



(86) Date de dépôt PCT/PCT Filing Date: 2012/03/30
(87) Date publication PCT/PCT Publication Date: 2012/10/04
(85) Entrée phase nationale/National Entry: 2013/09/13
(86) N° demande PCT/PCT Application No.: US 2012/031417
(87) N° publication PCT/PCT Publication No.: 2012/135603
(30) Priorité/Priority: 2011/04/01 (US13/078,774)

(51) Cl.Int./Int.Cl. *A61L 27/14* (2006.01),
A61F 2/24 (2006.01), *A61L 27/40* (2006.01)

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(54) Titre : COMPOSITE POLYMERE DURABLE DE RESISTANCE ELEVEE POUR IMPLANT ET ARTICLES PRODUITS
A PARTIR DE CELUI-CI

(54) Title: DURABLE HIGH STRENGTH POLYMER COMPOSITE SUITABLE FOR IMPLANT AND ARTICLES
PRODUCED THEREFROM

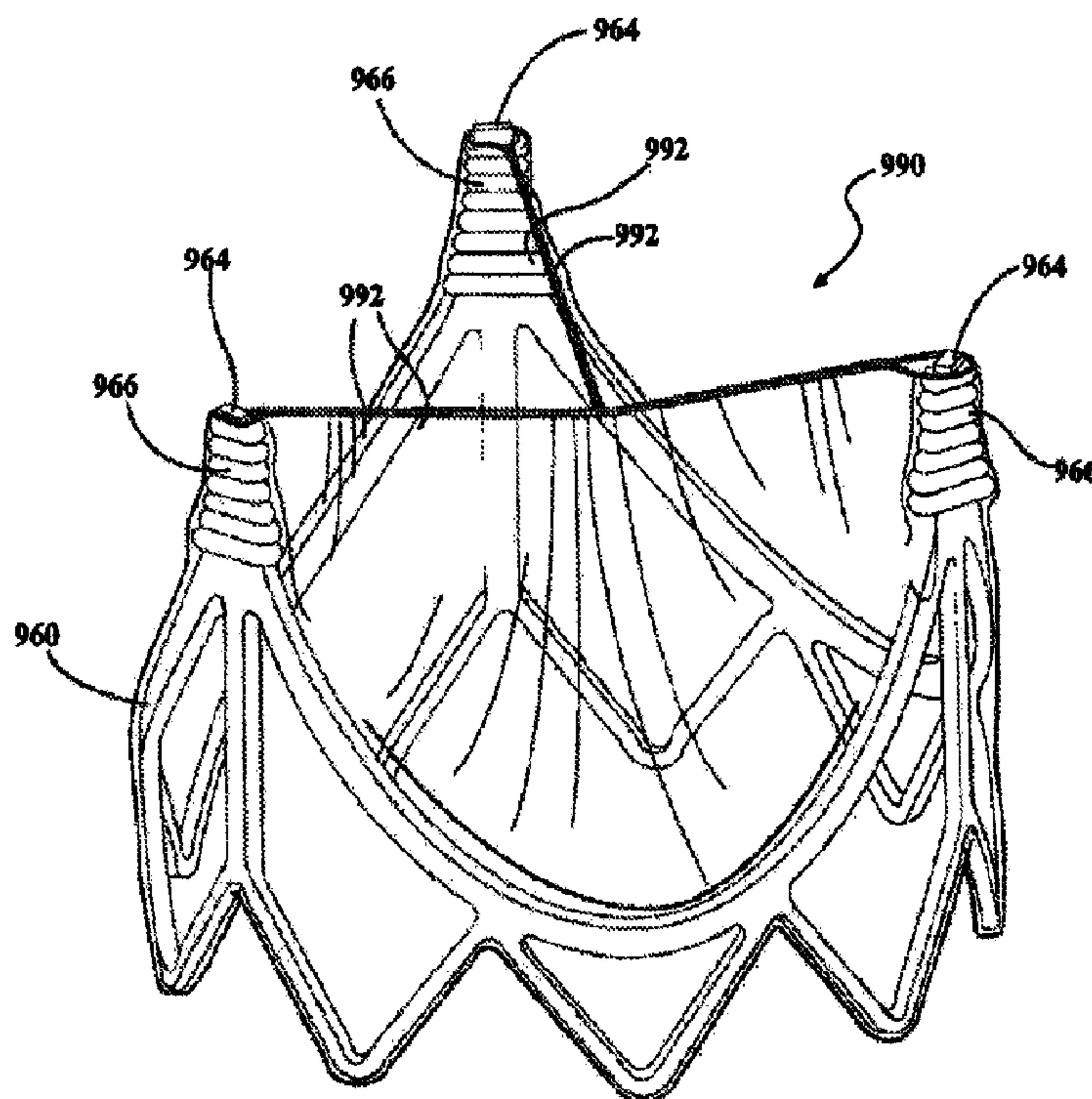


FIG. 23

(57) Abrégé/Abstract:

A thin, biocompatible, high-strength, composite material is disclosed that is suitable for use in various implanted configurations. In one aspect, the composite material maintains flexibility in high-cycle flexural applications, making it particularly applicable to high-flex implants such as heart pacing lead or heart valve leaflet. The composite material includes a porous expanded fluoropolymer

(57) **Abrégé(suite)/Abstract(continued):**

membrane and an elastomer, wherein the elastomer is present in substantially all of the pores of the porous expanded fluoropolymer, and the composite material comprising less than about 80% fluoropolymer by weight.

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

(19) World Intellectual Property
Organization
International Bureau(10) International Publication Number
WO 2012/135603 A3(43) International Publication Date
4 October 2012 (04.10.2012)

(51) International Patent Classification:

A61L 27/14 (2006.01) *A61L 27/40* (2006.01)
A61F 2/24 (2006.01)

(21) International Application Number:

PCT/US2012/031417

(22) International Filing Date:

30 March 2012 (30.03.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

13/078,774 1 April 2011 (01.04.2011) US

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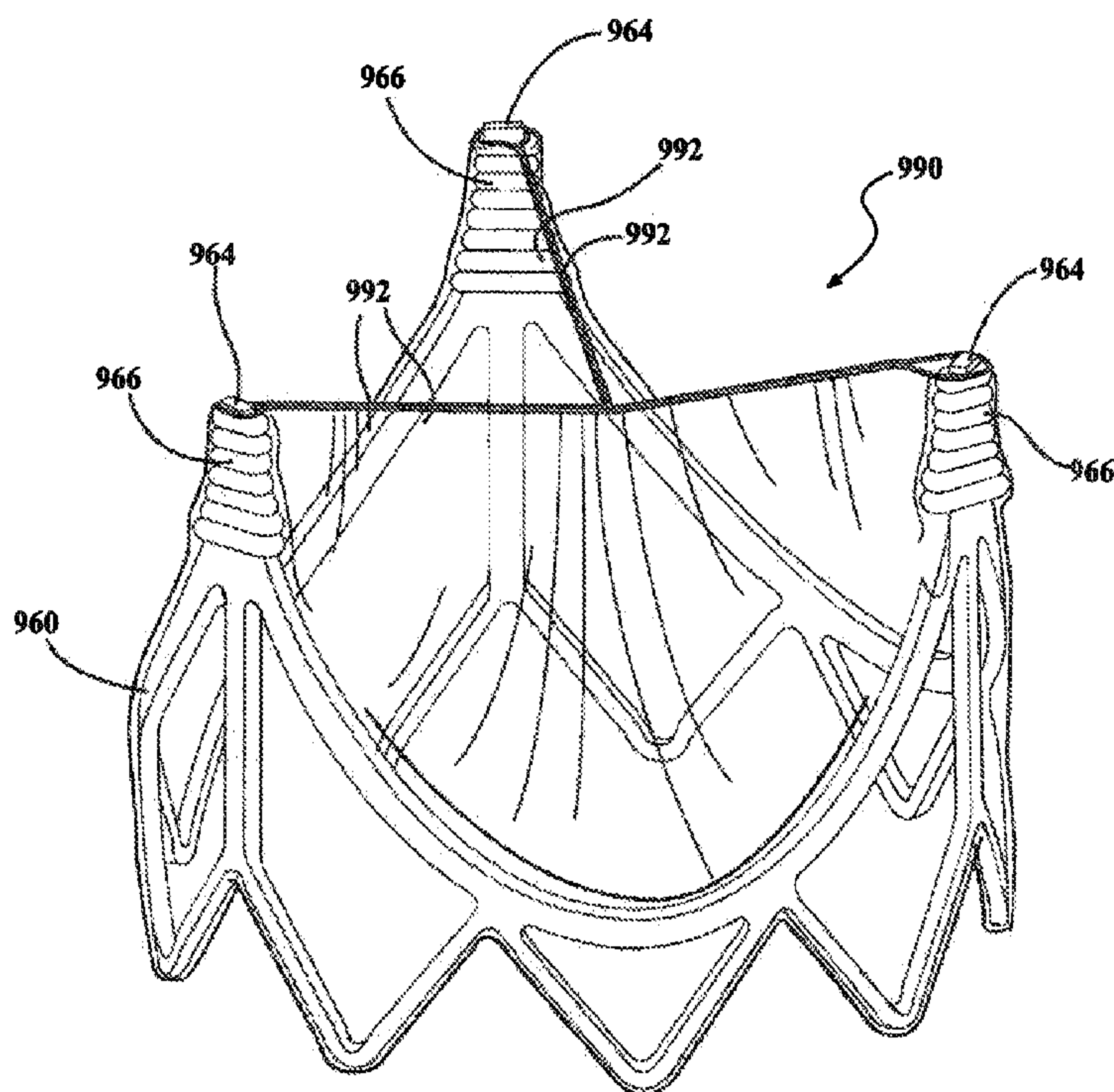
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, 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, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, 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.

[Continued on next page]

(54) Title: DURABLE HIGH STRENGTH POLYMER COMPOSITE SUITABLE FOR IMPLANT AND ARTICLES PRODUCED THEREFROM

**FIG. 23**

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WO 2012/135603 A3

(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, MD, 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, ML, MR, NE, SN, TD, TG).

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:

6 December 2012

DURABLE HIGH STRENGTH POLYMER COMPOSITE SUITABLE FOR IMPLANT AND ARTICLES PRODUCED THEREFROM

BACKGROUND OF THE INVENTION

Field of the Invention

[001] The invention relates to materials used in medical implants. More particularly, the invention relates to a biocompatible material suitable for use in high-cycle flexural applications including artificial heart valves.

Background

[002] Artificial heart valves preferably should last at least ten years in vivo. To last that long, artificial heart valves should exhibit sufficient durability for at least four hundred million cycles or more. The valves, and more specifically heart valve leaflets, must resist structural degradation including the formation of holes, tears, and the like as well as adverse biological consequences including calcification and thrombosis.

[003] Fluoropolymers, such as expanded and non-expanded forms of polytetrafluoroethylene (PTFE), modified PTFE, and copolymers of PTFE, offer a number of desirable properties, including excellent inertness and superior biocompatibility, and, therefore make ideal candidate materials. PTFE and expanded PTFE (ePTFE) have been used to create heart valve leaflets. It has been shown, however, that PTFE stiffens with repeated flexure, which can lead to unacceptable flow performance. Failure due to formation of holes and tears in the material has also been observed. A variety of polymeric materials has previously been employed as prosthetic heart valve leaflets. Failure of these leaflets due to stiffening and hole formation occurred within two years of implant. Efforts to improve leaflet durability by thickening the leaflets resulted in unacceptable hemodynamic performance of the valves, that is, the pressure drop across the open valve was too high.

[004] As such, it remains desirable to provide a biocompatible artificial heart valve design that lasts beyond ten years in vivo by exhibiting sufficient durability for at least about four hundred million cycles of flexure or more.

SUMMARY OF THE INVENTION

[005] According to one aspect of the invention, an implantable article is provided for regulating blood flow direction in a human patient. In one embodiment, the implantable article includes a leaflet

t comprising a composite material with at least one fluoropolymer layer having a plurality of pores and an elastomer present in substantially all of the pores of the at least one fluoropolymer layer, wherein the composite material comprises less than about 80% fluoropolymer by weight.

[006] In another embodiment, the implantable article includes a support structure; a leaflet supported on the support structure and movable between open and closed positions to regulate blood flow through the implantable article; and a cushion member located between at least a portion of the support structure and at least a portion of the leaflet, wherein the cushion member is formed from a composite material with at least one fluoropolymer layer having a plurality of pores and an elastomer present in substantially all of the pores.

[007] In another embodiment, the implantable article includes a generally annular shaped support structure having a first end and an opposite second end. The first end of the support structure has a longitudinally extending post. A sheet of leaflet material extends along an outer periphery of the support structure and forms first and second leaflets extending along on opposite sides of the post. A cushion member is coupled to the post and provides a cushion between the post and the leaflets to minimize stress and wear on the leaflets as the leaflets cycle between open and closed positions.

BRIEF DESCRIPTION OF THE DRAWINGS

[008] The accompanying drawings are included to provide a further understanding of the invention and are incorporated in and constitute a part of this specification, illustrate embodiments of the invention, and together with the description serve to explain the principles of the invention.

[009] Figures 1A, 1B, 1C, and 1D are front, side and top elevational views, and a perspective view, respectively, of a tool for forming a heart valve leaflet;

[010] Figure 2A is a perspective view of a cushion pad being stretched over a leaflet tool;

[011] Figure 2B is a perspective view of a release layer being stretched over the cushion pad covered leaflet tool in Figure 2A;

[012] Figures 3A, 3B and 3C are top, side and front elevational views illustrating a step in the formation of a valve leaflet, in which the leaflet tool covered by the cushion pad and release layer (shown in Figures 2A and 2B, respectively) is positioned over a composite material for cutting and further assembly;

[013] Figure 4 is a top elevational view of a tri-leaflet assembly prior to cutting excess leaflet material;

[014] Figure 5A is a perspective view of the tri-leaflet assembly and a base tool.

[015] Figure 5B is a perspective view of the tri-leaflet assembly and base tool aligned and assembled to form a base tool assembly;

[016] Figure 6A is a flattened plane view of a stent frame or support structure;

[017] Figure 6B is a flattened plane view of the support structure covered in a polymer coating;

[018] Figures 7A, 7B and 7C are scanning electron micrograph images of expanded fluoropolymer membranes used to form the valve leaflets;

[019] Figure 8 is a perspective view of a valve assembly;

[020] Figures 9A and 9B are top elevational views of the heart valve assembly of Figure 8 shown illustratively in closed and open positions, respectively;

[021] Figure 10 is a graph of measured outputs from a heart flow pulse duplicator system used for measuring performance of the valve assemblies;

[022] Figures 11A and 11B are a graph and data chart of measured outputs from a high rate fatigue tester used for measuring performance of the valve assemblies;

[023] Figures 12A and 12B are graphs of measured outputs from the heart flow pulse duplicator system taken while testing valve assemblies according to the invention at zero cycles and after about 207 million cycles, respectively;

[024] Figures 13A and 13B are graphs of measured outputs from the heart flow pulse duplicator system taken while testing valve assemblies at about 79 million cycles and after about 198 million cycles, respectively;

[025] Figure 14 is a perspective view of a mandrel for manufacturing a heart valve assembly;

[026] Figure 15 is a perspective view of a valve frame for a heart valve;

[027] Figure 16 is a perspective view of the valve frame of Figure 15 nested together with the mandrel Figure 14;

[028] Figure 17 is a perspective view of a molded valve;

[029] Figure 18 is a perspective view of a molded valve, showing an attachment member for reinforcing a bond between adjacent valve leaflets and a post of a valve frame;

[030] Figure 19 is a perspective view of a valve frame;

[031] Figure 20 is a perspective view of the valve frame of Figure 19 with posts that are cushion-wrapped;

[032] Figure 21 is a perspective view of a stereolithography-formed mandrel;

[033] Figure 22 is a perspective view of the cushion-wrapped valve frame of Figure 20 mounted onto the mandrel of Figure 21; and

[034] Figure 23 is a perspective view of a valve having valve leaflets coupled to and supported on the cushion-wrapped valve frame of Figure 20.

DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

[035] Definitions for some terms used herein are provided below in the Appendix.

[036] The present invention addresses a long-felt need for a material that meets the durability and biocompatibility requirements of high-cycle flexural implant applications, such as heart valve leaflets. It has been observed that heart valve leaflets formed from porous fluoropolymer materials or, more particularly, from ePTFE containing no elastomer suffer from stiffening in high-cycle flex testing and animal implantation.

[037] In one embodiment, described in greater detail below, the flexural durability of porous fluoropolymer heart valve leaflets was significantly increased by adding a relatively high-percentage of relatively lower strength elastomer to the

pores. Optionally, additional layers of the elastomer may be added between the composite layers. Surprisingly, in embodiments wherein porous fluoropolymer membranes are imbibed with elastomer the presence of the elastomer increased overall thickness of the leaflet, the resulting increased thickness of the fluoropolymer members due to the addition of the elastomer did not hinder or diminish flexural durability. Further, after reaching a minimum percent by weight of elastomer, it was found that fluoropolymer members in general performed better with increasing percentages of elastomer resulting in significantly increased cycle lives exceeding 40 million cycles in vitro, as well as by showing no signs of calcification under certain controlled laboratory conditions.

[038] A material according to one embodiment includes a composite material comprising an expanded fluoropolymer membrane and an elastomeric material. It should be readily appreciated that multiple types of fluoropolymer membranes and multiple types of elastomeric materials can be combined while within the spirit of the present invention. It should also be readily appreciated that the elastomeric material can include multiple elastomers, multiple types of non-elastomeric components, such as inorganic fillers, therapeutic agents, radiopaque markers, and the like while within the spirit of the present invention.

[039] In one embodiment, the composite material includes an expanded fluoropolymer material made from porous ePTFE membrane, for instance as generally described in U.S. Patent No. 7,306,729.

[040] The expandable fluoropolymer, used to form the expanded fluoropolymer material described, may comprise PTFE homopolymer. In alternative embodiments, blends of PTFE, expandable modified PTFE and/or expanded copolymers of PTFE may be used. Non-limiting examples of suitable fluoropolymer materials are described in, for example, U.S. Patent No. 5,708,044, to Branca, U.S. Patent No. 6,541,589, to Baillie, U.S. Patent No. 7,531,611, to Sabol et al., U.S. Patent Application No. 11/906,877, to Ford, and U.S. Patent Application No. 12/410,050, to Xu et al.

[041] The expanded fluoropolymer of the present invention may comprise any suitable microstructure for achieving the desired leaflet performance. In one embodiment, the expanded fluoropolymer may comprise a microstructure of nodes interconnected by fibrils, such as described in U.S. Patent No. 3,953,566 to Gore. In

one embodiment, the microstructure of an expanded fluoropolymer membrane comprises nodes interconnected by fibrils as shown in the scanning electron micrograph image in Figure 7A. The fibrils extend from the nodes in a plurality of directions, and the membrane has a generally homogeneous structure. Membranes having this microstructure may typically exhibit a ratio of matrix tensile strength in two orthogonal directions of less than 2, and possibly less than 1.5.

[042] In another embodiment, the expanded fluoropolymer may have a microstructure of substantially only fibrils, such as, for example, depicted in Figure 7B and 7C, as is generally taught by U.S. Patent No. 7,306,729, to Bacino. Figure 7C is a higher magnification of the expanded fluoropolymer membrane shown in Figure 7B, and more clearly shows the homogeneous microstructure having substantially only fibrils. The expanded fluoropolymer membrane having substantially only fibrils as depicted in Figures 7B and 7C, may possess a high surface area, such as greater than $20\text{m}^2/\text{g}$, or greater than $25\text{m}^2/\text{g}$, and in some embodiments may provide a highly balanced strength material having a product of matrix tensile strengths in two orthogonal directions of at least $1.5 \times 10^5 \text{MPa}^2$, and/or a ratio of matrix tensile strengths in two orthogonal directions of less than 2, and possibly less than 1.5.

[043] The expanded fluoropolymer of the present invention may be tailored to have any suitable thickness and mass to achieve the desired leaflet performance. In some cases, it may be desirable to use a very thin expanded fluoropolymer membrane having a thickness less than $1.0 \mu\text{m}$. In other embodiments, it may be desirable to use an expanded fluoropolymer membrane having a thickness greater than $0.1 \mu\text{m}$ and less than $20 \mu\text{m}$. The expanded fluoropolymer membranes can possess a specific mass less than about $1\text{g}/\text{m}^2$ to greater than about $50\text{g}/\text{m}^2$.

[044] Membranes according to an embodiment of the invention can have matrix tensile strengths ranging from about 50 MPa to about 400 MPa or greater, based on a density of about $2.2 \text{g}/\text{cm}^3$ for PTFE.

[045] Additional materials may be incorporated into the pores or within the material of the membranes or in between the layers of the membranes to enhance desired properties of the leaflet. Composites according to one embodiment can include fluoropolymer membranes having thicknesses ranging from about $500 \mu\text{m}$ to less than $0.3 \mu\text{m}$.

[046] The expanded fluoropolymer membrane combined with elastomer provides the elements of the present invention with the performance attributes required for use in high-cycle flexural implant applications, such as heart valve leaflets, in at least several significant ways. For example, the addition of the elastomer improves the fatigue performance of the leaflet by eliminating or reducing the stiffening observed with ePTFE-only materials. In addition, it reduces the likelihood that the material will undergo permanent set deformation, such as wrinkling or creasing, that could result in compromised performance. In one embodiment, the elastomer occupies substantially all of the pore volume or space within the porous structure of the expanded fluoropolymer membrane. In another embodiment the elastomer is present in substantially all of the pores of the at least one fluoropolymer layer. Having elastomer filling the pore volume or present in substantially all of the pores reduces the space in which foreign materials can be undesirably incorporated into the composite. An example of such foreign material is calcium. If calcium becomes incorporated into the composite material, as used in a heart valve leaflet, for example, mechanical damage can occur during cycling, thus leading to the formation of holes in the leaflet and degradation in hemodynamics.

[047] In one embodiment, the elastomer that is combined with the ePTFE is a thermoplastic copolymer of tetrafluoroethylene (TFE) and perfluoromethyl vinyl ether (PMVE), such as described in U.S. Patent No. 7,462,675. As discussed above, the elastomer is combined with the expanded fluoropolymer membrane such that the elastomer occupies substantially all of the void space or pores within the expanded fluoropolymer membrane. This filling of the pores of the expanded fluoropolymer membrane with elastomer can be performed by a variety of methods. In one embodiment, a method of filling the pores of the expanded fluoropolymer membrane includes the steps of dissolving the elastomer in a solvent suitable to create a solution with a viscosity and surface tension that is appropriate to partially or fully flow into the pores of the expanded fluoropolymer membrane and allow the solvent to evaporate, leaving the filler behind.

[048] In another embodiment, a method of filling the pores of the expanded fluoropolymer membrane includes the steps of delivering the filler via a dispersion to partially or fully fill the pores of the expanded fluoropolymer membrane;

[049] In another embodiment, a method of filling the pores of the expanded fluoropolymer membrane includes the steps of bringing the porous expanded fluoropolymer membrane into contact with a sheet of the elastomer under conditions of heat and/or pressure that allow elastomer to flow into the pores of the expanded fluoropolymer membrane.

[050] In another embodiment, a method of filling the pores of the expanded fluoropolymer membrane includes the steps of polymerizing the elastomer within the pores of the expanded fluoropolymer membrane by first filling the pores with a prepolymer of the elastomer and then at least partially curing the elastomer.

[051] After reaching a minimum percent by weight of elastomer, the leaflets constructed from fluoropolymer materials or ePTFE generally performed better with increasing percentages of elastomer resulting in significantly increased cycle lives. In one embodiment, the elastomer combined with the ePTFE is a thermoplastic copolymer of tetrafluoroethylene and perfluoromethyl vinyl ether, such as described in U.S. Patent No. 7,462,675, and other references that would be known to those of skill in the art. For instance, in another embodiment shown in Example 1, a leaflet was formed from a composite of 53% by weight of elastomer to ePTFE and was subjected to cycle testing. Some stiffening was observed by around 200 million test cycles, though with only modest effect on hydrodynamics. When the weight percent of elastomer was raised to about 83% by weight, as in the embodiment of Example 2, no stiffening or negative changes in hydrodynamics were observed at about 200 million cycles. In contrast, with non-composite leaflets, i.e. all ePTFE with no elastomer, as in the Comparative Example B, severe stiffening was apparent by 40 million test cycles. As demonstrated by these examples, the durability of porous fluoropolymer members can be significantly increased by adding a relatively high-percentage of relatively lower strength elastomer to the pores of the fluoropolymer members. The high material strength of the fluoropolymer membranes also permits specific configurations to be very thin.

[052] Other biocompatible polymers which may be suitable for use in this invention may include but not be limited to the groups of urethanes, silicones(organopolysiloxanes), copolymers of silicon-urethane, styrene/isobutylene copolymers, polyisobutylene, polyethylene-co-poly(vinyl acetate), polyester

copolymers, nylon copolymers, fluorinated hydrocarbon polymers and copolymers or mixtures of each of the foregoing.

[053] The following non-limiting examples are provided to further illustrate embodiments of the present invention.

