(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 January 2015 (29.01.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/013536 A2

(51) **International Patent Classification**:
G06F 19/00 (2011.01)

(21) **International Application Number**:
PCT/US2014/048059

(22) **International Filing Date**:
24 July 2014 (24.07.2014)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:

61/858,059	24 July 2013 (24.07.2013)	US
61/857,989	24 July 2013 (24.07.2013)	US
61/864,337	9 August 2013 (09.08.2013)	US
61/895,892	25 October 2013 (25.10.2013)	US

(71) **Applicant**: **SHIFAMED HOLDINGS, LLC** [US/US]; 745A Camden Avenue, Campbell, CA 95008 (US).

(72) **Inventors**: **KROLIK, Jeffery, A.**; 745A Camden Avenue, Campbell, CA 95008 (US). **CLAUDE, John, P.**; 745A Camden Avenue, Campbell, CA 95008 (US). **ARGENTO, Claudio**; 745A Camden Avenue, Campbell, CA 95008 (US). **SALAHIEH, Ali**; 745A Camden Avenue, Campbell, CA 95008 (US). **SALAHIEH, Amr**; 745A Camden Avenue, Campbell, CA 95008 (US). **SUMANAWEERA, Thilaka**; 745A Camden Avenue, Campbell, CA 95008 (US). **MERCHANT, Adnan**; 745A Camden Avenue, Campbell, CA 95008 (US). **SAUL, Tom**; 745A Camden Avenue, Campbell, CA 95008 (US). **BOYETTE, Jeremy**; 745A Camden Avenue, Campbell, CA 95008 (US). **BITOUN, Marc**; 745A Camden Avenue, Campbell, CA 95008 (US).

(74) **Agents**: **ZLOGAR, Thomas, M.** et al.; Shay Glenn LLP, 2755 Campus Drive, Suite 210, San Mateo, CA 94403 (US).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2015/013536 A2

(54) **Title**: HEART VALVE SIZING

(57) **Abstract**: Methods and devices for sizing a replacement heart valve.

HEART VALVE SIZING

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to the following U.S. Provisional Applications: 61/857,989, filed July 24, 2013; 61/858,059, filed July 24, 2013; 61/864,337, filed August 9, 2013; and 61/895,892, filed October 25, 2013, the disclosures of which are incorporated by reference herein.

INCORPORATION BY REFERENCE

[0002] All publications and patent applications mentioned in this specification 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.

BACKGROUND

[0003] Replacement heart valves are used to replace or support the natural functioning of a heart valve. The replacement valve can be positioned in a surgical procedure or in a minimally invasive procedure via catheter delivery.

[0004] Before the replacement heart valve is inserted into place, a determination needs to be made about the size (e.g., diameter) of the replacement valve that is to be implanted. Under-sizing can lead to paravalvular leak, while oversizing can cause aortic injury.

[0005] Existing approaches have inflated or expanded a device within the annulus to a known/desired pressure while deforming the annulus, and then determine a diameter to select for the valve based on the expansion at the known pressure.

[0006] Procedural fluoroscopy has been used to gauge the relative stiffness of the aortic root by way of balloons, intentionally under-expanded valves, intentionally under-sized valves, and unintentionally under-expanded valves. One disadvantage of procedural fluoroscopy with balloons or transitional devices include higher stroke risk, cost, and when not retrievable adds a significant procedural risk.

[0007] Approaches and devices are needed that allow a more accurate sizing of the valve to ensure a properly sized valve is implanted.

SUMMARY OF THE DISCLOSURE

[0008] One aspect of the disclosure is a method of calibrating an expandable device used for determining a size of a replacement heart valve to be implanted, comprising establishing a mathematical relationship between a degree of expansion less than a full expansion of the device and a stiffness of an object disposed radially outside the device. In some embodiments the degree of expansion is a percent under-expansion relative to a fully expanded diameter of the device. In some embodiments the degree of expansion less than a full expansion of the device is at a location of the object. In some embodiments the establishing step comprises establishing a mathematical relationship between a degree of expansion less

than a full expansion of a self-expanding device. In some embodiments the establishing step comprises expanding the device within the object and measuring a radial distance between a fully expanded portion of the device and a portion of the device at the location of the object. The method can also comprise computing a degree of perimeter expansion less than a full perimeter expansion, and establishing a mathematical relationship between a degree of perimeter expansion less than a full perimeter expansion of the device and a stiffness of an object disposed radially outside the device. The method can also include comprise computing a degree of area under-expansion, and establishing a mathematical relationship between a degree of area expansion less than a full area expansion of the device and a stiffness of an object disposed radially outside the device. In some embodiments the establishing step comprises imaging the native valve to obtain major and minor axis diameters in at least one of the annular plane, left ventricular outflow tract plane, and sinus of valsalva plane. In some embodiments the establishing step comprises imaging the device while the device is expanded adjacent a native valve. In some embodiments imaging comprises using a 3-D C-arm. In some embodiments imaging comprises using computed tomography. In some embodiments imaging comprises using a 3-D transesophageal echocardiogram. In some embodiments imaging comprises using 3-D multideterctor CT. In some embodiments the method further comprises storing the relationship in a memory device.

[0009] One aspect of the disclosure is a method of using a calibrated sizing tool to determine a size of a replacement heart valve to be implanted, comprising establishing a mathematical relationship between a degree of expansion less than a full expansion of a compliant sizing device and a stiffness of an object disposed radially outside the device. In some embodiments the degree of expansion is percent under-expansion relative to a fully expanded diameter of the device. In some embodiments the degree of expansion less than a full expansion of the compliant sizing device is at a location of the object. In some embodiments the establishing step comprises establishing a mathematical relationship between a degree of expansion less than a full expansion of a self-expanding sizing device. In some embodiments the establishing step comprises expanding the sizing device within the object and measuring a radial distance between a fully expanded portion of the sizing device and a portion of the sizing device at the location of the object. The method can further comprise computing a degree of perimeter or area expansion less than a full perimeter expansion, and establishing a mathematical relationship between a degree of perimeter or area expansion less than a full perimeter or area expansion of the sizing device and a stiffness of an object disposed radially outside the sizing device. In some embodiments the establishing step comprises imaging the native valve to obtain major and minor axis diameters in at least one of the annular plane, left ventricular outflow tract plane, and sinus of valsalva plane. In some embodiments the establishing step comprises imaging the sizing device while the sizing device is expanded adjacent a native valve. In some embodiments imaging comprises using a 3-D C-arm. In some embodiments imaging comprises using computed tomography. In some embodiments imaging comprises using a 3-D transesophageal echocardiogram. In some embodiments imaging comprises using 3-D multidetector CT. In some embodiments the method further comprises storing the relationship in a memory device.

[00010] One aspect is a method of determining a size of a replacement heart valve to be implanted, comprising determining major and minor diameters of an aortic heart valve annulus; endovascularly delivering an expandable calibrated sizing device to a location adjacent the aortic valve annulus and expanding the sizing device within the annulus and into contact with tissue; obtaining an image of the expanded device in a plane that is in alignment with at least one of the major and minor annular diameters; measuring a dimension of the device using the obtained image; determining a degree of expansion of the device less than full expansion, and relating the degree of expansion to an estimated annular stiffness; and selecting a replacement valve size based on the estimated stiffness. In some embodiments expanding the sizing device comprises allowing the sizing device to fully self-expand.

[00011] One aspect is a compliant self-expandable medical device, comprising an expandable compliant device with a central portion that is configured to foreshorten substantially less than proximal and distal portions when the device is allowed to self-expand.

[00012] One aspect is a method of selecting a valve size for implantation within a heart valve annulus, comprising: generating a mathematical relationship between measured changes in a patient's blood pressure and displacement of a native heart valve annulus; and selecting a heart valve size to be implanted within the annulus based on the mathematical relationship. In some embodiments the generating step comprises taking arterial pressure measurements of the patient and obtaining a plurality of images of the heart valve annulus during a cardiac cycle. In some embodiments selecting the heart valve size is based on the mathematical relationship between change in pressure and a dimensional change in the annulus.

[00013] One aspect is a method of selecting a valve size for implantation within a heart valve annulus, comprising generating a mathematical relationship between at least one of radial force and pressure applied to a heart valve annulus, and displacement of the annulus as a result of the at least one of force and pressure; and selecting a heart valve size to be implanted within the annulus based on the mathematical relationship. In some embodiments the method further comprises obtaining an initial dimension of the annulus. In some embodiments the method comprises deforming the annulus with an expandable device at known forces and/or known pressures, and obtaining a plurality of annulus size measurements at a plurality of the know forces and/or know pressures, and generating a plot of the displacement versus the force/pressure. In some embodiments the method comprises deforming the annulus with known forces, and measuring a diameter of the annulus. The method can include analyzing the plot and selecting the heart valve size based on a characteristic of the plot. The characteristic of the plot can be an indication of a change in stiffness, such as an increase in the stiffness.

[00014] In some embodiments the generating step comprises obtaining initial dimensions of the annulus along major and minor annular dimensions. The generating step can further comprise expanding a radial expanding device inside the annulus to deform the annulus at a plurality of known forces, and making a plurality of dimensional measurements of the annulus along the major and minor annular directions in response to each of the known forces. Selecting the heart valve size can comprise analyzing plots of displacement versus force for each of the major and minor directions.

BRIEF DESCRIPTION OF THE DRAWINGS

[00015] Figure 1A illustrates imaging of the basal plane of the aortic valve.

[00016] Figure 1B illustrates a best-fit ellipse showing major and minor annular diameters.

[00017] Figure 1C illustrates major and minor diameters of the sinus of Valsalva.

[00018] Figure 2A illustrates a lateral imaged view of an exemplary self-expanding sizing device.

[00019] Figure 2B illustrates a lateral imaged view of an exemplary self-expanding sizing device.

[00020] Figures 3A, 3B, 3C illustrate a self-expanding sizing device being calibrated.

[00021] Figure 4 illustrates exemplary calibration curves for a sizing device and known exemplary replacement heart valves.

[00022] Figures 5A and 5B illustrate guidelines for recommending certain valve sizes for two of Edwards's Sapien valve.

[00023] Figure 6 illustrates guidelines for recommending certain valve sizes for the CoreValve valve.

[00024] Figure 7 illustrates an exemplary plot of displacement vs force for an exemplary annulus.

[00025] Figure 8 illustrates two curves for a single device, wherein the curves are generated based on the measured distances D1 and D2 during expansion at known forces.

[00026] Figures 9A and 9B illustrate a process for creating a 3-D reconstructing an valve.

[00027] Figures 10A, 10B, 11A, 11B, 12A, and 12B illustrate cross sections of exemplary measurement devices for assessing the shape and size of a heart valve in situ.

[00028] Figures 13A and 13B illustrate an exemplary measurement device with a camera.

[00029] Figures 14 and 15 illustrate an exemplary device for measuring the internal dimensions of a lumen inside the body.

[00030] Figure 16 illustrates a valvuloplasty balloon that incorporates reflectors on one or both ends of the balloon to enhance balloon internal illumination.

[00031] Figures 17A, 17B, 18, 19, and 20 illustrate exemplary masks for painting markers on a balloon.

[00032] Figures 21A, 21B, 21C, and 21D illustrate the effects of valvular disease on a tri-leaflet aortic valve.

[00033] Figures 22A and 22B show the inflation of a valvuloplasty balloon in a healthy valve and in a diseased valve.

[00034] Figure 23 shows an exemplary embodiment of a balloon sizing device.

[00035] Figure 24 shows an exemplary flowchart of the data collection, analysis, and display for the exemplary embodiment in figure 23.

[00036] Figure 25 shows an alternative embodiment of the valvuloplasty catheter described in figure 23.

[00037] Figure 26 shows a further embodiment of a valvuloplasty catheter.

[00038] Figures 27A and 27B illustrate an exemplary embodiment where the internal geometry of the annulus is measured using a plurality of piezoelectric transducers.

[00039] Figures 28A and 28B show an exemplary embodiment in which the piezoelectric transducers are formed using the balloon material itself.

[00040] Figure 29 illustrates an exemplary camera geometry.

[00041] Figures 30A, 30B, 30C, and 30D illustrate an exemplary method of obtaining 3D geometry of the balloon using images acquired from the cameras.

[00042] Figure 31 illustrates an exemplary method of obtaining 3D geometry of the balloon using images acquired from the cameras.

[00043] Figures 32A-32E illustrate an exemplary method of obtaining 3D geometry of the balloon using images acquired from the cameras.

[00044] Figures 33A and 33B illustrate an exemplary method of obtaining 3D geometry of the balloon.

[00045] Figures 34A and 34B illustrate an exemplary embodiment of a valvuloplasty balloon with a user set outer diameter.

[00046] Figures 35A, 35B, and 35C illustrate an exemplary embodiment of an expandable valvuloplasty device.

[00047] Figure 36 depicts an alternative embodiment of a valvuloplasty balloon.

[00048] Figures 37A and 37B illustrates a valvuloplasty balloon with perfusion ports.

[00049] Figure 38 illustrates a valvuloplasty device with an ablation electrode.

DETAILED DESCRIPTION

[00050] The disclosure is related to methods of and devices configured for selecting a size of a replacement heart valve that is to be implanted within a heart valve annulus.

[00051] One aspect of the disclosure includes methods of using a calibrated expandable sizing device to determine the size of the replacement valve that should be implanted. At a high level, a calibrated sizing device is expanded within the native valve, and an amount, or percent, that the sizing device is under-expanded relative to a full expansion size is determined. The amount of under-expansion that occurs can then be used, based on a calibration of the device, to provide an estimate of the stiffness of the annulus in which the sizing device was expanded. The estimated stiffness can then be used to determine the type of replacement valve and/or the replacement valve size that should be implanted. While sizing for a replacement aortic valve is described herein, any suitable valve can be sized using the methods herein, and they can be used for any type of lumen.

[00052] An exemplary step in the methods herein is imaging the valve to determine major and minor annular diameters of a best-fit ellipse of the valve. Imaging techniques can be used to locate the basal plane 003 of the aortic valve annulus, as shown in figure 1A. Additional planes used in combination or separately for determination of a size are the left ventricular outflow tract, and sinus of valsalva. An exemplary method for use at the time of surgery for characterizing valve size involves creating a 3-dimensional reconstruction of the valve region using, for example, a C-arm. Alternative methods, or methods used in concert with the C-arm reconstruction, may include trans esophageal ultrasound, or other forms of volumetric ultrasound, or when a major and minor axis are known multiple planes of 2D ultrasound. The appropriate planes may be determined before the surgery via for instance a multi detector CT. The identified planes may be referenced to anatomical structures such as native leaflet attachments, coronaries. 3D C-Arm reconstruction is currently already being used in some minimally invasive

replacement heart valve procedures as an initial step to determine orientation of the aortic root, so this would not require extra equipment. As set forth above, known software can determine a best-fit ellipse for the annulus (or LVOT or sinus of Valsalva) in the basal plane, and major annular diameter 006 and minor annular diameter 007 of that ellipse in that plane 003 are determined, as shown in figure 1B. The perimeter and area of the best-fit ellipse can also be calculated using the major and minor axis dimensions. The position of the imaging device used to obtain images in the annular plane 003 is stored in memory so the device can be returned to the same position to further image the aortic valve.

[00053] At a point in time after the above imaging step, the calibrated expandable sizing device (explained in more detail below) is endovascularly delivered adjacent the aortic valve. The sizing device is in this embodiment a completely self-expanding compliant device that will expand towards its fully expanded configuration when released from a delivery device (or from any other type of radial restraint). When expanded, a section of the device will not be expanded to the fully expanded configuration where it engages with the annular region. Proximal and distal regions of the device will expand to the fully expanded configuration. The imaging device (e.g., a C-arm) is repositioned to the stored positions and images are taken, with the sizing device expanded in place, in planes that are in alignment with the major and minor annular diameters previously determined. Exemplary lateral profiles of the expanded device are shown in figures 2A and 2B, with figure 2A being in a plane perpendicular to the basal plane and including the major axis diameter, while figure 2B is in a plane perpendicular to the basal plane and including the minor axis diameter. The image planes are orthogonal to one another. Images at the LVOT and sinus of Valsalva are also obtained, as shown in figure 1C.

[00054] In this embodiment the sizing device is configured to self-expand to a fully expanded configuration. That is, additional forces to expand the device are not required, but in other embodiments the device could be configured to be at least partially expanded via expansion forces. The constrained central portion 009 of the expandable device (i.e., the "waist") can be seen in figures 2A and 2B, while distal and proximal portions have expanded to a greater extent to the fully expanded configuration. The central portion of the device includes visual markers 008 (in this embodiment they are radiopaque markers). When imaged, as shown in figures 2A and 2B, the markers 008 can be used to determine the dimension at the waist. Since the fully expanded diameter of the device is known, the amount of "under-expansion" of the device at the waist can be determined. The amount of "under-expansion" is considered the amount by which the device, at the waist portion (but it can be any other portion along its length), is not fully expanded. The degree of expansion of the waist portion could similarly be characterized as the percent of expansion (i.e., rather than under-expansion).

[00055] The waist dimensions (in the two directions) can also be used to calculate the sizing device perimeter and area at the annulus using known relationships. The amount of under-expansion of the device perimeter and area at the annulus can thus also be determined. The device under-expansion can be an under-expansion in one or two dimensions (e.g., comparing it with native major and minor annular diameters), a perimeter under-expansion (comparing it with the fully expanded perimeter), or an area under-expansion (comparing it with the area of the device when expanded). Any type of under-expansion

can be used, depending on the measurements taken. In some embodiments the under-expansion is a perimeter under-expansion. In some embodiments it is an area under-expansion. The degree of under-expansion after expanding the device will be used as described below.

[00056] In this embodiment the sizing device is calibrated so that an amount, or degree, or under-expansion (which could alternatively be characterized as "percent expansion") is related to a known stiffness (N/mm^2) of an object radially disposed at the location of the under-expansion. That is, a mathematical relationship is known between a percent of under-expansion and radially applied stiffness at the location of under-expansion. In this embodiment the sizing device is calibrated by expanding it within a plurality of annuluses or representations of annuluses with known stiffnesses. The sizing device has a pre-set manufactured diameter. Figures 3A-3C illustrate an exemplary method of calibrating the sizing device. Figure 3A shows the device fully self-expanded 011 wherein the device has substantially the same diameter in the most expanded portion. In figure 3B the device is positioned within an O-ring 010 and allowed to self-expand within the O-ring, wherein the O-ring has a known stiffness. Because the O-ring has a diameter less than the fully expanded size, a central portion of the sizing device does not expand to the fully expanded size, and forms a "waist." The device is thus expanded within an "annulus" that has a known stiffness. The distance between the outer edge of the fully expanded device and the outer edge of the device at the annulus 012 is measured, and is considered to be the under-expansion distance at the annulus (i.e., the distance that represents how much under-expanded the sizing device is at the annulus.) For the particular stiffness the percentage of under-expansion is recorded. The sizing device is then expanded within as many annuluses (real or representative) as possible, and the resulting percentage of under-expansion of the device is recorded. Figure 3C illustrates an expansion within two O-rings. Based on these recordings, a plot (mathematical relationship) of annulus stiffness vs percentage under-expansion is generated for the sizing device. Thus, for any measured percentage of under-expansion of the device, an estimate can be made for the stiffness of the annulus (real or representative) in which it was expanded. The sizing device is thus calibrated based on annulus stiffness and under-expansion.

[00057] The sizer can be calibrated initially with bench tests, such as using O-rings or other known stiffness devices. The calibration can also be improved over time using, for example, cadaver or clinical results from actual implantations. The calibration is thus not necessarily a static calibration for a particular device. Data can be compiled from a variety of sources and used to improve the sizing device's calibration. In this way the accuracy of the calibration can improve over time.

[00058] In this embodiment, relationships between vessel stiffness and replacement valve under-expansion are also similarly created for minimally invasive replacement heart valves. For example, the Sapian valve manufactured by Edwards and the Corevalve valve are also tested so that a mathematical relationship can be established for annular stiffness and valve under-expansion. Figure 4 illustrates exemplary calibration curves for a sizing device ("sizer") as well as three known exemplary minimally invasive replacement heart valves.

[00059] As set forth above, the amount of under-expansion for the sizing device is determined at the annulus (e.g., perimeter, area, one or two dimensions). Using the calibration for the sizing device, the estimated stiffness is easily determined, as shown in Figure 4. The amount of under-expansion for as many different possible replacement valves can then be determined using the estimated stiffness from the sizing measurements and calibration curve. For example, in figure 4 a percent of under-expansion for each of the three exemplary replacement valves can be determined based on the estimated annular stiffness.

