



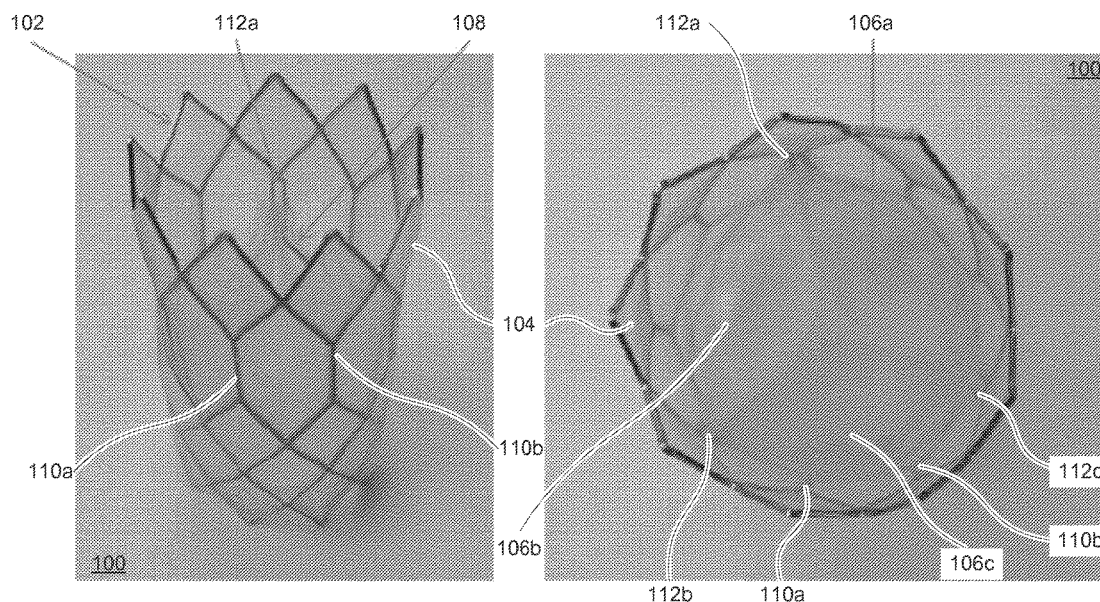
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(19) **United States**(12) **Patent Application Publication**
Justino et al.(10) **Pub. No.: US 2017/0189175 A1**(43) **Pub. Date: Jul. 6, 2017**(54) **ARTIFICIAL, FLEXIBLE VALVES AND
METHODS OF FABRICATING AND
SERIALLY EXPANDING THE SAME**(71) Applicants: **Baylor College of Medicine**, Houston,
TX (US); **William Marsh Rice
University**, Houston, TX (US)(72) Inventors: **Henri Justino**, Houston, TX (US);
Daniel Harrington, Houston, TX (US);
Kwonsoo Chun, Katy, TX (US)(73) Assignees: **Baylor College of Medicine**, Houston,
TX (US); **William Marsh Rice
University**, Houston, TX (US)(21) Appl. No.: **15/308,667**(22) PCT Filed: **May 6, 2015**(86) PCT No.: **PCT/US15/29442**

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7, 2014.**Publication Classification**(51) **Int. Cl.**
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(2013.01); **A61F 2230/0069** (2013.01); **A61F**
2230/0008 (2013.01); **A61F 2220/0008**
(2013.01); **A61F 2250/0098** (2013.01)(57) **ABSTRACT**

One aspect of the invention provides an artificial, flexible valve including: a stent defining a wall and a plurality of leaflets extending from the wall of the stent. The plurality of leaflets form a plurality of coaptation regions between two adjacent leaflets. The coaptation regions include extensions along a z-axis and adapted and are configured to form a releasable, but substantially complete seal when the leaflets are in a closed position. Another aspect of the invention provides an artificial, flexible valve including: a stent defining a wall and a plurality of leaflets extending from the wall of the stent. Each of the plurality of leaflets terminates in a commissure line. The commissure lines deviate from a hyperbola formed in the x-y plane by at least one deviation selected from the group consisting of: a deviation in the z-direction and one or more curves relative to the hyperbola.



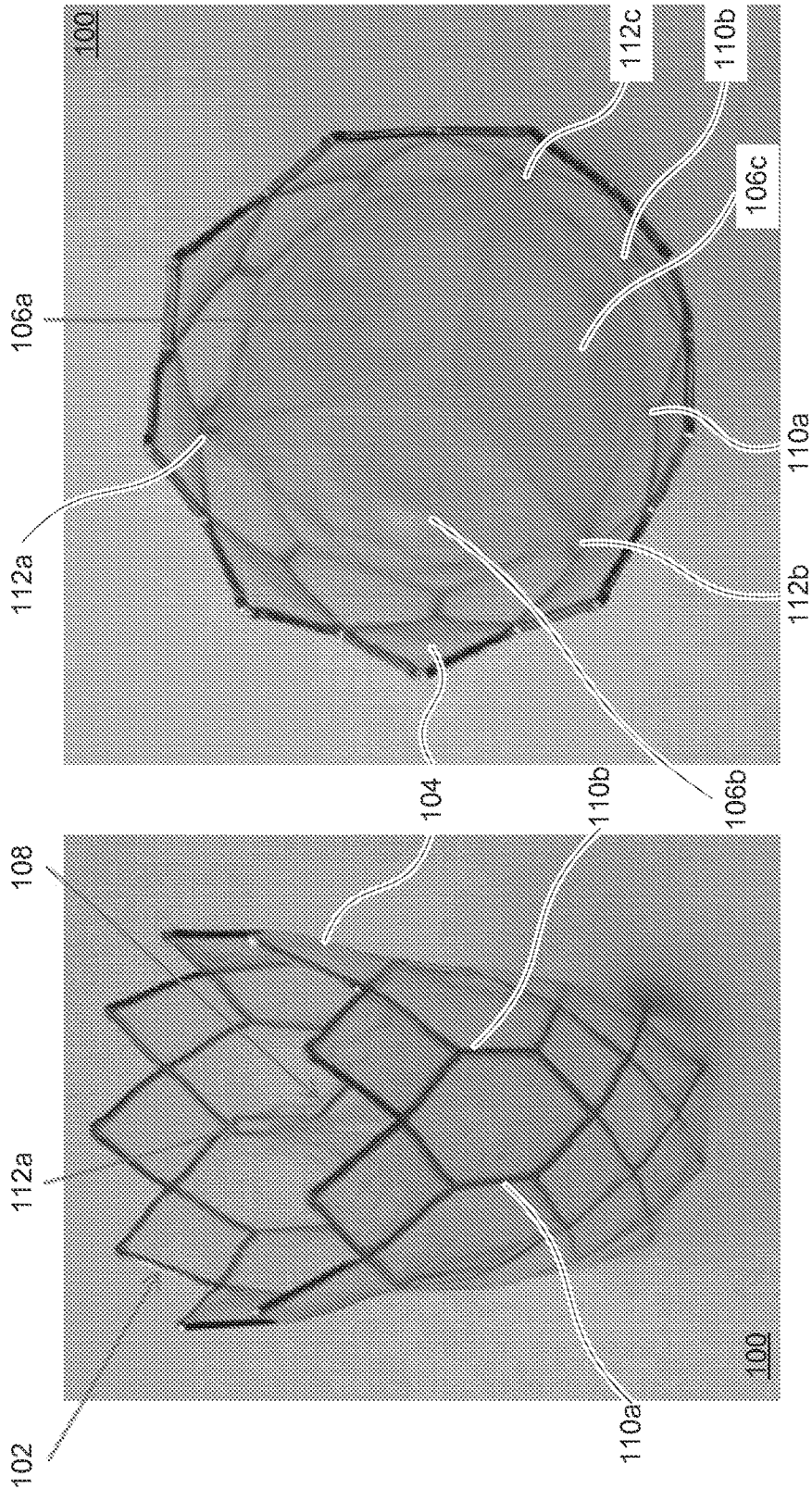


FIG. 1B

FIG. 1A

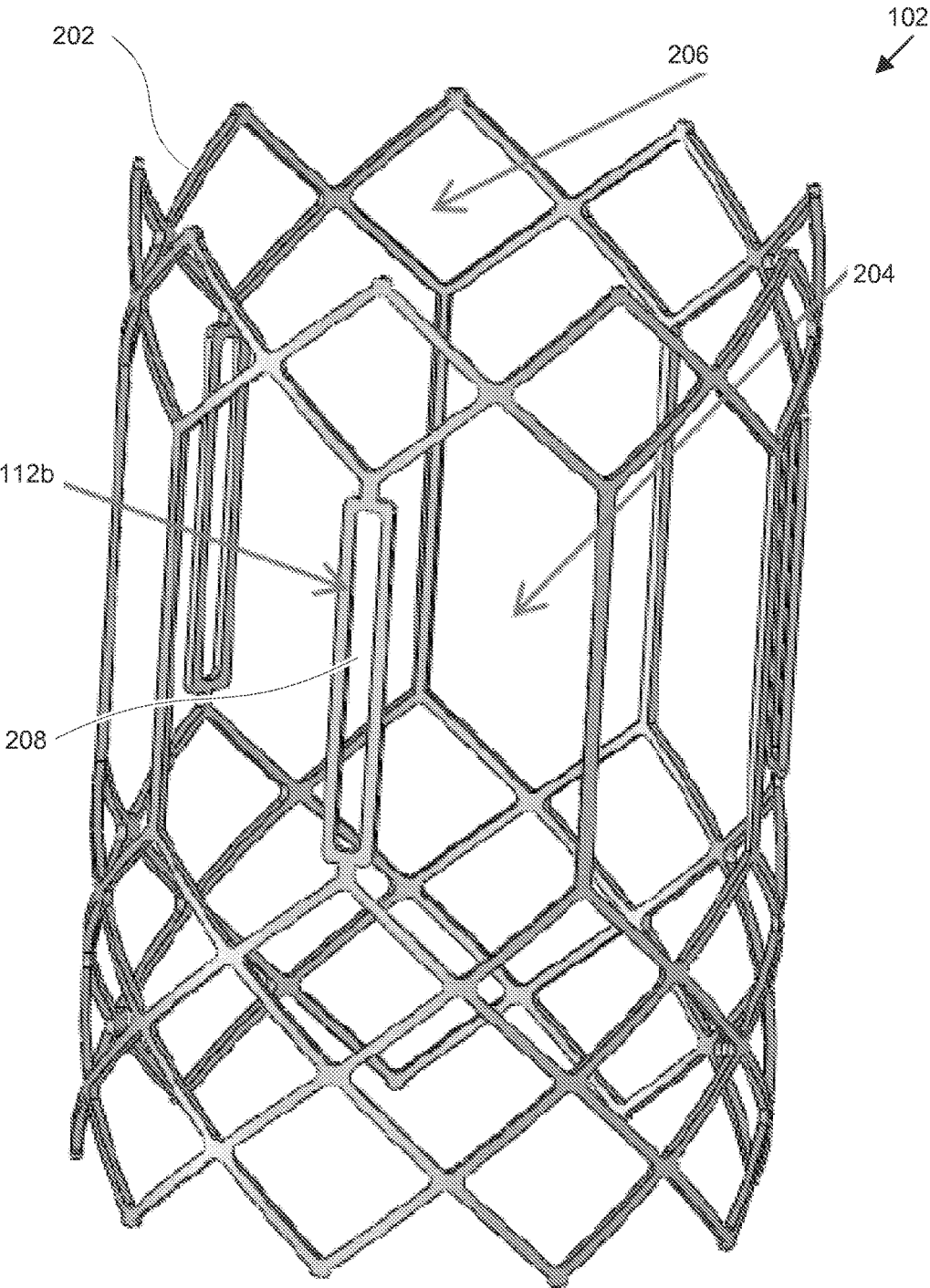


FIG. 2

FIG. 3A

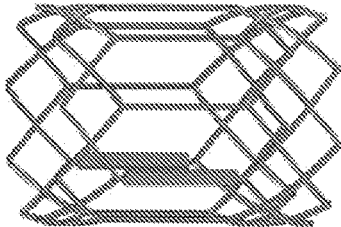


FIG. 3B

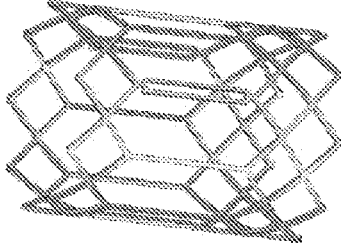


FIG. 3C

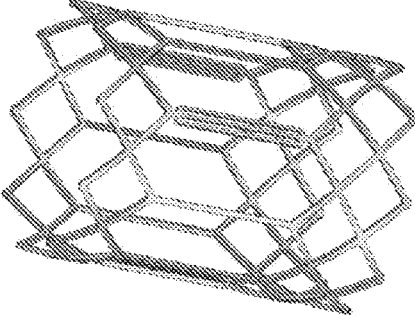
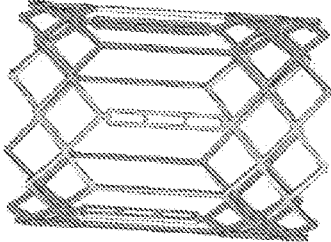


