *sheet having one or more folds* defining cusps or leaflets. The examiner disagrees. Bailey discloses graft (sheet) *everted* (folded) into leaflets (28). See figure 10 which clearly shows leaflets (28) as a continuum of sheet (graft 11b) that is folded at 27, (see col.9, lines 19-27 which discussed everting the graft material). Bailey's additional cuff fold is when 11a is a continuum of 11b (col.9, lines 27-32) and sheet (graft 11a) is folded inward to form sheet (graft 11b).

The applicant has also argued that Bailey does not disclose the valve body entirely within the inner space of the stent. The examiner disagrees. When the valve body is considered 11b+26, it is entirely within the stent. When the valve body is considered 11a+11b+26, at least

11b+26 is within the valve body (as the *entirety* of the valve is not required by the claims to reside within the inner space).

The applicant has also argued that Bailey does not anticipate the claims as Bailey's device requires valve struts on the leaflets. The examiner disagrees as the applicant's claims do not preclude the use of additional elements such as struts. Although the struts help regulate the flow by helping the leaflets open and close by their bias, the leaflets themselves also help regulate the flow (as flow would not be regulated without the leaflets, if the struts were used alone).

The applicant further argues that patentable weight must be given to the process in a product by process claim. The examiner disagrees. Patentable weight is given only to the end product structure.

It is noted that although Bailey 578' has not been applied herein, the parent patent (Bailey et al. US 6,458,153 B1) has as it is believed to be applicable as a 102(b), see Priority section below. The same response to arguments for the 578' patent corresponds to the 153' patent.

Declaration

The declaration filed on December 15, 2008 under 37 CFR 1.131 has been considered but is ineffective to overcome the Bailey (US 6,652,578 B2) reference.

The evidence submitted is insufficient to establish a conception of the invention prior to the effective date of the Bailey reference. While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a complete disclosure

to another. Conception is more than a vague idea of how to solve a problem. The requisite means themselves and their interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897). Portions of the declaration that are declared to have occurred prior to December 31, 1999 do not provide sufficient support for a valve being *unslit or uncut* and also *an inner and an outer fold*.

Priority

Claims 1-10 and 27-37 have been given the priority date of July 10, 2004.

Regarding claims 1-10, 27-29, and 33-37, the language "unslit", "without slits", and "uncut" are not present in parent application 10/037,266. Although the parent application does not disclose cutting or slitting the valve body, it does not disclose the valve body to be unslit or uncut either. From the figures of the valve in the parent application (fig.1, 2, and 3b for example that best show the leaflets), it is unclear whether or not the leaflets have slits or cuts, as the leaflets appear to have an arcuate shape. Also, the negative limitation of "uncut", "unslit" and "without slits" precludes the use of cutting or slitting, which was not necessarily precluded in the parent application. As such, the limitation "unslit" and "without slits" are given the priority date of July 10, 2004.

The language of claims 5, 6, and 8 is not contained in the parent application (10/037,266) and is given the priority date of July 10, 2004.

Claims 27-32, and 34-35 require an upper border fold and lower border fold, which is not present in the parent application (10/037,266) and is given the priority date of July 10, 2004.

Claims 31 and 35 require two separate sheets attached to one another, not present in parent application (10/037,266) and receive the priority date of July 10, 2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 35 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification and drawings do not seem to provide support for two separate sheets of material, each having a fold, wherein the "upper border of said first sheet joined to said lower border of said second sheet". Although an embodiment of having two separate sheets is disclosed (not shown), the location of the attachment (where joined) is not disclosed. Thus applicant does not have support for the “upper border of said first sheet joined to said lower border of said second sheet”.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 7-10, 27-28, 30-34, and 36-37 are rejected under **35 U.S.C. 102(b)** as being anticipated by Bailey et al. (US 6,458,153 B1; assuming all claims receive a priority date of July 10, 2004). Bailey discloses an implantable heart valve (figs.1-5 for example) comprising an expandable stent (12) and an inner flexible compressible valve (11b+26) made of biocompatible material (col.8, lines 37-40) disposed within the stent (12) and affixed to the stent (see figs) the valve having leaflets without slits (see fig.2; valve body disclosed as a tubular graft 11b extension, col.9, lines 11-20). Bailey discloses the stent (12) to be made of the materials claimed (nitinol; col.8, lines 4-8). Bailey discloses the valve to be formed of biological or synthetic materials (col.8, lines 37-40). Bailey's valve is capable of self-expansion or balloon expansion (col.8, lines 4-8). Bailey discloses an outer cuff portion (considered 11a; which may be integral to 11b and 26; see col.9, lines 20-24). Bailey discloses the sheet of tissue (11b) having an upper border (top of device in fig.4) with an outward fold (material 11b is folded outwardly at 11a; col.9, lines 20-24) and a lower border (bottom of 11b in fig.4) having an inward fold (inward fold/eversion located at 27 forms cusps/leaflets 28). See col.9, lines 11-20. Folds of sheet may be considered 27, 29 or where 11a folds into 11b (see col.9, lines 20-24, this embodiment not shown). Bailey discloses first sheet coupled to second sheet (by seams 29; col.9, lines 48-52).

