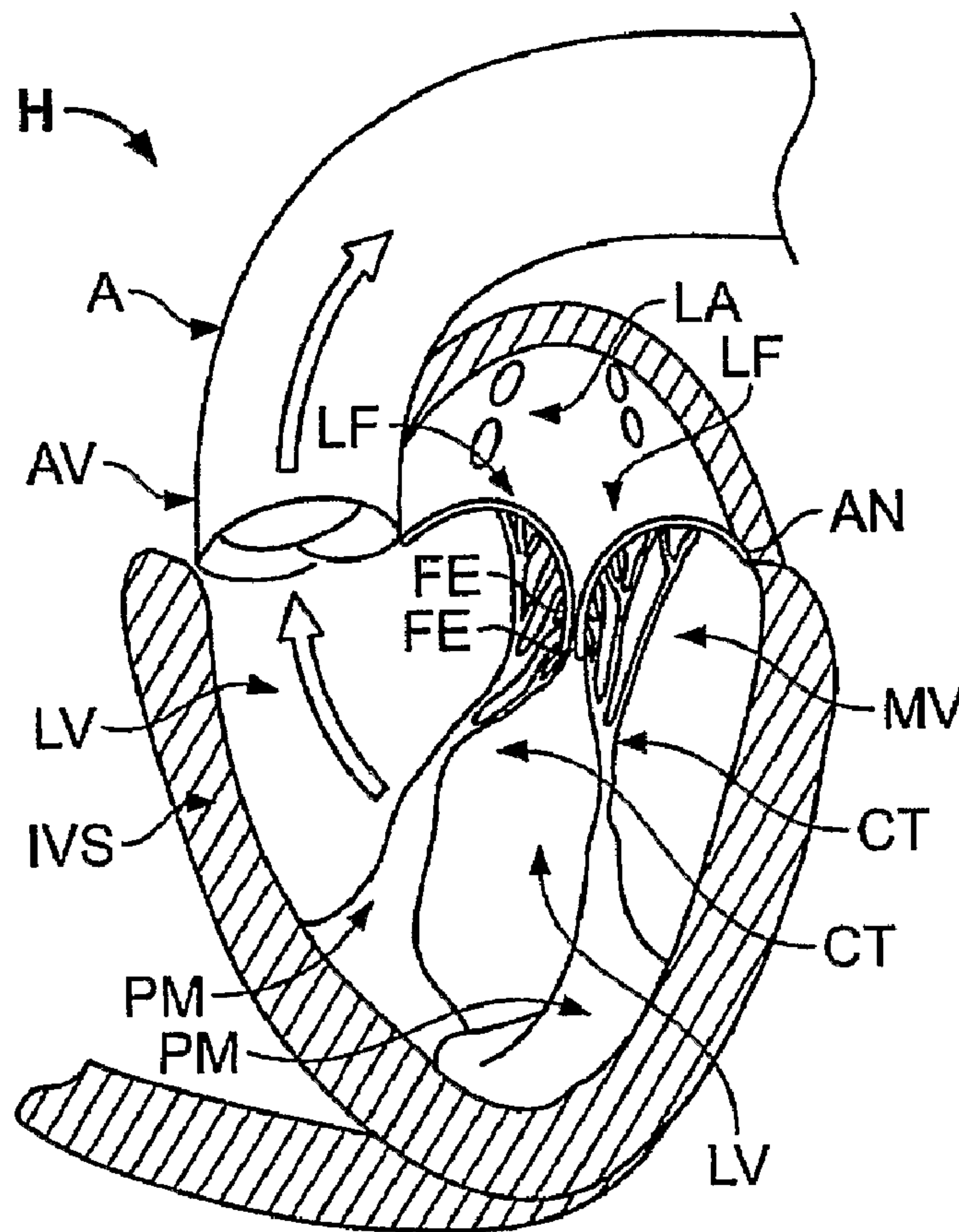




(86) Date de dépôt PCT/PCT Filing Date: 2006/02/07
 (87) Date publication PCT/PCT Publication Date: 2006/08/17
 (45) Date de délivrance/Issue Date: 2014/04/15
 (85) Entrée phase nationale/National Entry: 2007/08/07
 (86) N° demande PCT/PCT Application No.: US 2006/004368
 (87) N° publication PCT/PCT Publication No.: 2006/086434
 (30) Priorités/Priorities: 2005/02/07 (US60/650,918);
 2005/06/21 (US60/692,802)

(51) Cl.Int./Int.Cl. *A61F 2/24* (2006.01),
A61B 17/04 (2006.01)
 (72) Inventeurs/Inventors:
 POWELL, FEROLYN T., US;
 THORNTON, TROY L., US;
 GOLDFARB, ERIC A., US;
 KOMTEBEDDE, JAN, US;
 DELL, KENT D., US;
 LUCATERO, PEDRO B., US;
 VALENCIA, FRANCISCO J., US;
 ...
 (73) Propriétaire/Owner:
 EVALVE, INC., US
 (74) Agent: SMART & BIGGAR

(54) Titre : PROCÉDES, SYSTEMES ET DISPOSITIFS POUR REPARER UNE VALVULE CARDIAQUE
 (54) Title: METHODS, SYSTEMS AND DEVICES FOR CARDIAC VALVE REPAIR



(57) Abrégé/Abstract:

Disclosed are methods, systems, and devices for the endovascular repair of cardiac valves, particularly the atrioventricular valves which inhibit back flow of blood from a heart ventricle during contraction. The procedures described herein can be performed with



(72) **Inventeurs(suite)/Inventors(continued)**: SRINIVASAN, MURLI, US; GOODGION, ROGER A., US; SAENZ, SANDRA, US; FAN, SYLVIA WENCHIN, US; LUCATERO, SYLVESTER B., US; LIAO, YEN C., US; MADDEN, JOHN P., US; SARABIA, JAIME E., US

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

interventional tools, guides and supporting catheters and other equipment introduced to the heart chambers from the patient's arterial or venous vasculature remote from the heart. The interventional tools and other equipment may be introduced percutaneously or may be introduced via a surgical cut down, and then advanced from the remote access site through the vasculature until they reach the heart.

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

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
17 August 2006 (17.08.2006)

PCT

(10) International Publication Number
WO 2006/086434 A1

(51) International Patent Classification:

A61F 2/24 (2006.01)

(21) International Application Number:

PCT/US2006/004368

(22) International Filing Date: 7 February 2006 (07.02.2006)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/650,918 7 February 2005 (07.02.2005) US
60/692,802 21 June 2005 (21.06.2005) US(71) Applicant (for all designated States except US): **EVALVE, INC.** [US/US]; 4045 Campbell Avenue, Menlo Park, California 94025 (US).

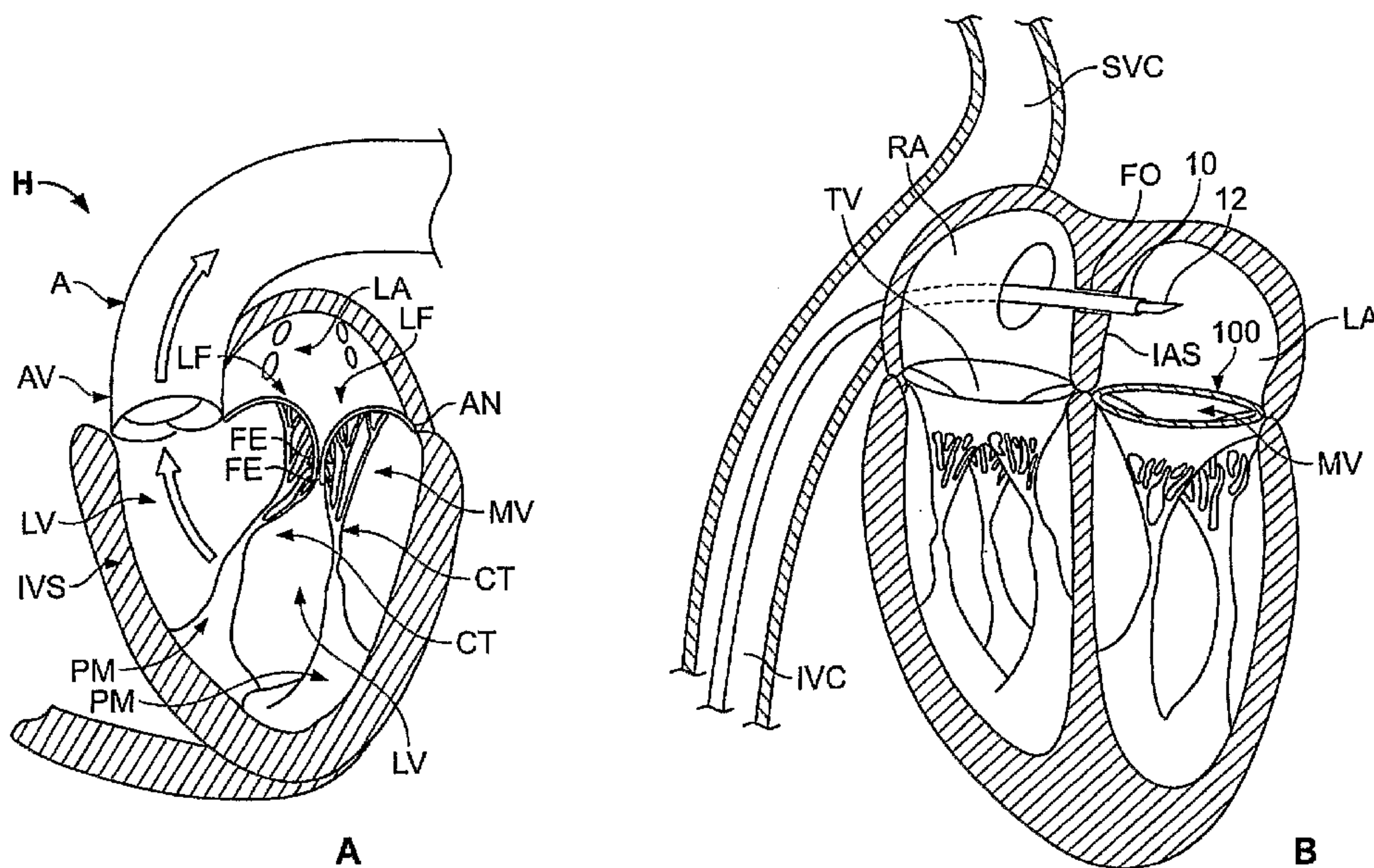
(72) Inventors; and

(75) Inventors/Applicants (for US only): **POWELL, Ferolyn, T.** [US/US]; 55 Caselli Avenue, San Francisco, California 94114 (US). **THORNTON, Troy, L.** [US/US]; 743 Carolina Street, San Francisco, California 941007 (US). **GOLDFARB, Eric, A.** [US/US]; 140 Jersey Street, San Francisco, California 94114 (US). **KOMTEBEDDE,****Jan** [US/US]; 23360 Deerfield Road, Los Gatos, California 95033 (US). **DELL, Kent, D.** [US/US]; 1131 Grand Avenue, Redwood City, California 94061 (US). **LUCATERO, Pedro, B.** [US/US]; 501 Runnymede Street, East Palo Alto, California 94303 (US). **VALENCIA, Francisco, J.** [US/US]; #14, 417 Harrison Avenue, Redwood City, California 94062 (US). **SRINIVASAN, Murli** [US/US]; 40940 Cascado Place, Fremont, California 94539 (US). **GOODGION, Roger, A.** [US/US]; 340 Ritch Street, #6, San Francisco, California 94107 (US). **SAENZ, Sandra** [US/US]; 1530 38th Avenue, Seattle, Washington 98122 (US). **FAN, Sylvia, Wenchin** [US/US]; 1336 Capuchino Avenue, Burlingame, California 94010 (US). **LUCATERO, Sylvester, B.** [US/US]; 501 Runnymede Street, East Palo Alto, California 94303 (US). **LIAO, Yen, C.** [US/US]; 27 11th Avenue, San Mateo, California 94401 (US). **MADDEN, John, P.** [US/US]; 3636 Jefferson Avenue, Redwood City, California 94062 (US). **SARABIA, Jaime, E.** [US/US]; 1832 Cooper Lake Drive, Smyrna, GA 30080 (US).(74) Agent: **HERNANDEZ, Fred, C.**; 12390 El Camino Real, San Diego, California 92130 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

[Continued on next page]

(54) Title: METHODS, SYSTEMS AND DEVICES FOR CARDIAC VALVE REPAIR



(57) Abstract: Disclosed are methods, systems, and devices for the endovascular repair of cardiac valves, particularly the atrioventricular valves which inhibit back flow of blood from a heart ventricle during contraction. The procedures described herein can be performed with interventional tools, guides and supporting catheters and other equipment introduced to the heart chambers from the patient's arterial or venous vasculature remote from the heart. The interventional tools and other equipment may be introduced percutaneously or may be introduced via a surgical cut down, and then advanced from the remote access site through the vasculature until they reach the heart.

WO 2006/086434 A1

WO 2006/086434 A1

AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,

FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

METHODS, SYSTEMS AND DEVICES FOR CARDIAC VALVE REPAIR**BACKGROUND**

[0001] The present invention relates generally to medical methods, devices, and systems. In particular, the present invention relates to methods, devices, and systems for the endovascular or minimally invasive surgical repair of the atrioventricular valves of the heart, particularly the mitral valve.

[0002] Mitral valve regurgitation is characterized by retrograde flow from the left ventricle of a heart through an incompetent mitral valve into the left atrium. During a normal cycle of heart contraction (systole), the mitral valve acts as a check valve to prevent flow of oxygenated blood back into the left atrium. In this way, the oxygenated blood is pumped into the aorta through the aortic valve. Regurgitation of the valve can significantly decrease the pumping efficiency of the heart, placing the patient at risk of severe, progressive heart failure.

[0003] Mitral valve regurgitation can result from a number of different mechanical defects in the mitral valve. The valve leaflets, the valve chordae which connect the leaflets to the papillary muscles, or the papillary muscles themselves may be damaged or otherwise dysfunctional. Commonly, the valve annulus may be damaged, dilated, or weakened limiting the ability of the mitral valve to close adequately against the high pressures of the left ventricle. In some cases the mitral valve leaflets detach from the chordae tendinae, the structure that tethers them to the ventricular wall so that they are positioned to coapt or close against the other valve leaflet during systole. In this case, the leaflet "flails" or billows into the left atrium during systole instead of coopting or sealing against the neighboring leaflet

allowing blood from the ventricle to surge into the left atrium during systole. In addition, mitral valve disease can include functional mitral valve disease which is usually characterized by the failure of the mitral valve leaflets to coapt due to an enlarged ventricle, or other impediment to the leaflets rising up far enough toward each other to close the gap or seal against each other during systole.

[0004] The most common treatments for mitral valve regurgitation rely on valve replacement or strengthening of the valve annulus by implanting a mechanical support ring or other structure. The latter is generally referred to as valve annuloplasty. A recent technique for mitral valve repair which relies on suturing adjacent segments of the opposed valve leaflets together is referred to as the "bow-tie" or "edge-to-edge" technique. While all these techniques can be very effective, they usually rely on open heart surgery where the patient's chest is opened, typically via a sternotomy, and the patient placed on cardiopulmonary bypass. The need to both open the chest and place the patient on bypass is traumatic and has associated morbidity.

SUMMARY

[0005] For the foregoing reasons, it would be desirable to provide alternative and additional methods, devices, and systems for performing the repair of mitral and other cardiac valves, including the tricuspid valve, which is the other atrioventricular valve. In some embodiments of the present invention, methods and devices may be deployed directly into the heart chambers via a trans-thoracic approach, utilizing a small incision in the chest wall, or the placement of a cannula or a port. In other embodiments, such methods, devices, and systems may not require open chest access and be capable of being performed endovascularly, i.e., using devices which are advanced to the heart from a point in the patient's vasculature

64166-43

remote from the heart. In some embodiments, the methods, devices, and systems should not require that the heart be bypassed, although the methods, devices, and systems should be useful with patients who are bypassed and/or whose heart may be temporarily stopped by drugs or other techniques.

5 [0005a] According to one aspect of the present invention, there is provided a system for treating a heart, comprising: a first anchor that attaches to a first location of a wall of a left ventricle of the heart; a second anchor that attaches to a second location of the heart, wherein the second location is located opposite the first location; and a mechanism that moves the first anchor and the second anchor toward one
10 another to cause the first location and second location to move toward one another so as to re-shape at least one of the mitral valve annulus or the left ventricle in a manner that reduces backflow through the mitral valve, wherein the mechanism comprises a tether that interconnects the first and second anchors.

[0005b] According to another aspect of the present invention, there is provided
15 a system for treating a heart, comprising: a steerable delivery device adapted to be percutaneously introduced into the heart; a valve removably coupled to the steerable delivery device, wherein the valve is adapted for placement in a pulmonary vein of the heart such that the valve regulates blood flow into the left ventricle of the heart when positioned in the pulmonary vein.

20 [0005c] According to another aspect of the present invention, there is provided a device for treating a heart, comprising: a steerable delivery device adapted to be percutaneously introduced into the heart; a first wedge-shaped device removably coupled to the steerable delivery device, wherein the first wedge-shaped device has a contact surface adapted to be positioned adjacent a first mitral valve leaflet of the
25 heart.

[0006] In another aspect, there is disclosed a method of treating a heart, comprising attaching a first device to a first location of a wall of a left ventricle of the heart; attaching a second device to a second location of the heart, wherein the second

64166-43

location is located opposite the first location; and moving the first device and the second device toward one another to cause the first location and second location to move toward one another so as to re-shape at least one of the mitral valve annulus or the left ventricle in a manner that reduces backflow through the mitral valve.

- 5 [0007] In another aspect, there is disclosed a method of treating a heart, comprising coupling at least one valve to a steerable delivery device; percutaneously introducing the valve into the heart using the steerable delivery device; and placing the valve in a pulmonary vein of the heart, wherein the valve regulates blood flow into the left ventricle of the heart.

- 10 [0008] In another aspect, there is disclosed a method of treating a heart, comprising coupling a first wedge-shaped device to a steerable delivery device, wherein the first device has a contact surface adapted to be positioned adjacent a first mitral valve leaflet of the heart; percutaneously introducing the first device into the heart using the steerable delivery device; and securing the first device to the

heart such that the first mitral valve leaflet is positioned adjacent the contact surface of the device.

[0009] In another aspect, there is disclosed a device for treating heart disease comprising a prosthetic comprising a wedge having a length that is about equal to a length of a line of coaptation of a mitral valve and a depth sufficient to prevent prolapse of a mitral valve when the wedge is placed atop an annulus of the mitral valve along the line of coaptation; and one or more anchors protruding from the wedge for coupling the wedge to the annulus of the mitral valve.

[0010] Other features and advantages should be apparent from the following description of various embodiments, which illustrate, by way of example, the principles of the disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Figure 1A is a schematic illustration of the left ventricle of a heart showing blood flow during systole with arrows.

[0012] Figure 1B shows a cross-sectional view of the heart wherein a flexible stent is positioned at or near the mitral valve.

[0013] Figure 2A shows a cross-sectional view of the heart showing one or more magnets positioned around the annulus of the mitral valve.

[0014] Figure 2B shows an annular band with magnets that can be positioned on the mitral valve annulus.

[0015] Figure 3 shows a cross-sectional view of the heart identifying locations for placement of valves.

[0016] Figure 4 show a cross-sectional view of the heart with a pair of flaps mounted at or near the mitral valve.

[0017] Figure 5A shows a schematic side view of the mitral valve leaflets with a flap positioned immediately below each leaflet.

[0018] Figure 5B shows a downward view of the mitral valve with a pair of exemplary flaps superimposed over the leaflets.

[0019] Figure 5C shows a pair of mitral valve leaflet flaps having complementary shapes.

[0020] Figure 6A shows a cross-sectional view of the heart with a membrane ring positioned at the mitral valve annulus.

[0021] Figure 6B shows a schematic view of the membrane ring, which includes an annular ring on which is mounted a membrane.

[0022] Figure 7A shows a cross-sectional view of a heart with a bladder device positioned partially within the left ventricle and partially within the left atrium.

[0023] Figure 7B shows a schematic side view of the mitral valve leaflets failing to coapt.

[0024] Figure 7C shows a schematic side view of the mitral valve leaflets with a bladder positioned between the leaflets.

[0025] Figure 7D shows a plan view of the mitral valve with the leaflets in an abnormal closure state such that a gap is present between the leaflets.

[0026] Figure 8 shows a cross-sectional view of the heart wherein a one-way valve device is located in the left atrium.

[0027] Figure 9A shows a prosthetic ring that is sized to fit within a mitral valve.

[0028] Figure 9B shows another embodiment of a prosthetic ring wherein a one-way valve is positioned inside the ring.

[0029] Figure 10 shows a prosthetic with one or more tongues or flaps that are configured to be positioned adjacent the flaps of the mitral valve

[0030] Figure 11A shows an exemplary embodiment of one or more clips that are positioned on free edges of the leaflets.

[0031] Figure 11B shows pair of leaflets with a magnetic clip attached to the underside of each leaflet.

[0032] Figure 11C shows the leaflets coapted as a result of the magnetic attraction between the magnetic clips.

[0033] Figure 11D shows a pair of leaflets with a single clip attached to one of the leaflets.

[0034] Figure 12 shows a schematic, cross-sectional view of the heart with a wedge positioned below at least one of the leaflets of the mitral valve.

[0035] Figure 13A shows an artificial chordae tendon.

[0036] Figures 13B and 13C show attachment devices for attaching the artificial chordae tendon to a heart wall.

[0037] Figure 14 shows a cross-sectional view of the heart with a first and second anchor attached to a wall of the heart.

[0038] Figure 15 shows a catheter that has been introduced into the heart.

[0039] Figure 16 shows a schematic view of a papillary muscle with a ring positioned over the muscle.

[0040] Figure 17 shows a cross-sectional view of the heart with one or more magnets attached to a wall of the left ventricle.

[0041] Figure 18A shows another embodiment of a procedure wherein magnets are implanted in the heart to geometrically reshape the annulus or the left ventricle.

[0042] Figure 18B shows the heart wherein tethered magnets are implanted in various locations to geometrically reshape the annulus or the left ventricle.

[0043] Figure 18C shows the heart wherein magnets are implanted in various locations to geometrically reshape the annulus or the left ventricle.

[0044] Figure 19 shows another embodiment of a procedure wherein magnets are implanted in the heart to geometrically reshape the annulus or the left ventricle.

[0045] Figure 20 shows a cross-sectional view of the left ventricle with a tether positioned therein.

[0046] Figure 21 shows a cross-sectional view of the left ventricle with a delivery catheter positioned therein.

[0047] Figure 22 shows a cross-sectional view of the left ventricle with the delivery catheter penetrating a wall of the left ventricle.

[0048] Figure 23 shows a cross-sectional view of the left ventricle with the delivery catheter delivering a patch to the wall of the left ventricle.

[0049] Figure 24 shows a cross-sectional view of the left ventricle with the delivery penetrating delivering a second patch.

[0050] Figure 25 shows a cross-sectional view of the left ventricle with two tethers attached together at opposite ends from the patches mounted in the heart.

[0051] Figure 26 shows a cross-sectional view of the left ventricle with a needle or delivery catheter passed transthoracically into the left ventricle LV to deliver a patch to the exterior of the ventricular wall.

[0052] Figure 27 shows a schematic, cross-sectional view of the left ventricle in a healthy state with the mitral valve closed.

[0053] Figure 28 shows the left ventricle in a dysfunctional state.

[0054] Figure 29 shows the left ventricle with a biasing member mounted between the papillary muscles.

[0055] Figure 30 shows the left ventricle with a suture mounted between the papillary muscles.

[0056] Figure 31 shows the left ventricle with a snare positioned around the chordae at or near the location where the chordae attach with the papillary muscles.

[0057] Figure 32 shows a leaflet grasping device that is configured to grasp and secure the leaflets of the mitral valve.

[0058] Figures 33A-33C show the leaflet grasping device grasping leaflets of the mitral valve.

[0059] Figure 34 shows the left ventricle with a needle being advanced from the left atrium into the left ventricle via the leaflet grasping device.

[0060] Figure 35 shows the left ventricle with sutures holding the papillary muscles in a desired position.

[0061] Figure 36 shows a cross-sectional view of the heart with one or more clips clipped to each of the papillary muscles.

[0062] Figure 37 shows a cross-sectional view of the heart with tethered clips attached to opposed walls of the left ventricle.

DETAILED DESCRIPTION

[0063] The present invention provides methods, systems, and devices for the endovascular repair of cardiac valves, particularly the atrioventricular valves which inhibit back flow of blood from a heart ventricle during contraction (systole), most particularly the mitral valve between the left atrium and the left ventricle. By "endovascular," it is meant that the procedure(s) of the present invention are performed with interventional tools, guides and supporting catheters and other equipment introduced to the heart chambers from the patient's arterial or venous vasculature remote from the heart. The interventional tools and other equipment may

be introduced percutaneously, i.e., through an access sheath, or may be introduced via a surgical cut down, and then advanced from the remote access site through the vasculature until they reach the heart. Thus, the procedures of the present invention will generally not require penetrations made directly through the exterior heart muscle, i.e., myocardium, although there may be some instances where penetrations will be made interior to the heart, e.g., through the interatrial septum to provide for a desired access route.

[0064] While the procedures of the present invention will usually be percutaneous and intravascular, many of the tools will find use in minimally invasive and open surgical procedures as well that includes a surgical incision or port access through the heart wall. In particular, the tools for capturing the valve leaflets prior to attachment can find use in virtually any type of procedure for modifying cardiac valve function.

[0065] The atrioventricular valves are located at the junctions of the atria and their respective ventricles. The atrioventricular valve between the right atrium and the right ventricle has three valve leaflets (cusps) and is referred to as the tricuspid or right atrioventricular valve. The atrioventricular valve between the left atrium and the left ventricle is a bicuspid valve having only two leaflets (cusps) and is generally referred to as the mitral valve. In both cases, the valve leaflets are connected to the base of the atrial chamber in a region referred to as the valve annulus, and the valve leaflets extend generally downwardly from the annulus into the associated ventricle. In this way, the valve leaflets open during diastole when the heart atria fill with blood, allowing the blood to pass into the ventricle.

[0066] During systole, however, the valve leaflets are pushed together and closed to prevent back flow of blood into the atria. The lower ends of the valve leaflets are connected through tendon-like tissue structures called the chordae, which in turn are connected at their lower ends to the papillary muscles.

Interventions according to the present invention may be directed at any one of the leaflets, chordae, annulus, or papillary muscles, or combinations thereof. It will be the general purpose of such interventions to modify the manner in which the valve leaflets coapt or close during systole so that back flow or regurgitation is minimized or prevented.

[0067] The left ventricle LV of a normal heart H in systole is illustrated in Figure 1A. The left ventricle LV is contracting and blood flows outwardly through the tricuspid (aortic) valve AV in the direction of the arrows. Back flow of blood or "regurgitation" through the mitral valve MV is prevented since the mitral valve is configured as a "check valve" which prevents back flow when pressure in the left ventricle is higher than that in the left atrium LA. The mitral valve MV comprises a pair of leaflets having free edges FE which meet evenly to close, as illustrated in Figure 1A. The opposite ends of the leaflets LF are attached to the surrounding heart structure along an annular region referred to as the annulus AN. The free edges FE of the leaflets LF are secured to the lower portions of the left ventricle LV through chordae tendineae CT (referred to hereinafter as the chordae) which include plurality of branching tendons secured over the lower surfaces of each of the valve leaflets LF. The chordae CT in turn, are attached to the papillary muscles PM which extend upwardly from the lower portions of the left ventricle and interventricular septum IVS.

64166-43

[0068] While the procedures of the present invention will be most useful with the atrioventricular valves, at least some of the tools described hereinafter may be useful in the repair of other cardiac valves, such as peripheral valves or valves on the venous side of the cardiac circulation, or the aortic valve.

[0069] The methods of the present invention can comprise accessing a patient's vasculature at a location remote from the heart, advancing an interventional tool through the vasculature to a ventricle and/or atrium, and engaging the tool against a tissue structure which forms or supports the atrioventricular valve. By engaging the tool against the tissue structure, the tissue structure is modified in a manner that reduces valve leakage or regurgitation during ventricular systole. The tissue structure may be any of one or more of the group consisting of the valve leaflets, chordae, the valve annulus, and the papillary muscles, atrial wall, ventricular wall or adjacent structures. Optionally, the interventional tool will be oriented relative to the atrioventricular valve and/or tissue structure prior to engaging the tool against the tissue structure. The interventional tool may be self-orienting (e.g., pre-shaped) or may include active mechanisms to steer, adjust, or otherwise position the tool.

[0070] Alternatively, orientation of the interventional tool may be accomplished in whole or in part using a separate guide catheter, where the guide catheter may be pre-shaped and/or include active steering or other positioning means such as those devices set forth in United States Patent Application Serial Numbers 10/441,753 filed May 19, 2003, 10/441,508 filed May 19, 2003 and 10/441,687 filed May 19, 2003.

In all cases, it will usually be desirable to confirm the position prior to engaging the valve leaflets or other tissue structures. Such orienting step may comprise positioning the tool relative to a line of coaptation in the atrioventricular

valve, e.g., engaging positioning elements in the valve commissures and confirming the desired location using a variety of imaging means such as magnetic resonant imaging (MRI), intracardiac echocardiography (ICE), transesophageal echo (TEE), fluoroscopy, endoscopy, intravascular ultrasound (IVUS) and the like.

[0071] In some embodiments, heart disease in general, and valve repair in particular, are treated by targeting the pacing of the heartbeat. In one embodiment, heart disease is treated by introducing one or more pacing leads into a heart chamber. The pacing leads are placed in contact with a heart muscle and are in electrical communication with a power source. The power source provides paced electrical stimuli to the heart muscle. The electrical stimuli are provided during or immediately after systole to extend systolic contraction of the heart, thereby extending the range of systole during each heartbeat. This extension of systole extends the amount of time in which the heart muscle tightens when it would otherwise be relaxing, when there is most mitral regurgitation in diseased mitral valves.

[0072] Other embodiments are directed to annuloplasty to treat heart disease in general and valve repair in particular. In one embodiment, shown generally in Figure 1B, a stent is used to treat the mitral valve. Figure 1B shows a cross-sectional view of the heart wherein a flexible stent 100 is positioned at or near the mitral valve MV. The stent 100 is annular and is sized and shaped to be positioned on the annulus of the mitral valve. The stent 100 can transition between a collapsed state of reduced size and an expanded state of enlarged size relative to the collapsed state.

[0073] The flexible stent 100 can be percutaneously introduced into an individual's heart while being biased toward the collapsed state. The stent is advanced partially through the annulus of the mitral valve so that it is coaxially positioned within the annulus, as shown in Figure 1B. The stent 100 is then secured to the annulus such that the stent exerts an inward force on the annulus thereby causing the annulus to resist dilation during diastole of the heart.

[0074] In yet another embodiment, a device is disclosed for treating the mitral valve. The device can be a stent, such as the stent 100, that is sized to fit coaxially within an annulus of a mitral valve. The stent includes a hollow frame. The frame can be annular such that it has a cross-sectional diameter that is sized such that an outer surface of the frame is in continuous coaxial contact with the annulus. The frame also includes one or more anchors protruding from it for securing the stent to the annulus. The anchors can be prongs, barbs, protrusions, or any structure adapted to secure the stent to the annulus. The stent is flexible between an expanded configuration and a contracted configuration and is biased toward the contracted configuration so that it exerts an inward force on the annulus.

[0075] In one embodiment, the stent 100 is delivered using a delivery catheter 10 that is advanced from the inferior vena cava IVC into the right atrium RA. Once the catheter 10 reaches the anterior side of the interatrial septum IAS, a needle 12 may be advanced so that it penetrates through the septum at the fossa ovalis FO or the foramen ovale into the left atrium LA. At this point, a delivery device can be exchanged for the needle and the delivery device used to deliver the stent 100. The catheter 10 can also approach the heart in other manners.

[0076] Figure 2A shows a cross-sectional view of the heart showing one or more magnets 210 positioned around the annulus of the mitral valve MV. A corresponding method of treating heart disease involves the use of magnets. The method includes percutaneously introducing at least a first magnet 205 into an individual's heart and securing it to the mitral valve MV annulus. At least a second magnet 210 is percutaneously introduced into the heart and advanced so that it is within a magnetic field of the first magnet. The second magnet is secured to the heart. The polarity of one of the two magnets is then cyclically changed in synchronization with the heart beat so that the magnets attract and repel each other in synchronization with the heart beat. The first magnet therefore moves in relation to the second magnet and exerts an inward closing force on the mitral valve during systole. The magnets 210 can be positioned on an annular band 215 (shown in Figure 2B) that is sized and shaped to be implanted on the annulus of the mitral valve. The band 215 can be, for example, a stent.

[0077] In one embodiment, the magnets 210 or the annular band 215 are delivered using a delivery catheter 10 that is advanced from the inferior vena cava IVC into the right atrium RA, as described above with reference to Figure 1. Any of the devices described herein can be percutaneously delivered into the heart by coupling the device to a delivery device, such as a steerable delivery catheter.

[0078] In yet another embodiment involving magnets, two or more magnets are percutaneously introduced into an individual's coronary sinus such that they attract or repel each other to reshape the coronary sinus and an underlying mitral valve annulus.

64166-43

{0079] Other embodiments involve various prosthetics for treating heart disease in general and defective or diseased mitral valves in particular. In one embodiment, a method of treatment includes placing one or more one-way valves in one or more pulmonary veins of an individual either near the ostium of the vein or at some point along the length of the PV. Valves that may be used, for example may be stentless valves such as designs similar to the TORONTO SPV® (Stentless Porcine Valve) valve, mechanical or tissue heart valves or percutaneous heart valves as are known in the art provided they are sized appropriately to fit within the lumen of the pulmonary vein, as shown in Figure 3. In Figure 3, the locations in the left atrium LA where valves can be positioned in pulmonary vein orifices are represented by an "X". In addition, certain venous valve devices and techniques may be employed such as those described in United States Patent, 6,299,637 and 6,585,761, and United States Patent Applications 20040215339 and 20050273160.