FIG. 3D

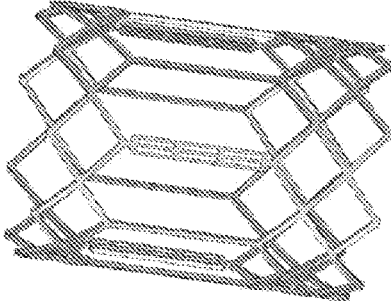


FIG. 3E

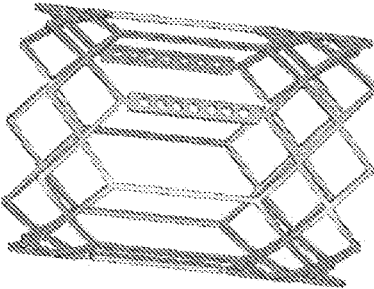


FIG. 3F

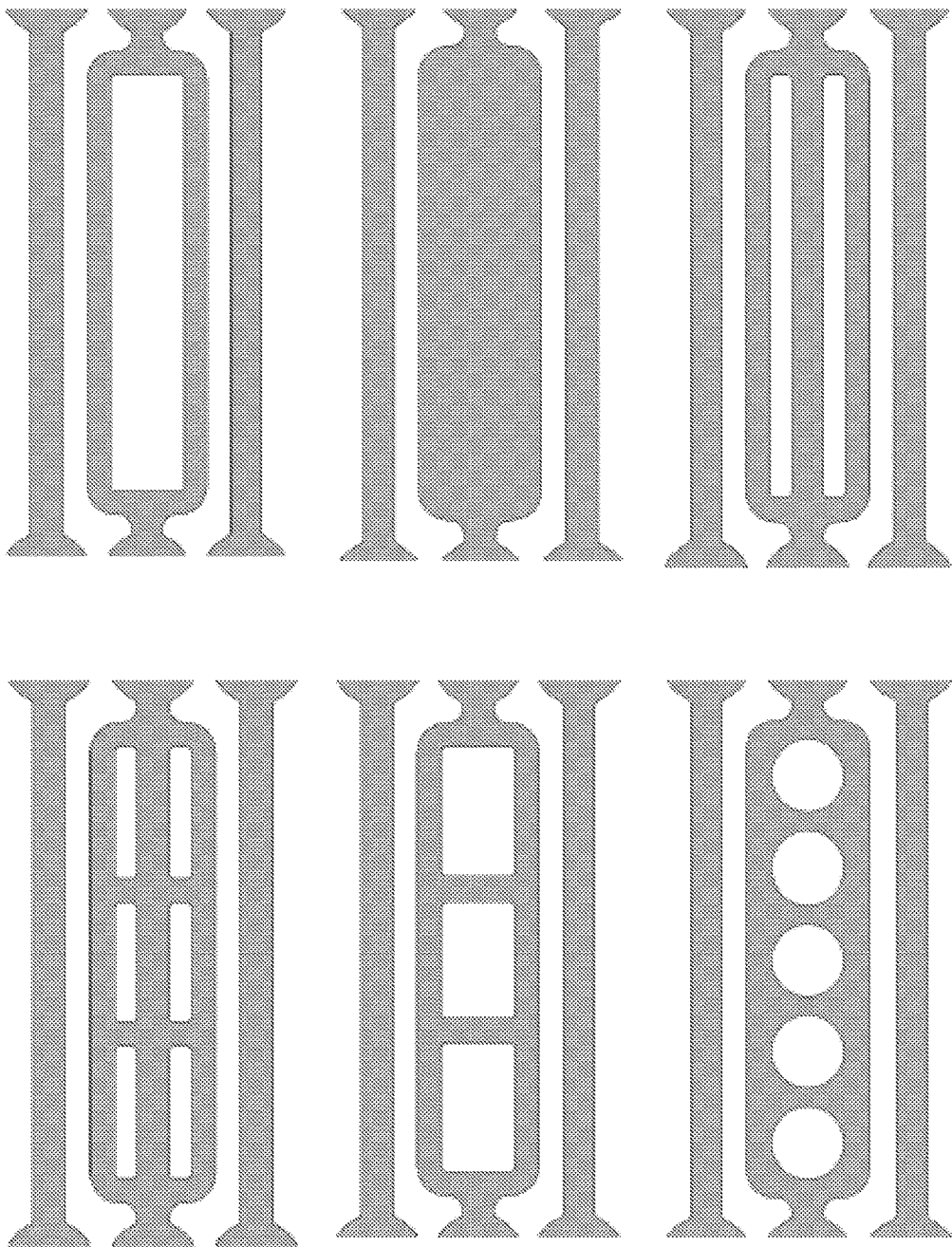


FIG. 4

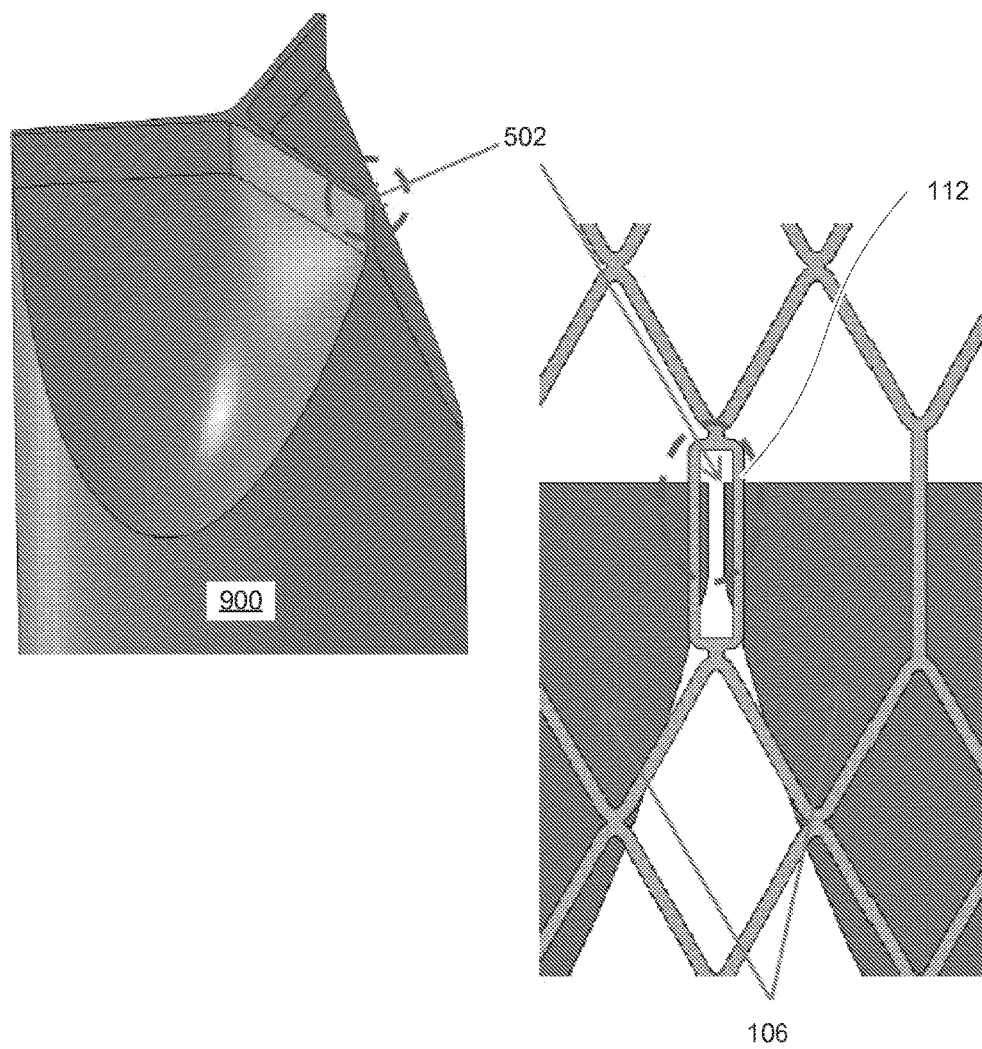


FIG. 5A

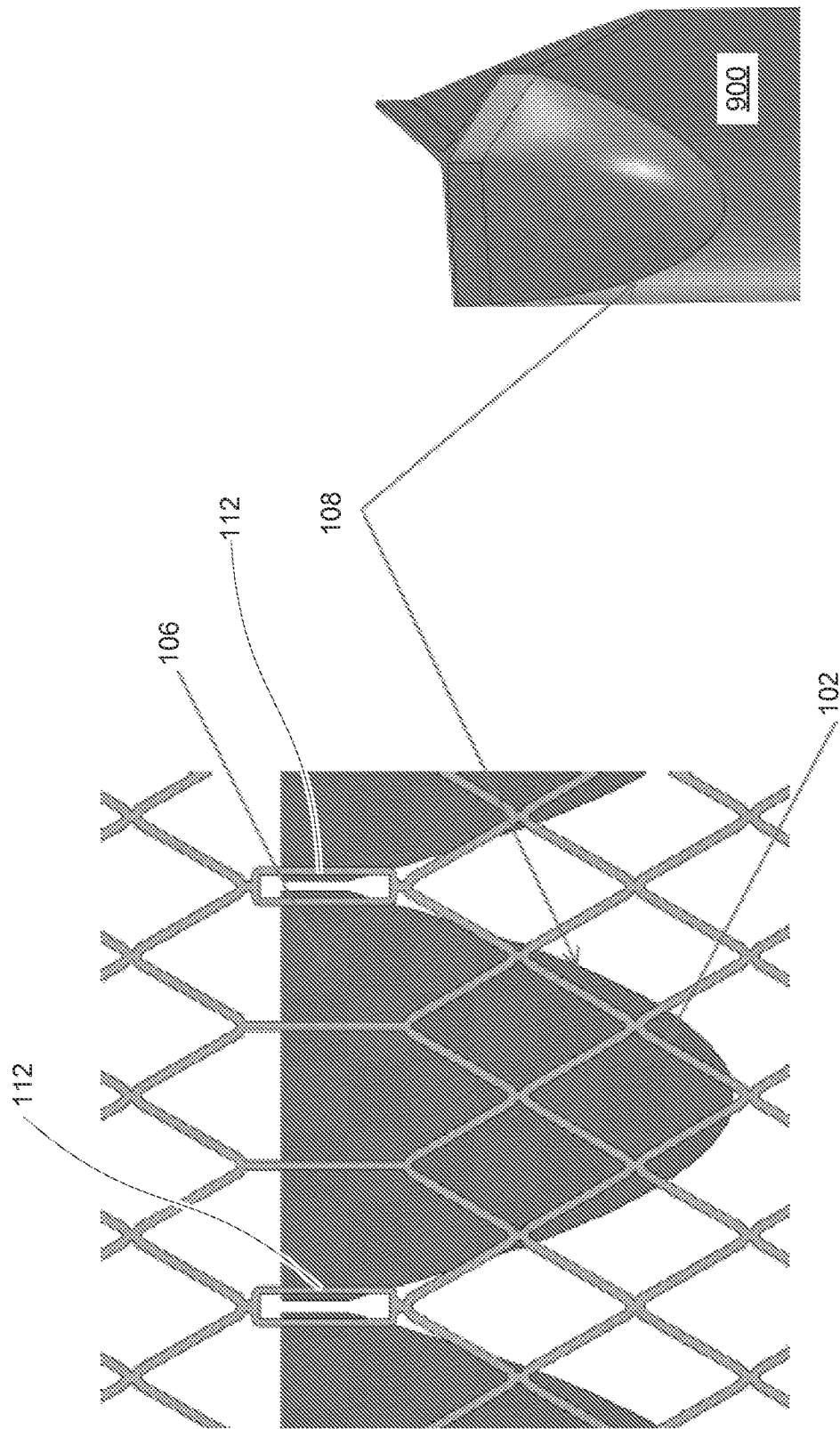


FIG. 5B

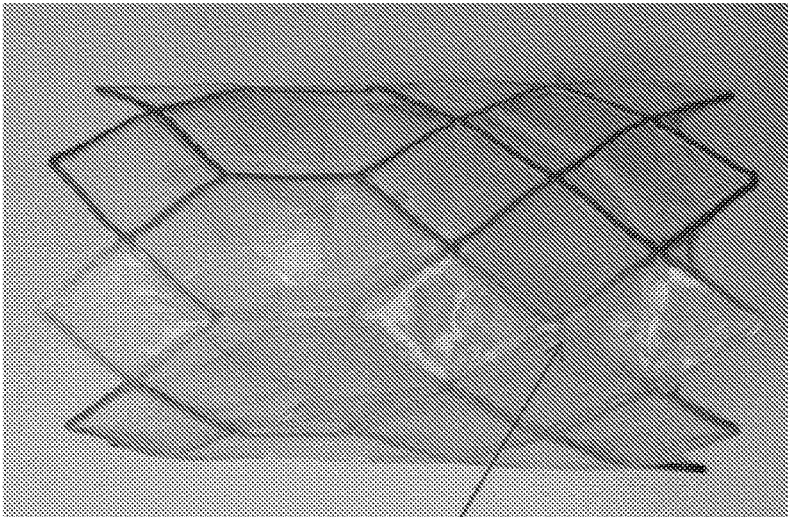


FIG. 5D

Glue line close to
metal frames