[00060] In general, slight overexpansion of the replacement valve in the annulus is preferred to make sure the replacement valve anchors sufficiently in the annulus. In general, because different types of expandable replacement valves are different, the amount of desired overexpansion for each type of replacement valve will be slightly different. Currently, physicians use general guidelines for valve size based on original aortic root measurements. The guidelines that are used are on based on studies, that is, after the implantation investigators went back and figured out how much overexpansion provided adequate valve anchoring. This is obviously not an exact approach. In some embodiments the replacement valve (of the possible replacement valves) with the under-expansion value or "device oversizing" amount most in line with sizing guidelines for that particular replacement valve is selected. The emerging multi-detector computed tomography ("MDCT") sizing guidelines are device specific and expressed in terms of an "oversizing" percent defined as nominal valve dimension / MDCT annular dimension. For the Sapien valve the recommended oversizing is about 5-20% by area or about 2.5 - 9.5% by perimeter (using MDCT area derived diameters). For the CoreValve valve the recommended oversizing is about 20-35% by area or about 9.5-16.2% by perimeter (using MDCT perimeter derived diameters). The current practice is thus to obtain the native annular dimension(s) using the CT multi-detector, then implant a valve with that has an "oversizing" percentage in the ranges above. This is how the current guidelines are used to select a replacement valve that is slightly oversized relative to the native annulus.

[00061] Figures 5A and 5B illustrate guidelines for recommending certain valve sizes for two of Edwards's Sapien valve. Figure 6 illustrates guidelines for recommending certain valve sizes for the CoreValve valve. The "annulus range" portion of the guidelines provides ranges for particular sized valves. For example, if the area of the annulus from CT measurements is between 300 mm^2 and 380 mm^2, a 23 mm diameter valve may be best for oversizing.

[00062] Using the curves in figure 4, once the estimated stiffness is determined, the valve that provides the optimal oversizing based on the guidelines can then be selected for implantation.

[00063] The sizing devices can be manufactured using a variety of techniques and materials. In some embodiments, the device is a nitinol tube that formed by two sections, each of which is laser cut with a particular pattern at one end portion. The end portions are then expanded and shape set into the expanded configuration. The ends are then attached together, in some embodiments being crimped together with radiopaque markers. In some embodiments the central section (axially) is configured not to foreshorten

when the device is expanded (contrary to the proximal and distal expandable portions). This can make making measurements easier.

[00064] A retractable sizing frame is safer and more affordable than non-compliant balloons or the transitional replacement heart valves that have been used for sizing.

[00065] A second aspect of the disclosure is estimating the stiffness of the annulus by making more than one measurement with a radially expandable device, and then determining a valve size based on the estimated stiffness of the aorta. In some embodiments this aspect includes generating a mathematical relationship between at least one of radial force and pressure applied to a heart valve annulus, and displacement of the annulus as a result of the at least one of force and pressure, and selecting a heart valve size to be implanted within the annulus based on the mathematical relationship.

[00066] Methods of endovascularly accessing the locations of heart valves are known, and any of the methods herein can include delivering a delivery catheter to the location of a heart valve using known techniques and access routes.

[00067] Some embodiments are a method of determining a replacement valve size that includes positioning a radial expander within the valve annulus, expanding the radial expander, and making a plurality of measurements about the size of the radial expander as the expander is expanded. A radial expander is used herein to refer to a device configured to radially expand, and can be compliant or non-compliant. An example is the compliant self-expanding sizer shown in figures 2A and 2B. Radial expanders include without limitation compliant and non-compliant balloons and other expandable structures (e.g., stents or braided devices). In some embodiments the radial expander comprises a plurality of markers that are adapted to be used to make measurements about the size of the expander as it is radially expanded.

[00068] The devices can be configured so that the force and/or pressure of the device are known throughout the expansion of the device. For example, the device can be calibrated so that the pressure in an expandable balloon is directly known throughout the expansion of the balloon (e.g., with a pressure sensor). Alternatively, the device can be calibrated so that the radial force is known throughout the expansion of the device. A relationship can thus be determined between radial force (or pressure) and the size of the device (via the markers or other indicators)

[00069] When a device is expanded within a heart valve annulus and into contact with tissue, there is an amount of initial elasticity in the tissue. As the device continues to be expanded, the expansion will be met with greater and greater resistance from the tissue. By expanding a calibrated radial expander within an annulus, size measurements taken using markers on radially outermost portions of the device can be used to create a mathematical relationship between the force and the size of the device as it is expanded. For example, a stiffness (Force / displacement) of the annulus can be estimated using the relationship between force (calibrated from the device) and tissue displacement (which is determined by measuring distances between markers on the radial expander).

[00070] Figure 7 illustrates an exemplary plot of displacement vs force for an exemplary annulus. The curve was obtained by plotting the points indicated, and the points were obtained during the expansion of

a radial expander. A device calibrated with known radial forces and with markers on the radially outer portions thereon was expanded in an annulus. A collecting of images were taken, and correlated to known radial forces from the device. The diameter of the device is then determined using the collected images at the known forces. The curve can then be plotted, which represents the compliance of the annulus tissue.

[00071] The curve illustrates an initial elasticity of the tissue as radial force is initially increased, followed by a general plateauing of the curve as radial force continues to be increased. The plateauing illustrates a greater radial resistance from the tissue against the expansion of the device. One consideration when determining the size of a valve to implant is a desire to avoid undersizing. One way in which the curve can be used is to select a size (displacement) is to select a size that is on the curve and to the right of where the curve starts to plateau. By selecting this size there is confidence that the heart valve will be anchored into tissue when there is sufficient stiffness in the tissue.

[00072] In alternative embodiments a mathematical relationship can be created between pressures applied and displacement.

[00073] In some alternative embodiments different views of the device can be obtained during the device expansion. Obtaining different views of a calibrated and marked device during expansion can be used to correlate known radial forces to different sizes of the device in the different views, which can provide a better indication about the size and shape of the annulus. Images can be obtained in the same manner as in figures 1 and 2, or using other techniques described herien.

[00074] Knowing major and minor annular diameters allows for the radial expander to be (once positioned within the annulus) imaged in those planes (similar to figures 2A and 2B above) and so that changes in the size of the device can be related to the initial dimension of the annulus. Mathematical relationships can thus be created for the stiffness of the annulus at different places. In this example, the stiffness along the major and minor annular axes can be determined.

[00075] Figure 1B again illustrates the major and minor annular diameters of the annulus. Figures 2A and 2B represent an image of the device once positioned within the annulus expanded into contact with tissue. The 2-D image plane in figure 2A is the same as a plane that includes the major annular diameter. The dimension D1 thus represents the outer dimension (in this case diameter) of the device measured along the major axis diameter line. The 2-D image plane in figure 2A is the same as a plane that includes the minor annular diameter. The image planes in figures 2A and 2B in this case are orthogonal to each other. They need not be orthogonal if, for example, other initial dimensions of the annulus can be reliably obtained. In this example the images are obtained using a C-arm device used in the imaging in figures 1A-1C. To do this the positions of the major and minor axes are stored once obtained, allowing images to be taken along those axes with the C-arm device.

[00076] The images shown in figures 2A and 2B illustrate an expansion state of the device at one point in time. Images would be obtained in each of the views throughout the expansion of the device. Thus, the device calibrated with radial force can be used to expand the tissue, and measurements D1 and D2 are obtained during the expansion. The diameters of the device (D1 and D2) in different fields of view can

be related to known radial forces applied to the device. Mathematical relationships can thus be created at multiple annular locations between the applied force and the size of the device, which can represent the displacement of tissue.

[00077] Figure 8 illustrates two such curves for a single device, wherein the curves are generated based on the measured distances D1 and D2 during expansion at known forces. Distances D1 and D2 at zero force represent initial dimensions of the major and minor annular diameters.

[00078] Having two stiffness curves provides a better understanding about the size and shape of the annulus. For example, a protrusion in the valve could be revealed with two mathematical relationships rather than just one.

[00079] Views along more than two imaging planes can provide even more detail about the annulus and its stiffness.

[00080] Figures 9A and 9B represent how the images from figures 2A and 2B can be used to re-create the annulus in 3-D, which provides a better understanding about the complete size and shape of the valve.

[00081] Figures 10A-12B illustrate cross sections of exemplary measurement devices for assessing the shape and size of a heart valve in situ.

[00082] In some embodiments the measurement device includes an optical camera (e.g., UV to IR), figuratively represented as 820, in figures 10A and 10B within an expandable balloon 801, the balloon filled with a media clear to the optical energy to which the camera is tuned. There can be two cameras, or more, in the balloon situated to provide a substantially 360 degree view of some circumference of the balloon. The device can include a set of markers 810 whose size remains substantially constant and in the field of view of the camera and proximate to the surface being measured. The above features can be carried at or near the distal end of a percutaneous delivery system 802, or carried at or near the distal end of an endovascular delivery system.

[00083] The markers can be used to calibrate distance as a function of location within an image captured by the camera. The markers can be comprised of markings or features on the surface of the balloon. The markings or features can exhibit a strain of less than 2% when the balloon is inflated to its operating pressure.

[00084] The markers can be a feature such as a transition associated with a necked region 918 of a balloon 917. The necked transition can strain less than 2% at the operating pressure of the balloon as illustrated in cross section figures 11A and 11B. Such features are imaged in the field of view 923 of camera 920. Figure 11B illustrates the transition regions 916 and 919, the most proximal and distal regions associated with the necked region 918.

[00085] Some embodiments include an algorithm adapted to make measurements of a body lumen whose image has been captured by the camera wherein the image incorporates images of the markers and the images of the markers are used to create a mapping of distance between pixels to distance between features in the image. Individual local values of the mapping may differ as a function of location in the image. The local values of the mapping can be approximately equal for pixels that fall within a ring perpendicular to the optical axis. The system and algorithm can be used to estimate the diameter of a

heart valve. The system and algorithm can be used to estimate the circumference of a heart valve. The system and algorithm can be used to measure the compliance estimate.

[00086] The markers can be in a random pattern or in a regular pattern. The markers can be in a thin layer of elastomeric material affixed to the outer or inner surface of the balloon. The elastomeric material can be created by dip coating.

[00087] In some embodiments the balloon is comprised of a material capable of sustaining less than 2% strain at operational pressures where the markers are either an integral feature of the balloon such as a variation in thickness, or affixed to the surface of the balloon such as by printing.

[00088] The balloon can be comprised of a material capable of sustaining greater than 2 to 10 percent strain. The balloon can be comprised of a material capable of sustaining greater than 10 percent strain.

[00089] The device can include a set of markers used to locate an expansible section of the balloon within the valve.

[00090] The balloon can comprise a central section which is substantially more compliant than the balloon's proximal and/or distal portions. "Substantially" can be a factor of greater than 20%. "Substantial" can imply capable of sustaining strains of 25% at 4 atm. The compliant section can comprise markers which in situ strain less than 2% when the balloon is subjected to 4 atm.

[00091] In some embodiments, shown in cross section figures 12A-13B, the device 1001 includes an optical camera 1020 in a balloon filled with a clear fluid, the camera being at a known and fixed distance from a necked region in a central region of the balloon. The proximal and/or distal regions of the necked region can be substantially less compliant then the mid-section of the necked region. The camera is located at a proximal location on the balloon. Alternatively the entire necked region can exhibit less than 2% strain at up to 4 atm. The circumference and diameter of the proximal and/or distal transitions or edges 1016 and 1018 in figure 12B of the necked region are known and in some embodiments imaged by the camera prior to use of the balloon. The image of the diameter and circumference of the edge region can be used to calibrate and image the central necked region. The calibration can be used on an image of the balloon and or tissue surrounding the balloon, to measure a heart valve diameter and/or circumference. The calibration can be used in the assessment of the shape of the perimeter of the heart valve. The balloon can be percutaneously delivered to a heart valve in a patient. The balloon can be endovascularly delivered to a heart valve of a patient. The balloon can also be used to perform a valvuloplasty.

[00092] Figures 14 and 15 illustrate an exemplary device for measuring the internal dimensions of a lumen inside the body. The device has a distal inflatable member 1219 designed to be placed inside the section of the lumen to be measured. The device has an imaging system 1210 capable of imaging the internal surface of the inflatable member and therefore creating an image of the internal surface of the lumen to be measured. The imaging system can be connected to computational means, which can be capable of performing image analysis on the image created of the inside surface of the inflatable member. The image analysis can be designed in such a way as to compute the internal dimensions of the inside surface of the lumen. The device includes a guidewire lumen for carrying a guide wire 1212 placed

through the inflatable member, in such a way as it is centered on the inflatable member. The device includes one or more cameras comprised in a camera housing 1224 disposed around the guidewire lumen and placed in such a way as to allow imaging of the internal surface of the inflatable member. The device includes a plurality of light sources comprised in a light source housing 1225 to illuminate the internal surface of the inflatable member. In some embodiments the most proximal surface of the balloon 1219, that surface closest to the camera housing, is coated with a diffuse reflective material and the light source is directed towards the diffuse reflector. The inflatable member may include features in its surface to facilitate imaging analysis and computation. The inflatable member may comprise variable wall thickness to allow for variable compliance.

[00093] The devices can have any combination of the following: one or more imaging devices herein imaging device; one or more light sources herein light source; a pressure sensor; a balloon; an elongate shaft; a fluid source capable of delivering fluid pressures in excess of 1 atm and more preferably 4 atm at fluid flows of greater than 1.25mL/min and more preferably 20ml/sec; the balloon affixed the distal end of the elongate shaft; the elongate shaft comprising a guide wire lumen; the elongate shaft comprising a pressure monitoring lumen; the elongate shaft comprising a balloon pressurization lumen; the proximal end of the pressurization lumen in fluid communication with the fluid pressure source; the distal end of the pressurization lumen in fluid communication with the internal volume of the balloon; the imaging device comprised within the balloon; the light source comprised within the balloon; the imaging device carried on the elongate shaft; the balloon comprising means to calibrate length in the images captured by the imaging device, said means comprising markings on the balloon; the balloon comprising reflective surfaces, said surfaces having a reflectivity greater than that associated with the miss match in refractive index between the balloon filling media and the balloon material refractive index, or the reflective surfaces comprised of metalized coatings on the balloon surface; a pressure control system usable to control the fluid source; a fluid flow control system usable to control in the fluid source, where the flow and pressure control is the physician.

[00094] The devices can be configured for any of the following: imaging in 3D of an included angle of between 270 to 360 degree, measured normal to the longitudinal axis, portion of a heart valve annular surface profile; spanning longitudinally at least the annulus or at least 10 mm and more optimally 50mm; where imaging is carried out using light energy in the band pass of between 200 nm and 3000nm; 3D mappings of the heart valve at each of a number of balloon inflation pressures. Typically spanning pressures from 6 atm to .1 atm gage (typically at greater then 40Hz); Measurement of inflation pressure through remote lumen or internal sensor; where the pressure change as a function of time and volume may be controlled in a non-linear fashion; where the pressure is allowed to change at a faster rate at higher pressures; where the pressure is allowed to change at a faster rate at lower pressures; where the pressure is allowed change at a slower rate at intermediate pressures; where the pressure is changed in an incremental fashion such as to synchronize with the imaging device frame rate; an algorithm and its use for the translation of a balloon internal pressure to a pressure delivered at the surface or interface of the balloon and the heart valve; where surface pressure is the delta between the balloon pressure and the

pressure required to distend the balloon to the size required to stretch the balloon segment to the measured perimeter (The balloon compliance can be in the range of 1% to 5% at burst pressure; 5% to 10% at burst pressure, or 10% to 30% at burst pressure); this delta calculated both with and without correction for the shear in the balloon. The interface pressure can be used to calculate a compliance measure associated with a portion of the valve perimeter, where that valve perimeter comprises the valve annulus. The mapping can be gathered during the depressurization of the balloon post annuloplasty pressurization. Generation of the data sets can comprise valve perimeter, min diameter, max diameter, eccentricity, sectional area, compliance, each as a function of pressure, such data sets comprising both average and segmental data in both the radial and longitudinal directions. The data sets can be used as the partial or total basis in a selection procedure for the identification of a type and or size of TAVR heart valve, said selection procedure comprising the incorporation of compliance data for the TAVR valves under selection consideration, or said selection procedure comprising planning with integration in combination of any of the data sets and any combination of CT, TGE, TEE, MRI, or any other visualization modality data. A database can be maintained as a basis for improving said selection procedure wherein final sizing information is fed back to the size selection algorithm. A tool can be used to evaluate implant compliance for the purpose of providing input into such a sizing procedure.

[00095] The valvuloplasty balloon can incorporate reflectors on one or both ends 1426 and 1428 of balloon to enhance balloon internal illumination (see fig 16). Said reflectors can comprise a metalized coating on the balloon on the proximal end of the balloon, or a non specular (diffuse) reflecting coating on the surface of the balloon. The reflectors 1427 can be on a cylindrical portion of the balloon and/or the distal portion of the balloon 1428. The balloon material can be a diffuse material, such as by nature of the material (e.g., nylon), by using a filler such as BaSO4, or TiO2 coating, for example. The balloon can include a LED illumination internal to the balloon. The illumination can be maintained at a constant level. The illumination can be ramped to achieve selective illumination proximal and distal to the imager. The LED's 1430 can be placed at one or more positions longitudinally with respect to the camera not shown at the proximal end. The LED's can be mounted within a diffuser to prevent specular reflection. The illumination can be pulsed, where the LED pulsations are synced with any or any combination of: incremental pressure changes; pressure set points; image frame capture period. The pass band of the illumination can be: narrow such as a red LED, matched to either or the sensitivity of the camera or the absorbance of materials on the surface of the balloon; selected so as to excite fluorescence at a wavelength distinct from the illumination wavelength; where a circular polarizer is used in front of the imager to reduce the effect of specular reflections.

[00096] The balloon can include markers for use in calibrating length measurements in the images captured by the imaging system. The markers can be of known dimension such as a grid. The markings can be markings on the surface of the balloon. The markings can be comprised of a material with equal or greater compliance that the balloon. The markers can be fibers within the wall of the balloon, or texturing on the surface of the balloon, for example. The markers can be a series of longitudinal lines configured to provide perspective correction, such as is illustrated in masks for painting markers on a

balloon in figures 17-20. The markers can be an ordered or random pattern of discrete marks, and can be a material that fluoresces or a material that contrasts with the surrounding balloon. The markers can be uniquely identifiable fiducials placed to allow stereoscopic reconstruction of the pattern. The system can include an algorithm to determine the change in dimension of the markers or fiducials to compensate for their change in dimension associated with pressurizing the balloon. The device can include an internal shaft comprising markings indicative of distance along the shaft.

[00097] Some existing approaches to valve sizing include 2-D fluoroscopic images of a balloon inflation using a marker of known size to determine the annulus size under balloon inflation. The disclosure now expands upon the concept of using the balloon to assess the annulus dimensions, but includes a number of strategies to provide a more accurate assessment, and also provide a more granular understanding of the relationship between pressure applied by the balloon and the resulting annulus dimensions.

[00098] Figures 21A-D show the effects of valvular disease on a tri-leaflet aortic valve. An annulus 2432 exists in the heart of a patient. Three leaflets 2433 exist within the annulus, and are shaped from a strong, thin tissue such that they are moveable between an open and closed configuration. Figures 21a and 21c show the valves in a closed configuration for a healthy valve and a diseased valve, respectively. The closed configuration serves to prevent blood flow back into the heart from the aorta. Figures 21b and 21d show the valves in an open configuration for the healthy valve and diseased valve respectively. The open configuration serves to allow blood to be ejected from the ventricle of the heart, and into the aorta. The healthy valve shown in figures 21a and 21b can be completely closed and opened during the cardiac cycle, allowing proper hemodynamic performance of the heart. Figures 21c and 21d show the diseased valve, where diseased areas (3) affect the opening and closing of the leaflets. In figure 21d, it can be appreciated that the valve leaflets are not opening to the same degree as in figure 21b, resulting in a suboptimal hemodynamic performance due to the increased resistance of blood passing through the valve.

[00099] Figured 22A and 22B show the inflation of a valvuloplasty balloon (2536, 2537) in a healthy valve (fig 22a) and in a diseased valve (fig 22b). The balloon expands to fill the area within the leaflets and push them against the annulus. A healthy valve, shown in figure 22a, results in a substantially round balloon cross section (2536) as the leaflets are free to move with the balloon during expansion. A diseased valve, shown in figure 22b, is not able to expand evenly, resulting in an irregular balloon cross section (2537). In the traditional method of evaluating the annulus size, an interventionalist eye 2535 would look at a 2-dimensional image of the balloon inflation to determine the size of the annulus during balloon inflation. One issue that can be appreciated in figures 22a and 22b is that a single 2-D image may give a false representation of the true condition of the valve during valvuloplasty. Figures 22a and 22b would look very similar when viewed in a side projection as shown, leaving the interventionalist the impression that these two valves should use the same valve size for both figure 22a and 22b. In the case of Figure 22b, that valve would have an over-sized valve placed, potentially resulting in poor valve implant performance and/or valve reliability issues. Additionally, an improperly sized valve may result in damage to the heart's natural pacing mechanism. Knowing that 2-D images are imperfect indicators of true annulus size may also lead interventionalists to estimate the annulus to be smaller than is truly is,

resulting in an under-sized valve replacement, potentially resulting in poor valve fixation or para-valvular leaks.