[054] **Example 1**

[055] Heart valve leaflets according to one embodiment were formed from a composite material having an expanded fluoropolymer membrane and an elastomeric material and joined to a metallic balloon expandable stent, as described by the following process:

[056] 1) A thick, sacrificial tooling cushion pad or layer was formed by folding a ePTFE layer over upon itself to create a total of four layers. The ePTFE layer was about 5 cm (2") wide, about 0.5mm (0.02") thick and had a high degree of compressibility, forming a cushion pad. Referring to Figures 1 and 2, the cushion pad 200 was then stretched (Figure 2) onto a leaflet tool, generally indicated at 100. The leaflet tool 100 has a leaflet portion 102, a body portion 104 and a bottom end 106. The leaflet portion 102 of the leaflet tool 100 has a generally arcuate, convex end surface 103. The cushion pad 200 was stretched and smoothed over the end surface 103 of the leaflet portion 102 of the leaflet tool 100 by forcing the leaflet tool 100 in the direction depicted by the arrow (Figure 2A). A peripheral edge 202 of the cushion pad 200 was stretched over the bottom end 106 of the leaflet tool 100 and twisted to hold the cushion pad 200 in place (Figure 2B).

[057] 2) Referring to Figure 2B, a release layer 204 was then stretched over the leaflet portion 102 of the leaflet tool 100 which in the previous step was covered with the cushion pad 200. In one embodiment, the release layer 204 was made from a substantially nonporous ePTFE having a layer of fluorinated ethylene propylene (FEP) disposed along an outer surface or side thereof. The release layer 204 was stretched over the leaflet tool 100 such that the FEP layer faced toward the cushion pad 200 and the substantially nonporous ePTFE faced outwardly or away from the cushion pad 200. The release layer was about 25 μ m thick and of sufficient length and width to allow the release layer 204 to be pulled over the bottom end 106 of the leaflet tool 100. As with the cushion pad 200 in the previous step, a peripheral edge 206 of the release layer 204 was pulled toward the bottom end 106 of the leaflet tool 100 and then twisted onto the bottom end 106 of the leaflet tool 100 to retain or hold

the release layer 204 in place. The FEP layer of the release layer 204 was then spot-melted and thereby fixedly secured to the cushion pad 200, as required, by the use of a hot soldering iron.

[058] 3) The processes of Steps 1) and 2) were repeated to prepare three separate leaflet tools, each having a cushion pad covered by a release layer.

[059] 4) A leaflet material according to one embodiment was formed from a composite material comprising a membrane of ePTFE imbibed with a fluoroelastomer. A piece of the composite material approximately 10 cm wide was wrapped onto a circular mandrel to form a tube. The composite material was comprised of three layers: two outer layers of ePTFE and an inner layer of a fluoroelastomer disposed therebetween. The ePTFE membrane was manufactured according to the general teachings described in U.S. Patent No. 7,306,729. The fluoroelastomer was formulated according to the general teachings described in U.S. Patent No. 7,462,675. Additional fluoroelastomers may be suitable and are described in U.S. Publication No. 2004/0024448.

[060] The ePTFE membrane had the following properties: thickness = about 15 μm ; MTS in the highest strength direction = about 400 MPa; MTS strength in the orthogonal direction = about 250 MPa; Density = about 0.34 g/cm^3 ; IBP = about 660 KPa.

[061] The copolymer consists essentially of between about 65 and 70 weight percent perfluoromethyl vinyl ether and complementally about 35 and 30 weight percent tetrafluoroethylene.

[062] The percent weight of the fluoroelastomer relative to the ePTFE was about 53%.

[063] The multi-layered composite had the following properties: thickness of about 40 μm ; density of about 1.2 g/cm^3 ; force to break/width in the highest strength direction = about 0.953 kg/cm; tensile strength in the highest strength direction = about 23.5 MPa (3,400 psi); force to break/width in the orthogonal direction = about 0.87 kg/cm; tensile strength in the orthogonal direction = about 21.4 MPa (3100 psi), IPA bubble point greater than about 12.3 MPa, Gurley Number greater than about 1,800 seconds, and mass/area = about 14 g/m^2 .

[064] The following test methods were used to characterize the ePTFE layers and the multi-layered composite.

[065] The thickness was measured with a Mutitoyo Snap Gage Absolute, 12.7 mm (0.50") diameter foot, Model ID-C112E, Serial # 10299, made in Japan. The density was determined by a weight/volume calculation using an Analytical Balance Mettler PM400 New Jersey, USA. The force to break and tensile strengths were measured using an Instron Model #5500R Norwood, MA, load cell 50 kg, gage length = 25.4 cm, crosshead speed = 25 mm/minute (strain rate = 100% per minute) with flat faced jaws. The IPA Bubble Point was measured by an IPA bubble point tester, Pressure Regulator Industrial Data Systems Model LG-APOK, Salt Lake City, UT, USA, with a Ramp Rate of 1.38 KPa/s (0.2 psi/s), 3.14 cm² test area. The Gurley Number was determined as the time in seconds for 100 cm³ of air to flow through a 6.45 cm² sample at 124 mm of water pressure using a Gurley Tester, Model #4110, Troy, NY, USA.

[066] Unless otherwise noted, these test methods were used to generate the data in subsequent examples.

[067] Layers of the composite material, each having two outer layers of ePTFE and an inner layer of a fluoroelastomer disposed therebetween, was wrapped onto a mandrel having a diameter of about 28 mm (1.1") such that the higher strength direction of the membrane was oriented in the axial direction of the mandrel. In one embodiment, four layers of the composite material were wrapped in a non-helical, generally circumferential fashion onto the mandrel. The composite material had a slight degree of tackiness that allowed the material to adhere to itself. While still on the mandrel, the composite material was slit longitudinally generally along the mandrel long axis to form a sheet about 10 cm (4") by about 90 mm (3.5").

[068] 5) The resulting sheet of leaflet material (or composite material from Step 4) was then cut and wrapped onto the leaflet tool 100 having a cushion pad 200 covered by a release layer 204. More specifically, as shown in Figures 3A – 3C, the leaflet material 300 was placed onto a flat cutting surface. The leaflet tool 100 with the cushion pad 200 and release layer 204 was then aligned onto the leaflet material 300 approximately as shown. Four slits 302, 304, 306, 308 were then formed in the leaflet material 300 with a razor blade. One pair of slits 302, 304 extends from one side of the leaflet tool 100 and terminates at one edge 300a of the leaflet material 300, and the other pair of slits 306, 308 extends from an opposite side of the leaflet tool 100 and terminates at an opposite edge 300b of the leaflet material 300. The

slits 302, 304, 306, 308 were spaced apart from the leaflet portion 102 of the leaflet tool 100. The slits 302, 304, 306, 308 did not protrude under the leaflet tool 100. It should be appreciated that the widths of the individual slits are shown not to scale. The slits 302, 304, 306, 308 in the leaflet material 300 resulted in the formation of a folding portion 310, a pair of straps 312, 314 and excess material of leaflet material 315. The folding portions 310 were then folded in the general direction indicated by the arrows 316 in Figure 3 and smoothed over the leaflet tool 100, which was covered by the cushion pad 200 and the release layer 204 in the previous steps.

[069] 6) The leaflet material 315 was then stretched and smoothed over the leaflet portion 102, particularly the end surface 103 of the leaflet tool 100. The Steps 4) and 5) were repeated to form three separate leaflet assemblies. The three leaflet assemblies 402, 404, 406 were then clamped together to form a tri-leaflet assembly 400, as shown in Figure 4. Shown are the three separate leaflet assemblies 402, 404, 406, each having an excess material of leaflet material 315 extending generally radially beyond the periphery of the tri-leaflet assembly 400.

[070] 7) A base tool was then provided having cavities for engaging the end surfaces of the leaflet tools of the tri-leaflet assembly and trimming the excess leaflet area to form three leaflets. Referring to Figure 5A, the base tool is generally indicated at 500 and extends longitudinally between an end 501 and an opposite bottom end 503. Three concave cavities 502, 504, 506 are formed in the end 501 of the base tool 500. Each concave cavity 502, 504, 506 is formed to match fit or nestingly seat the end surface 103 of one of the three leaflet assemblies 402, 404, 406. Three radially extending elements 508, 510, 512 extend outwardly from the end of the base tool 500. Each element 508, 510, 512 is disposed between an adjacent pair of concave cavities 502, 504, 506.

[071] The base tool 500 was then prepared having a compression pad and a release layer (not shown) similar to how the leaflet tool was prepared in Steps 1 and 2. As described for each leaflet tool in Steps 1 and 2, the compression pad and the release layer were similarly stretched and affixed to the base tool 500 to form a base tool assembly.

[072] 8) Referring to Figure 5B, the base tool assembly (illustrated for convenience as the base tool 500 without showing the cushion pad and the release layer) and the tri-leaflet assembly, generally indicated at 400, were then generally

axially aligned together so that the end surface (not shown) of each leaflet tool 100 was seated into one of the concave cavities (not shown) in the end 501 of the base tool, generally indicated at 500, to form a combined tool assembly.

[073] 9) A metallic balloon expandable stent was then fabricated. A tube of 316 stainless steel having a wall thickness of about 0.5mm (0.020") and a diameter of about 2.5cm (1.0") was laser cut. A pattern was cut into the tube to form an annular-shaped cut stent frame or support structure, which is generally indicated at 600 and shown illustratively in a flat, plane view in Figure 6a. The support structure 600, includes a plurality of small closed cells 602, a plurality of large closed cells 604, and a plurality of leaflet closed cells 606. Note that one of the plurality of leaflet closed cells 606 appears as an open cell in Figure 6A due to the flat plane view. The cells 602, 604, 606 are generally arranged along rows forming the annular shape of the support structure 600.

[074] 10) Polymeric materials were then adhered to the laser cut stent frame. First, a sacrificial compression layer of ePTFE membrane was wrapped without overlap onto a mandrel (not shown) having a diameter of about 2.5 cm (1.0"). The sacrificial compression layer of ePTFE membrane had a thickness of about 0.5 mm (0.02") and a width of about 10 cm (4"), and was compliant and compressible to provide a soft, sacrificial compression layer.

[075] 11) Four layers of a substantially nonporous, ePTFE film were then wrapped onto the mandrel on top of the compression layer membrane. The substantially nonporous, ePTFE film had a thickness of about 25 μm (0.001"), was about 10 cm (4") wide and had a layer of FEP on one side. The substantially nonporous, ePTFE film was wrapped with the FEP facing away from the mandrel. The substantially nonporous, ePTFE film had the properties of the release layer previously described in Step 2).

[076] 12) A thin film of type 1 (ASTM D3368) FEP was constructed using melt extrusion and stretching. An additional 10 layers of this type 1 (ASTM D3368) FEP film was added to the mandrel, which was previously wrapped in the compression layer membrane in Step 10 and the four layers of substantially nonporous, ePTFE film in Step 11. The type 1 (ASTM D3368) FEP film was about 40 μm (0.0016") thick and was about 7.7 cm (3") wide.

[077] 13) The wrapped mandrel was then heat treated in an air convection oven at about 320 °C for about 5 minutes and allowed to cool.

[078] 14) The support structure (indicated at 600 in Figure 6A) was then placed onto the heat treated and wrapped mandrel. Two additional layers of type 1 (ASTM D3368) FEP film (provided in Step 12) were then wrapped onto the support structure, which was previously placed on the wrapped mandrel.

[079] 15) The wrapped mandrel and the support structure supported thereon were then heat treated in an air convection oven at about 320 °C for about 10 minutes and allowed to cool, forming a polymeric-coated support structure.

[080] 16) The polymeric-coated support structure was then trimmed with a scalpel to form a trimmed stent frame, which is generally indicated at 700 and shown illustratively in a flat, plane view in Figure 6B. More specifically, in one manner, the polymeric coating was trimmed about 2 mm (0.08") past the edges of the support structure (600, Figure 6A) to form a variety of edge profiles 708. In another manner, the polymeric coating was allowed to span entire cells to form a web in each cell. In either case, the support structure 600 was fully encapsulated within a polymeric coating 702 to form the trimmed stent frame 700. The trimmed stent frame 700 includes a plurality of leaflet openings 704 corresponding in number and generally in shape to the plurality of leaflet closed cells 606 (Figure 6A). Further, a slit 706 is formed in the polymeric coating 702 of each of the small closed cells as shown in Figure 6B. Specifically, each slit 706 is linear and generally parallel to a longitudinal center axis (not shown) of the annular-shaped support structure 600.

[081] 17) The trimmed stent frame was then placed onto the combined tool assembly from Step 8. The leaflet portions (102) of the leaflet tools were aligned to the leaflet openings (704 in Figure 6B) in the trimmed stent frame. The three excess leaflet material areas (315 in Figure 4) were pulled through the leaflet openings of the stent frame. Each of the three pairs of straps (312, 314 in Figure 3A) was pulled through one of the slits (706 in Figure 6B) and wrapped around the trimmed stent frame. Each pair of straps were wrapped in opposing directions relative to each other. The six straps were then heat tacked to the trimmed stent frame using a hot soldering iron.

[082] 18) The combined tool assembly (Step 8) and the trimmed stent frame having the wrapped and heat tacked straps were then mounted into a rotary

chuck mechanism. The rotary chuck mechanism was then adjusted to apply a light, longitudinal compressive load. The excess leaflet material areas (315 in Figure 4) were then heat tacked to the base tool (500 in Figure 5) using a hot soldering iron.

[083] 19) The combined tools of Step 18 were then wrapped with an additional 2 layers of type 1 (ASTM D3368) FEP film (from Step 12). Three additional layers of the composite (Step 4) were then overwrapped and tacked down to the trimmed stent frame.

[084] 20) In preparation for a final heat treat, release and sacrificial layers of a compression tape and compression fiber were applied both circumferentially and longitudinally to the assembly from Step 19. The compression tape/fiber contact and compress the assembly both circumferentially and longitudinally during the subsequent heat treat. A sacrificial layer of compression tape was circumferentially wrapped in a helical fashion onto the assembly from Step 19. This compression tape had the properties of the sacrificial compression layer of ePTFE previously described in Step 10. An ePTFE compression fiber was then tightly wrapped onto the compression tape. Approximately 100 turns of the compression fiber were circumferentially applied in a closely spaced helical pattern. The ePTFE compression fiber was about 1 mm (0.04") in diameter and was structured to shrink longitudinally when sufficiently heated. The clamped assembly was then removed from the rotary chuck mechanism. Three layers of sacrificial compression tape were then wrapped in a longitudinal fashion around the assembly. Approximately 20 wraps of the compression fiber was then longitudinally wrapped over the longitudinal compression tape.

[085] 21). The assembly from Step 20 was then heat treated in an air convection oven at about 280°C for about 90 minutes and then room temperature water quenched. This heat treatment step facilitates the flow of the thermoplastic fluoroelastomer into the pores of the ePTFE membrane used to create the leaflet material described in step 4.

[086] 22) The sacrificial compression tapes/fibers were then removed. The polymeric materials were trimmed to allow the leaflet and base tools to be separated. The stent polymeric layers were then trimmed to allow removal of the stent frame with the attached leaflets. The leaflets were then trimmed, resulting in a valve assembly as shown in Figure 8 and generally indicated at 800.

[087] The resulting valve assembly 800, according to one embodiment, includes leaflets 802 formed from a composite material with at least one fluoropolymer layer having a plurality of pores and an elastomer present in substantially all of the pores of the at least one fluoropolymer layer. Each leaflet 802 is movable between a closed position, shown illustratively in Figure 9A, in which blood is prevented from flowing through the valve assembly, and an open position, shown illustratively in Figure 9B, in which blood is allowed to flow through the valve assembly. Thus, the leaflets 802 of the valve assembly 800 cycle between the closed and open positions generally to regulate blood flow direction in a human patient,

[088] The performance of the valve leaflets in each valve assembly was characterized on a real-time pulse duplicator that measured typical anatomical pressures and flows across the valve, generating an initial or “zero fatigue” set of data for that particular valve assembly. The valve assembly was then transferred to a high-rate fatigue tester and was subjected to approximately 207 million cycles. After each block of about 100 million cycles, the valve was then returned to the real-time pulse duplicator and the performance parameters re-measured.

[089] The flow performance was characterized by the following process:

[090] 1) The valve assembly was potted into a silicone annular ring (support structure) to allow the valve assembly to be subsequently evaluated in a real-time pulse duplicator. The potting process was performed according to the recommendations of the pulse duplicator manufacturer (ViVitro Laboratories Inc., Victoria BC, Canada)

[091] 2) The potted valve assembly was then placed into a real-time left heart flow pulse duplicator system. The flow pulse duplicator system included the following components supplied by VSI Vivitro Systems Inc., Victoria BC, Canada: a Super Pump, Servo Power Amplifier Part Number SPA 3891; a Super Pump Head, Part Number SPH 5891B, 38.320 cm² cylinder area; a valve station/fixture; a Wave Form Generator, TriPack Part Number TP 2001; a Sensor Interface, Part Number VB 2004; a Sensor Amplifier Component, Part Number AM 9991; and a Square Wave Electro Magnetic Flow Meter, Carolina Medical Electronics Inc., East Bend, NC, USA.

[092] In general, the flow pulse duplicator system uses a fixed displacement, piston pump to produce a desired fluid flow through the valve under test.

[093] 3) The heart flow pulse duplicator system was adjusted to produce the desired flow, mean pressure, and simulated pulse rate. The valve under test was then cycled for about 5 to 20 minutes.

[094] 4) Pressure and flow data were measured and collected during the test period, including ventricular pressures, aortic pressures, flow rates, and pump piston position. Shown illustratively in Figure 10 is a graph of typical data outputs from the heart flow pulse duplicator system.

[095] 5) Parameters used to characterize the valve and to compare to post-fatigue values are pressure drop across the open valve during the positive pressure portion of forward flow, effective orifice area, and regurgitant fraction.

[096] Following characterization, the valve assembly was then removed from the flow pulse duplicator system and placed into a high-rate fatigue tester. A Six Position Heart Valve Durability Tester, Part Number M6 was supplied by Dynatek, Galena, MO, USA and was driven by a Dynatek Delta DC 7000 Controller. This high rate fatigue tester displaces fluid through a valve assembly with a typical cycle rate of about 780 cycles per minute. During the test, the valve assembly can be visually examined using a tuned strobe light. The pressure drop across the closed valve can also be monitored as displayed in Figures 11A and 11B. Shown in Figures 11A and 11B is a typical data set verifying that the high-rate fatigue tester was producing consistent pressure wave forms.

[097] The valve assembly was continuously cycled and periodically monitored for visual and pressure drop changes. After approximately 200 million cycles, the valve assembly was removed from the high-rate tester and returned to the real-time pulse duplicator. The pressure and flow data were collected and compared to the original data collected.

[098] Shown in Figure 12A is a screen shot displaying typical measured data outputs from the real-time heart flow pulse duplicator system. Shown are Ventricular Pressures, Aortic Pressures and Flow Rate. The initial or zero fatigue data for a particular valve is shown illustratively in Figure 12A. The same measurements were taken and data were collected for the same particular valve after 207 million cycles. The 207 million cycle data for the particular valve is shown illustratively in Figure

12B. Both sets of measurements were taken at 5 liters per minute flow rate and 70 cycles per minute rate. Comparing Figures 12A and 12B, it should be readily appreciated that the waveforms are substantially similar, indicating no substantial change in the valve leaflet performance after about 207 million cycles. Pressure drop, effective orifice area (EOA), and regurgitant fraction measured at zero and 207 million cycles are summarized in Table 1 below.

Number of cycles (Million)	Pressure Drop (mm Hg)	EOA (cm ²)	Regurgitant Fraction (%)
0	5.7	2.78	12.7
207	7.7	2.38	9.6

Table 1

[099] Generally, it was observed that the valve leaflets constructed according to the embodiments described herein exhibited no physical or mechanical degradation, such as tears, holes, permanent set and the like, after 207 million cycles. As a result, there was also no observable change or degradation in the closed and open configurations of the valve leaflets even after 207 million cycles.

[0100] **Example 2**

[0101] A heart valve having polymeric leaflets joined to a rigid metallic frame was constructed according to the following process:

[0102] A mandrel 900 was machined from PTFE having a shape shown in Figure 14. The mandrel 900 has a first end 902 and an opposite second end 904, and extends longitudinally therebetween. The mandrel 900 has an outer surface 910 having three (two shown) generally arcuate, convex lobes 912, each generally for forming leaflets (not shown) of a finished valve assembly (not shown). The outer surface 910 also includes a frame seating area 920 for positioning a valve frame (930 in Figure 15) relative to the convex lobes 912 prior to formation of leaflets onto the valve frame.

[0103] As shown in Figure 15, a valve frame 930 was laser cut from a length of 316 stainless steel tube with an outside diameter of about 25.4mm and a wall

thickness of about 0.5mm in the shape shown in Figure 15. In the embodiment shown, the valve frame 930 extends axially between a bottom end 932 and an opposite top end defined generally by a plurality of axially extending, generally spire shaped posts 934 corresponding to the number of leaflets in the intended finished valve assembly (not shown). In the specific embodiment shown, three posts 934 are formed in the valve frame 930.

[0104] Two layers of an about 4 μm thick film of FEP (not shown) was wrapped around the valve frame 930 and baked in an oven for about 30 minutes at about 270°C and allowed to cool. The resulting covered valve frame (for clarity, shown uncovered and indicated at 930) was then slid onto the mandrel 900 so that the complementary features between the valve frame 930 and mandrel 900 are nested together, as shown in Figure 16.

[0105] A leaflet material was then prepared having a membrane layer of ePTFE imbibed with a fluoroelastomer. More specifically, the membrane layer of ePTFE was manufactured according to the general teachings described in U.S. Patent No. 7,306,729. The ePTFE membrane was tested in accordance with the methods described in the Appendix. The ePTFE membrane had a mass per area of about 0.57 g/m^2 , a porosity of about 90.4%, a thickness of about 2.5 μm , a bubble point of about 458 KPa, a matrix tensile strength of about 339 MPa in the longitudinal direction and about 257 MPa in the transverse direction. This membrane was imbibed with the same fluoroelastomer as described in Example 1. The fluoroelastomer was dissolved in Novec HFE7500, 3M, St Paul, MN, USA in an about 2.5% concentration. The solution was coated using a mayer bar onto the ePTFE membrane (while being supported by a polypropylene release film) and dried in a convection oven set to about 145°C for about 30 seconds. After two coating steps, the resulting composite material of ePTFE/fluoroelastomer had a mass per area of about 3.6 g/m^2 .

[0106] The composite material (not shown) was then wound around the assembled mandrel 900 and valve frame 930. In one embodiment, a total of 20 layers of the ePTFE/fluoroelastomer composite was used. Any excess composite material that extended beyond the ends of mandrel 900 were twisted and pressed lightly against the ends 902, 904 of the mandrel 900.

[0107] The composite material wrapped mandrel was then mounted in a pressure vessel so that a vent port 906 (Figure 14) in the base or second end 904 of the mandrel 900 was plumbed to atmosphere. The vent port 906 extends from the second end 904 axially through the mandrel 900 and communicates to a generally orthogonally extending vent port 908 that extends through the outer surface 910 of the mandrel 900. The vent ports 906, 908, in addition to other vent ports which may be provided in the mandrel as needed (not shown), allow trapped air between the composite material and the mandrel to escape during the molding process.

[0108] About 690 KPa (100 psi) of nitrogen pressure was applied to the pressure vessel, forcing the ePTFE/fluoroelastomer composite against the mandrel 900 and the valve frame 930. Heat was applied to the pressure vessel until the temperature inside the vessel reached about 300° C, about 3 hours later. The heater was turned off and the pressure vessel was allowed to cool to room temperature overnight. This process thermally bonded the layers of ePTFE/fluoroelastomer composite to each other and to the FEP coating on the valve frame 930. The pressure was released and the mandrel was removed from the pressure vessel.

[0109] The ePTFE/fluoroelastomer composite was trimmed circumferentially in two places: first, at the bottom end 932 of the valve frame 930, and second, near the top end of the valve frame 930 along a circle generally intersecting near the mid-point of each post 934. The resulting valve assembly 940 consisting of the valve frame 930 and the trimmed composite material was separated from and slid off the mandrel. The molded valve assembly 940, as shown in Figure 17, includes the valve frame 930 and a plurality of leaflets 950 formed from the trimmed composite material. In one embodiment, the valve assembly 940 included three leaflets. In another embodiment, each leaflet 950 in the valve assembly 940 was approximately 40 μ m thick.

[0110] To help control the degree of opening of the valve, adjacent leaflets about each post were bonded together. As shown in Figure 18, the adjacent leaflets 950a, 950b were wrapped around the post 934 and bonded together to form a seam 954. The seam 954 had a depth 956 extending to at least about 2mm from the post 934. To support the bond between the adjacent leaflets 950a, 950b, an attachment member 952 was fixedly secured to inner surfaces of the adjacent leaflets 950a,

950b thereby bridging the seam 954 between the adjacent leaflets 950a, 950b. As shown in Figure 18, the attachment member 952 was generally rectangular. It should be appreciated, however, that other shapes for the attachment member may be utilized. The attachment member 952 was formed from the same type of composite material used to form the leaflets 950. The attachment member 952 was fixedly secured to the inner surfaces of the adjacent leaflets 950a, 950b using the fluoroelastomer solution previously described. These steps were repeated for the other pairs of adjacent leaflets of the valve assembly.