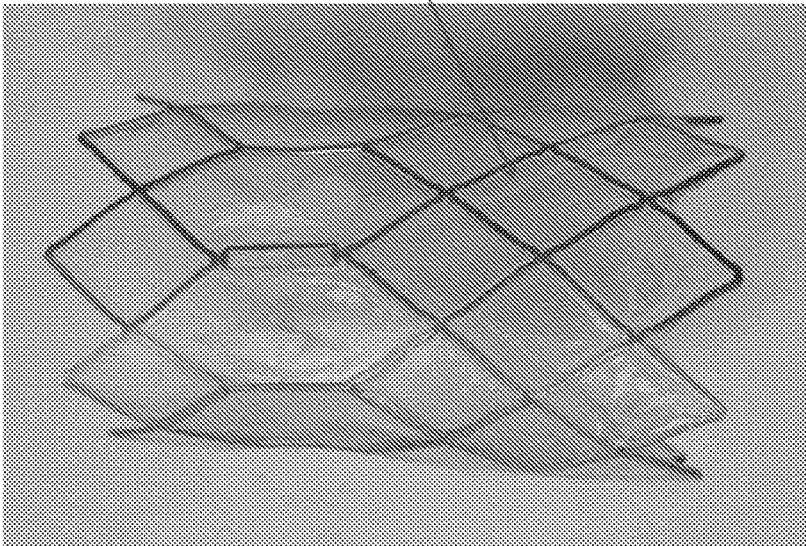


FIG. 5C

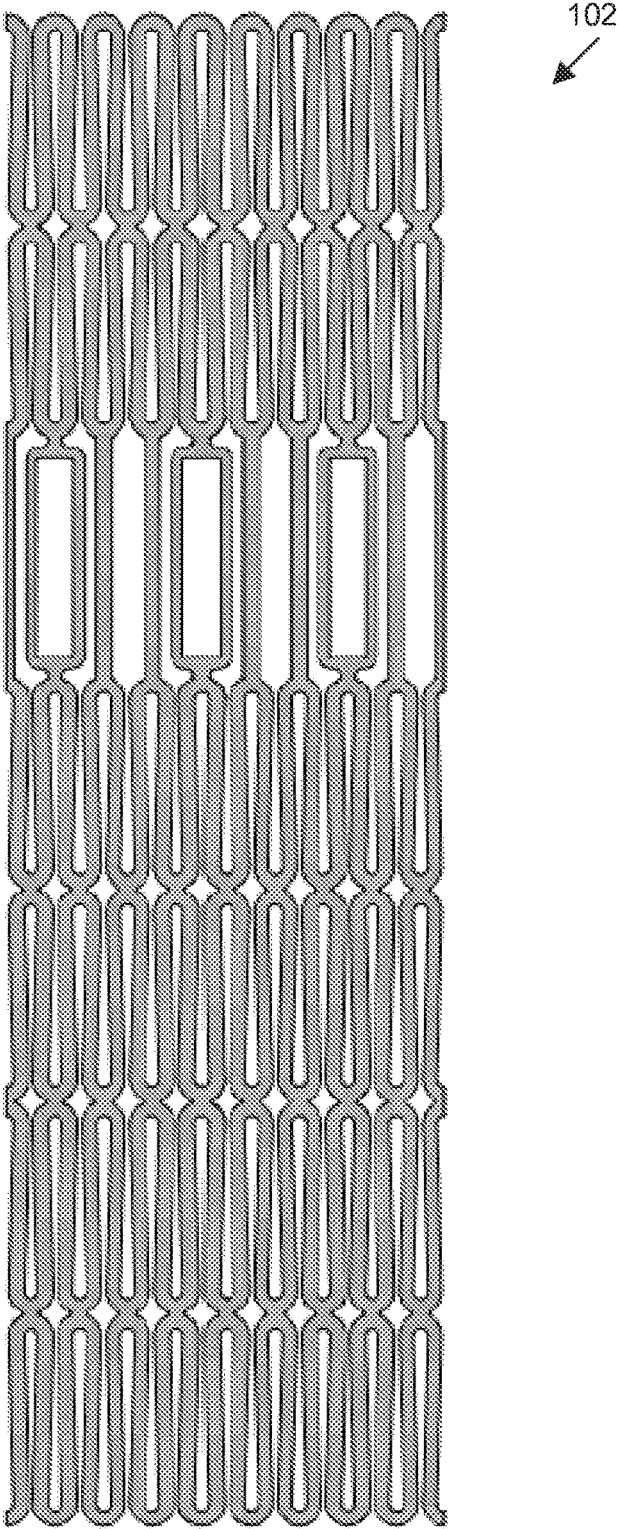


FIG. 6

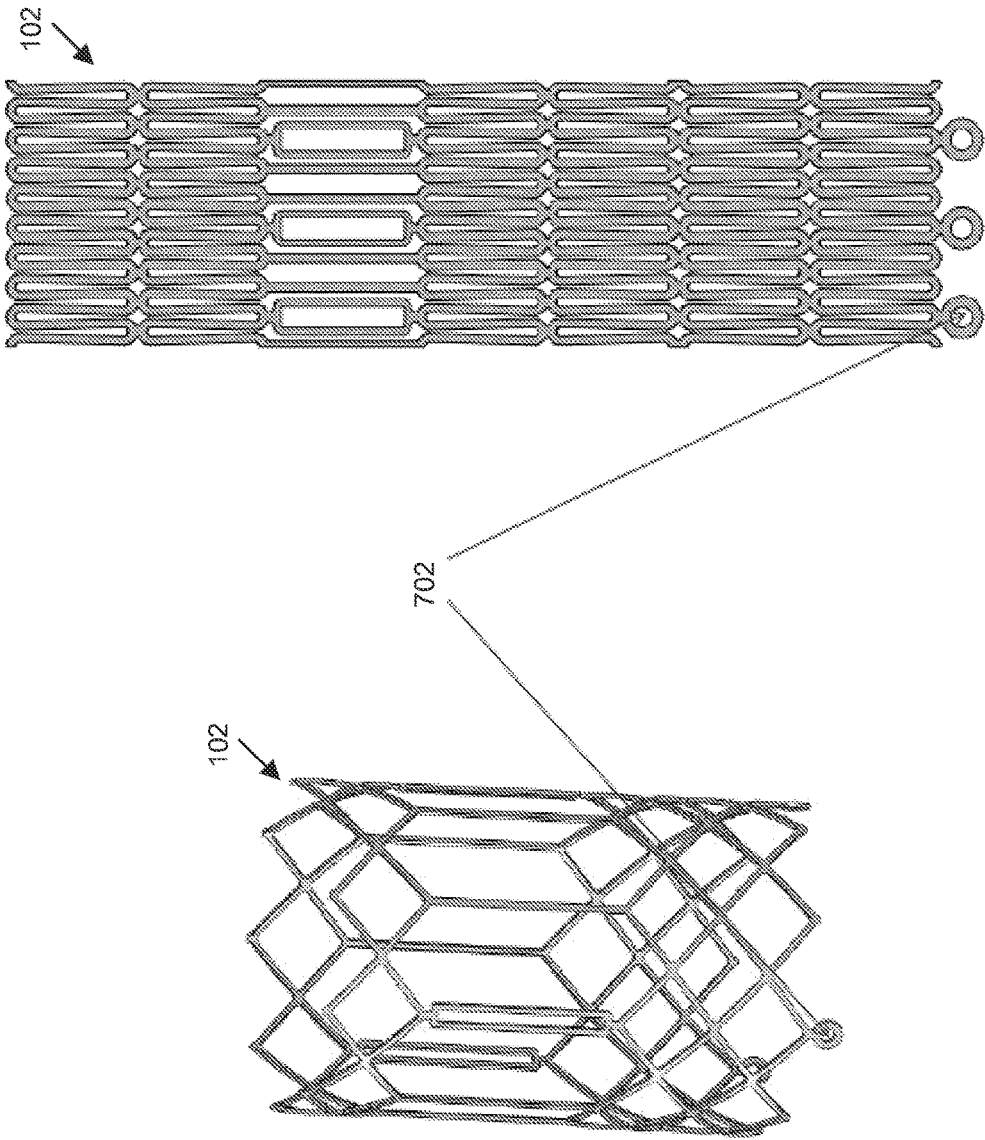


FIG. 7

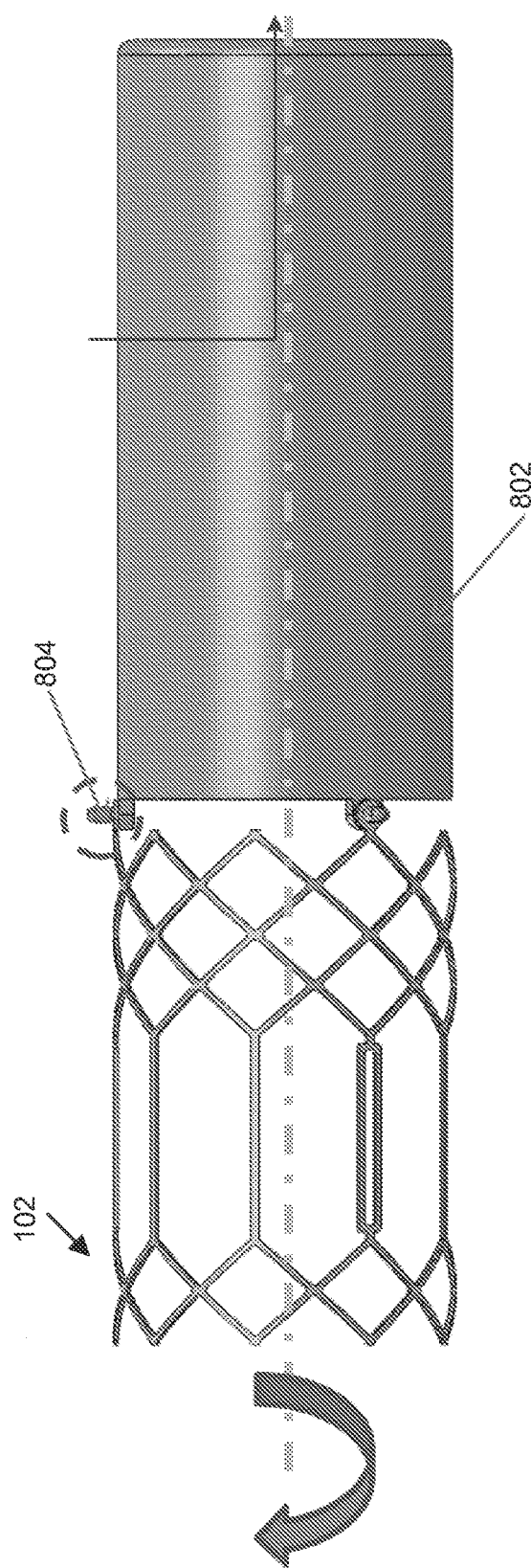


FIG. 8

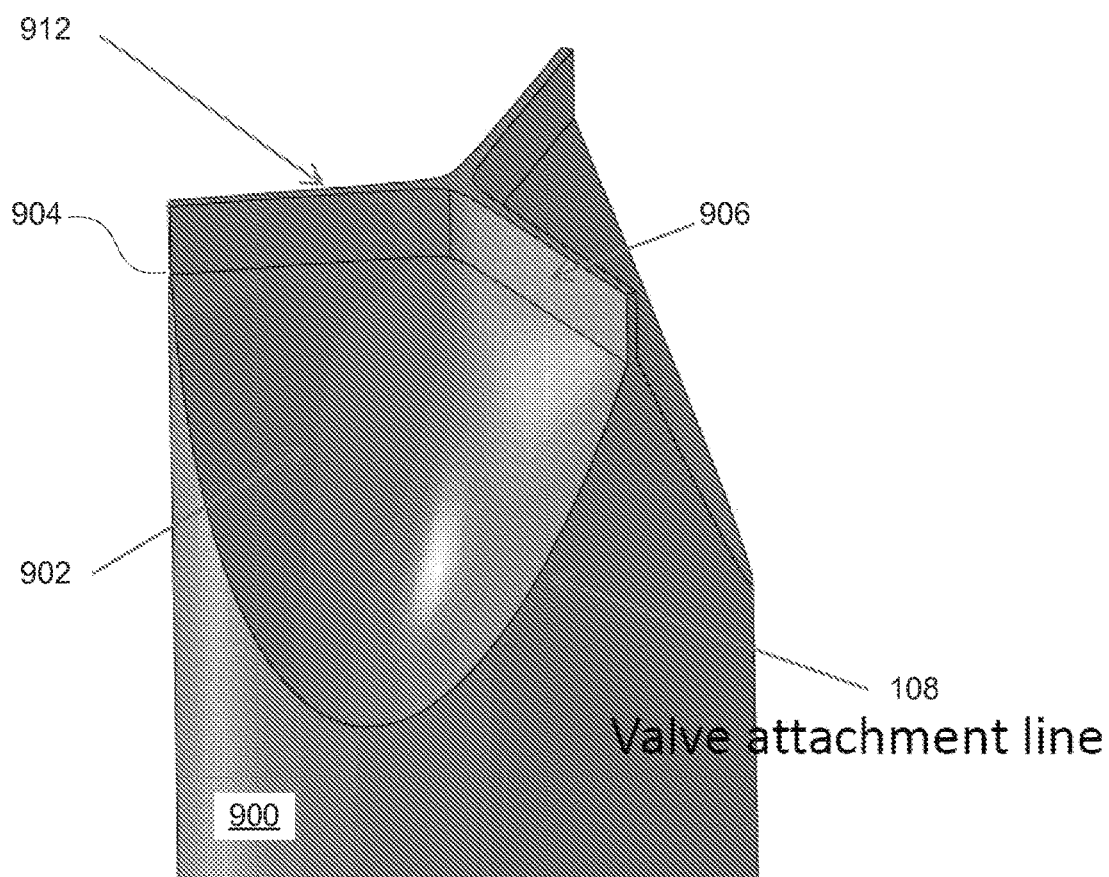


FIG. 9A

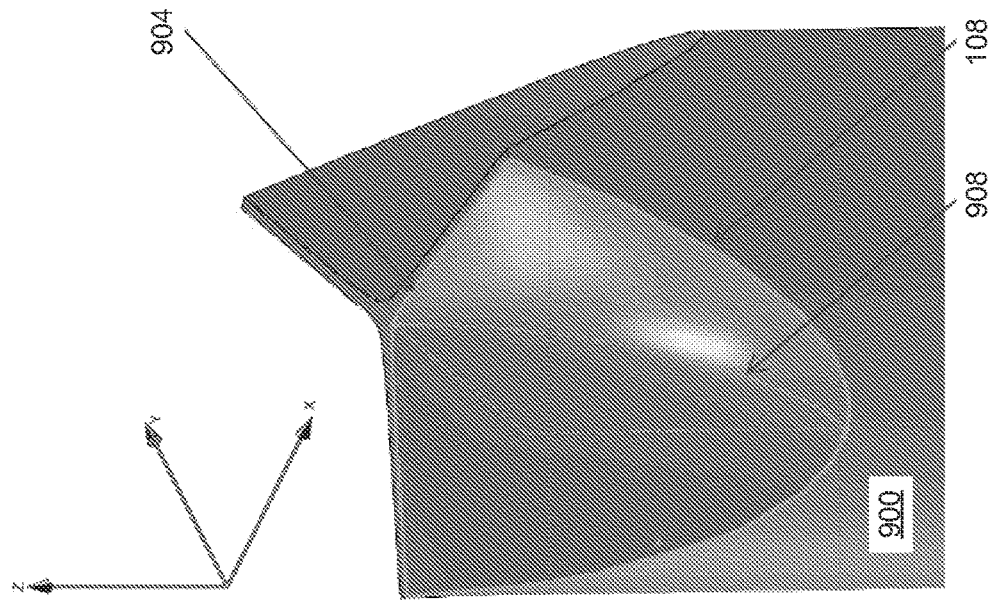


FIG. 9B

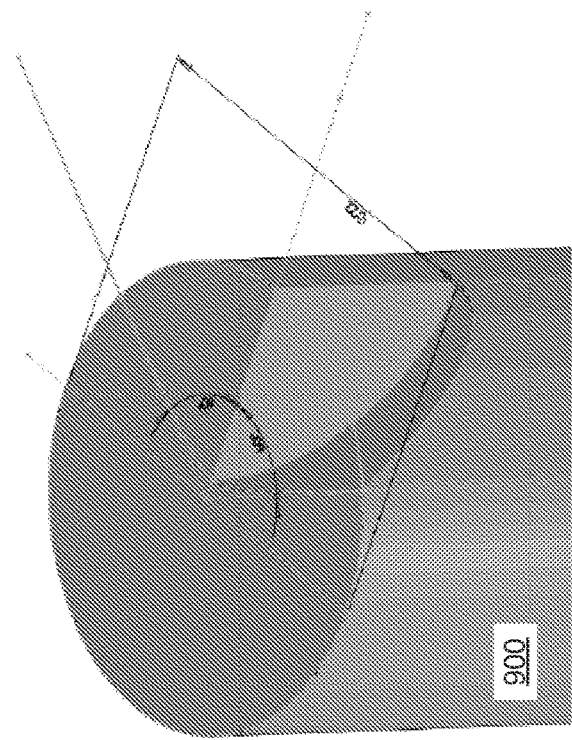


FIG. 9C

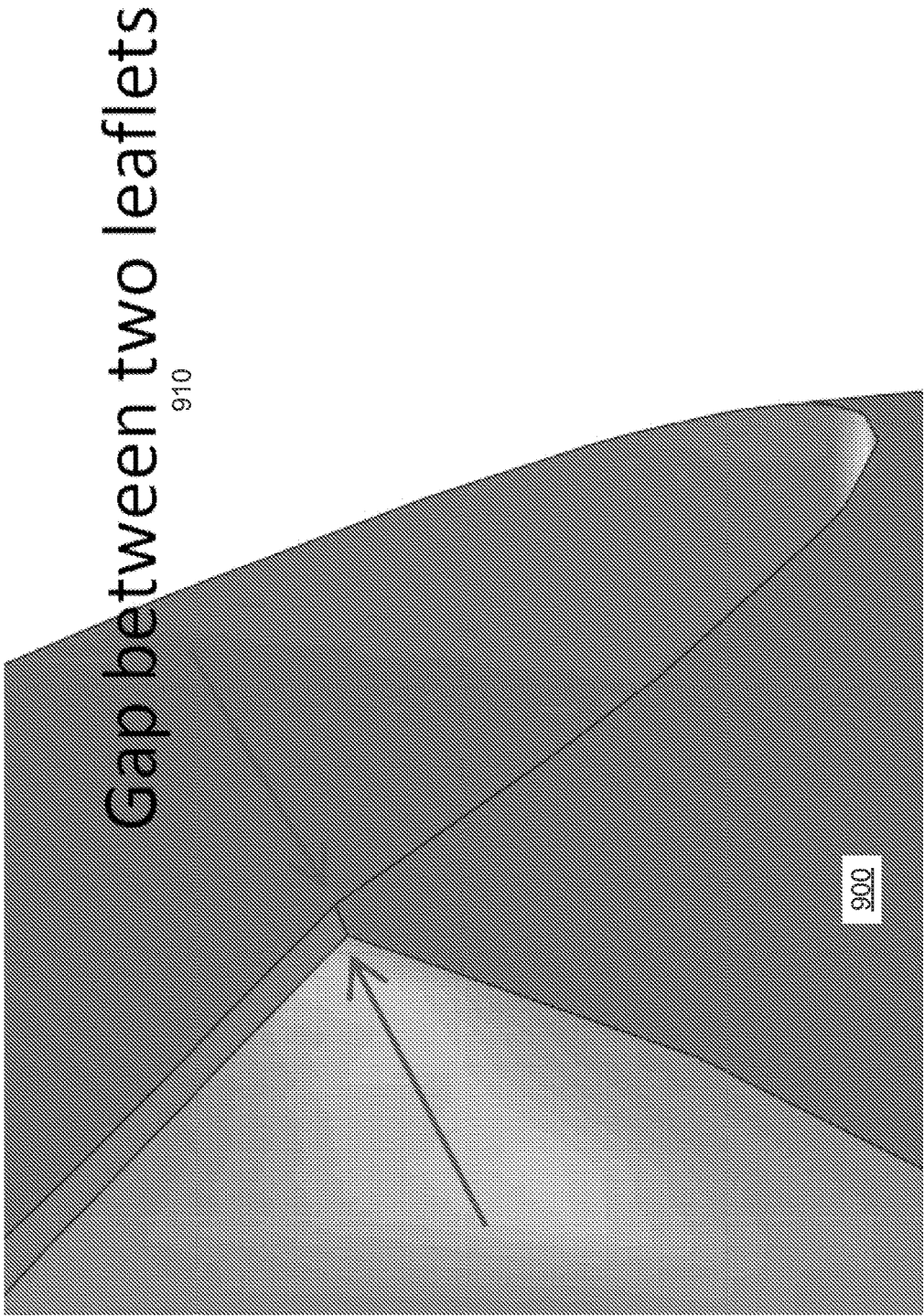