A valve

prosthesis for placement in the ostia of the pulmonary vein from the left atrium may be in the range of 6-20mm in diameter. Placement of individual valves in the pulmonary vein ostia (where the pulmonary veins open or take off from the left atrium) may be achieved by obtaining trans septal access to the left atrium with a steerable catheter, positioning a guidewire through the catheter and into the targeted pulmonary vein, and deploying a valve delivery catheter over the guidewire and deploying the valve out of the delivery catheter. The valve may be formed of a deformable material, such as stainless steel, or of a self-expanding material such as NiTi, and include tissue leaflets or leaflets formed of a synthetic material, such as is known in the art. A line of +++++ symbols in Figure 3 represents a mid-atrial location above the mitral valve where a single valve can be positioned as disclosed later in this specification.

64166-43

[0080] The following references describe devices (such as steerable catheters) and methods for delivering interventional devices to a target location within a body: United States Patent Application Serial Numbers 10/441,753 filed May 19, 2003, 10/441,508 filed May 19, 2003 and 10/441,687 filed May 19, 2003.

[0081] Figure 4 show a cross-sectional view of the heart with a pair of flaps mounted at or near the mitral valve. Figure 5A shows a schematic side view of the mitral valve leaflets LF with a flap 300 positioned immediately below each leaflet. The flap 300 can be contoured so as to conform at least approximately to the shape of a leaflet, or the flap 300 can be straight as shown in Figure 4. Figure 5B shows a downward view of the mitral valve with a pair of exemplary flaps superimposed over the leaflets LF. As shown in Figure 5C, the flaps can have complementary shapes with a first flap having a protrusion that mates with a corresponding recess in a second flap.

[0082] In corresponding method of treatment, shown in Figures 4 and 5C, a first flap 300 with an attachment end 305 and a free end 310 is provided. The attachment end 305 of the first flap 300 is secured to the inside wall of the ventricle below the mitral valve. A second flap 315 with an attachment end 320 and a free end 330 is provided and is also secured to the inside wall of the ventricle below the mitral valve. The first and second flaps 300, 315 are oriented so that they face each other and the free ends 310, 330 are biased toward each other and approximate against each other during systole. This system provides a redundant valving system to assist the function of the native mitral valve.

[0083] In other embodiments, devices and methods that involve prosthetic discs are disclosed. For example, Figure 6A shows a cross-sectional view of the heart with a membrane ring 610 positioned at the mitral valve annulus. Figure 6B shows a schematic view of the membrane ring 610, which includes an annular ring on which is mounted a membrane. The membrane includes a series of perforations 615 extending through the membrane surface. One or more anchor devices, such as prongs, can be located on the ring for securing the ring to the mitral valve.

[0084] In one embodiment, a device for treating heart disease in general and defective or diseased mitral valves in particular includes a disc having a ring, a membrane stretched across an opening of the ring, and one or more anchors for securing the disc to an annulus of a mitral valve. The disc is sized to cover the annulus of the mitral valve, and the membrane includes one or more perforations that permit one way fluid flow through the disc. Methods of treatment using the device are also provided.

[0085] In other embodiments, devices and methods that involve fluid-filled bladders are disclosed. Figure 7A shows a cross-sectional view of a heart with a bladder device positioned partially within the left ventricle and partially within the left atrium. A device for treating heart disease in general and defective or diseased mitral valves in particular includes a fluid-filled bladder 600. The bladder 600 is placed across the mitral valve between the left atrium and the left ventricle. Upon compression of the left ventricle, the volume of the bladder is expanded on the left atrial side of the heart, providing a baffle or sealing volume to which the leaflets of the mitral valve coapt. The bladder may also act as a blocking device in the case of flail of a leaflet, blocking said flailing leaflet from billowing into the left atrium causing regurgitation. The bladder also includes one or more anchors for securing the

bladder to an annulus of a mitral valve, or may be formed on a cage or other infrastructure to position it within the line of coaptation of the mitral valve.

[0086] A bladder can also be used to treat functional mitral valve disease. As mentioned, functional mitral valve disease is usually characterized by the failure of the mitral valve leaflets to coapt due to an enlarged ventricle, or other impediment to the leaflets rising up far enough toward each other to close the gap or seal against each other during systole. Figure 7B shows a schematic side view of the mitral valve leaflets LF failing to coapt such that regurgitation can occur (as represented by the arrow RF.) With reference to Figure 7C, a baffle or bladder 630 is positioned between the leaflets LF along the line of coaptation of the leaflets. The bladder 630 provides a surface against which at least a portion of the leaflets LF can seal against. The bladder 630 thus serves as a coaptation device for the leaflets. The bladder can be attached to various locations adjacent to or on the mitral valve. Figure 7D shows a plan view of the mitral valve with the leaflets LF in an abnormal closure state such that a gap G is present between the leaflets. In one embodiment, the bladder is attached or anchored to the mitral valve at opposite edges E of the gap G.

[0087] Methods of treatment using the bladder include providing the bladder and inserting it through an annulus of a mitral valve such that the bladder is coaxially positioned through the mitral valve. An atrial portion of the bladder extends into the left atrium, and a ventricular portion of the bladder extends into the left ventricle. A mid portion of the bladder may be secured to the annulus of the mitral valve such that the mid portion remains stationary while the atrial and ventricular portions expand and contract passively between the atrium and ventricle based on pressure differentials during systole and diastole.

[0088] Figure 8 shows a cross-sectional view of the heart wherein a one-way valve device 700 is located in the left atrium. The valve device is represented schematically in Figure 8. A corresponding method of treating heart disease includes introducing a one-way valve device 700 into the left atrium of an individual's heart proximal the mitral valve. The valve device 700 is configured to permit fluid flow in one direction while preventing fluid flow in an opposite direction. The valve device can have various structures. For example, the device can comprise a valve that is mounted on a stent that is sized to be positioned in the left atrium. Valves that may be used, for example may be stentless valves such as the TORONTO SPV® (Stentless Porcine Valve) valve, mechanical or tissue heart valves or percutaneous heart valves as are known in the art. The outer wall of the one-way valve device is sealed to the inner wall of the atrium so that a fluid-tight seal is formed between the outer wall of the one-way valve device and the inner wall of the left atrium. In this regard, the valve device can include a seal member that is configured to seal to the inner wall of the atrium.

[0089] Another embodiment involves a prosthetic for treating heart disease in general and defective or diseased mitral valves in particular. Figure 9A shows a prosthetic ring 800 that is sized to fit within a mitral valve annulus. The ring includes one or more anchors 805 that extend around the periphery of the ring 800. In addition, one or more struts 810 struts extend across the diameter of the ring, and can be made of a material that includes nitinol or magnetic wires for selectively adjusting the shape of the ring. The struts can also be instrumental in baffling mitral valve leaflet "flail". Figure 9B shows another embodiment of a prosthetic ring 807 wherein a one-way valve 815 is positioned inside the ring such that blood flow BF

can flow through the valve in only one direction. The valve can be manufactured of various materials, such as silicone.

[0090] Figure 10 shows a prosthetic with one or more tongues or flaps that are configured to be positioned adjacent the flaps of the mitral valve. The prosthetic includes a ring 900 sized to fit within a mitral valve annulus. At least two tongues 910 project from the ring 900 in a caudal direction when the ring is implanted into a heart of an individual. The ring is flexible between an expanded configuration and a contracted configuration and is biased toward the contracted configuration. One or more anchors 920 protrude from the flexible ring for coupling the ring coaxially to the annulus such that the contracted configuration of the ring exerts an inward force to the annulus. Alternatively, or in addition, the two tongues can each have a length sufficient to prevent prolapse of a mitral valve when the ring is placed atop the leaflets of the mitral valve. In a further embodiment the tongue elements may be attached at a central point.

[0091] In yet another embodiment, a prosthetic for treating heart disease in general and a defective or diseased mitral valve in particular includes a wedge. The wedge has a length that is about equal to a length of the line of coaptation of a mitral valve. The wedge has a depth sufficient to prevent prolapse of a mitral valve when the wedge is placed atop an annulus of the mitral valve along the line of coaptation, and may provide a point of coaptation for each leaflet. One or more anchors protrude from the wedge for coupling the wedge to the annulus of the mitral valve. Methods of treatment using the wedge are also disclosed. The methods include inserting the wedge into an individual's heart, placing the wedge lengthwise along the line of coaptation of the mitral valve. The wedge is then secured to an annulus of

the mitral valve along the line of coaptation. The wedge may be positioned also just under one segment of the leaflet (likely P2 in the case of functional MR).

[0092] In yet another embodiment, a device for treating heart disease includes a clip for attachment to a free end of a heart valve leaflet. Figure 11A shows an exemplary embodiment of one or more clips 1101 that are positioned on free edges of the leaflets LF. Each of the clips 1101 has a shape that prevents flail of the leaflet by catching against an underside of an opposing leaflet. Methods of treatment using the clip are also disclosed. The methods include introducing the clip into an individual's heart and attaching the clip to a free end of a heart valve leaflet opposite the free end of an opposing leaflet of the heart valve so that the clip catches to the underside of the opposing leaflet during systole. In a further embodiment, a clip may be placed on both leaflets such that the clips meet or catch when the leaflets are in proximity. The clips may attach momentarily during systole, and then detach during diastole, or may clip permanently resulting in a double orifice mitral valve anatomy. The clips of this embodiment may include a magnetic element, or one may be magnetic and the other of a metal material attracted to said electromagnetic field of the magnetic clip.

[0093] In the case of magnetic clips, the clip elements may be placed on the underside of the leaflets (e.g. not necessarily on the free edge of the leaflet), provided that the magnetic field of the clip is sufficient to attract the opposing magnetic or metal clip element. This is further described with reference to Figure 11B, which shows pair of leaflets LF with a clip 1101 attached to the underside of each leaflet. At least one of the clips is magnetic, while the other clip is of an opposite magnetic polarity than the first clip or of a metal attracted to the magnetic field of the first clip. The magnetic field is sufficiently strong such that the clips 1101

can attach to one another either momentarily or permanently to coapt the leaflets, as shown in Figure 11C.

[0094] In another embodiment, shown in Figure 11D, a single clip 1101 is attached to one of the leaflets. The clip 1101 is sufficiently long to increase the likelihood that the clip 1101 will coapt with the opposite leaflet.

[0095] In yet another embodiment, a device for treating heart disease includes a wedge for placement under a heart valve leaflet. Figure 12 shows a schematic, cross-sectional view of the heart with a wedge 1205 positioned below at least one of the leaflets of the mitral valve. The wedge 1205 can be positioned below one or both of the leaflets. The wedge 1205 is sized to fit under the valve leaflet and caudal the annulus of the heart valve. The wedge 1205 can have a shape that is contoured so as to provide support to a lower surface of the leaflet. (In Figure 12, the left atrium is labeled LA and the left ventricle is labeled LV.) An anchor is attached to the wedge for coupling the wedge to a wall of the heart chamber adjacent the heart valve. The wedge forms a fixed backstop against the bottom side of the heart valve leaflet, thereby providing a location for the leaflet to coapt against, and/or providing support or "pushing up" a restricted leaflet.

[0096] Other embodiments are directed to altering the size, shape, chemistry, stiffness, or other physical attributes of heart valve leaflets. In one embodiment in particular, a method of treating heart disease includes obtaining access to a heart valve leaflet and injecting a stiffening agent into the leaflet to stiffen the leaflet and minimize flail.

[0097] Other embodiments are directed to the chordae that connect heart valve leaflets to the inner walls of the heart. In one embodiment in particular, a

method of treating heart disease includes obtaining access to a heart valve chord and cutting it mechanically or with energy such as a laser, or by heating the chordae to elongate them, thereby allowing the previously restricted leaflet to be less restricted so that it can coapt with the opposing leaflet.

[0098] In another embodiment directed to the chordae that connect heart valve leaflets to the inner walls of the heart, a cam-shaped ring is disclosed. The cam-shaped ring is sized to fit within a left ventricle of a heart. The ring forms a hole that is sized to receive two or more chordae tendineae. The ring is formed by connecting two detachable ends of the ring.

[0099] Methods of treatment using the cam-shaped ring are also disclosed. One method in particular includes introducing the ring into a left ventricle of a heart. One or more chordae tendineae are then surrounded by the ring, and the two ends of the ring are then attached to form a closed ring around the chordae tendineae. The ring is then rotated such that one or more of the chordae tendineae are shifted away from their initial orientation by the rotation of the cam-shaped ring. The ring may then be fixed in the rotated or tightened position.

[0100] An embodiment directed at the chordae of heart valve leaflets is now described. Figure 13A shows a device that can be used to alter a chordae. A method includes obtaining access to a chordae tendinea (chord) within an individual's heart chamber. The chordae is then cut at a point along its length so that a length of the chorda tendinea is freed from the heart chamber leaving behind a length of chorda tendinea having a free end and an end attached to an edge of a heart valve.

[0101] With reference to Figure 13A, a synthetic chord 1005 of greater length than the free length of chordae is introduced into the heart chamber. One end of the synthetic chordae 1005 is connected to a wall 1305 of the heart chamber or to a muscle attached to the wall of the heart chamber. Another end of the synthetic chord is attached to the free end of the chorda tendinea or to the leaflet.

[0102] In this regard, the end of the chord 1005 that is attached the wall 1305 can have any of a variety of devices that facilitate such attachment. Figures 13B and 13C show enlarged views of attachment devices contained within box 13 of Figure 13A. The attachment devices can be used to attach the chord 1005 to the wall 1305. In Figure 13B, the attachment device 1310 is an enlarged ball having a distal trocar for penetrating the wall 1305. In Figure 13C, the attachment device 1310 is a hook that is configured to penetrate through the wall 1305. It should be appreciated that the attachment device 1310 can have other structures and it not limited to the structures shown in Figures 13B and 13C. In variations of these embodiments, it may be advantageous to adjust the length of the chordae (synthetic, or modified), determine the therapeutic effect of the shortening or lengthening, and then fix the chordae at the most efficacious location.

[0103] Other embodiments are directed to atrial or ventricular remodeling to alter the shape of an atrium or ventricle. Figure 14 shows a cross-sectional view of the heart with a first and second anchor attached to a wall of the heart. The system includes a first anchor 1410a having a screw portion 1415 for screwing into a wall of the heart and a connector portion. The connector portion is rotatable around an axis of rotation. The first anchor includes a power source to power rotation of the connector portion and a receiver for receiving telemetric signals from an external controller for controlling the rotation of the connector portion. The system includes a

second anchor 1410b having a screw portion 1415b for screwing into a wall of the heart and a connector portion. Also included is a tether 1420 having two free ends. One of the free ends is coupled to the connector portion of the first anchor, and the other free end is coupled to the connector portion of the second anchor. An external controller is also included. The external controller has a telemetric transmitter for communicating with the receiver and controls the rotation of the connector portion. Alternatively, the anchors may be placed with a torqueable catheter.

[0104] In another embodiment, a method of altering a geometry of a heart includes introducing a first coupler into a heart chamber. The first coupler has an anchor portion and a connector portion. The connector portion is rotatable around an axis of rotation and is connected to a power source to power rotation of the connector portion. The power source is in communication with a telemetric signal receiver. The first coupler is secured to the wall of the heart chamber by anchoring the anchor portion to the wall. A second coupler is introduced into the heart chamber. The second coupler includes an anchor portion and a connector portion. The second coupler is secured to the wall of the heart chamber by anchoring the anchor portion to the wall at a distance from the first coupler.

[0105] A tensile member is introduced into the heart chamber. One end of the tensile member is connected to the connector portion of the first coupler, and another end of the tensile member is connected to the connector portion of the second coupler. The distance between the first and second couplers is adjusted by transmitting a telemetric signal to the receiver, thus causing the connector portion to rotate around the axis of rotation and threading the tensile member around the connector portion to reduce the distance between the first and second couplers.

[0106] In another embodiment, a system for altering the geometry of a heart chamber includes a planar tensile member having substantially inelastic material. At least two anchors are included for anchoring the planar tensile member to an inner wall of a heart chamber. The planar tensile member is substantially shorter in length than a left ventricle of a heart so that when the planar tensile member is anchored in a caudal direction along a length of the left ventricle a tensile force exerted by the planar tensile member between the two anchors prevents the left ventricle from dilating caudally.

[0107] In another embodiment, a method for altering the geometry of a heart includes providing a tensile member having a substantially inelastic material. The tensile member is substantially shorter in length than a left ventricle of a heart. The tensile member is inserted into the left ventricle of the heart and a proximal end of the tensile member is anchored to the left ventricle adjacent the mitral valve. A distal end of the tensile member is anchored to the left ventricle caudal the proximal end so that a tensile force exerted by the tensile member between the two anchors prevents the left ventricle from dilating caudally.

[0108] Other embodiments are directed to strengthening or reshaping the left ventricle of the heart. In one embodiment in particular, a method of reinforcing the left ventricle includes injecting a strengthening agent into a wall of the left ventricle in an enlarged region of the ventricle, as shown in Figure 15. Figure 15 shows a catheter 1510 that has been introduced into the heart. The catheter 1510 has an internal lumen through which the strengthening agent 1512 can be injected. A proximal end of the catheter is connected to a source of the strengthening agent and a distal end of the catheter is configured to release the strengthening agent. As

shown in Figure 15, the distal end of the catheter is positioned at or near a wall of the heart and the strengthening agent 1512 is injected into the wall of the heart.

[0109] In another embodiment, a method is directed to altering the geometry of a heart. The method includes injecting a polymerizing agent into a pericardial space adjacent a left ventricle, thereby exerting a medial (inward) force against the left ventricle.

[0110] In yet another embodiment, a method of altering the geometry of a heart includes inserting a balloon into a pericardial space adjacent to a left ventricle of the heart, or extend into the pericardium of the heart. The balloon is inflated by injecting it with a fluid, and it exerts a medial force against the left ventricle upon inflation. In certain embodiments, the balloon can be inflated at the time of implantation, or at a later time. If inflated at a later time, the balloon would be self-sealing, and may be inflated by accessing the balloon with a needle placed through the chest wall.

[0111] Other embodiments are directed to adjusting the length or orientation of papillary muscles. Figure 16 shows a schematic view of the heart showing the papillary muscles PM. With reference to Figure 16, a method of treating heart disease includes inserting an anchor, cuff or sleeve 1205 into the left ventricle of an individual's heart, and sliding a cuff or sleeve around a papillary muscle P. The size of the cuff or sleeve is reduced so that the cuff or sleeve squeezes the papillary muscle. As the size of the cuff or sleeve is reduced, the papillary muscle stretches and increased in length.

[0112] In yet another embodiment, a method of treating heart disease includes obtaining access to a papillary muscle in a left ventricle of the heart. The

papillary muscle is cut and reattached at a new location on an inner wall of the ventricle closer to the mitral valve.

[0113] Additional embodiments that employ magnets in the heart are now described with reference to Figures 17-19, which show cross-sectional views of the heart. With reference to Figure 17, in one embodiment one or more magnets 1705 are implanted or otherwise attached to a wall 1710 of the left ventricle LV. One or more other magnets 1715 are implanted or otherwise attached to a wall 1720 of the right ventricle. The magnets 1705 and 1715 are attached to the walls 1710 and 1720 such that they assert an attractive magnetic force (as represented by the arrows 1725 in Figure 17) toward each other. The magnetic force 1725 assists in remodeling of the left ventricle during pumping of the heart. That is, the magnets 1705 and 1715 are urged toward one another (thereby also urging the walls 1710 and 1720 toward one another) to re-shape either the annulus AN or the left ventricle LV. The annulus or the left ventricle LV are re-shaped in a manner that reduces or eliminates backflow through the mitral valve MV. It should be appreciated that a similar procedure can be performed on the right ventricle RV and associated valves.

[0114] Figure 18A shows another embodiment of a procedure wherein magnets are implanted in the heart to geometrically reshape the annulus or the left ventricle. One or more magnets 1705 are implanted or otherwise attached to a first wall 1710a of the left ventricle LV. One or more magnets 1705 are also implanted or otherwise attached to a second, opposed wall 1710b of the left ventricle. The magnets on the opposed walls 1710a, 1710b exert an attractive magnetic force toward one another to draw the walls 1710a, 1710b toward one another and re-shape the left ventricle LV or the annulus AN.

[0115] Another embodiment of a procedure uses magnets to anchor tethers within the heart at various locations to optimize the shape of cardiac structures to improve cardiac function. The tethers are placed to either reshape the cardiac structure or to prevent dilatation of the structure over time. The tethers must be securely anchored to the heart structures. A method of anchoring which enables tethering in various positions and directions within the cardiac structures is important for the clinician to optimize cardiac reshaping based on each individual patient anatomy and disease state. A method of anchoring which is atraumatic is also desirable.

[0116] Figure 18B shows a side view of the heart with sets of magnets A, A1, B, and B1 positioned to various locations of the heart or to anatomical structures adjacent the heart. In one embodiment, at least one magnet A is placed on the interventricular septum within the right ventricle RV. At least one magnet A1 is placed within the left ventricle LV opposite magnet A. The magnetic force between A and A1 maintains the position of the magnets. The magnets may be enclosed in materials that will promote tissue in-growth and healing to the interventricular septum to ensure stability of location and to eliminate the need for long term anti-coagulation. Additionally, the enclosure material which is flexible and can be delivered in a low profile can be significantly larger in size than the magnets to increase the surface area of contact with the heart wall which will increase the tension that can ultimately be placed on the anchor over time.

[0117] A second set of magnets B and B1 are then delivered to another location selected within or adjacent to the heart. The set of magnets A/A1 are attached to the set of magnets B/B1 using at least one tether 1805, as shown in Figure 18B. The tether 1805 can be attached to either or both of the magnets A/A1

at one end and to either of both of the magnets B/B1 at an opposite end. When the set of magnets B/B1 are tethered under tension to the set of magnets A/A1, a change in the shape of the cardiac structure results to improve cardiac function. Figure 18B shows magnet B positioned in the LV and B1 positioned in a blood vessel BV adjacent to the heart. The magnetic force between B and B1 maintains the location of B and B1. Magnets B and B1 are delivered on or within materials and structures which promote healing and increase the amount of tension that can be placed on the anchor over time. For example, magnet B1 can be delivered on a stent which is of a length, diameter and material which will heal within the BV to provide sufficient resistance to forces placed on it by the tethers.

[0118] The tethers may be pre-attached to the magnets A and B1 or they may be attached after A and B1 have been positioned. The tether length may be shortened and/or adjusted after placement of the anchors. Alternatively the final tether length may be pre-selected based on the patient's cardiac structure geometry and the effect the clinician desires. Placing sets of magnets in this method, enables anchoring of tethers within the heart in various positions and angles which provides increased flexibility and variation for clinicians to select optimal re-shaping of the cardiac structures based on specific patient characteristics.

[0119] Examples which demonstrate the flexibility of this approach include placing anchors at the annulus and at the apex of the heart and tethered to shorten the length of the LV; anchors can be placed in the around the annulus and tethered to change the shape of the annulus. More specifically, one or more sets of magnets can be placed in the RA and LA at the level of the mitral valve annulus (on the anterior side of the annulus) and one or more sets of magnets can be placed in the LA and LV on opposite sides of the annulus on the posterior portion of the annulus.

The posterior sets of magnets can then be tethered to the anterior sets of magnets to change the shape of the annulus. Alternatively, the magnet anchors can be placed at the level of the annulus in the LA and in a BV adjacent to the heart at the level of the annulus and these then tethered to the anterior annulus magnet anchor described above.

[0120] The magnets A and A1 can also be a single magnet that extends through the interventricular septum. Moreover, only one of the magnets A or A1 need be implanted. One or more magnets B and/or B2 are located opposite the location of the magnet(s) A and/or A1. The magnet(s) B is located within the left ventricle opposite the magnets A/A1, such as on the left ventricular wall. The magnet B1 is located on an anatomical structure adjacent the heart, such as on a blood vessel BV.

[0121] In another embodiment shown in Figure 18C, the magnets A, A1, B, and B1, or combinations thereof, are implanted in the heart without tethers. The magnets A, A1, B, and B1 can be positioned in various combinations so as to exert magnetic attractions to one another to re-shape the left ventricle or the mitral valve annulus. For example, the magnets A and B can be implanted such that they exert an attractive magnetic force relative to one another. The magnets A and B2 can alternately be implanted. Other possible combinations are the magnets A1 and B or the magnets A1 and B2. The magnets can be implanted without tethers such that an attractive magnetic force F causes the magnets and the attached region of the heart to move toward one another to re-shape the heart. Alternately, the magnets can be attached to one another with tethers.

[0122] In yet another embodiment, one or more magnets 1705 are implanted in the walls 1710 of the left ventricle LV and/or the right ventricle RV, as shown in Figure 19. The magnets 1705 are positioned in opposed locations on the walls 1710 and one or more tethers 1905 attach opposed pairs of magnets 1705 to one another. One or more of the tethers 1905 extend through the interventricular septum to connect a first magnet disposed in the left ventricle and a second magnet disposed in the right ventricle. In certain embodiments, magnet elements do not include tethers, but rely on the magnetic attraction to each other to remodel the tissue between them. For example, a magnetic element may be placed on either side of the interventricular septum, or one element within the septum. Another magnetic element may be placed on or within the opposite left ventricular wall, or in an adjacent vessel on the left ventricular wall. The electromagnetic field of such elements can then interact to cause a remodeling of the left ventricle to assist with ventricular function.

[0123] The tethers 1905 can be elastic so to exert an attractive force between the attached magnets 1705 and re-shape the left ventricle LV or annulus AN. Alternately, or in combination with elastic tethers, the tethers 1905 can be shortened in length after placement to thereby pull the walls of the left ventricle LV toward one another and re-shape the left ventricle LV or the annulus AN. In combination with the force provided by the tethers 1905, the magnets 1705 exert an attractive magnetic force toward one another to assist in pulling the heart walls toward each other.

[0124] It should be appreciated that one or more magnets can be positioned in other locations of the heart or adjacent anatomical structures for re-shaping of the heart. For example, one or more magnets can be positioned around

the annulus AN or can be positioned in the coronary sinus in such a manner that the magnets exert attractive forces toward one another to cause re-shaping of a desired portion of the heart.

[0125] In another embodiment, cardiac re-shaping is achieved through percutaneous placement of one or more tethers that are cinched or anchored in the walls of the left ventricle LV. The tethers provide tension between the walls of the left ventricle to reshape the left ventricle LV in a desired manner. Figure 20 shows a cross-sectional view of the left ventricle LV with a tether 2010 positioned therein. The tether 2010 has a first end anchored to a first wall of the left ventricle LV and a second end anchored to an opposed wall of the left ventricle LV. The tether 2010 is tensioned to pull the walls toward one another (as represented by the phantom lines 2012 in Figure 20) and re-shape the left ventricle LV. It should be appreciated that the phantom lines 2012 in Figure 20 are merely representative of the geometric re-shaping. The left ventricle LV can be re-shaped in various manners and the amount of re-shaping can vary depending on the tension applied to the tether 2010 and the location of attachment to the walls of the left ventricle LV. The tether may be inelastic or somewhat elastic.

[0126] The tether 2010 can be anchored or otherwise attached to the walls in various manners. In an exemplary embodiment, a patch 2015 (shown in Figure 20) of material is positioned on an exterior surface of the ventricular wall and is attached to one end of the tether 2010. A similar patch can also be positioned on the opposed wall and attached to the opposite end of the tether.

[0127] With reference to Figure 21, the patch is delivered to a desired location using a catheter 2105 having a sharpened distal end 2110 that is positioned

within the left ventricle LV. The catheter 2105 can be delivered to the left ventricle LV in various manners, including trans-aortically (via the aorta), trans-septally (by piercing the interventricular septum), and trans-atrially (via the left atrium) pursuant to well-known methods. As shown in Figure 22, the sharpened distal end 2110 pierces the ventricular wall such that the distal end 2110 is positioned exterior to the ventricular wall. The catheter 2105 has an internal delivery lumen having an opening at the distal end 2110. The patch 2015 is configured to be transported in a contracted state through the delivery lumen and delivered out of the opening at the distal end 2110, where the patch 2015 expands into an expanded state at the exterior of the ventricular wall to seal against the exterior of the left ventricular wall.

[0128] When positioned at the exterior of the ventricular wall, the patch 2015 is configured to act as a reservoir that receives a fluid material that can be delivered to the patch via the delivery lumen of the catheter 2105. The fluid material has a first viscous state of sufficient fluidity such that the material can flow through the delivery lumen of the catheter 2105 and out of the distal end 2110 to the location of the patch 2015. The fluid material changes to a second viscous state when positioned exterior to the ventricular wall at the patch 2015. The second viscous state is of greater viscosity (i.e., more resistant to flow) than the first viscous state such that the fluid material provides support and a level of rigidity to the patch 2015 and to the left ventricular wall. The fluid material can change to the second viscous state after a predetermined time period, after contact with the patch, or when the patch is completely filled. A catalyst can be injected into the fluid material to cause it to change to the second viscous state.

[0129] As shown in Figure 23, the catheter 2105 can then be disengaged from the patch 2015 such that the patch 2015 is disposed exterior to the ventricular

wall. The patch 2015 can be firmly attached to the ventricular wall (such as using an adhesive) to minimize wear or friction between the patch and the ventricular wall. Next, an end of the tether 2010 is attached to the patch 2015. The catheter 2105 can be used to deliver the tether 2010 to the patch 2015 or, alternately, a second catheter can be used. In one embodiment, the tether 2015 is already positioned in a delivery lumen of the catheter 2010 while the patch 2015 is being delivered. The catheter 2010 is then pulled back while the end of the tether 2015 remains attached to the patch 2015 to thereby let the tether 2010 out from the catheter 2010, as shown in Figure 23.

[0130] With reference now to Figure 24, a second patch 2415 is deployed in or exterior to an opposed ventricular wall in a manner similar to that described above. The opposite end of the tether 2010 is then attached to the second anchor 2415 such that the tether 2010 extends between the two anchors, as shown in Figure 20. Alternately, as shown in Figure 24, a second tether 2420 is attached at a first end to the second anchor 2415. As shown in Figure 25, the two tethers 2010 and 2420 can then be attached together at opposite ends from the patches, such as by using a clip 2510, to form a single attachment tether between the patches 2015 and 2415. The tether 2510 can be twisted or adjusted within the clip to tension the resulting attachment tether between the patches 2415 and 2015 and pull the ventricular walls toward one another via the tether. Once properly tensioned, the tether can be clipped or clamped to maintain its position.

[0131] In another embodiment, shown in Figure 26, a needle 2610 or delivery catheter is passed trans-thoracically into the left ventricle LV to deliver a patch 2615 to the exterior of the ventricular wall, as described above. A sealing means, such as a sealing balloon, can be used to seal one or more puncture holes in

the wall of the left ventricle caused by the needle 26 during delivery of the patch 2615. Visualization means, such as fluoroscopy, can be used to visualize proper placement of the needle 2610. A second patch is attached to an opposed wall to form a tether attachment between the walls, as shown in Figure 20. The tether is then tensioned to pull the walls together and re-shape the left ventricle or annulus of the mitral valve in a desired manner.

[0132] In other embodiments, described with reference to Figures 27-31, cardiac re-shaping is achieved by manipulation of the papillary muscles. Figure 27 shows a schematic, cross-sectional view of the left ventricle LV in a healthy state with the mitral valve closed. The valve chordae CH connect the leaflets LF of the mitral valve to the papillary muscles PM. The papillary muscles PM and the chordae CH are positioned such that at least a portion of the leaflets LF contact one another when the mitral valve is in the closed state, resulting in functional coaptation of the leaflets.

[0133] Figure 28 shows the left ventricle LV in a dysfunctional state. The valve chordae CH or the papillary muscles PM are damaged or otherwise dysfunctional such that the leaflets LF do not properly coapt (contact one another). The dysfunction can be manifested by excess tension in the chordae CH such that a gap is located between the leaflets LF, or in some cases one leaflet may function at a different level from the other (e.g. lower (prolapse) or higher (flail)) thereby limiting the ability of the mitral valve to close resulting in mitral regurgitation. The dysfunctional left ventricle LV and in some cases leaflet prolapse or flail, can be treated by manipulating papillary muscles PM to adjust the position of the leaflets LF. In one embodiment, the papillary muscles PM are repositioned toward one another to reduce the distance between the papillary muscles PM.

[0134] In an embodiment described with reference to Figure 29, a biasing member, such as a rod of adjustable length, or a spring 2910, is mounted between the papillary muscles PM with a first end of the spring 2910 attached to a first papillary muscle and a second end of the spring 2910 attached to a second papillary muscle. The spring 2910 has a pre-load such that the spring 2910 provides a biasing force (represented by the arrows 2915 in Figure 29) that pulls the papillary muscles PM toward one another. Such a spring may be covered with polyester fabric or other coating to promote ingrowth into the muscle tissue and minimize the potential for clot formation. The repositioning of the papillary muscles PM re-shapes the left ventricle and/or changes the distance that the leaflets need to move on the chordae CH such that the leaflets LF contact one another to close the mitral valve. The tension provided by the spring 2910 can be varied or different springs can be used to achieve a proper repositioning of the papillary muscles PM. The tension may be modified at the time of the procedure or during a subsequent procedure if it is determined that additional coaptation is required.

[0135] In another embodiment, described with reference to Figure 30, a suture 3010 is mounted between the papillary muscles PM with a first end of the suture 3010 attached to a first papillary muscle and a second end of the suture 3010 attached to a second papillary muscle. The suture 3010 can be attached to the papillary muscles in various manners. For example, an attachment device 3015, such as an anchor, cuff or sleeve, can be positioned around or partially around each of the papillary muscles. The ends of the suture 3010 are attached to the attachment devices 3015 to secure the suture 3010 to the suture to the papillary muscles.

64166-43

[0136] The suture 3010 is tensioned such that it provides a force that pulls the papillary muscles PM toward one another. The suture 3010 can be tensioned, for example, by twisting the suture 3010 to reduce its the overall length and thereby reduce the distance between the papillary muscles PM, and fixing the suture with a crimping element or other stay element. The amount of twisting or shortening can be varied to vary the tension provided by the suture 3010. In addition, a crimping member may be used to fix the sutures once a desired tension between the muscles is reached. Exemplary crimping members are described in International Patent Application Number PCT/US03/06149.