[0111] The performance and durability of the valve leaflets in this example were analyzed in the same manner as described in Example 1. The valve assembly was initially characterized on the same real-time pulse duplicator as described in Example 1 that measured typical anatomical pressures and flows across the valve, generating an initial or “zero fatigue” set of data for that particular valve assembly. The valve was then subjected to accelerated testing as in Example 1. After about 79 million cycles, the valve was removed from the high rate fatigue tester and the hydrodynamic performance again characterized as in Example 1. The valve was removed finally at about 198 million cycles. Pressure drop, EOA and regurgitant fraction measured at about 79 million cycles and about 198 cycles are summarized in Table 2 below.

[0112] Figures 13A and 13B display similar results for a similar valve. Figure 13A is a graph of measured data output from the heart flow pulse duplicator system taken after about 79 million cycles. The same measurements were taken for the similar valve after about 198 million cycles, a graph of which is shown illustratively in Figure 13B. Both sets of measurements were taken at about 4 liters per minute flow rate and about 70 cycles per minute rate. Comparing Figures 13A and 13B, it should be again appreciated that the waveforms are significantly similar, indicating no substantial change in the valve leaflet performance after about 198 million cycles. Pressure drop, effective orifice area (EOA), and regurgitant fraction measured at 0, about 79, and about 198 million cycles are summarized in Table 2 below. These data indicate no substantial change in the valve leaflet performance after about 198 million cycles.

Number of Cycles (Million)	Pressure Drop (mm Hg)	EOA (cm ²)	Regurgitant Fraction (%)
0	6.8	2.56	7.8
79	5.4	2.58	10.25
198	4.4	2.60	10.1

Table 2

[0113] **Example 3**

[0114] A heart valve having polymeric leaflets joined to a rigid metallic frame was constructed according to the following process:

[0115] A valve support structure or frame 960 was laser cut from a length of 316 stainless steel tube with an outside diameter of about 25.4mm and a wall thickness of about 0.5mm in the shape shown in Figure 19. In the embodiment shown, the frame 960 extends axially between a bottom end 962 and an opposite top end defined generally by a plurality of axially extending, generally spire shaped posts 964 corresponding to the number of leaflets in the intended finished valve assembly (not shown). A parabolically shaped top edge 968 extends between adjacent posts 964. In the specific embodiment shown, three posts 964 and three top edges 968 form the top end of the frame 960. The corners of the frame that would be in contact with the leaflet material were rounded using a rotary sander and hand polished. The frame was rinsed with water and then plasma cleaned using a PT2000P plasma treatment system, Tri-Star Technologies, El Segundo, CA, USA.

[0116] In one embodiment, a cushion member is provided between at least a portion of the frame and at least a portion of the leaflet to minimize stress related to direct contact between the frame and the leaflet. A composite fiber of ePTFE and silicone was created by first imbibing an ePTFE membrane with silicone MED-6215 (NuSil, Carpinteria, CA, USA), slitting it to a width of about 25 mm, and rolling into a substantially round fiber. The ePTFE used in this fiber was tested in accordance with the methods described in the Appendix. The ePTFE membrane had a bubble point of about 217 KPa, a thickness of about 10 μ m, a mass per area of about 5.2

g/m², a porosity of about 78%, a matrix tensile strength in one direction of about 96 MPa, and a matrix tensile strength of about 55 MPa in an orthogonal direction. The composite fiber 966 was wrapped around each of the posts 964 of the frame 960 as shown in Figure 20.

[0117] A mandrel 970 was formed using stereolithography in a shape shown in Figure 21. The mandrel 970 has a first end 972 and an opposite second end 974, and extends longitudinally therebetween. The mandrel 970 has an outer surface 980 having three (two shown) generally arcuate, convex lobes 982, each generally for forming leaflets (not shown) of a finished valve assembly (not shown). The outer surface 980 also includes a frame seating area 984 for positioning the frame (960 in Figure 19) relative to the convex lobes 982 prior to formation of the valve leaflets onto the valve frame.

[0118] The mandrel 970 was then spray coated with a PTFE mold release agent. Four layers of the ePTFE membrane previously described in this example were wrapped around the mandrel. MED-6215 was wiped onto the ePTFE and allowed to wet into and substantially fill the pores of the ePTFE. Excess MED-6215 was blotted off and the frame 960 with the composite fiber 966 wrapped posts 964 was positioned on the mandrel 970 along the frame seating area 984, as shown in Figure 22. Silicone MED-4720, NuSil, Carpinteria, CA, USA was placed along the top edges 968 of the frame 960 and along the posts 964 of the frame 960 to create a strain relief within the leaflet (not shown). Eight additional layers of ePTFE were wrapped around the frame 960 and mandrel 970. Additional MED-6215 was wiped onto the ePTFE and allowed to wet into and substantially fill the pores of the ePTFE. Another 8 layers of ePTFE were wrapped around the frame 960 and mandrel 970. These layers form a blotter to absorb any excess silicone during the molding process and were removed after the silicone had cured.

[0119] Silicone rubber forms (not shown) molded with one surface exactly matching the inverse shape of the mandrel surface were previously fabricated for each of the 3 leaflet-forming features. These forms were spray coated with PTFE mold release and then mated to the matching feature of the mandrel. Approximately 50 wraps of an ePTFE fiber (not shown) were wound around the silicone forms to apply generally radial pressure to the valve against the mandrel.

[0120] This assembly was then placed in an oven at about 100°C for about 1 hour to cure the silicone. After cooling, the fiber and silicone forms were removed, the 8 layers of blotter ePTFE were peeled away and discarded, and the resulting valve (not shown) was slid off of the mandrel. The posts were trimmed using wire cutters and the excess length of leaflet material and excess length of material at the base of the frame was carefully trimmed using scissors to form a completed valve assembly, which is shown and generally indicated at 990 in Figure 23. Thus, in one embodiment, the valve assembly 990 was formed having the frame or support structure 960; a plurality of leaflets 992 supported on the support structure 960 and movable between open and closed positions to regulate blood flow through the valve assembly 990; and a composite fiber 966 wrapped post 964 located between at least a portion of the support structure 960 and at least a portion of each leaflet 992 to minimize stress in the leaflets due to the coupling and/or proximity of the leaflets to the support structure. In another embodiment, the cushion member is formed from a composite material with at least one fluoropolymer layer having a plurality of pores and an elastomer present in substantially all of the pores, as described above.

[0121] It should be appreciated that support structures other than as specifically shown in the figures may be utilized. Further, cushion members may be utilized anywhere along the support structure as necessary to minimize stress in the leaflets due to the coupling and/or proximity of the leaflets to the support structure. For example, cushion member(s) may be coupled to the support structure along the parabolically shaped top edge.

[0122] It should also be appreciated that the cushion members may be formed as sheets and wrapped around desired locations along the support structure, or be formed from fibers of various cross sectional shapes and sizes.

[0123] It should also be appreciated that the cushion members may be formed as tubes and slid over the ends of the support structure, or be slit longitudinally and positioned around the desired location along the support structure.

[0124] The leaflets of the complete valve assembly were measured and determined to have an average thickness at the center of each leaflet of about 120 μm .

[0125] The valve assembly was then characterized for flow performance and subjected to accelerated testing as in Example 1. After each block of about 50 million

cycles, the valve assembly was removed from the high rate fatigue tester and the hydrodynamic performance again characterized as in Example 1. The valve assembly was removed finally at about 150 million cycles and demonstrated acceptable performance and no hole formation.

[0126] Comparative Example A

[0127] Six valves were constructed in the manner of Example 1 with the exception that the elastomer was not incorporated. The ePTFE material was the same as that described in Example 1, but it was not imbibed with the fluoroelastomer copolymer and was instead coated with a discontinuous layer of FEP copolymer that served as a thermoplastic adhesive. Valves were constructed as in Example 1 with each leaflet comprising 3 layers of membrane resulting in a final leaflet thickness averaging about 20 μm . After hydrodynamic characterization, the valves were mounted in the Dynatek accelerated tester described in Example 1. By about 40 million cycles, edge delamination and hole formation in the leaflets was observed and the test was stopped.

[0128] Comparative Example B

[0129] Two valves were constructed in the manner of Example 1 but did not incorporate the elastomer portion of the current invention. The material employed was thin ePTFE membrane possessing properties similar to the following: a mass per area of about 2.43 g/m^2 , a porosity of about 88%, an IBP of about 4.8 KPa, a thickness of about 13.8 μm , a matrix tensile strength in one direction of about 662 MPa, and a matrix tensile strength of about 1.2 MPa in the orthogonal direction. The ePTFE membrane was tested in accordance with the methods described in the Appendix. Ten layers of the membrane were placed in alternating directions onto a stack and then placed on the tooling as described in Example 1. The tooling was then exposed to about 350°C in a convection air oven for about 25 minutes, removed and quenched in a water bath. The three pieces of tooling were then inserted into the stent frame and the leaflets bonded to the valve assembly with FEP as in Example 1.

[0130] Each valve was subjected to high-rate fatigue testing using the real-time heart flow pulse duplicator system, as described above. After about 30 million cycles on one valve and about 40 million cycles on another valve, visual degradation, including stiffening and deformation, was observed and measurable

decrease in performance was noted. In addition to the visual and measurable degradation in performance, Table 3 below summarizes the pressure drop, effective orifice area (EOA), and regurgitant fraction measured after about 40 million cycles.

Number of Cycles (Millions)	Pressure Drop (mm Hg)	EOA (cm ²)	Regurgitant Fraction (%)
0	3.9	3.11	8.1
40x10 ⁶	6.5	2.85	14.1

Table 3

[0131] It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

APPENDIX

[0132] As used in this application, matrix tensile strength refers to the tensile strength of a porous fluoropolymer specimen under specified conditions. The porosity of the specimen is accounted for by multiplying the tensile strength by the ratio of density of the polymer to the density of the specimen.

[0133] As used herein the term “membrane” refers to a porous fluoropolymer article, “composite” refers to imbibed porous fluoropolymers, and a “leaflet” is a component of an implantable article for regulating blood flow direction. Leaflets of the present invention are one or more layers of a composite.

[0134] The term “imbibe” used herein refers to any process used to at least partially fill pores with a secondary material.

[0135] For porous fluoropolymer leaflets having pores substantially filled with elastomer, the elastomer can be dissolved or degraded and rinsed away using an appropriate solvent in order to measure desired properties.

[0136] As the term “elastomer” is used herein it defines a polymer, mixture of polymers, or mixture of one or more polymers with one or more non-polymeric

components that has the ability to be stretched to at least 1.3 times its original length and to retract rapidly to approximately its original length when released. The term "elastomeric" is intended to describe a property whereby a polymer displays stretch and recovery properties similar to an elastomer, although not necessarily to the same degree of stretch and/or recovery.

[0137] As the term "thermoplastic" is used herein it defines a polymer that softens when exposed to heat and returns to its original condition when cooled to room temperature. Such a polymer can be made to soften, flow or take on new shapes, without significant degradation or alteration of the polymer's original condition, by the application of heat or heat and pressure. In contrast to a thermoplastic polymer, a "thermoset" polymer is hereby defined as a polymer that solidifies or "sets" irreversibly when cured. A determination of whether a polymer is a "thermoplastic" polymer within the meaning of the present invention can be made by slowly elevating the temperature of a stressed specimen and watching for deformation. If the polymer can be made to soften, flow, or take on a new shape, without significant degradation or alteration of the polymer's original chemical condition, then the polymer is considered to be a thermoplastic. If only small amounts of material are available it may be necessary to use a hot stage microscope for this determination.

[0138] One measure of the quality of a valve is the effective orifice area (EOA), which can be calculated as follows: $EOA(\text{cm}^2) = Q_{\text{rms}} / (51.6 * (\Delta P)^{1/2})$ where Q_{rms} is the root mean square systolic/diastolic flow rate (cm^3/s) and ΔP is the mean systolic/diastolic pressure drop (mmHg).

[0139] As used in this application, the surface area per unit mass, expressed in units of m^2/g , was measured using the Brunauer-Emmett-Teller (BET) method on a Coulter SA3100 Gas Adsorption Analyzer, Beckman Coulter Inc. Fullerton CA, USA. To perform the measurement, a sample was cut from the center of the expanded fluoropolymer membrane and placed into a small sample tube. The mass of the sample was approximately 0.1 to 0.2 g. The tube was placed into the Coulter SA-Prep Surface Area Outgasser (Model SA-Prep, P/n 5102014) from Beckman Coulter, Fullerton CA, USA and purged at about 110°C for about two hours with helium. The sample tube was then removed from the SA-Prep Outgasser and weighed. The sample tube was then placed into the SA3100 Gas adsorption

Analyzer and the BET surface area analysis was run in accordance with the instrument instructions using helium to calculate the free space and nitrogen as the adsorbate gas.

[0140] Bubble point and mean flow pore size were measured according to the general teachings of ASTM F31 6-03 using a capillary flow Porometer, Model CFP 1500AEXL from Porous Materials, Inc., Ithaca NY, USA. The sample membrane was placed into the sample chamber and wet with SilWick Silicone Fluid (available from Porous Materials Inc.) having a surface tension of about 20.1 dynes/cm. The bottom clamp of the sample chamber had an about 2.54 cm diameter hole. Using the Capwin software version 7.73.012 the following parameters were set as specified in the table below.

[0141] <u>Parameter</u>	<u>Set Point</u>
[0142] Maxflow (cm ³ /m)	200000
[0143] Bubflow(cm ³ /m)	100
[0144] F/PT (old bubltime)	50
[0145] Minbpress (PSI)	0
[0146] Zerotime (sec)	1
[0147] V2incr(cts)	10
[0148] Preginc (cts)	1
[0149] Pulse delay(sec)	2
[0150] Maxpre (PSI)	500
[0151] Pulse width (sec)	0.2
[0152] Mineqtime (sec)	30
[0153] Presslew (cts)	10
[0154] Flowslew (cts)	50
[0155] Eqiter	3
[0156] Aveiter	20
[0157] Maxpdif (PSI)	0.1
[0158] Maxfdif (PSI)	50
[0159] Sartp(PSI)	1
[0160] Sartf (cm ³ /m)	500

[0161] Membrane thickness was measured by placing the membrane between the two plates of a Käfer FZ1000/30 thickness snap gauge Käfer Messuhrenfabrik

GmbH, Villingen-Schwenningen, Germany. The average of the three measurements was reported.

[0162] The presence of elastomer within the pores can be determined by several methods known to those having ordinary skill in the art, such as surface and/or cross section visual, or other analyses. These analyses can be performed prior to and after the removal of elastomer from the leaflet.

[0163] Membrane samples were die cut to form rectangular sections about 2.54 cm by about 15.24 cm to measure the weight (using a Mettler-Toledo analytical balance model AG204) and thickness (using a Käfer Fz1000/30 snap gauge). Using these data, density was calculated with the following formula: $\rho = m/w \cdot l \cdot t$, in which: ρ = density (g/cm^3): m = mass (g), w = width (cm), l = length (cm), and t = thickness (cm). The average of three measurements was reported.

Tensile break load was measured using an INSTRON 122 tensile test machine equipped with flat-faced grips and a 0.445 kN load cell. The gauge length was about 5.08 cm and the cross-head speed was about 50.8 cm/min. The sample dimensions were about 2.54 cm by about 15.24 cm. For longitudinal measurements, the longer dimension of the sample was oriented in the highest strength direction. For the orthogonal MTS measurements, the larger dimension of the sample was oriented perpendicular to the highest strength direction. Each sample was weighed using a Mettler Toledo Scale Model AG204, then the thickness measured using the Käfer FZ1000/30 snap gauge. The samples were then tested individually on the tensile tester. Three different sections of each sample were measured. The average of the three maximum loads (i.e., peak force) measurements was reported. The longitudinal and transverse matrix tensile strengths (MTS) were calculated using the following equation: $\text{MTS} = (\text{maximum load/cross-section area}) \cdot (\text{bulk density of PTFE}) / (\text{density of the porous membrane})$, wherein the bulk density of the PTFE was taken to be about 2.2 g/cm^3 . Flexural stiffness was measured by following the general procedures set forth in ASTM D790. Unless large test specimens are available, the test specimen must be scaled down. The test conditions were as follows. The leaflet specimens were measured on a three-point bending test apparatus employing sharp posts placed horizontally about 5.08 mm from one another. An about 1.34 mm diameter steel bar weighing about 80 mg was used to cause deflection in the y (downward) direction, and the specimens were not

restrained in the x direction. The steel bar was slowly placed on the center point of the membrane specimen. After waiting about 5 minutes, the y deflection was measured. Deflection of elastic beams supported as above can be represented by : $d = F \cdot L^3 / 48 \cdot EI$, where F (in Newtons) is the load applied at the center of the beam length, L (meters), so $L = 1/2$ distance between suspending posts, and EI is the bending stiffness (Nm). From this relationship the value of EI can be calculated. For a rectangular cross-section: $I = t^3 \cdot w / 12$, where I = cross-sectional moment of inertia, t = specimen thickness (meters), w = specimen width (meters). With this relationship, the average modulus of elasticity over the measured range of bending deflection can be calculated.

WHAT IS CLAIMED IS:

1. An implantable article for regulating blood flow direction in a human patient, comprising:
a leaflet comprising a composite material having at least one fluoropolymer layer having a plurality of pores and an elastomer present in substantially all of the pores of the at least one fluoropolymer layer, the composite material comprising less than about 80% fluoropolymer by weight.
2. The implantable article as set forth in claim 1, wherein the composite material comprises less than about 70% fluoropolymer by weight.
3. The implantable article as set forth in claim 1, wherein the composite material comprises less than about 60% fluoropolymer by weight.
4. The implantable article as set forth in claim 1, wherein the composite material comprises less than about 50% fluoropolymer by weight.
5. The implantable article as set forth in claim 1, wherein the composite material further includes a layer of the elastomer.
6. The implantable article as set forth in claim 5, wherein the elastomer is a fluoroelastomer.
7. The implantable article as set forth in claim 6, wherein the elastomer is a TFE/PMVE copolymer.
8. The implantable article as set forth in claim 7, wherein the copolymer comprises essentially of between about 40 and 80 weight percent perfluoromethyl vinyl ether and complementally 60 and 20 weight percent tetrafluoroethylene.
9. The implantable article as set forth in claim 5, wherein the fluoropolymer is PTFE.

10. The implantable article as set forth in claim 9, wherein the PTFE is ePTFE.
11. The implantable article as set forth in claim 10, wherein the at least one fluoropolymer layer has a matrix tensile strength in at least one direction greater than about 96 MPa.
12. The implantable article as set forth in claim 1, wherein the elastomer is a fluoroelastomer.
13. The implantable article as set forth in claim 12, wherein the elastomer is a TFE/PMVE copolymer.
14. The implantable article as set forth in claim 13, wherein the copolymer comprises essentially of between about 40 and 80 weight percent perfluoromethyl vinyl ether and complementally about 60 and 20 weight percent tetrafluoroethylene.
15. The implantable article as set forth in claim 1, wherein the fluoropolymer is PTFE.
16. The implantable article as set forth in claim 15, wherein the PTFE is ePTFE.
17. The implantable article as set forth in claim 16, wherein the at least one fluoropolymer layer has a matrix tensile strength in at least one direction greater than about 96 MPa.
18. The implantable article as set forth in claim 1, wherein the leaflet has a thickness of less than about 350 μm .
19. The implantable article as set forth in claim 1, wherein the leaflet has a thickness of less than about 300 μm .

20. The implantable article as set forth in claim 1, wherein the leaflet has a thickness of less than about 200 μm .
21. The implantable article as set forth in claim 1, wherein the leaflet has a thickness of less than about 100 μm .
22. The implantable article as set forth in claim 1, wherein the leaflet has a thickness of less than about 50 μm .
23. The implantable article as set forth in claim 1, wherein the leaflet has a thickness of less than about 25 μm .
24. The implantable article as set forth in claim 1, wherein an EOA across the implantable article for regulating blood flow direction is maintained within about 10% after about 40 million cycles.
25. The implantable article as set forth in claim 1, wherein a regurgitant fraction across the implantable article for regulating blood flow direction is maintained below about 15% after about 40 million cycles.
26. The implantable article as set forth in claim 1, wherein the leaflet is devoid of edge delamination or hole formation after about 40 million cycles.
27. A method of forming the composite material of the implantable article of claim 1, the method comprising:
- dissolving an elastomer in a solvent suitable to create a solution to substantially fill the pores of the at least one fluoropolymer layer;
 - substantially fill the pores of the at least one fluoropolymer layer; and
 - allowing the solvent to evaporate so that the elastomer remains in substantially all of the pores of the at least one fluoropolymer layer.

28. A method of forming the composite material of the implantable article of claim 1, the method comprising the step of delivering the elastomer via a dispersion to substantially fill substantially all of the pores of the at least one fluoropolymer layer.
29. A method of forming the composite material of the implantable article of claim 1, the method comprising the step of bringing the at least one fluoropolymer layer into contact with a sheet of the elastomer under conditions of heat or pressure that allow elastomer to substantially fill substantially all of the pores of the at least one fluoropolymer layer.
30. A method of forming the composite material of the implantable article of claim 1, the method comprising the step of polymerizing the elastomer within the pores of the at least one fluoropolymer layer.
31. The implantable article as set forth in claim 10, wherein the composite material comprises less than about 50% fluoropolymer by weight.
32. An implantable article for regulating blood flow direction in a human patient, the implantable article comprising:
- a support structure;
 - a leaflet supported on the support structure and movable between open and closed positions to regulate blood flow through the implantable article; and
 - a cushion member located between at least a portion of the support structure and at least a portion of the leaflet, wherein the cushion member is formed from a composite material with at least one fluoropolymer layer having a plurality of pores and an elastomer present in substantially all of the pores.
33. The implantable article as set forth in claim 32, wherein the cushion member includes expanded fluoropolymer.
34. The implantable article as set forth in claim 32, wherein the cushion member is formed as a fiber.

35. The implantable article as set forth in claim 32, wherein the cushion member is formed as a sheet.
36. The implantable article as set forth in claim 32, wherein the cushion member is formed as a tube.
37. The implantable article as set forth in claim 34, wherein the cushion member is wrapped generally helically about the at least a portion of the support structure to provide a cushion between the at least a portion of the support structure and the leaflet.
38. The implantable article as set forth in claim 32, wherein the support structure includes a longitudinally extending post about which a portion of the leaflet is wrapped to secure the leaflet to the support structure.
39. The implantable article as set forth in claim 38, wherein the at least one fluoropolymer layer of the cushion member is formed from porous ePTFE.
40. The implantable article as set forth in claim 39, wherein the cushion member is formed as a fiber.
41. The implantable article as set forth in claim 40, wherein the fiber is wrapped generally helically about the post to provide a cushion between the post and the portion of the leaflet wrapped about the post.
42. The implantable article as set forth in claim 40, wherein the fiber is formed from a sheet of ePTFE having a plurality of pores and an elastomer present in substantially all of the pores.

43. An implantable article for regulating blood flow direction in a human patient, the implantable article comprising:

a generally annular shaped support structure, the support structure having a first end and an opposite second end, the first end having a longitudinally extending post;

a sheet of leaflet material extending along an outer periphery of the support structure and forming a first leaflet and a second leaflet each extending along opposite sides of the post; and

a cushion member coupled to the post to provide a cushion between the post and the leaflets.

44. The implantable article as set forth in claim 43, wherein the cushion member is a fiber formed from a sheet of ePTFE having a plurality of pores and an elastomer present in substantially all of the pores.

45. An implantable article for regulating blood flow direction in a human patient, the implantable article comprising:

a leaflet comprising a composite material having at least one fluoropolymer layer having a plurality of pores and an elastomer substantially filling the pores of the at least one fluoropolymer layer, the composite material comprising less than about 80% fluoropolymer by weight.

46. An implantable heart valve for regulating blood flow direction in a human patient, the heart valve comprising:

a leaflet cyclable between a first configuration for allowing blood flow through the implantable heart valve and a second configuration for substantially preventing blood flow through the implantable heart valve, the leaflet comprising a composite material having at least one fluoropolymer layer having a plurality of pores and an elastomer present in substantially all of the pores of the at least one fluoropolymer layer,

wherein the composite material has less than about 55% fluoropolymer by weight and a thickness of less than 120 μm .

47. The implantable heart valve as set forth in claim 46, wherein an EOA across the implantable heart valve is maintained within about 10% after about 40 million cycles.

48. The implantable heart valve as set forth in claim 46, wherein a regurgitant fraction across the implantable heart valve is maintained below about 15% after about 40 million cycles.

49. The implantable heart valve as set forth in claim 46, wherein the leaflet is devoid of edge delamination or hole formation after about 40 million cycles.