FIG. 9D

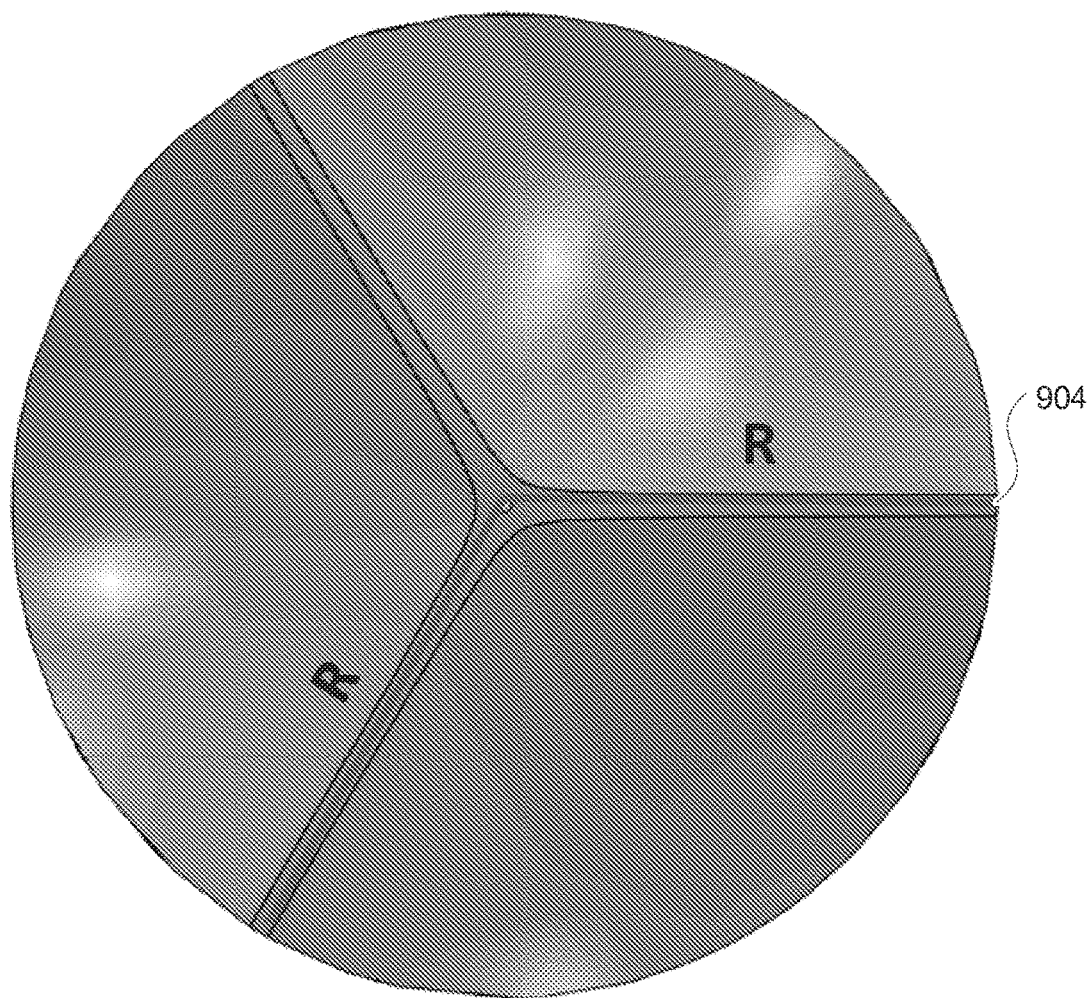


FIG. 9E

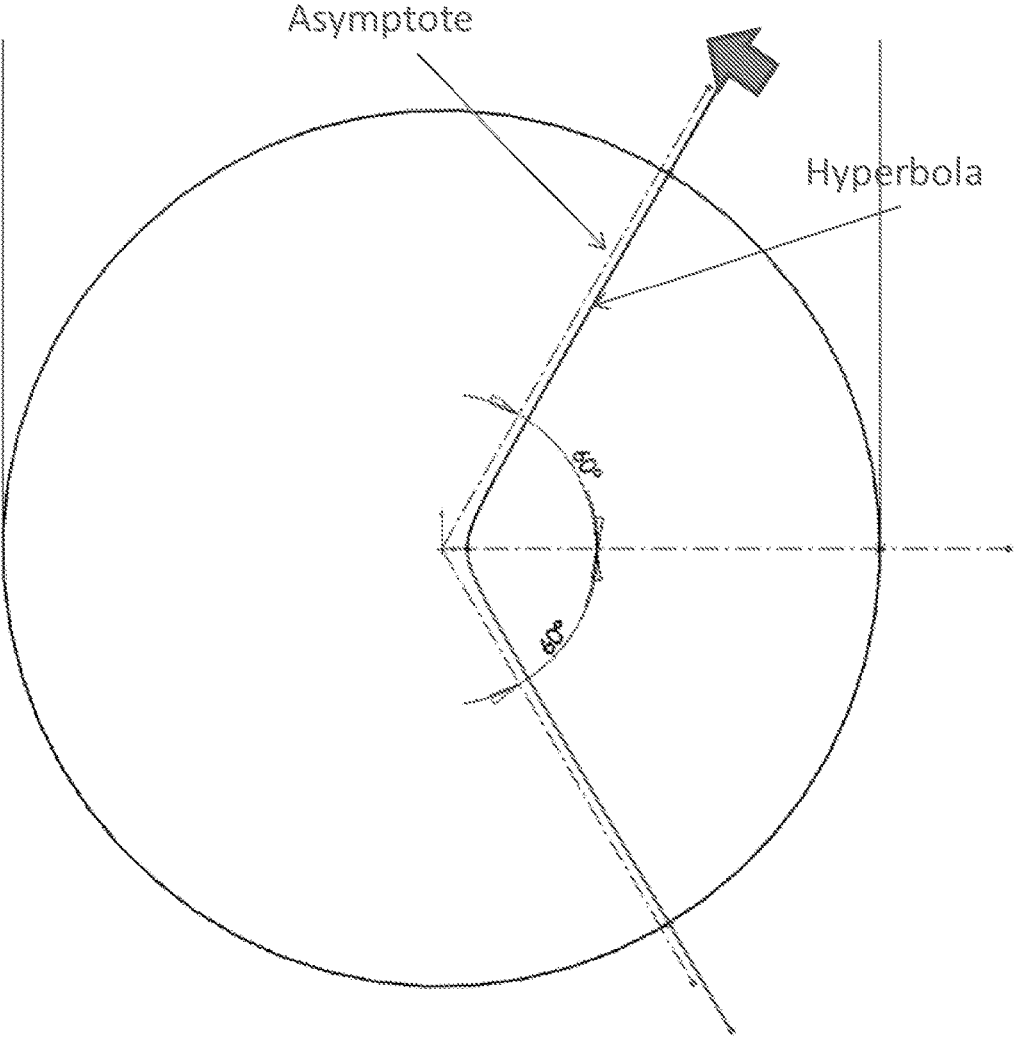
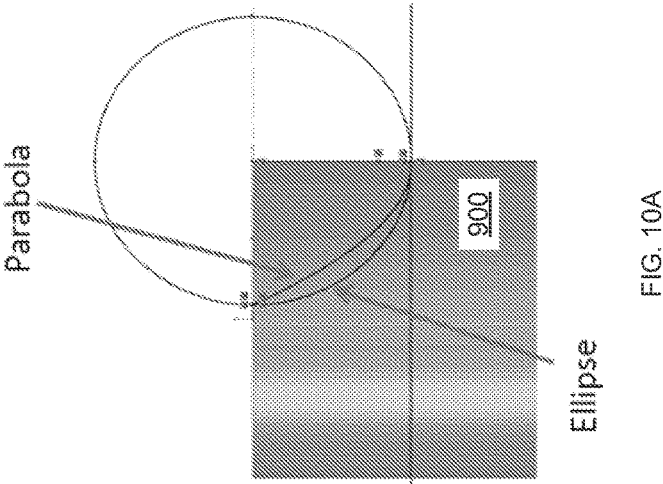
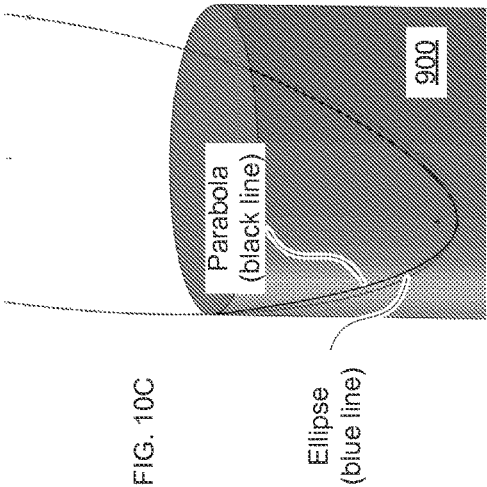
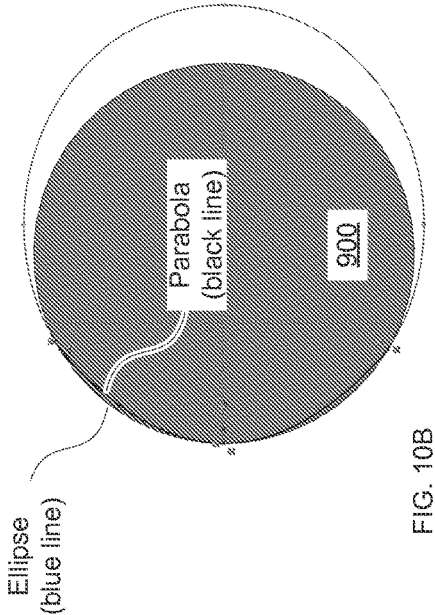
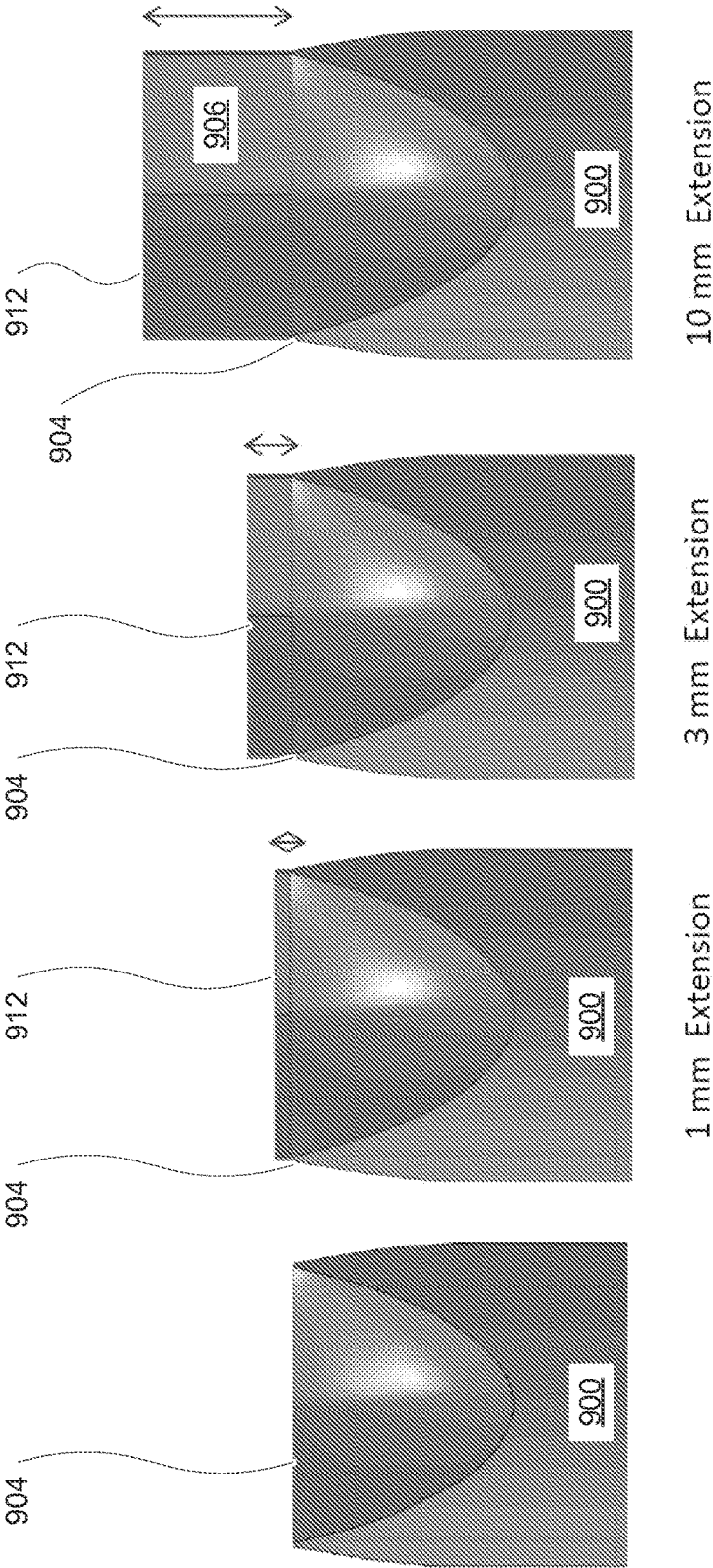
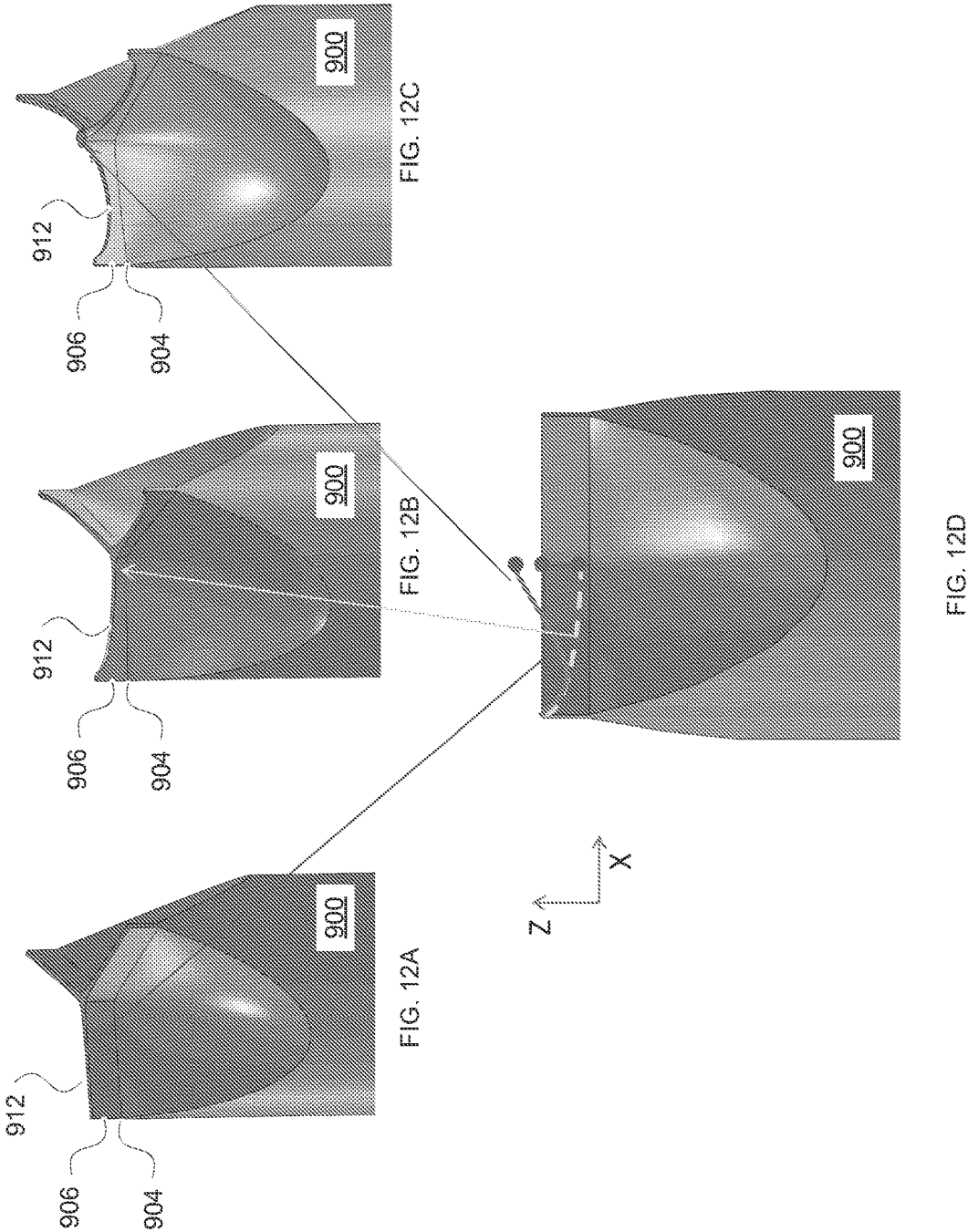
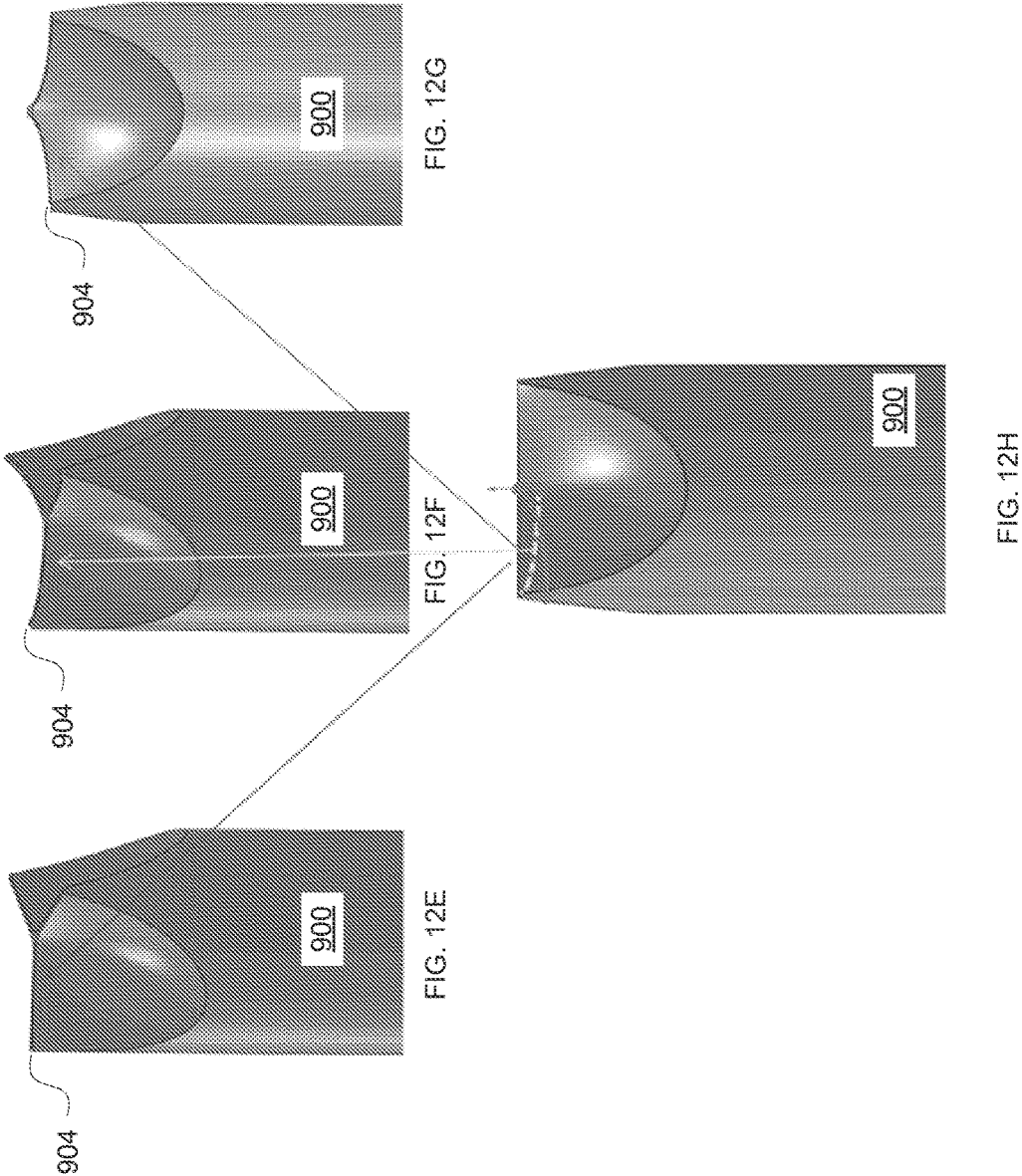