In the alternative to the above rejection, claims 1, 2, 7-10, 27-28, 30-34, and 36-37 are rejected under **35 U.S.C. 102(e)** as being anticipated by Bailey et al. (US 6,458,153 B1;in the case that the claims receive the priority date of the parent application January 4, 2002). Bailey discloses an implantable heart valve (figs.1-5 for example) comprising an expandable stent (12) and an inner flexible compressible valve (11b+26) made of biocompatible material (col.8, lines

37-40) disposed within the stent (12) and affixed to the stent (see figs) the valve having leaflets without slits (see fig.2; valve body disclosed as a tubular graft 11b extension, col.9, lines 11-20). Bailey discloses the stent (12) to be made of the materials claimed (nitinol; col.8, lines 4-8). Bailey discloses the valve to be formed of biological or synthetic materials (col.8, lines 37-40). Bailey's valve is capable of self-expansion or balloon expansion (col.8, lines 4-8). Bailey discloses an outer cuff portion (considered 11a; which may be integral to 11b and 26; see col.9, lines 20-24). Bailey discloses the sheet of tissue (11b) having an upper border (top of device in fig.4) with an outward fold (material 11b is folded outwardly at 11a; col.9, lines 20-24) and a lower border (bottom of 11b in fig.4) having an inward fold (inward fold/eversion located at 27 forms cusps/leaflets 28). See col.9, lines 11-20. Folds of sheet may be considered 27, 29 or where 11a folds into 11b (see col.9, lines 20-24, this embodiment not shown). Bailey discloses first sheet coupled to second sheet (by seams 29; col.9, lines 48-52).

Claims 1, 2, 7, 9-10, 27, 30, 36, and 37 are rejected under **35 U.S.C. 102(b)** as being anticipated by Garrison et al. (US 6,425,916 B1, cited previously). See figures 32-38 and respective portions of the specification. Garrison discloses a valve device comprising an expandable stent member (111+26d+8d) having an inner space and a flexible compressible valve (6d) disposed in the inner space and affixed to the stent member (see fig.37, 38 for example), the valve (6d) comprising a sheet of biocompatible material (col.10, lines 55-57; col.5, lines 45-60) having at least one fold (folds shown at commissures of valve seen in fig.34, 38; and along the circumference of valve when inverted seen in fig.35) forming the leaflets and no slits (see figs). Garrison discloses the stent to be made of the materials claimed that are self-expandable or

balloon expandable materials (col.5, lines 4-7; col.10, lines 38-50, 59-61). Garrison discloses a first sheet (upper valve 6d having leaflets) folded (at commissures) and a second sheet (cuff attached to 26d and 111) folded (when inverted in figs.35-37), the sheet portions are attached/affixed (integral and connected).

In the alternative to the above rejection, claims 1, 2, 7, 9-10, 27, 30, 36, and 37 are rejected under **35 U.S.C. 102(e)** as being anticipated by Garrison et al. (US 6,425,916 B1, cited previously). See figures 32-38 and respective portions of the specification. Garrison discloses a valve device comprising an expandable stent member (111+26d+8d) having an inner space and a flexible compressible valve (6d) disposed in the inner space and affixed to the stent member (see fig.37, 38 for example), the valve (6d) comprising a sheet of biocompatible material (col.10, lines 55-57; col.5, lines 45-60) having at least one fold (folds shown at commissures of valve seen in fig.34, 38; and along the circumference of valve when inverted seen in fig.35) forming the leaflets and no slits (see figs). Garrison discloses the stent to be made of the materials claimed that are self-expandable or balloon expandable materials (col.5, lines 4-7; col.10, lines 38-50, 59-61). Garrison discloses a first sheet (upper valve 6d having leaflets) folded (at commissures) and a second sheet (cuff attached to 26d and 111) folded (when inverted in figs.35-37), the sheet portions are attached/affixed (integral and connected).