As in the previous embodiment, the repositioning of the papillary muscles PM re-shapes the left ventricle and/or changes the tension on the chordae CH such that the leaflets LF contact one another to close the mitral valve. Cuffs or sleeves may be placed around the papillary muscles PM to such as those previously described, to affect the repositioning.

[0137] With reference now to Figure 31, the papillary muscles PM can also be repositioned by snaring the papillary muscles. A snare 3110 comprised of a looped strand of material is positioned around the chordae CH at or near the location where the chordae attach with the papillary muscles PM. The snare 3110 is tightened to draw the papillary muscles PM toward one another and re-shape the left ventricle and/or changes the distance that the leaflets need to travel during systole such that the leaflets LF contact one another to close the mitral valve.

[0138] In yet another embodiment, shown in Figure 36, one or more clips 3610 are clipped to each of the papillary muscles PM. The structure of the clips 3610 can vary. A tether 3615 attaches the clips 3610 to one another. The tether 3615 is cinched to shorten the length of the tether 3615 and pull the papillary

muscles PM toward one another and re-shape the left ventricle and/or changes the distance that the leaflets need to travel during systole such that the leaflets LF contact one another to close the mitral valve.

[0139] In yet another embodiment, shown in Figure 37, one or more clips 3610 are clipped to opposed walls of the left ventricle LV. The clips 3610 can be delivered to the left ventricle using a delivery catheter 2105. A tether attaches the clips to one another. The tether is cinched to shorten the length of the tether and pull the ventricular walls toward one another and re-shape the left ventricle and/or changes the distance that the leaflets need to travel during systole such that the leaflets LF contact one another to close the mitral valve.

[0140] In all embodiments, once the papillary muscles are fixed or repositioned, it may be advantageous to further treat the area by selectively elongating or shortening the chordae tendinae to achieve further optimal valve function. In addition, a mitral valve clip may be deployed to augment the desired valve function, either before papillary or chordal manipulation, or after, if the desired leaflet coaptation is not achieved with one particular approach.

[0141] As discussed above with reference to Figure 28, a dysfunctional left ventricle can be manifested by excess tension in the chordae CH such that a gap is positioned between the valve leaflets LF. It can be desirable to eliminate or relieve the excess tension by cutting the chordae CH, and/or cutting the chordae and replacing them with artificial chordae. Prior to cutting the chordae, it can be desirable to evaluate the placement of the artificial chordae to confirm that implantation of the chordae will indeed provide the desired clinical result. This process is now described with reference to Figures 32-35.

64166-43

[0142] Figure 32 shows a leaflet grasping device 1100 that is configured to grasp and secure the leaflets of the mitral valve. The device 1100 and corresponding methods of use are described in more detail in U.S. Patent Application Serial No. 10/635,776, entitled "Methods and Apparatus For Cardiac Valve Repair", which is incorporated herein by reference in its entirety. Additional leaflet grasping devices are described in U.S. Patent Application Serial No. 10/441,508, filed May 19, 2003, U.S. Patent No. 6,269,819, issued August 7, 2001, and U.S. Patent No. 6,461,366, issued October 8, 2002.

[0143] Referring to Figure 32, the device 1100 is comprised of a catheter shaft 1102 having a distal end 1104 and a proximal end 1106. The catheter shaft 1102 is comprised of, among others, a conduit 1108, a coaxial outer sheath 1110, a central lumen 1111 through which a double-jaw grasper 1113 may be inserted, and a central guidewire lumen 1105. The catheter shaft 1102 can have additional lumens for the passage of one or more needles, as described more fully below.

[0144] Toward the distal end 1104, an optional pair of stabilizers 1112 are fixedly mounted on the outer sheath 1110 at their proximal end 1114 and fixedly attached to extenders 1116 at their distal end 1118. The stabilizers 1112 are shown in an outwardly bowed position, however they may be inwardly collapsed by either extending the extenders 1116 or retracting the outer sheath 1110. Bowing may be achieved by the reverse process.

[0145] The double-jaw grasper 1113 is comprised of two articulating jaw arms 1120 which may be opened and closed against the central shaft 1122 (movement depicted by arrows) either independently or in tandem. The grasper

1113 is shown in the open position in Figure 32. The surfaces of the jaw arms 1120 and central shaft 1122 may be toothed, as shown, or may have differing surface textures for varying degrees of friction. The jaw arms 1120 each include a needle passageway 1121 comprised of a cutout or a slot that extends at least partially along the length of each jaw arm 1120. As described in more detail below, the needle passageway provides a location where a needle can pass through the jaw arm 1120 during manipulation of the papillary muscle.

[0146] The above described components may be manipulated and controlled by a handle 1126 connected to the proximal end 1106 of the catheter shaft 1102, as shown in fig. 86. the handle 1026 permits independent control of the components described above.

[0147] Referring to Figures 33A-C, the device 1100 may be used at least temporarily grasp and restrain the valve leaflets LF of the mitral valve MV. The double-jaw grasper 1113 extends through the valve such that the leaflets L1, L2 are grasped from below. Thus, the device 1100 is termed "atrial-ventricular."

[0148] Referring to Figure 33A, the atrial device 1100 may be stabilized against the mitral valve MV. The stabilizers 1112 may be positioned on the superior surface of the valve leaflets LF1, LF2 at a 90 degree angle to the line of coaptation. The grasper 1113 may be advanced in its closed position from the conduit 1108 between the leaflets LF1, LF2 until the jaw arms 1120 are fully below the leaflets in the ventricle. At this point, the grasper 1113 may be opened and retracted so that the jaw arms 1120 engage the inferior surface of the leaflets LF1, LF2. In this manner, the leaflets are secured between the stabilizers 1112 and the jaw arms 1120.

[0149] Referring to Figure 33B, the grasper 1113 will gradually close, drawing the leaflets LF1, LF2 together while maintaining a secure hold on the leaflets between the jaw arms 1120 and the stabilizers 1112. This may be accomplished by number of methods. For example, the stabilizers 1112 may be gradually collapsed by either extending the extenders 1116 or retracting the outer sheath 1110. As the stabilizers 1112 collapse, the jaw arms 1120 may collapse due to spring loading to gradually close the grasper 1113. Alternatively, the jaw arms 1120 may be actuated to close against the central shaft 1122 applying force to the stabilizers 1112 causing them to collapse. In either case, such action allows the stabilizers 1112 to simultaneously vertically retract and withdraw from the leaflets as the leaflets are clamped between the jaw arms 1120 and the central shaft 1122. In this manner, the leaflets are effectively "transferred" to the grasper 1113. Referring to Figure 33C, once the collapsed stabilizers 1112 are completely withdrawn, the leaflets LF1, LF2 are held in vertical opposition by the grasper 1113 in a more natural coaptation geometry.

[0150] With reference now to Figure 34, a needle 3410 is advanced from the left atrium into the left ventricle. The needle 3410 can be passed through a lumen in the device 1100 or it can be passed external to the device 1100. In any event, the needle 3410 passes through a leaflet LF and into a papillary muscle PM. As mentioned, the jaw arms 1120 have needle passageways 1121 (shown in Figure 32) that permit passage of the needle through the jaw arms 1120.

[0151] The needle 3410 is attached to a suture 3415 that extends distally through the device 1100. The suture 3415 is then anchored to the papillary muscle PM such that the suture 3415 provides an attachment for holding, pulling, or otherwise manipulating the papillary muscle PM. The tension in the suture 3415 can

64166-43

be adjusted to re-position the papillary muscle PM such that the leaflets LF contact one another to close the mitral valve. The same process can be performed with the other papillary muscle.

[0152] With the sutures 3415 holding the papillary muscles PM in a desired position, as shown in Figure 35, the chordae CH may be cut. The sutures 3415 function as artificial chordae that retain the leaflets LF and papillary muscles PM in a desired orientation.

[0153] A fixation device such as a clip can then be attached to the leaflets using methods and device described in U.S. Patent Application Serial No. 10/635,776, filed August 5, 2003, U.S. Patent Application Serial No. 10/441,508, filed May 19, 2003, U.S. Patent No. 6,269,819, issued August 7, 2001, and U.S. Patent No. 6,461,366, issued October 8, 2002.

The sutures 3415 can be attached to the clip 3510 or directly to the leaflets LF. It should be appreciated that any quantity of sutures 3415 can be used as artificial chordae between the leaflets and the papillary muscles. It should be appreciated that the leaflet clips can also be used in conjunction with cutting, elongating, or shortening of the chordae pursuant to the methods described above.

[0154] Prior to permanently placing the chordae or clips, the result can be previewed on ultrasound (TEE, ICE, echocardiography), to determine if the appropriate valve coaptation is restored. In addition, it is within the scope of the present invention to implant a mitral valve clip in addition to performed papillary muscle approximation or chordal implantation.

[0155] Although embodiments of various methods and devices are described herein in detail with reference to certain versions, it should be appreciated

64166-43

that other versions, embodiments, methods of use, and combinations thereof are also possible. Therefore the scope of the appended claims should not be limited to the description of the embodiments contained herein.

64166-43

CLAIMS:

1. A system for treating a heart, comprising:
a first anchor that attaches to a first location of a wall of a left ventricle of the heart;
5 a second anchor that attaches to a second location of the heart, wherein the second location is located opposite the first location; and
a mechanism that moves the first anchor and the second anchor toward one another to cause the first location and second location to move toward one another so as to re-shape at least one of the mitral valve annulus or the left ventricle
10 in a manner that reduces backflow through the mitral valve,
wherein the mechanism comprises a tether that interconnects the first and second anchors.
2. The system of claim 1, wherein the second location is on a wall of a right ventricle of the heart.
- 15 3. The system of claim 1, wherein the second location is on a wall of the left ventricle of the heart.
4. The system of claim 1, wherein the second location is on an interventricular septum of the heart.
5. The system of any one of claims 1 to 4, wherein at least one of the first
20 and second anchors comprises a magnet, and wherein the mechanism comprises a magnetic force that causes the first and second anchors to move toward one another.
6. The system of any one of claims 1 to 5, wherein the tether is elastic such that the tether exerts an attractive force between the first and second anchors to cause the first and second anchors to move toward one another.

64166-43

7. The system of any one of claims 1 to 6, further comprising a mechanism for shortening the length of the tether so as to move the first anchor and second anchor toward one another.