[000100] Figure 23 shows an exemplary embodiment of a balloon sizing device. The device includes an elongate shaft 2638 having a proximal end 2639 and a distal end 2640. A balloon 2601 is mounted on the shaft, and an inflation lumen is contained within the shaft to inflate or deflate the balloon. A guidewire lumen 2612 is also provided, and the device may be tracked over a guidewire and into the annulus. The device functions similarly to any valvuloplasty balloon, in that the balloon is inflated to expand the leaflets, and may also stretch the annulus and any diseased areas on the leaflets as a result of pressure applied within the balloon envelope. Unique to this embodiment is the inclusion of an optical coherence tomography (OCT) instrument 2641 contained within or adjacent to the shaft. Similarly, a pressure monitoring instrument is contained on the proximal end of the device, or preferably near or within the balloon envelope. The OCT instrument 2641 has a field of view directed at the portion of the balloon that expands the leaflets and annulus. In use, the balloon is positioned within the native valve, inflated, maintained at a desired pressure, and then deflated. During the inflation, pressure maintenance, and deflation, the OCT and pressure measurement instruments are actively collecting data on the geometry of the inflated valve and the associated pressure within the balloon.

[000101] Figure 24 shows an exemplary flowchart of the data collection, analysis, and display for this exemplary embodiment. The process starts with the initial collection of data, including valve dimensional data and pressure data. This step may be completed using simple electronic collection and storage hardware contained within a disposable handpiece. Alternatively, the data may be collected and simultaneously transmitted to data analysis hardware. In the next step, analysis is performed on the data. This may include post-processing of the raw data collected by the handpiece (i.e. post-processing of the OCT sensor signal, or other sensor signals). Additionally, the data is combined with the pressure data to create an estimate of compliance of the annulus, with the compliance (comp) defined as: $comp=\delta/F$, where δ is the displacement of a segment of the annulus and F is the force applied to that segment of the annulus. The compliance may be calculated for many small segments of the annulus to aid in the definition of areas that have more compliance, and areas that have less compliance within the annulus. This estimation is similar to annulus compliance estimation provided above.

[000102] Lastly, the analyzed data is presented to the user to aid their understanding of the annulus prior to valve implantation. Data presented to the user may include compliance (or a compliance map), shape of the annulus, size of the annulus, and any irregularities such as protrusions or other deviations from the typical annulus shape.

[000103] Figure 25 shows an alternative embodiment of the valvuloplasty catheter described in figure 23. Instead of the OCT sensor, this embodiment includes an ultrasound transducer 2842 within the balloon. The ultrasound transducer emits ultrasound energy 2843, and receives any ultrasound energy that is reflected back by the balloon internal surface. The time required for the ultrasound energy to pass from the transducer and be reflected back to the transducer can be used to calculate the distance from the transducer to the inside of the balloon envelope. The transducer can be rotated about the long axis of the

device, and also moved axially along that axis to cover the entire internal surface of the balloon. Similarly to the OCT probe in Figure 2, this information can be used to drive the analysis described in Figure 24.

[000104] Figure 26 shows a further embodiment of the valvuloplasty catheter. In this embodiment, a light detection and ranging (LIDAR) sensor 2944 is included within the balloon. Similar to the ultrasound sensor described in Figure 25, the LIDAR sensor can measure the distance from the sensor to the inside of the balloon, and is similarly rotated and moves axially along the balloon to map its internal surface geometry. Again, similarly to figures 23 and 25, the geometry data is used in the process described in figure 24 to provide annulus information for valve sizing and placement. In this case, rays of light 2945 are transmitted to the balloon inside surface, and the returned reflections are used to determine distance from the sensor.

[000105] Figures 27A and 27B show a further embodiment, where the internal geometry of the annulus is measured using a plurality of piezoelectric transducers 3046. To determine the internal geometry of the annulus, a transducer emits an ultrasonic pulse 3047, and the other transducers measure the time required to receive the pulse. This is repeated for the other transducers, resulting in a data set that can be used to triangulate the relative position of each of the sensors against the other sensors. Given the known position of the sensors relative to the annulus, the geometry of the annulus can be modeled.

[000106] In an alternate embodiment the peizo electric elements in the embodiment in figures 27 may be replaced with magnetic sensors, such as but not limited to hall effect devices, magnetostrictive devices, or coils printed on the balloon. An antenna or antennas may then be mounted on the central guide wire lumen. The distance between the sensors and the central lumen may then be ascertained by measuring the changes in field strength measured by the sensors. In some embodiments when using a hall effect or magnetostrictive device the central antenna may be replaced with a magnet or electromagnet. In yet other embodiments the antenna or set of antennas may be placed outside the body, and the 3D location of the sensors calculated to characterize the shape of the polygon they form when expanding into the valve. In yet other embodiments the sensors may be mounted on the cage like structures such as those of figures 2 and 3. In figures 3B or 3C the sensors would optimally be placed around the central axis along the plane passing through the rings wrapping around the cage. The sensors can be communicated with via traditional flex circuits and/or cables fixed to the surface of the balloon or cage, depending on the expandable structure. The sensors can also be disposed on the surface of the balloon or other expandable structure.

[000107] Figures 28A and 28B show an exemplary embodiment. In this figure, the piezoelectric transducers 3146 are formed using the balloon material itself. The material undergoes a bi-axial elongation during the balloon blowing process, and can be poled (i.e. the magnetic poles of the polymeric structure being aligned) by applying a strong magnetic field to the desired locations on the balloon during the blowing process. Electrical connections to the transducers may be made with a conductive layer within the balloon 3148 and conductive traces 3149 to each transducer formed on the outside of the

balloon. The conductive elements on both the inside and outside of the balloon may be formed via a material deposition process (i.e. sputtering, direct painting, spraying, and the like).

[000108] Embodiments in which an expandable balloon is used to determine the size of a replacement valve. An exemplary method includes inserting a balloon into the aortic valve; images from one or more cameras inside the balloon are acquired during the inflation and deflation phases of the balloon; the 3-D geometry of the balloon is continuously measured using the images; the pressure inside the balloon is also measured synchronous with the images; the minimum cross-section of the balloon is determined from the 3D geometry of the balloon; one or more metrics characterizing the size of the minimum cross-section is estimated and plotted against the pressure inside the balloon; the size of the minimum cross-section corresponding to a preset pressure is output as the size of the replacement valve; and based on the shape of the minimum cross-section, a particular model and make of the replacement valve is also output.

[000109] Considering the camera geometry shown in Figure 29, let (u, v) be the coordinates of a pixel in the image. Then the azimuth and elevation angles of the ray cast from the focal point of the camera through the pixel is given by:

$$\tan\alpha = \frac{u}{f}$$

$$\tan\beta = \frac{v}{f}$$

[000110] Outlined below are different embodiments of the method of obtaining 3D geometry of the balloon using the images acquired from the cameras.

[000111] One exemplary method is the dead-reckoning method. In this embodiment, images from a single camera can be used to determine the shape of the balloon as follows. The geometry of the balloon is shown in Figure 30A. The location of a camera inside the balloon is shown in Figure 30D. A grid pattern visible in the images from the camera is placed on the balloon. The distance, d_n, between the (n-1)th ring and the nth ring is known. Figure 30B shows the grid pattern when the balloon is not distorted. The line AB corresponds to a longitudinal line in the grid pattern. Figure 30C shows the grid pattern after the balloon has been distorted. The line AB' is now distorted accordingly.

[000112] Assume that the most proximal ring visible in the image is undistorted. Assume also that the balloon is made of a material that does not stretch.

[000113] Consider line AB and AB' as seen in Figure 30D. The quantities $\{p_n\}$ correspond to the 3-D coordinates of grid points along line AB'. Let d_{n-1} be the distance between the (n-1)th ring and the nth ring. Then:

$$d_{n-1}^2 = (x_n - x_{n-1})^2 + (y_n - y_{n-1})^2 + (z_n - z_{n-1})^2$$

[000114] Assume p_{n-1} is known. The azimuth and elevation angles (α_n, β_n) are also known from the images. Then:

$$x_n = z_n \tan \alpha_n$$

$$y_n = z_n \tan \beta_n$$

[000115] Substituting last two equations in 1 yields a quadratic equation for z_n, which can be readily solved. Hence p_n can be computed once p_{n-1} is known. Using mathematical induction once p_0 is known, all of $\{p_n\}$ are known.

[000116] Figure 31 illustrates an exemplary method of stereo reconstruction method. Two or more cameras 2120 and 2120' are mounted inside the balloon 2101 comprising guide wire lumen 2112 with a fixed relationship to each other. The fields of view 2123 and 2123'of the cameras overlap. The 3D shape of the balloon inside the common field of view can be reconstructed using images from pairs of cameras providing overlapping fields of view by employing stereo reconstruction techniques known in the prior art.

[000117] To make the reconstruction robust one or more markers inside the balloon may be provided. Figures 32A-32E show one such embodiment. As shown in Figures 32A-32E, a set of rings may be provided on the surface of the balloon 2255. Figure 32B and 32C show the images acquired by the two cameras. A set of features lying on a straight or curved line in one image 32B lies in a corresponding straight line (or more general curved line) in the other image. Such lines are called "epipolar" lines in the prior art.

[000118] The spatial relationship between the epipolar lines depends only on the camera geometry and the spatial relationship between the two cameras. Therefore, it is known at the factory. The points of intersection of a given ring with an epipolar line in figure 32B (e.g. point A) correspond to the points of intersection of the same ring with the same epipolar line in figure 32C. Let the coordinates of the point A in image figure 32B be (u_1, v_1) and in image 32C be (u_2, v_2). Then the 3-D coordinates of the point on the balloon that painted point A in images 32B and 32C is given by: (x, y, z), where:

[000119]

$$x = X(u_1, v_1, u_2, v_2)$$

$$y = Y(u_1, v_1, u_2, v_2)$$

$$z = Z(u_1, v_1, u_2, v_2)$$

[000120] X, Y and Z are stereo projection transformations known at the factory. Thus the coordinates of the points along each ring can be determined, and from which the 3-D shape of the balloon can be determined.

[000121] The 3D shape of the balloon when it is deformed can also be determined using images such as those shown in Figures 32D and 32E.

[000122] Figures 33A and 33B illustrate a mono reconstruction method, in which images from a single camera can be used to determine the shape of the balloon as follows. Figure 33A shows the longitudinal view of the balloon. The location of a point on a ring is marked A. When the balloon is deformed, this point moves to a new location, A'. The displacements in a plane normal to the axis of the balloon are Δx and Δy, while that along the longitudinal direction is Δz.

[000123] Assume that Δz is negligible compared to Δx and Δy.

[000124] Then each ring in Figures 33A and 33B correspond to a fixed z value, z_0. Consider a pixel, (u, v) in an image whose azimuth and elevation coordinates are (α, β). The coordinates of A' can thus be calculated as:

$$\begin{bmatrix} z_0 \tan\alpha - x_c \\ z_0 \tan\beta - y_c \\ z_0 \end{bmatrix}$$

[000125] where, (x_c, y_c) are the camera offset from the axis in the z = 0 plane.

[000126] In some alternative embodiments, optical flow-based or cross-correlation based motion tracking algorithms may be used for determining the 3-D coordinates of a series of markers on the balloon. The markings in the balloon can be made using multiple colors to facilitate robust detection using red, green and blue channels of the camera. The markings in the balloon can be made using a material that reflects light back at wavelengths different from the illumination wavelengths (i.e. Fluorescence). The distal part of the balloon can be illuminated differently from the proximal part of the balloon. This can include using different wavelength, or not illuminating parts of the balloon. The device can also make use of structured lighting, like projecting markers on to the balloon. The device can also make use of laser range finding inside the balloon. As with other embodiments described herein, the balloon can also make use of IVUS, OCT, Fluoro, TEE Ultrasound, or other time series 3D ultrasound image to characterize its shape.

[000127] Figures 34A and 34B illustrate an exemplary embodiment of a valvuloplasty balloon 3201 with a user set outer diameter. A expandable braided structure is on the balloon 3261. Inner and outer sheaths 3262 and 3264 are axially movable relative to one another. Moving the sheaths in the direction of arrows shown in figure 34A causes the balloon to lengthen for a reduced profile for delivery. The balloon is pressurized with an inflation fluid to inflate and expand the balloon, and thus the braid, as shown in figure 34B. The inner shaft 3262 can retract proximally at higher pressure, in the direction of the arrow in figure 34B. The same balloon can used in multiple sized braided devices since the outer diameter can be set after delivery but before inflation by adjusting the distance between the inner and outer shafts.

[000128] This disclosure will now describe valvuloplasty devices which comprise means for "cracking" and or modifying the size, shape, and confirmation of a heart valve. The valvuloplasty devices can be used during percutaneous valve replacement treatments. A common percutaneous valve replacement treatment is the replacement of the aortic valve. In such treatments it is often required to remodel the aortic root in one or some combination of the following ways: enlargement of the annulus, reshaping the annulus, and flattening the cusps against the aortic wall. Tissues in the native valve to be replaced are often highly calcified and in the process of reshaping them the calcium compounds are "cracked" thereby allowing the tissue to be reformed into a shape and configuration compatible with a percutaneously delivered replacement valve. Such procedures are currently carried out using a stiff

balloon which is delivered to the site of the valve in a deflated state, placed within the valve, and then inflated under up to many tens of atmospheres. The coronary arteries, which provide blood flow to the heart, are fed from ostia just above (i.e., downstream of) the aortic valve. As such, when the balloon is inflated, the balloon blocks the flow of blood to the heart through the coronary arteries. A valvuloplasty balloon is therefore typically inflated and deflated as quickly as possible to minimize the risk to the patient. It is also possible to create a tear in the aortic wall during such a procedure and thereby create an aneurysm in the aorta. When this happens the surgical team has a short period of time to open the patient's chest and attempt a repair. The valvuloplasty devices described herein provide alternatives to the standard devices available incorporating features that provide an additional measure of safety and performance.

[000129] In some embodiments, particularly useful for aortic valve treatment, the valvuloplasty device may provide for blood flow to the coronaries during the procedure. In some embodiments the balloon may form a seal against the aortic wall and aortic root such that if there is a tear in the aortic wall or root, the balloon provides a seal which precludes or limits blood flow out of the vascular system through the tear. The balloon configuration may also support blood flow to the coronaries but restrict access to other portions of the interface between the balloon and the aortic root. The balloon may additionally comprise a check valve which limits or stops blood flow in one direction while allowing blood flow in the opposite direction. Such a valvuloplasty balloon would have great value in minimizing morbidity and mortality in patients receiving percutaneously delivered heart valves. The device may additionally incorporate features which facilitate the locating of the cracking portion of the balloon and help to hold it in place while performing its function. The valvuloplasty balloon may incorporate features which allow for imaging the valve, or structures associated with the valve during the procedure. The valvuloplasty device may additionally incorporate means which allow it to be more easily captured within a delivery device.

[000130] The following embodiment provides an exemplary method of using a valvuloplasty device in an aortic valve. The system is tracked to the site of the aortic valve typically from a femoral access point. During this portion of the treatment the visualization system may be used to facilitate tracking and orienting the system prior to complete deployment. Once at the site and deployed the physician can visualize and evaluate the state of the diseased valve and the associated tissues. At this point it is possible for the physician to choose to abort the valve replacement procedure if the extent and form of the damage indicate that the risks of completion of the treatment outweigh the possible gains. This can be done at minimal additional risk to the patient. If the physician chooses to proceed, an expandable member portion of the system can be inflated under pressure to crack the diseased native heart valve. Calcified tissues in the diseased heart valve are fractured by expansion of the expandable member. After being fractured, the site of the diseased valve is more compliant and able to more snugly conform to the perimeter of the replacement valve. Additionally, such inspection can be used to help the physician choose which of the available percutaneously deliverable valves best fit the patient's anatomy or possibly even that no such valve would be sufficient and that the patient should be taken immediately

to a traditional surgery for an open heart valve replacement procedure. In some embodiments, the physician may at this time choose to use ablation elements carried by the valvuloplasty device to shrink the tissues at the site of the implant to better fit the available valves. In the event of a tear in the aortic wall the physician may use the ablation elements to cauterize the blood at the tear.

[000131] Figures 35A-C illustrate an exemplary embodiment of an expandable valvuloplasty device. Figure 35A illustrates a valvuloplasty balloon 3501, incorporating primary perfusion ports 3502, which are located at the proximal and distal ends. The valvuloplasty balloon 3501 additionally comprises side perfusion ports 3505, located in webbing 3507. The valvuloplasty balloon 3501 includes a set of toroidal balloons 3503 and 3504. Cracking balloons 3503 have a smaller outer diameter than and are located axially between locating balloons 3504. In valvuloplasty balloon 3501 all of the balloons are in fluid communication by the 3 fill lumens 3506. Alternate embodiments may incorporate more or fewer fill lumens. Additionally, in some embodiments a single or multiple balloon element sets may be fluidly interconnected with a single or multiple lumen sets whereas a different single or multiple balloon element set is filled by a different single or multiple lumen set. The device can have more or less than 3 cracking balloons, and more or less than 2 locating balloons.

[000132] Figure 35B is a cross section of the valvuloplasty device shown of Figure 35. Blood flow, as would be experienced during a percutaneously delivered aortic valve procedure using a standard femoral approach, is illustrated by arrows 3509 where blood is leaving the left ventricle and 3508 where blood is entering the aorta. As embodied in Figure 35B, blood also passes through side perfusion ports 3505 such that the coronaries may be supplied during the valvuloplasty procedure. Guide wire lumens 3512 provide for delivery of the balloon, techniques for which are known. In the embodiment of Figure 35B the fill lumens distal ends 3511 are allowed to extend past the distal locating balloon 3504, and provide a stiffening and locating function. Distal refers to the direction along the device away from the access point, while proximal refers to the direction along the device towards the access point.

[000133] Figure 35C illustrates the proximal end of the valvuloplasty device comprising the interface between the dual lumen delivery shaft 3513 and fill lumens 3506. The delivery shaft 3513 is comprised of a fill lumen 3506 and a guide wire lumen 3512. In some embodiments, the delivery shaft may incorporate more than one fill lumen 3506. In some embodiments the guide wire lumen may be fabricated such that it can be actuated to stretch, or lengthen, the balloon in a proximal to distal fashion (i.e., axially) to facilitate sheathing the balloon in a delivery catheter.

[000134] Figure 36 depicts an alternative embodiment of valvuloplasty balloon 3601 incorporating an outflow valve comprised of membrane 3614 at the outflow end, which is affixed to delivery shaft 3613 and seals against perfusion ports 3602 (beneath membrane) on the proximal end of the balloon. Fill lumens 3606 are enlarged to be comparable in size to the toroid balloons of the cracking portion 3603, by so doing the interface between the surface of the cracking portion of the balloon and the aortic or other organ wall forms distinct sealed chambers 3615. As depicted in Figure 36 each chamber has its own outflow port 3605. In alternate embodiments, only a selection of one or more chambers 3615 may be provided with side outflow ports 3605.

[000135] Figure 37A illustrates a valvuloplasty balloon with only two of the sealed chambers 3715 provided with perfusion ports 3705. In an aortic valve procedure such a configuration provides added safety if the aortic wall tears during the procedure. Figure 37B is a cut away view of Figure 37A incorporating indications of blood flow to the coronaries, as shown by the large arrows 3708.

[000136] Figure 38 depicts alternative embodiment of the valvuloplasty device of Figure 37A, incorporating two camera assemblies similar to those described in co-pending U.S. Application No. 12/616,758, filed 11/11/2009, and in co-pending U.S. Application No. 13/106,658, filed May 12, 2011, both of which are incorporated by reference herein. The surface of the balloon over one of the cameras has been cut away to show the position of the camera 3820 and flexible circuit interface 3822. Fields of vision for the two cameras are set to overlap such that they can be knit together by electronic hardware or software to create a larger field of view than obtainable by a single camera in such a configuration. The valvuloplasty balloon in such an embodiment is fabricated of a clear polymer such as PET, high durometer polyurethane, or other such material known in the art, and inflated with a saline or a clear contrast media. The toroidal section within which the camera sits and its clear contents displace the blood and the cameras can view the surface of the aorta or other lumen wall against which the toroidal section is pressing. Using such an arrangement the visualization capability of the valvuloplasty device can first be used to assess the state of the aortic valve and then to orient it such that perfusion ports 3805 are aligned with the coronaries. Aligning the perfusion ports with the coronaries can better ensure that blood flow to the coronaries is not blocked.