Claims 30 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Bessler et al. (US 5,855,601, cited previously). Bessler discloses a valve device (see figs.1-5) comprising a sheet of biocompatible material (col.4, lines 9-11) folded to form a tubular cuff portion (25; folded to form a cylinder, see figs also shows a folded top edge, see dotted lines in fig.4) and

folded further to form and upstanding cusp or leaflet portion (35) disposed in the inner space of cuff portion (25; see figs.1-5), the cups/leaflets opening and closing in response to blood flow (col.5, lines 37-38).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-6 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bailey et al. (US 6,458,153 B1). Referring to claims 3-6, Bailey discloses an implantable valve, the valve being formed of either biological tissue or biocompatible synthetic polymer (col.8, lines 37-40). Bailey does not however, disclose a specific type of biological material (such as claimed, mammal, porcine, or juvenile pericardium or PTFE or polyester biopolymers). It would have been obvious to one having ordinary skill in the art at the time the invention was made to have the specific biological materials claimed, since it has been held to be within the general skill of a worker in the art to select a known material (mammal, porcine, juvenile pericardium) on the basis of its suitability for the intended use (valve replacement) as a matter of obvious design choice. *In re Leshin*, 125 USPQ 416.

Referring to claim 29, Bailey discloses attachment of the cuff first sheet (11a) to the valve second sheet (11b+26; col.9, lines 47-52 by longitudinal seams), however is silent to mention how the members are coupled (what types of seam). It would have been obvious to one having ordinary skill in the art at the time the invention was made to use sutures, double sutures

to attach the two membranes (cuff and valve) since suturing is a common means of attachment in the vascular art and would be applicable to Bailey's invention. See Fogarty et al, US 6,491,719 B1, cited previously; col.10, lines 5-8 as evidence of common means of attaching layers of material (31, 32) in the vascular art which include stitching, welding, adhering.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHERYL MILLER whose telephone number is (571)272-4755. The examiner can normally be reached on Monday-Friday 7:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Corrine McDermott can be reached at 571-272-4754. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cheryl Miller/
Examiner, Art Unit 3738

/Corrine M McDermott/
Supervisory Patent Examiner, Art Unit 3738

Notice of References Cited	Application/Control No. 10/887,688	Applicant(s)/Patent Under Reexamination PANIAGUA ET AL.	
	Examiner CHERYL MILLER	Art Unit 3738	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,458,153 B1	10-2002	Bailey et al.	623/1.24
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10887688	PANIAGUA ET AL.
	Examiner	Art Unit
	CHERYL MILLER	3738

SEARCHED			
Class	Subclass	Date	Examiner
623	1.24, 1.26, 2.1-2.19	3/12/2009	cm

SEARCH NOTES		
Search Notes	Date	Examiner

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/887,688	07/10/2004	David Paniagua	51458.010100	4909

54353 7590 06/12/2009

MANUEL VALCACEL
c/o GREENBERG TRAURIG, P.A.
1221 BRICKELL AVENUE
MIAMI, FL 33131

EXAMINER	
MILLER, CHERYL L	
ART UNIT	PAPER NUMBER
3738	

MAIL DATE	DELIVERY MODE
06/12/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Interview Summary	Application No.	Applicant(s)	
	10/887,688	PANIAGUA ET AL.	
	Examiner	Art Unit	
	CHERYL MILLER	3738	

All participants (applicant, applicant's representative, PTO personnel):

(1) *CHERYL MILLER (Examiner)*. (3)_____.

(2) *Manuel Valcarcel (Reg No.41,360)*. (4)_____.

Date of Interview: *09 June 2009*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____.

Claim(s) discussed: _____.

Identification of prior art discussed: *Bailey (US 6,458,153), Garrison (US 6,425,916), and Bessler (US 5,855,601)*.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Attorney for applicant argued that support for unslit or uncut is provided in the parent application. When applicant responds, they intend to include references to the parent application which will be evaluated in more detail at that time. Applicant further noted that a prototype was submitted as exhibit b and c, which is not in the electronic file and the examiner will have to search for the location of the prototype. The applicant argued that Bailey shows an external graft. Language such as "including" following the preamble, and the sheet of biocompatible material or valve, "disposed entirely within the inner space of the stent" was discussed which potentially could overcome the Bailey rejections. Language such as "without suturing" the leaflets was discussed with regards to the Garrison reference. Applicant plans to file an official response which will be considered in more detail at that point in time. The applicant may also want to consider claiming the location of the folds, or the inner and outer cuff or entire sheet positioned interior of the stent* .