8. The system of any one of claims 1 to 7, wherein the first and second
5 anchors comprise magnets.

9. The system of any one of claims 1 to 8, wherein the tether extends through an interventricular septum of the heart.

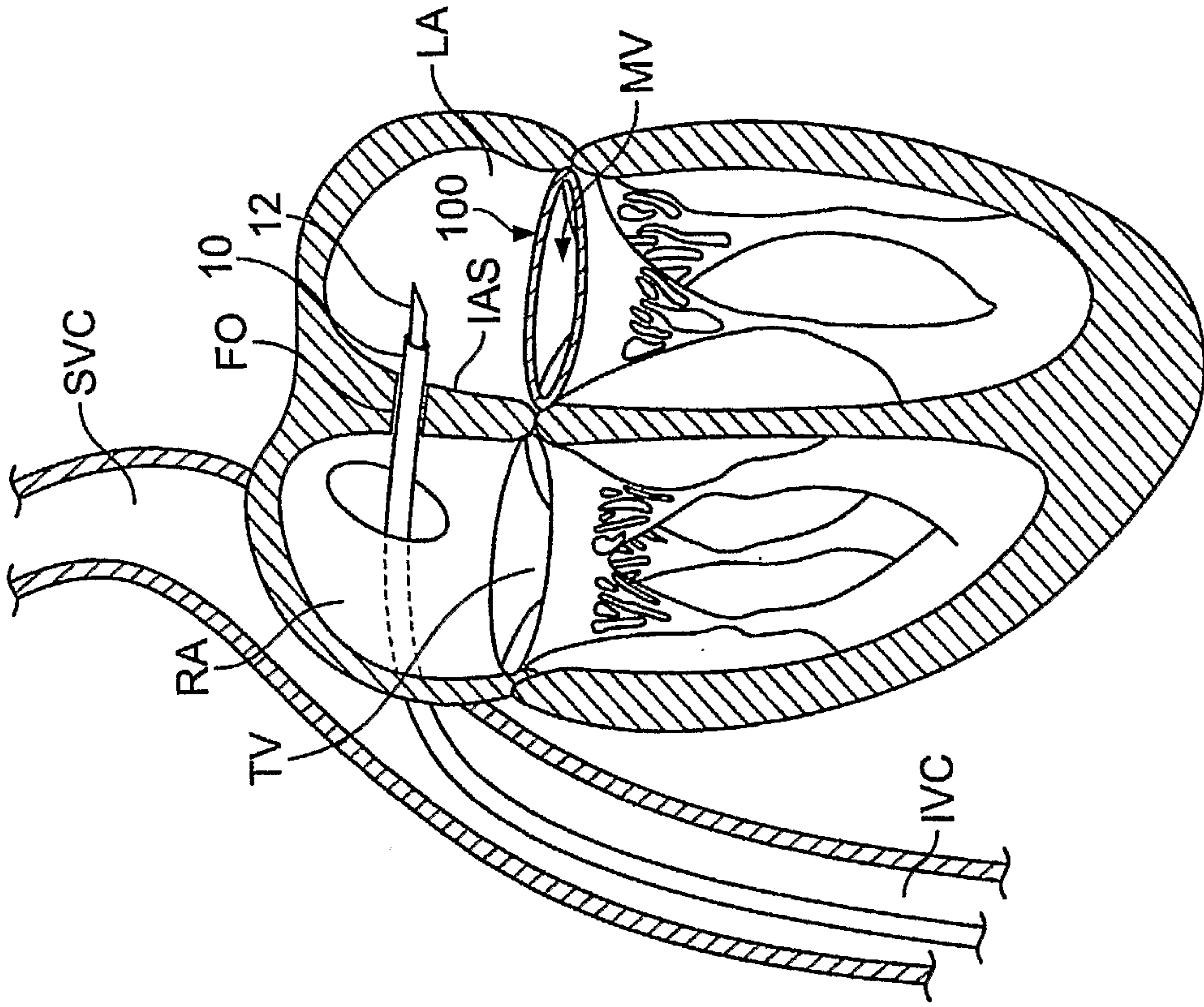


FIG. 1B

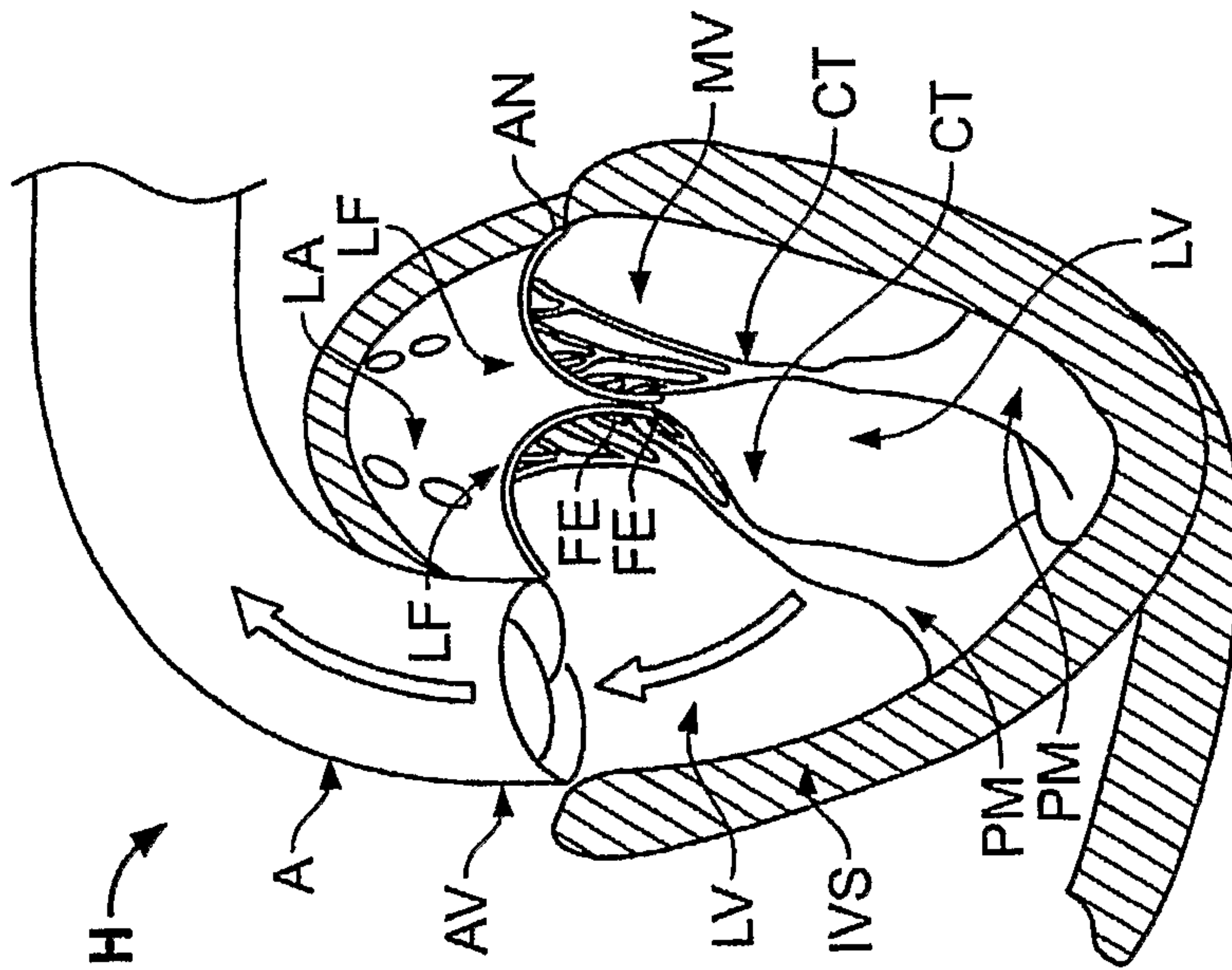


FIG. 1A

2/19

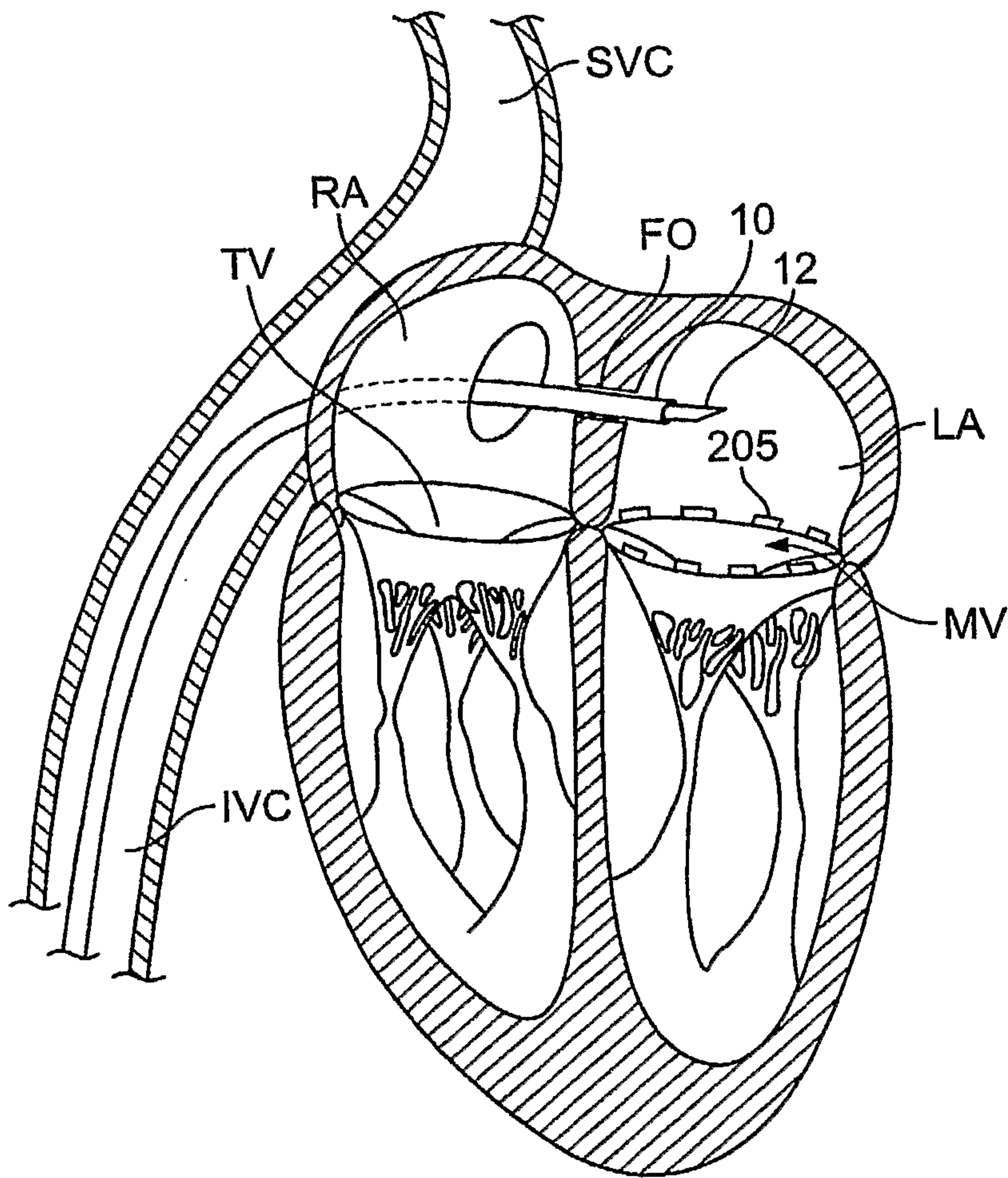


FIG. 2A

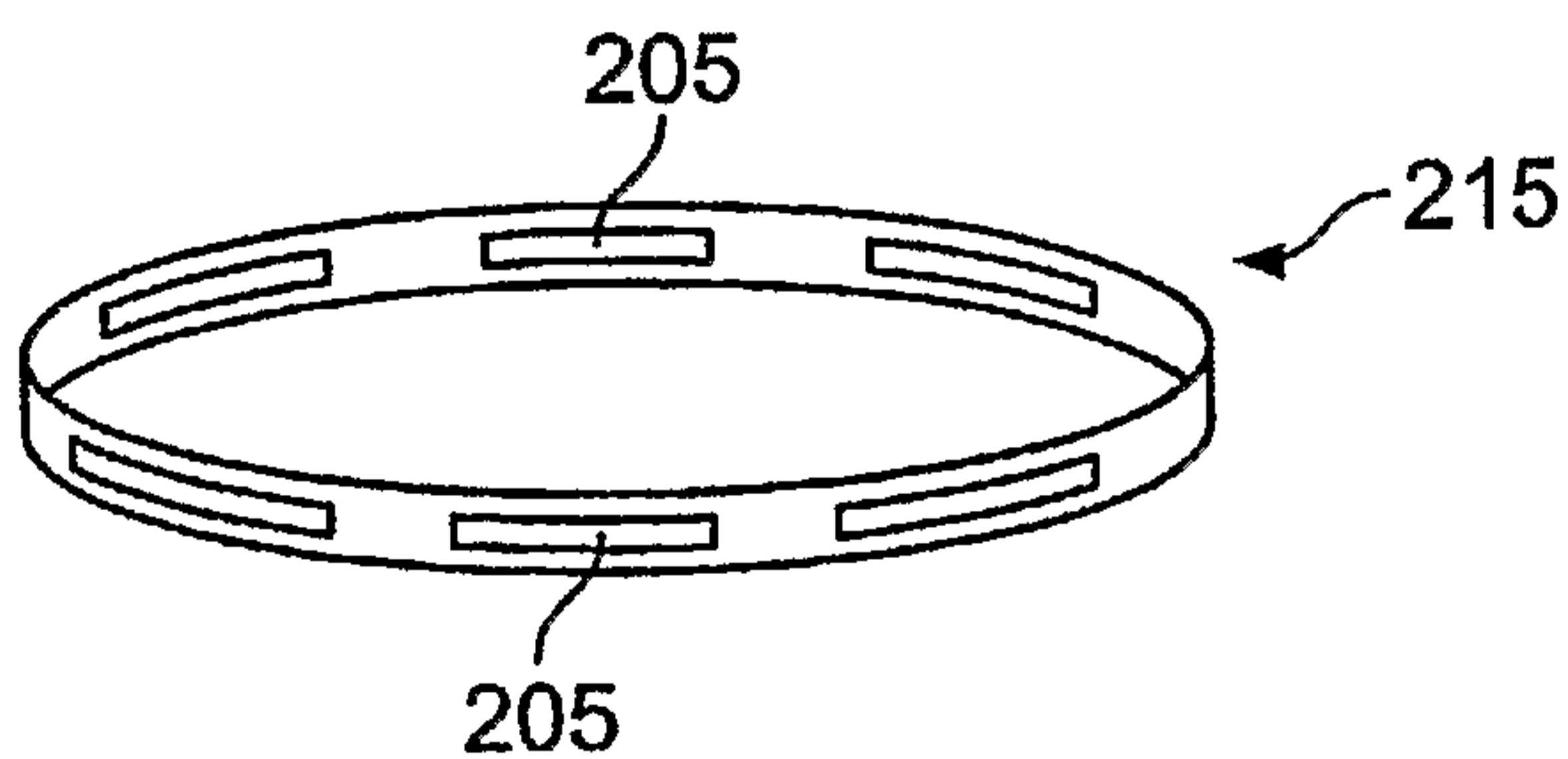


FIG. 2B

3/19

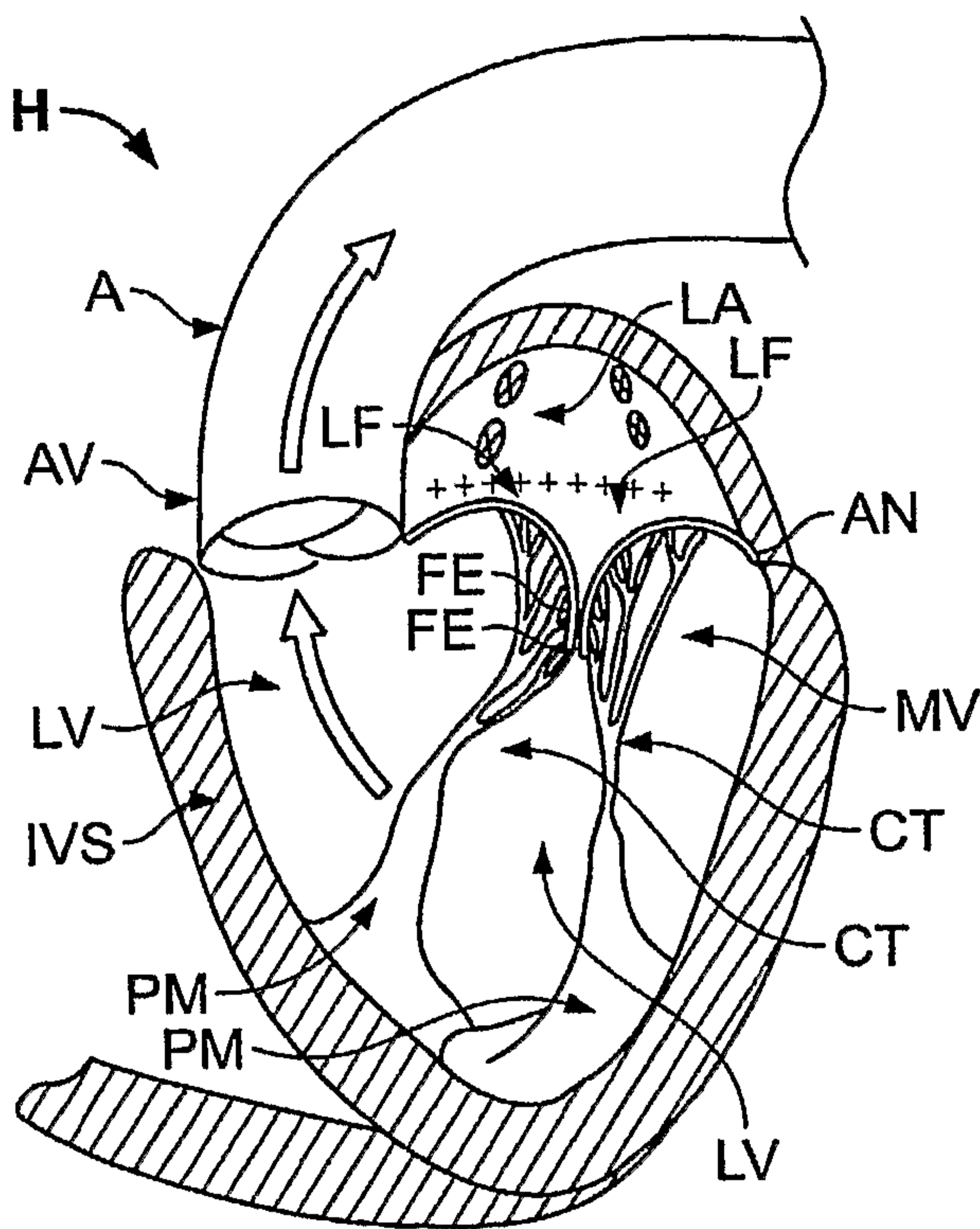


FIG. 3

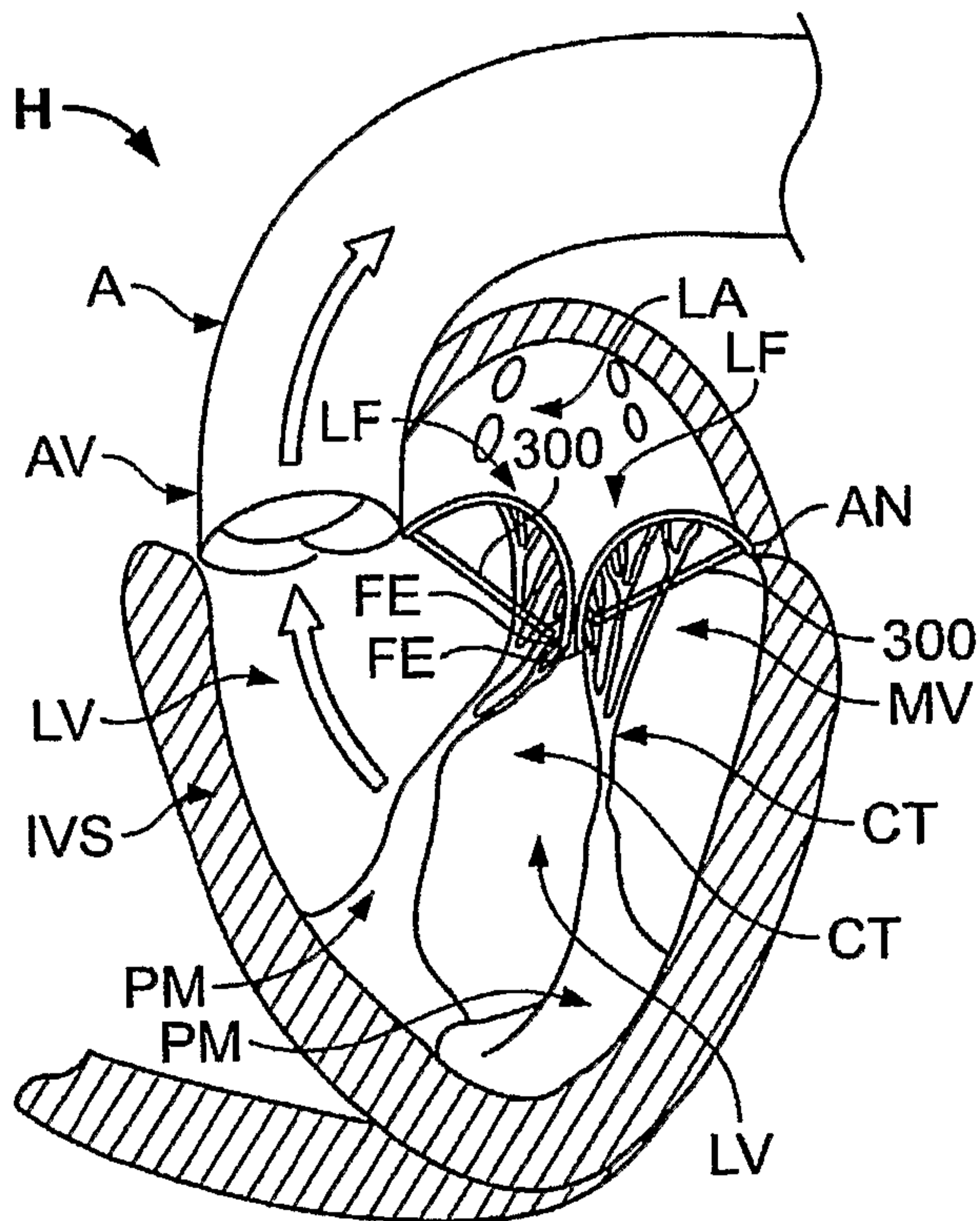


FIG. 4

4/19

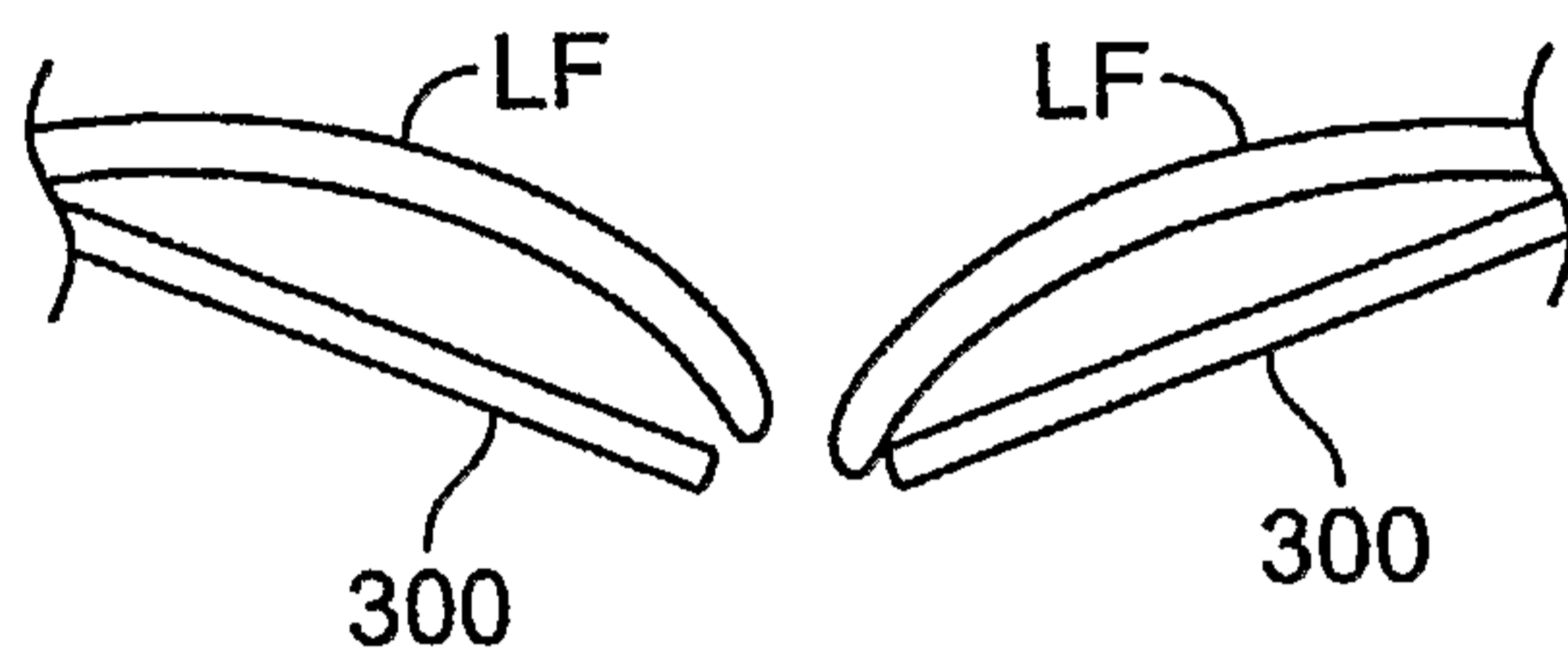


FIG. 5A