FIG. 9F









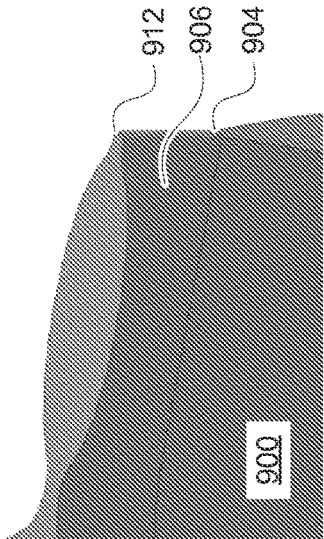


FIG. 12I

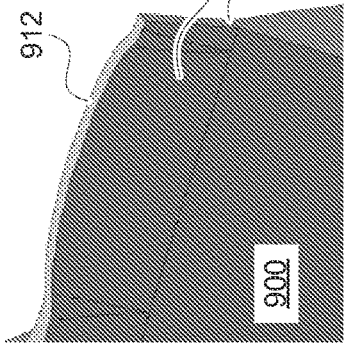


FIG. 12J

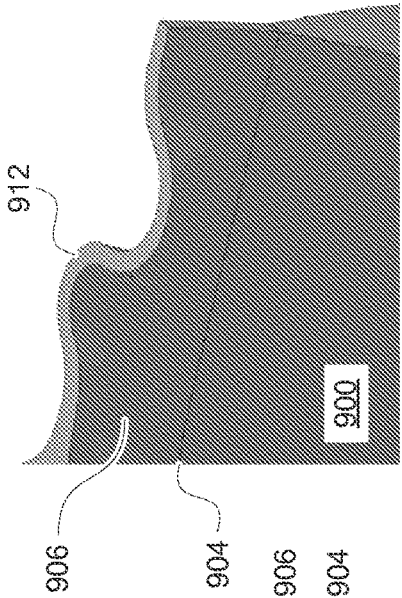


FIG. 12K

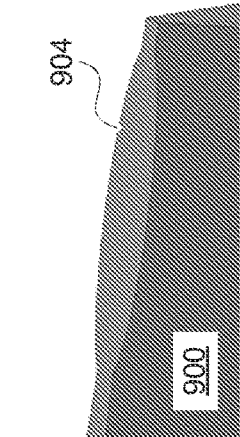


FIG. 12L

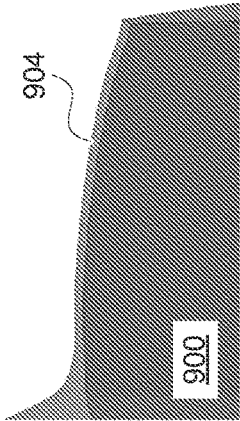


FIG. 12M

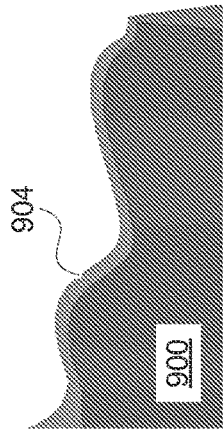


FIG. 12N

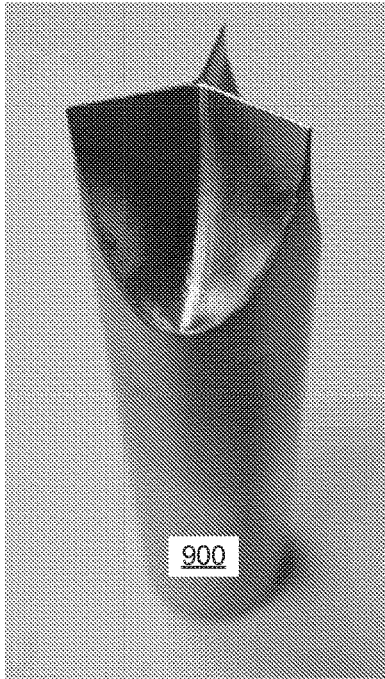


FIG. 13A

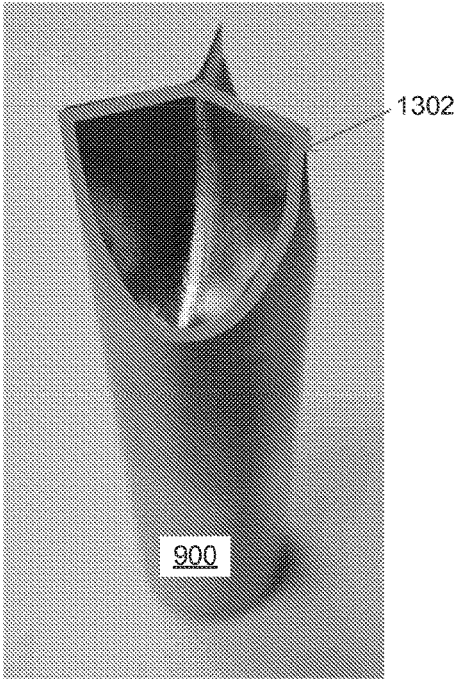


FIG. 13B

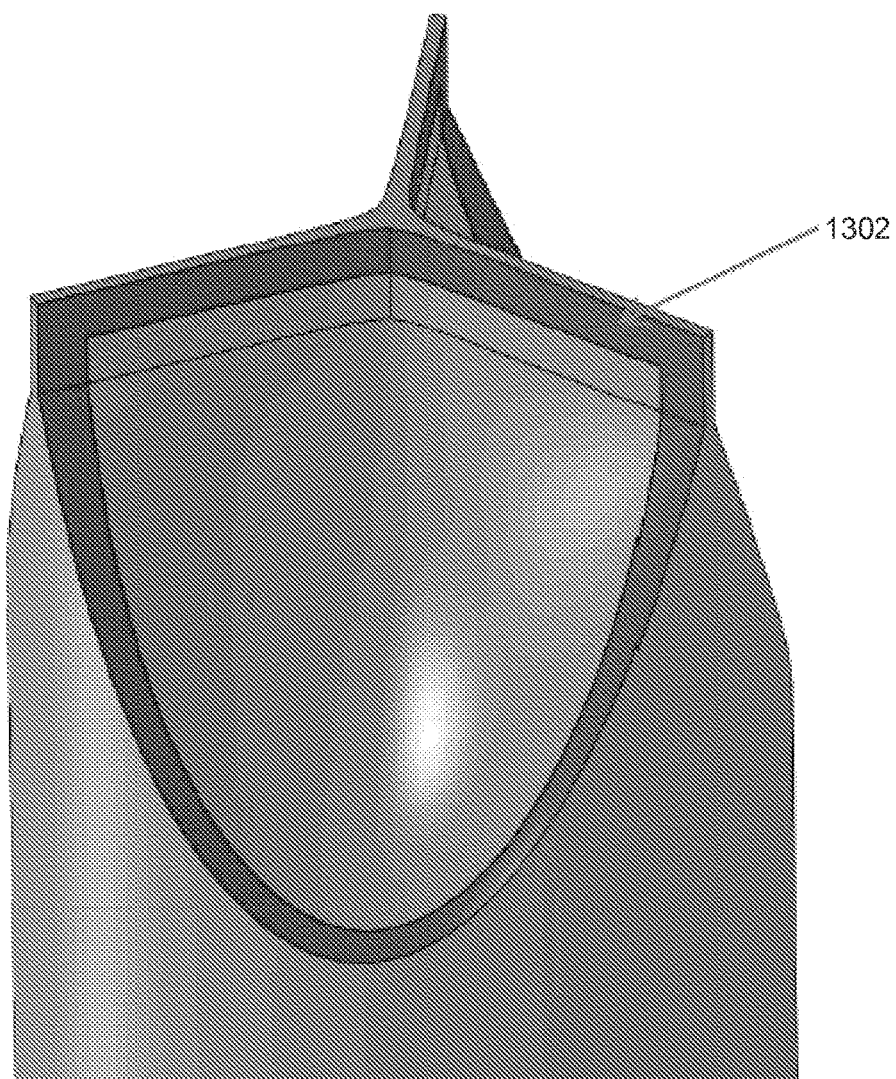


FIG. 13C

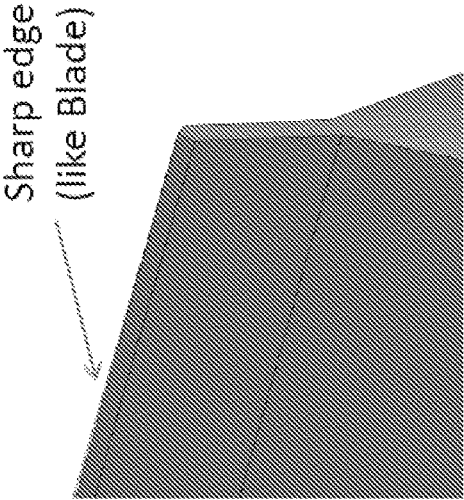


FIG. 14C

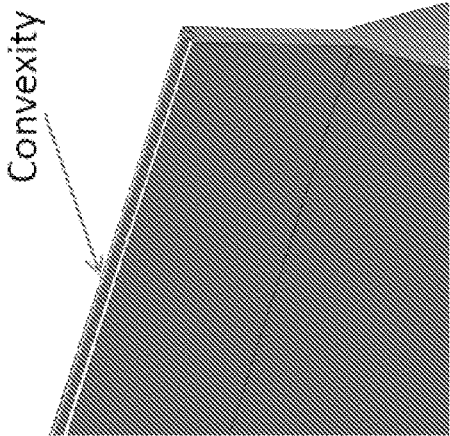


FIG. 14B

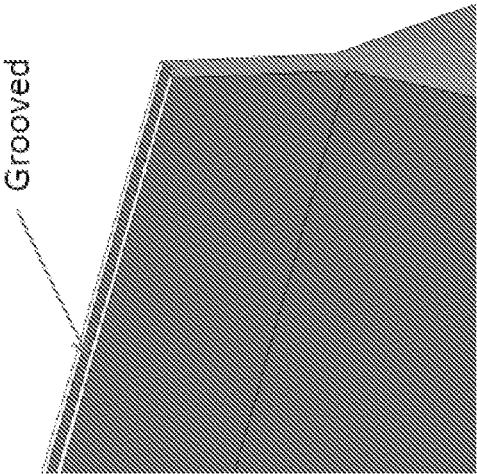


FIG. 14A

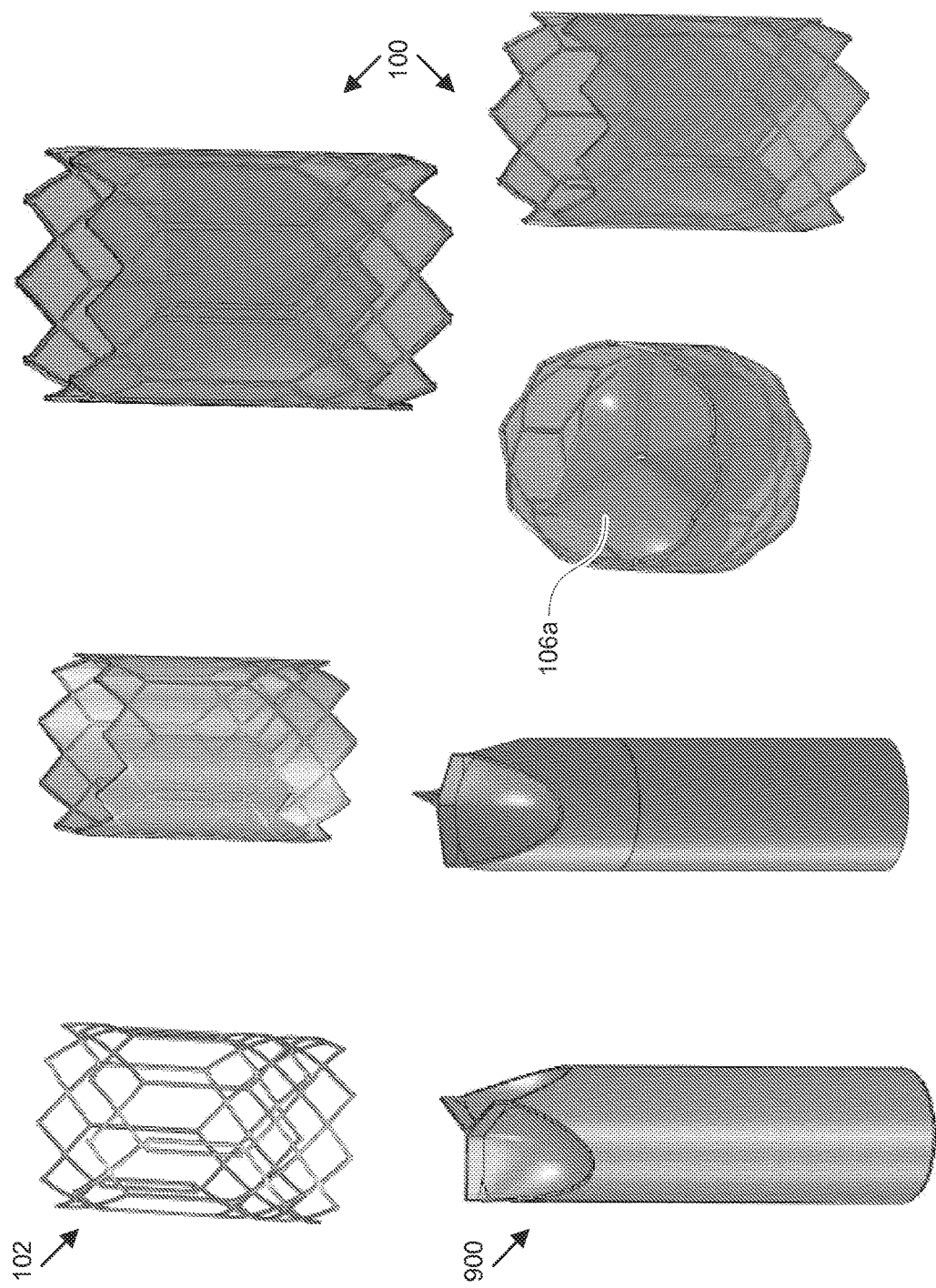


FIG. 15A

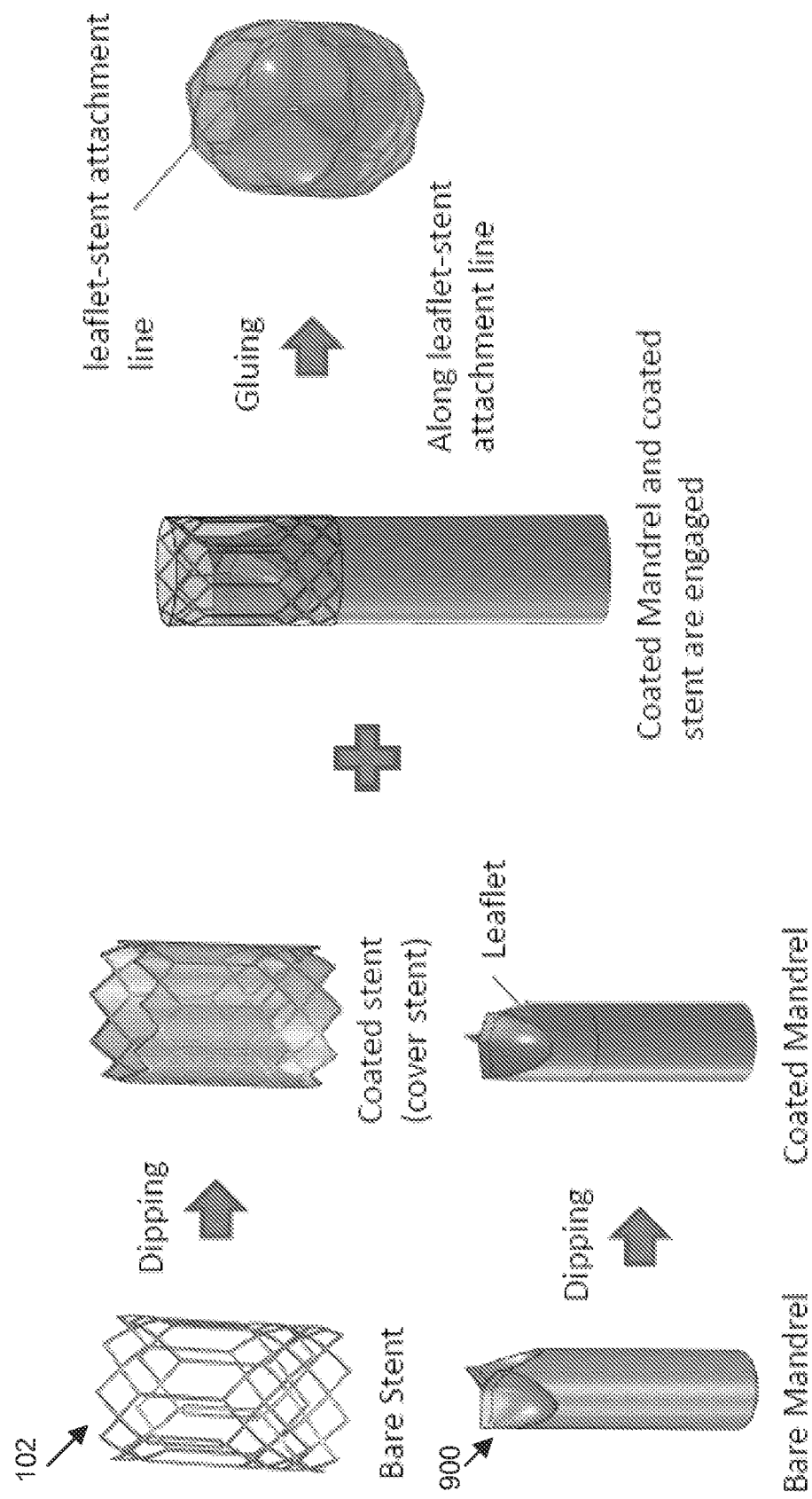
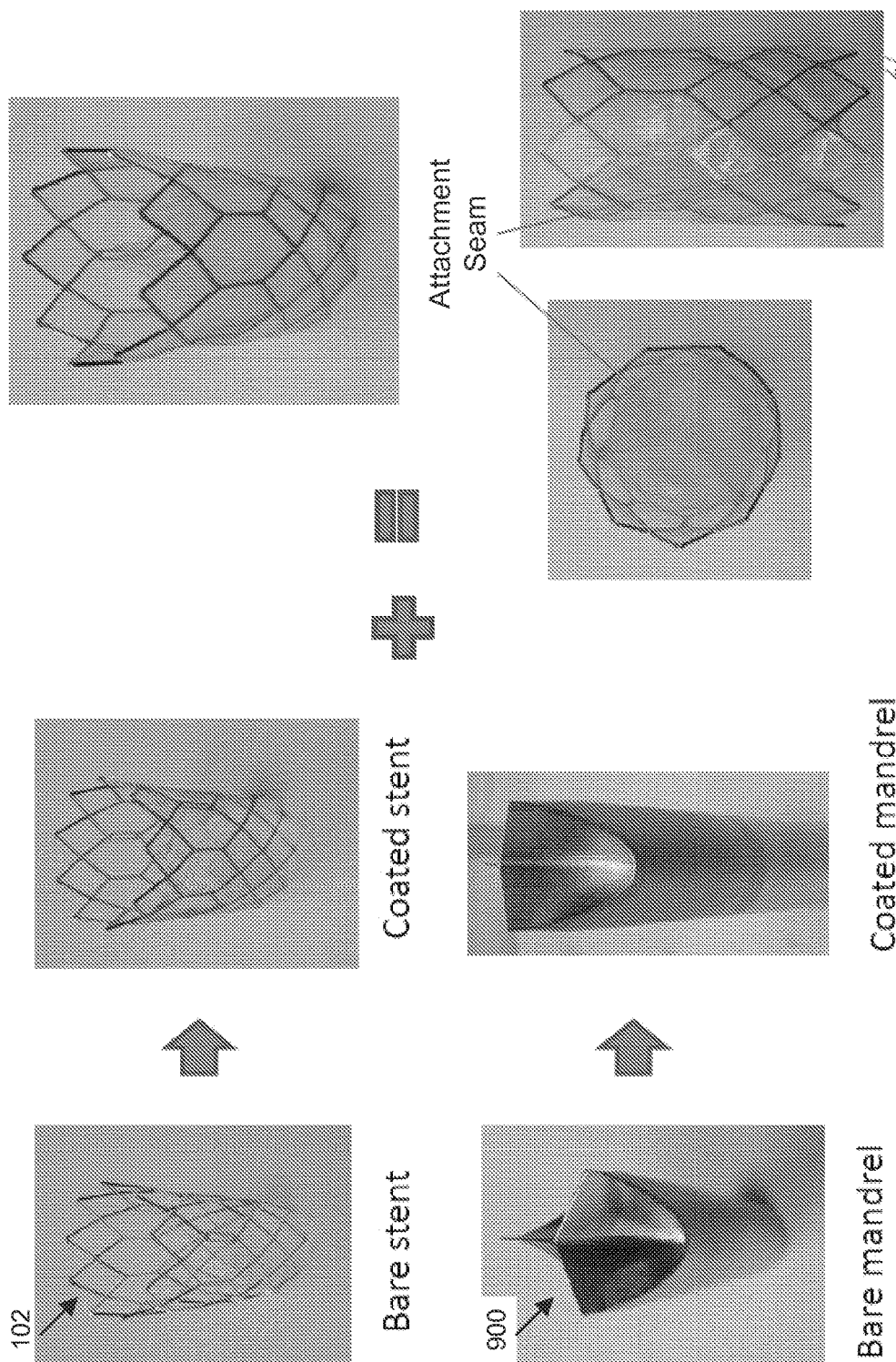