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

/Cheryl Miller/ Examiner, Art Unit 3738	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

———

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

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PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	10/887,688
Filing Date	07/10/2004
First Named Inventor	Paniagua
Art Unit	3738
Examiner Name	Miller, Cheryl
Attorney Docket Number	051458.010100

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		US- 3,671,979	06-27-1972	Moulopoulos	
		US- 4,056,854	11-08-1977	Boretos et al.	
		US- 4,218,782	08-26-1980	Rygg	
		US- 4,222,126	09-16-1980	Boretos et al.	
		US- 4,759,758	07-26-1988	Gabbay	
		US- 5,163,955	11-17-1992	Love et al.	
		US- 5,509,930	04-23-1996	Love	
		US- 5,571,174	11-05-1996	Love et al.	
		US- 5,653,749	08-05-1997	Love et al.	
		US- 6,126,686	10-03-2000	Badylak et al.	
		US- 6,494,909 B2	08-08-2002	Greenhalgh	
		US- 6,626,938 B1	09-30-2003	Butaric et al.	
		US- 6,773,456 B1	08-10-2004	Gordon et al.	
		US- 7,331,993 B2	10-27-2005	White	
		US-			
		US-			
		US-			
		US-			
		US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
		WO 03/092554 A1	11-13-2003	White/The Gen. Hosp. Corp		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

PTO/SB/08b (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	10/887,688
Filing Date	07/10/2004
First Named Inventor	Paniagua
Art Unit	3738
Examiner Name	Miller, Cheryl
Attorney Docket Number	051458.010100

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		CRIBIER, ALAIN, ET AL., Percut.Transcatheter Implant. of an Aortic Valve Prosthesis for Calcific Aortic Stensosis: First Human Case Descr., Circulation 2002, 3006-08, AHA, US.	
		PANIAGUA, DAVID, ET AL., Percutaneous Heart Valve In the Chronic In Vitro Testing Model, Circulation, 2002, pp.e51-52, Vol. 106, American Heart Association, US.	
		PANIAGUA, DAVID ET AL., First Human Case of Retrograde Transcatheter Implantation of an Aortic Valve Prosthesis, Texas Heart Institute Journal, 2005, pp.91-96, Vol. 32, US.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

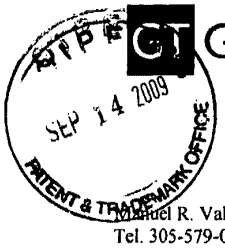
1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

09-15-09

IFW



GT GreenbergTraurig

Manuel R. Valcarcel, Esq.
Tel. 305-579-0812
Fax 305-961-5812
mrv@gtlaw.com

September 14, 2009

VIA EXPRESS MAIL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Re: U.S. Patent Application No. 10/887,688
Invention: Percutaneously implantable replacement heart valve device and method of making same
Revocation/New Power of Attorney, Statement Under 3.73(b), Petition for Extension of Time, Response to Office Action Dated March 16, 2009, Declarations and Information Disclosure Statement
Our Ref. No. 051458.010100

Dear Sir:

Enclosed under cover of this transmittal letter are the following documents:

1. Revocation of Power of Attorney and New Power of Attorney executed by the assignee of the above-referenced application, appointing the undersigned, together with an executed Statement Under 37 CFR Section 3.73(b);

2. Petition for Extension of Time (three months) Under 37 CFR Section 1.136(a), including authorization to charge the small entity petition fee under 37 CFR Section 1.17(a)(3) ($555) and any other required fees to Deposit Account No. 50-1792;

3. Response to the office action dated March 16, 2009 in the above-referenced application, canceling 1 independent claim and 15 dependent claims, and adding 10 new independent claims, 3 new dependent claims and 6 multiple dependent claims (5 multiple dependent claims referring to 16 prior claims and 1 multiple dependent claim referring to 15 prior claims), including authorization to charge the small entity fee for 9 net additional independent claims in excess of 3 under 37 CFR Section 1.16(i) ($110 x9=$990), the small entity fee for 92 net additional claims in excess of 20 under 37 CFR 1.16(i) ($26 x 92=$2392) and the small entity multiple dependent claim fee under 37 CFR Section 1.16(j) ($195) (total claims fees $3,577) to Deposit Account No. 50-1792;

EXPRESS MAIL MAILING LABEL NO. EH 796550831 US

4. Supplemental Declaration Under 37 CFR Section 1.131 together with exhibits including Affidavits of Dr. Gervasio A. Lamas, M.D. and Dr. Paolo Angelini, M.D.;

5. Utility Patent Application Declaration; and

6. Information Disclosure Statement, Form PTO/SB/08a and copies of non-U.S. patent documents listed therein including authorization to charge the Information Disclosure Statement Fee under 37 CFR Section 1.17(p) ($180) to Deposit Account No. 50-1792.