Application number / Numéro de demande: 2830355

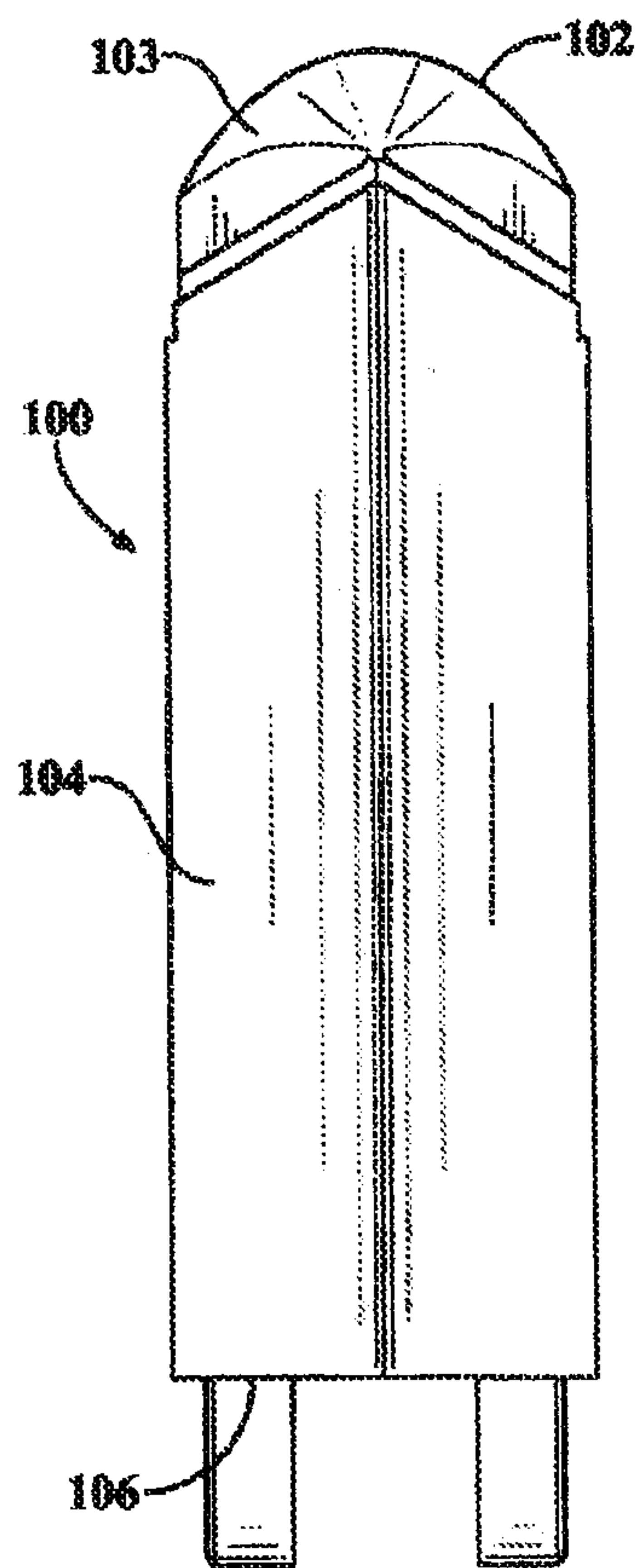
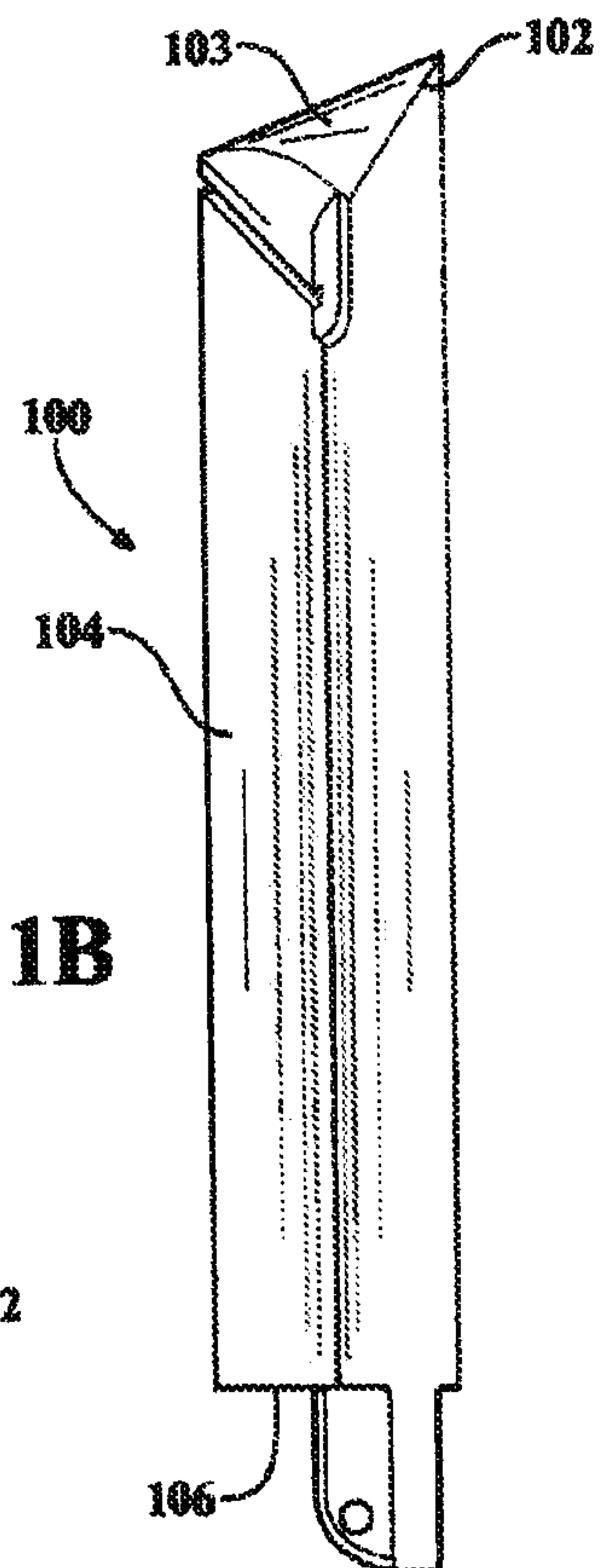
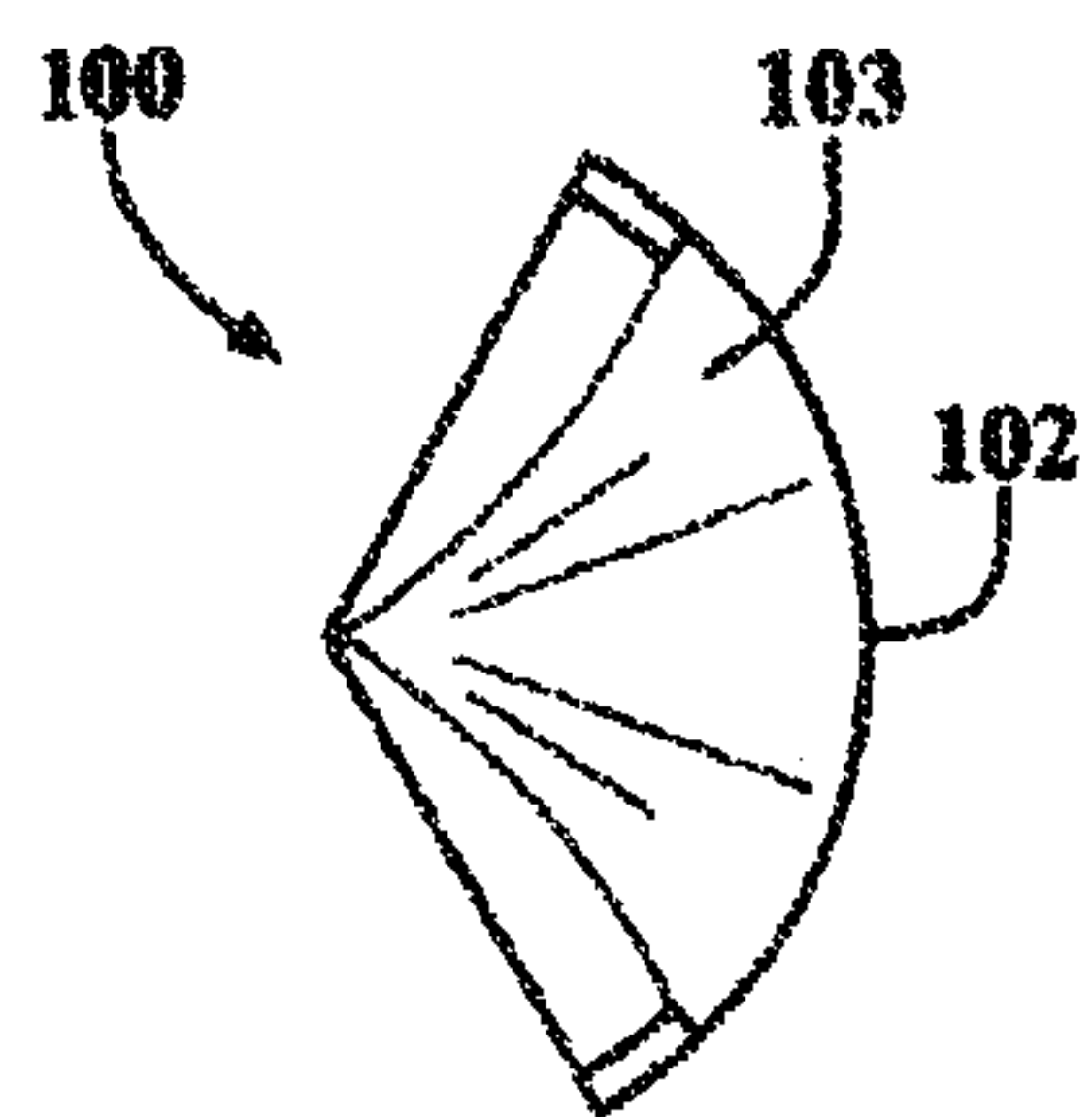
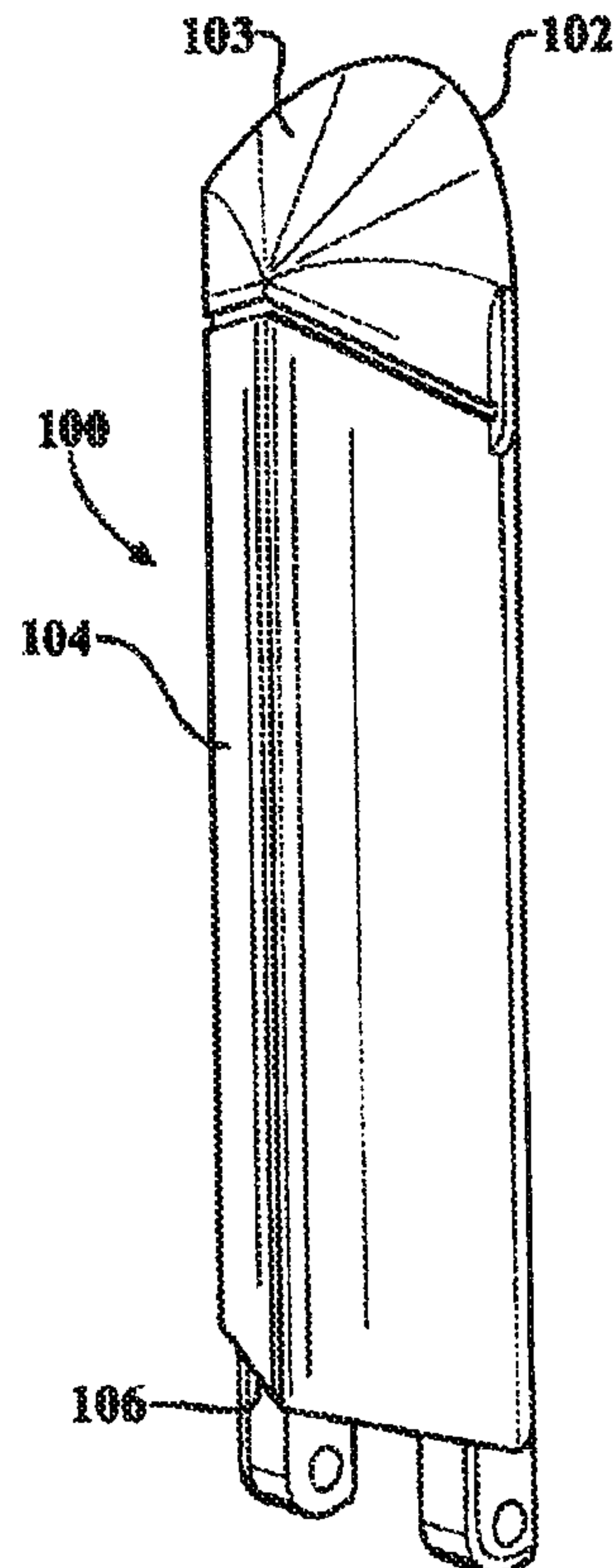
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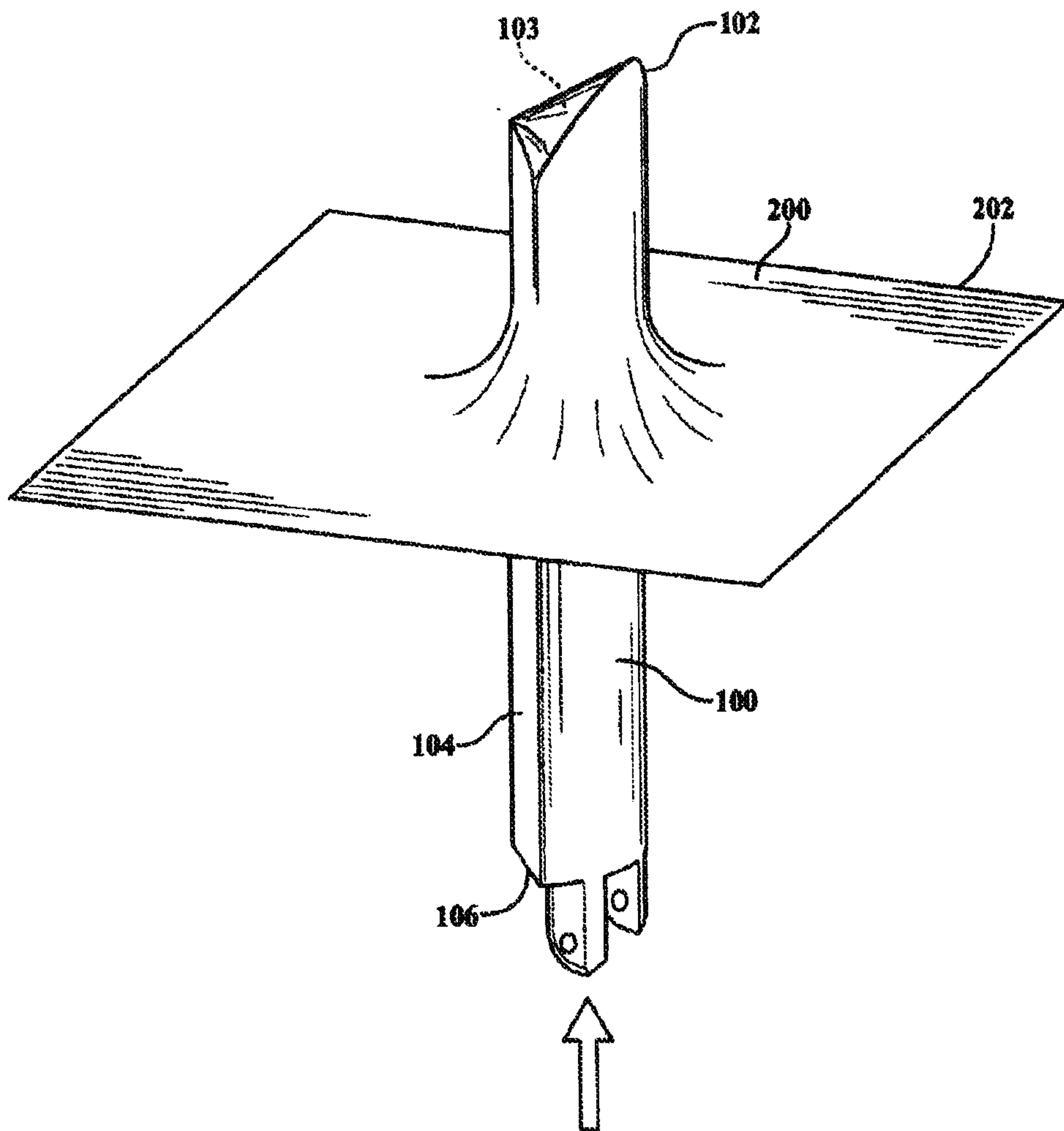
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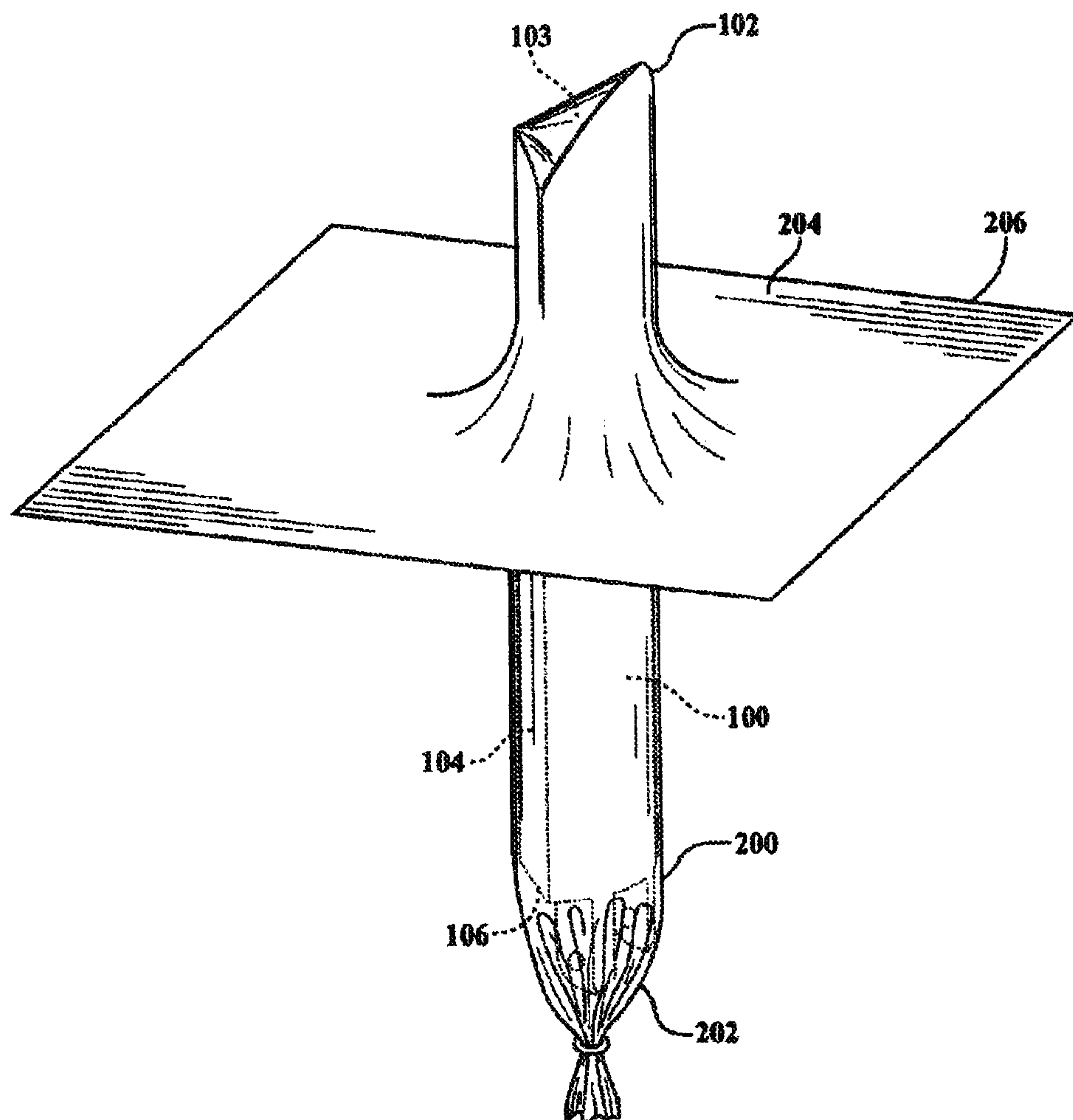
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**FIG. 1A****FIG. 1B****FIG. 1C****FIG. 1D**

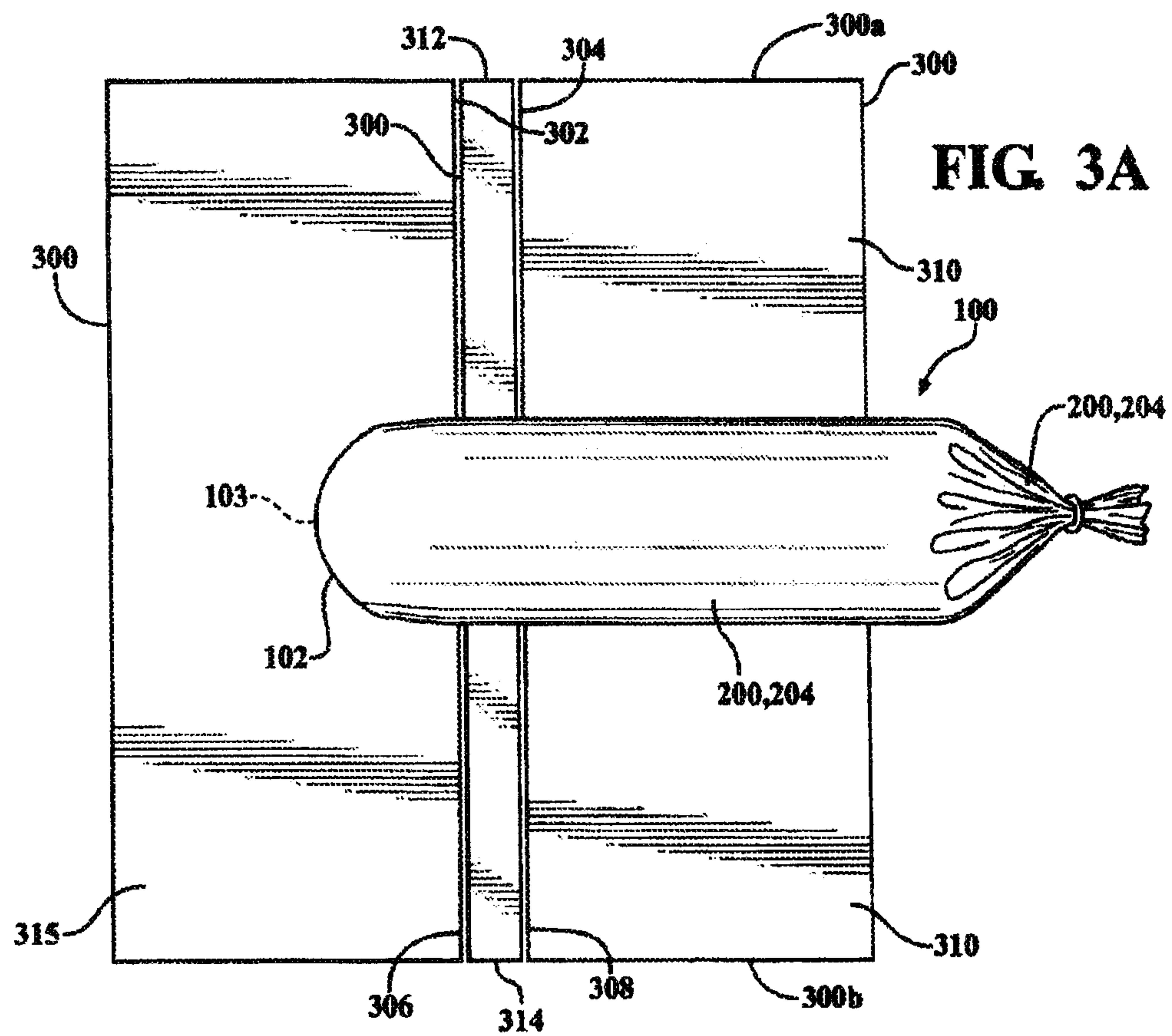
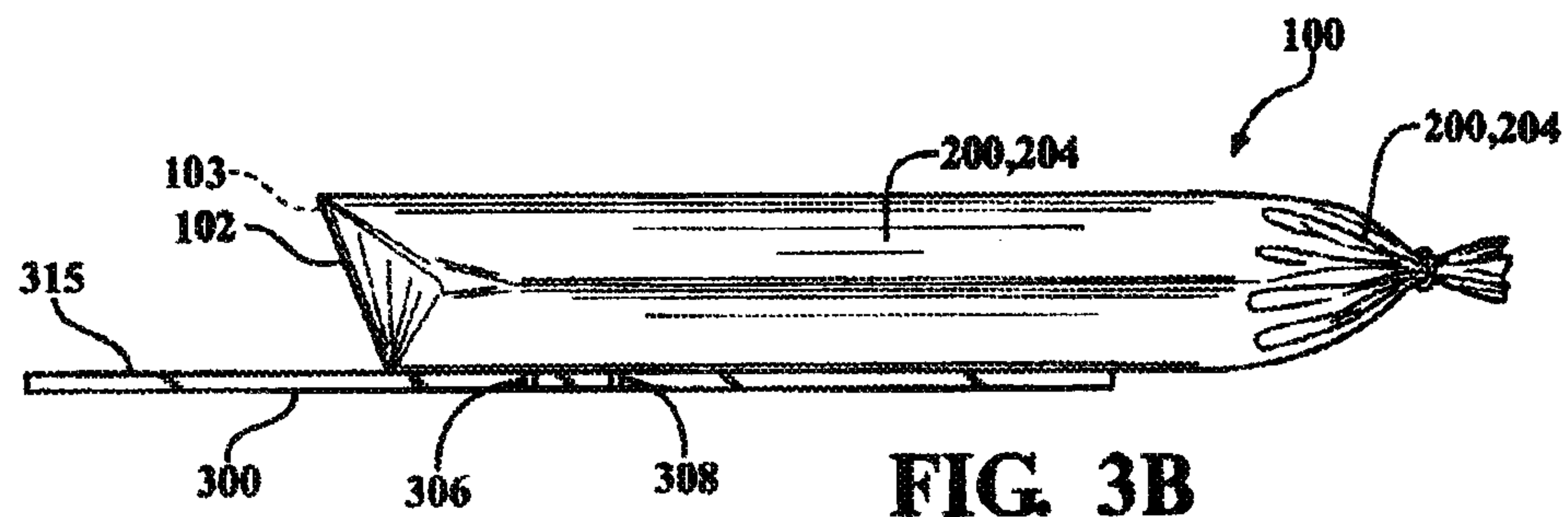
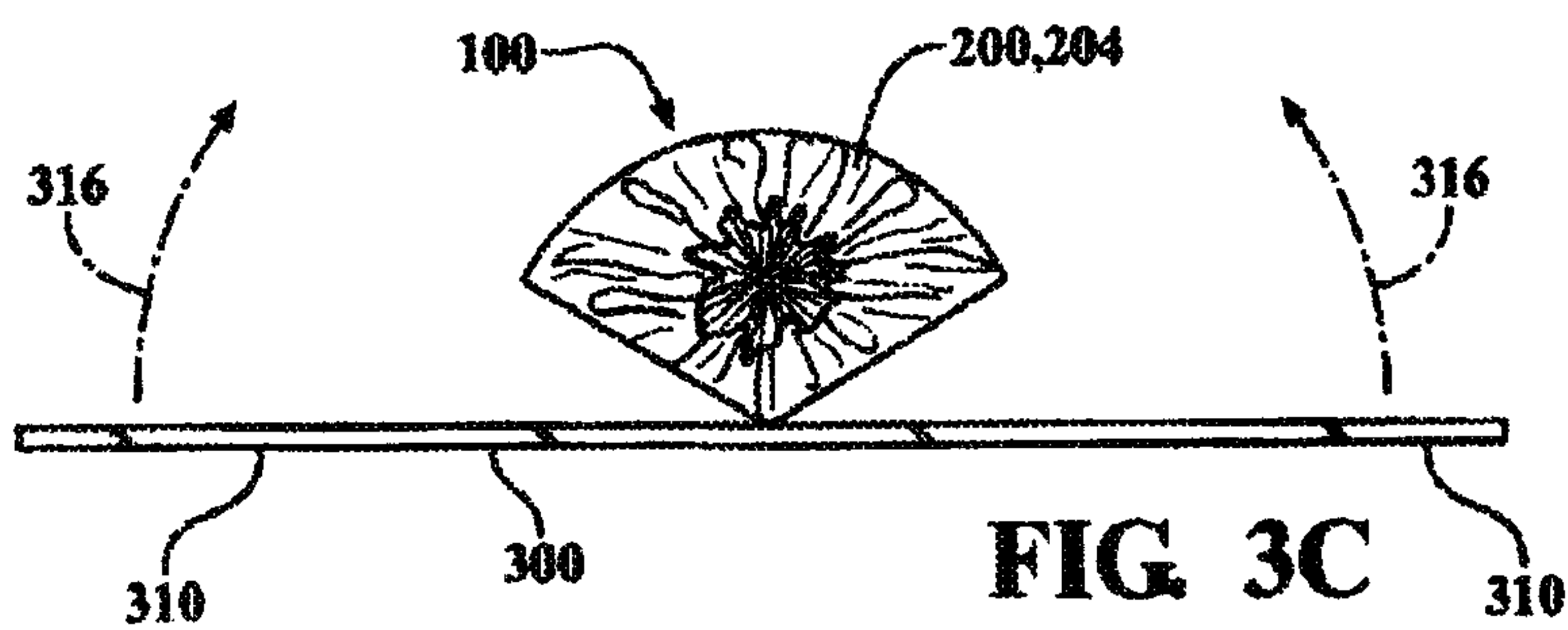
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**FIG. 2A**