FIG. 15B



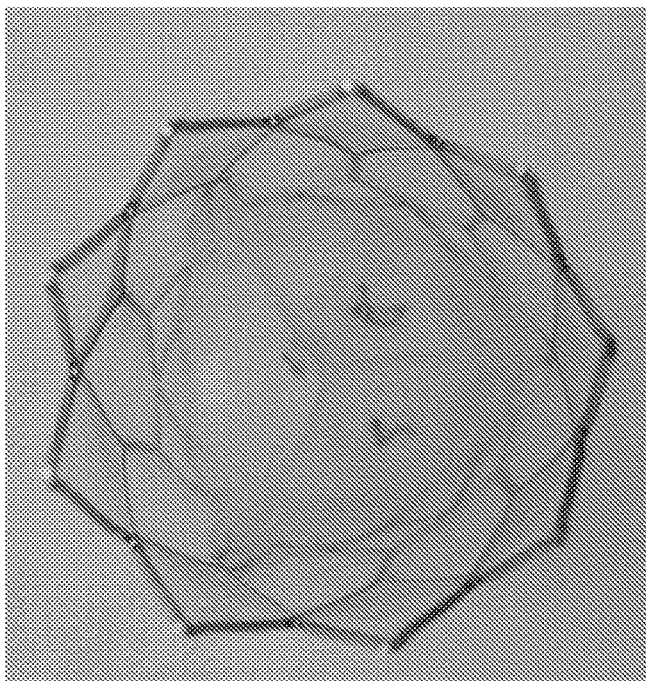


FIG. 17B

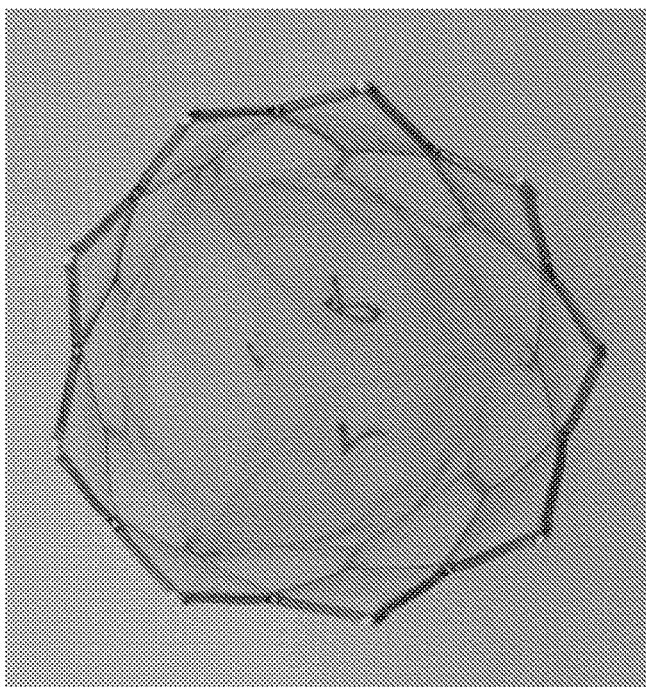


FIG. 17A

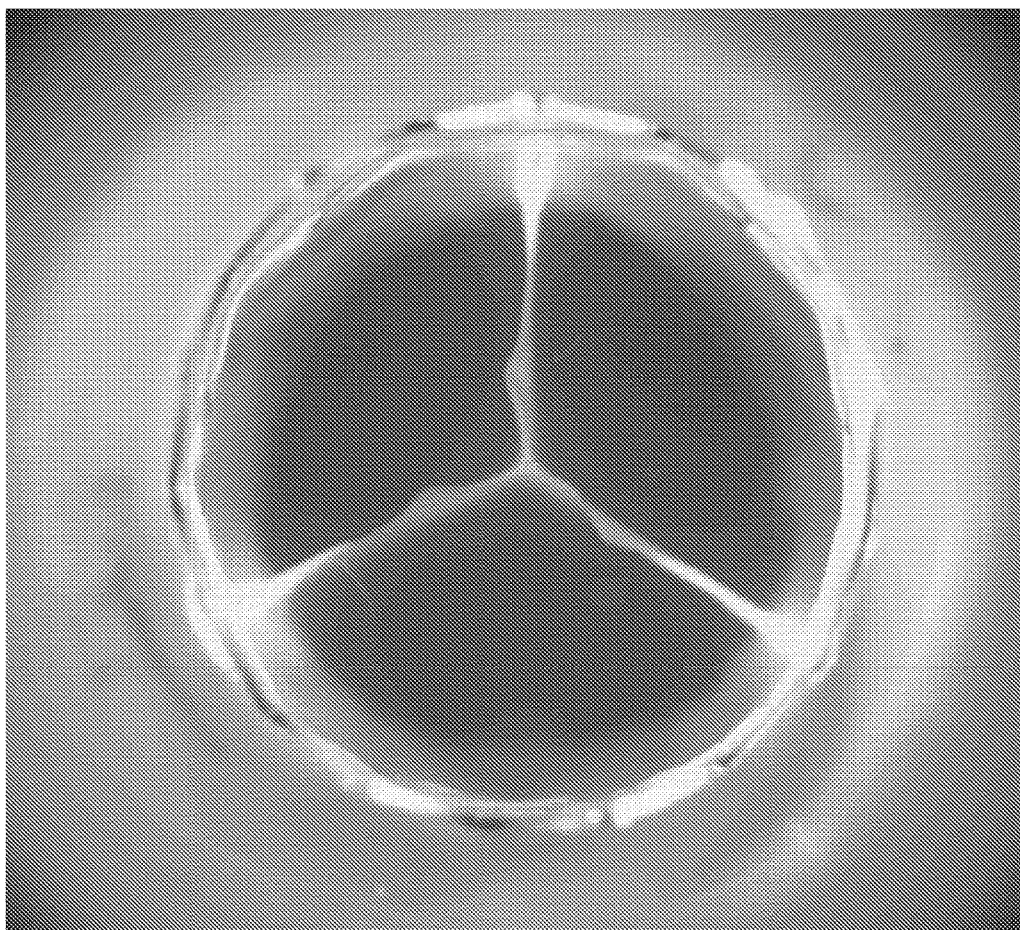


FIG. 17C

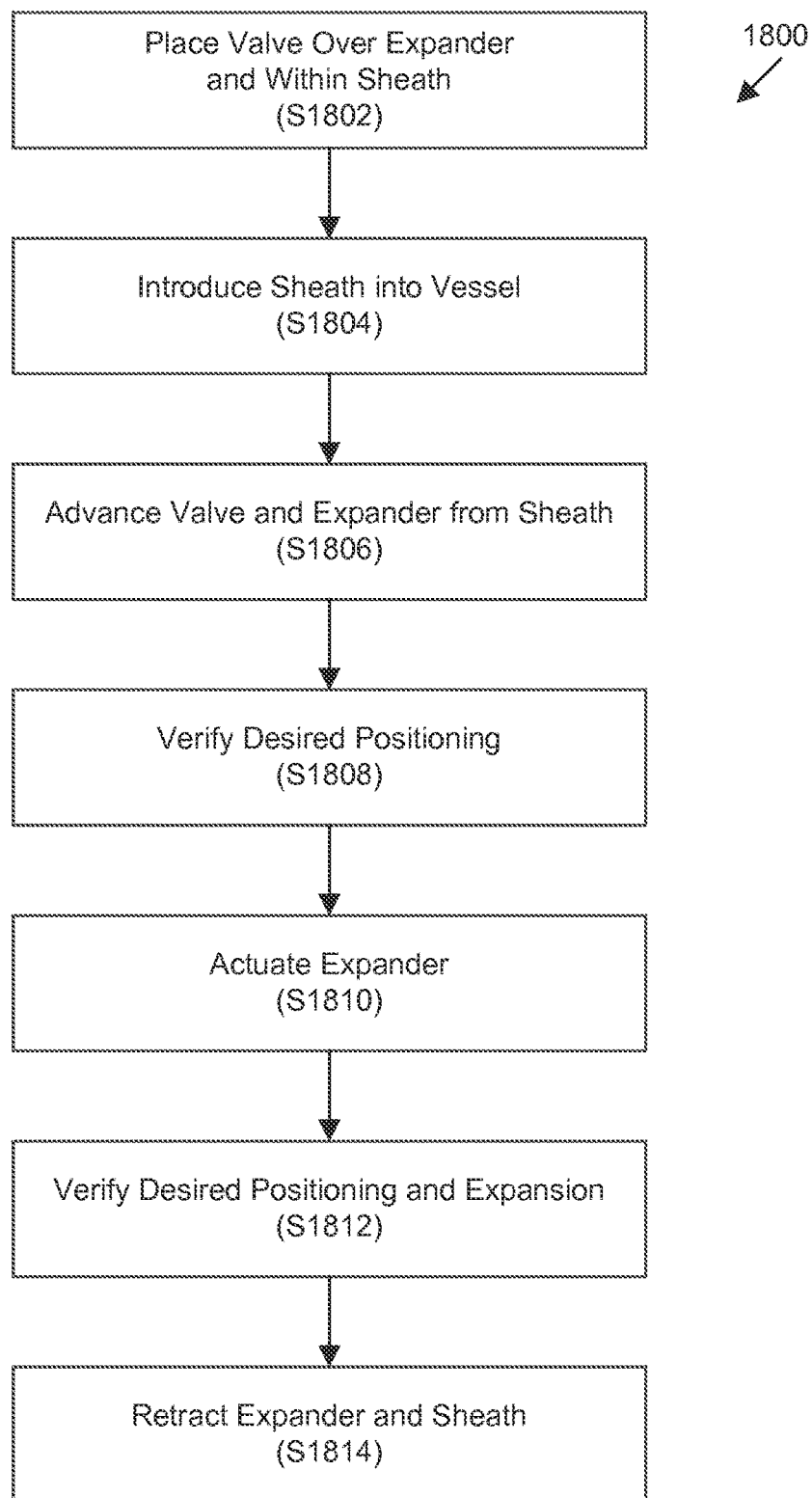


FIG. 18

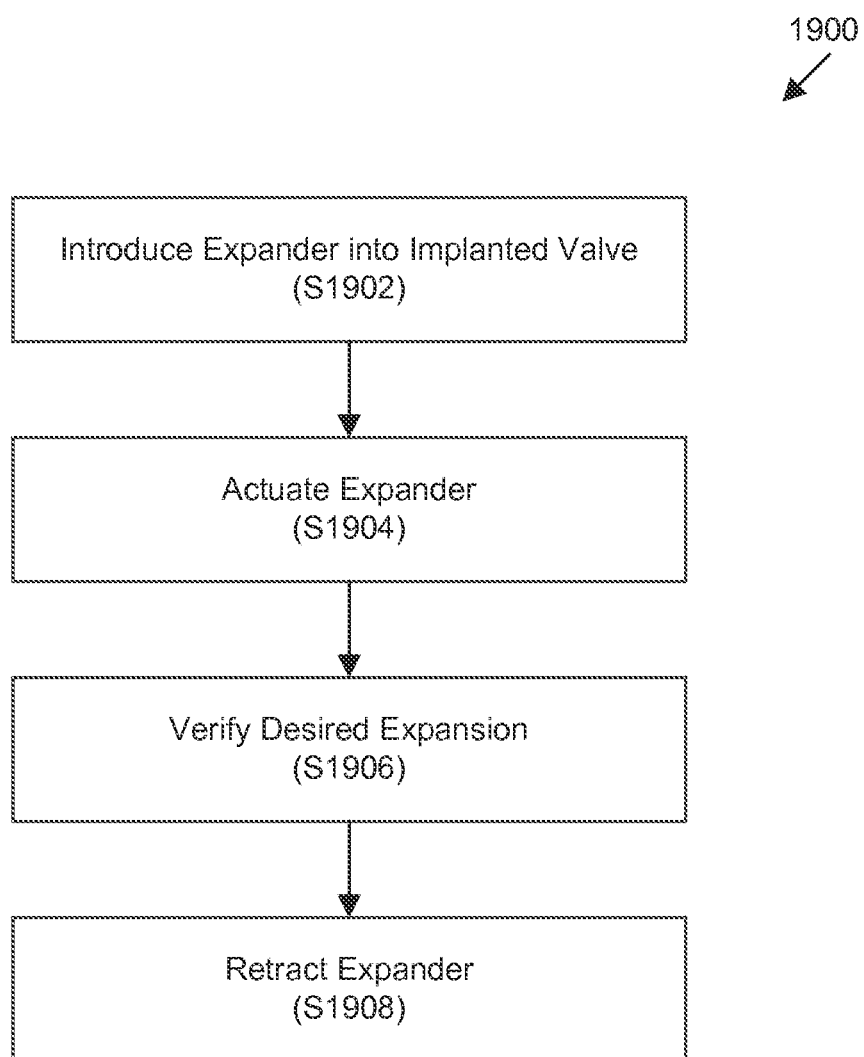


FIG. 19

ARTIFICIAL, FLEXIBLE VALVES AND METHODS OF FABRICATING AND SERIALLY EXPANDING THE SAME

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to U.S. Provisional Patent Application Ser. No. 61/989,820, filed May 7, 2014. The entire content of this application is hereby incorporated by reference herein.

BACKGROUND OF THE INVENTION

[0002] Valves exist in the body (e.g., in the heart and the systemic veins) to allow unidirectional blood flow. A variety of congenital conditions, infectious diseases (e.g., rheumatic heart disease), endocarditis, and age-related impairments (e.g., senile stenosis) can necessitate implantation of an artificial valve.

SUMMARY OF THE INVENTION

[0003] One aspect of the invention provides an artificial, flexible valve including: a stent defining a wall and a plurality of leaflets extending from the wall of the stent. The plurality of leaflets form a plurality of coaptation regions between two adjacent leaflets. The coaptation regions include extensions along a z-axis and adapted and are configured to form a releasable, but substantially complete seal when the leaflets are in a closed position.

[0004] This aspect of the invention can have a variety of embodiments. The extensions can have a length along the z-axis between about 1 mm and about 10 mm. The extensions can have a curved profile. The curved profile can lie in an x-y plane. The curved profile can be a variance in extension length along the z-axis.

[0005] The coaptation regions can have a substantially hyperbolic profile. Each of the plurality of leaflets can have a substantially elliptical leaflet-stent attachment line. The stent can be an expandable, cylindrical stent. The leaflets can be reinforced with one or more selected from the group consisting of: reinforcing materials and directional fibers. One or more selected from the group consisting of: coaptation regions and leaflet-stent attachment lines can be reinforced with one or more selected from the group consisting of: additional polymer thickness, reinforcing materials, and directional fibers.

[0006] Adjacent leaflets can be coupled to a wide post of the stent. The wide post can include one or more windows. The wide post can have a width between about 0.5 mm and about 3 mm.

[0007] The stent can include metal or plastic. The metal can be selected from the group consisting of: stainless steel, 316L stainless steel, cobalt-chromium alloys, and nickel-titanium alloys.

[0008] The leaflets can be formed from a first polymer. The first polymer can be selected from the group consisting of: polytetrafluoroethylene, polyethylene, polyurethane, silicone, and copolymers thereof.

[0009] The stent can be dip-coated in a second polymer. The second polymer can be selected from the group consisting of: polytetrafluoroethylene, polyethylene, polyurethane, silicone, and copolymers thereof. The leaflets can be coupled to the second polymer. The leaflets can be mechanically coupled to the second polymer. The leaflets can be

chemically coupled to the second polymer. The leaflets can be coupled to the second polymer by one or more techniques selected from the group consisting of: gluing, chemical fusing, thermal fusing, sonic welding, stitching, and mechanical fastening.

[0010] A leaflet-stent attachment line for each of the plurality of leaflets can substantially approximate a frame of the stent. The leaflet-stent attachment line can lie within about 3 mm of the frame of the stent.

[0011] The stent can include one or more anchor points. The anchor points can contain a radio-opaque material.

[0012] The valve can be adapted and configured for replacement of one or more cardiac valves selected from the group consisting of: aortic, mitral, tricuspid, and pulmonary.

[0013] The valve can be adapted and configured for insertion in a subject's veins in order to treat venous insufficiency. The valve can be adapted and configured for serial expansion as the subject ages.

[0014] Another aspect of the invention provides an artificial, flexible valve including: a stent defining a wall and a plurality of leaflets extending from the wall of the stent. Each of the plurality of leaflets terminates in a commissure line. The commissure lines deviate from a hyperbola formed in the x-y plane by at least one deviation selected from the group consisting of: a deviation in the z-direction and one or more curves relative to the hyperbola.

[0015] This aspect of the invention can have a variety of embodiments. The leaflets can further include extensions beyond the commissure lines along a z-axis. The extensions can have a length along the z-axis between about 1 mm and about 10 mm. The extensions can have a curved profile. The curved profile can lie in an x-y plane. The curved profile can be a variance in extension length along the z-axis.

[0016] Each of the plurality of leaflets can have a substantially elliptical leaflet-stent attachment line. The stent can have an expandable, cylindrical stent. The leaflets can be reinforced with one or more selected from the group consisting of: reinforcing materials and directional fibers.

[0017] One or more selected from the group consisting of: coaptation regions and leaflet-stent attachment lines can be reinforced with one or more selected from the group consisting of: additional polymer thickness, reinforcing materials, and directional fibers.

[0018] Adjacent leaflets can be coupled to a wide post of the stent. The wide post can include one or more windows. The wide post can have a width between about 0.5 mm and about 3 mm.

[0019] The stent can include metal or plastic. The metal can be selected from the group consisting of: stainless steel, 316L stainless steel, cobalt-chromium alloys, and nickel-titanium alloys.

[0020] The leaflets can be formed from a first polymer. The first polymer can be selected from the group consisting of: polytetrafluoroethylene, polyethylene, polyurethane, silicone, and copolymers thereof.

[0021] The stent can be dip-coated in a second polymer. The second polymer can be selected from the group consisting of: polytetrafluoroethylene, polyethylene, polyurethane, silicone, and copolymers thereof. The leaflets can be coupled to the second polymer. The leaflets can be mechanically coupled to the second polymer. The leaflets can be chemically coupled to the second polymer. The leaflets can be coupled to the second polymer by one or more techniques

selected from the group consisting of: gluing, chemical fusing, thermal fusing, sonic welding, stitching, and mechanical fastening.