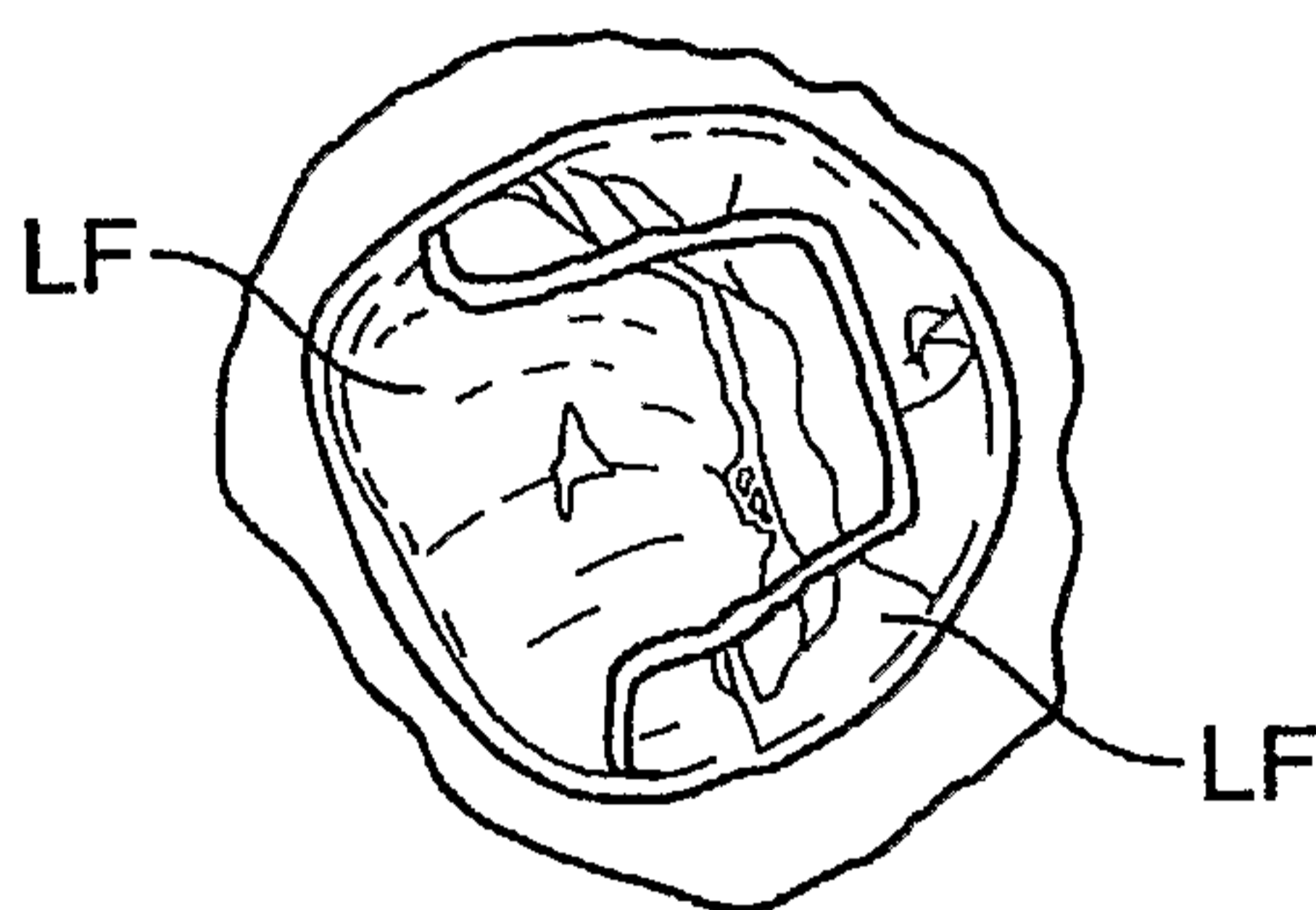


FIG. 5B

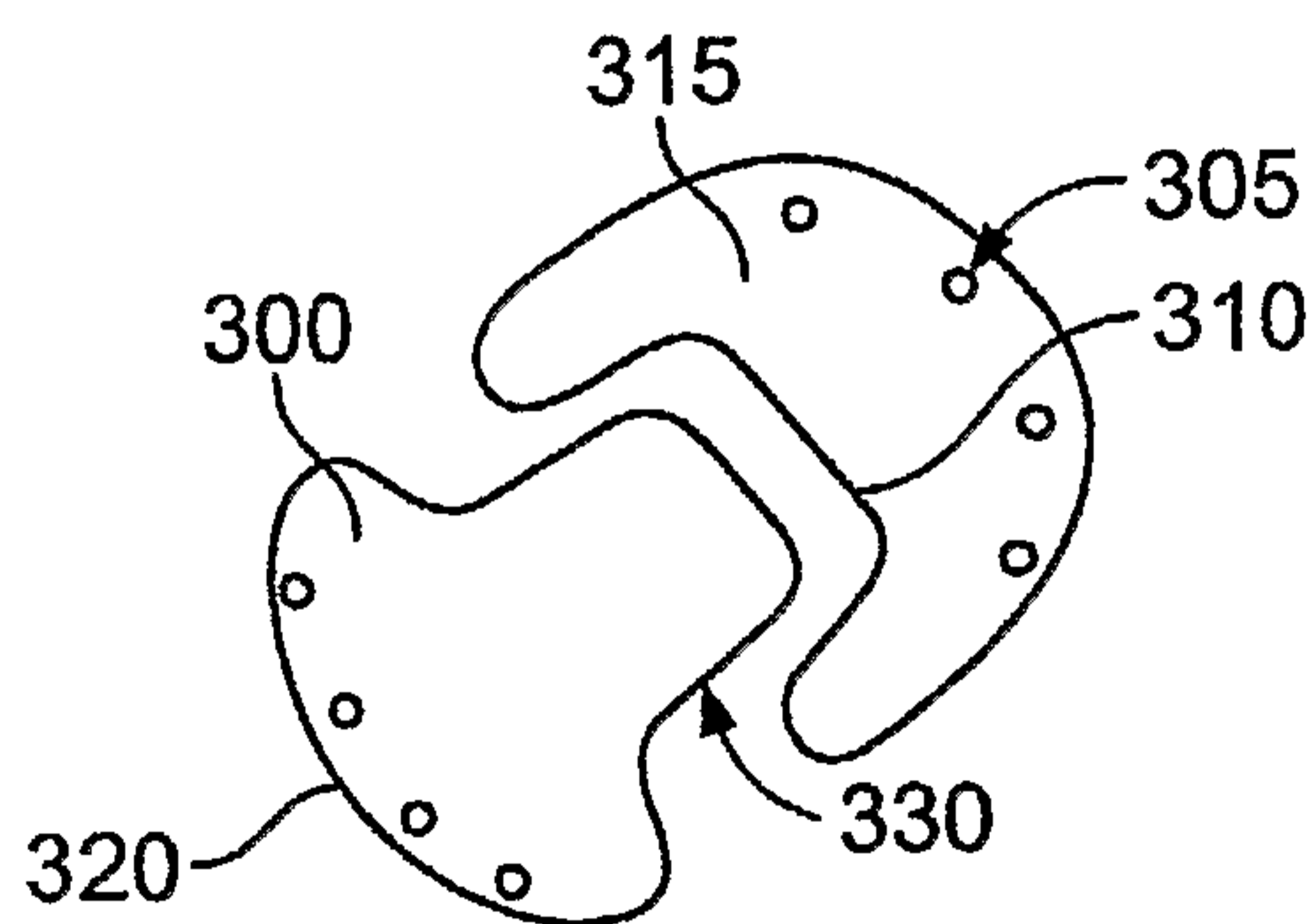


FIG. 5C

5/19

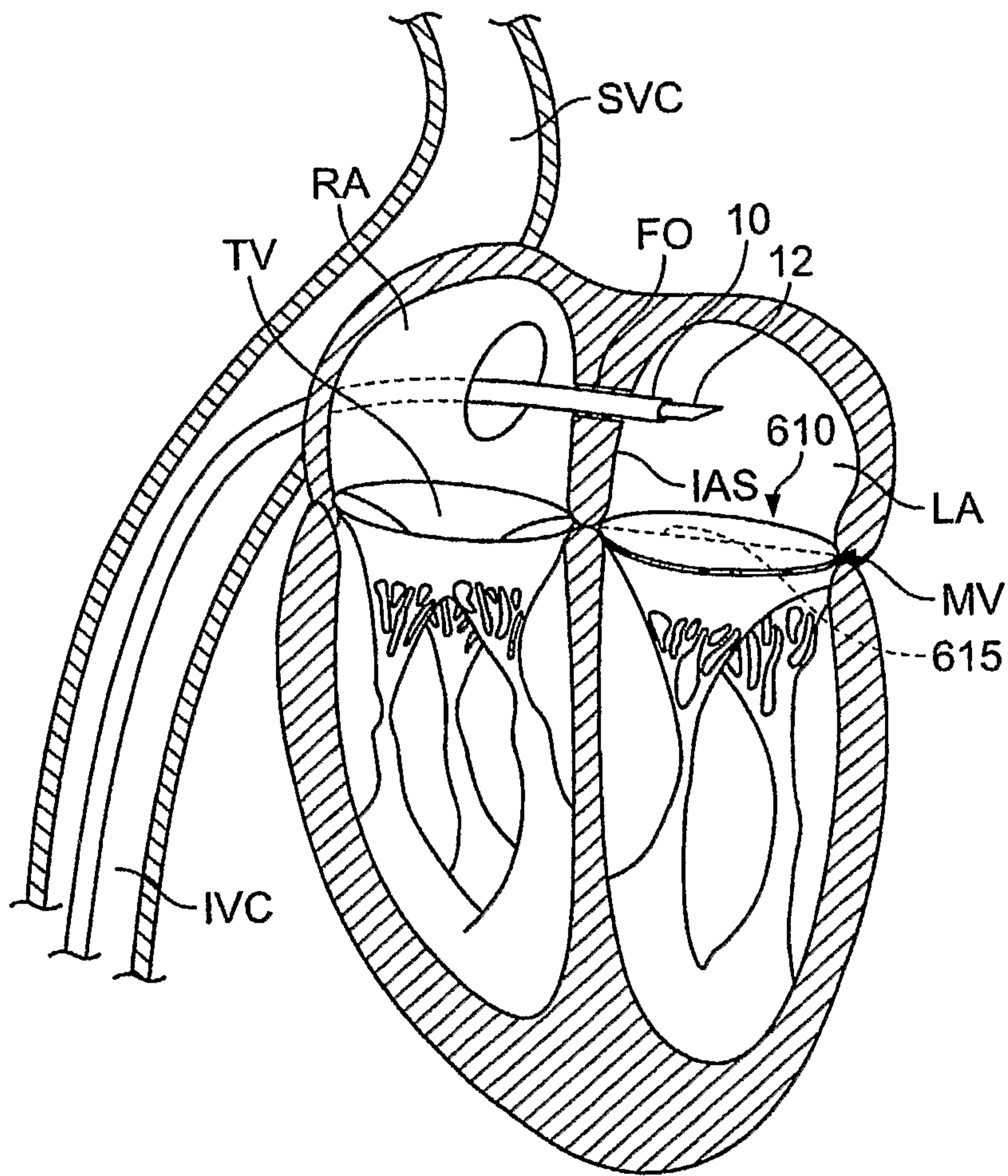


FIG. 6A

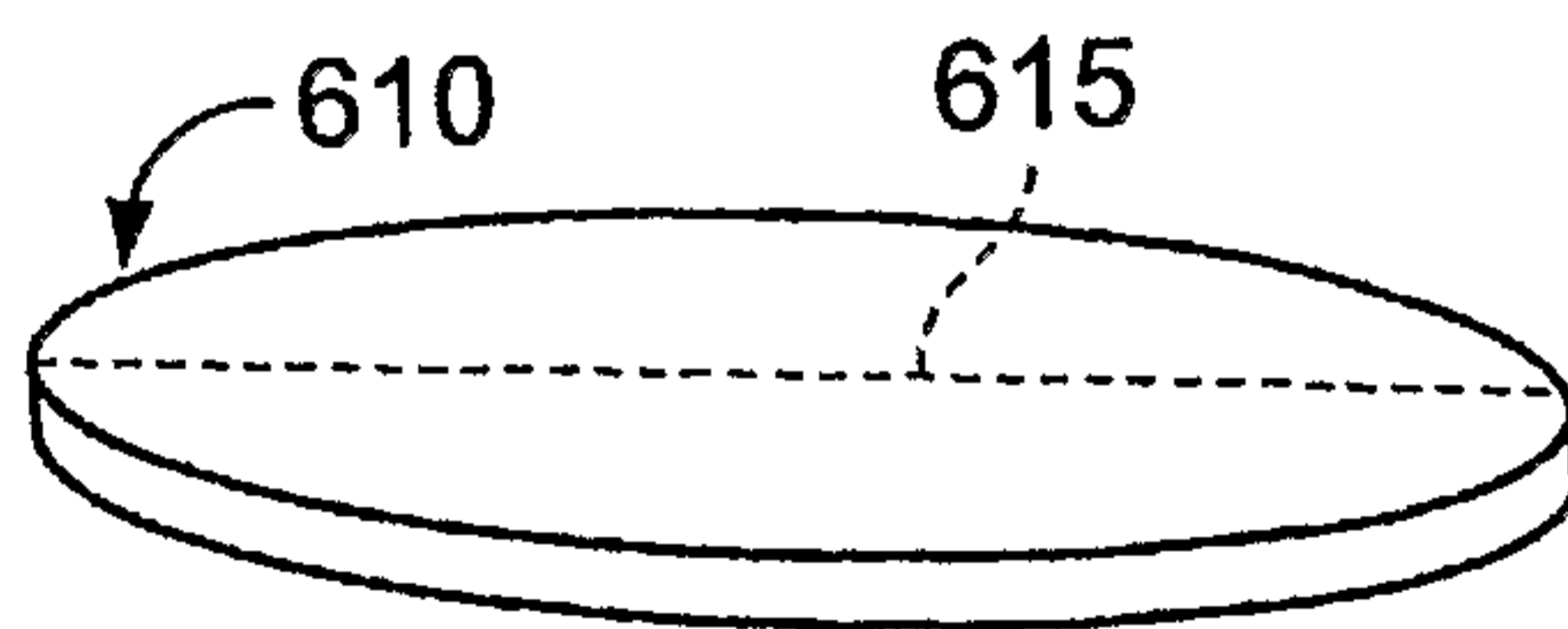


FIG. 6B

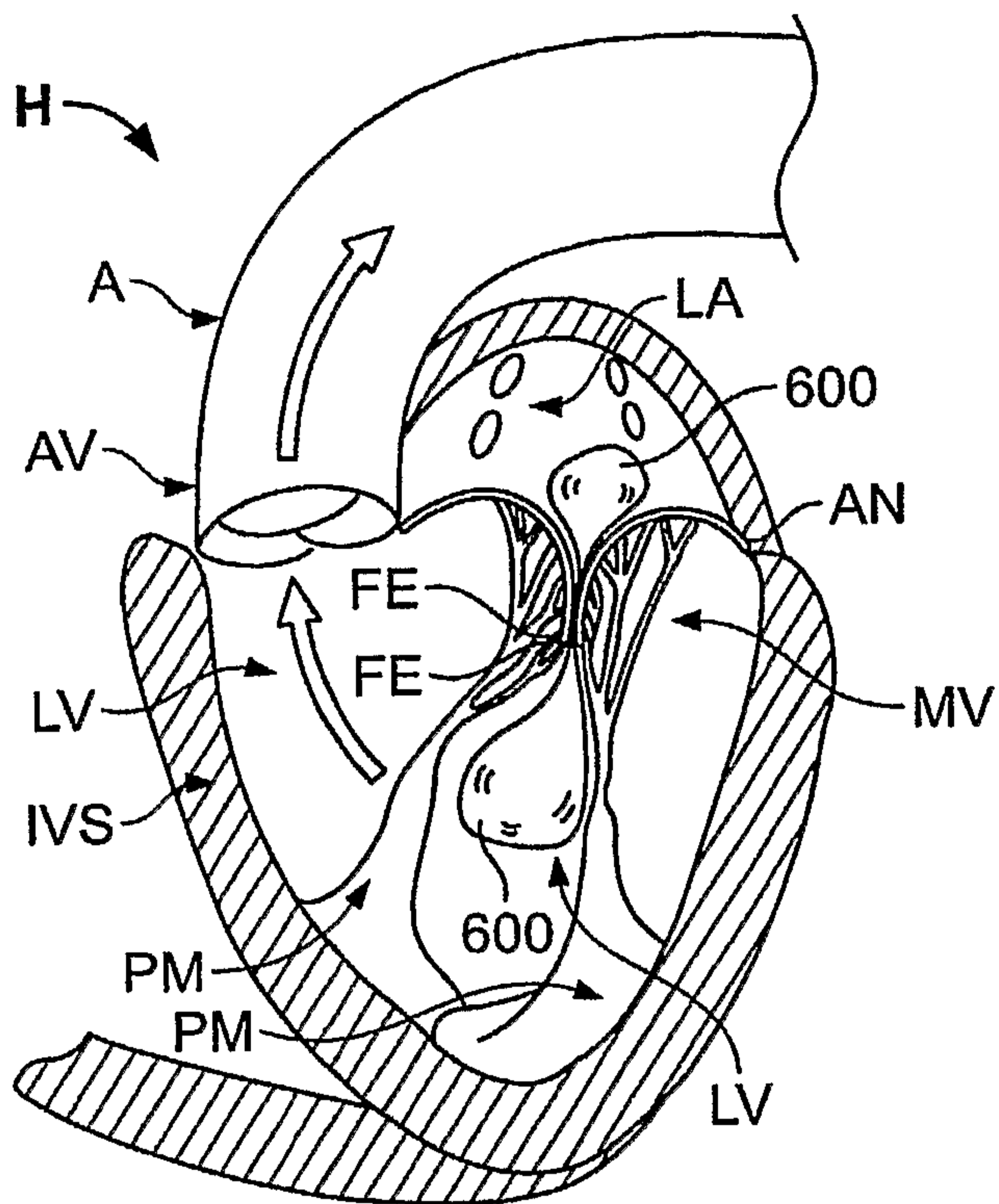


FIG. 7A

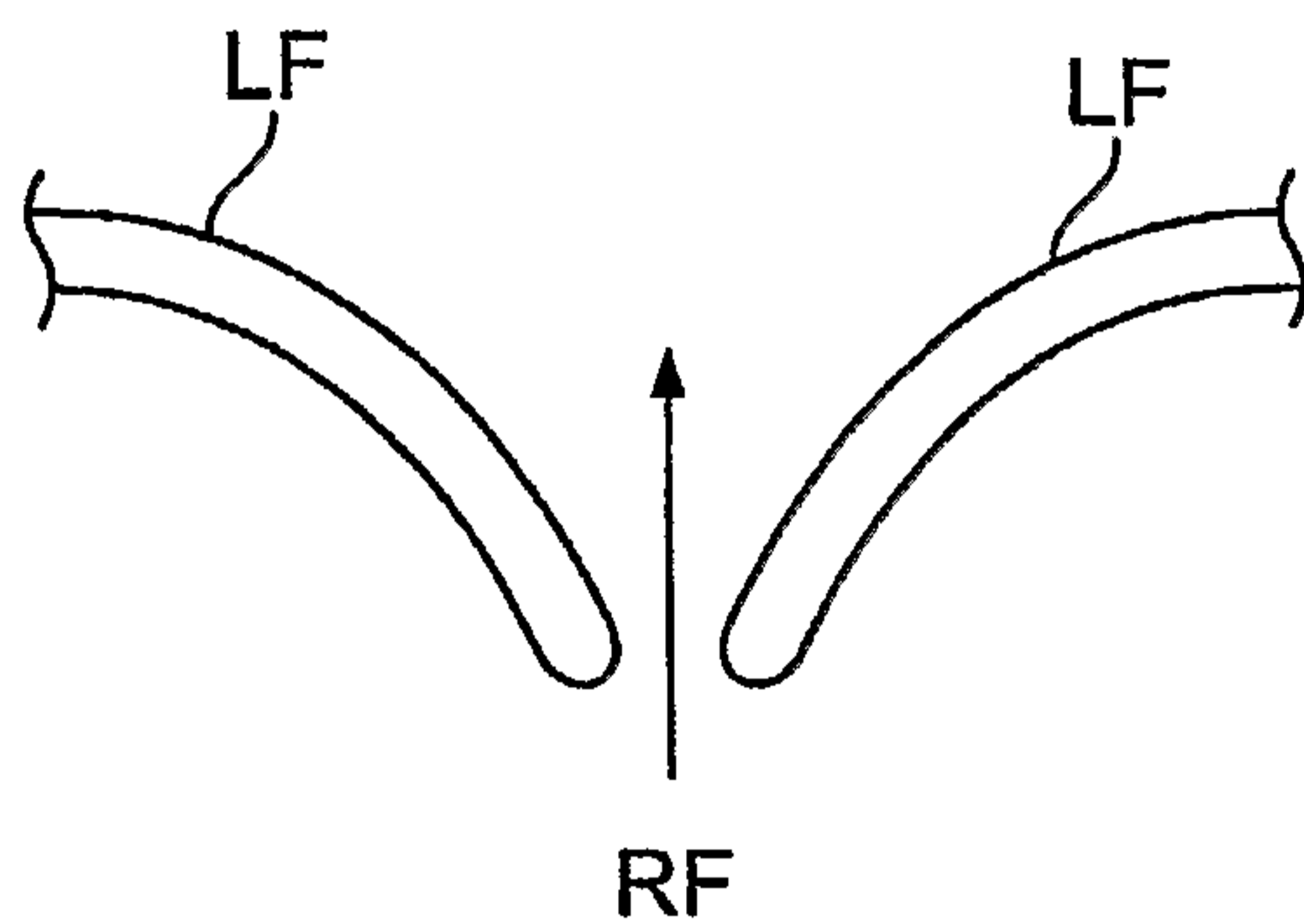


FIG. 7B

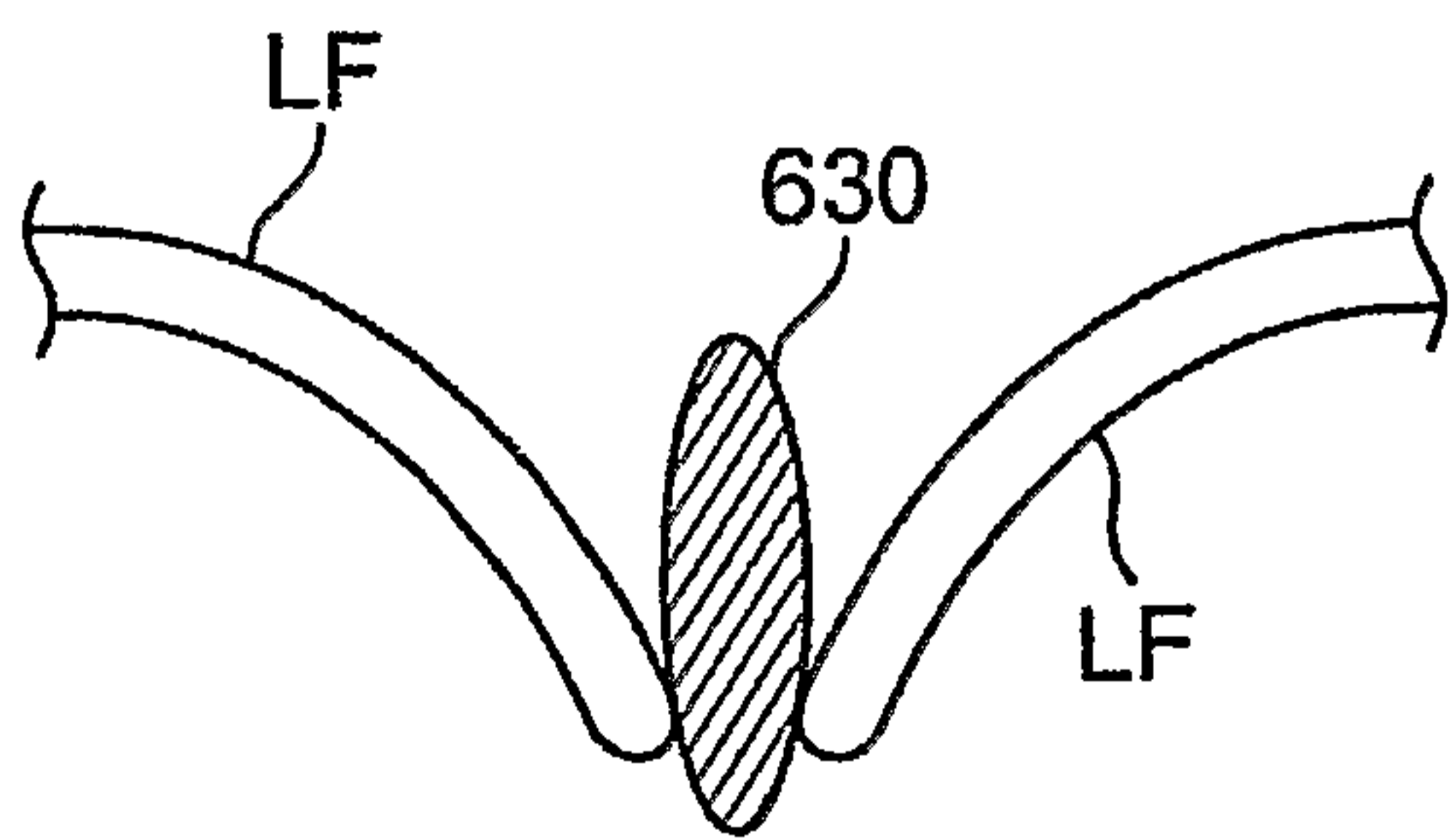


FIG. 7C

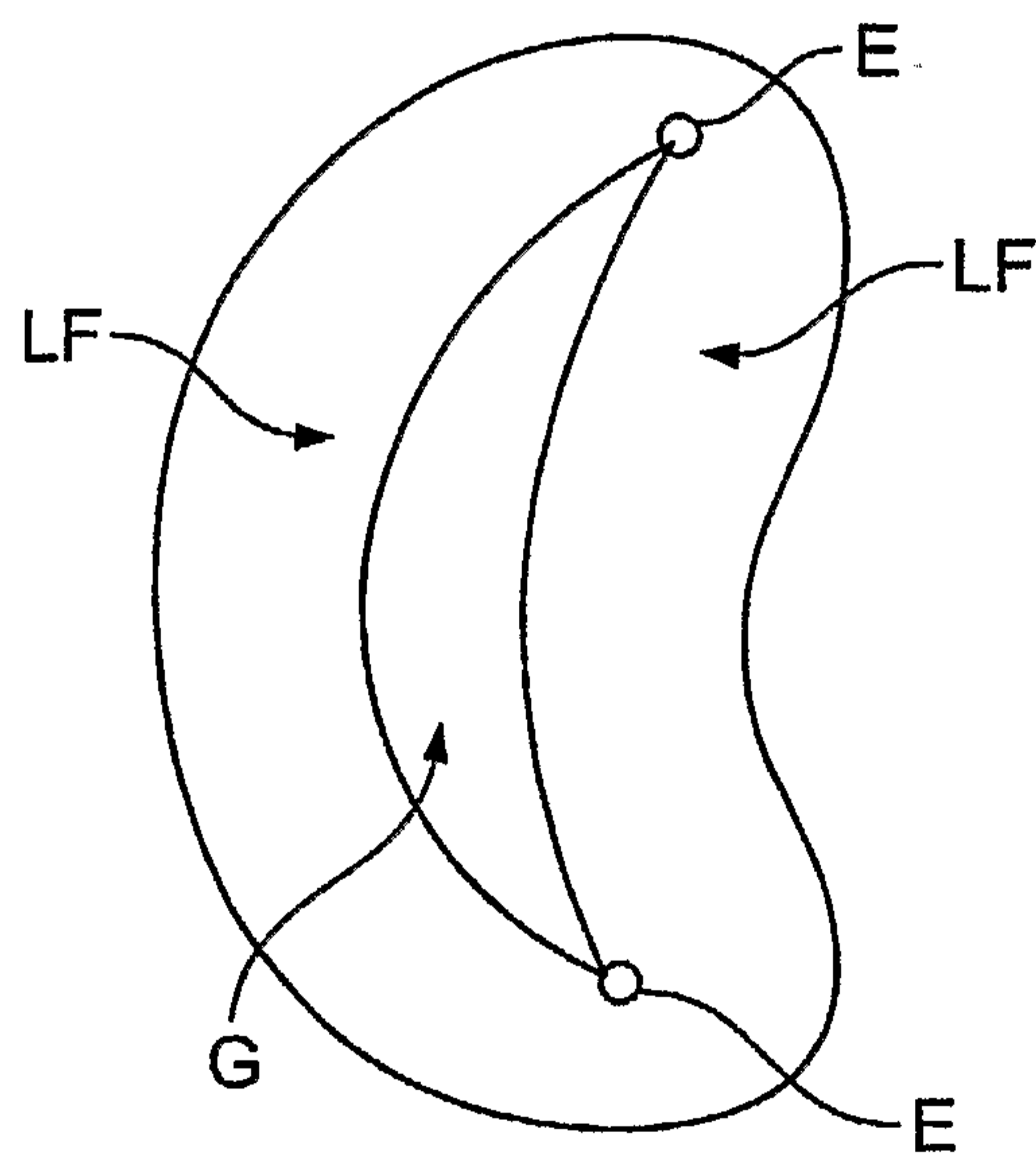


FIG. 7D

7/19

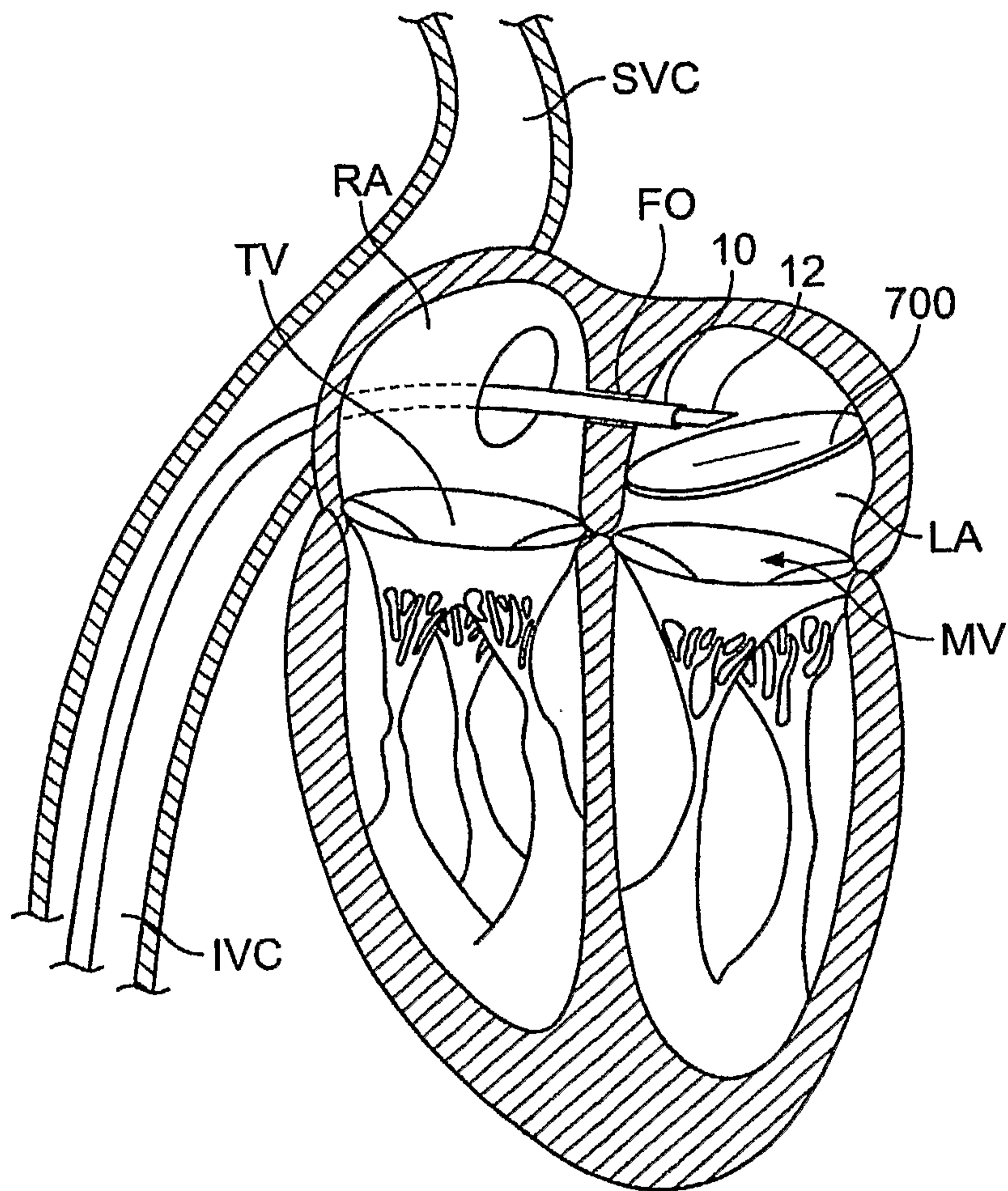


FIG. 8

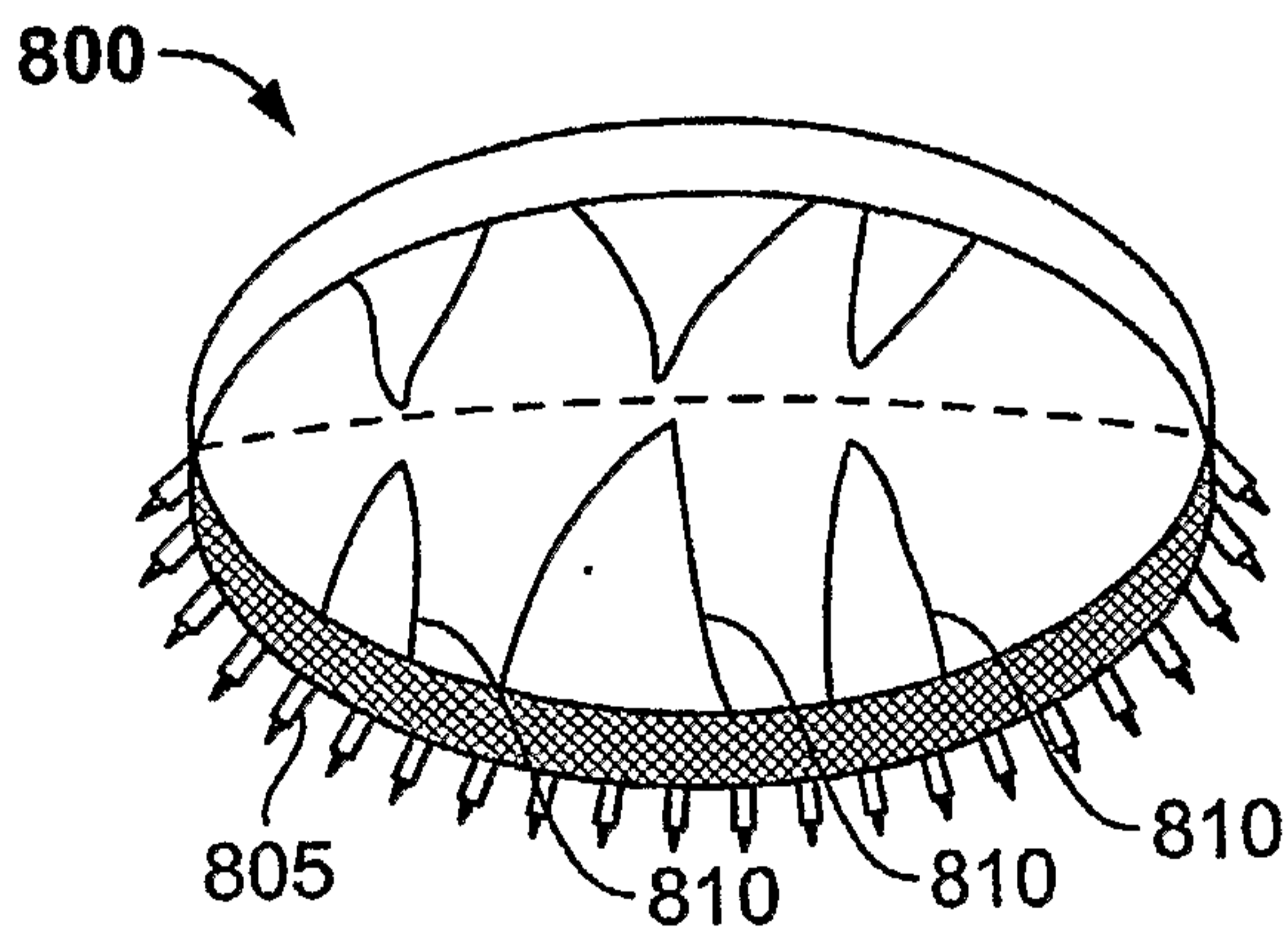


FIG. 9A

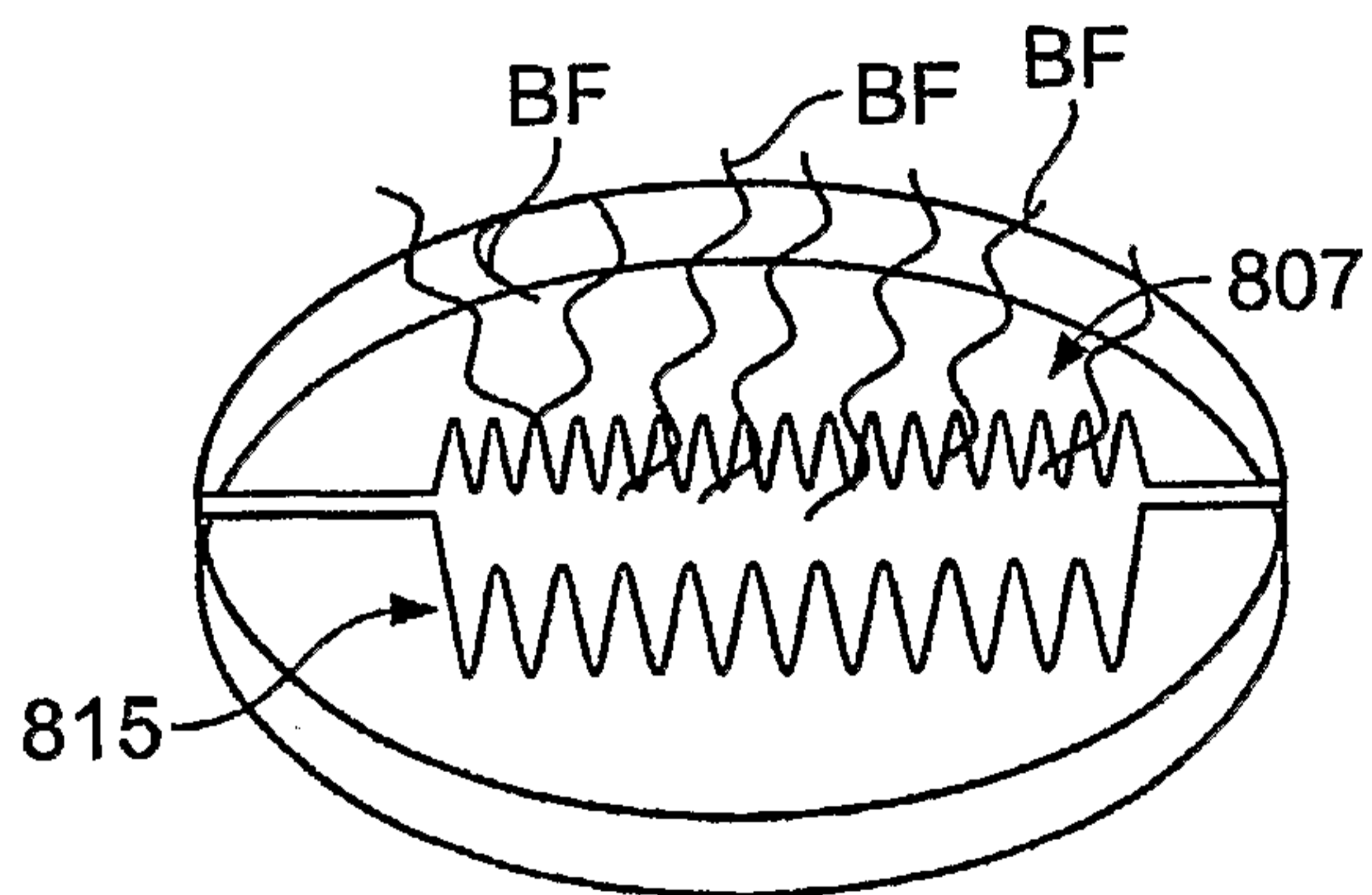


FIG. 9B

8/19

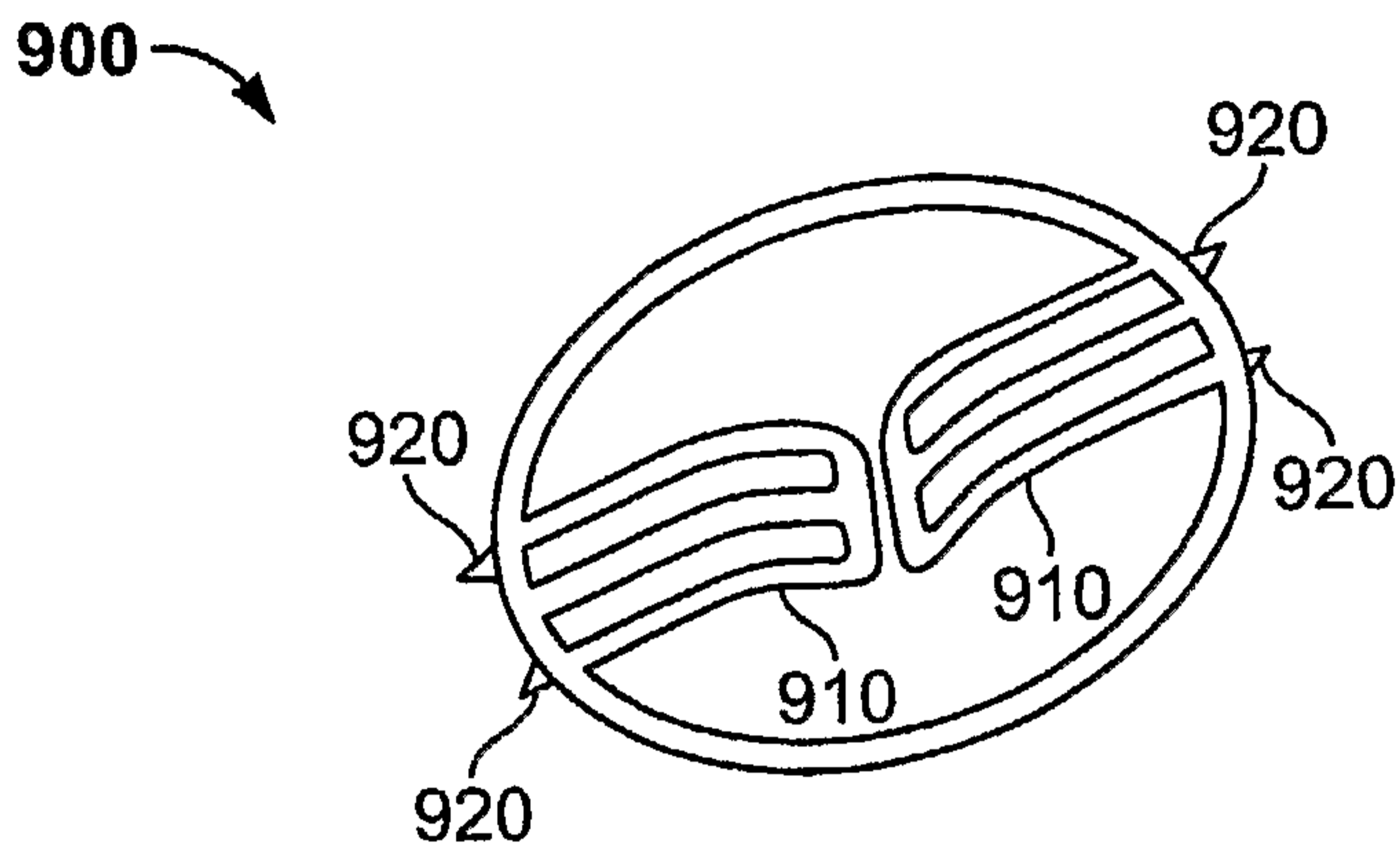