Please charge all required fees noted above and any other required fees for the enclosed submission to Deposit Account No. 50-1792.

Please confirm receipt of the enclosed documents by date-stamping and returning the enclosed postage paid return postcard. Please direct all communications regarding the foregoing to the undersigned.

Respectfully submitted,

GREENBERG TRAURIG, P.A.

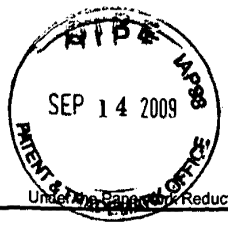
Manuel R. Valcarcel, Esq.
Reg. No. 41,360

EXPRESS MAIL MAILING LABEL NO. EH 796550831 US

MRV/mam
Enclosures

cc: David Paniagua, M.D.
R. David Fish
Endoluminal Technology LLC

MIA 180,806,014v1



PTO/SB/22 (8-00)
Approved for use through 10/31/2002 OMB 0651-0031
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 051458.010100

In re Application of Paniagua, et al.	
Application Number 10/887,688	Filed July 10, 2004
Group Art Unit 3738	Examiner: Miller, Cheryl L.

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows:
(check time period desired):

- ☐ One month (37 CFR 1.17(a)(1)) $ _____
- ☐ Two months (37 CFR 1.17(a)(2)) $ _____
- ☒ Three months (37 CFR 1.17(a)(3)) $ 1110.00
- ☐ Four months (37 CFR 1.17(a)(4)) $ _____
- ☐ Five months (37 CFR 1.17(a)(5)) $ _____

☒ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: $ **555.00**

A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Commissioner has already been authorized to charge fees in this application to a Deposit Account.

☒ The Commissioner is hereby authorized to charge the fee and any additional fees which may be required, or credit any overpayment, to Deposit Account Number 50-1792.

I have enclosed a duplicate copy of this sheet.

I am the
- ☐ assignee of record of the entire interest.
- ☐ applicant.
- ☒ attorney or agent of record.
- ☐ attorney or agent under 37 CFR 1.34(a).
  Registration number if acting under 37 CFR 1.34(a) _____.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

September 14, 2009
Date

Signature

Manuel Valcarcel, Esq.
Typed or printed name (Reg. 41,360)

Burden Hour Statement: This form is estimated to take 0.1 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

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MIA 180,806,008v1

09/15/2009 RMEBRAHT 00000073 501792 10887688

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: Paniagua, et al.
Patent Application Serial No. 10/887,688
Filing Date: July 10, 2004
Title: Percutaneously Implantable Replacement Heart Valve Device and Method of Making Same

REVOCATION OF POWER OF ATTORNEY
AND
NEW POWER OF ATTORNEY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The undersigned assignee and owner of the above-referenced patent application hereby revokes all Powers of Attorney previously granted and hereby appoints **Manuel R. Valcarcel, attorney at law, of the firm of GREENBERG TRAURIG, P.A., with an address at 1221 Brickell Avenue, Miami, Florida 33131**, to transact all business in the United States Patent and Trademark Office in connection therewith. **The correspondence address in the above-referenced patent application shall remain the same, namely: Manuel Valcarcel, Esq., Greenberg Traurig, P.A., 1221 Brickell Avenue, Miami, Florida 33131.** Please direct all future correspondence to this address.

Date: September 3, 2009

Assignee/Owner:

ENDOLUMINAL TECHNOLOGY LLC

Signature: RDFish
Name: R. David Fish
Title: Managing Officer

cc: Manuel R. Valcarcel, Esq.
Greenberg Traurig, P.A.
1221 Brickell Avenue
Miami, Florida 33131

MIA 180,790,817v1

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Endoluminal Technology LLC

Application No./Patent No.: 10/887,688 Filed/Issue Date: July 10, 2004

Titled: Percutaneously implantable replacement heart valve device and method of making same

Endoluminal Technology LLC, a limited liability company
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☑ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

OR

B. ☑ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: D.Paniagua, E. Induni, C.Mejia and F. Lopez To: Endoluminal Technology Research, LLC
The document was recorded in the United States Patent and Trademark Office at
Reel 022532, Frame 0213, or for which a copy thereof is attached.