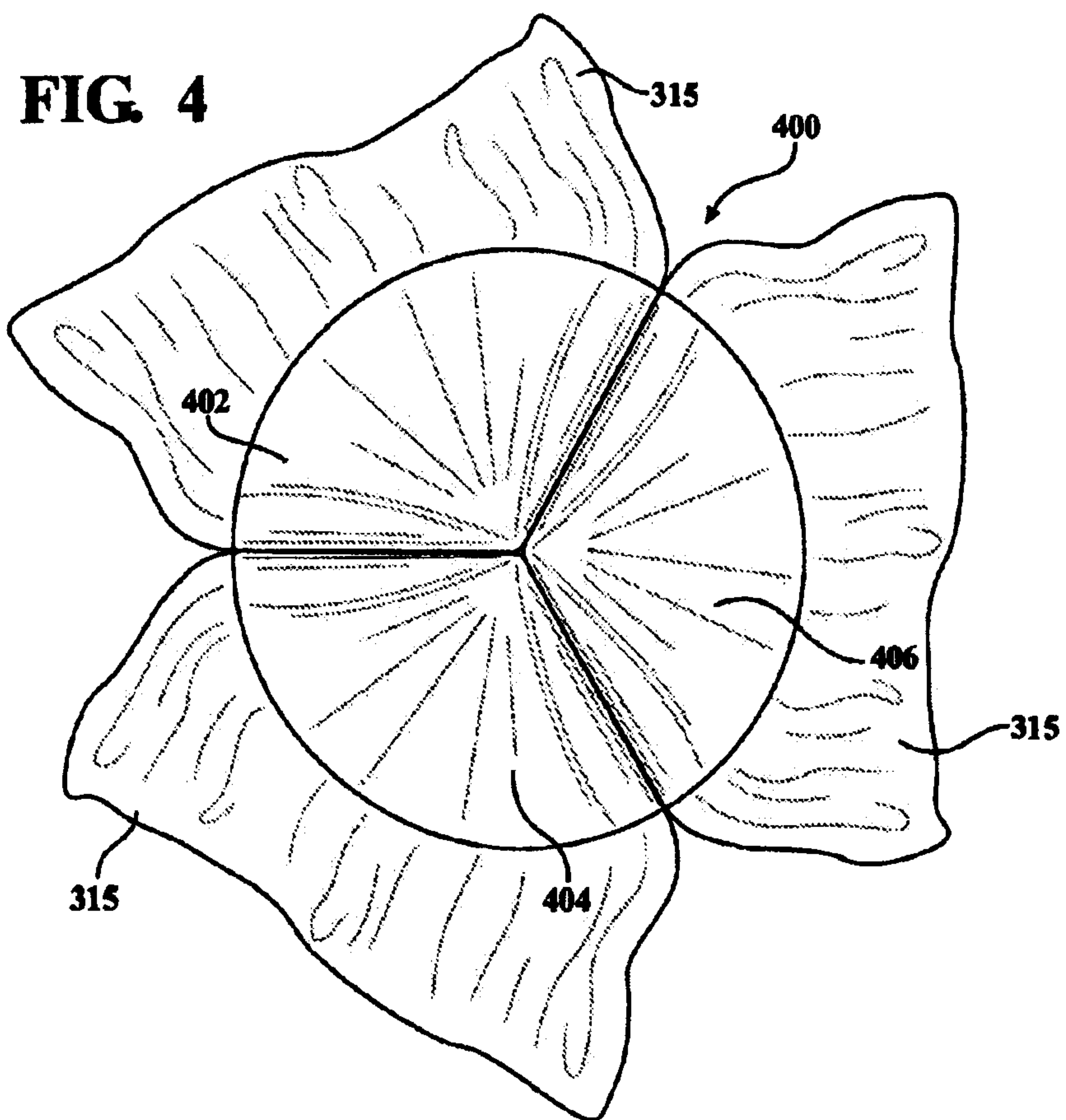
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**FIG. 2B**

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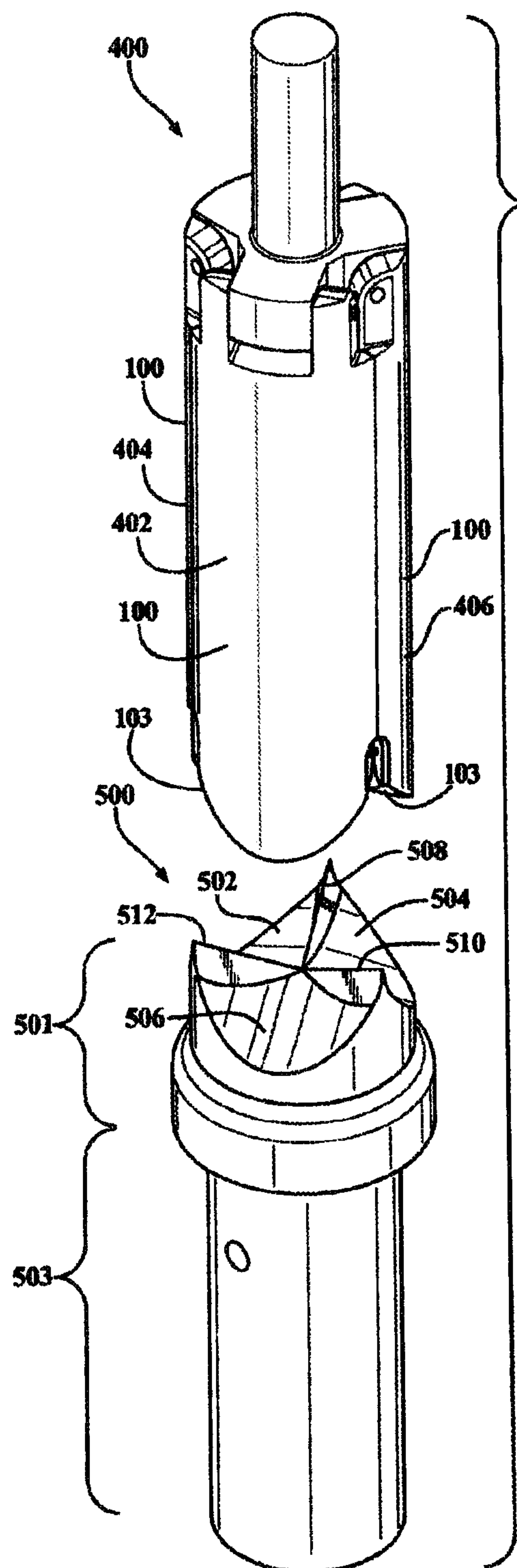


FIG. 5A

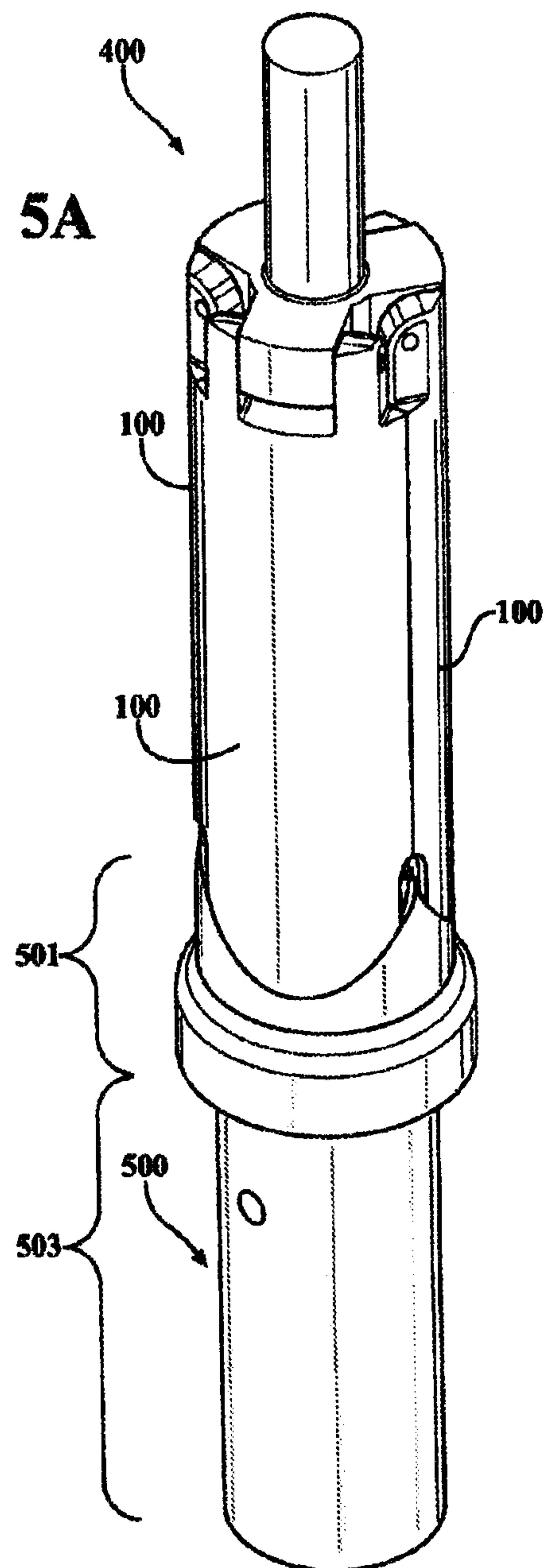
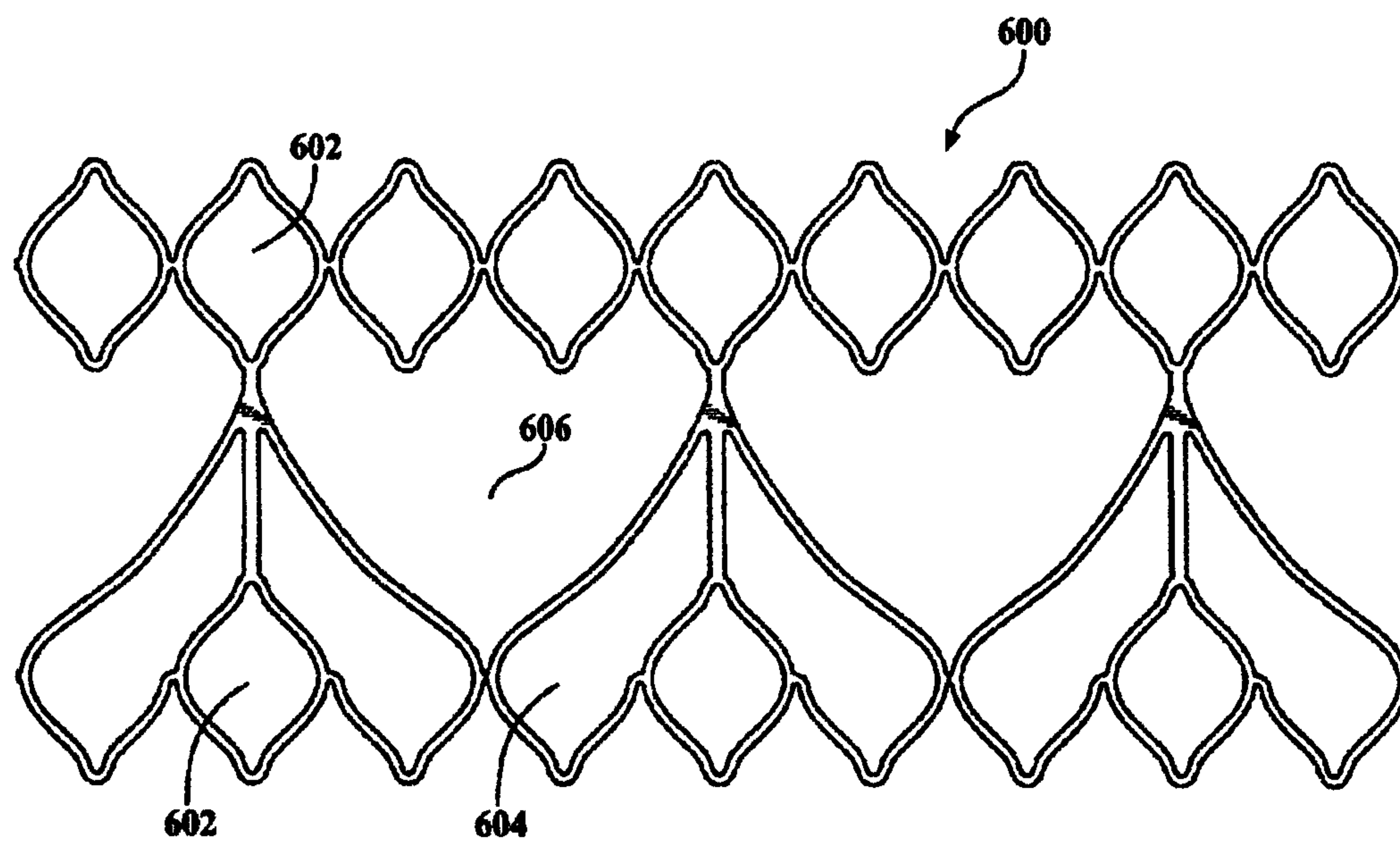
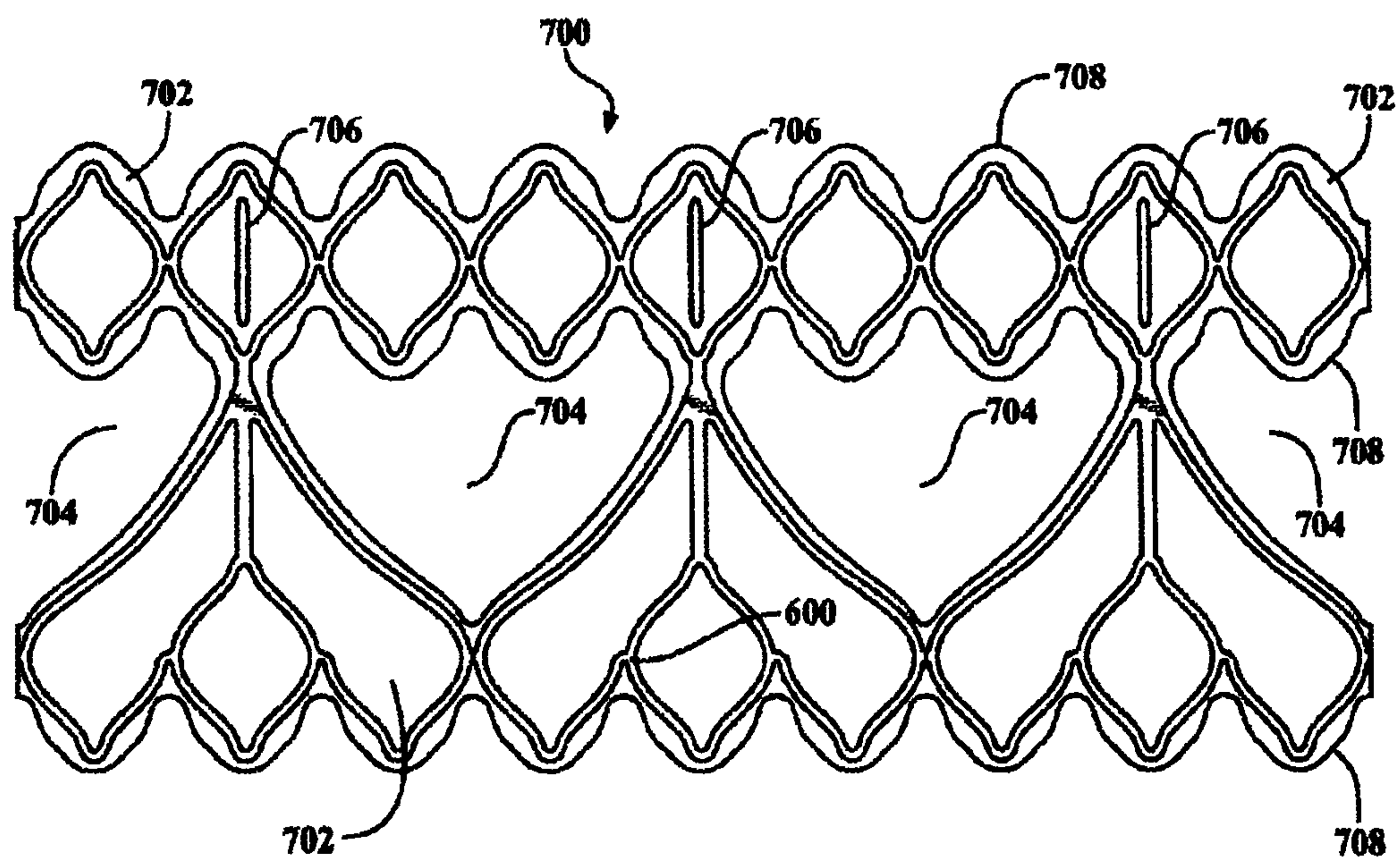
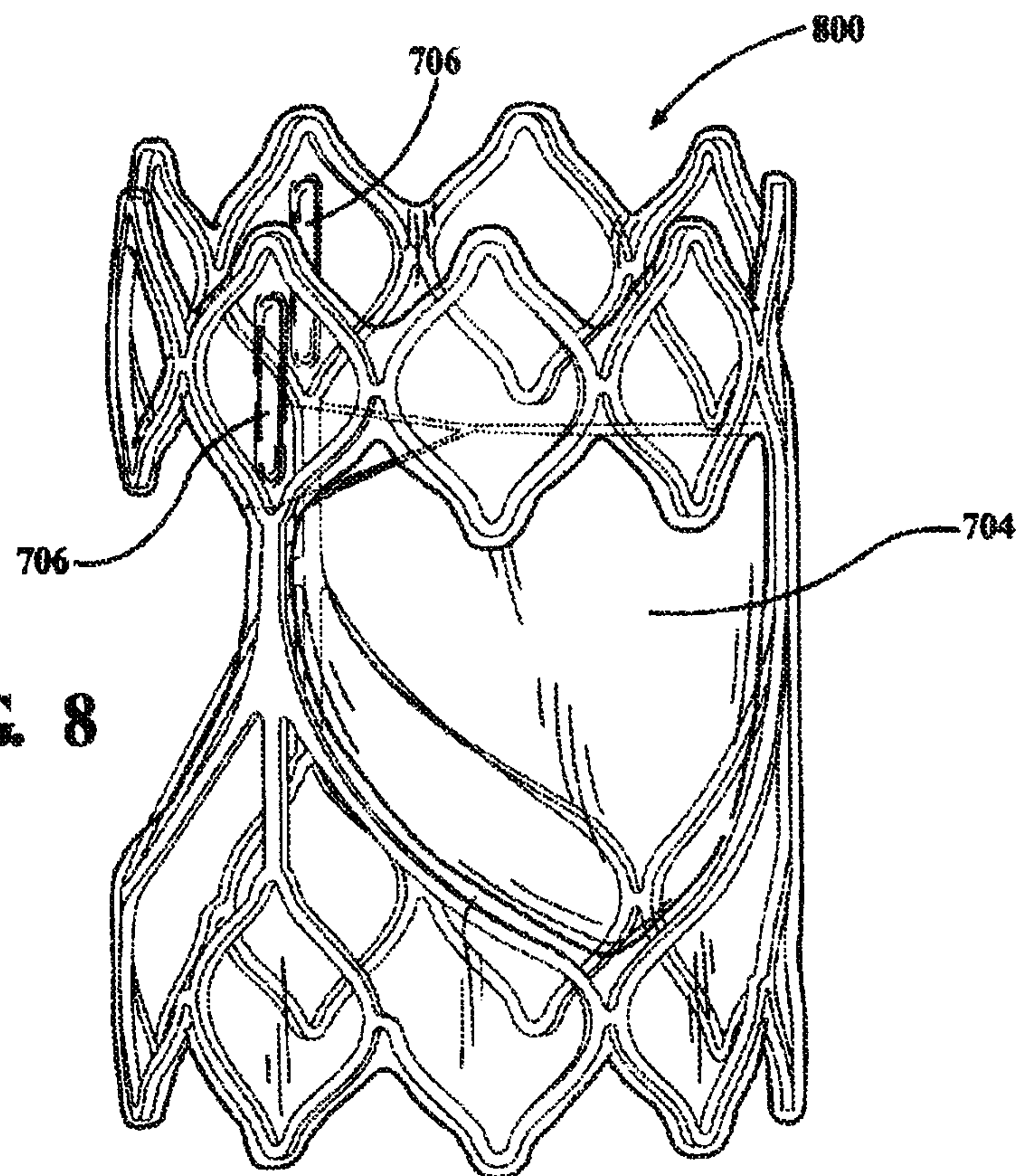