FIG. 10

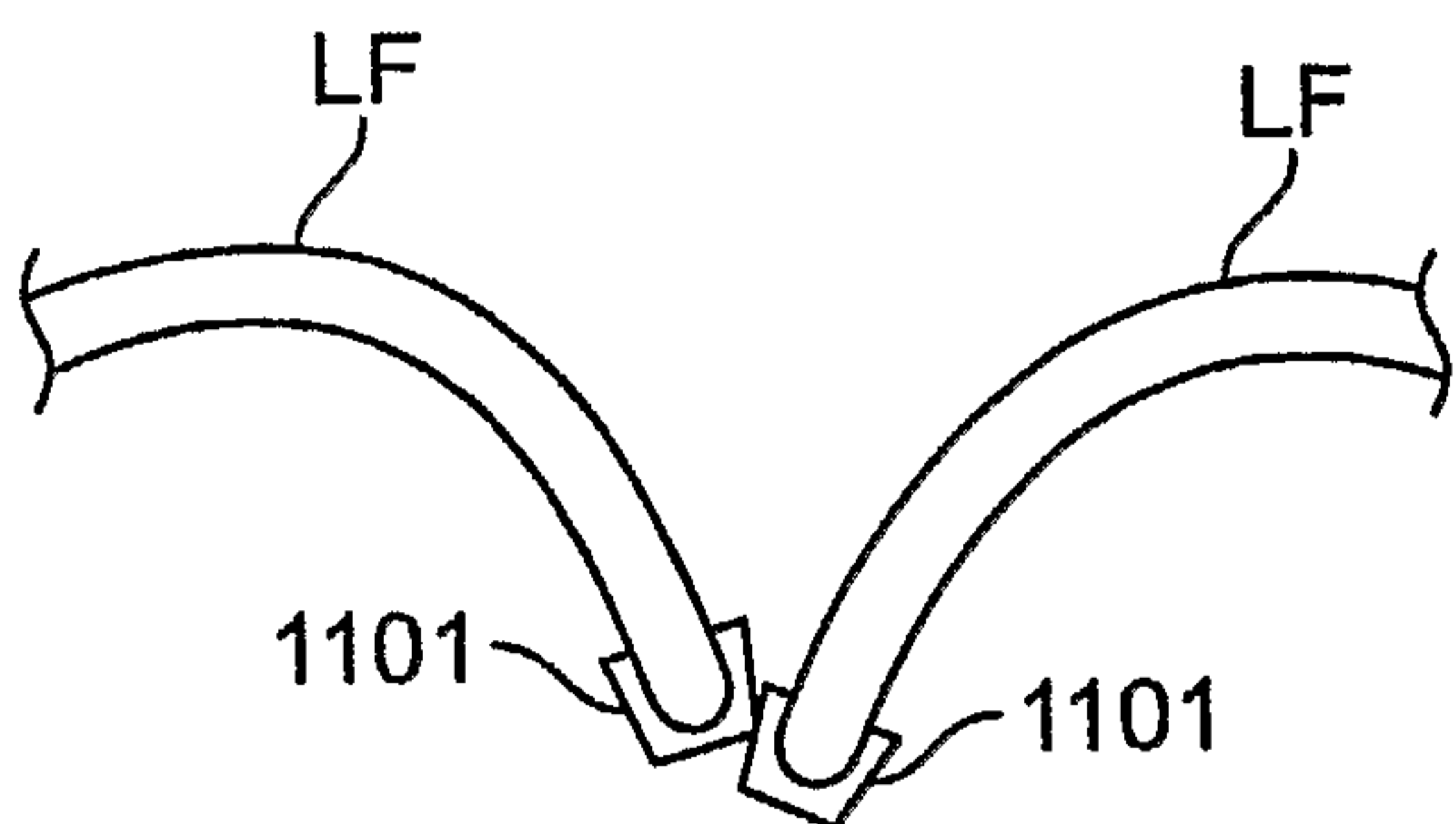


FIG. 11A

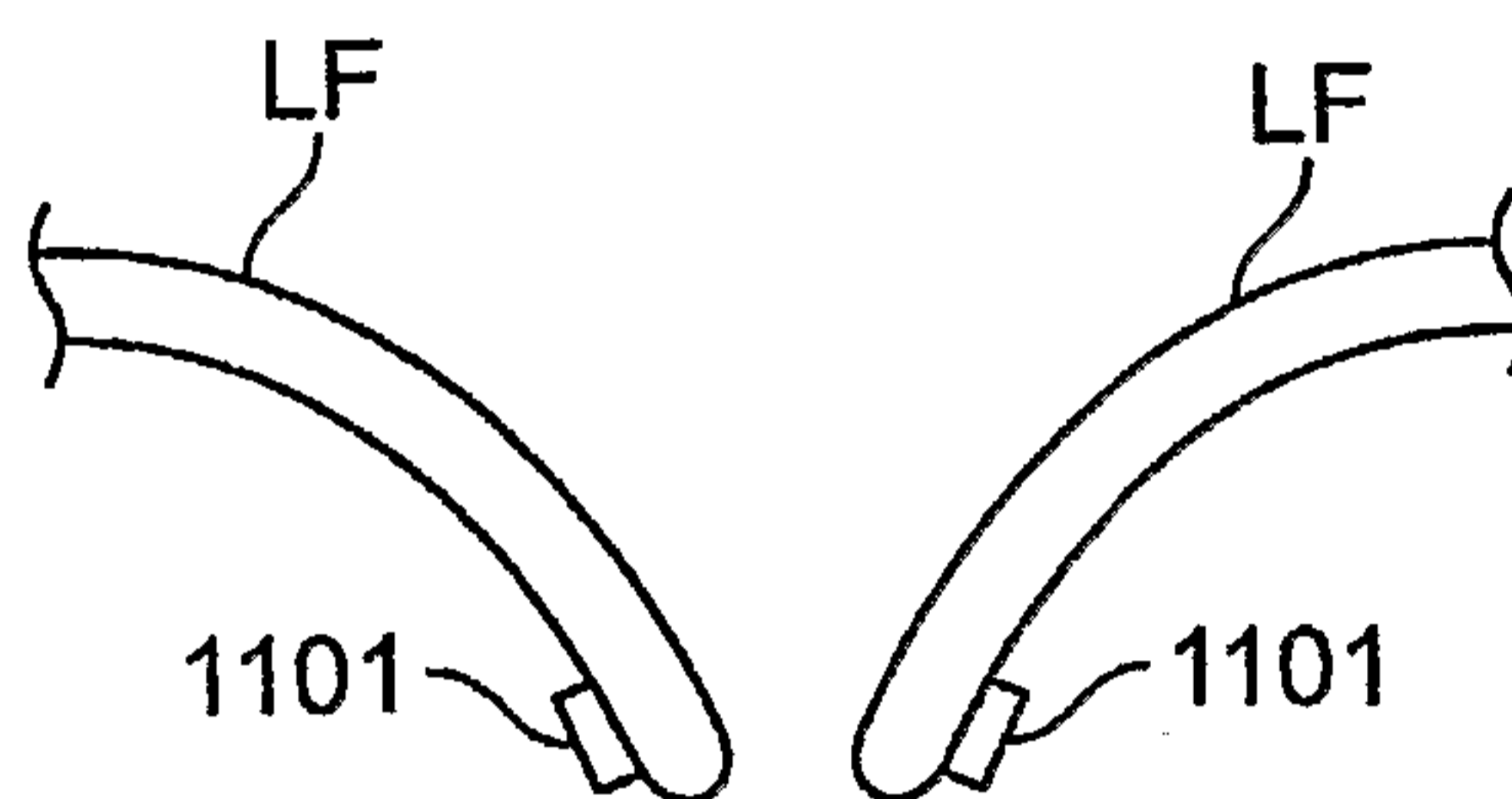


FIG. 11B

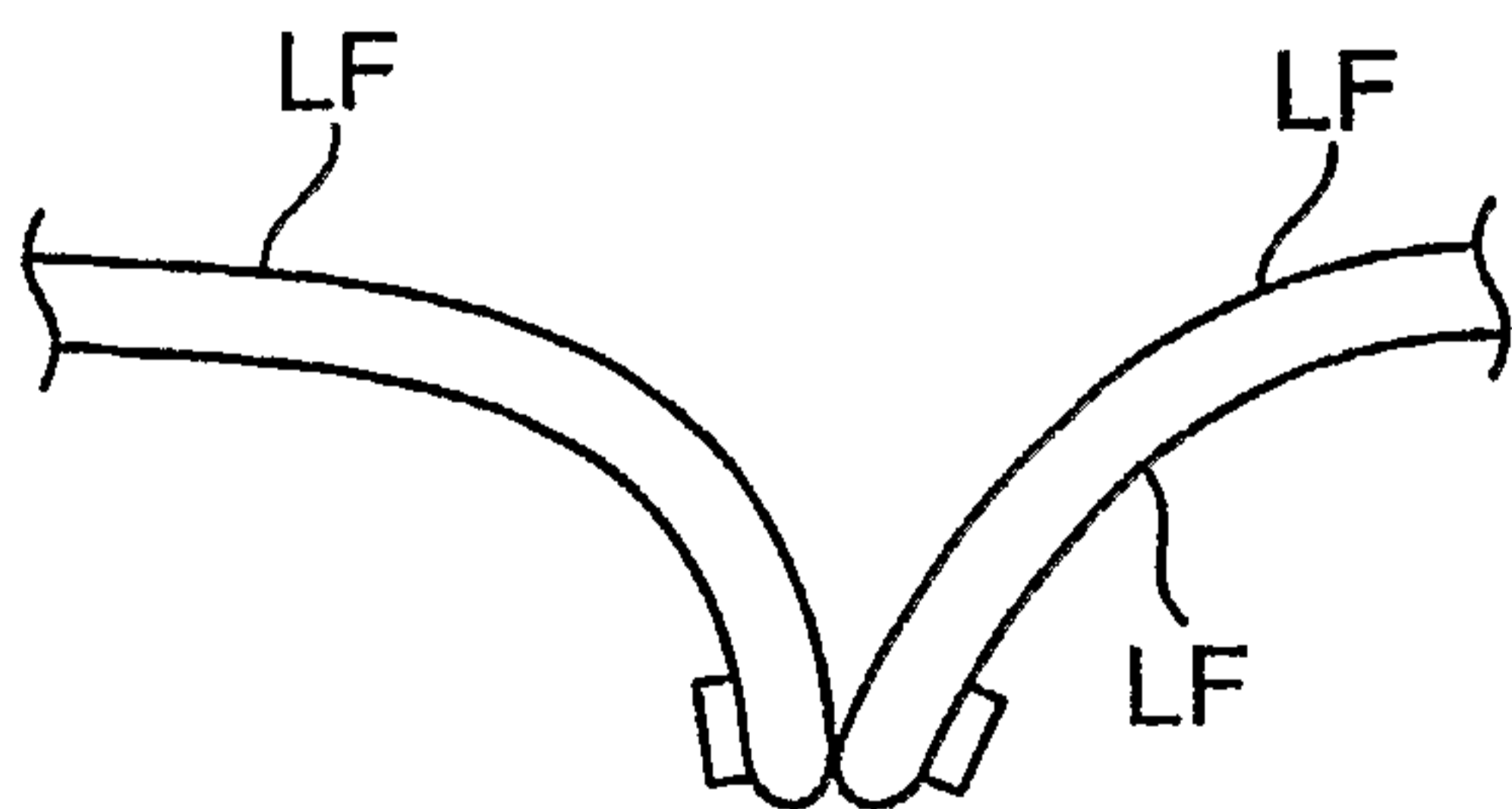


FIG. 11C

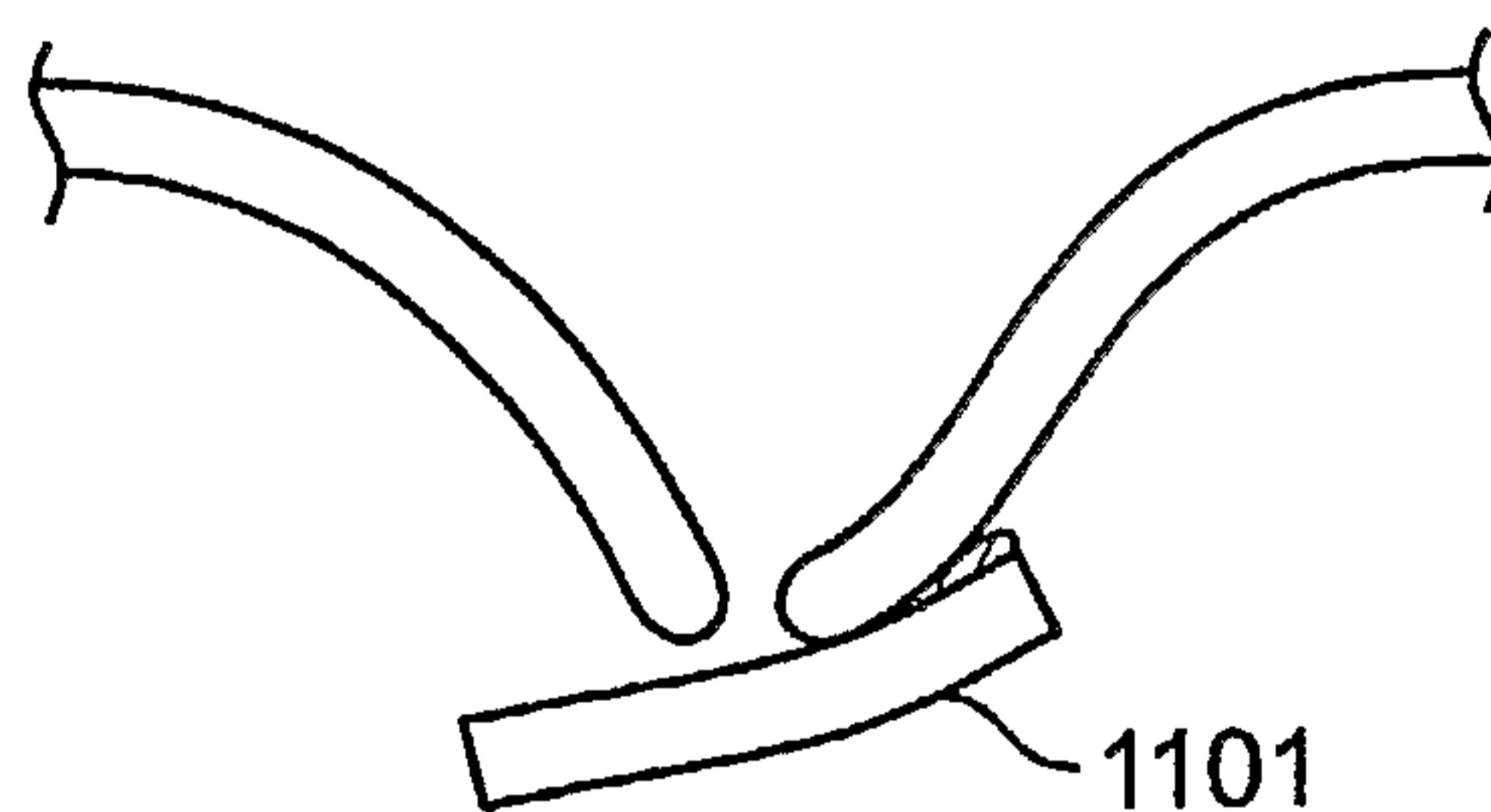


FIG. 11D

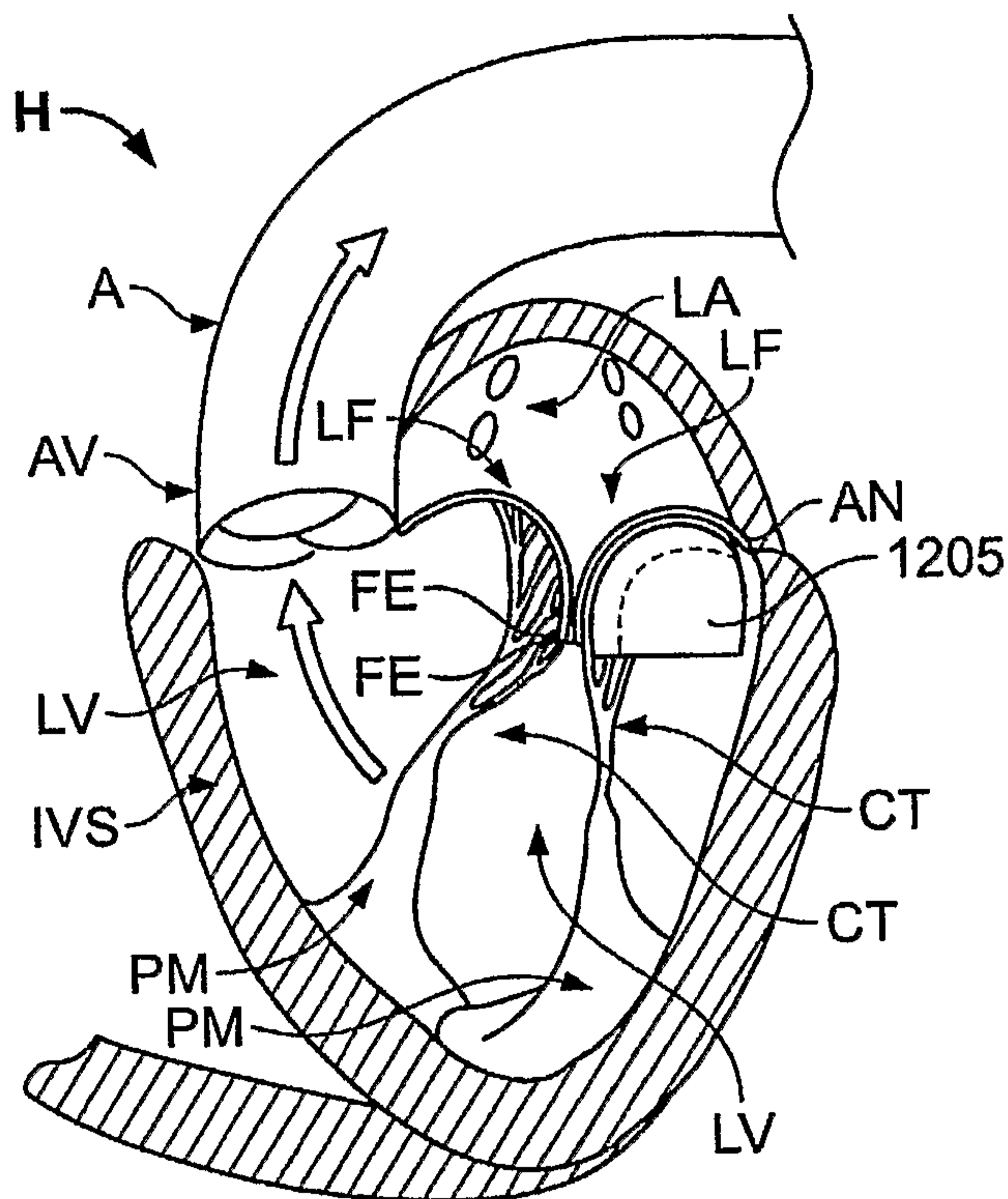


FIG. 12

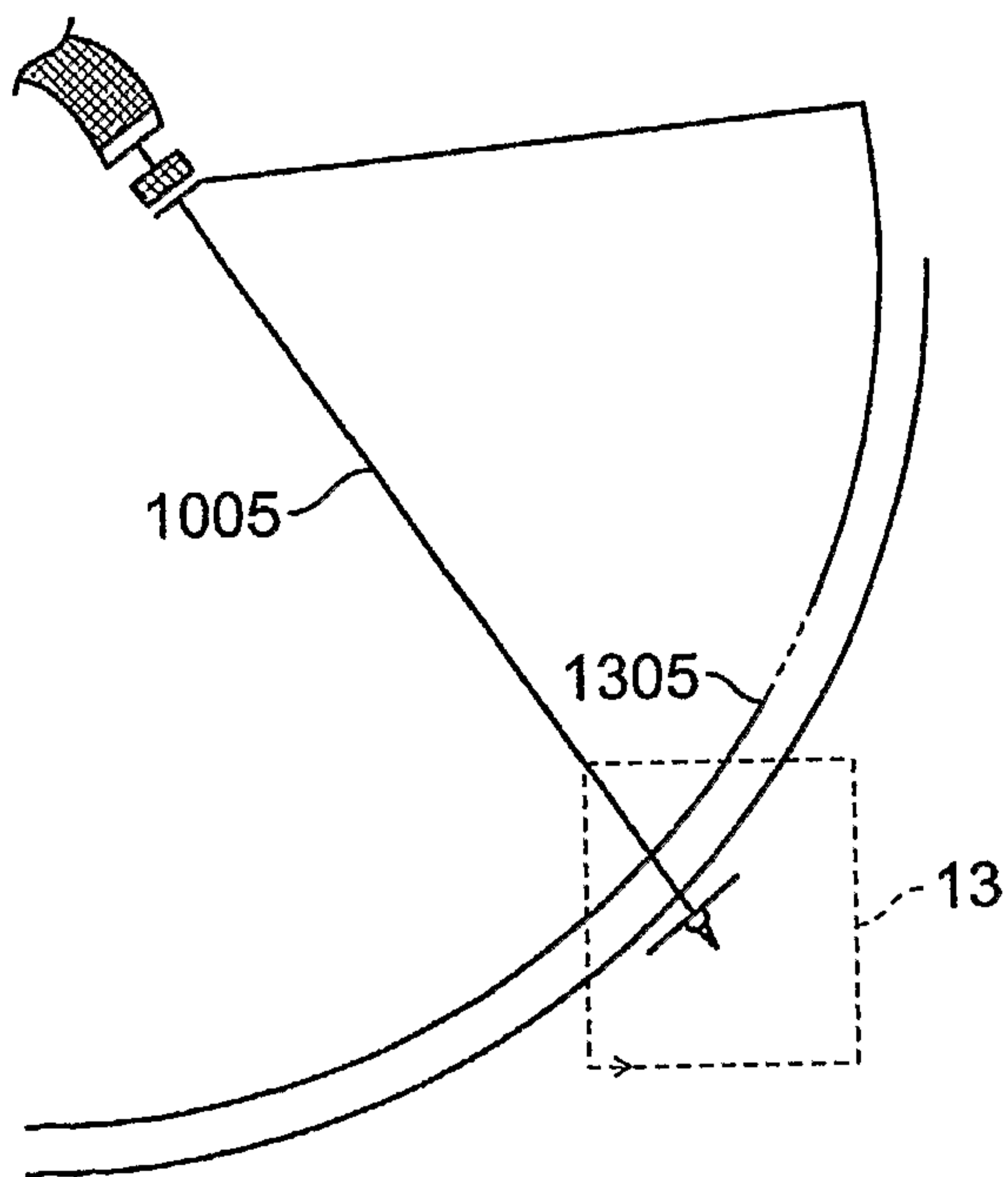


FIG. 13A

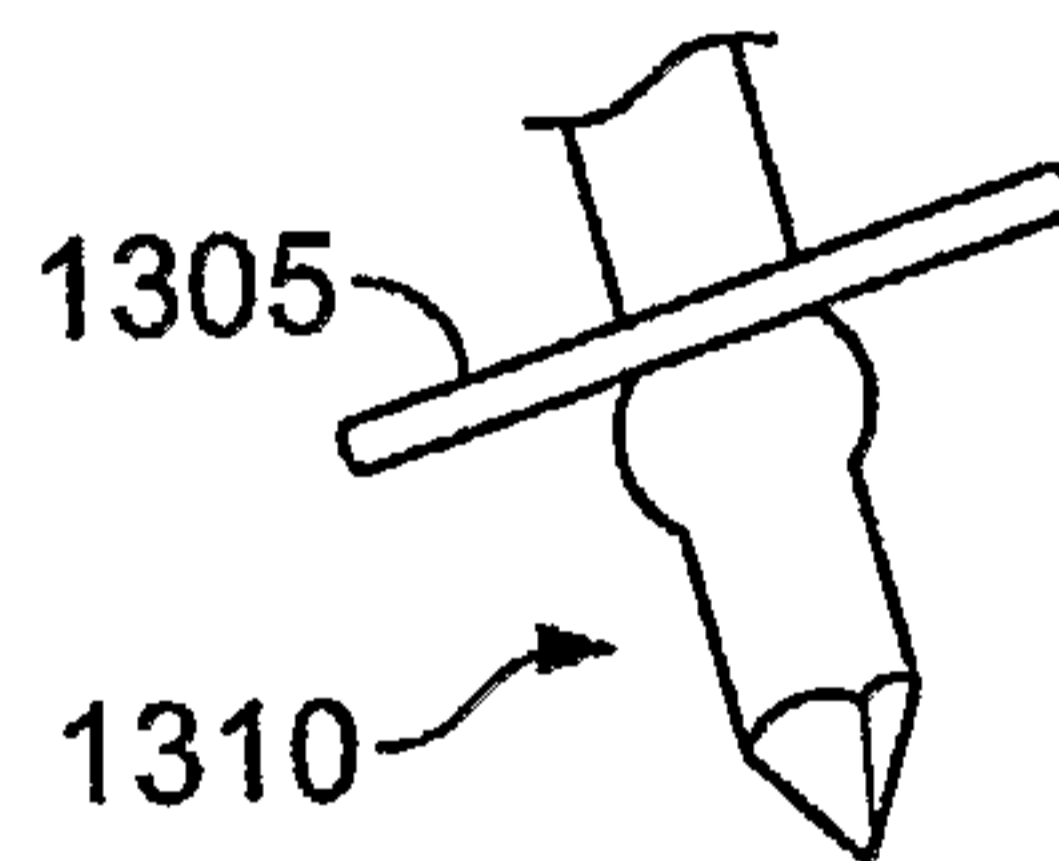


FIG. 13B

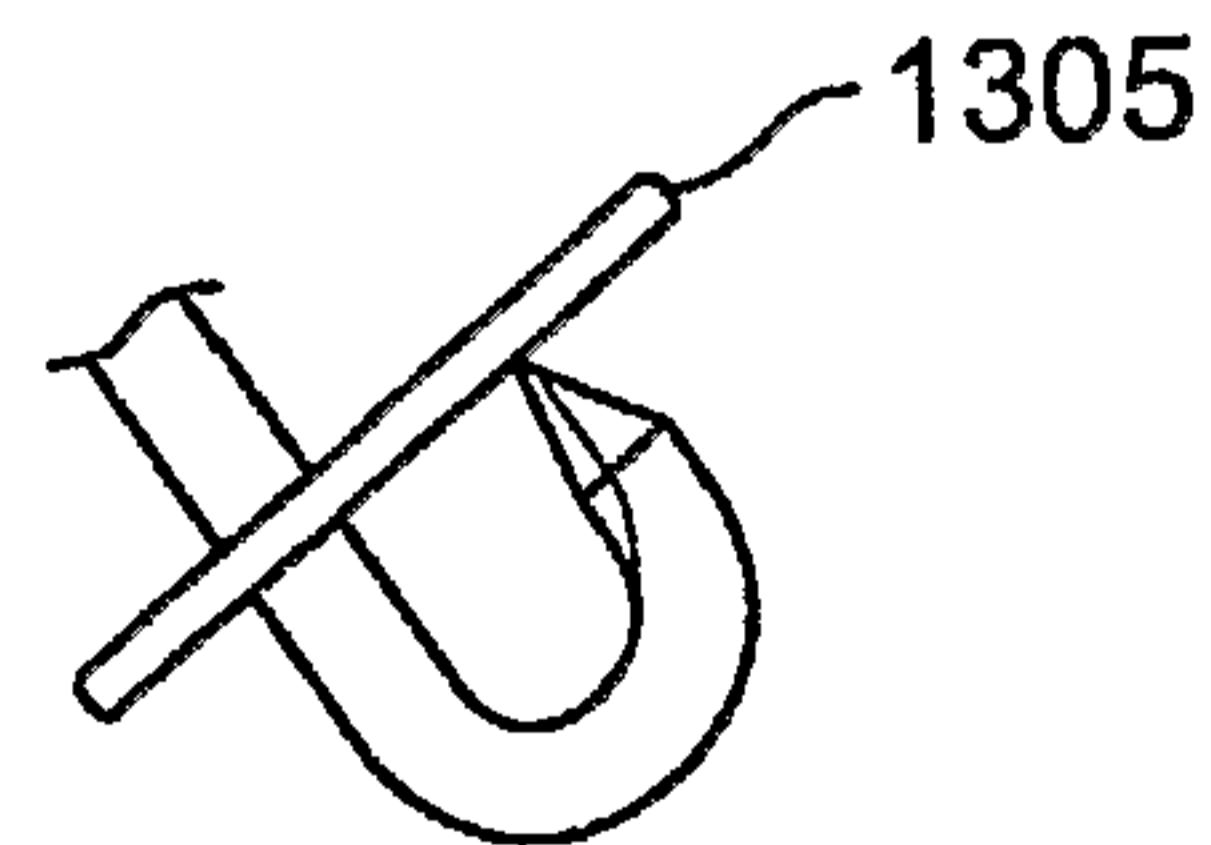


FIG. 13C

10/19

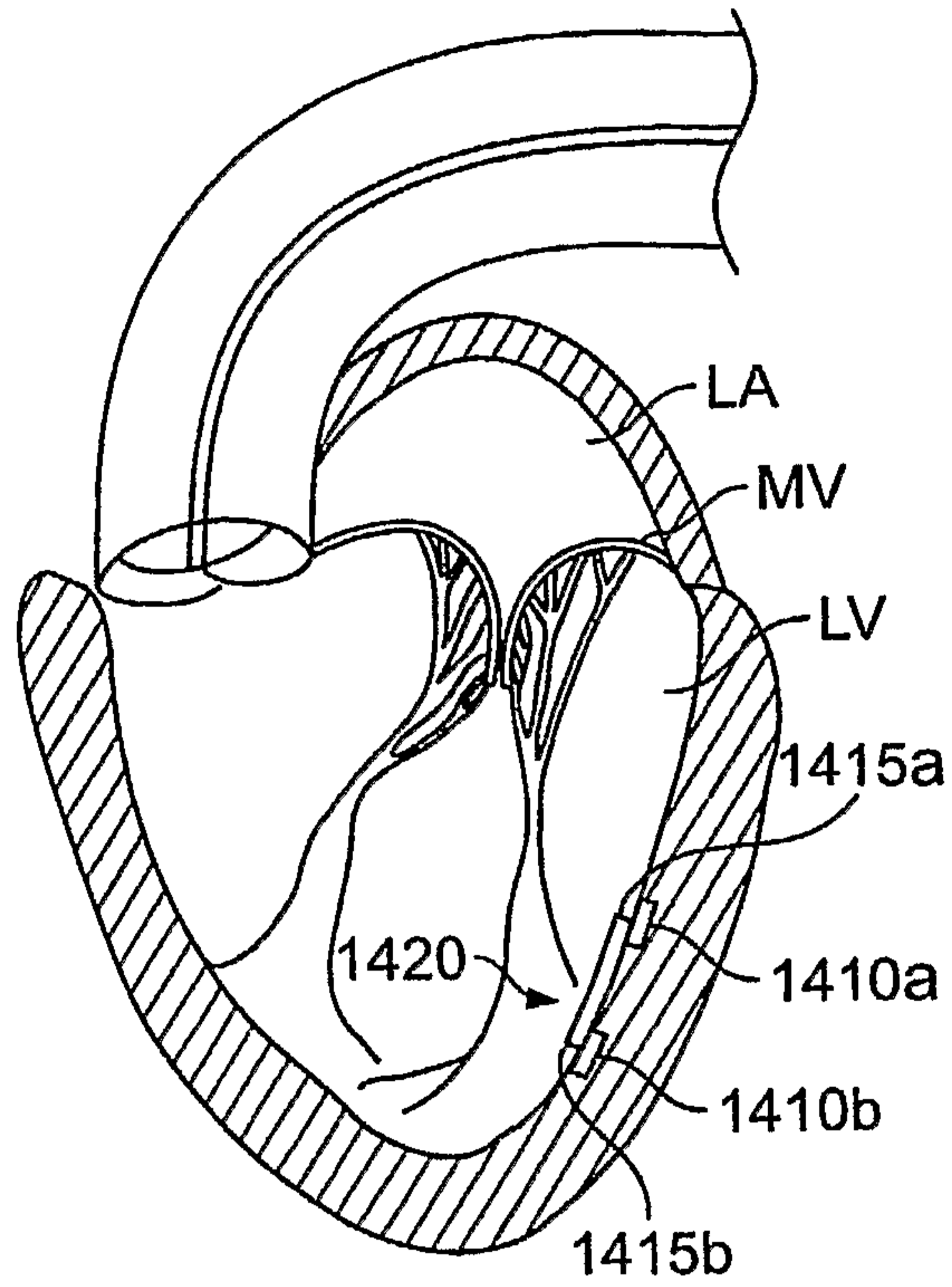


FIG. 14

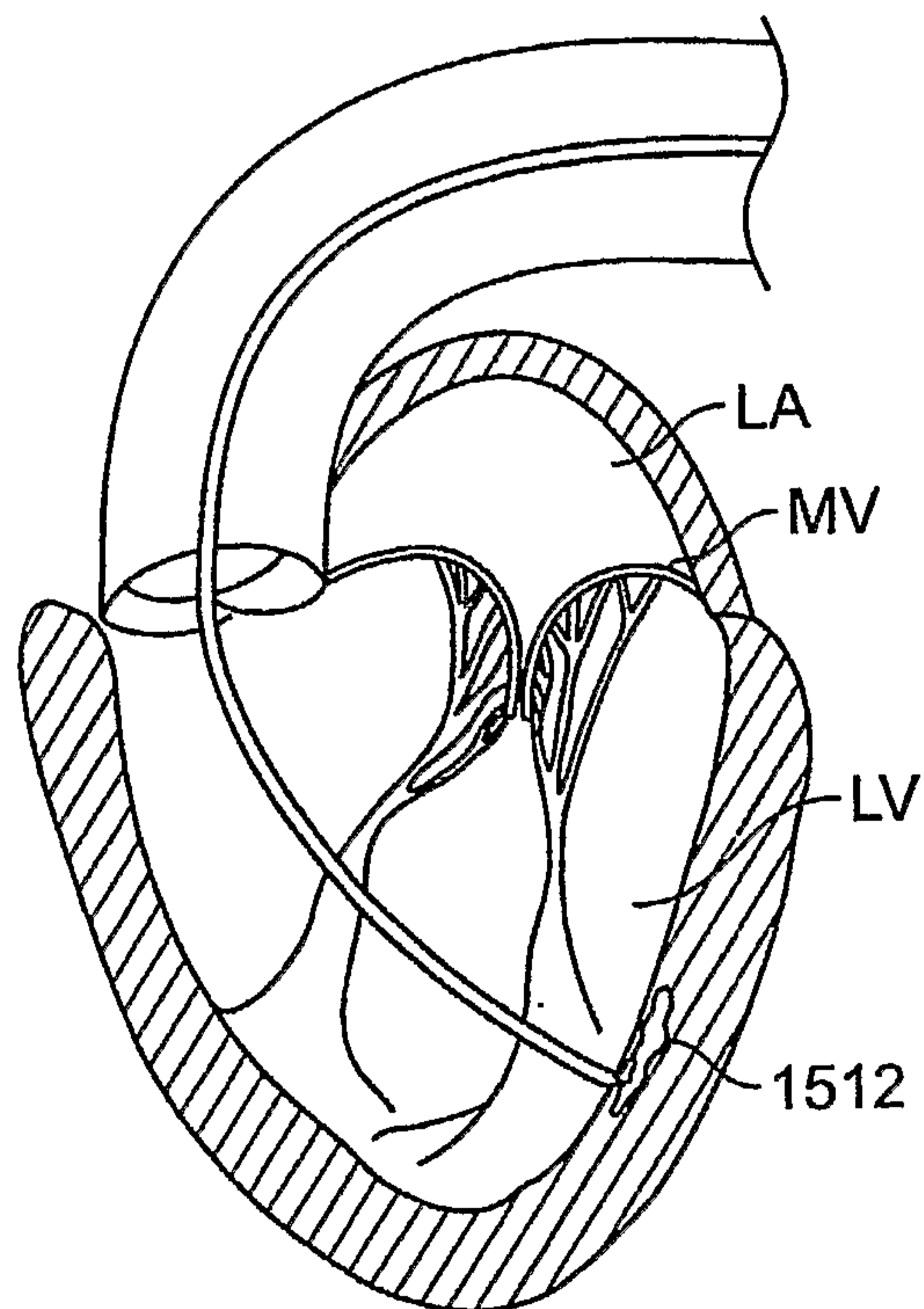


FIG. 15

11/19

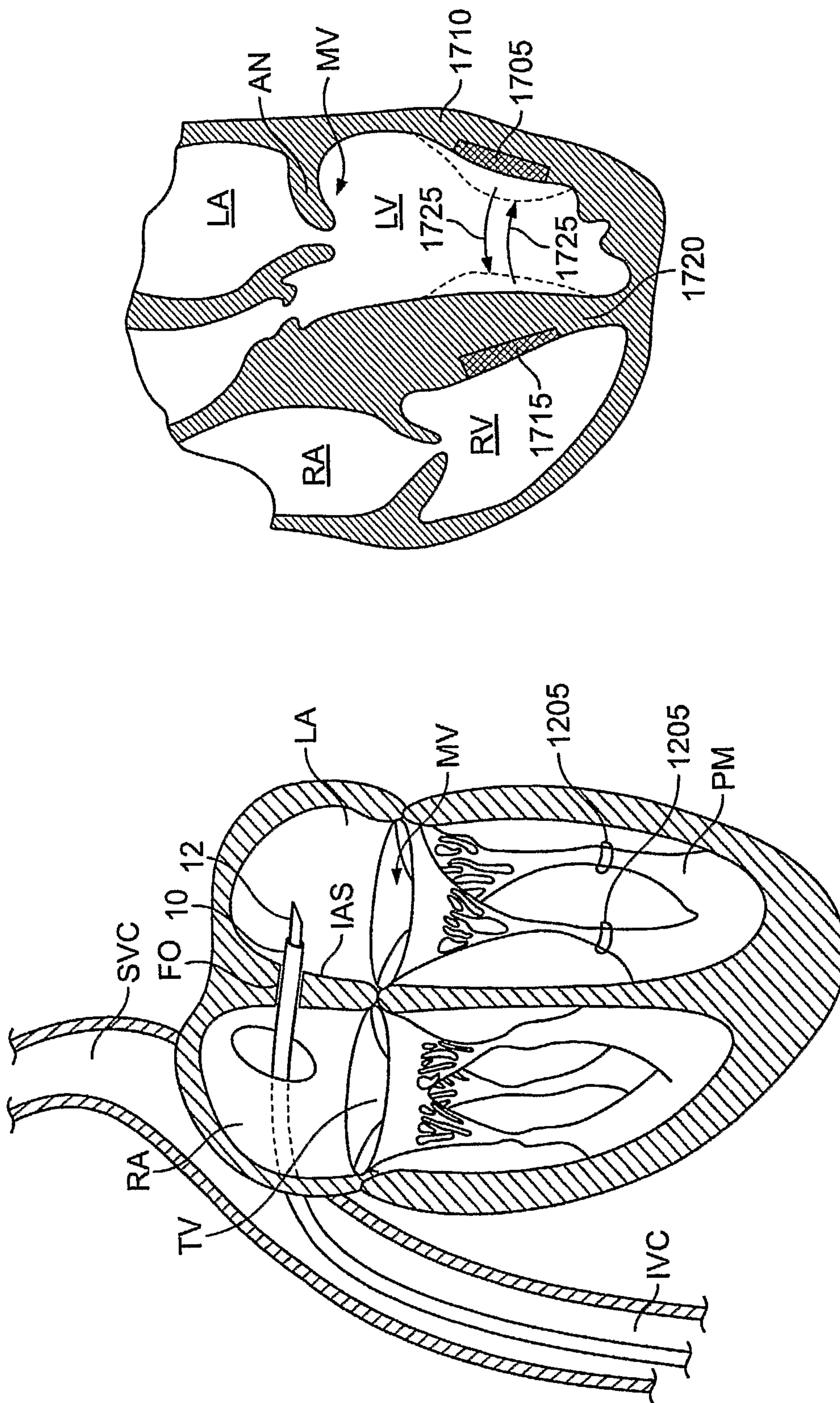