2. From: Endoluminal Technology Research, LLC To: Endoluminal Technology LLC
The document was recorded in the United States Patent and Trademark Office at
Reel 022532, Frame 0275, or for which a copy thereof is attached.

3. From: R. David Fish To: Endoluminal Technology LLC
The document was recorded in the United States Patent and Trademark Office at
Reel 022899, Frame 0819, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

RDFish
Signature

9.3.09
Date

R. David Fish
Printed or Typed Name

Managing Officer
Title

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No.: 051458.010100
First Named Inventor: Paniagua, David
Patent Application Serial No. 10/887,688
Filed: July 10, 2004
Art Unit: 3738
Examiner Name: Miller, Cheryl

UTILITY PATENT APPLICATION DECLARATION

As a below named inventor, I hereby declare that:

My mailing address, residence and citizenship are as stated below my name,

I believe I am an original, first and joint inventor of the subject matter claimed and for which a patent is sought on the invention entitled "Percutaneously Implantable Replacement Heart Valve Device and Method of Making Same," the specification, including the claims, of which was filed on July 10, 2004 as Application Serial No. 10/887,688, and as amended as attached hereto.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I hereby declare that the subject matter of the attached amendment was part of the invention and was invented before the filing date of the original application identified above for such invention.

I acknowledge the duty to disclose information that is known to me to be material to patentability in accordance with Title 37, Code of Federal Regulations, Section 1.56(a).

The benefit under Title 35, United States Code, Section 119 of United States provisional application(s), and/or Section 120 of any United States application(s) listed below has been claimed by or on behalf of the undersigned previously and said claim is reaffirmed, and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) that occurred between the filing date of the prior application and the filing date of this application:

Prior U.S. Application(s):

Serial No.	Filing Date	Status: Patented, Pending, Abandoned
10/037,266	January 4, 2002	Abandoned

Please direct all correspondence to the attorney of record:

Manuel Valcarcel, Esq.
Greenberg Traurig, P.A.
1221 Brickell Avenue
Miami, Florida 33131

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first joint inventor: David Paniagua

Inventor's signature: Date: September 5, 2009

Mailing Address: 3813 Drummond Street Houston Tx 77025

Citizenship: Costa Rica Residence (City, State, Country)(if different from mailing address):

Full name of second joint inventor: Eduardo Induni

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of third joint inventor: Carlos Mejia

Inventor's signature: Carlos Mejia A. Date: September 5, 2009

Mailing Address: 3503 Deal Street Houston Texas 77025

Citizenship: Colombia Residence (City, State, Country)(if different from mailing address):

Full name of third joint inventor: Francisco Lopez-Jimenez

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of fifth joint inventor: R. David Fish

Inventor's signature: Date: September __, 2009

Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first joint inventor: David Paniagua

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of second joint inventor: Eduardo Induni

Inventor's signature: Date: September _3_, 2009

Mailing Address: Resi Alajuela H 7 Alajuela 906 4050 Costa Rica

Citizenship: Costa Rica Residence (City, State, Country)(if different from mailing address):

Full name of third joint inventor: Carlos Mejia

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of third joint inventor: Francisco Lopez-Jimenez

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of fifth joint inventor: R. David Fish

Inventor's signature: Date: September __, 2009

Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first joint inventor: David Paniagua

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of second joint inventor: Eduardo Induni

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of third joint inventor: Carlos Mejia

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of third joint inventor: Francisco Lopez-Jimenez

Inventor's signature: Date: September 3, 2009

Mailing Address: 200 first St SW, Rochester, MN, USA

Citizenship: American. Residence (City, State, Country)(if different from mailing address):

Full name of fifth joint inventor: R. David Fish

Inventor's signature: Date: September __, 2009

Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first joint inventor: David Paniagua

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of second joint inventor: Eduardo Induni

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of third joint inventor: Carlos Mejia

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of third joint inventor: Francisco Lopez-Jimenez

Inventor's signature: Date: September __, 2009

Mailing Address:

Citizenship: Residence (City, State, Country)(if different from mailing address):

Full name of fifth joint inventor: R. David Fish

Inventor's signature: RDFish Date: September 3, 2009

Address: 6349 Vanderbilt St. Houston, Texas 77005 (Residence)

Citizenship: USA Residence (City, State, Country)(if different from mailing address):