[000137] In some embodiments, as depicted in Figure 38, an ablation electrode 3831 or multiple ablation electrodes may be incorporated on the surface of the valvuloplasty device. Such electrodes can be used to ablate tissues of the aorta and associated valve tissues, or other valve and associated tissues, to shrink the tissue and thereby decrease the diameter of the location where the percutaneously delivered valve will be placed. This has advantage where the available percutaneous valves are of sizes which do not match that of the patient. By appropriately shrinking the tissues at the implant location a better fit for the implant can be provided.

[000138] The valvuloplasty devices shown in Figures 35A - 38 are configured in such a fashion that they can be fabricated by heat sealing, laser welding, or otherwise affixing portions of two concentric balloons or tubular sections of material in appropriate patterns. The sealed chambers may be created in this fashion. In sealed chambers incorporating perfusion ports, some portion of the webbing remains as a means to create the seam between the inner and outer members.

[000139] The valvuloplasty devices can be incorporated into systems with proximal portions outside the patient that allow for the expanding fluid, such as saline, to be advanced through the fill lumens and expand the balloons. The proximal portions can additionally include actuators that can control the deployment of the valvuloplasty devices from a delivery catheter or sheath. The proximal portions may additionally incorporate means to monitor the state of inflation of the valvuloplasty device, such as a means of monitoring the volume of fluid introduced and removed from the device. This information can be used to estimate the size of the percutaneous valve used in the replacement procedure.

[000140] Any of the mathematical relationships herein can be stored in any kind of suitable memory device for later use, examples of which are well known.

CLAIMS

1. A method of calibrating an expandable device used for determining a size of a replacement heart valve to be implanted, comprising

establishing a mathematical relationship between a degree of expansion less than a full expansion of the device and a stiffness of an object disposed radially outside the device.

2. The method of claim 1 wherein the degree of expansion is percent under-expansion relative to a fully expanded diameter of the device.

3. The method of claim 1 wherein the degree of expansion less than a full expansion of the device is at a location of the object.

4. The method of claim 1 wherein the establishing step comprises establishing a mathematical relationship between a degree of expansion less than a full expansion of a self-expanding device.

5. The method of claim 1 wherein the establishing step comprises expanding the device within the object and measuring a radial distance between a fully expanded portion of the device and a portion of the device at the location of the object.

6. The method of claim 5 further comprising computing a degree of perimeter expansion less than a full perimeter expansion, and establishing a mathematical relationship between a degree of perimeter expansion less than a full perimeter expansion of the device and a stiffness of an object disposed radially outside the device.

7. The method of claim 5 further comprising computing a degree of area under-expansion, and establishing a mathematical relationship between a degree of area expansion less than a full area expansion of the device and a stiffness of an object disposed radially outside the device.

8. The method of claim 1 wherein the establishing step comprises imaging the native valve to obtain major and a minor axis diameters in at least one of the annular plane, left ventricular outflow tract plane, and sinus of valsalva plane.

9. The method of claim 1 wherein the establishing step comprises imaging the device while the device is expanded adjacent a native valve.

10. The method of claim 1 wherein imaging comprises using a 3-D C-arm.

11. The method of claim 1 wherein imaging comprises using computed tomography.

12. The method of claim 1 wherein imaging comprises using a 3-D transesophageal echocardiogram.

13. The method of claim 1 wherein imaging comprises using 3-D multideterctor CT.

14. The method of claim 1 further comprising storing the relationship in a memory device.

15. A method of using a calibrated sizing tool to determine a size of a replacement heart valve to be implanted, comprising

establishing a mathematical relationship between a degree of expansion less than a full expansion of a compliant sizing device and a stiffness of an object disposed radially outside the device.

16. The method of claim 15 wherein the degree of expansion is percent under-expansion relative to a fully expanded diameter of the device.

17. The method of claim 15 wherein the degree of expansion less than a full expansion of the compliant sizing device is at a location of the object.

18. The method of claim 15 wherein the establishing step comprises establishing a mathematical relationship between a degree of expansion less than a full expansion of a self-expanding sizing device.

19. The method of claim 15 wherein the establishing step comprises expanding the sizing device within the object and measuring a radial distance between a fully expanded portion of the sizing device and a portion of the sizing device at the location of the object.

20. The method of claim 19 further comprising computing a degree of perimeter expansion less than a full perimeter expansion, and establishing a mathematical relationship between a degree of perimeter expansion less than a full perimeter expansion of the sizing device and a stiffness of an object disposed radially outside the sizing device.

21. The method of claim 19 further comprising computing a degree of area under-expansion, and establishing a mathematical relationship between a degree of area expansion less than a full area expansion of the sizing device and a stiffness of an object disposed radially outside the sizing device.

22. The method of claim 15 wherein the establishing step comprises imaging the native valve to obtain major and minor axis diameters in at least one of the annular plane, left ventricular outflow tract plane, and sinus of valsalva plane.

23. The method of claim 15 wherein the establishing step comprises imaging the sizing device while the sizing device is expanded adjacent a native valve.

24. The method of claim 15 wherein imaging comprises using a 3-D C-arm.

25. The method of claim 15 wherein imaging comprises using computed tomography.

26. The method of claim 15 wherein imaging comprises using a 3-D transesophageal echocardiogram.

27. The method of claim 15 wherein imaging comprises using 3-D multideterctor CT.

28. The method of claim 15 further comprising storing the relationship in a memory device.

29. A method of determining a size of a replacement heart valve to be implanted, comprising

determining major and minor diameters of an aortic heart valve annulus;

endovascularly delivering an expandable calibrated sizing device to a location adjacent the aortic valve annulus and expanding the sizing device within the annulus and into contact with tissue;

obtaining an image of the expanded device in a plane that is in alignment with at least one of the major and minor annular diameters;

measuring a dimension of the device using the obtained image;

determining a degree of expansion of the device less than full expansion, and relating the degree of expansion to an estimated annular stiffness; and

selecting a replacement valve size based on the estimated stiffness.

30. The method of claim 29 wherein expanding the sizing device comprises allowing the sizing device to fully self-expand.

31. A compliant expandable medical device, comprising

an expandable compliant device with a central portion that is configured to foreshorten substantially less than proximal and distal portions when the device is allowed to self-expand.

32. A method of selecting a valve size for implantation within a heart valve annulus, comprising:

generating a mathematical relationship between measured changes in a patient's blood pressure and displacement of a native heart valve annulus; and

selecting a heart valve size to be implanted within the annulus based on the mathematical relationship.

33. The method of claim 32 wherein the generating step comprises taking arterial pressure measurements of the patient and obtaining a plurality of images of the heart valve annulus during a cardiac cycle.

34. The method of claim 32 wherein selecting the heart valve size is based on the mathematical relationship between change in pressure and a dimensional change in the annulus.

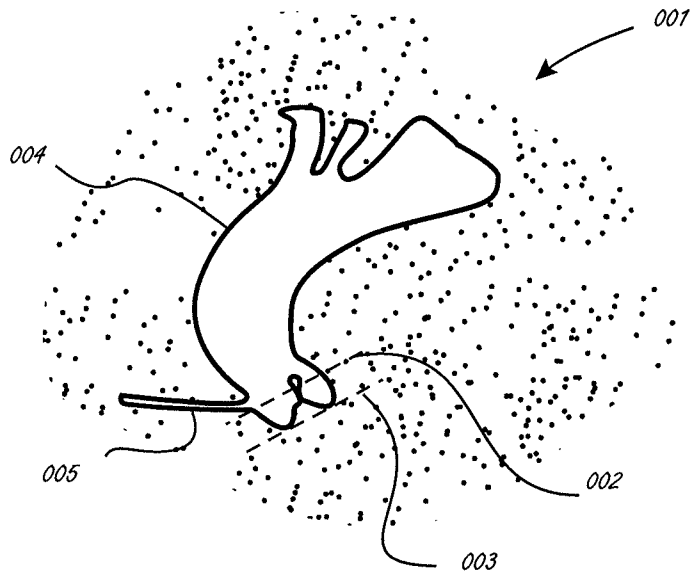


Fig. 1A

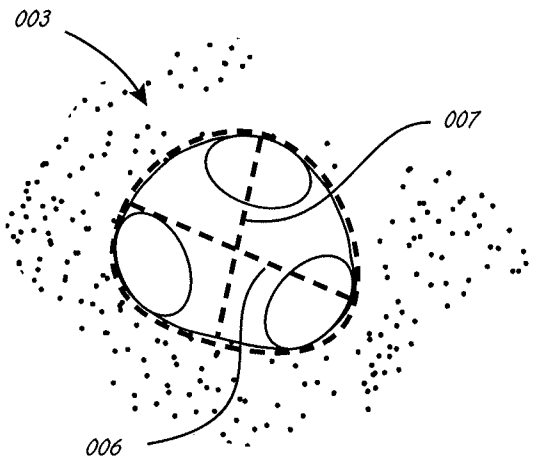


Fig. 1B

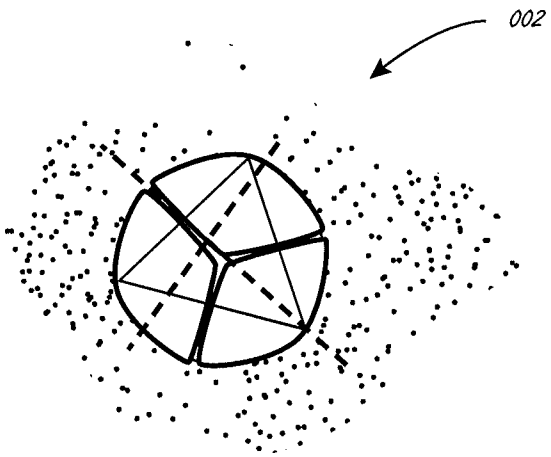


Fig. 1C

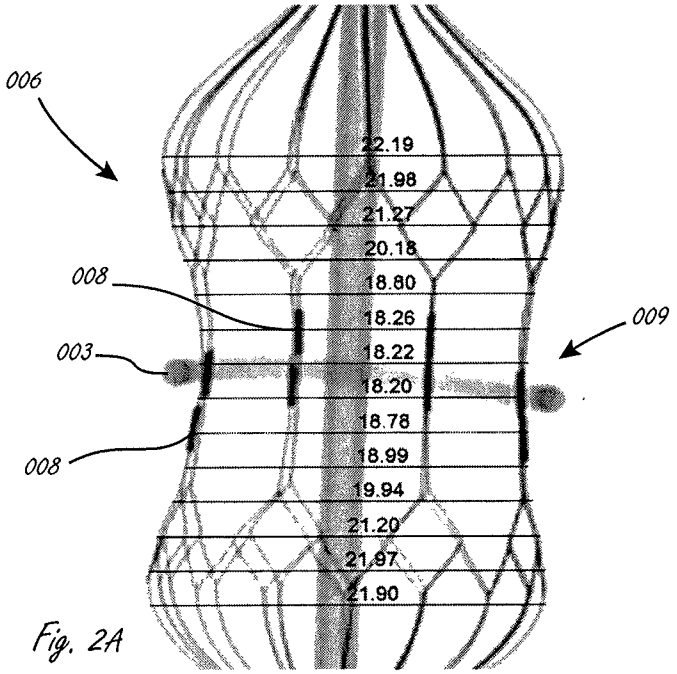


Fig. 2A

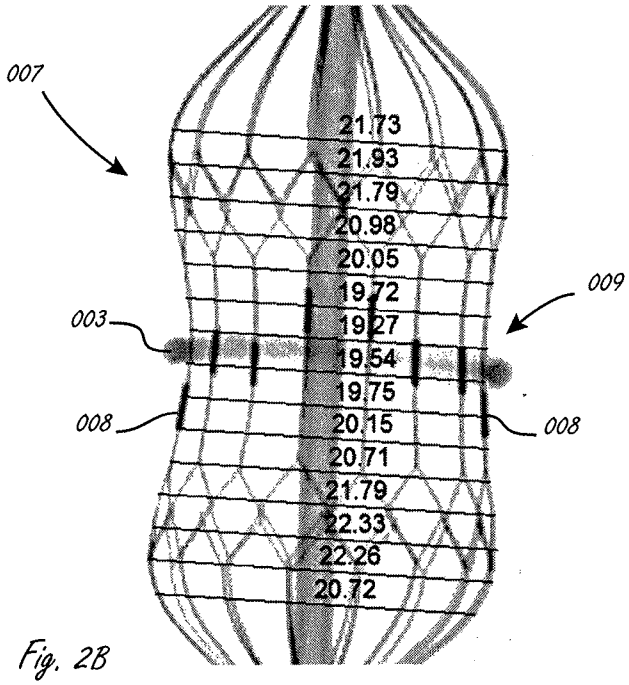


Fig. 2B

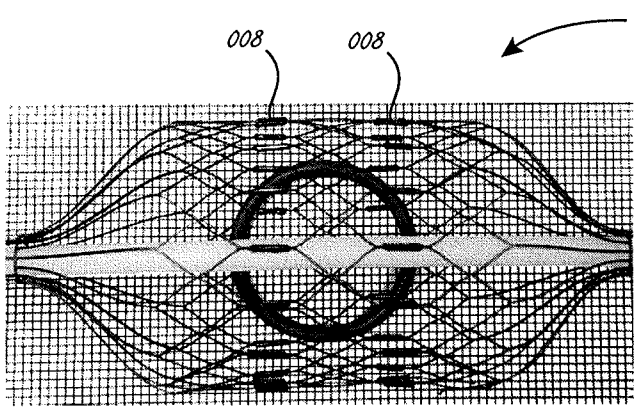


Fig. 3A

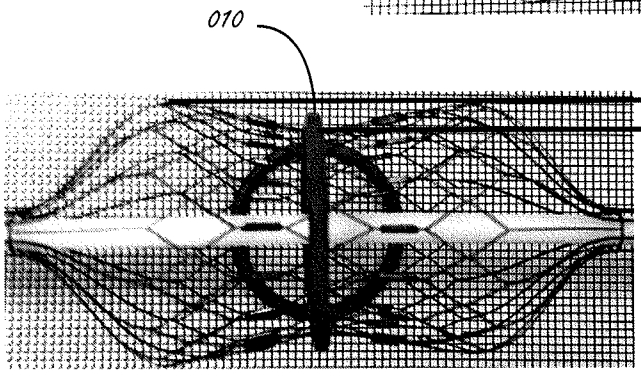


Fig. 3B

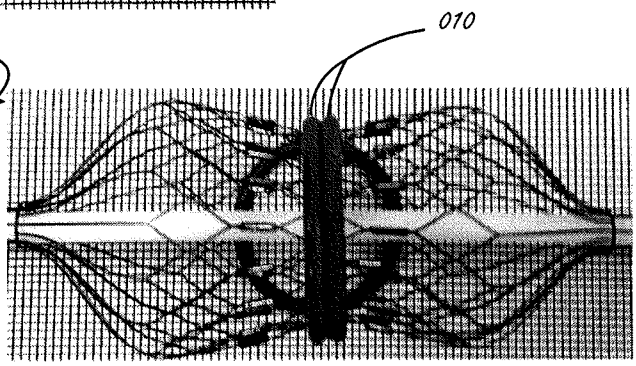


Fig. 3C

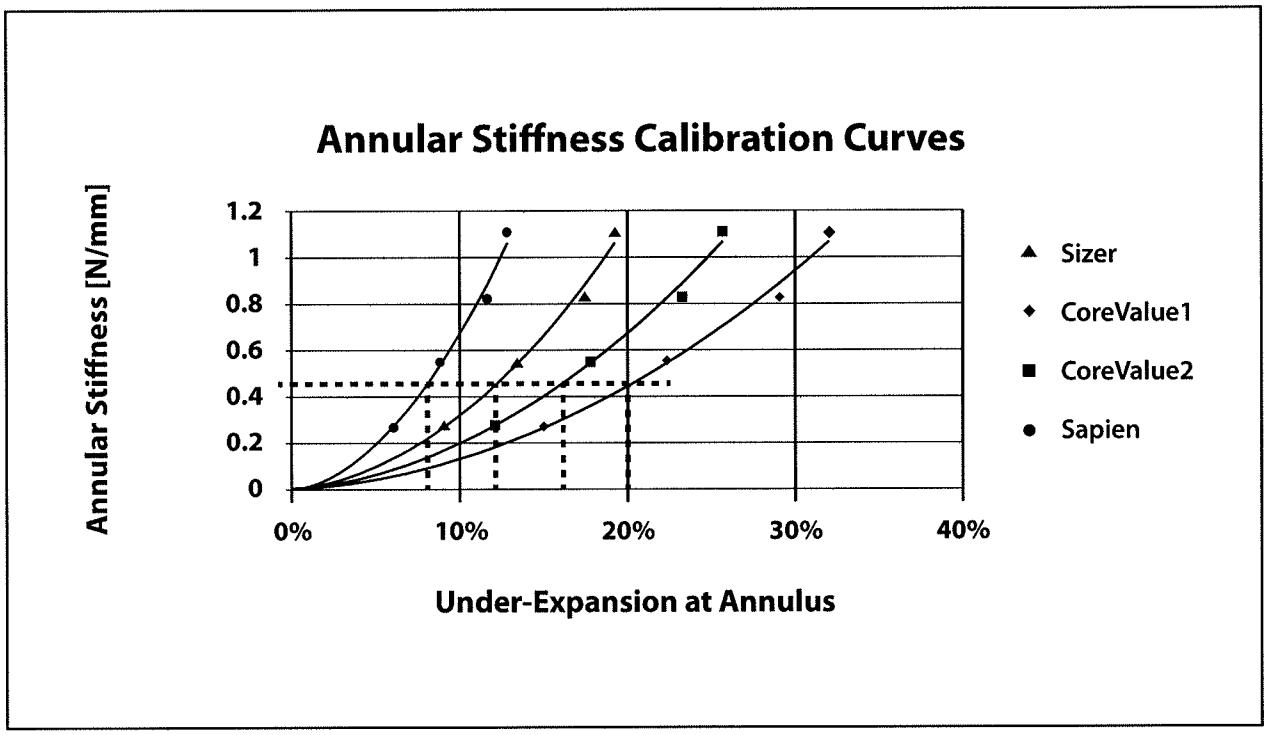

Annular Stiffness Calibration Curves
Annular Stiffness [N/mm]
1.2
1
0.8
0.6
0.4
0.2
0
0%
10%
20%
30%
40%
Under-Expansion at Annulus
Sizer
CoreValue1
CoreValue2
Sapien

Fig. 4

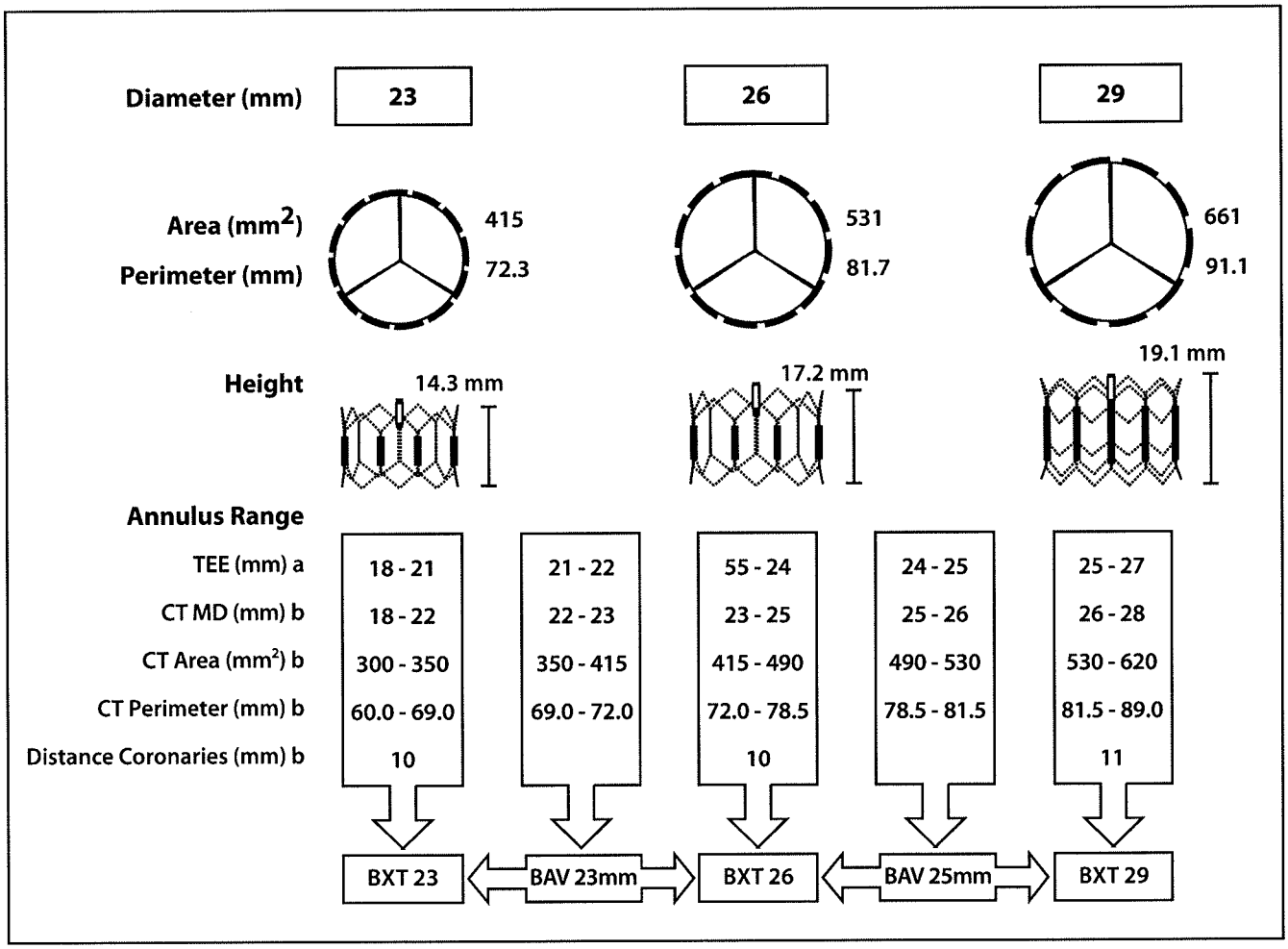

Diameter (mm)
23
26
29
Area (mm2)
415
531
661
Perimeter (mm)
72.3
81.7
91.1
Height
14.3 mm
17.2 mm
19.1 mm
Annulus Range
TEE (mm) a
CT MD (mm) b
CT Area (mm2) b
CT Perimeter (mm) b
Distance Coronaries (mm) b
18 - 21
18 - 22
300 - 350
60.0 - 69.0
10
21 - 22
22 - 23
350 - 415
69.0 - 72.0
55 - 24
23 - 25
415 - 490
72.0 - 78.5
10
24 - 25
25 - 26
490 - 530
78.5 - 81.5
25 - 27
26 - 28
530 - 620
81.5 - 89.0
11
BXT 23
BAV 23mm
BXT 26
BAV 25mm
BXT 29