[0022] A leaflet-stent attachment line for each of the plurality of leaflets can substantially approximate a frame of the stent. The leaflet-stent attachment line can lie within about 3 mm of the frame of the stent.

[0023] The stent can include one or more anchor points. The anchor points can contain a radio-opaque material.

[0024] The valve can be adapted and configured for replacement of one or more cardiac valves selected from the group consisting of: aortic, mitral, tricuspid, and pulmonary.

[0025] The valve can be adapted and configured for insertion in a subject's veins in order to treat venous insufficiency. The valve can be adapted and configured for serial expansion as the subject ages.

[0026] Another aspect of the invention provides an artificial, flexible valve including: an expandable, cylindrical stent defining a wall and a plurality of leaflets extending from the wall of the stent. Adjacent leaflets can be coupled to a relatively wide post of the stent.

[0027] The leaflets can further include extensions beyond the commissure lines along a z-axis. The extensions can have a length along the z-axis between about 1 mm and about 10 mm. The extensions can have a curved profile. The curved profile can lie in an x-y plane. The curved profile can be a variance in extension length along the z-axis.

[0028] The coaptation regions can have a substantially hyperbolic profile. Each of the plurality of leaflets can have a substantially elliptical leaflet-stent attachment line. The leaflets can be reinforced with one or more selected from the group consisting of: reinforcing materials and directional fibers.

[0029] One or more selected from the group consisting of: coaptation regions and leaflet-stent attachment lines can be reinforced with one or more selected from the group consisting of: additional polymer thickness, reinforcing materials, and directional fibers.

[0030] The relatively wide post can include one or more windows. The relatively wide post can have a width between about 0.5 mm and about 3 mm.

[0031] The stent can include metal or plastic. The metal can be selected from the group consisting of: stainless steel, 316L stainless steel, cobalt-chromium alloys, and nickel-titanium alloys.

[0032] The leaflets can be formed from a first polymer. The first polymer can be selected from the group consisting of: polytetrafluoroethylene, polyethylene, polyurethane, silicone, and copolymers thereof.

[0033] The stent can be dip-coated in a second polymer. The second polymer can be selected from the group consisting of: polytetrafluoroethylene, polyethylene, polyurethane, silicone, and copolymers thereof. The leaflets can be coupled to the second polymer. The leaflets can be mechanically coupled to the second polymer. The leaflets can be chemically coupled to the second polymer. The leaflets can be coupled to the second polymer by one or more techniques selected from the group consisting of: gluing, chemical fusing, thermal fusing, sonic welding, stitching, and mechanical fastening.

[0034] A leaflet-stent attachment line for each of the plurality of leaflets can substantially approximate a frame of the stent. The leaflet-stent attachment line can lie within about 3 mm of the frame of the stent.

[0035] The stent can include one or more anchor points. The anchor points can contain a radio-opaque material.

[0036] The valve can be adapted and configured for replacement of one or more cardiac valves selected from the group consisting of: aortic, mitral, tricuspid, and pulmonary. The valve can be adapted and configured for insertion in a subject's veins in order to treat venous insufficiency. The valve can be adapted and configured for serial expansion as the subject ages. The valve may not contain any animal-derived materials.

[0037] Another aspect of the invention provides a mandrel including: a cylindrical profile and a plurality of recesses adapted and configured to define a plurality of leaflets forming a plurality of coaptation regions between two adjacent leaflets. The coaptation regions can include extensions along a z-axis and be adapted and configured to form a releasable, but substantially complete seal when the leaflets are in a closed position.

[0038] This aspect of the invention can have a variety of embodiments. The mandrel can include one more cutting guides located between the plurality of recesses. The mandrel can include one or more heating elements.

[0039] Another aspect of the invention provides a mandrel including: a cylindrical profile and a plurality of recesses adapted and configured to define a plurality of leaflets. Each of the plurality of leaflets terminate in a commissure line. The commissure lines deviate from a hyperbola formed in the x-y plane by at least one deviation selected from the group consisting of: a deviation in the z-direction and one or more curves relative to the hyperbola.

[0040] This aspect of the invention can have a variety of embodiments. The mandrel can include one more cutting guides located between the plurality of recesses. The mandrel can include one or more heating elements.

[0041] Another aspect of the invention provides a method for fabricating an artificial, flexible valve. The method includes: dip coating a cylindrical mandrel having a plurality of recesses each approximating a profile of a leaflet and coupling the leaflets to an inner wall of a stent.

[0042] This aspect of the invention can have a variety of embodiments. The method can further include dip coating the stent prior to coupling the leaflets to the inner wall of the stent. The stent and the mandrel can have larger diameters than a target location for the valve. The method can further include separating adjacent leaflets from each other.

BRIEF DESCRIPTION OF THE DRAWINGS

[0043] For a fuller understanding of the nature and desired objects of the present invention, reference is made to the following detailed description taken in conjunction with the accompanying drawing figures wherein like reference characters denote corresponding parts throughout the several views and wherein:

[0044] FIGS. 1A and 1B provide perspective (in which fluid flows from the bottom of the stent toward the top of the stent) and top (in which fluid flows out of the page when the valve is open and flows down into the page to close the valve) views of a valve according to an embodiment of the invention;

[0045] FIG. 2 depicts a stent according to an embodiment of the invention;

[0046] FIGS. 3A-3F depict various stent geometries according to embodiments of the invention;

[0047] FIG. 4 depicts various vertical post geometries according to embodiments of the invention;

[0048] FIGS. 5A-5D depict the positioning of a leaflet joint adjacent to a window of a vertical post according to an embodiment of the invention;

[0049] FIG. 6 depicts a stent prior to expansion, dip coating, and leaflet installation according to an embodiment of the invention;

[0050] FIG. 7 depicts a stent including one or more anchor points according to an embodiment of the invention;

[0051] FIG. 8 depicts the engagement of a stent with a holder for dipping and rotation according to an embodiment of the invention;

[0052] FIGS. 9A-9E depict a mandrel according to an embodiment of the invention;

[0053] FIG. 9F depicts the positioning of a hyperbolic commissure line relative to defined asymptotes according to embodiments of the invention;

[0054] FIG. 10A depicts a comparison of elliptical vs. parabolic geometries leaflet valley lines according to embodiments of the invention;

[0055] FIGS. 10B and 10C depict a comparison of elliptical vs. parabolic leaflet stent attachment lines according to embodiments of the invention;

[0056] FIGS. 11A-11D depict mandrels for forming coaptation regions of varying height according to embodiments of the invention;

[0057] FIGS. 12A-12D depict mandrels for forming coaptation regions of varying radial length according to embodiments of the invention;

[0058] FIGS. 12E-12H depict mandrels for forming commissure lines having variable depths along the z-axis according to embodiments of the invention;

[0059] FIGS. 12I-12K depict mandrels for forming coaptation regions having curved profiles in an x-y plane, resulting in increased coaptation length, according to embodiments of the invention;

[0060] FIGS. 12L-12N depict mandrels for forming commissure lines having curved profiles in an x-y plane, resulting in increased coaptation length, according to embodiments of the invention;

[0061] FIG. 13A depicts a mandrel according to an embodiment of the invention;

[0062] FIGS. 13B and 13C depict the positioning of reinforcing zones on a mandrel according to an embodiment of the invention;

[0063] FIGS. 14A-14C depict various top profiles according to an embodiment of the invention;

[0064] FIGS. 15A and 15B depict the fabrication of valves according to embodiments of the invention;

[0065] FIG. 16 depicts the fabrication of valves according to an embodiment of the invention;

[0066] FIGS. 17A and 17B depict the compression of a valve after assembly in order to bring leaflets into contact with each other according to embodiments of the invention;

[0067] FIG. 17C is a high-speed photograph of a closed valve under pressure according to embodiments of the invention;

[0068] FIG. 18 depicts a method of implanting a valve according to embodiments of the invention; and

[0069] FIG. 19 depicts a method of expanding an implanted valve according to embodiments of the invention.

DEFINITIONS

[0070] The instant invention is most clearly understood with reference to the following definitions.

[0071] As used herein, the singular form “a,” “an,” and “the” include plural references unless the context clearly dictates otherwise.

[0072] Unless specifically stated or obvious from context, as used herein, the term “about” is understood as within a range of normal tolerance in the art, for example within 2 standard deviations of the mean. “About” can be understood as within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.05%, or 0.01% of the stated value. Unless otherwise clear from context, all numerical values provided herein are modified by the term about.

[0073] As used in the specification and claims, the terms “comprises,” “comprising,” “containing,” “having,” and the like can have the meaning ascribed to them in U.S. patent law and can mean “includes,” “including,” and the like.

[0074] Unless specifically stated or obvious from context, the term “or,” as used herein, is understood to be inclusive.

[0075] Ranges provided herein are understood to be shorthand for all of the values within the range. For example, a range of 1 to 50 is understood to include any number, combination of numbers, or sub-range from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 (as well as fractions thereof unless the context clearly dictates otherwise).

DETAILED DESCRIPTION OF THE INVENTION

[0076] Aspects of the invention provide a novel platform that allows development of polymeric valves of any size and shape. Aspects of the invention can be applied to valves designed for surgical implantation (e.g., through a sternotomy or thoracotomy) or valves designed for percutaneous, transcatheter implantation. Additionally, embodiments of the invention allow for possible percutaneous replacement of a dysfunctional valve, whether in adults or in small children. In addition, if implanted in a child, embodiments of the invention allow the valve to be serially expanded to accompany the child's growth.

Cardiac Applications

[0077] Multiple types of congenital heart defects require heart valve replacement surgery in infancy or childhood. In adults, the most commonly replaced valves are aortic and mitral, whereas in children, the pulmonary valve is the most commonly replaced valve. Heart valves are currently replaced using tissue valves (homograft or xenograft) or mechanical metal valves, each having their shortcomings. Homograft valves are in short supply, particularly in sizes suitable for use in children, and biologic tissue-based valves (whether bovine, porcine, or homograft) tend to induce an immunologic reaction which leads to failure of these valves. Mechanical valves generally require anticoagulation, and are almost never used in the pulmonary position due to an increased risk of thrombosis.

[0078] Furthermore, none of the surgically implanted valves can adapt to growing patients. The rapid growth of pediatric patients leads them to outgrow their implanted valves within a few years and induces a cycle of frequent

surgical valve replacements during childhood. Aspects of the invention provide valves having improved biocompatibility, durability, and hemodynamic performance and would reduce the frequency of recurrent open heart surgeries for valve replacement.

Venous Applications

[0079] Additionally, aspects of the invention can be used for venous valve replacement in patients having venous disease such as chronic venous insufficiency (leading to leg swelling). Because the polymer leaflets can be made extremely thin, the valves can even open under extremely low venous pressure gradients.

Artificial, Flexible Valves

[0080] Referring now to FIGS. 1A and 1B, one aspect of the invention provides an artificial, flexible valve 100. The valve includes an expandable, cylindrical stent 102 defining a wall 104. Valve 100 further includes a plurality of leaflets 106a-106c. Wall 104 can be formed by dip coating stent 102 in a polymer as further described herein. Leaflets 106 can be coupled to wall 104 along seams 108 using a variety of approaches (e.g., glue) as discussed further herein. Stent 102 can include one or more vertical posts 110, 112, which can be relatively narrow posts 110 or relatively wide posts 112. Preferably leaflet joints between adjacent leaflets 106 are positioned on or close to a vertical post 110, 112 of the stent 102.

[0081] The valve 100 will now be described in the context of its components and methods of fabrication.

Stents

[0082] Referring now to FIG. 2, stent 102 can be a metallic stent having plurality of wires, strips, and the like 202 defining a plurality of cells 204, 206 of various sizes. Stent 102 can be fabricated from a variety of malleable materials such as stainless steel, 316L stainless steel, cobalt-chromium alloys, nickel-titanium alloys (colloquially known as “nitinol”), and the like. Stent 102 can also be formed from various non-metallic materials such as plastics such as polyethylene, polyurethane, polytetrafluoroethylene (PTFE), silicone, poly(propylene) (PP), polyethylene terephthalate (PET), and the like.

[0083] Stent 102 can be completely enveloped by a polymer dip coating. Stent 102 and/or wall 104 can also be fabricated from a biocompatible material.

[0084] The stent 102 can be manufactured by laser cutting or wire forming. To increase bonding strength between metal and polymer, roughness of stent surface can be controlled. Some or all open cells 204, 206 of the stent can be covered as the bare 102 stent is dipped into the polymer solution.

[0085] FIG. 6 depicts a stent 102 prior to expansion, dip coating, and leaflet installation. Stents 102 typically have a diameter of between about 2 mm and 6 mm prior to expansion and can be expanded to between about 5 mm and about 30 mm for implantation into a subject.

[0086] The components of stent 102 can have a variety of dimensions that can be selected to achieve a desired flexibility, rigidity, resilience, and the like. For example, the thickness and width of components of the stent 102 can be between about 0.1 mm and about 2 mm.

[0087] As discussed above, stent 102 can include one or more vertical posts 110a-110c to enhance bonding with leaflets 106.

[0088] Stent 102 can include a plurality of vertical posts 110 that can serve a variety of functions. Some vertical posts 110 can include additional structure and are referred to herein as wide posts 112. Wide posts 112 are preferably located at leaflet joints where two leaflets 106 meet. For example, in a valve 100 having a three leaflets 106, wide posts 112 can be positioned at 120° intervals within cylindrical stent 102.

[0089] Wide posts 112 provide mechanical support to leaflets and prevent or substantially limit inward deformation of wall 104 due to tensile forces applied to leaflets 106 transferred to wall 104. Without being bound by theory, it is believed that the wide posts 112 provide increased strength and resiliency due to formation of polymer wall 104 through windows 206 and around wide posts 112, thus providing cohesive holding of the polymer to itself around the stent 102 instead of relying solely on adhesive bonding of the polymer wall 104 to the stent 102.

[0090] Wide posts 112 advantageously allow for relaxed tolerances in positioning leaflets 106 relative to wide posts 112. For example, window 208 can have a width of between about 0.5 mm and about 3 mm (e.g., about 1 mm) and a height of between about 1 mm and about 10 mm (e.g., about 5 mm).

[0091] A variety of additional wide post geometries are depicted in FIGS. 3A-3F. In FIG. 3A, the wide posts have a solid architecture without any windows. In FIG. 3B, the wide posts have a substantially rectangular architecture defining a single, long window as in FIGS. 1A, 1B, and 2. In FIG. 3C, the wide posts define a plurality of coaxial substantially rectangular windows. In FIG. 3D, the wide posts define a plurality of coaxial, substantially parallel windows. In FIG. 3E, the wide posts define a plurality of coaxial, substantially rectangular windows in a 2x3 arrangement. In FIG. 3F, the wide posts include a plurality of circular windows. These wide post architectures are further depicted in FIG. 4. Although substantially circular and rectangular window geometries are depicted, any geometry can be utilized including windows having a profile approximating a triangle, a square, an n-gon (e.g., a hexagon, an octagon, and the like), and the like.

[0092] Referring now to FIGS. 5A-5D, the positioning of a leaflet joint 502 (formed, e.g., on mandrel 900 as discussed herein) adjacent to window 206 of wide post 112 is depicted. (The polymer dip-coated wall 104 is completely transparent for ease and clarity in viewing, but can be transparent, translucent, or opaque.) FIG. 5B-5D further depict how a geometry of the stent 102 can be selected to substantially approximate the leaflet-stent attachment seam 108 discussed herein in order to provide added mechanical support and resiliency.

[0093] Referring now to FIG. 7, stent 102 can include one or more anchor points 702. Anchor points 702 advantageously facilitate holding, dipping, and rotation of the stent 102 during the dip coating process without interfering with the dip coating of the remainder of the stent architecture. Accordingly, the entire stent 102 can be dip coated in a single dipping, although multiple dippings can be utilized to control coating density, thickness, and the like. Anchor

points **702** can also receive one or more radio-opaque materials such as platinum to aid in placement and visualization of the valve.

[0094] In one embodiment depicted in FIG. 8, stent **102** can be engaged with a holder **802** (e.g., by posts **804**) for dipping and rotation. Once the polymer (again depicted as, but not necessarily, transparent) is wet on the stent **102**, the stent can be positioned horizontally and rotated axially.

Leaflets

[0095] Leaflets **106** can be formed using a variety of techniques including dip coating, 3D-printing (also known as additive manufacturing), molding, and the like.

[0096] Referring now to FIG. 9A, leaflets **106** can be fabricated by dip coating a mandrel **900** with a polymer. The mandrel **900** can be made with a solid such as a metal (e.g., stainless steel, titanium, aluminum, and the like), a plastic (e.g., polyethylene, polypropylene, polyvinyl chloride, polytetrafluoroethylene, polyoxymethylene, and the like), and the like. Since the coated polymer leaflets **106** will be removed from the mandrel **900** after the polymer dries, roughness of mandrel surface can be controlled using known machining and other manufacturing techniques. The mandrel **900** can be made from a cylinder. Preferably, the diameter of the mandrel **900** is a slightly (e.g., between about 0.05 and about 0.4 mm) smaller than inner diameter of stent **102** after expansion.

[0097] The mandrel **900** for the leaflets **106** can have novel features, including edges representing the leaflet attachment points that are mathematically defined and leaflet tips that are extended in order to increase the coaptation length of the leaflets. The mandrel **900** can be dimensioned to produce leaflets **106** having different regional thickness and supplementary materials such as directional fibers or reinforcing particles inserted between layers or mixed into the polymer solution in order to increase durability. For example, polymer interaction with particles on the nanoscale or microscale can greatly improve the physical properties or tear resistance of the polymer leaflets **106**.