FIG. 17

FIG. 16

12/19

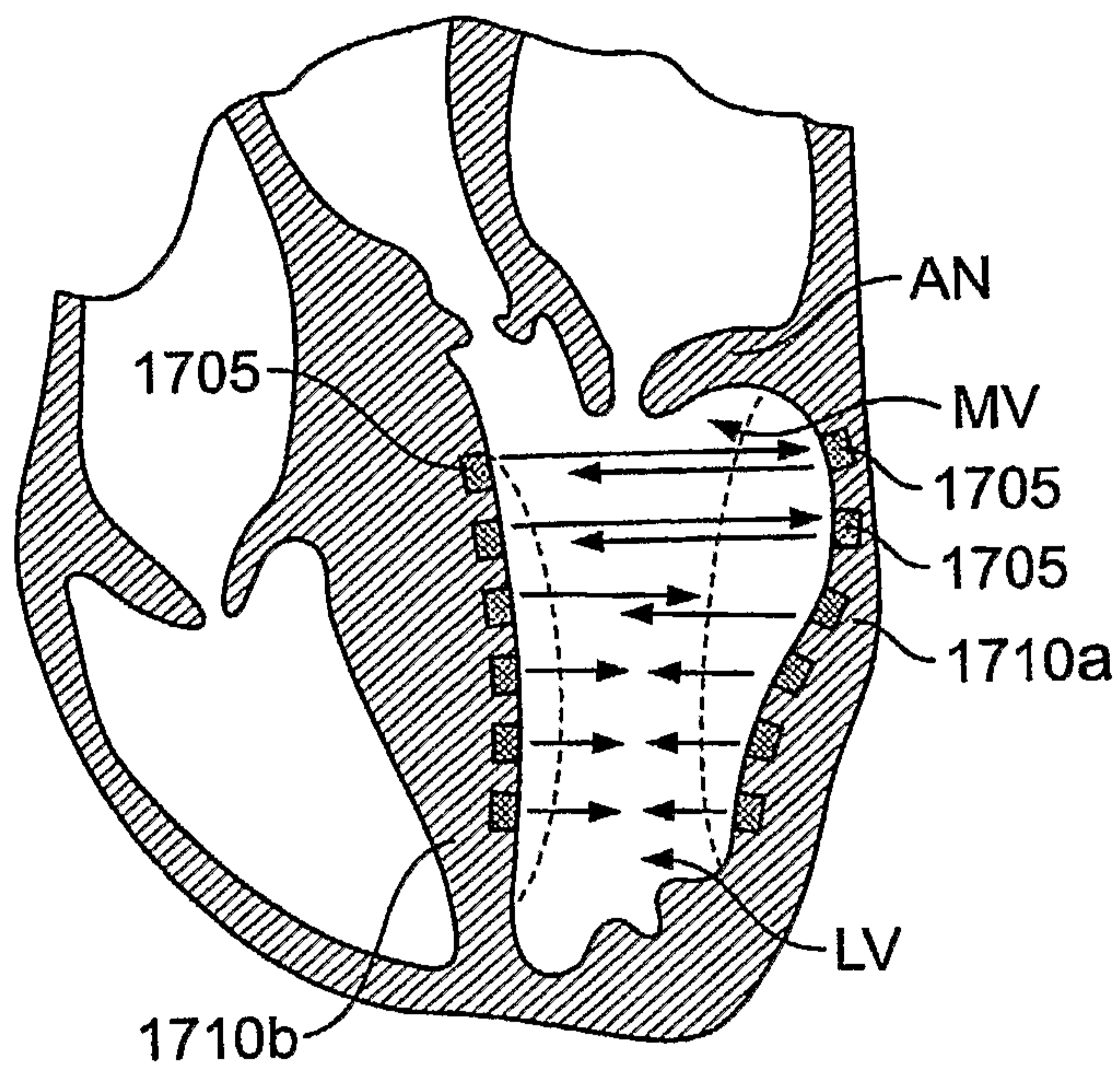


FIG. 18A

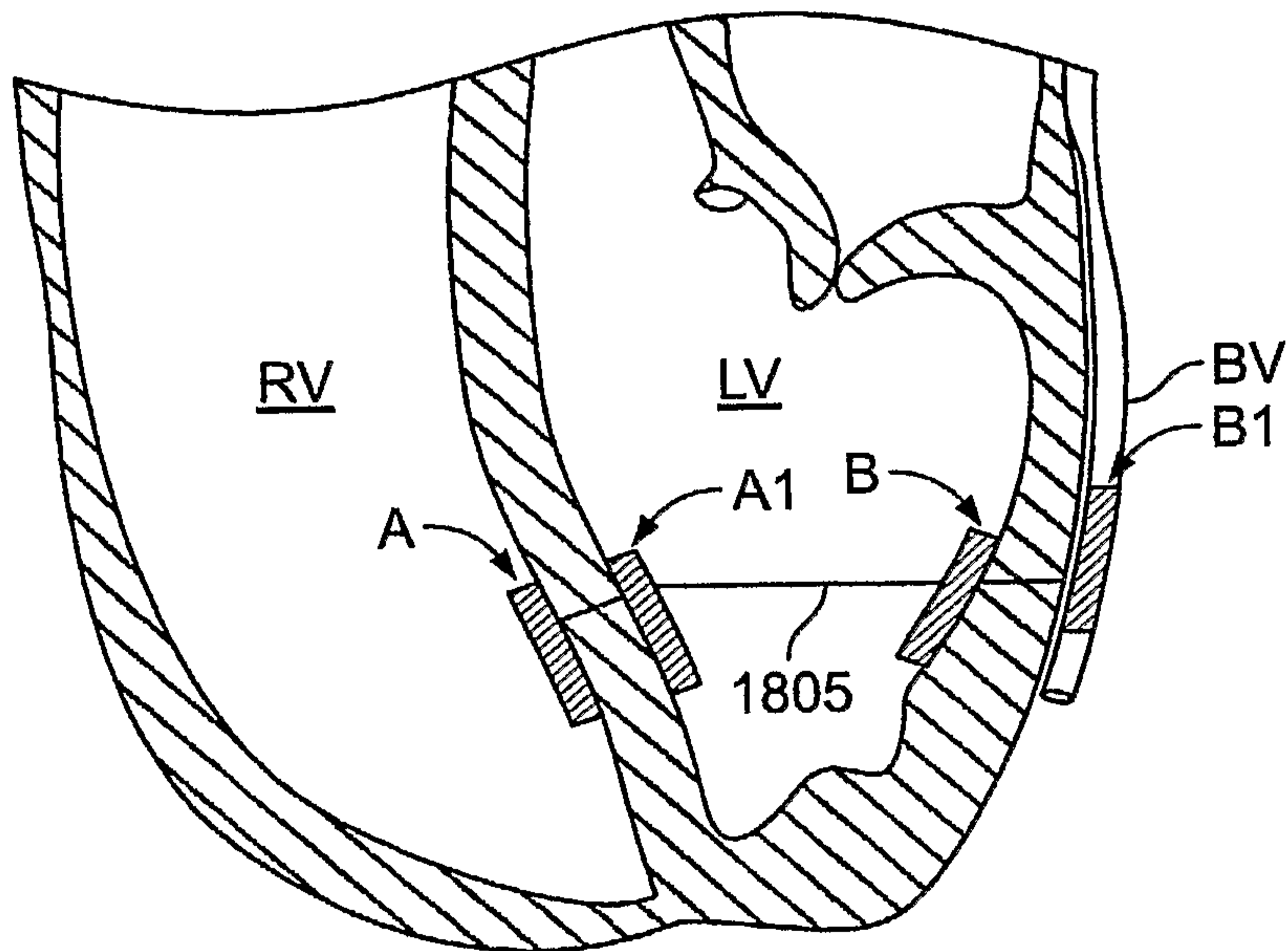


FIG. 18B

13/19

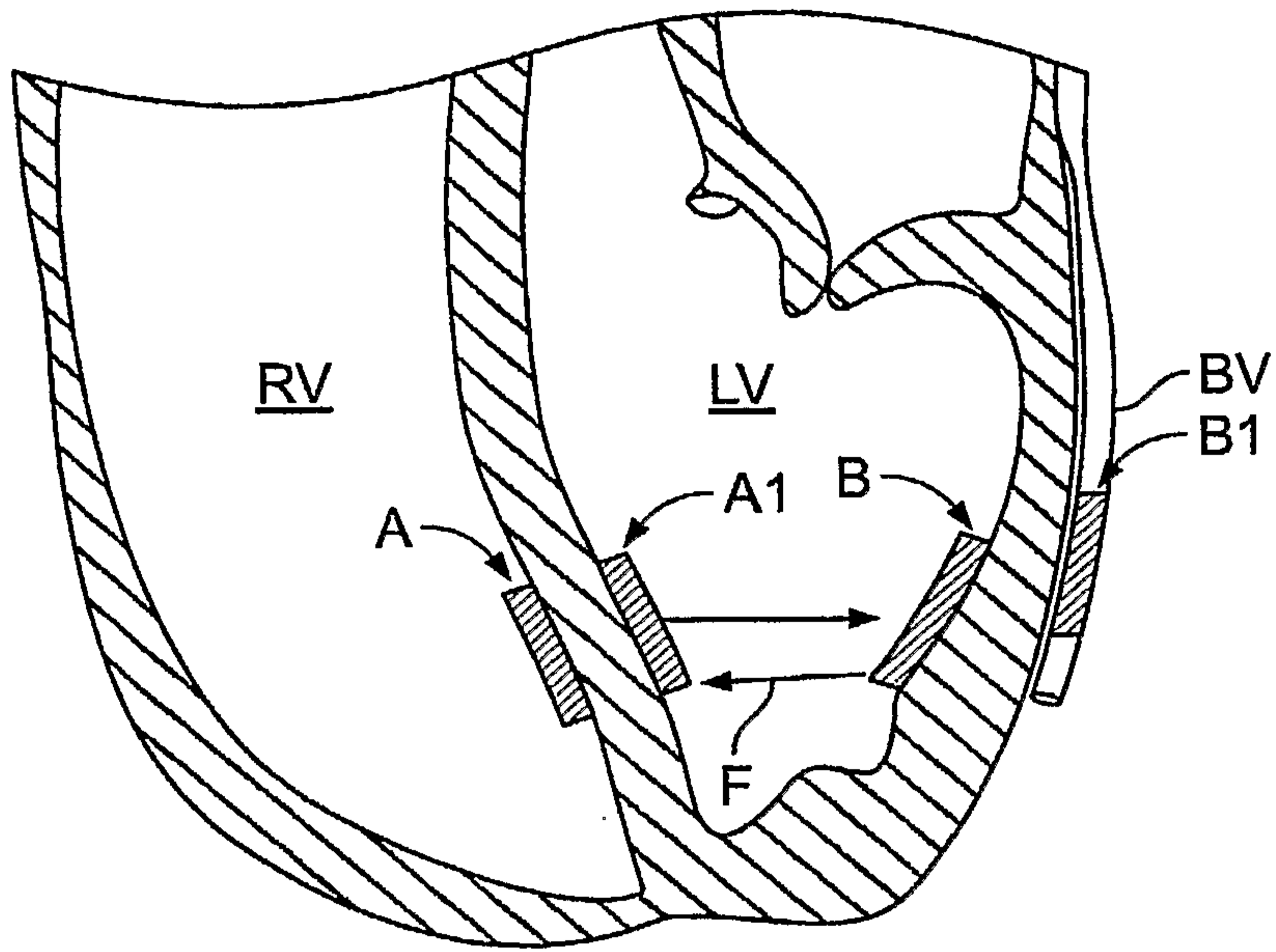


FIG. 18C

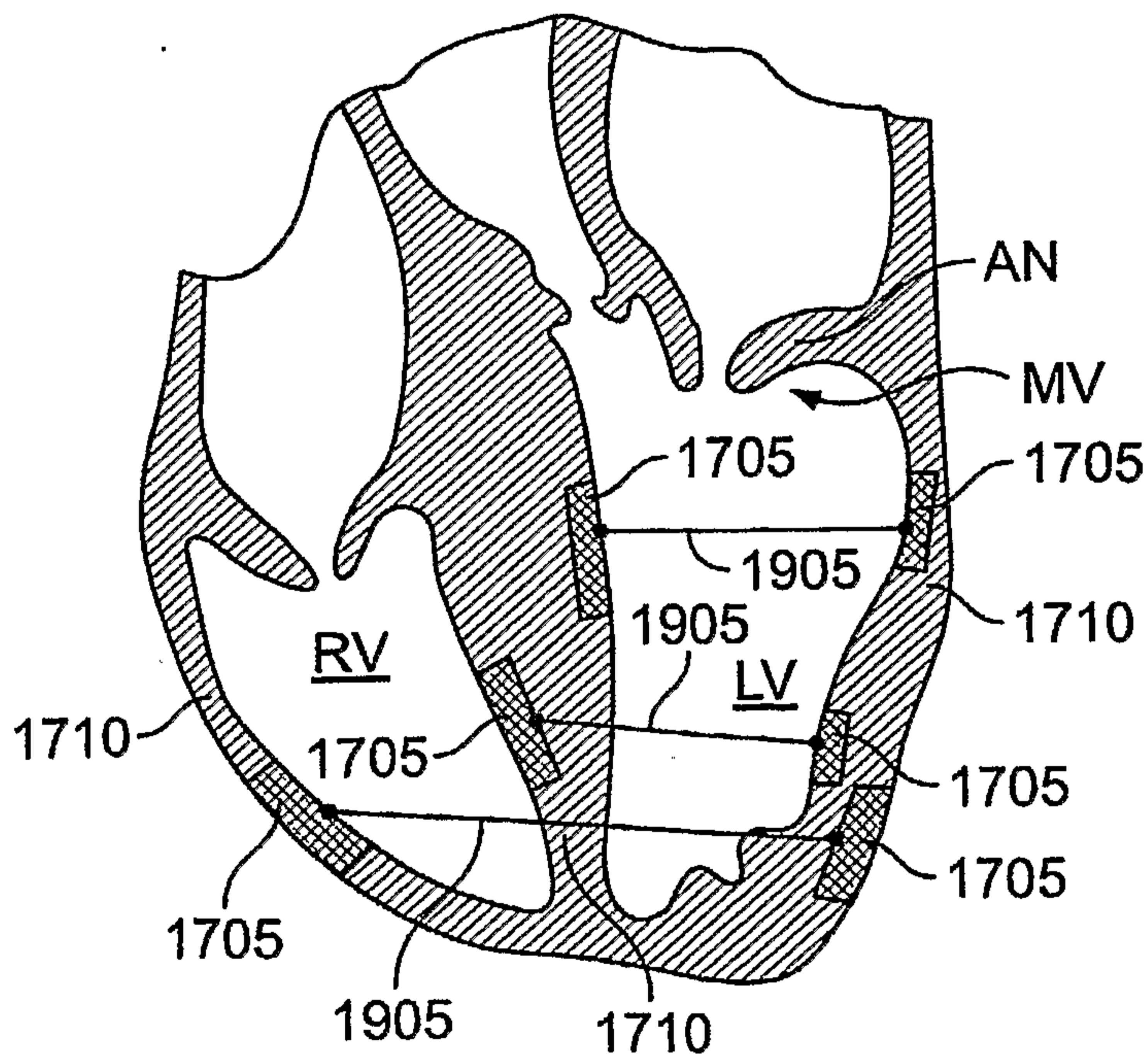


FIG. 19

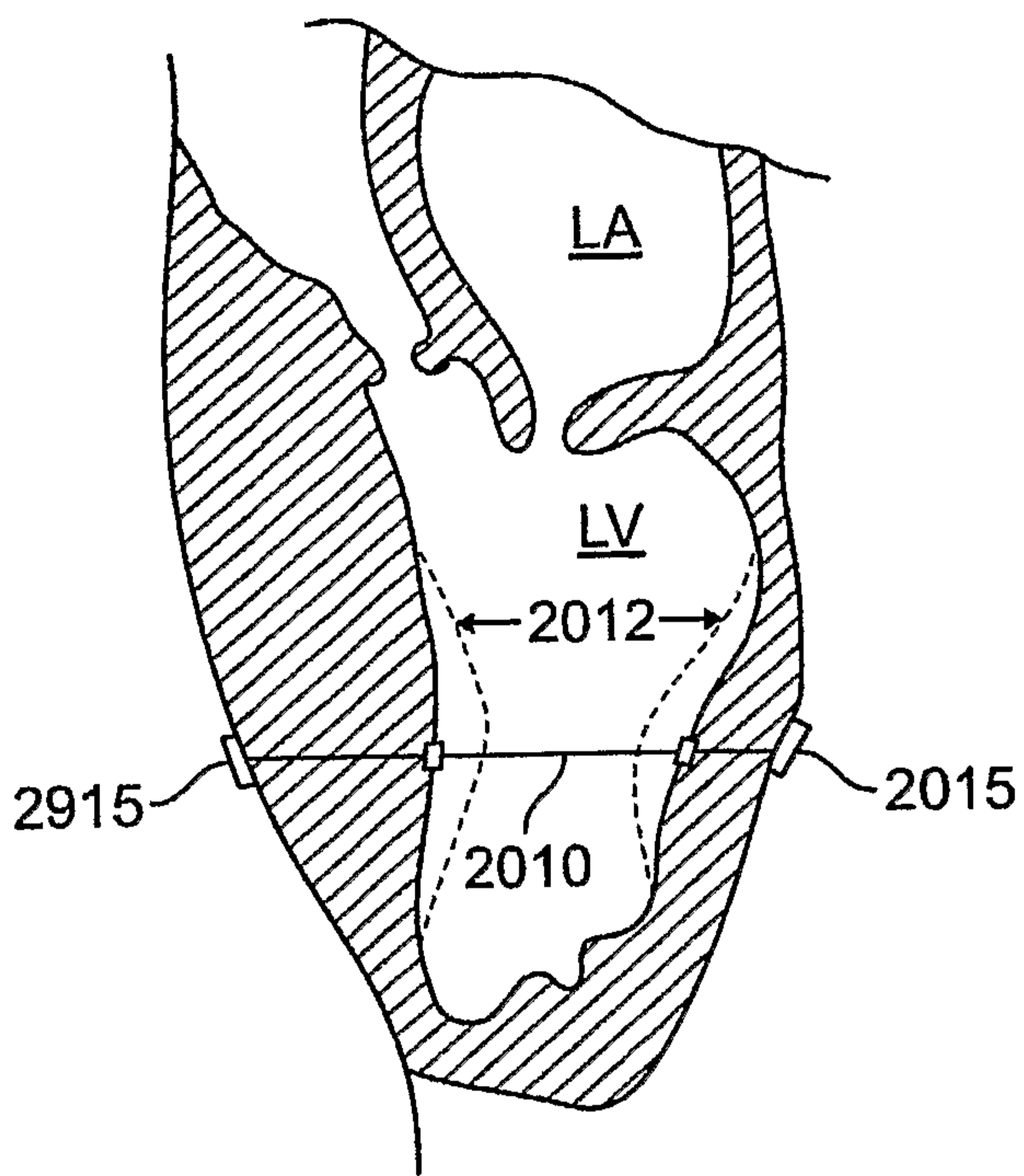


FIG. 20

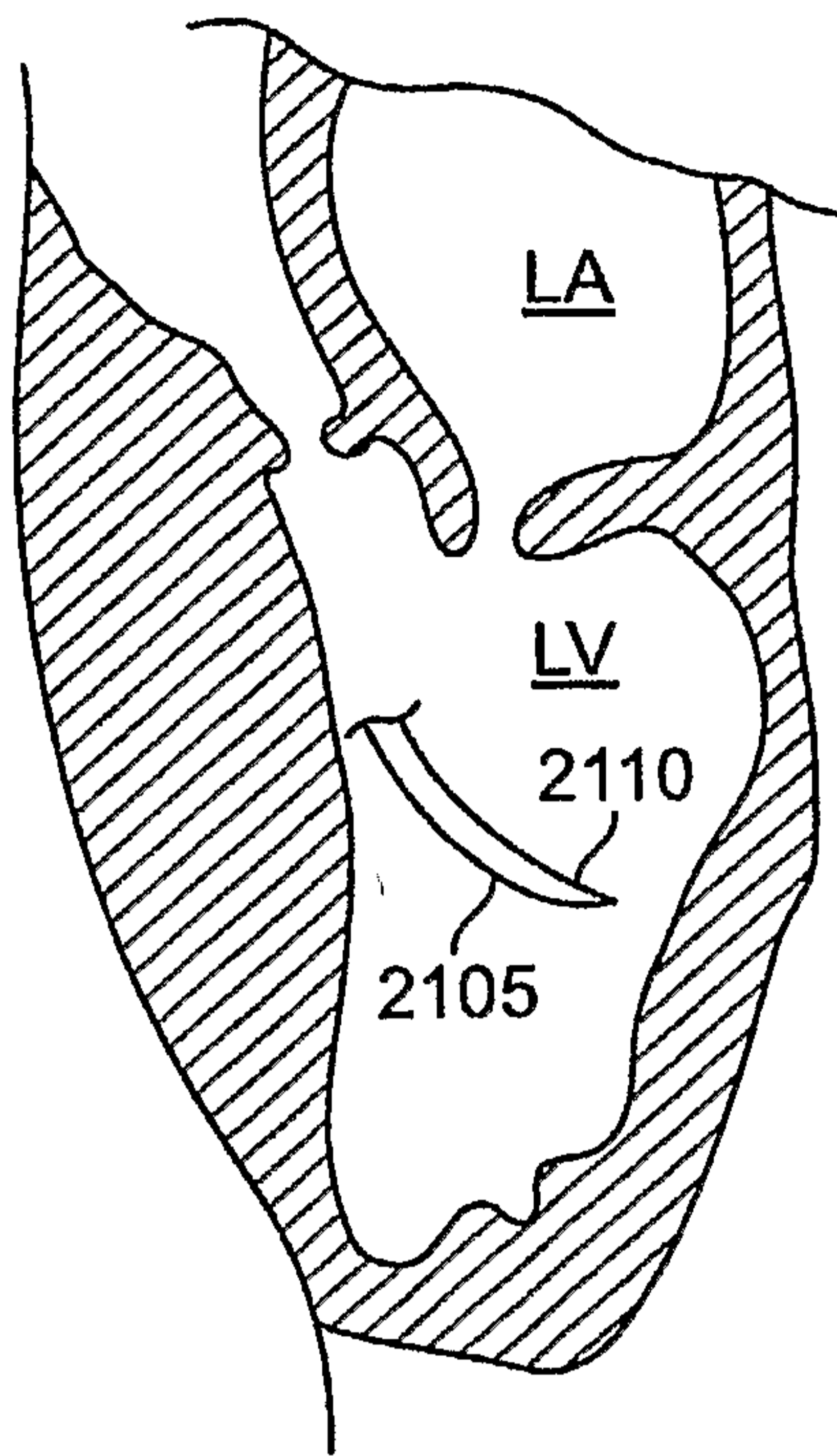


FIG. 21

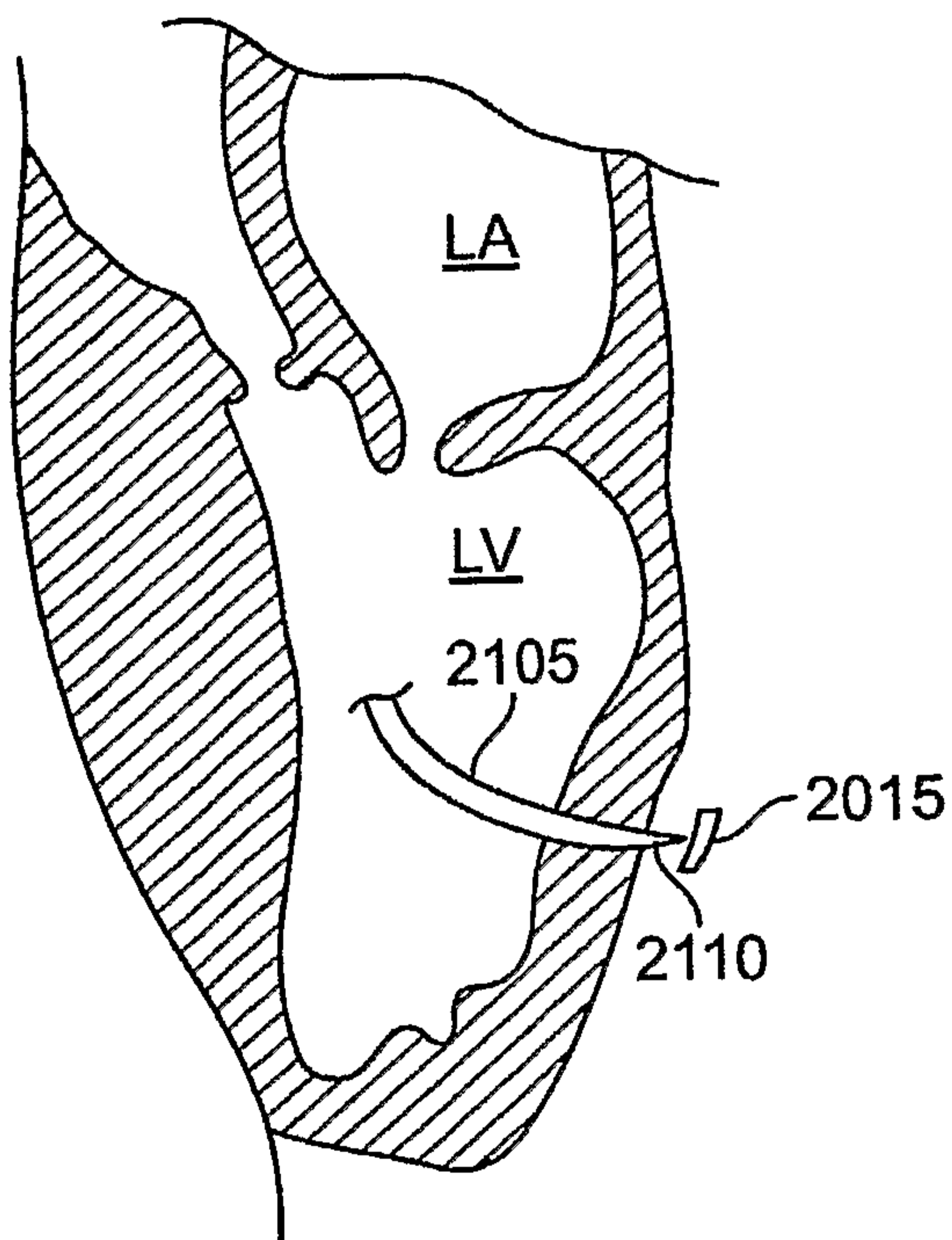


FIG. 22

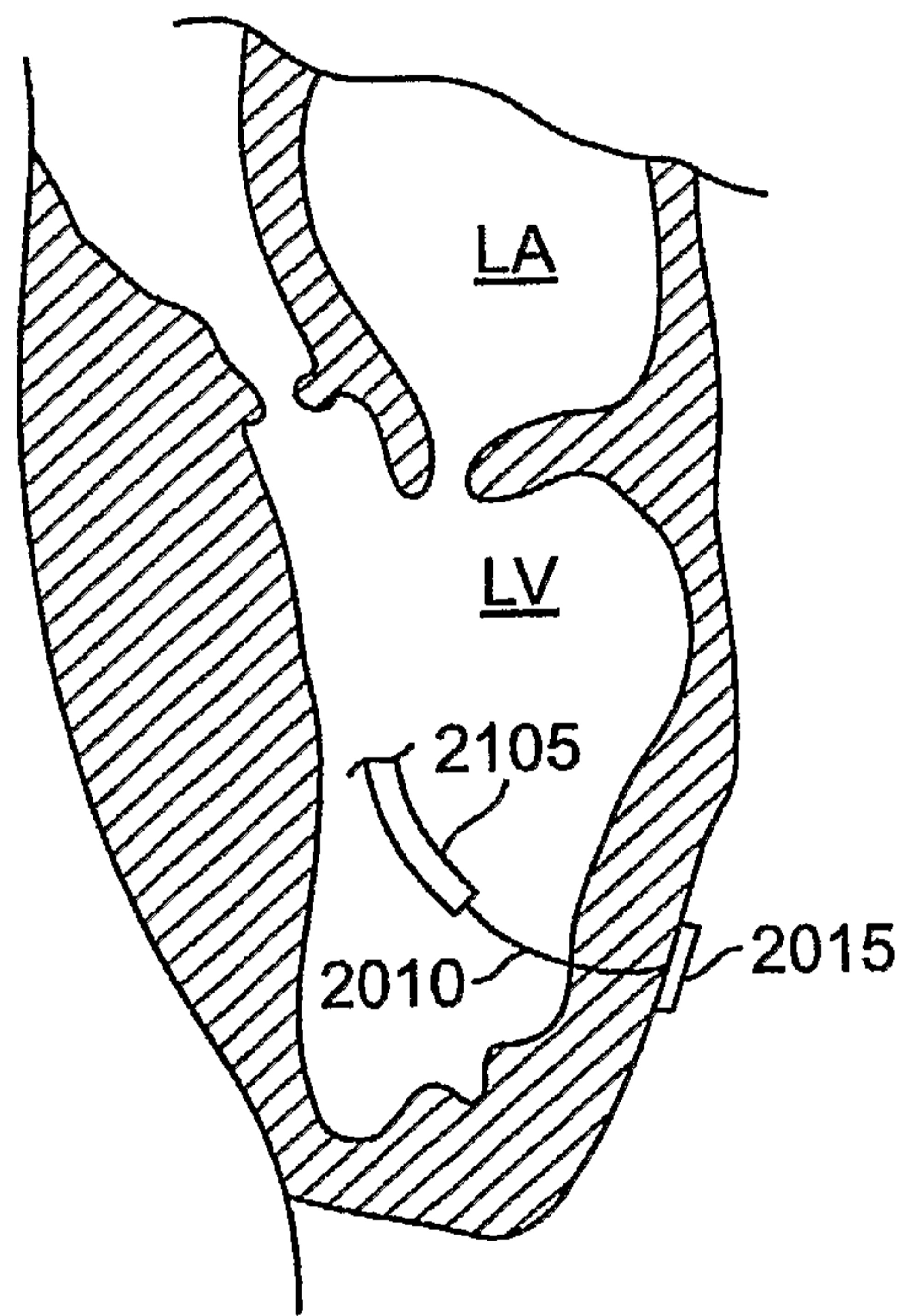


FIG. 23

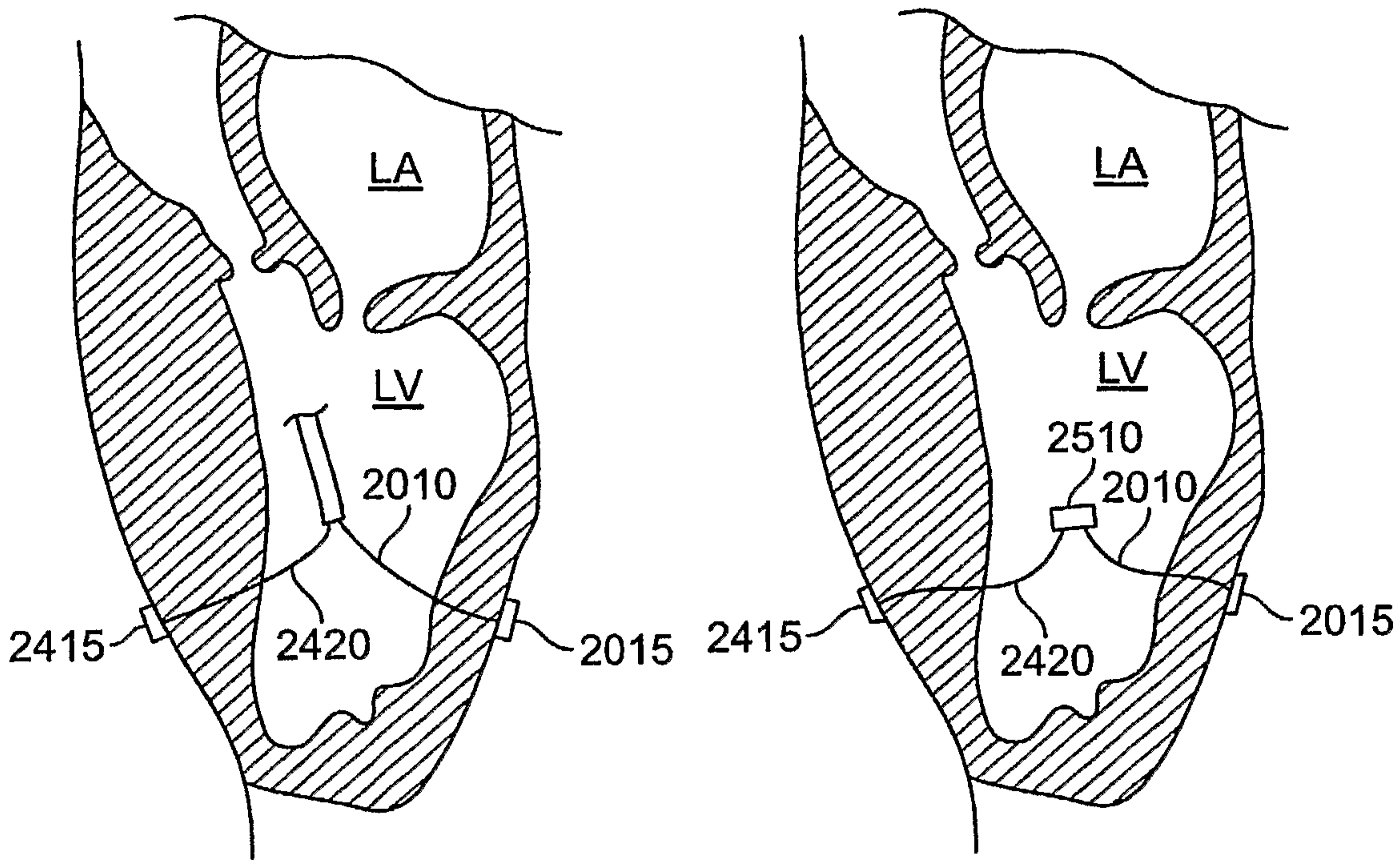


FIG. 24

FIG. 25

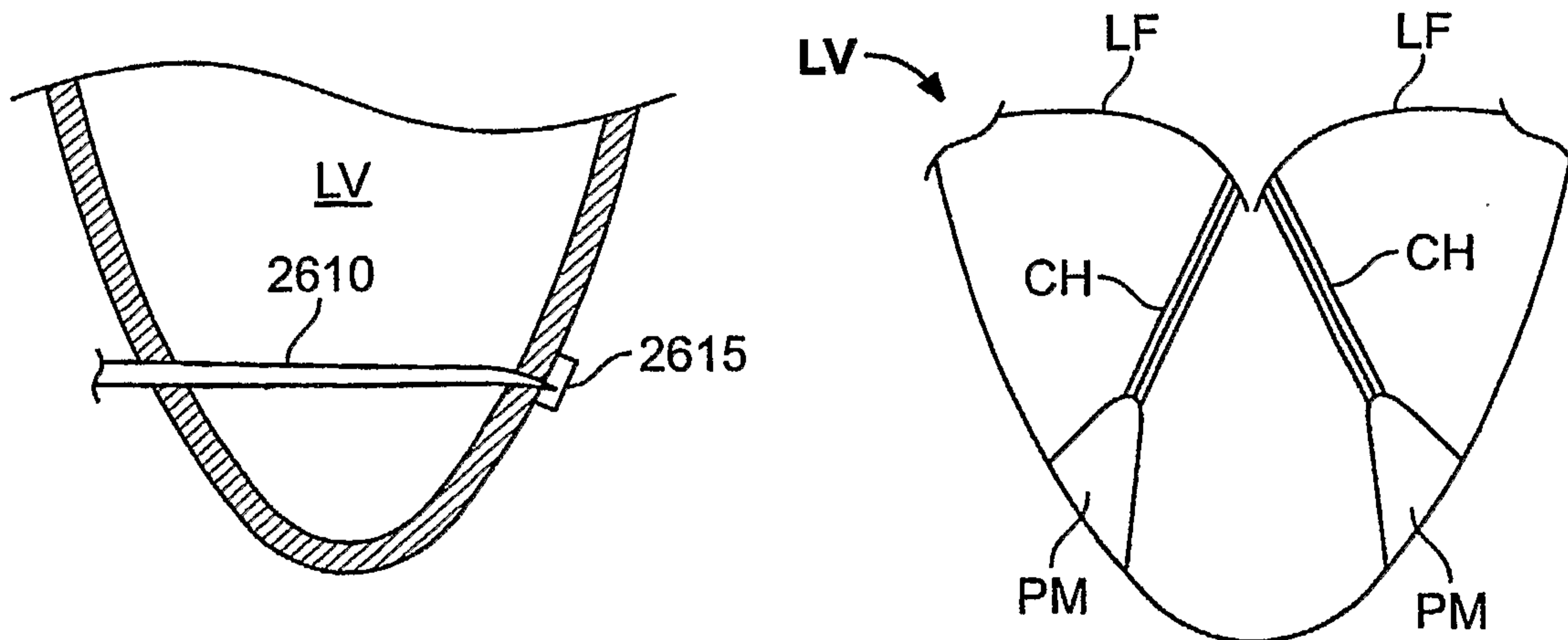


FIG. 26

FIG. 27

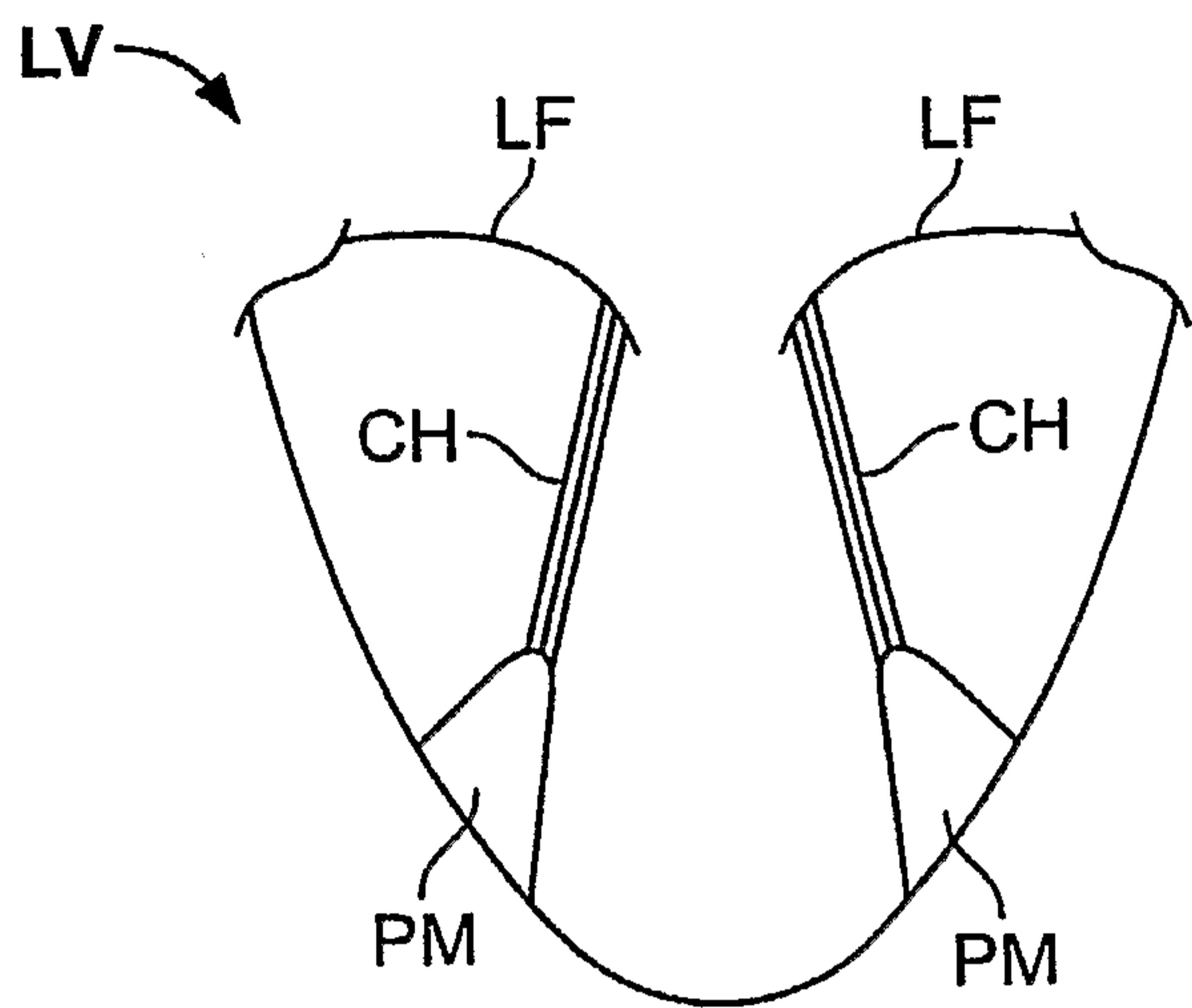