Fig. 5A

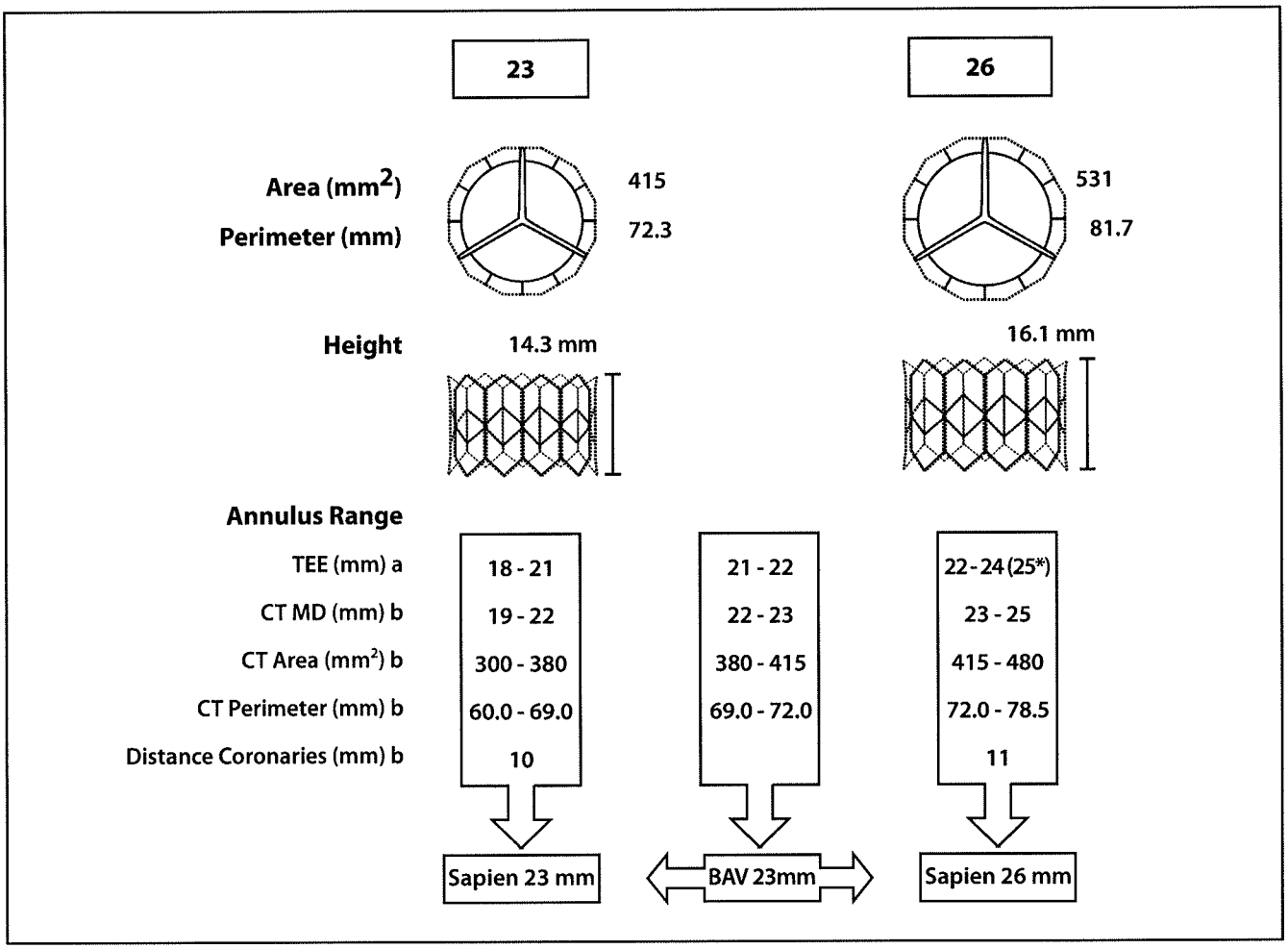

23
26
Area (mm2)
Perimeter (mm)
415
72.3
531
81.7
Height
14.3 mm
16.1 mm
Annulus Range
TEE (mm) a
CT MD (mm) b
CT Area (mm2) b
CT Perimeter (mm) b
Distance Coronaries (mm) b
18 - 21
19 - 22
300 - 380
60.0 - 69.0
10
21 - 22
22 - 23
380 - 415
69.0 - 72.0
22 - 24 (25*)
23 - 25
415 - 480
72.0 - 78.5
11
Sapien 23 mm
BAV 23mm
Sapien 26 mm

Fig. 5B

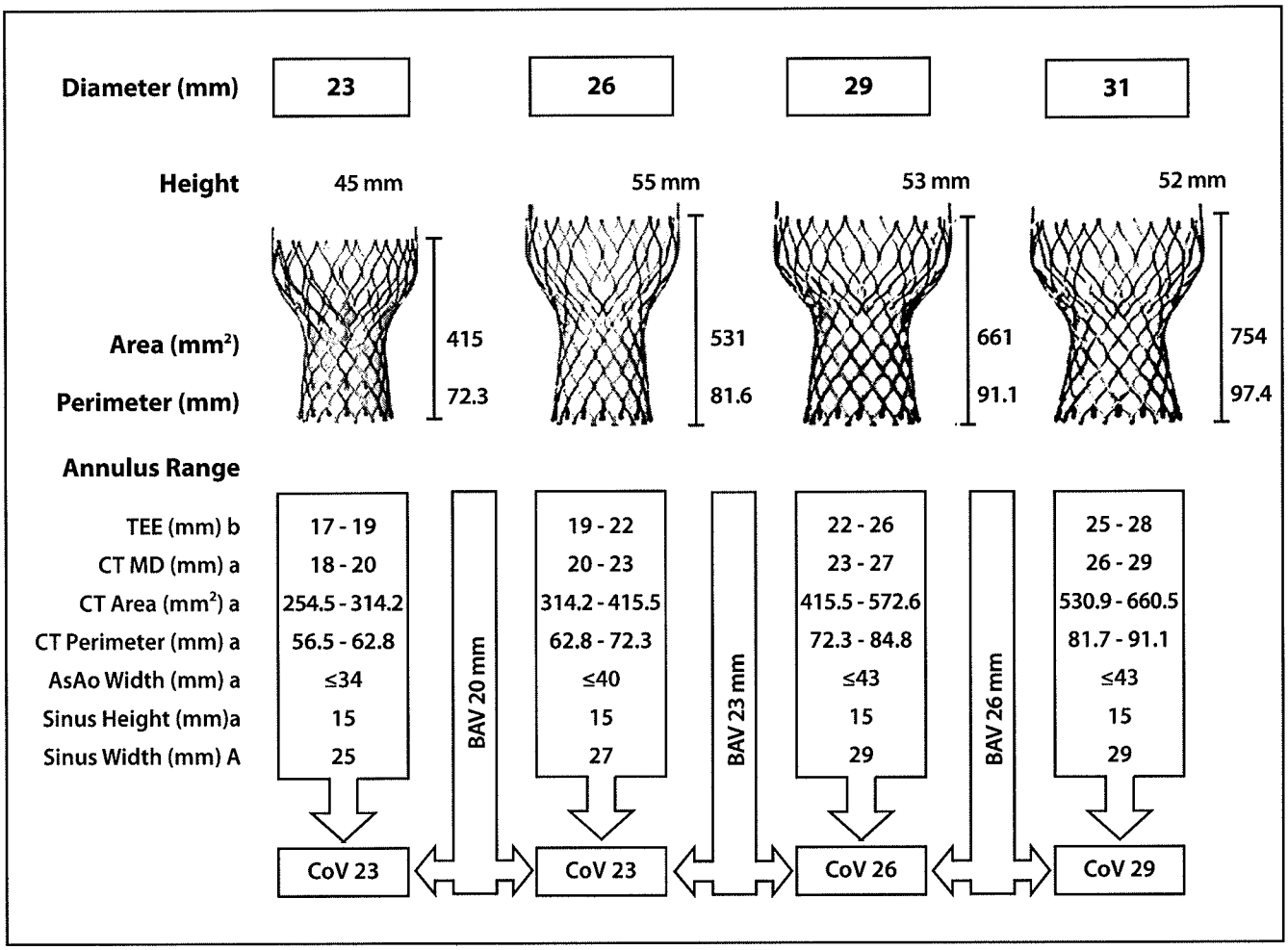

Diameter (mm)
23
26
29
31
Height
45 mm
55 mm
53 mm
52 mm
Area (mm²)
415
531
661
754
Perimeter (mm)
72.3
81.6
91.1
97.4
Annulus Range
TEE (mm) b
CT MD (mm) a
CT Area (mm²) a
CT Perimeter (mm) a
AsAo Width (mm) a
Sinus Height (mm)a
Sinus Width (mm) A
17 - 19
18 - 20
254.5 - 314.2
56.5 - 62.8
≤34
15
25
19 - 22
20 - 23
314.2 - 415.5
62.8 - 72.3
≤40
15
27
22 - 26
23 - 27
415.5 - 572.6
72.3 - 84.8
≤43
15
29
25 - 28
26 - 29
530.9 - 660.5
81.7 - 91.1
≤43
15
29
BAV 20 mm
BAV 23 mm
BAV 26 mm
CoV 23
CoV 23
CoV 26
CoV 29