FIG. 5B

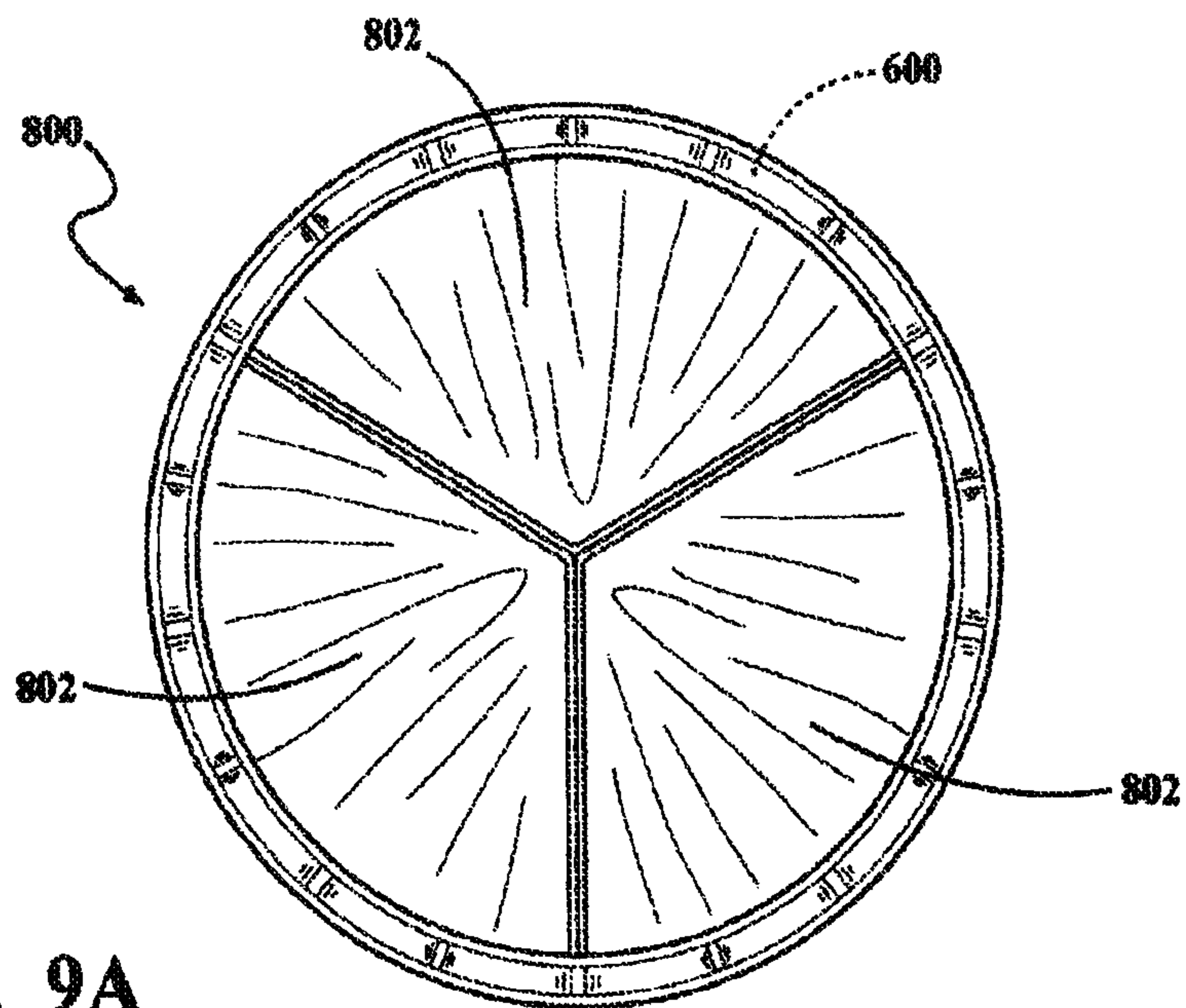
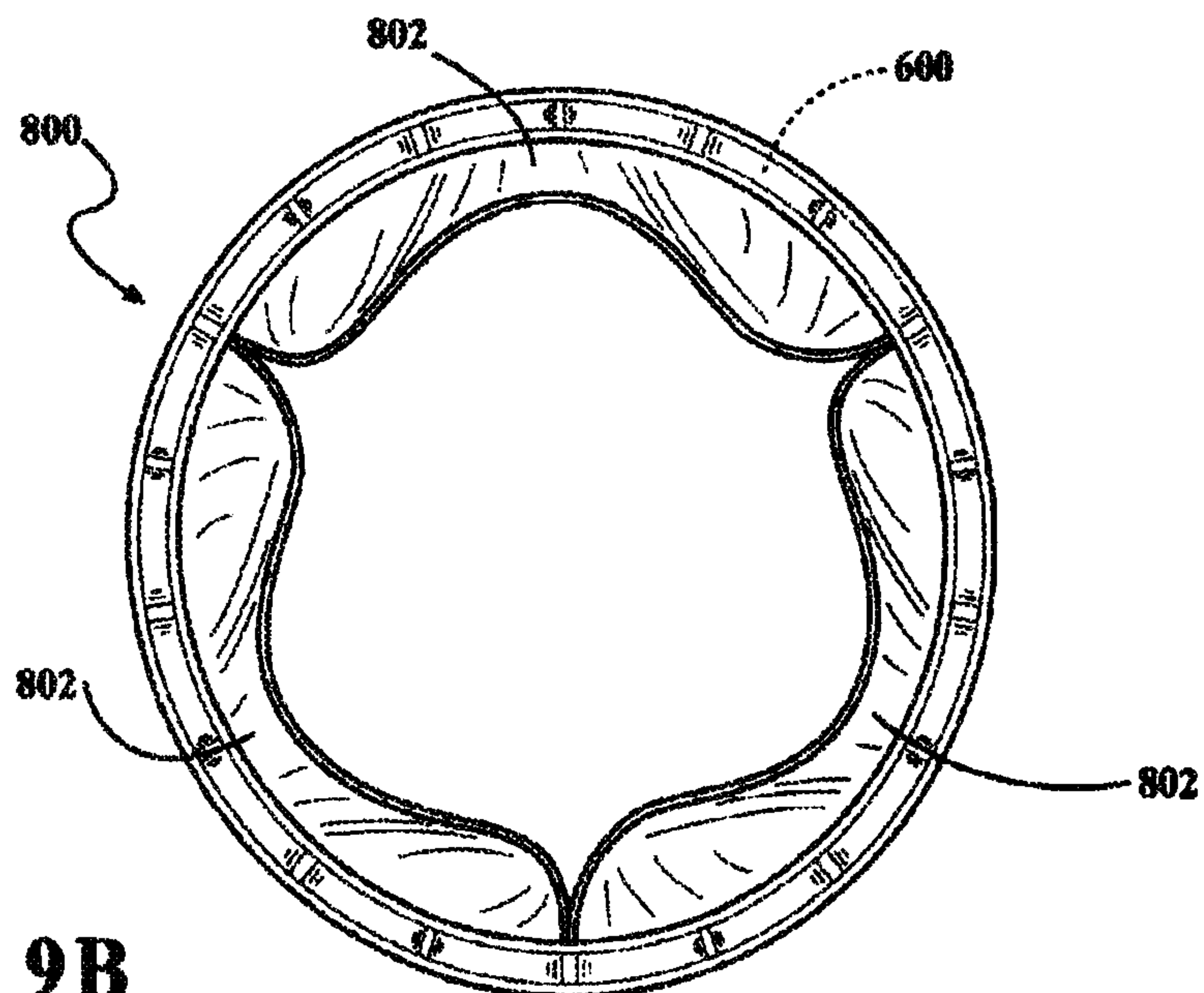
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**FIG. 6A****FIG. 6B**

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**FIG. 9A****FIG. 9B**

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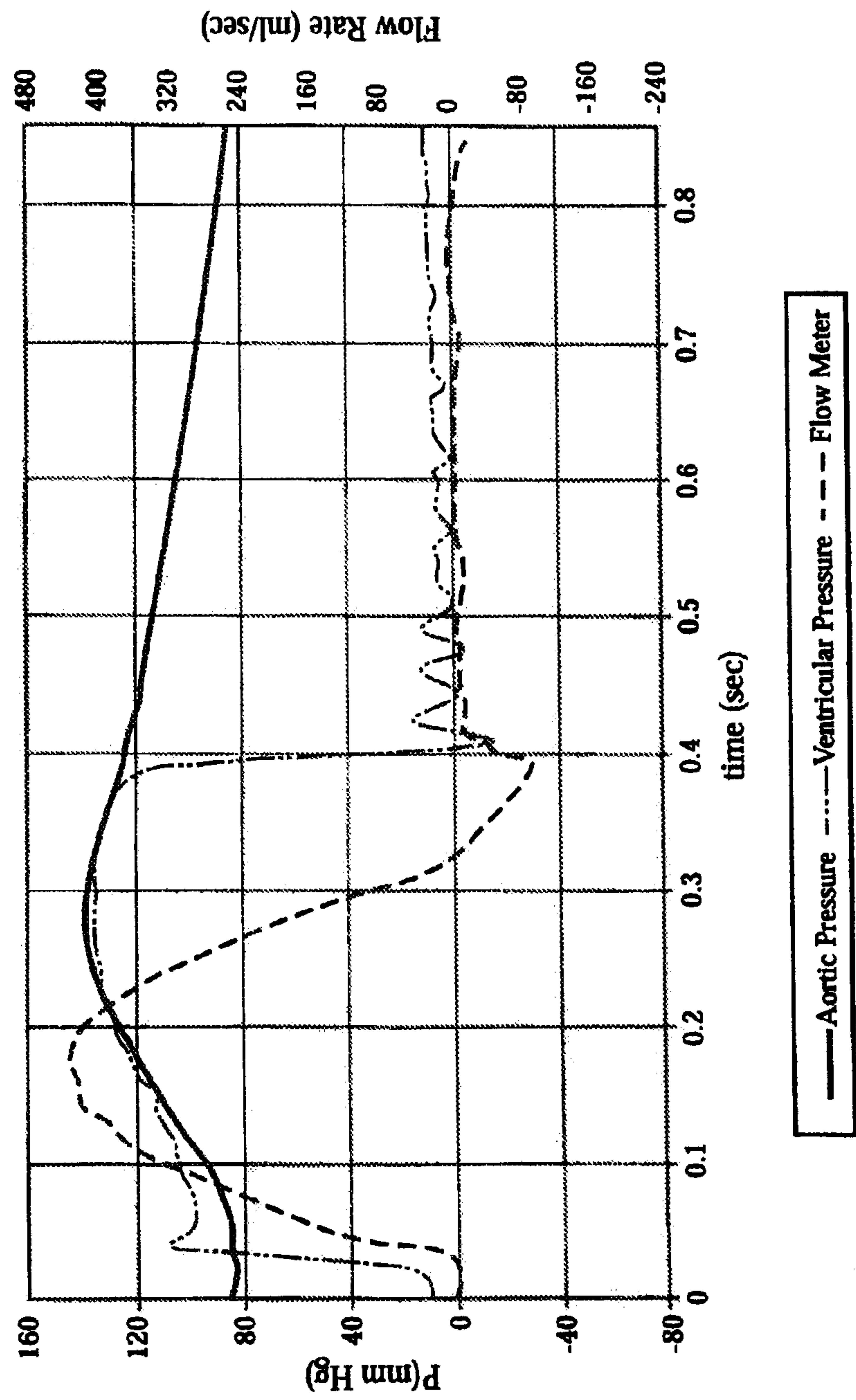


FIG. 10

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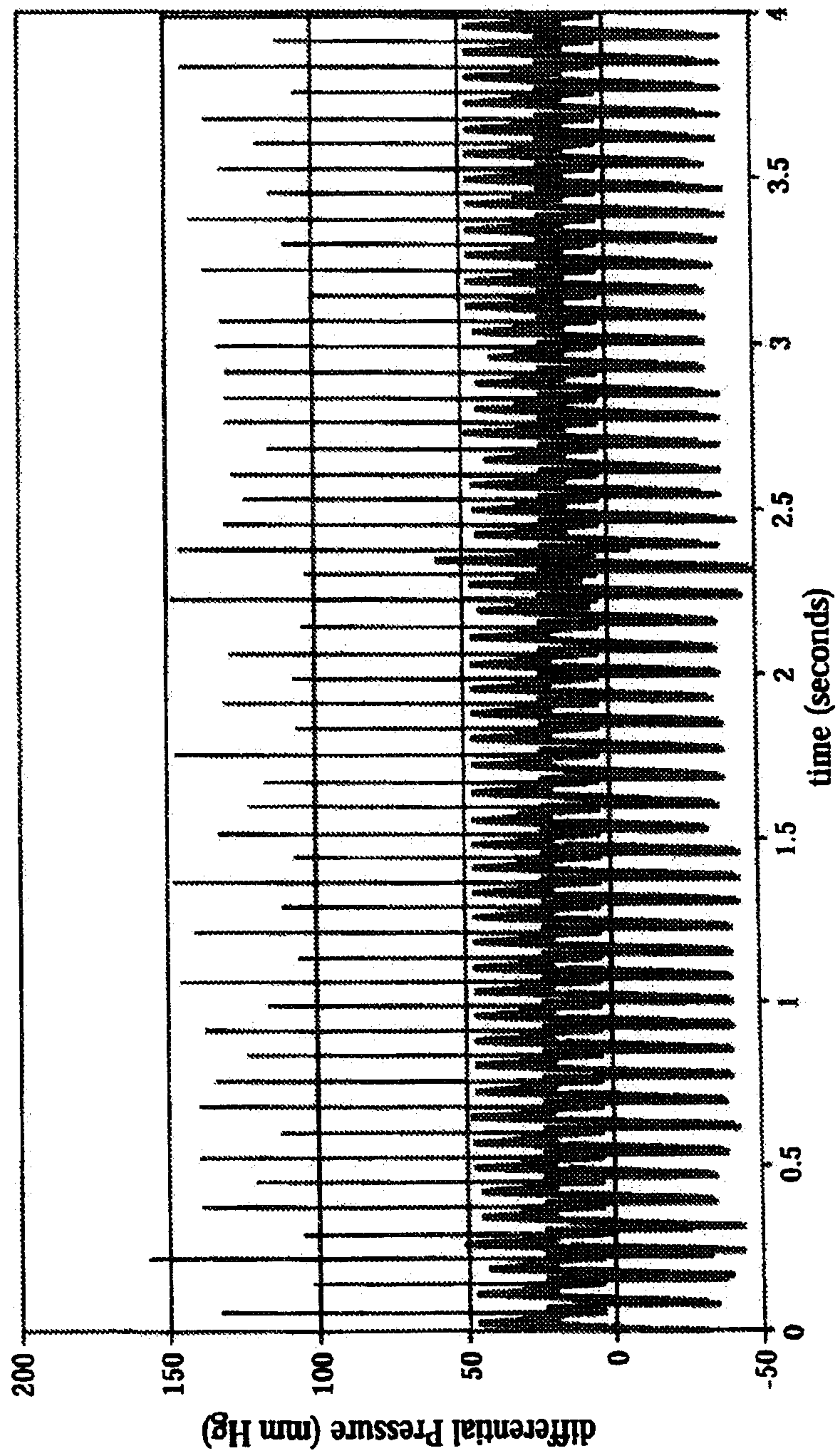
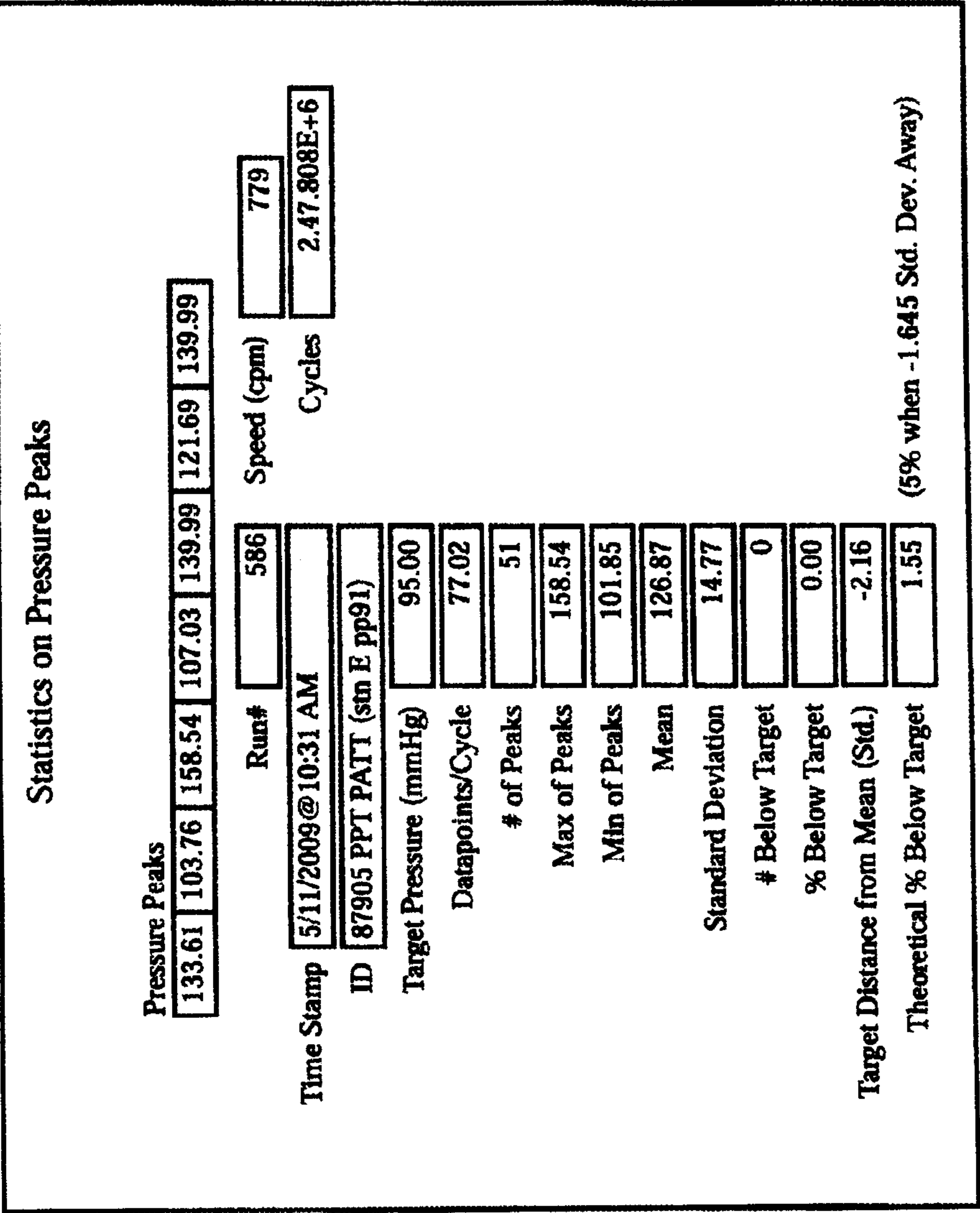
**FIG. 11A**

FIG 11B



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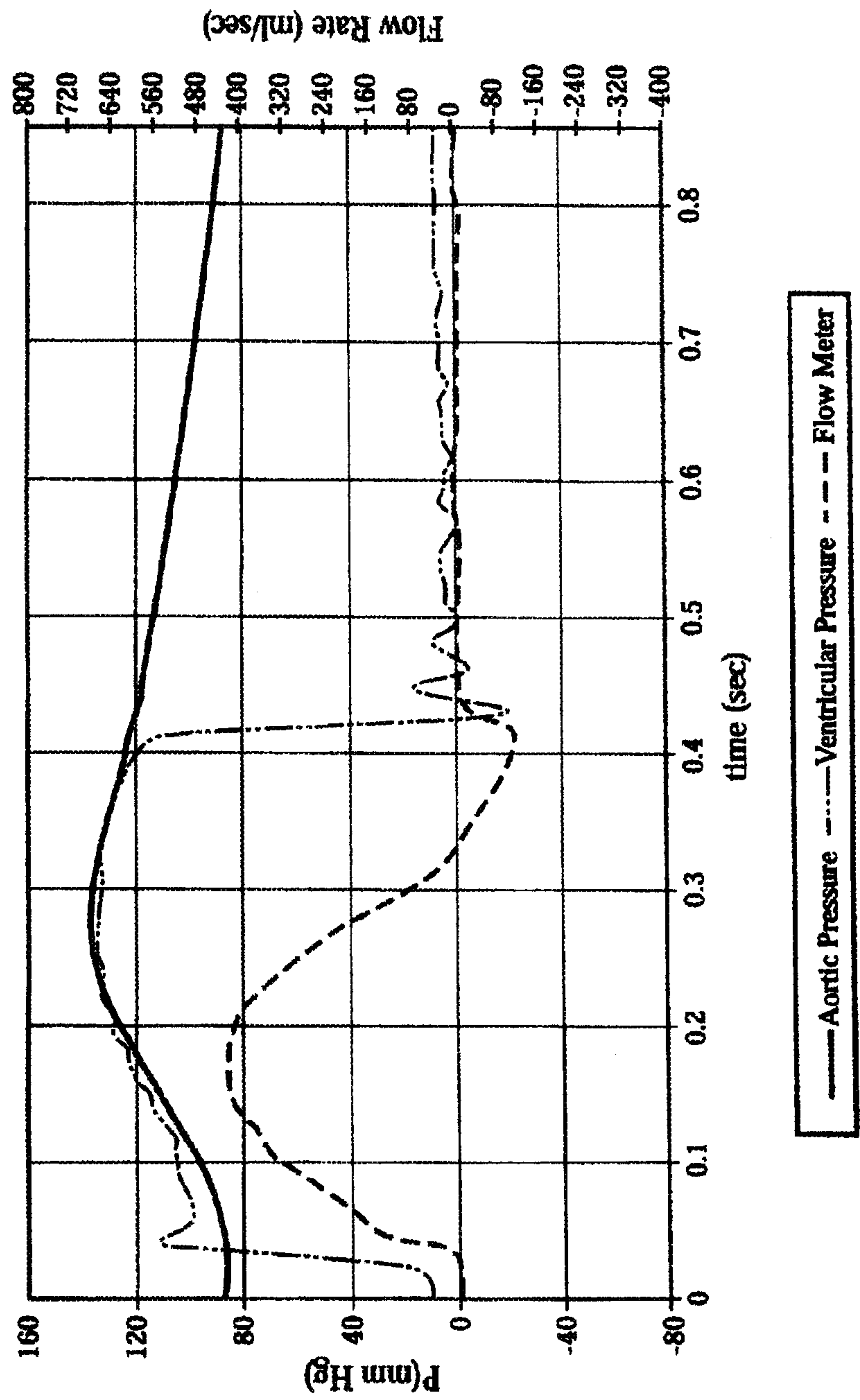


FIG. 12A

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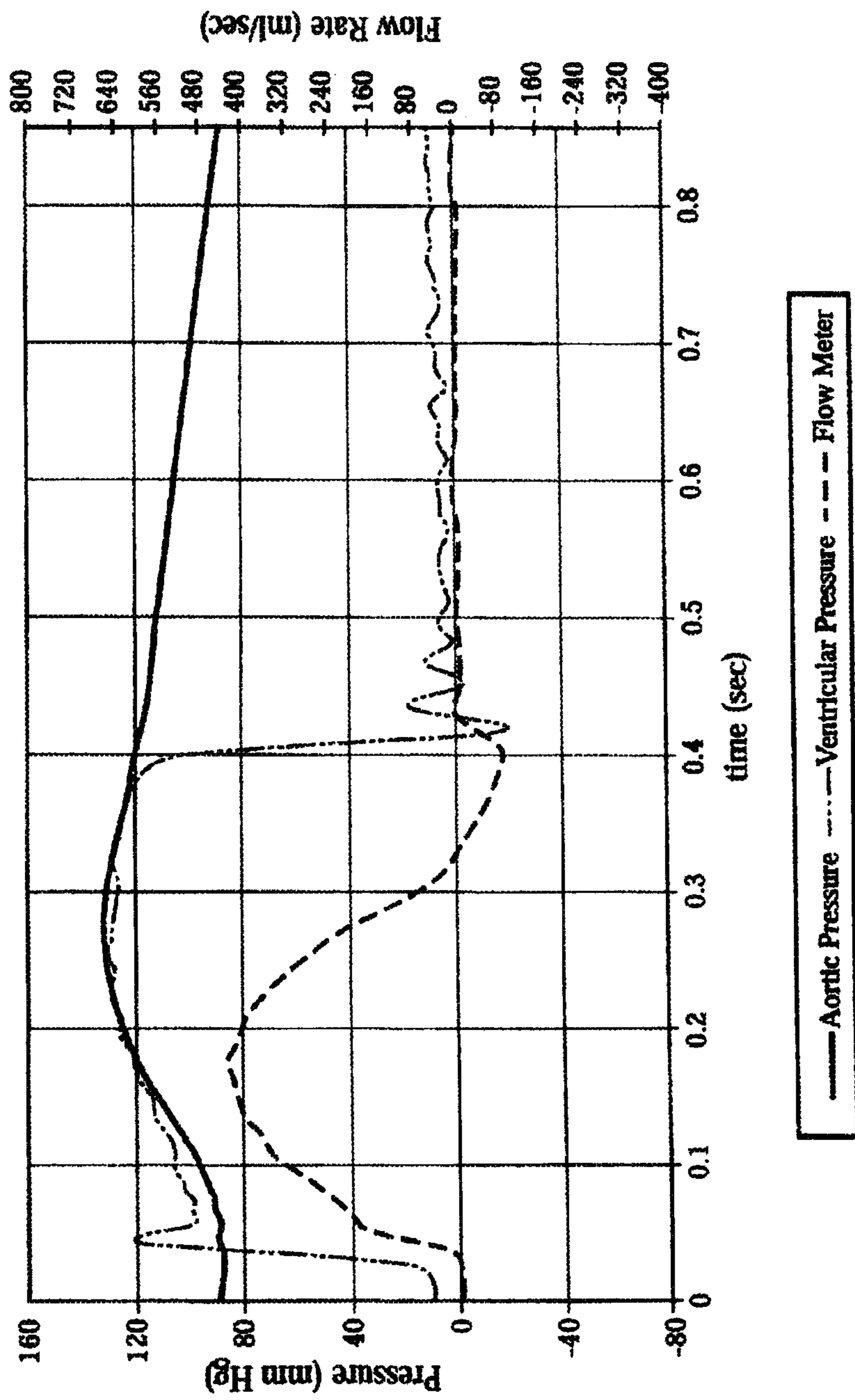