[0098] Mandrel **900** can be designed to have a complementary geometry to the desired leaflet shape and permits easier viewing of leaflet geometry. Although mandrel **900** is utilized to describe the geometry of the leaflet **106**, it should be recognized that the upstream surface of the resulting leaflets will have this geometry when formed by dip coating and that the complementary geometry of the leaflet(s) **106** can be produced using techniques other than dip coating. Mandrel **900** is preferably cylindrical and can have an outer profile substantially approximating an inner profile of stent **102**. Mandrel **900** can define a plurality of pockets **902** that each define a leaflet **106** as it hangs from wall **104** via attachment line **108**. Each leaflet **106** terminates in a commissure line **904** often, but not necessarily lying in a plane at the point where the elliptical or parabolic curve ends and where the leaflet often contacts the other leaflets. A substantially vertical coaptation region **906** can extend beyond the commissure line **904** to an extended commissure line **912** for improved sealing as will be discussed herein.

[0099] Referring now to FIGS. 9B and 9C, mandrel can be cast, machined, printed, or otherwise fabricated so that pockets **902** have a desired geometry. In one embodiment of the invention, the commissure line **904** (and optionally the coaptation region **906** and extended commissure line **912**) has a substantially hyperbolic profile when viewed in the x-y

plane. Additionally or alternatively, leaflet-stent attachment line **108** and/or a leaflet valley line **908** (formed by taking a cross-section in a z plane) can have substantially elliptical profiles. Although other quadratic profiles (e.g., parabolic) could be used, elliptical profiles better promote a secure pocket shape and the closure of the leaflet-stent attachment line **108** to the contour of the cylindrical mandrel **900**. A comparison of elliptical vs. parabolic leaflet valley lines is provided in FIG. 10A. A comparison of elliptical vs. parabolic leaflet-stent attachment lines is provided in FIGS. 10B and 10C.

[0100] Referring now to FIG. 9D, mandrel **900** can define a gap **910** between adjacent leaflets. Advantageously, leaflets **106** with a hyperbolic profile can produce smaller gaps than leaflets with parabolic profiles. For example, gaps **910** can be less than 1 mm or between about 0.1 mm and about 1 mm (e.g., between about 0.1 mm and about 0.2 mm, between about 0.2 mm and about 0.3 mm, between about 0.3 mm and about 0.4 mm, between about 0.4 mm and about 0.5 mm, between about 0.5 mm and about 0.6 mm, between about 0.6 mm and about 0.7 mm, between about 0.7 mm and about 0.8 mm, about 0.8 mm and about 0.9 mm, about 0.9 mm and about 1 mm, and the like).

[0101] As seen in FIG. 9E, the length of hyperbolic commissure line **904** is about twice the radius of the stent or mandrel. The positioning of a hyperbolic commissure line **904** relative to defined asymptotes is depicted in FIG. 9F.

[0102] Referring now to FIG. 11A, coaptation region can have minimal height in the z-axis so as to consist only of the commissure line **904**. Alternatively, coaptation region **906** can have a vertical extension in the z-axis to an extended commissure line **912** as depicted in FIGS. 11B-11D. The height of the coaptation region **906** can be selected to reduce the amount of regurgitation, while still allowing the valve to open. For example the coaptation region **906** can have a height between about 1 mm and about 10 mm (e.g., about 3 mm). Although FIGS. 11B-11D depict extensions of coaptation region **904** that extend solely in the z-axis, the same effect can be achieved using a smooth leaflet-stent attachment line that extends in the z-axis so that the adjacent leaflet-stent attachment lines (and/or the regions of leaflets hanging therebetween) approach and/or contact each other to form an extended coaptation region.

[0103] The zone of coaptation is affected by the pressure placed upon the closed valve **100**. The higher the pressure, the more downward tension is placed on the leaflets **106**, possibly leading to a failure of coaptation with consequent regurgitation. Proper coaptation also allows the leaflets **106** to support each other, so there is less stress placed on any individual leaflet **106**. Another benefit of enhancing height of the coaptation zone is that this allows the valve **100** to be re-dilated to a larger diameter late after implantation (such as to accommodate growth of a pediatric patient), while still maintaining competence of the valve **100**.

[0104] Options for enhancing the height of the coaptation zone include creating excess length of the leaflet free edges, so that the free edge length is greater than twice the radius of the stent or mandrel depicted in FIG. 9E. Lengthening of the leaflet free edges can be accomplished by curved edges in the x-y plane, or in the z-axis, or in all 3 axes.

[0105] Referring now to FIGS. 12A-12D, coaptation regions **906** can have varying heights in the z-axis between the commissure line **904** and extended commissure line **912**. For example, the height of coaptation region **906** can

increase toward the outside of the mandrel as depicted in FIG. 12B. In another embodiment, the height of the coaptation region 906 can dip to form a trough between the outside and the center of the mandrel 900 as depicted in FIG. 12C.

[0106] Referring now to FIGS. 12E-12H, the same profiles can be applied to commissure line 904 without any coaptation region 906.

[0107] Referring now to FIGS. 12I-12K, the commissure lines 904, coaptation regions 906 and/or extended commissure lines 912 can have curved profiles in an x-y plane (as opposed to a substantially hyperbolic profile) in order to increase the length of the commissure line 904, coaptation region 906, and/or extended commissure line 912. For example, the mandrel 900 can be thicker between the perimeter and the center as depicted in FIG. 12I to produce one or more scallops. In FIGS. 12J and 12K, the mandrel 900 can have either a single curve or multiple curves.

[0108] Referring now to FIGS. 12L-12N, the same profiles can be applied to commissure line 904 without any coaptation region 906.

[0109] In order to increase tear-resistance of the leaflets 106 and enhance bonding strength between leaflets 106 and stent 102, the thickness of the leaflets 106 can be controlled regionally. Because the most common failure points are at the outer edges of the leaflets 106 (such as commissure line 904 or extended commissure line 912 and leaflet-stent attachment line 108), increased thickness at outer areas of the leaflets 106 can improve the strength and durability. Also, if local areas are expected to have concentrated stress, the areas can be locally reinforced (e.g., made thicker than other areas). The thickness can be smoothly increased. The width of thickened area along leaflet-stent attachment line 108 can be large enough to cover the glued area for bonding the leaflets 106 and the covered stent 102. In some embodiments, the thickness of thickened areas of the leaflets is between about 0.1 mm and about 1 mm.

[0110] Multiple dippings can be performed to produce leaflets with a desired thickness. In some embodiments, the thickness of the leaflets is between about 0.01 mm and about 0.2 mm.

[0111] Different reinforcing materials such as strips, fibers and particles can be placed between the layers, or directly mixed into the polymer solution. The inserted material(s) can prevent tearing and reduce propagation of the tear if it occurs. The materials can have directional properties and can be layered onto, or embedded into, the leaflets in an optimal direction to prevent or limit tears.

[0112] Referring now to FIG. 13A, a photograph of a mandrel 900 is provided. Referring now to FIG. 13B, a reinforcing zone 1302 can be formed on the mandrel 900 prior either by removing mandrel material to allow for additional thickness in certain (e.g., outer) regions of leaflets 106 or by introducing one or more reinforcing fibers prior to, during, or after dip coating. Suitable reinforcing materials include fibers (e.g., polymers, nanotubules, aramids, para-aramids, and the like), wires, and the like. Transitions between reinforced and non-reinforced areas can be smooth in order to minimize any turbulence in the implanted valve 100.

[0113] After dipping the mandrel 900 into the polymer solution, the coated polymer dries in order to form the leaflet(s) 106. Because the formed leaflets 106 are connected, they need to be separated from each other. These can

be cut by a sharp cutter (e.g., a knife, a scalpel, a razor blade, a utility knife, and the like), a heated iron, a laser, a rotary tool, and the like. A guide on the top surface of the mandrel for cutting provides a clear, easy, and safe cutting path. The guide can be grooved/concave or convex. Also, the commissure edges of the mandrel can be sharp like a blade to facilitate leaflet separation and to improve on the quality of the cut edges.

[0114] Referring now to FIG. 14A-14C, the gap portion 910 of the mandrel can have various top profiles to facilitate sealing of the leaflets and/or separation of the leaflets prior to removal from mandrel 900. For example, the gap portion 910 can have a grooved profile as depicted in FIG. 14A, a concave profile as depicted in FIG. 14B, or an angled profile as depicted in FIG. 14C. Additionally or alternatively, a heating element (e.g., an Ohmic or resistive heating element such as a wire) can be included in the mandrel and can be actuated to melt the polymer to separate the leaflets and/or relax the polymer to facilitate removal of the leaflets from the mandrel 900.

[0115] The stent-mounted valve 100 can be implanted with smaller diameter than its manufactured diameter for reducing leakage and improving durability.

Methods of Fabricating Valves

[0116] Referring now to FIGS. 15A, 15B, and 16, a method for fabricating a valve is depicted. A bare stent 102 and a bare mandrel 900 are provided.

[0117] In some embodiments, the stent 102 can be first coated with a polymer such as PEEK or other metal surface modifier prior to further dip coating of the stent 102 in another polymer in order to improve adhesion of the leaflet polymer 106 to the metal stent 102.

[0118] The bare mandrel 900 can optionally be coated with a release agent to promote separation of the polymer leaflets from the mandrel 900.

[0119] Both the bare stent 102 and the mandrel 900 are dip coated separately in a polymer, which may be the same or different for the bare stent 102 and the mandrel 900.

[0120] The leaflets 106 formed on the mandrel 900 can be removed prior to introduction to the coated stent. Alternatively, the coated mandrel 900 can be introduced into the coated stent, the leaflets 106 can be bonded to the coated stent, and the mandrel 900 can be then be removed to leave the assembled valve 100.

[0121] Leaflets 106 can be bonded to the dip-coated stent using a variety of techniques including gluing, chemical fusing (i.e., dissolving the polymers) thermal fusing, sonic welding, stitching, mechanical fastening, and the like. For example, the same polymer solution used to coat either bare stent 102 and/or mandrel 900 can be applied to bond the leaflets 106 to the dip-coated stent.

[0122] Although separate fabrication of the polymer-coated stent and the leaflets 106 are currently preferred as a means of avoiding or minimizing air bubbles, the entire valve could be formed in a single dip coating (or series of dip coatings) through use of production-grade manufacturing techniques and other optimizations.

[0123] Although dipcoating was successfully used to fabricate prototypes of the valves described herein, any other manufacturing technique capable of producing flexible leaflets can be utilized. Exemplary techniques include injection molding and additive manufacturing or 3D printing.

[0124] Referring now to FIGS. 17A and 17B, stent 102 and leaflets 106 can be fabricated based on a diameter that is slightly larger than the placement location as depicted in FIG. 17A. When deployed to a location having a smaller diameter than the manufactured diameter, the leaflets 106 will be held in tight contact with each other as seen in FIG. 17B to form a tight seal. (In order to form a press fit with the vessel wall, the deployed diameter will be greater than the vessel diameter, but less than the manufactured diameter.)

[0125] As can be seen in FIGS. 17A and 17B, the coaptation regions of leaflets 106 have a substantially hyperbolic profile both at the manufactured diameter and the deployed diameter.

[0126] Referring now to FIG. 17C, a high-speed photograph of a closed valve under pressure during in vitro testing in a hemodynamic pulse duplicator is provided.

Polymers

[0127] The leaflets 106 can be formed from the same or different polymer with which the stent 102 is coated to form wall 104. For example, the leaflets 106 can be formed from polymers such as polyethylene, polyurethane, silicone, and the like. Wall 104 can be formed from polyethylene, polyurethane, silicone, and the like.

[0128] Supplementary materials such as directional fibers can be mixed into the polymer solution or applied to the leaflets between coatings in order to increase durability.

[0129] The selected polymer can be dissolved by a solvent such as tetrahydrofuran or dimethylacetamide. The thickness of the coated polymer can be controlled as a function of the density of the polymer solution and total number of dippings. When the polymer becomes dry after dipping, the coated stent and mandrel can be placed horizontally and axially rotated in order to produce a constant thickness and prevent the polymer from dripping.

Implantation of Valves

[0130] Referring now to FIG. 18, a method 1800 of implanting an artificial valve is provided. The valve to be implanted can be a valve 100 as described herein.

[0131] In step S1802, the valve is placed over an expander and within a sheath. Various surgical expanders and access devices exist in the cardiac surgery field. For example, a balloon catheter could be introduced into a patient's femoral artery and guided to the location of the implanted valve (e.g., within the patient's heart or systemic veins).

[0132] In step S1804, the sheath (containing the valve and the expander) is introduced into a vessel of the subject.

[0133] In step S1806, the valve and the expander are advanced from the sheath and positioned in the desired location.

[0134] In step S1808, the desired positioning can be verified using various imaging techniques such as fiber optics, ultrasound, X-ray, and the like.

[0135] In step S1810, the expander is actuated within the valve to expand the valve to form a press fit against the vessel in which the valve is implanted. For example, a balloon catheter can be expanded by introducing gas or a liquid into the balloon.

[0136] In step S1812, the desired positioning and expansion can be verified using various imaging techniques such as fiber optics, ultrasound, X-ray, and the like.

[0137] In step S1814, the expander and sheath can be retracted according to standard surgical techniques.

Expansion of Implanted Valves

[0138] Referring now to FIG. 19, a method 1900 of expanding an implanted valve is provided. The implanted valve can be a valve 100 as described herein.

[0139] In step S1902, an expander is introduced into the implanted valve.

[0140] In step S1904, the expander is actuated within the implanted valve to increase the diameter of the implanted valve.

[0141] In step S1906, the desired expansion can be verified using various imaging techniques.

[0142] In step S1908, the expander can be retracted according to standard surgical techniques.

Surgically-Implanted Valves

[0143] Although embodiments of the invention are described and depicted in the context of percutaneous, transcatheter valves having expandable, cylindrical stents, embodiments of the invention described herein can be applied to surgically-implanted valves that generally include anchors having fixed-diameter anchors supporting a plurality of leaflets (e.g., the CARPENTIER-EDWARDS™ series of valves available from Edwards Lifesciences Corporation of Irvine, Calif.). In such embodiments, the anchor replaces the expandable, cylindrical stents described herein.

EQUIVALENTS

[0144] Although preferred embodiments of the invention have been described using specific terms, such description is for illustrative purposes only, and it is to be understood that changes and variations may be made without departing from the spirit or scope of the following claims.

INCORPORATION BY REFERENCE

[0145] The entire contents of all patents, published patent applications, and other references cited herein are hereby expressly incorporated herein in their entireties by reference.

1. An artificial, flexible valve comprising:

a stent defining a wall; and

a plurality of leaflets extending from the wall of the stent, the plurality of leaflets forming a plurality of coaptation regions between two adjacent leaflets, the coaptation regions each having a substantially hyperbolic profile including extensions along a z-axis and adapted and configured to form a releasable, but substantially complete seal when the leaflets are in a closed position.

2. The valve of claim 1, wherein the extensions have a length along the z-axis between about 1 mm and about 10 mm.

3. The valve of claim 1, wherein the extensions have a curved profile.

4. The valve of claim 3, wherein the curved profile lies in an x-y plane.

5. The valve of claim 3, wherein the curved profile is a variance in extension length along the z-axis.

6. (canceled)

7. The valve of claim 1, wherein each of the plurality of leaflets has a substantially elliptical leaflet-stent attachment line.

8. (canceled)

9. The valve of claim 1, wherein one or more from the group consisting of: the leaflets, the coaptation regions, and the leaflet stent attachment lines are reinforced with one or more selected from the group consisting of: reinforcing materials and directional fibers.

10. (canceled)

11. The valve of claim 1, wherein adjacent leaflets are coupled to a wide post of the stent.

12. The valve of claim 11, wherein the wide post includes one or more windows.

13.-15. (canceled)

16. The valve of claim 1, wherein:

the leaflets are formed from a first polymer; and the stent is dip-coated in a second polymer; and the leaflets are coupled to the second polymer mechanically, chemically, or by one or more techniques selected from the group consisting of: gluing, chemical fusing, thermal fusing, sonic welding, stitching, and mechanical fastening.

17.-23. (canceled)

24. The valve of claim 1, wherein:

a leaflet-stent attachment line for each of the plurality of leaflets substantially approximates a frame of the stent; and

the leaflet-stent attachment line lies within about 3 mm of the frame of the stent.

25. (canceled)

26. The valve of claim 1, wherein the stent includes one or more anchor points.

27. (canceled)

28. The valve of claim 1, wherein the valve is adapted and configured for replacement of one or more cardiac valves selected from the group consisting of: aortic, mitral, tricuspid, and pulmonary or insertion in a subject's veins in order to treat venous insufficiency.

29. (canceled)

30. (canceled)

31. An artificial, flexible valve comprising:

a stent defining a wall; and

a plurality of leaflets extending from the wall of the stent, each of the plurality of leaflets terminating in a commissure line, the commissure lines deviating from a hyperbola formed in the x-y plane by at least one

deviation selected from the group consisting of: a deviation in the z-direction and one or more curves relative to the hyperbola.

32.-60. (canceled)

61. An artificial, flexible valve comprising:

an expandable, cylindrical stent defining a wall; and

a plurality of leaflets extending from the wall of the stent, wherein adjacent leaflets are coupled to a relatively wide post of the stent.

62.-90. (canceled)

91. A mandrel comprising:

a cylindrical profile; and

a plurality of recesses adapted and configured to define a plurality of leaflets forming a plurality of coaptation regions between two adjacent leaflets, the coaptation regions including extensions along a z-axis and adapted and configured to form a releasable, but substantially complete seal when the leaflets are in a closed position.

92. The mandrel of claim 91, further comprising:

one or more cutting guides located between the plurality of recesses.

93. The mandrel of claim 91, further comprising:

one or more heating elements.

94. A mandrel comprising:

a cylindrical profile; and

a plurality of recesses adapted and configured to define a plurality of leaflets, each of the plurality of leaflets terminating in a commissure line, the commissure lines deviating from a hyperbola formed in the x-y plane by at least one deviation selected from the group consisting of: a deviation in the z-direction and one or more curves relative to the hyperbola.

95. (canceled)

96. (canceled)

97. A method for fabricating an artificial, flexible valve, the method comprising:

dip coating a cylindrical mandrel having a plurality of recesses each approximating a profile of a leaflet; and coupling the leaflets to an inner wall of a stent;

wherein the stent and the mandrel have larger diameters than a target location for the valve.

98.-100. (canceled)

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