Fig. 6

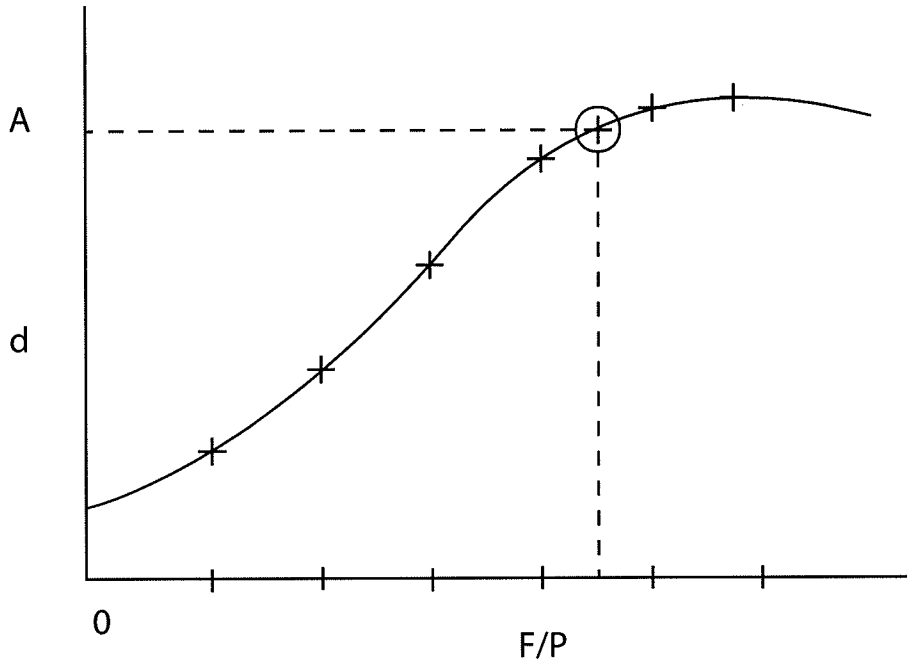


Fig. 7

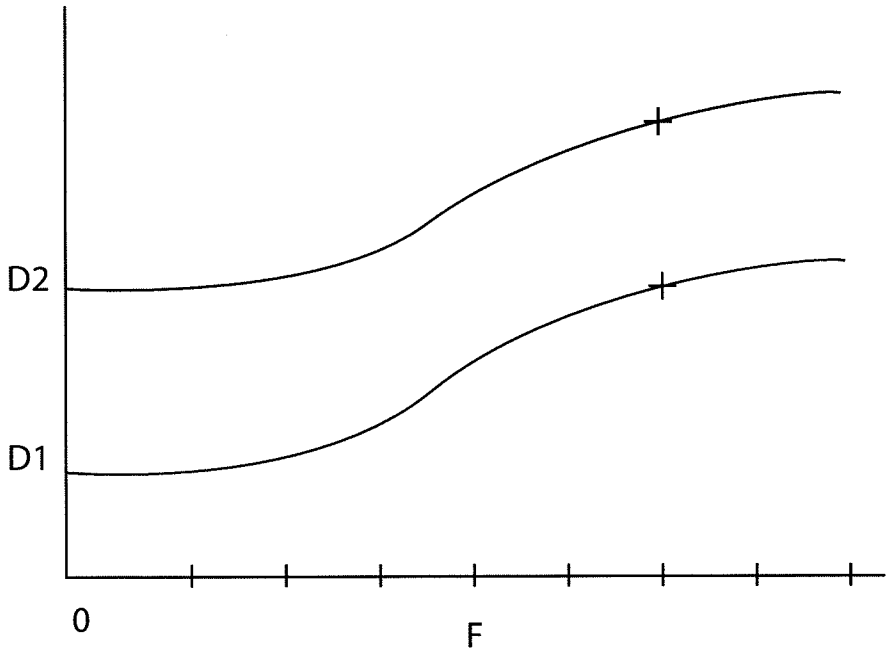


Fig. 8

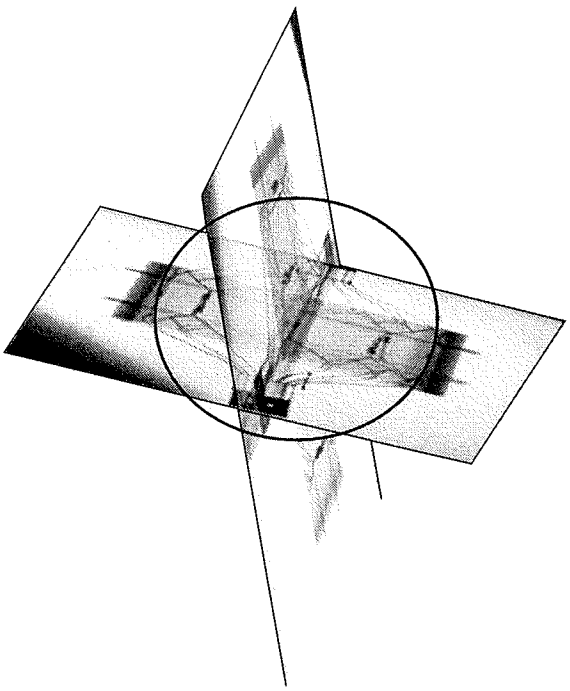


Fig. 9A

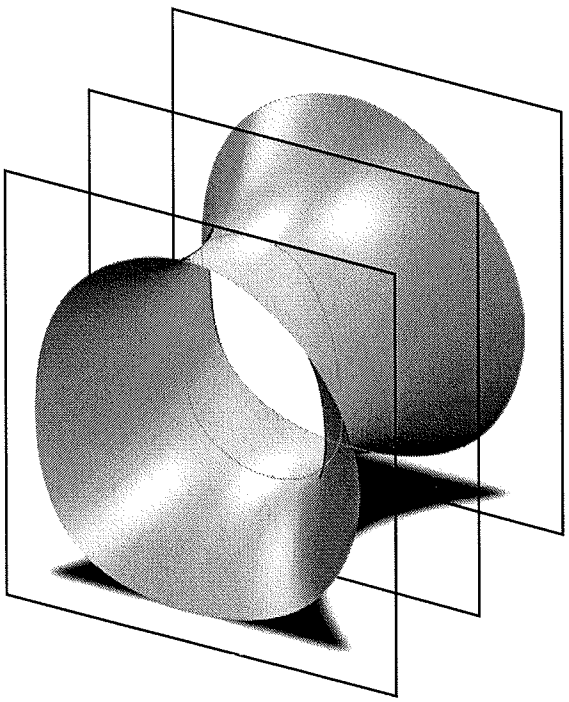


Fig. 9B

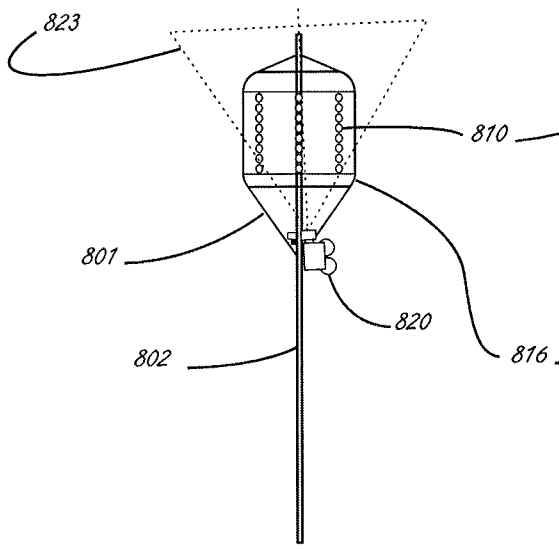


Fig. 10A

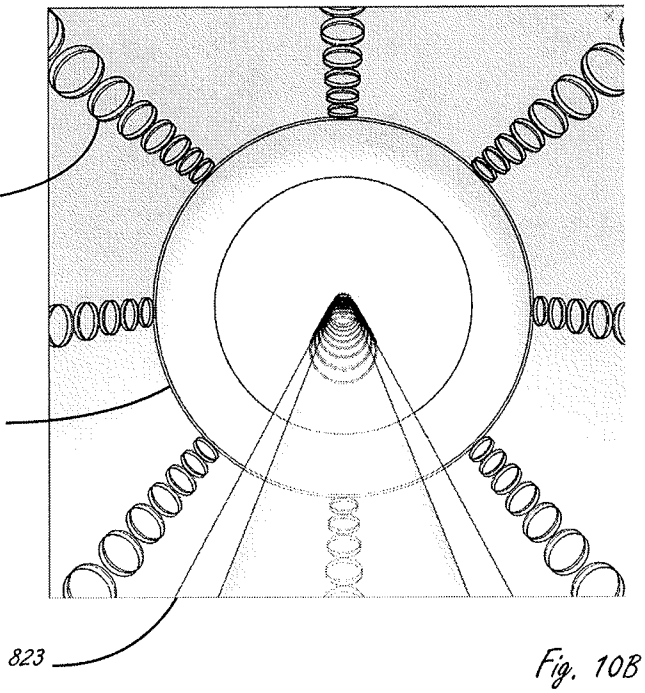


Fig. 10B

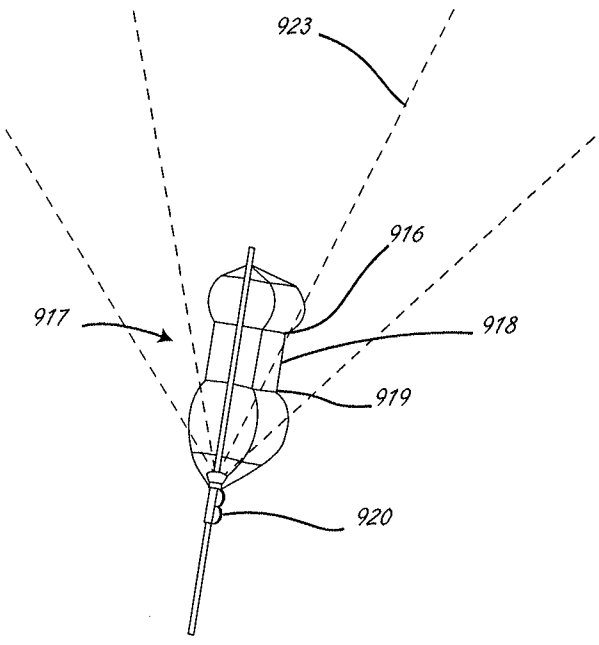


Fig. 11A

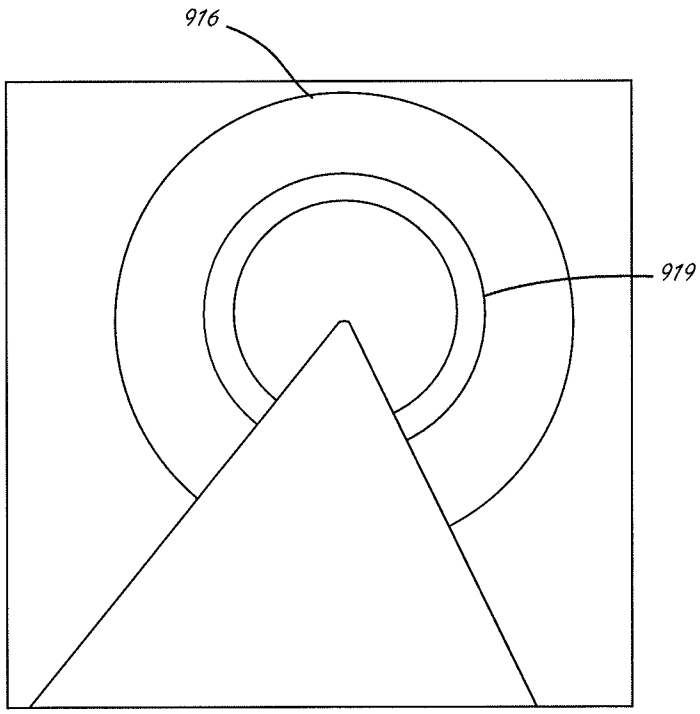


Fig. 11B

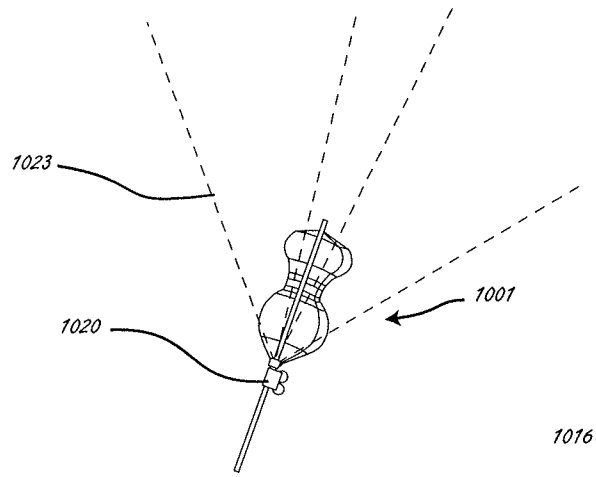


Fig. 12A

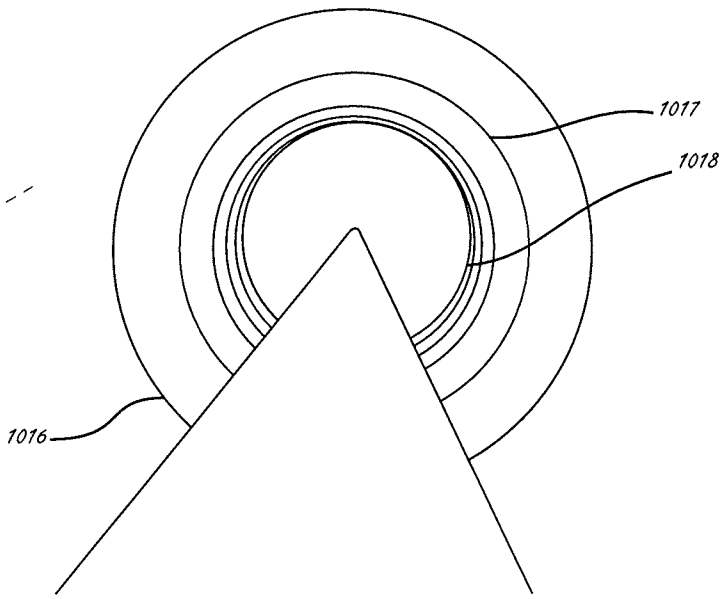


Fig. 12B

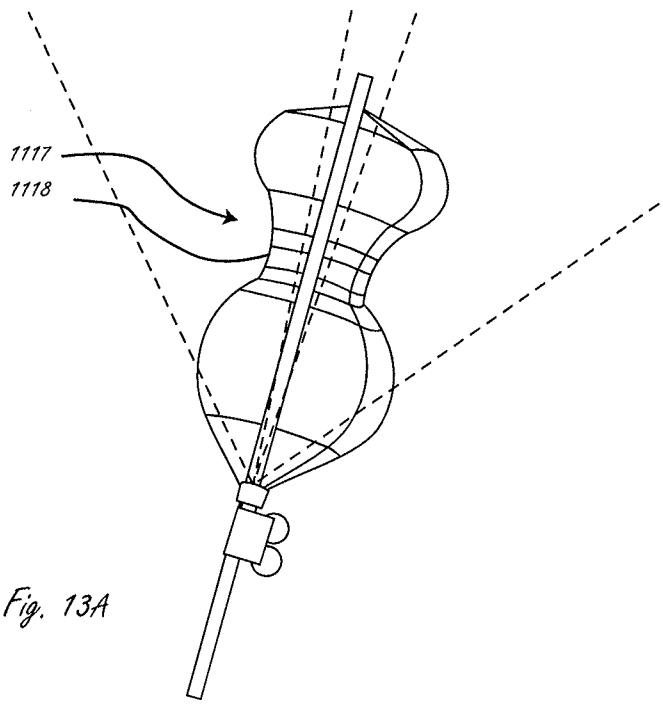


Fig. 13A

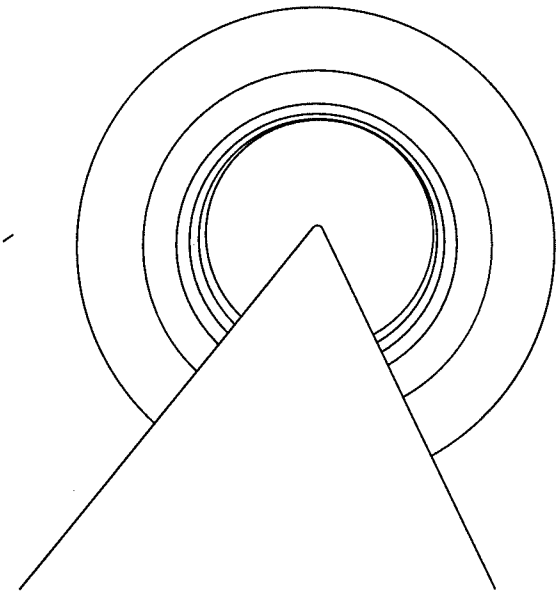


Fig. 13B

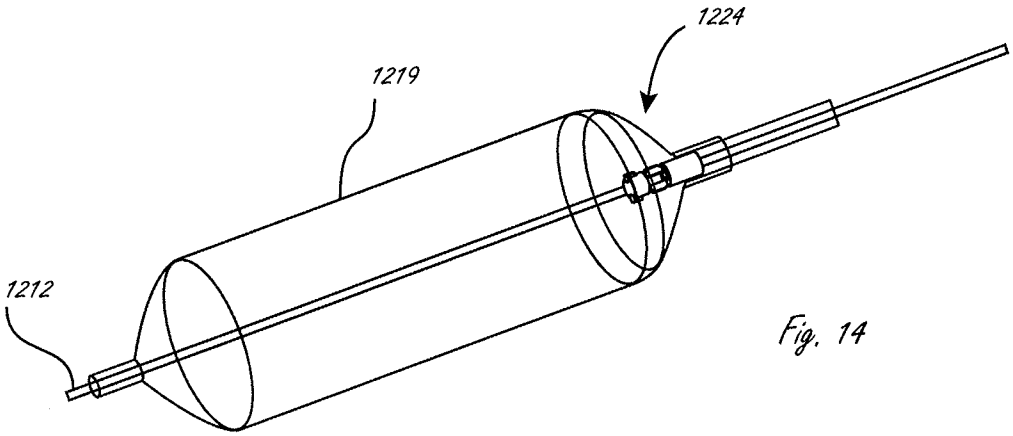


Fig. 14