FIG. 12B

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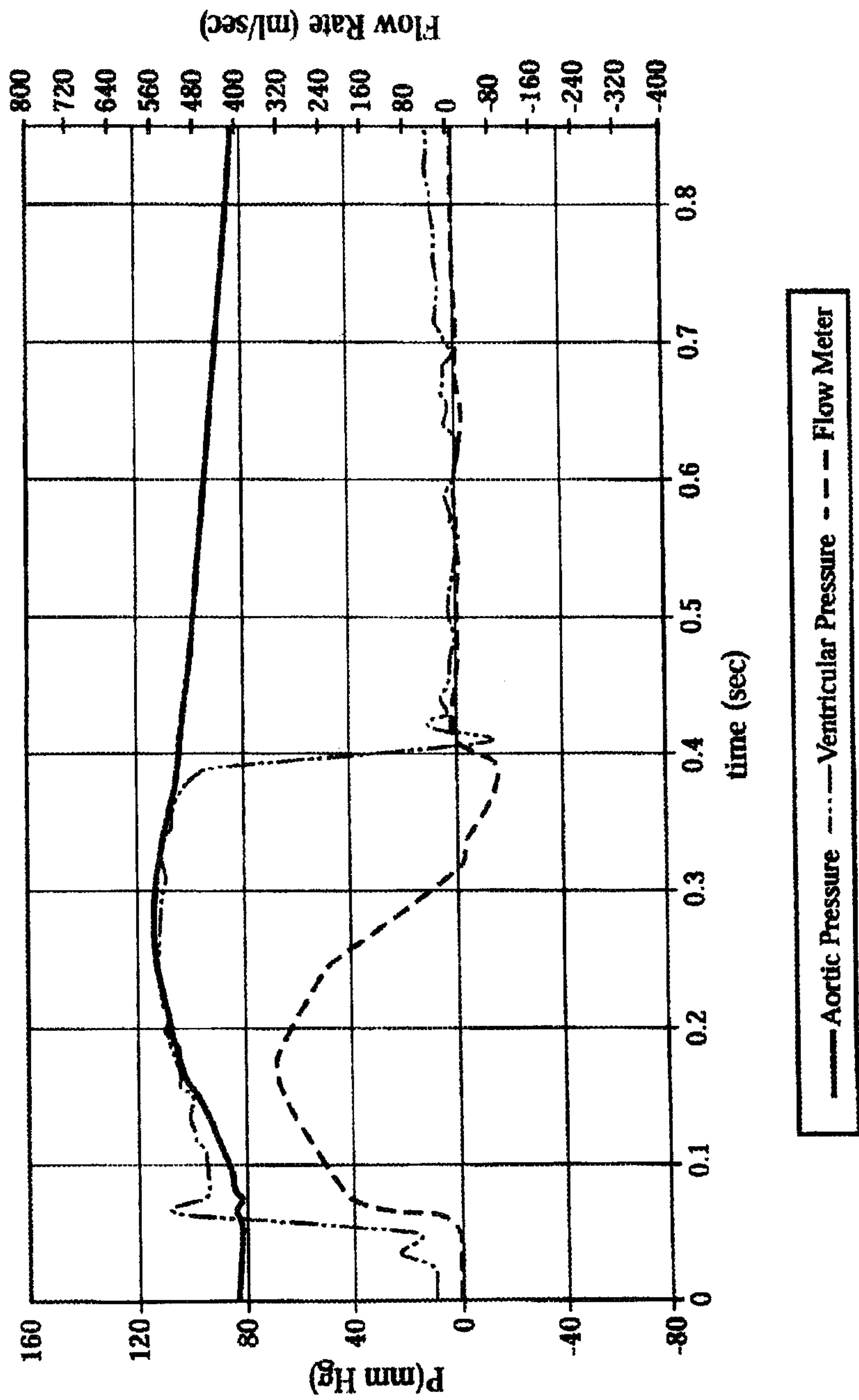


FIG. 13A

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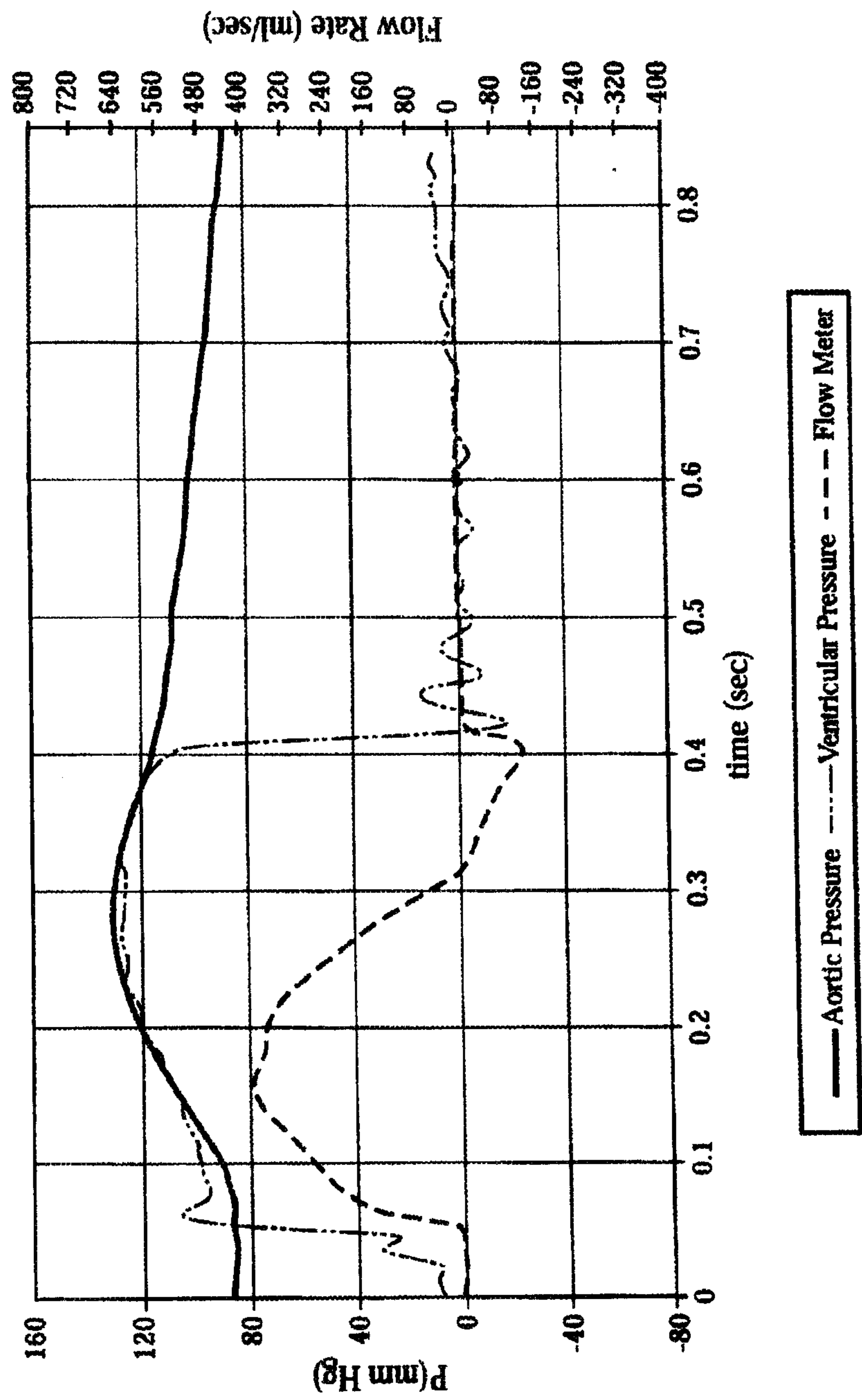
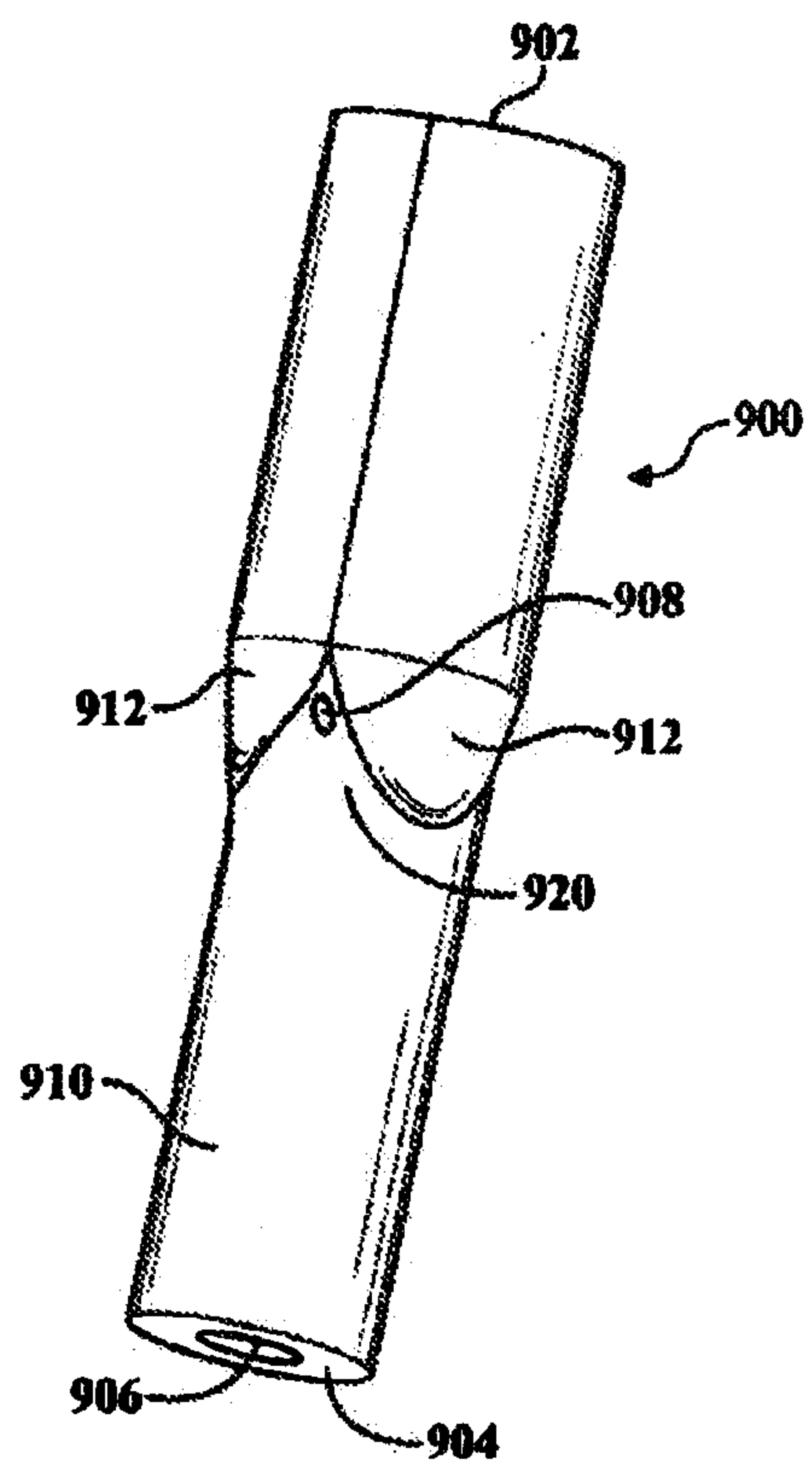
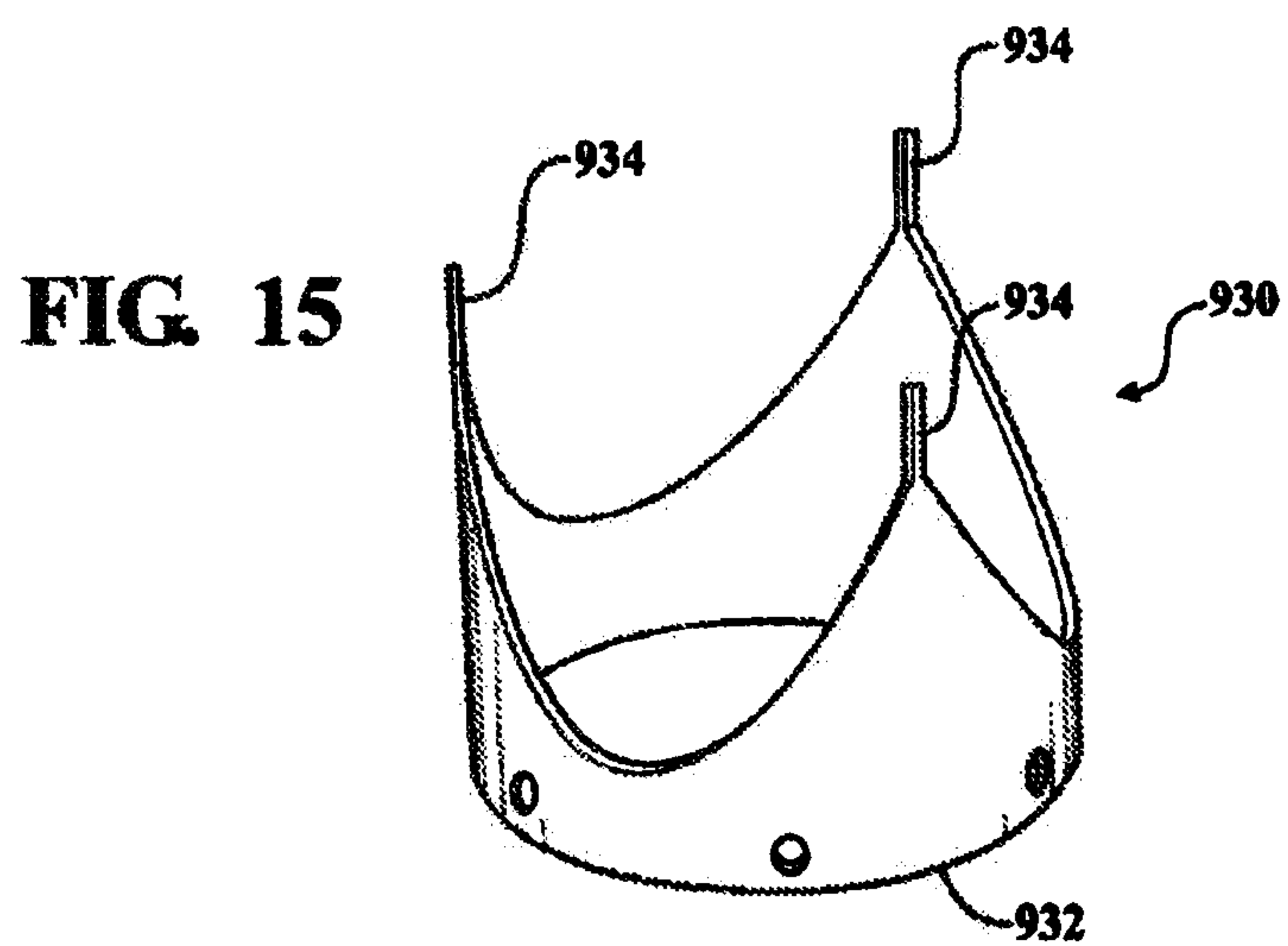
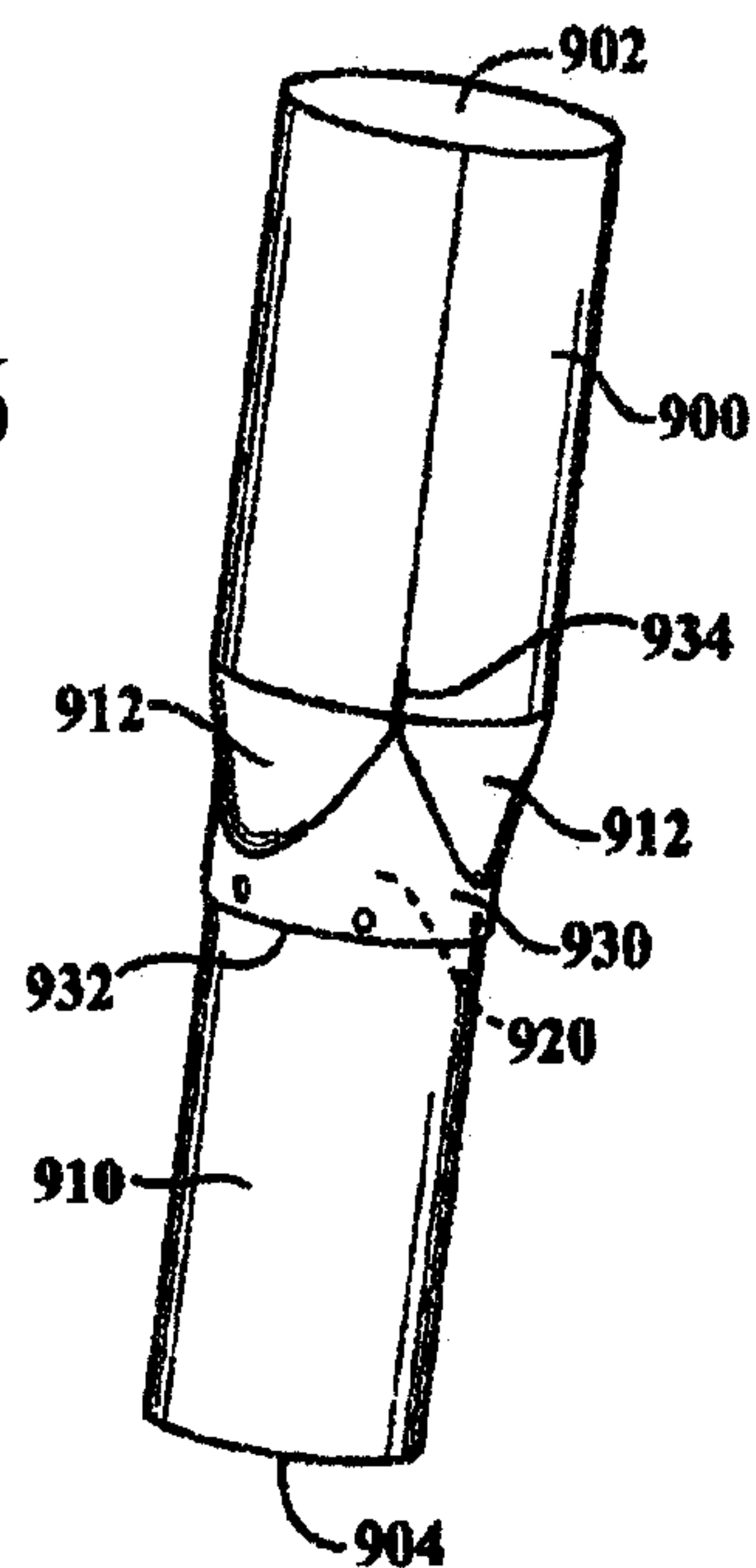
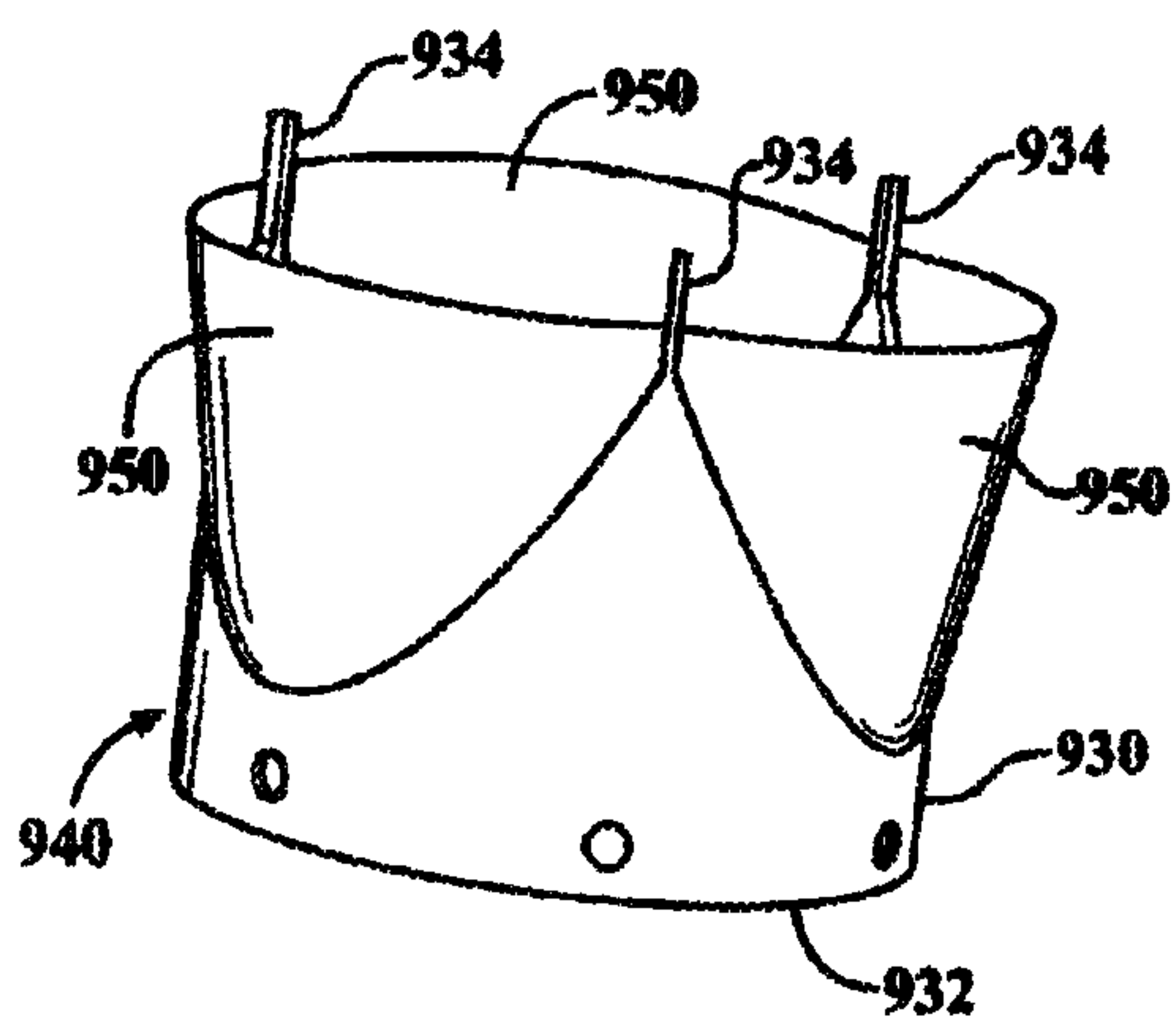
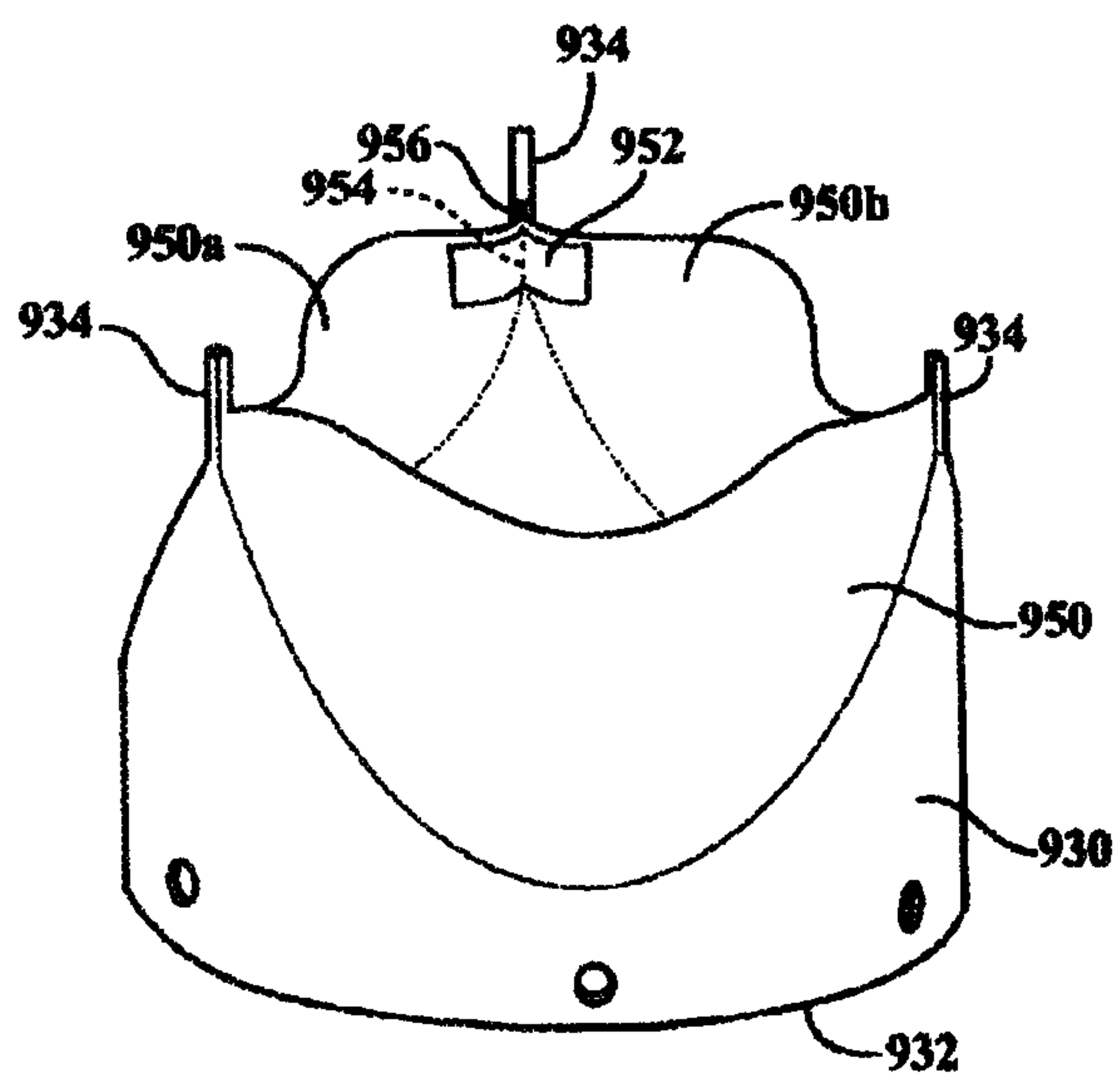