FIG. 28

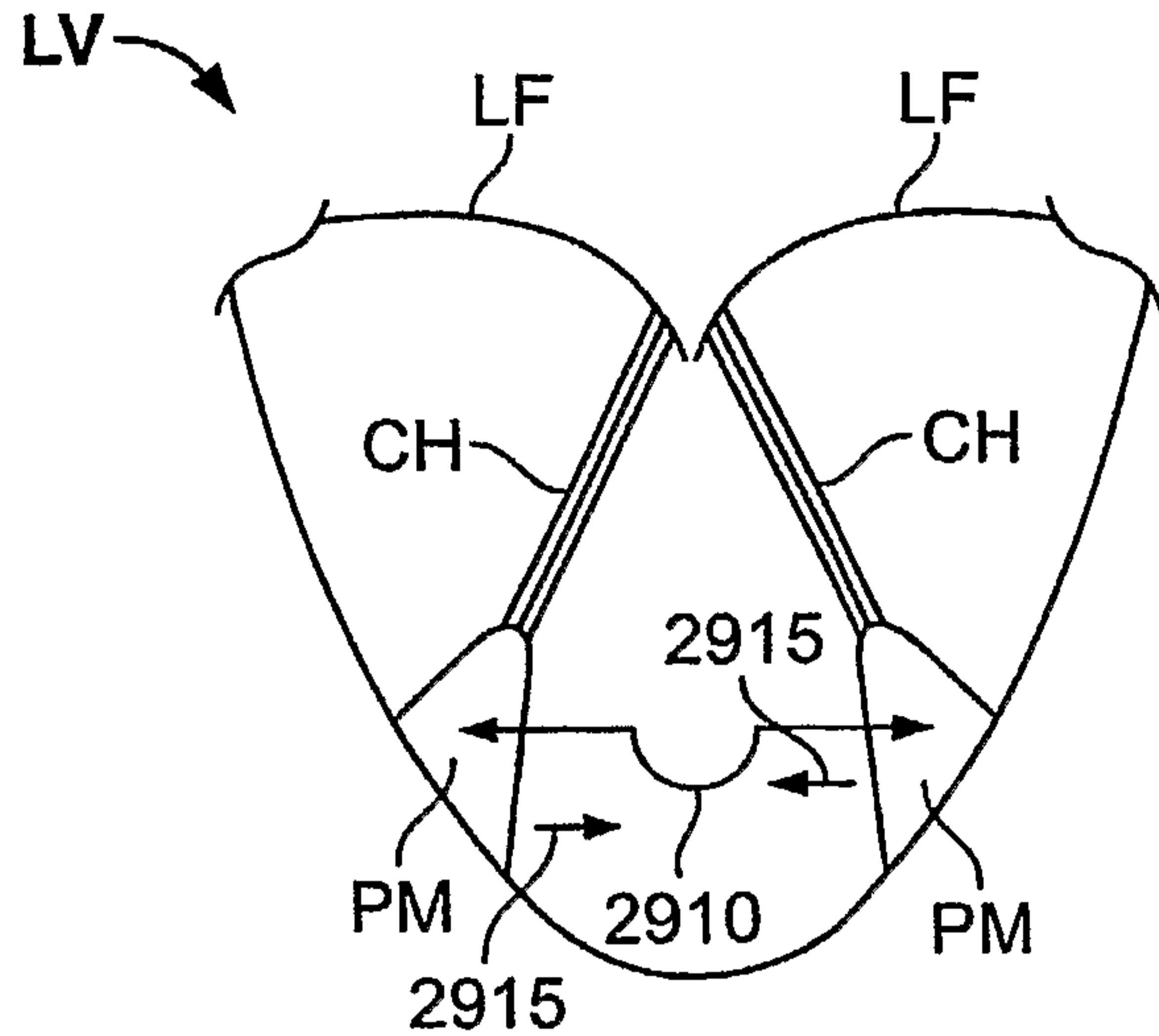


FIG. 29

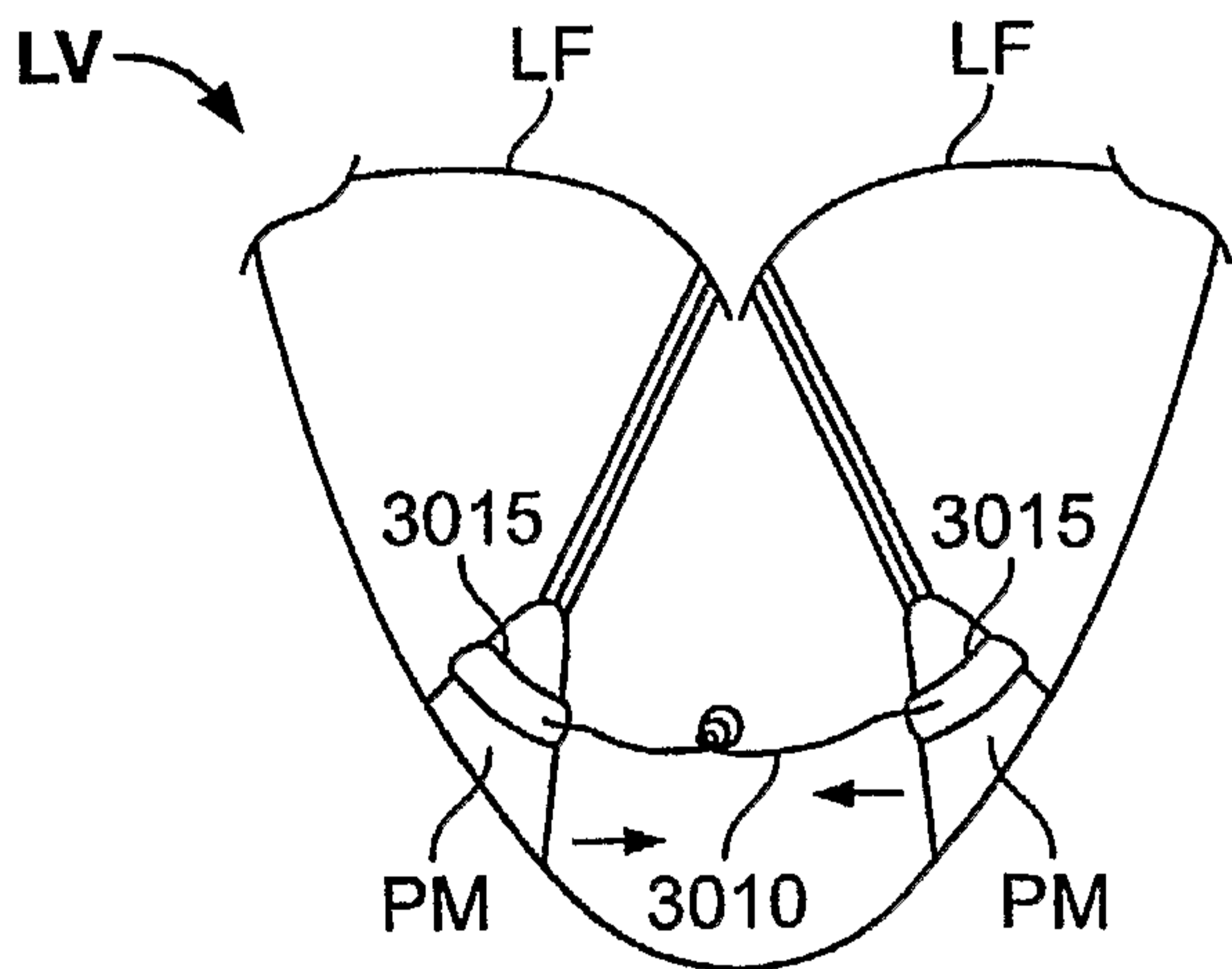


FIG. 30

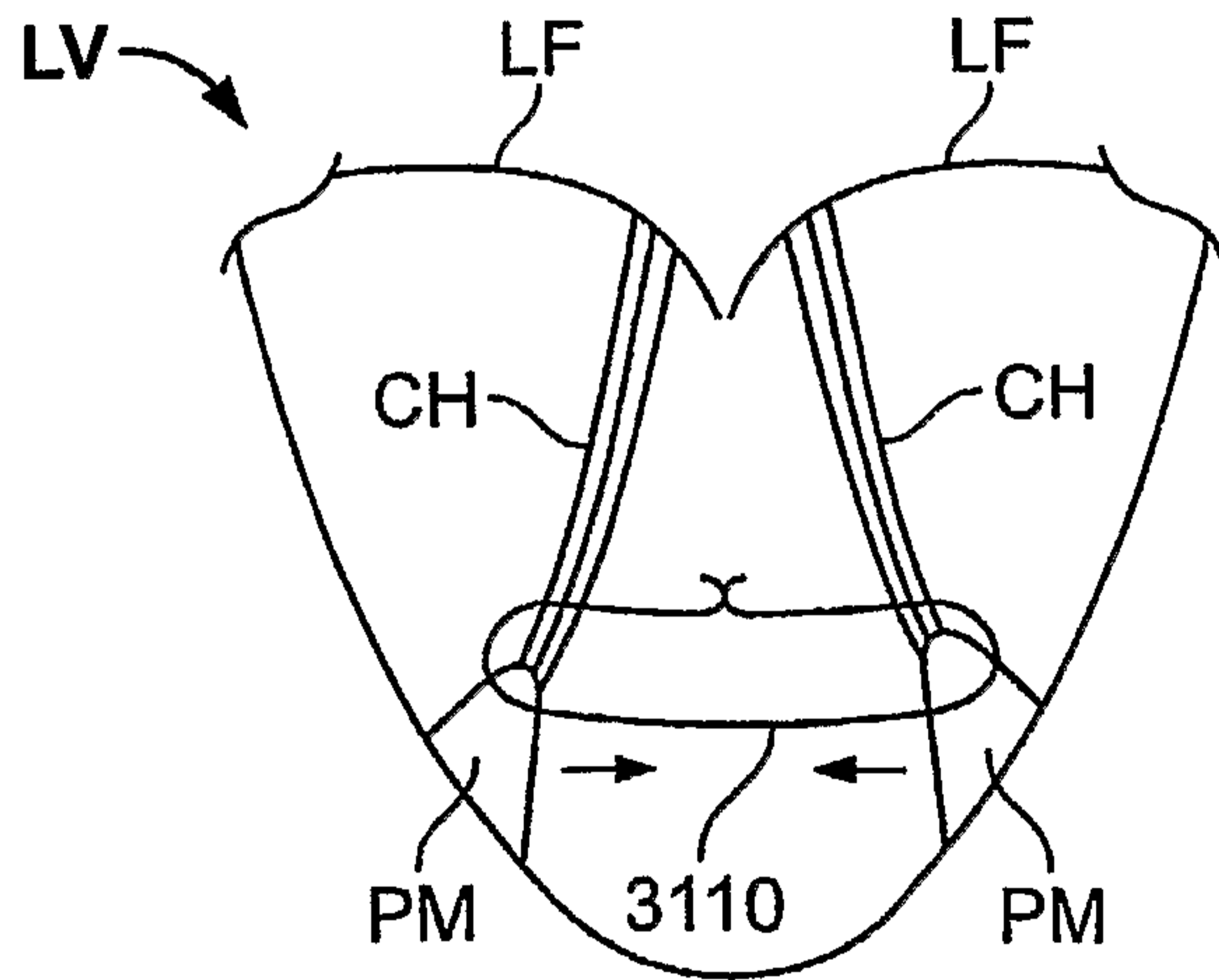


FIG. 31

17/19

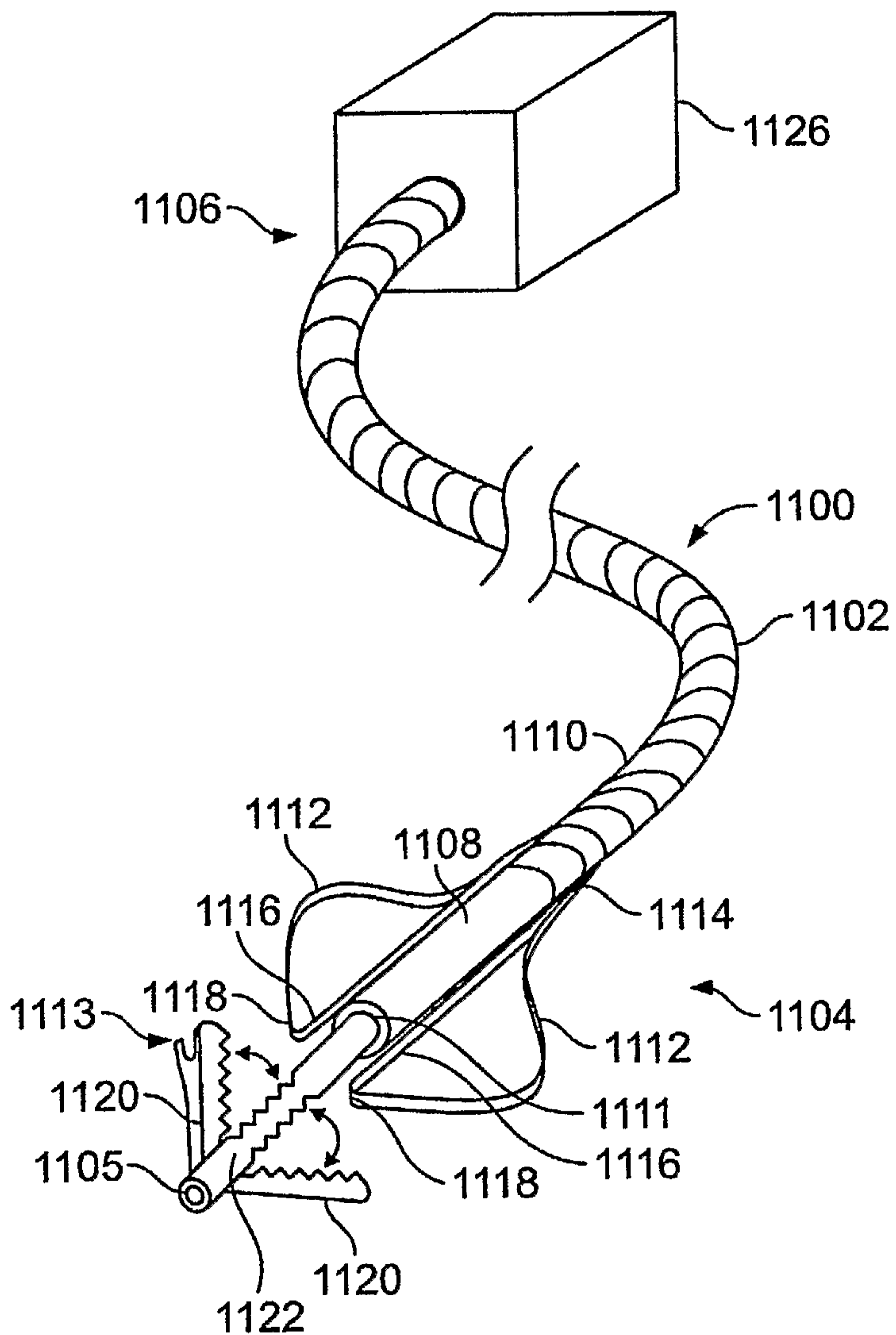


FIG. 32

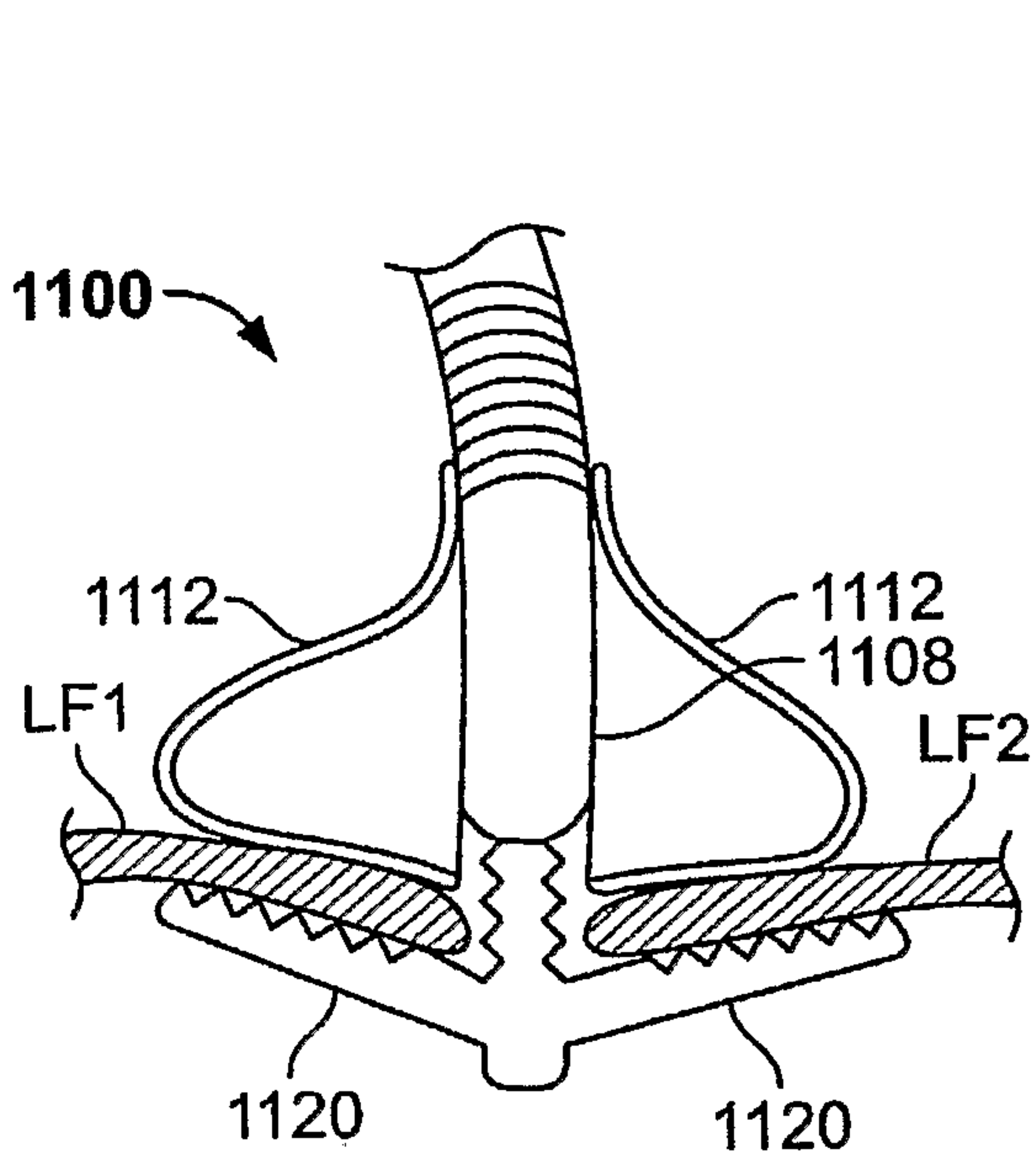


FIG. 33A

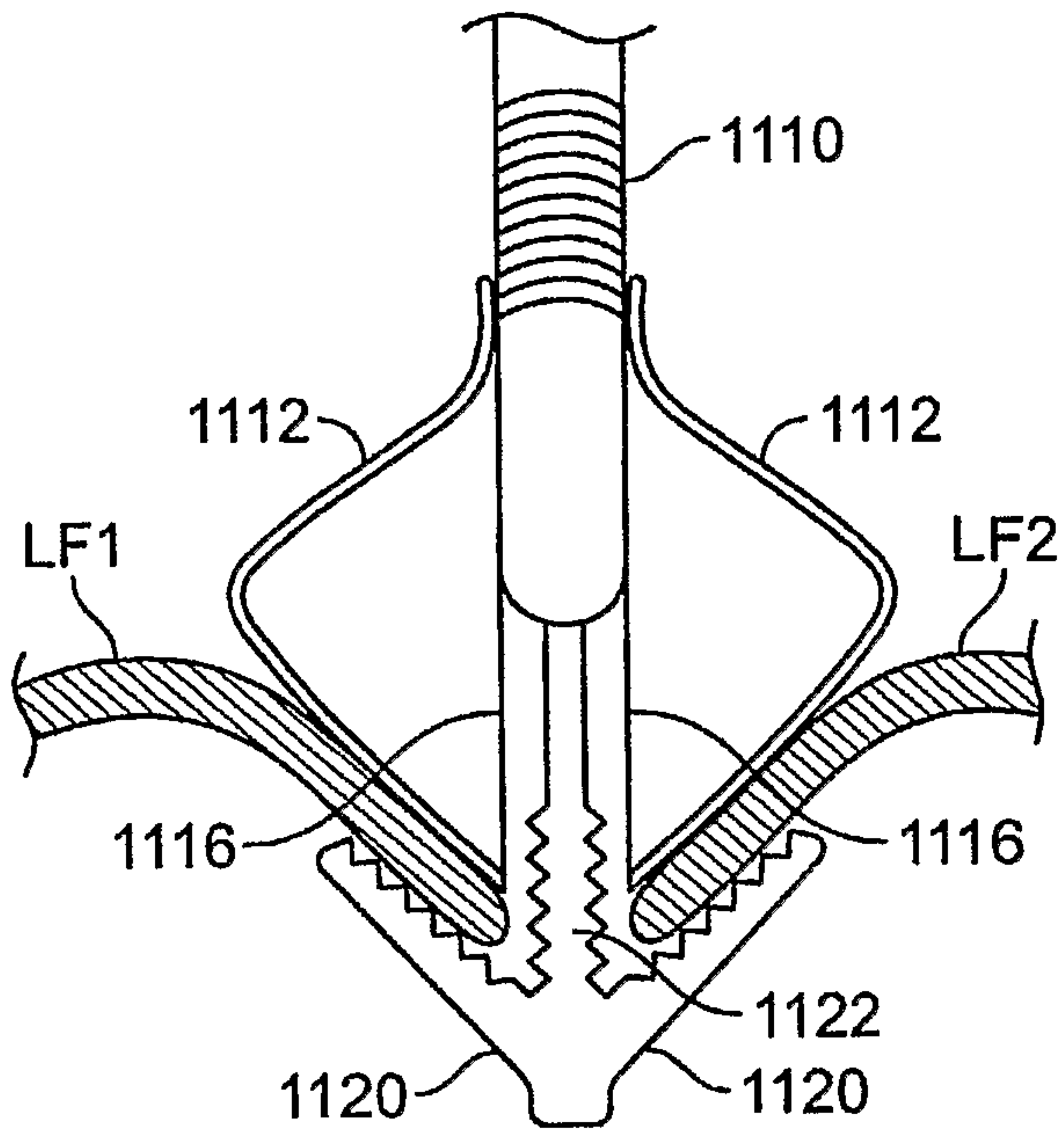


FIG. 33B

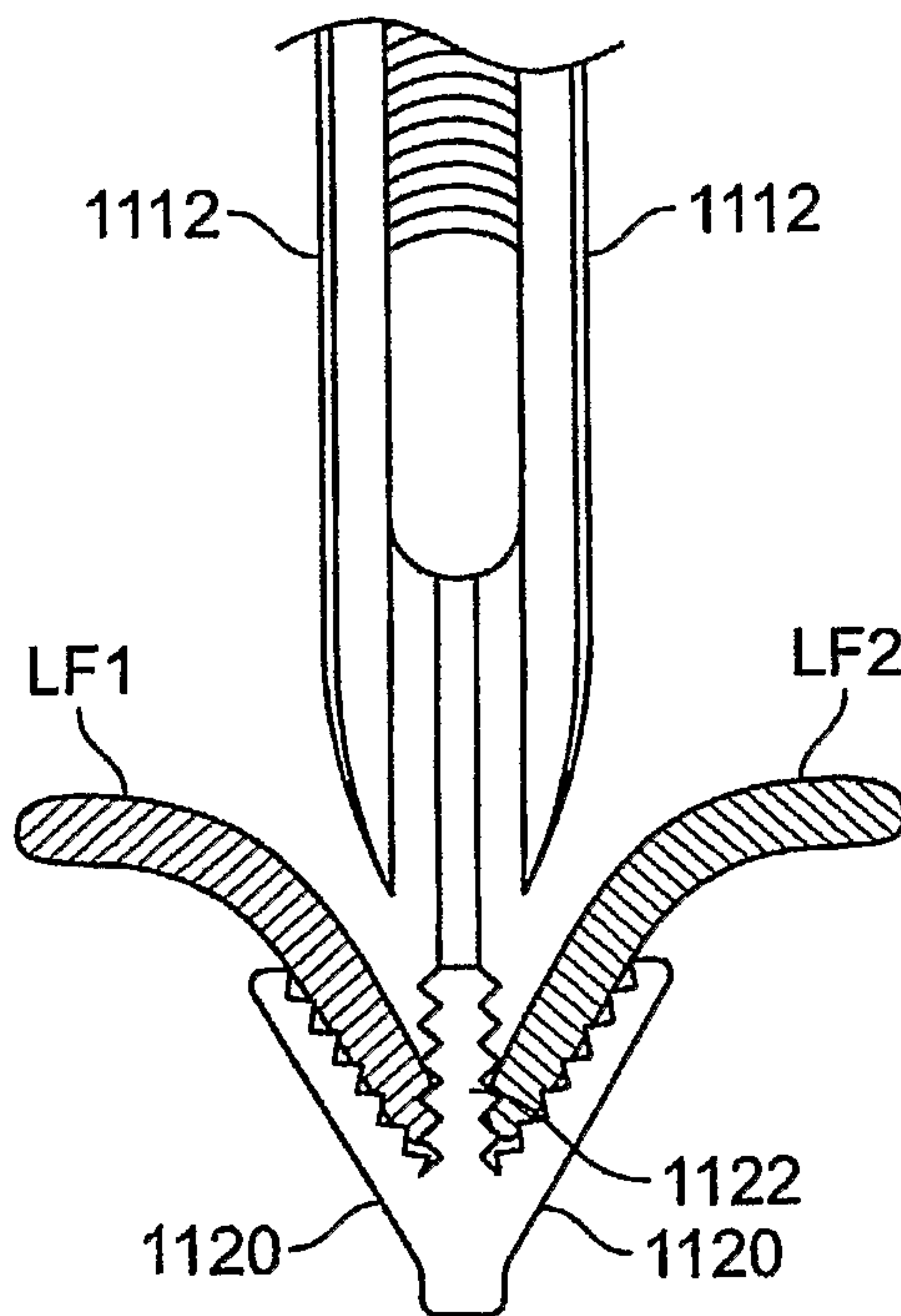


FIG. 33C

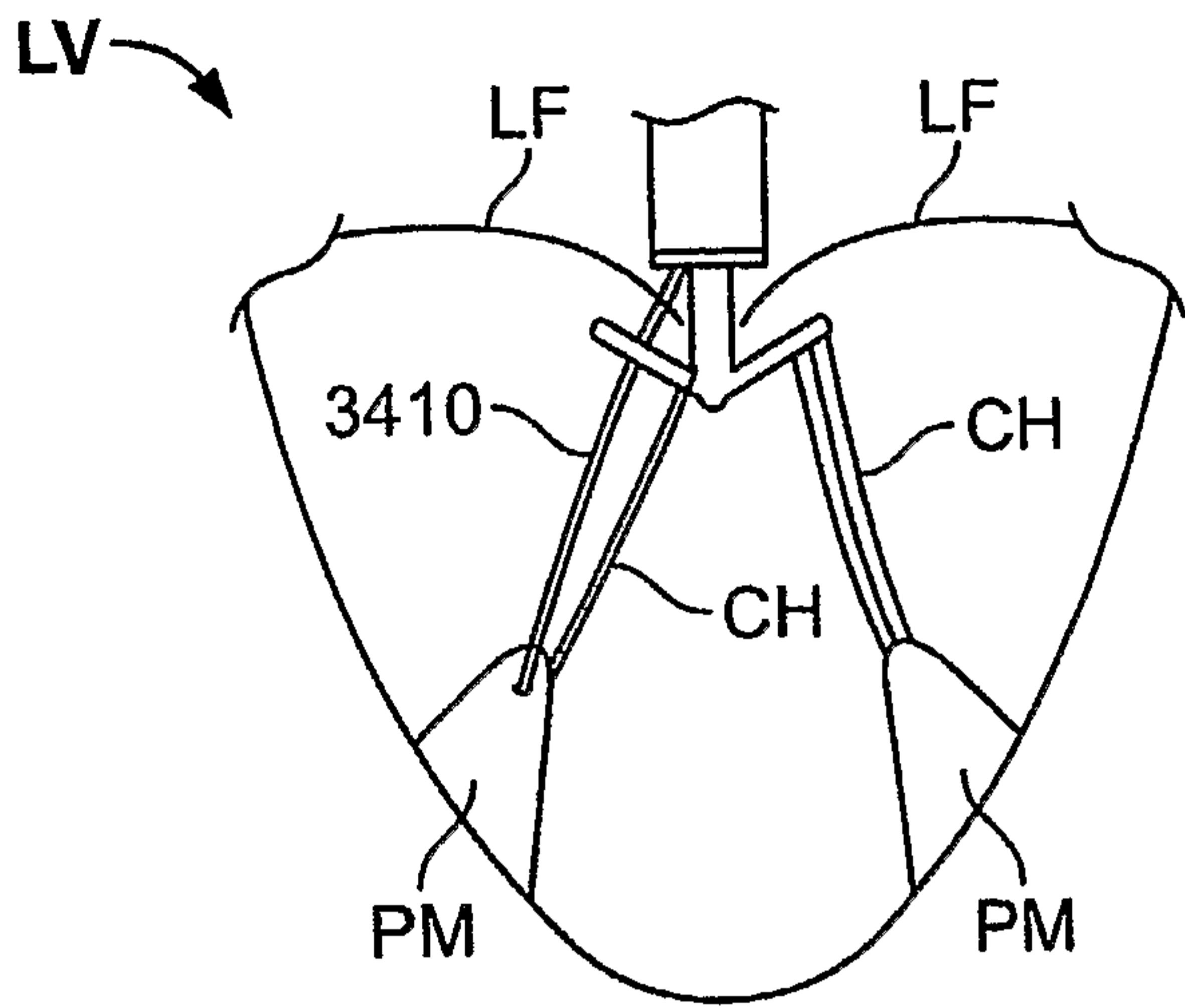


FIG. 34

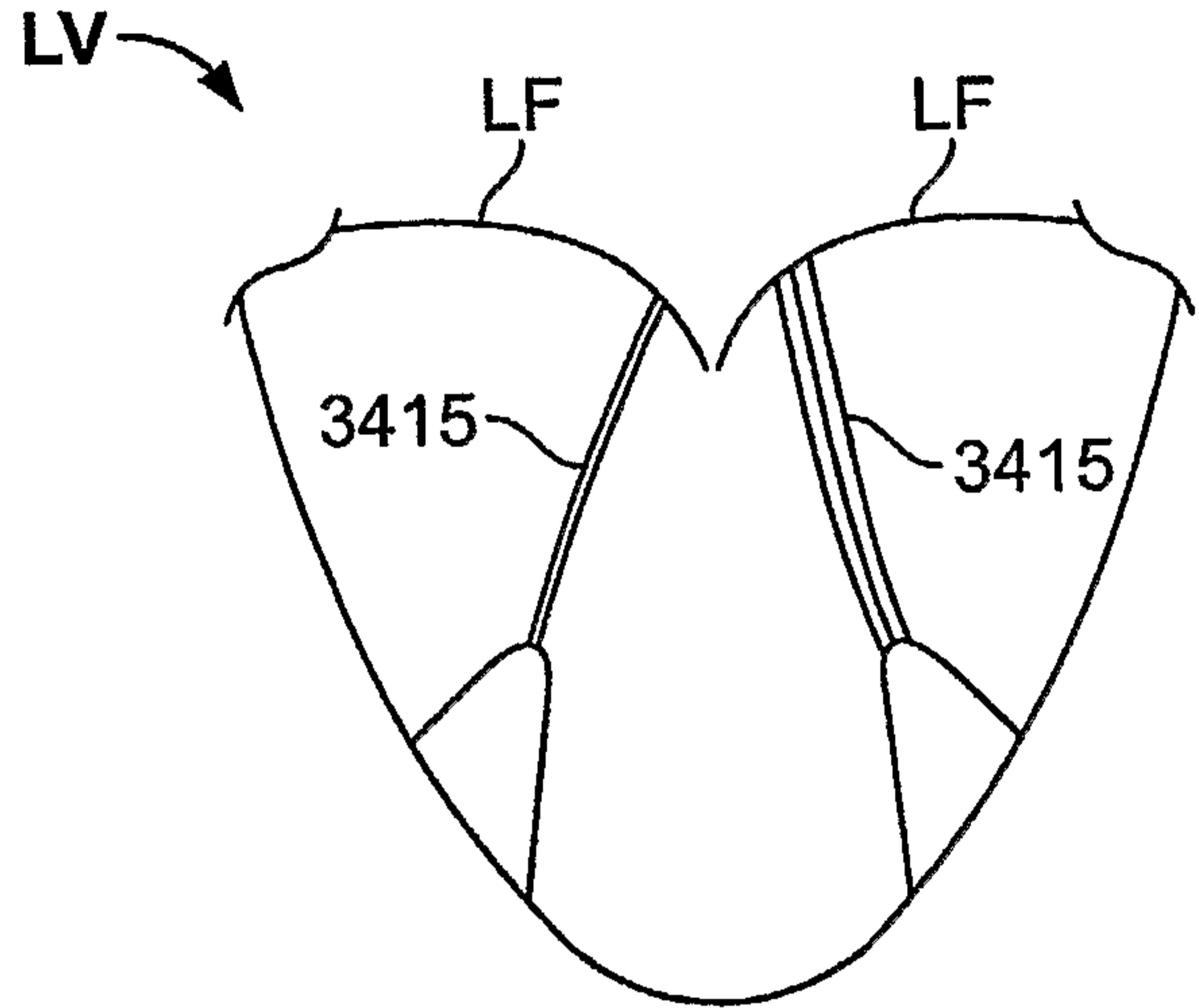


FIG. 35

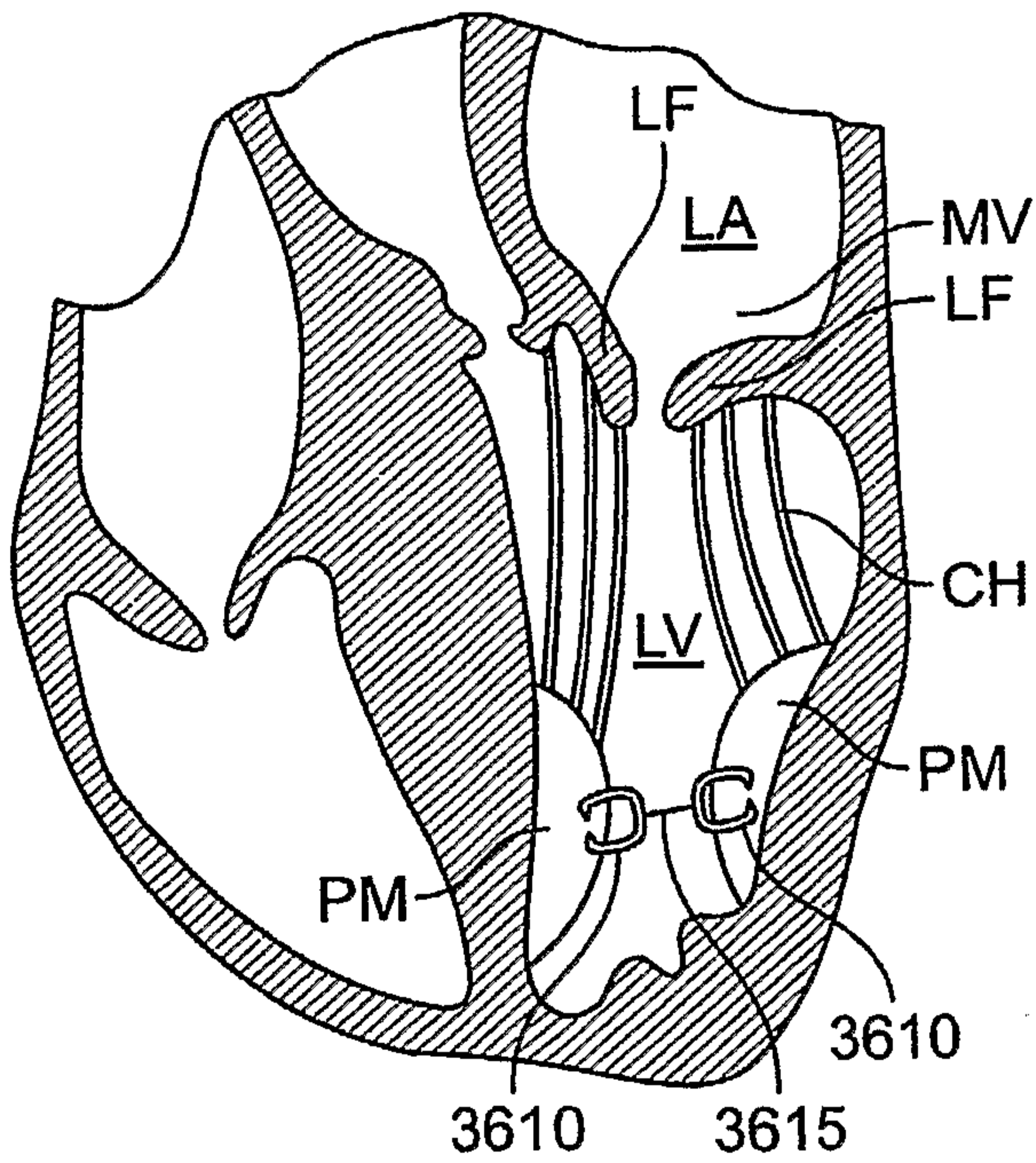


FIG. 36

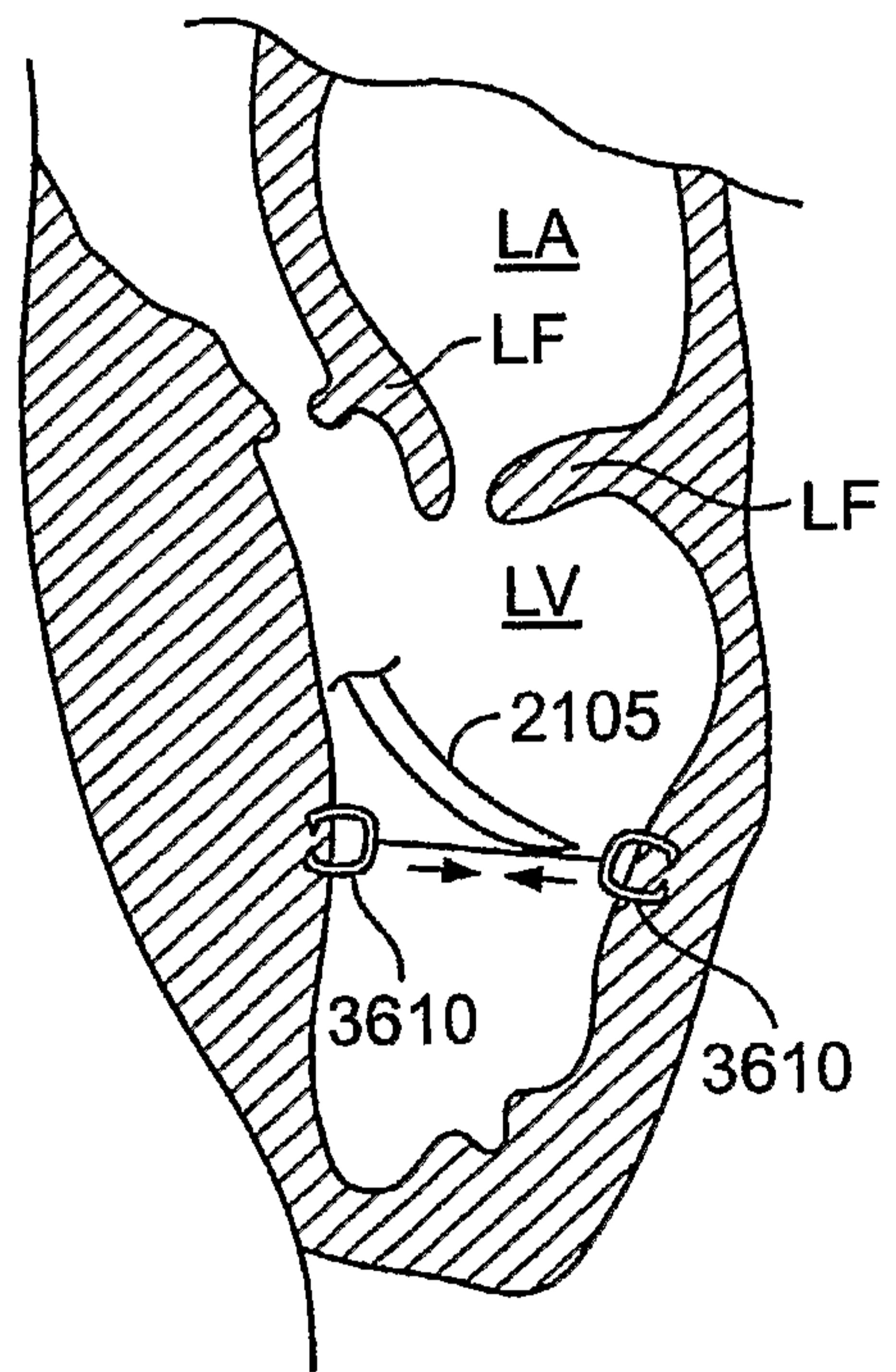


FIG. 37