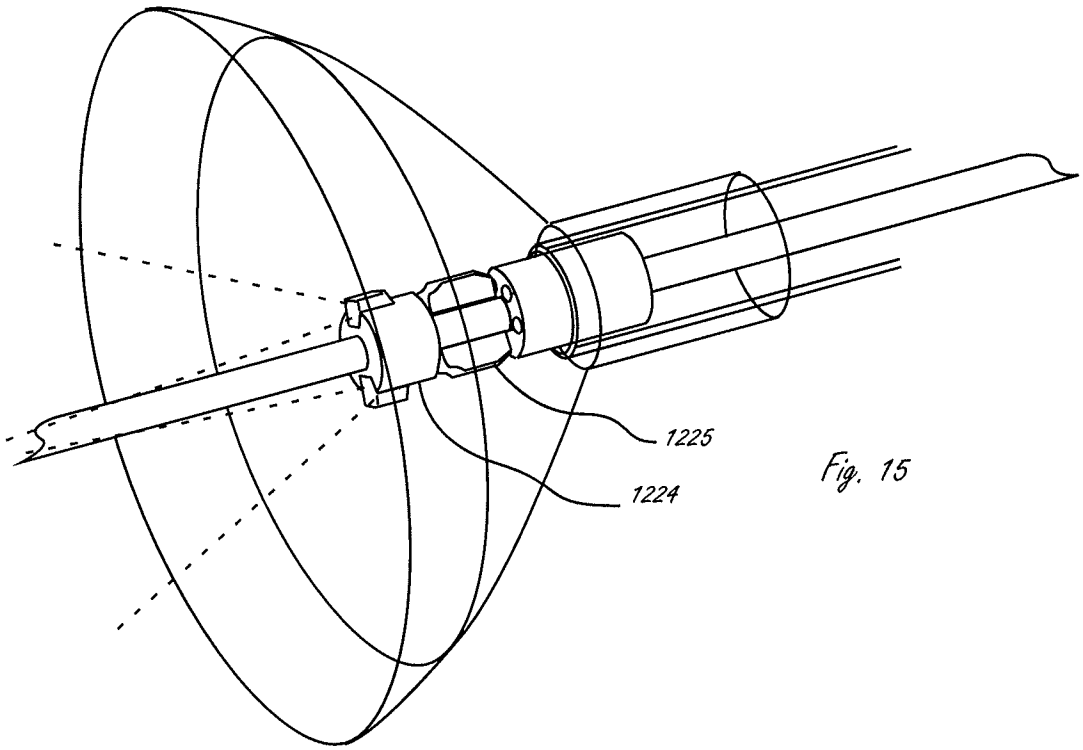


Fig. 15

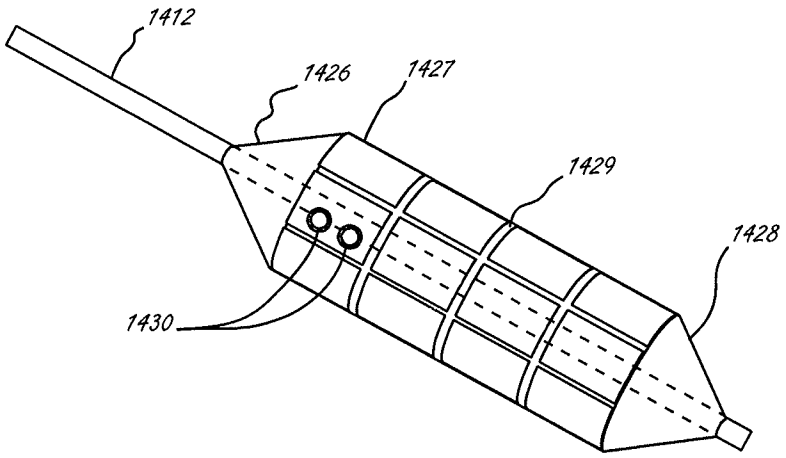


Fig. 16

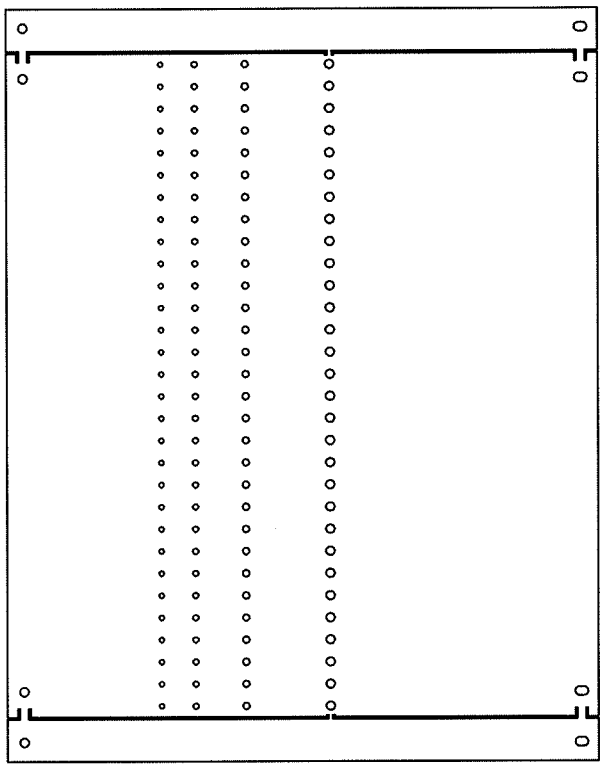


Fig. 17A

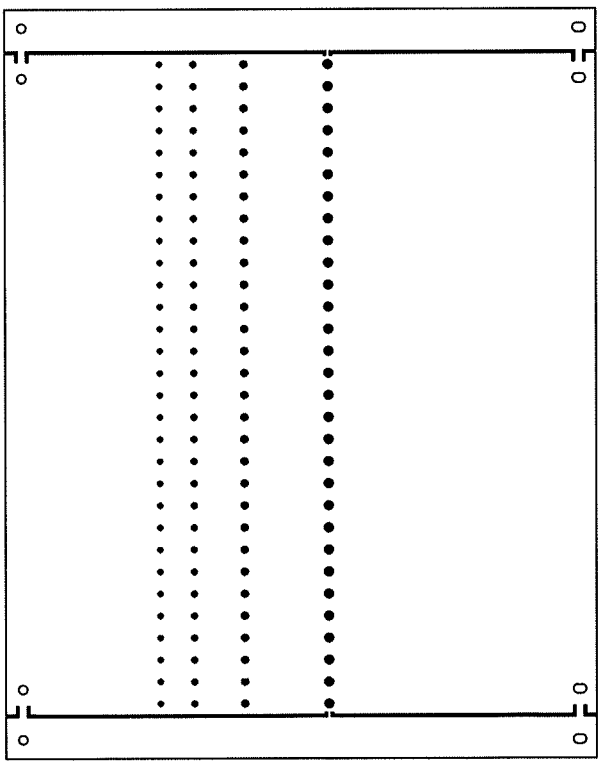


Fig. 17B

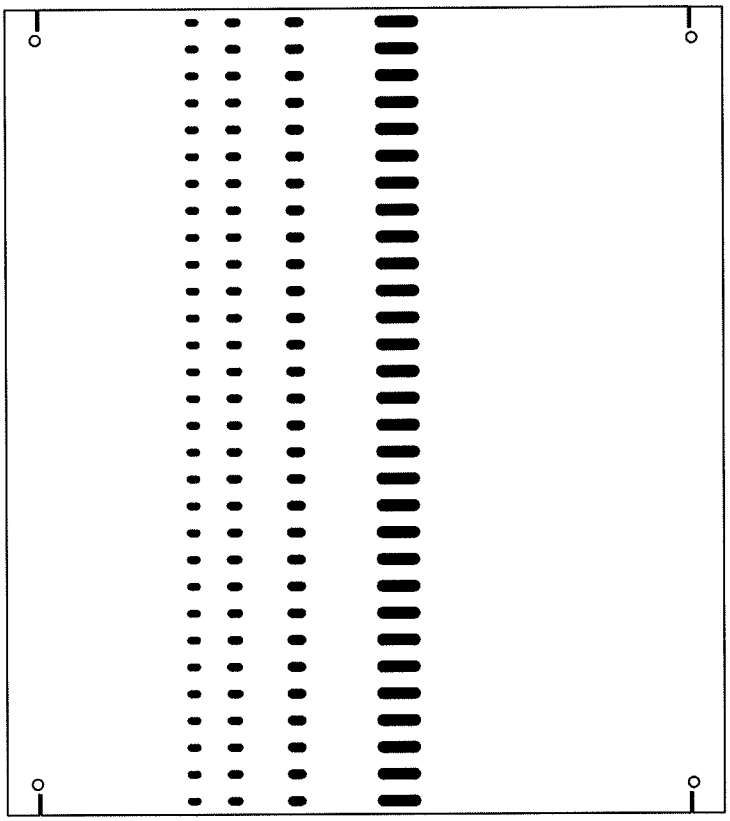


Fig. 18

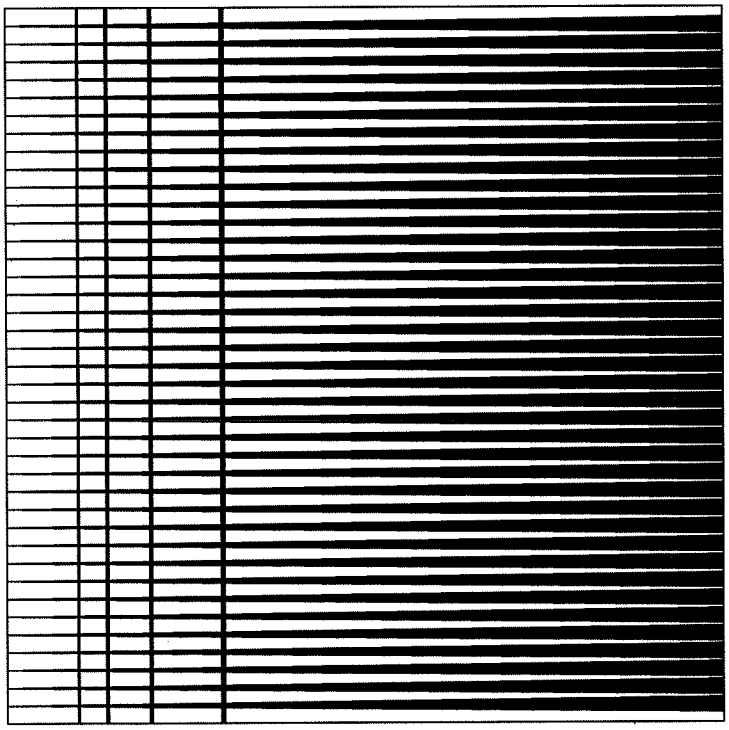


Fig. 19

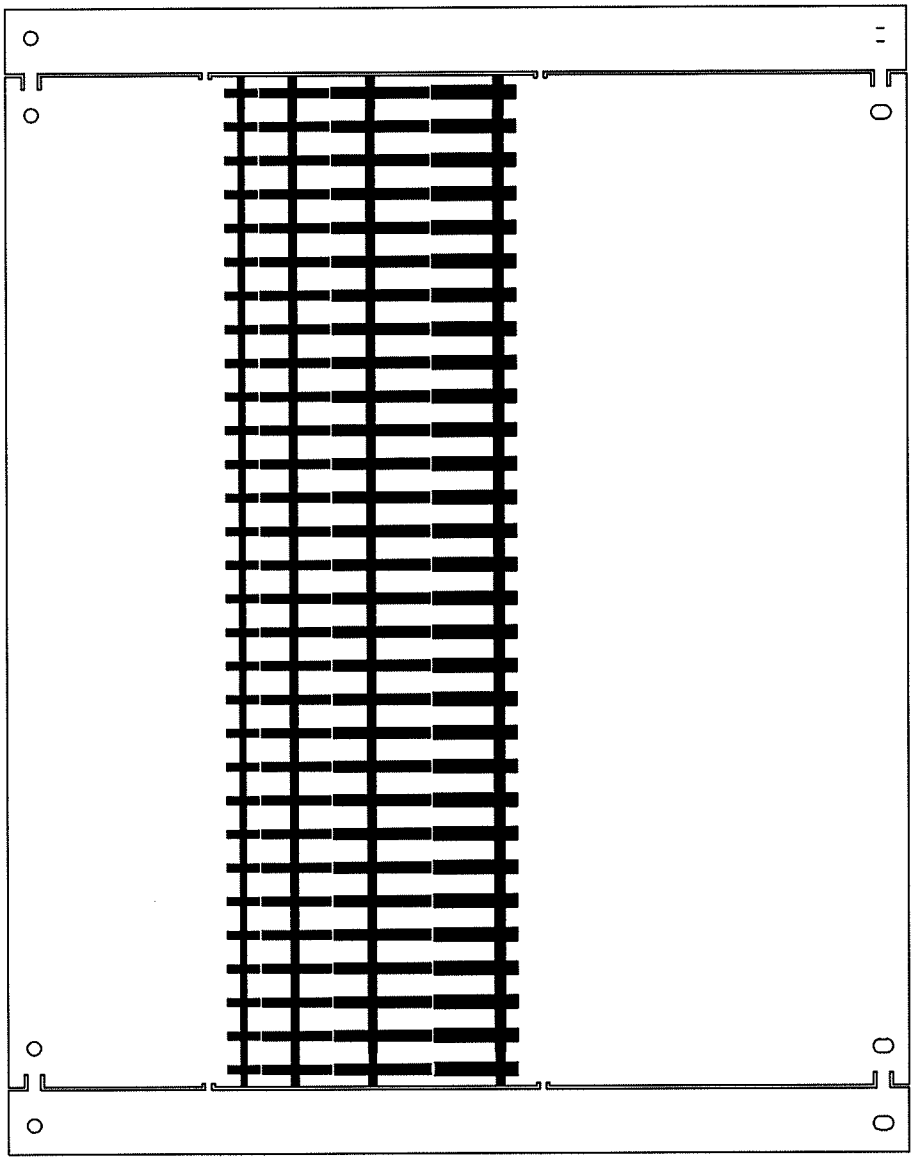


Fig. 20

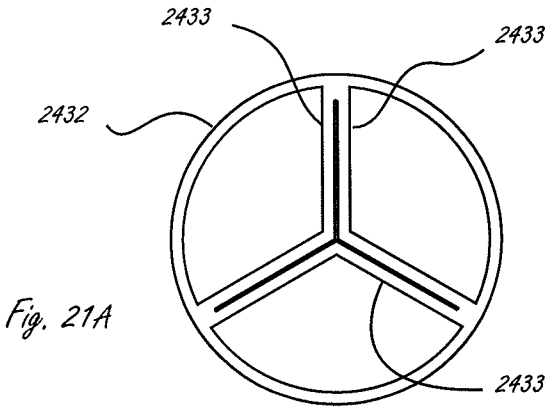


Fig. 21A

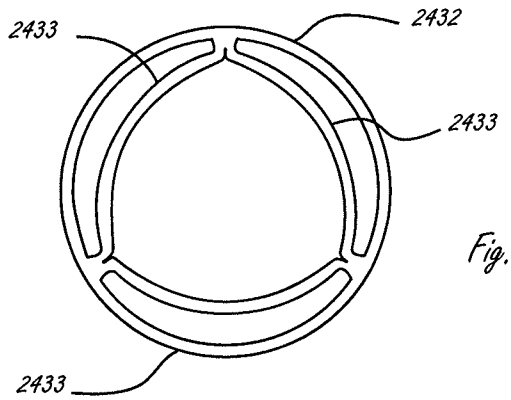


Fig. 21B

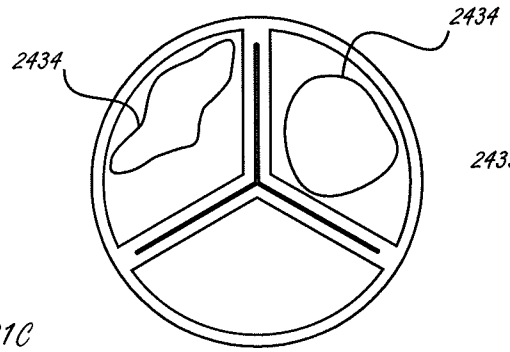


Fig. 21C

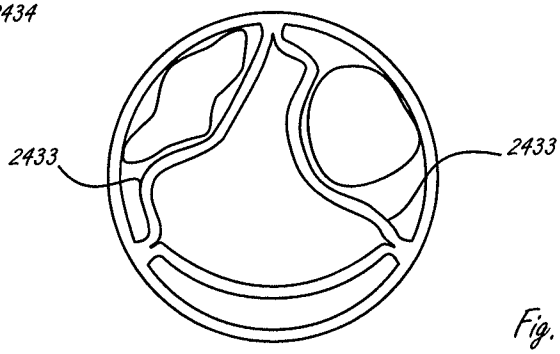


Fig. 21D

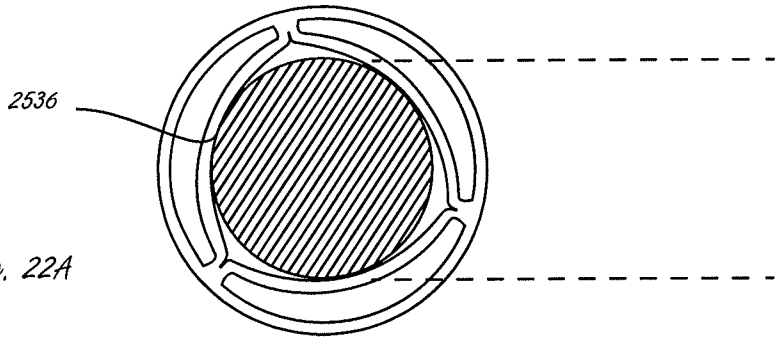


Fig. 22A

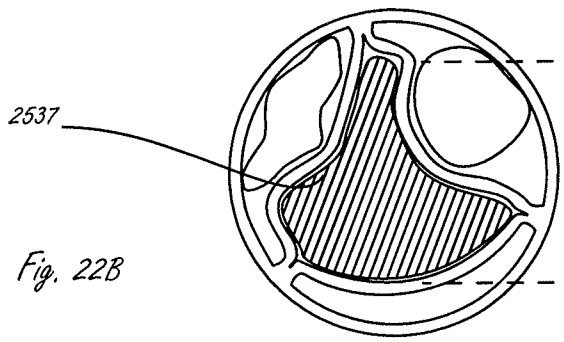
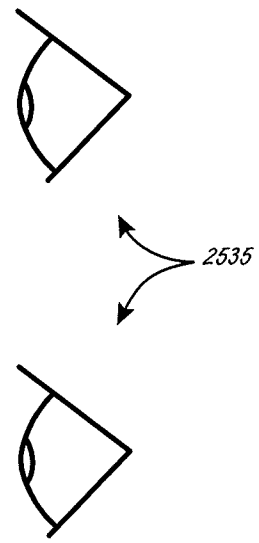