FIG. 13B

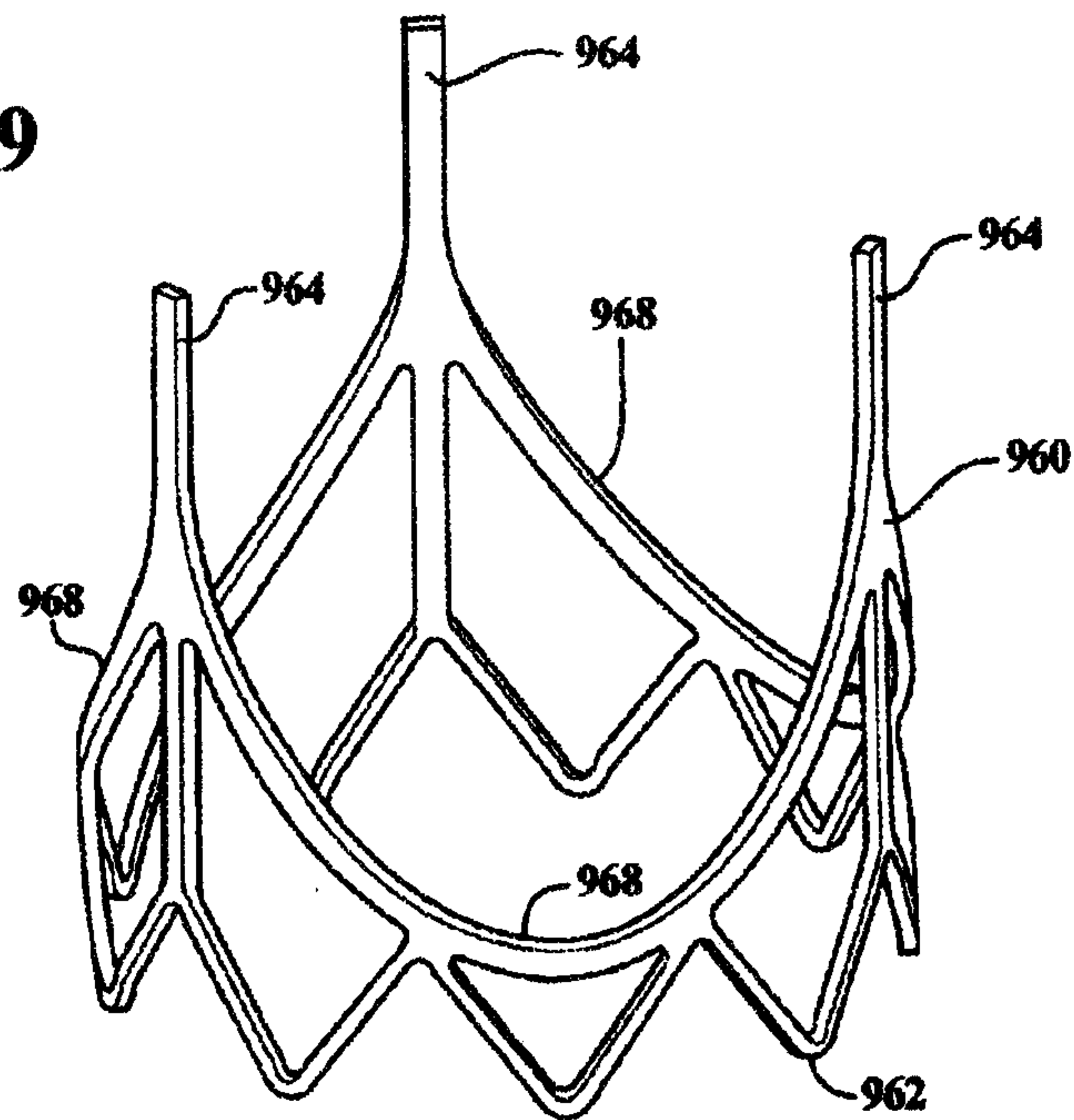
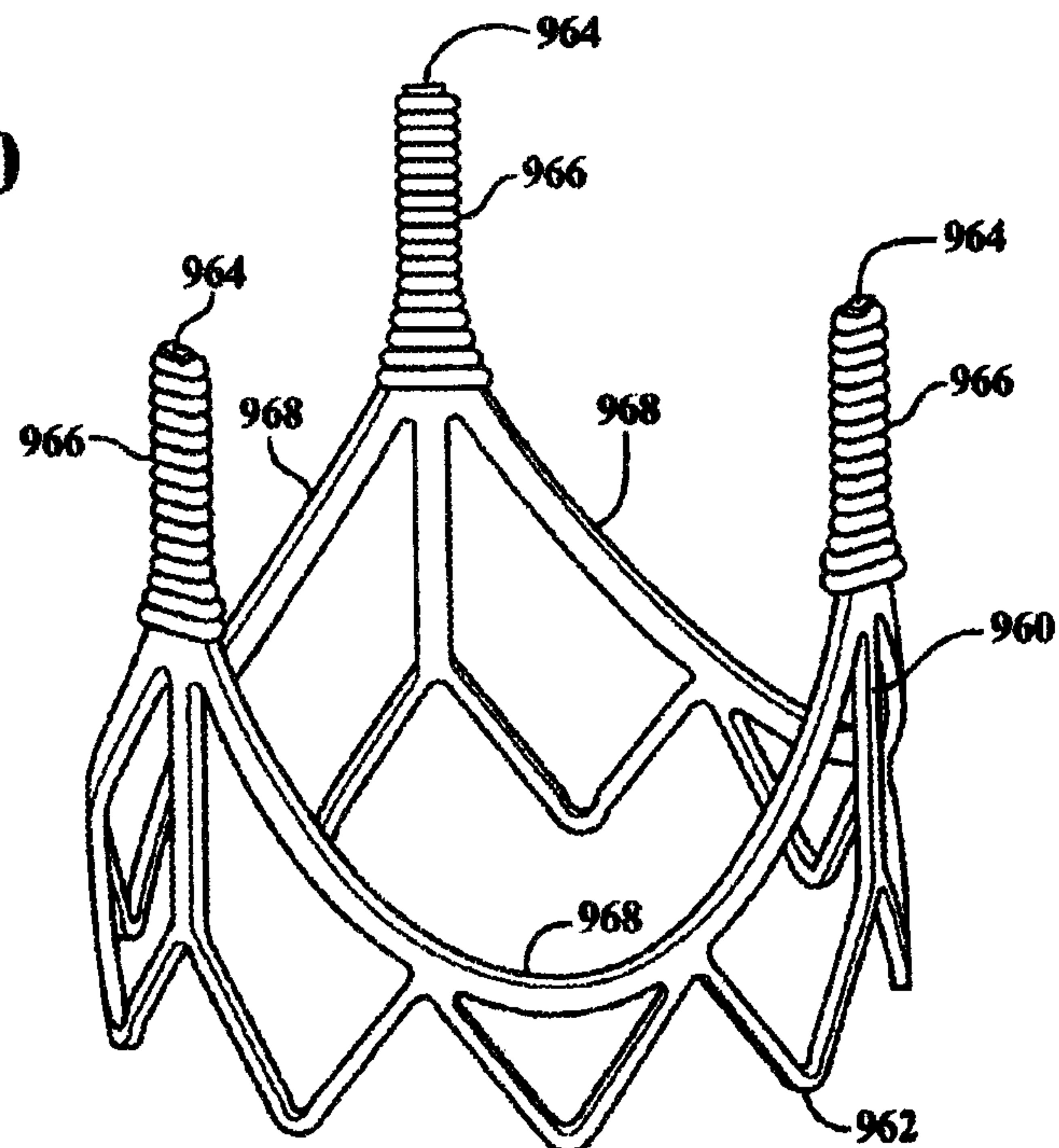
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**FIG. 14****FIG. 15**

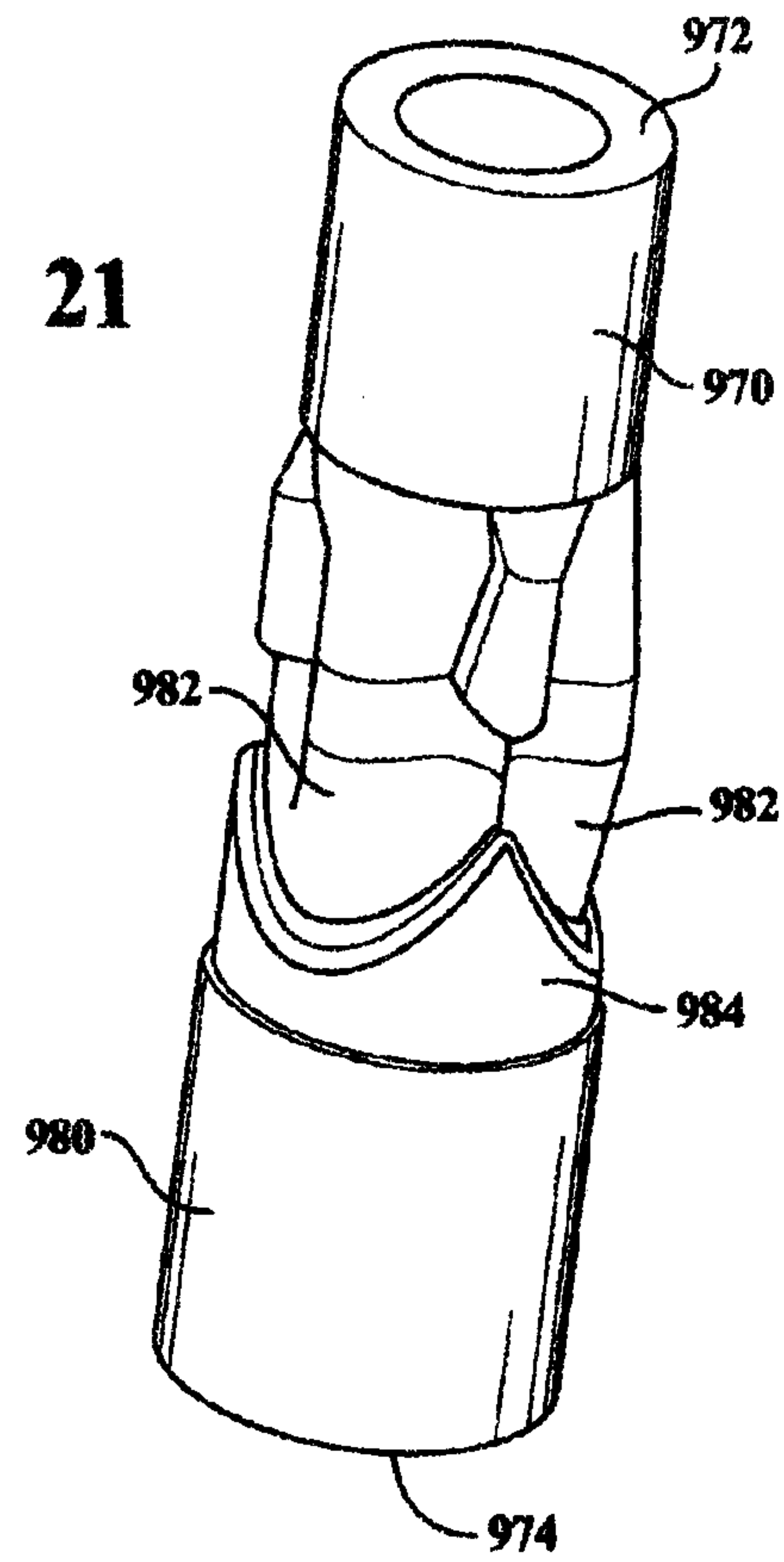
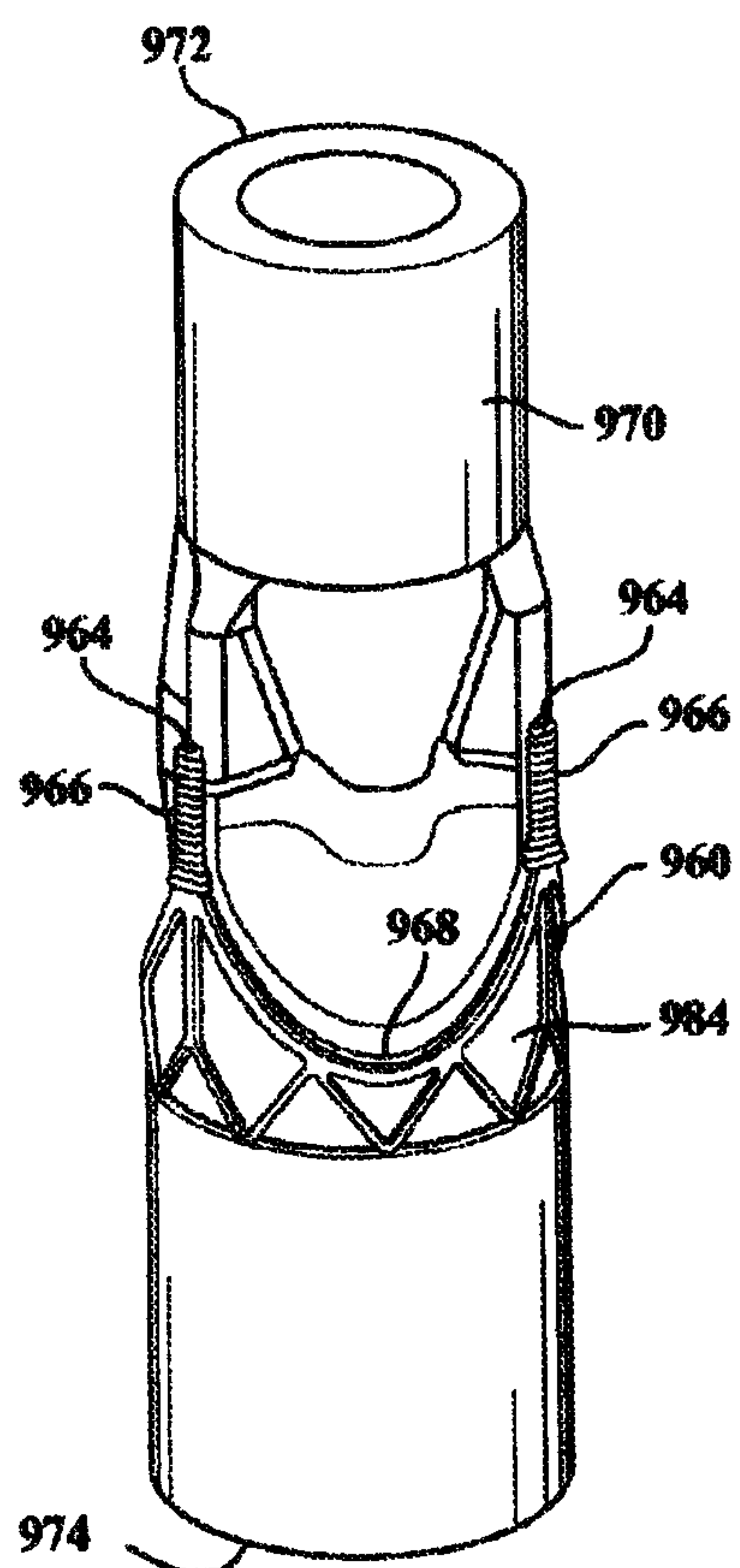
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FIG. 16**FIG. 17****FIG. 18**

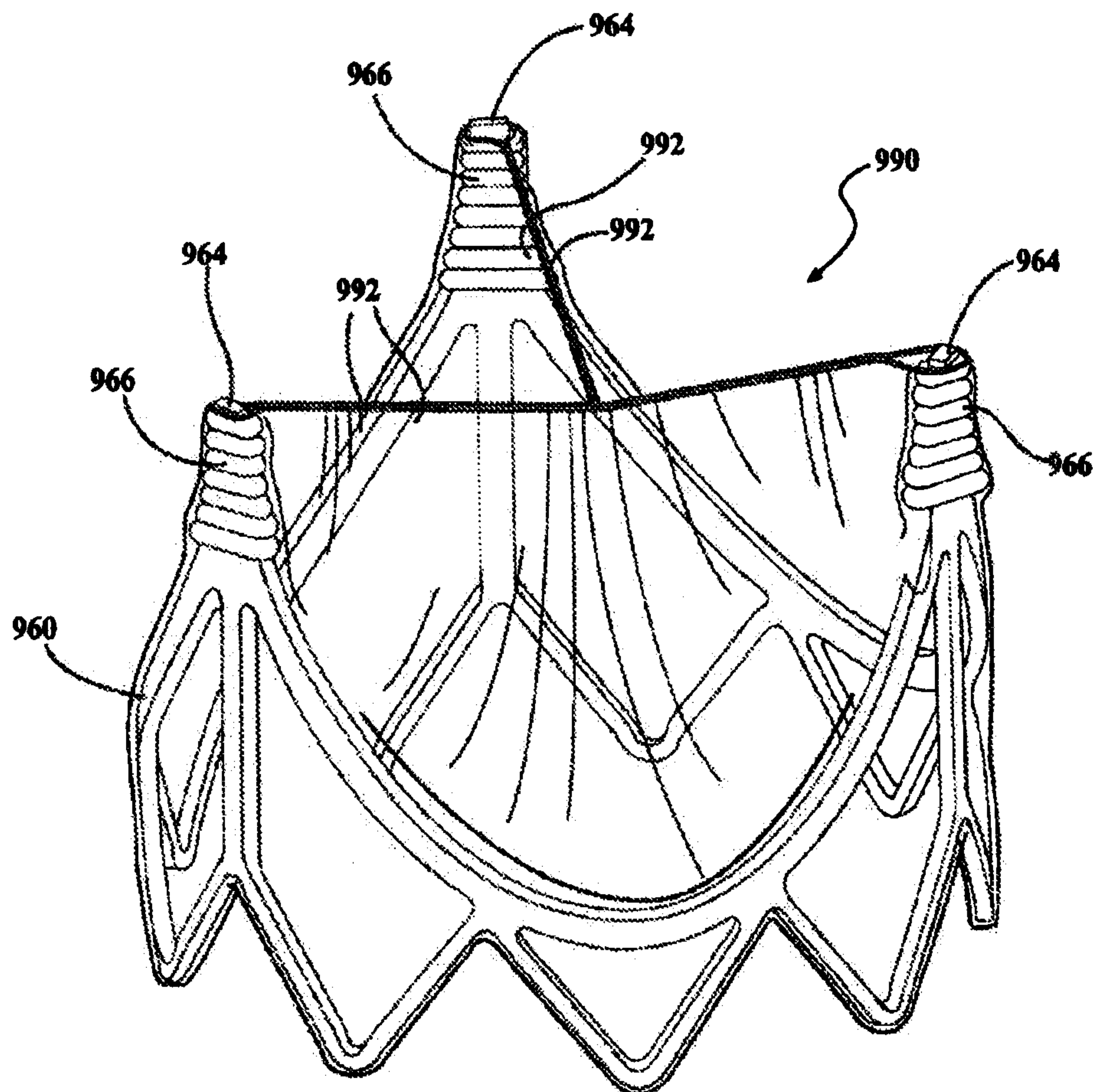
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FIG. 19**FIG. 20**

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FIG. 21**FIG. 22**

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**FIG. 23**

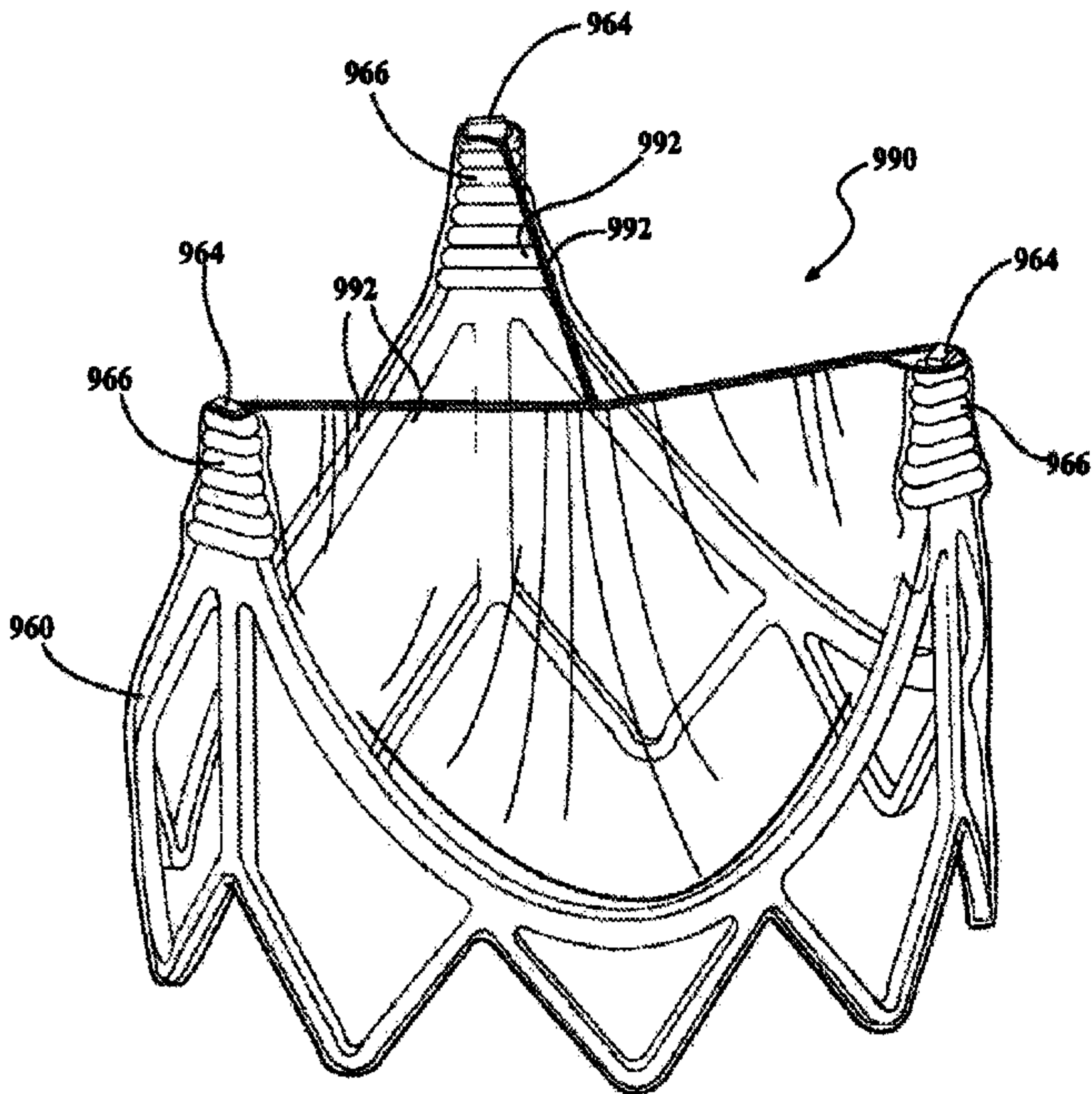


FIG. 23