Fig. 22B



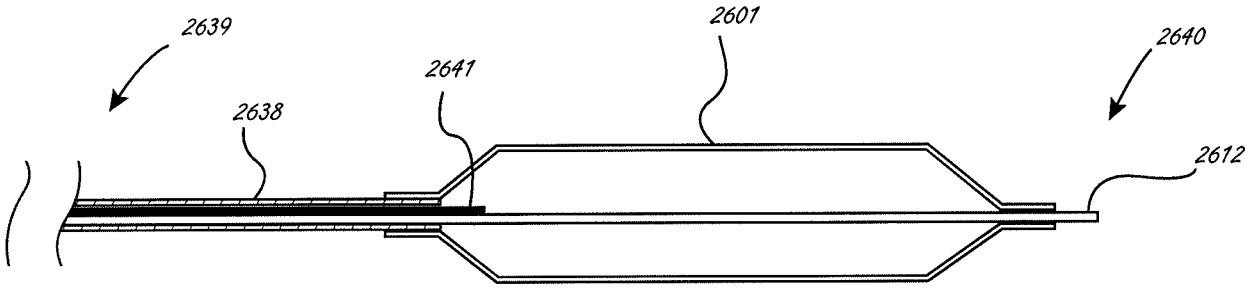


Fig. 23

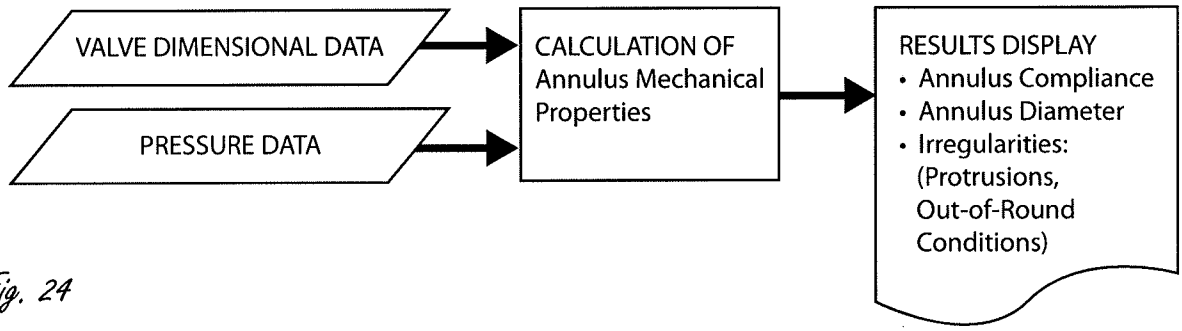


Fig. 24

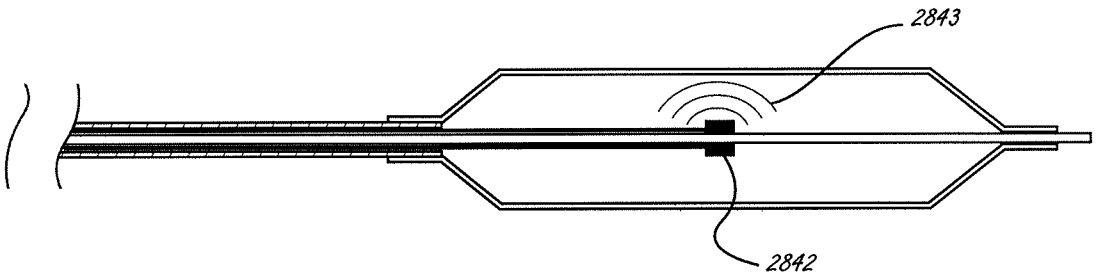


Fig. 25

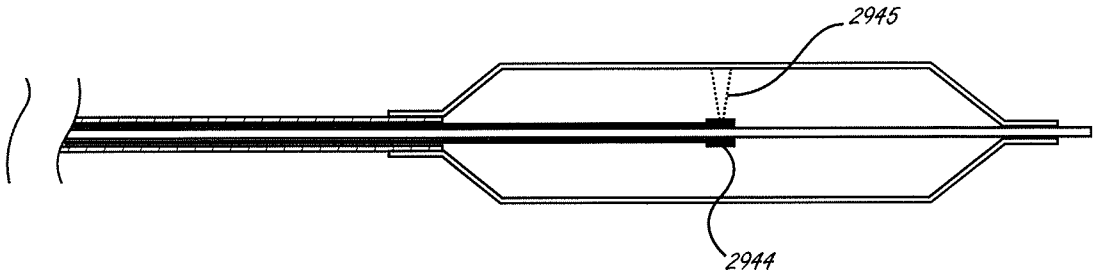


Fig. 26

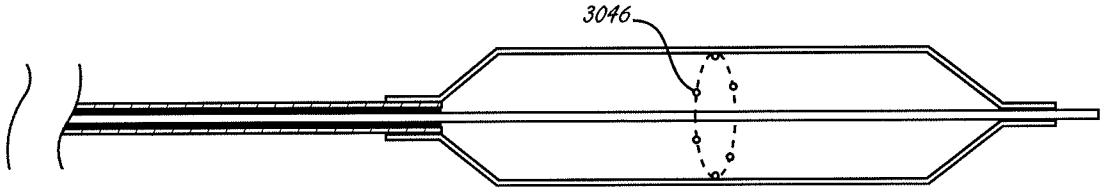


Fig. 27A

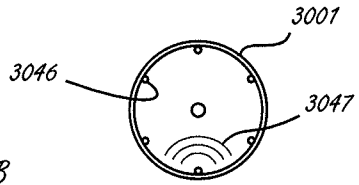


Fig. 27B

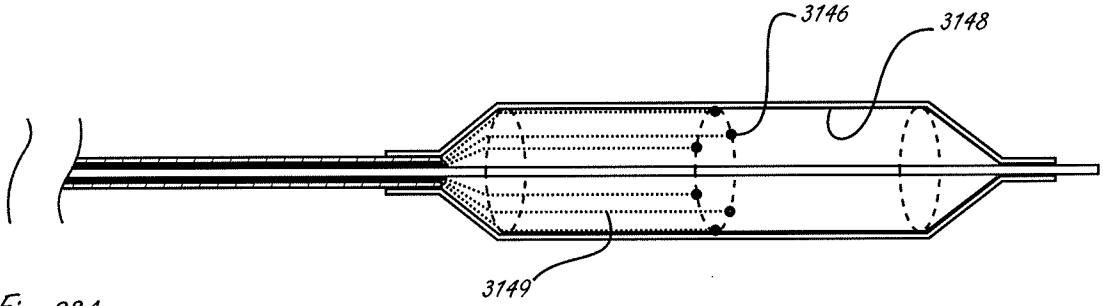


Fig. 28A

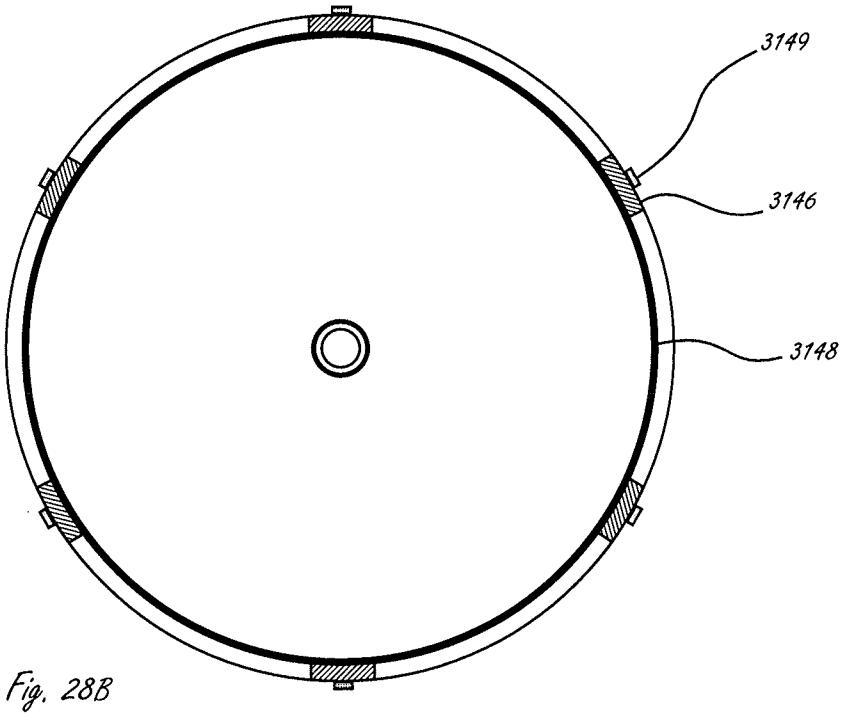


Fig. 28B

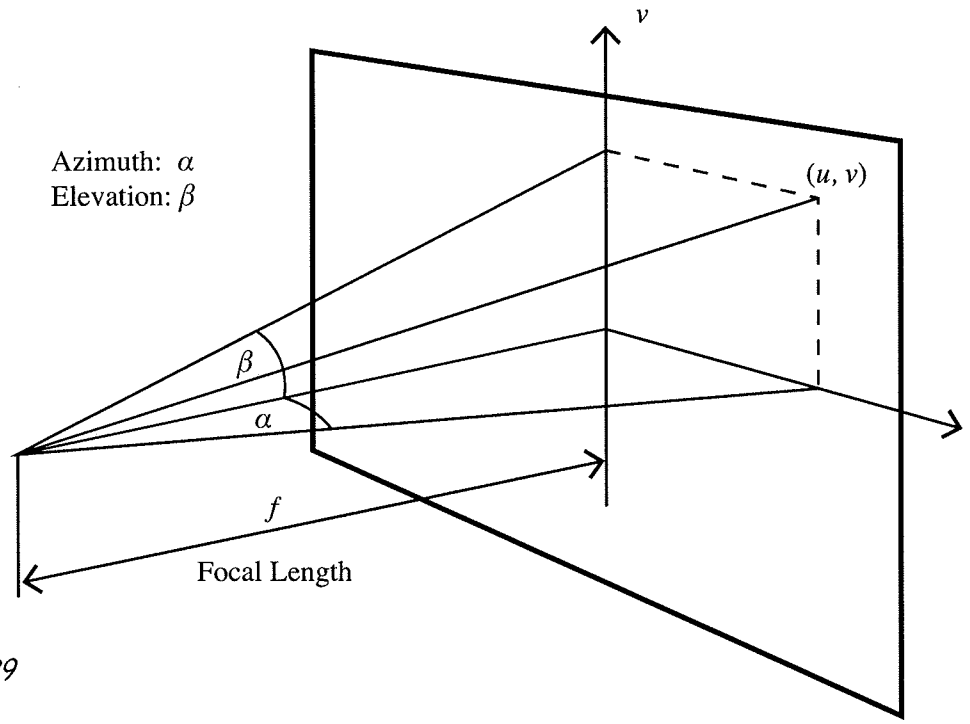


Fig. 29

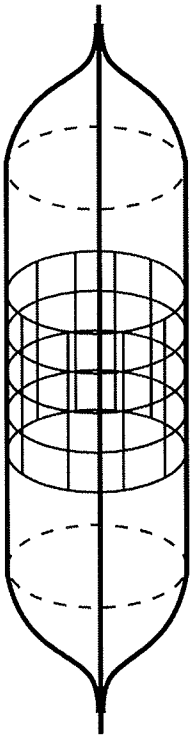


Fig. 30A

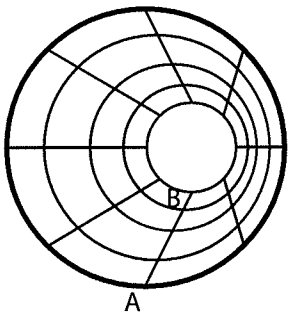


Fig. 30B

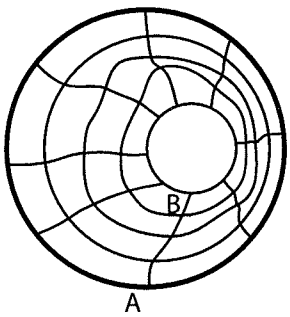


Fig. 30C

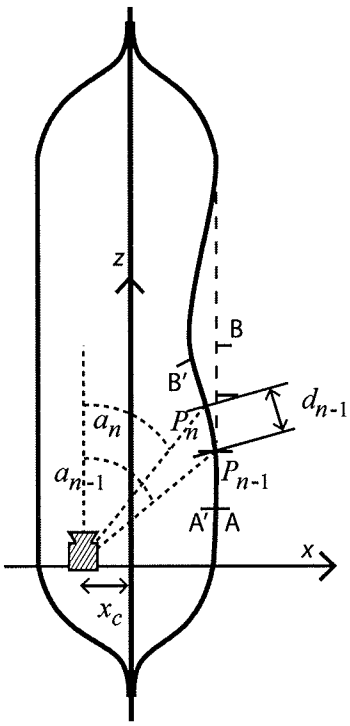


Fig. 30D

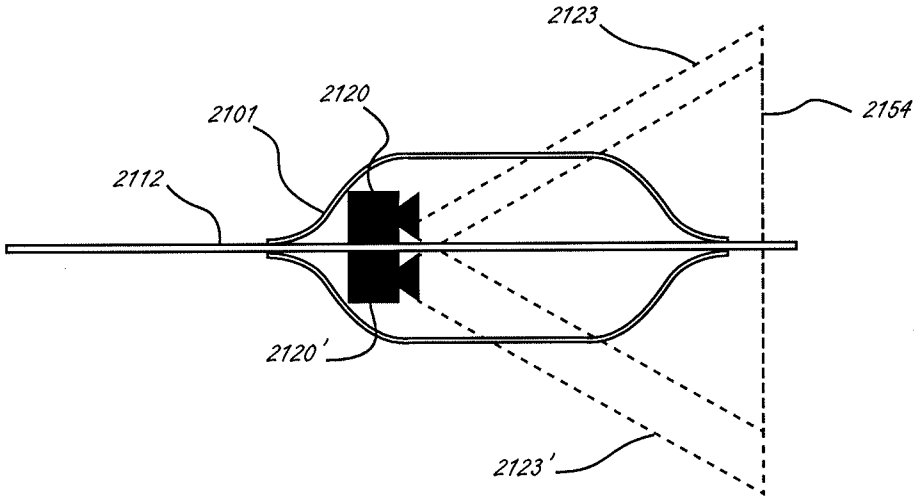


Fig. 31

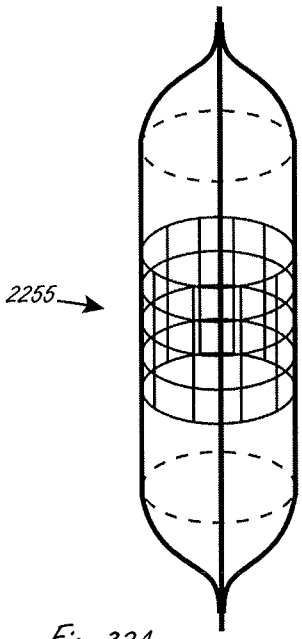


Fig. 32A

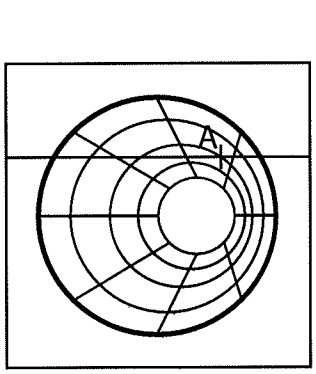


Fig. 32B

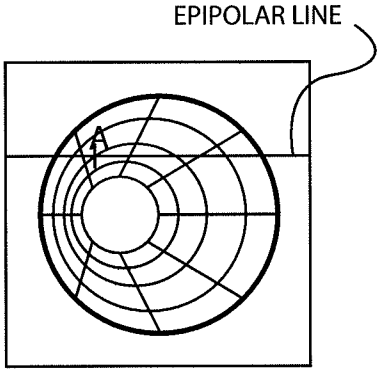


Fig. 32C

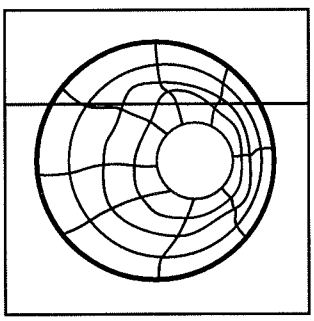


Fig. 32D

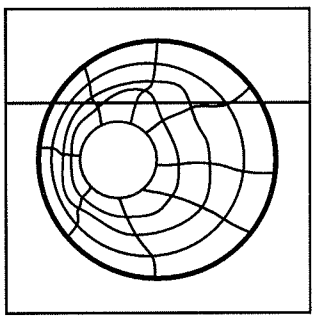


Fig. 32E

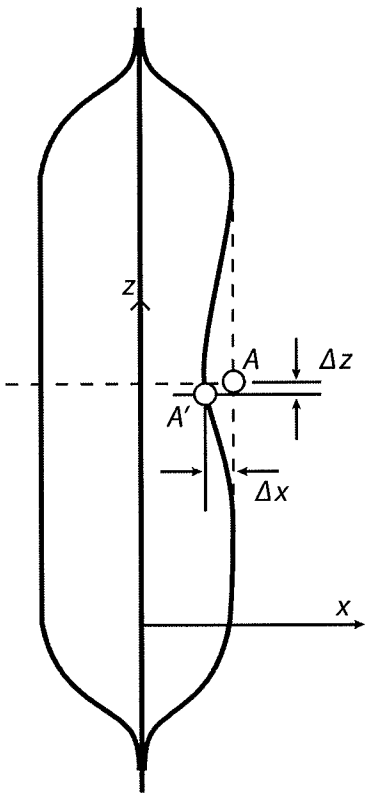


Fig. 33A

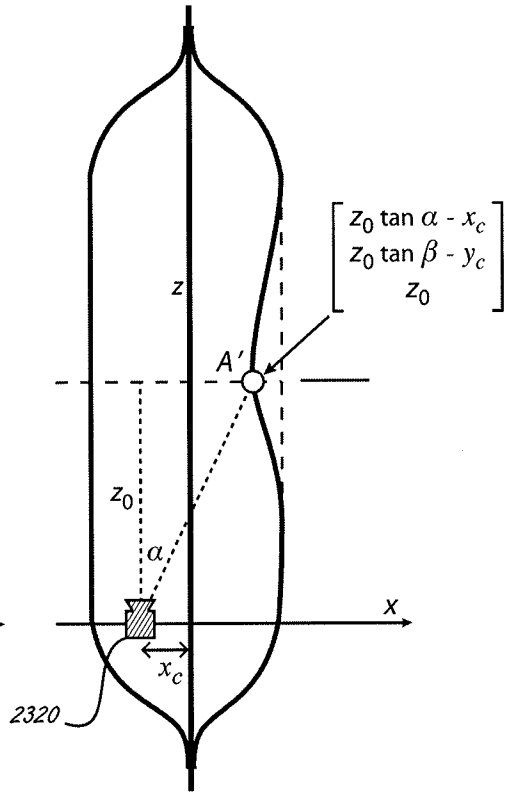


Fig. 33B

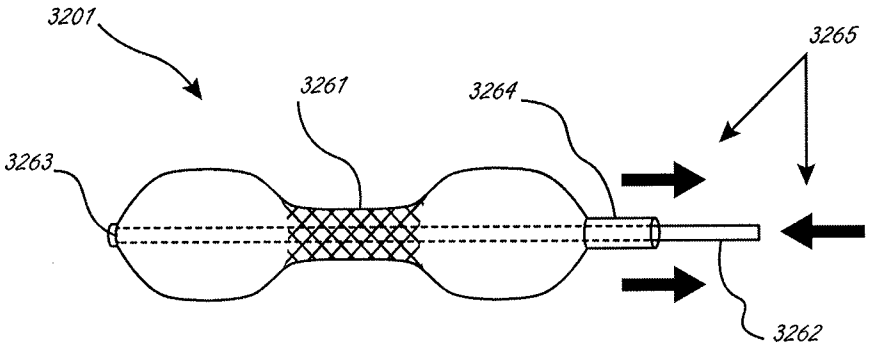


Fig. 34A

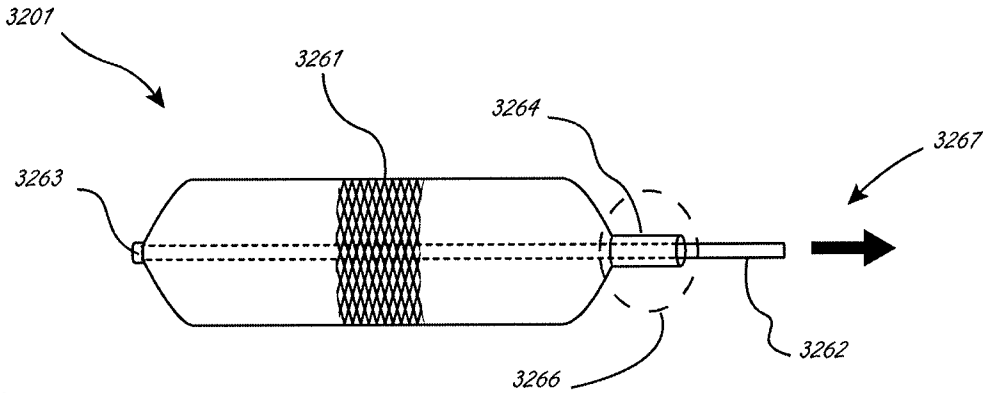


Fig. 34B

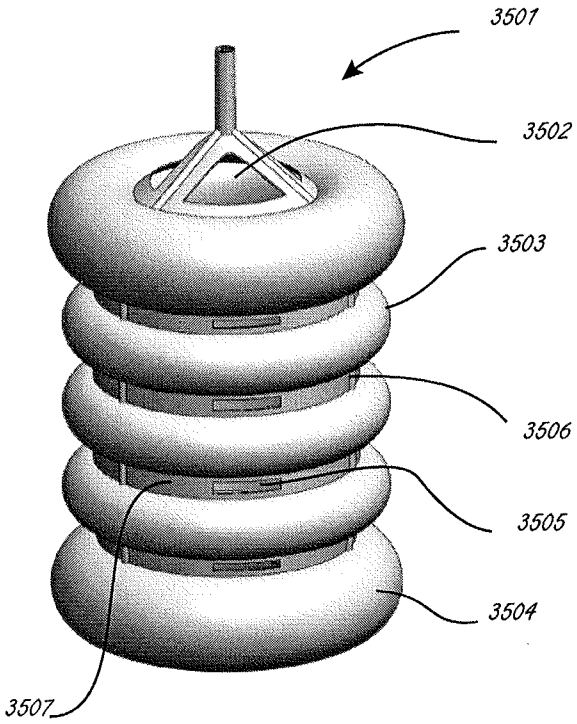


Fig. 35A

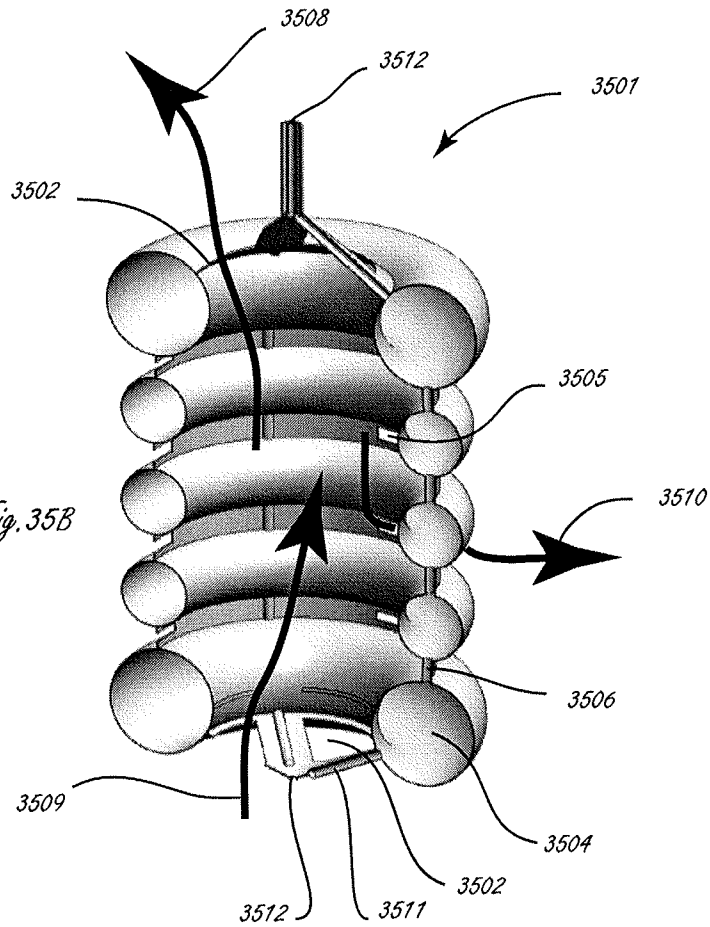


Fig. 35B

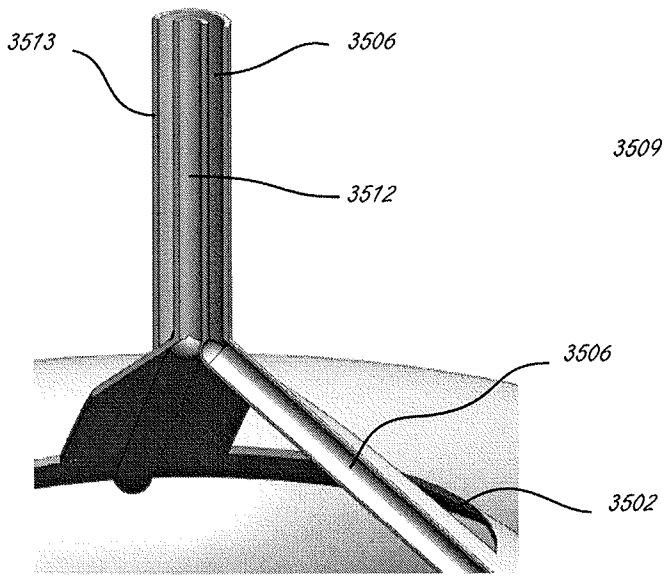


Fig. 35C

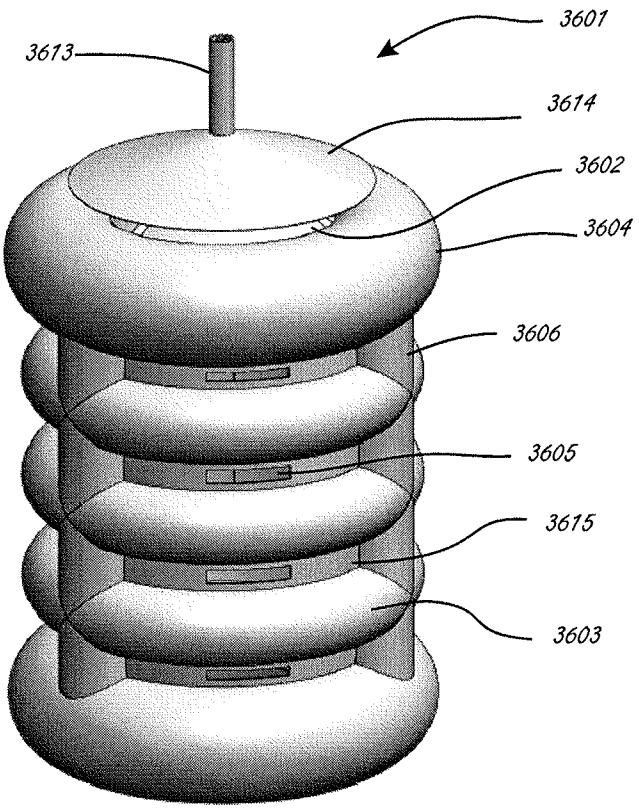


Fig. 36

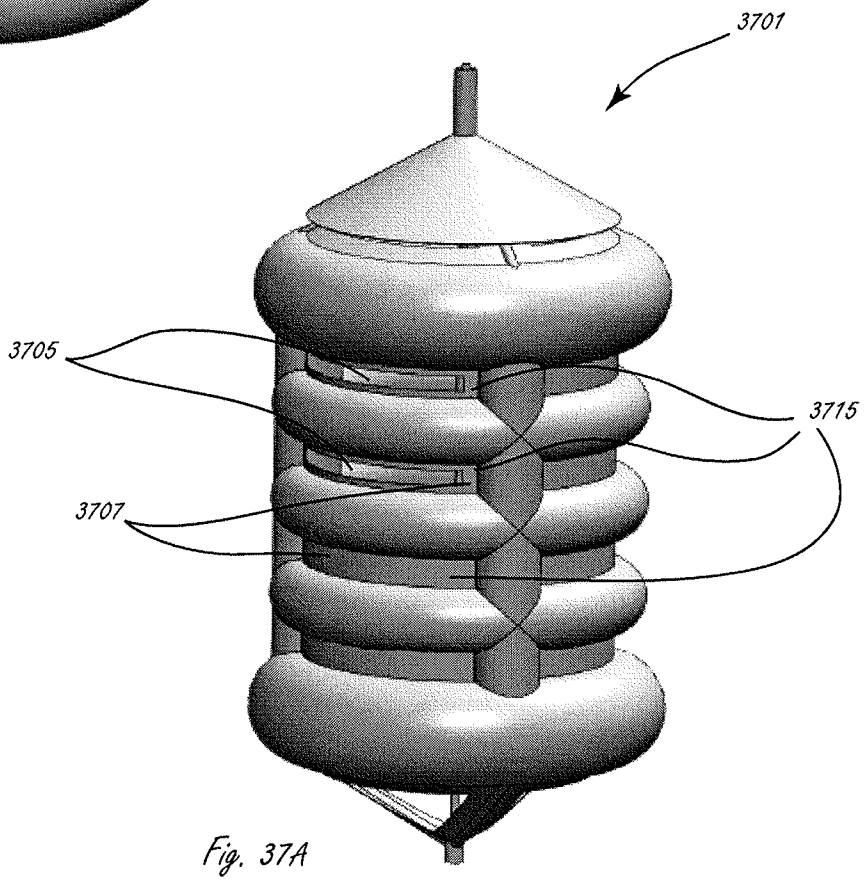


Fig. 37A

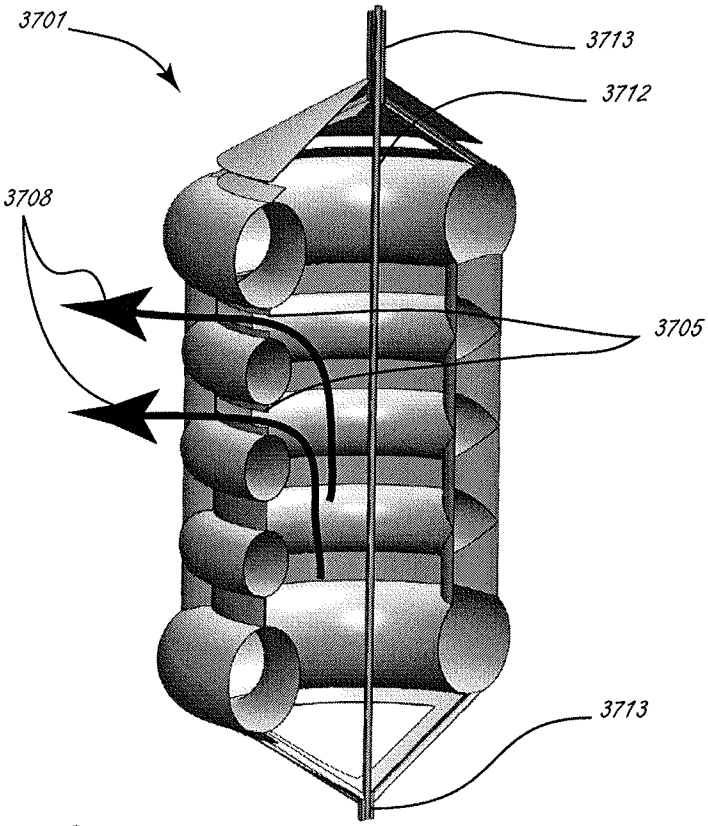


Fig. 37B

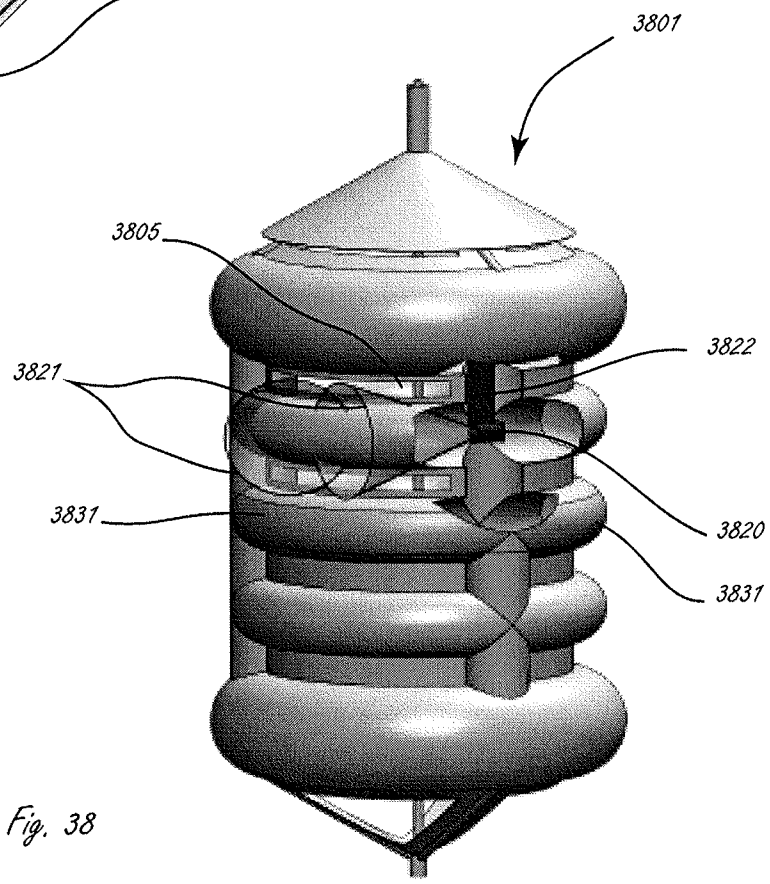


Fig. 38