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(54) Title: PLEURAL EFFUSION TREATMENT DEVICE, METHOD AND MATERIAL

(57) Abstract: The invention discloses a method of treating a patient for pleural effusion comprising percutaneously delivering an adhesive material to a pleural space of the patient. Suitable adhesive materials for performing any of the embodiments of the methods of the invention can be selected from the group consisting of hydrogels, collagen, poly(lactic acid), poly(glycolide), cyanoacrylates, glutaraldehyde, PEG, protein, and polysaccharide and derivatives thereof. The invention also discloses a pleural effusion treatment apparatus comprising an adhesive material adapted to adhere pleural membranes defining a pleural space and a pleural space access member adapted to deliver the adhesive material to the pleural space.

PLEURAL EFFUSION TREATMENT DEVICE, METHOD AND MATERIAL

CROSS-REFERENCE

This application claims the benefit of U.S. Provisional Application No. 60/586,887, filed July 8, 2004, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

Field of the Invention. The invention relates generally to methods, devices and materials for use in treating pleural effusion.

Description of the Related Art. In the thoracic cavity, a layer of visceral pleura covers the surface of the lung, and a layer of parietal pleura lines the inner surface of the thoracic cavity, including the inside of the ribs and diaphragm. These smooth membranes normally contain a small amount of clear, plasma-like pleural fluid that helps reduce the friction between the lung surface and its surroundings as the lung expands and contracts with respiration. The accumulation of an abnormal amount of fluid between the visceral and parietal pleuras is called pleural effusion. For example, a patient with lung cancer can have a plurality of parietal or visceral lesions that produce clear fluid that gets into the pleural space.

The etiology of pleural effusions is varied and includes congestive heart failure, pneumonia, and pulmonary malignancies among others. Patients with pleural effusion often present with dyspnea, minimal to moderate chest pain, dullness on percussion and possible pleural friction rub and/or mediastinal shift. The existence of an effusion can generally be confirmed with chest radiography or CT. There is significant potential for morbidity and mortality due to the tendency for the volume of the pleural effusion fluid to compress the lungs, thereby restricting their expansion.

If the pleural effusion is recurring or is caused by a progressive pulmonary malignancy, pleurodesis is generally indicated. Pleurodesis is a therapeutic procedure involving drainage of the pleural fluid and introduction of a sclerosing agent between the two pleural membranes to cause a scarring reaction, which effectively fuses the two layers to one another. The goal is to close the pleural space and preclude fluid from entering it again. See, e.g., US Patent No. 5,484,401, which describes some prior treatments for pleural effusion. Current treatments include, for example, surgical intervention to drain the fluid, distribute talc into the pleural space, draw a vacuum, and then monitor the patient in the hospital.

A variety of agents are currently used to perform chemical pleurodesis, including radioactive isotopes, tetracycline, chemotherapeutic agents and talc. Two things are necessary for a successful pleurodesis: (1) The sclerosing agent must be evenly distributed across the pleural surfaces; and (2) the lung must still be able to expand effectively after the procedure.

Treatment for pleural effusion currently involves introduction of a chest tube through the chest wall into the pleural space, followed by drainage of the fluid. The chest tube is then clamped, allowing the lung to partially collapse. A syringe containing a sclerosing agent is attached to the chest tube, and the agent is insufflated into the pleural space. The chest tube is unclamped, allowing the lung to inflate fully and to pull the agent further into the pleural space. The patient is rotated in bed over the following few hours to assist in the equal distribution of the agent. The chest tube is removed when there is less than $100cm^3$ of fluid per day removed from the pleural space. This pleurodesis procedure may be done at the bedside.

The sclerosing agents irritate the pleural membranes, eventually causing them to become inflamed and scarred, which fuses the layers together. Talc is the most commonly used sclerosing agent and has a reported 90% success rate. Although talc has demonstrated a high rate of success, there are complications associated with the procedure, most of which are caused by the sclerosing agent and the nature of its action. Patients commonly

experience pain during the installation of the agent, which is very irritating and inflammatory, and a narcotic is therefore usually administered prior to the procedure. Also, fever is common in more than 30% of patients undergoing talc pleurodesis, possibly due to the pleuritis it causes. The fever generally lasts for approximately 48 hours.

It is difficult to evenly distribute most sclerosing agents, especially talc, because they do not flow. Talc does not mix well with saline and has a tendency to clump. Incomplete lung expansion due to a partially trapped lung can occur when pleurodesis is only partially successful.

Additionally, pleurodesis is performed over several days. While waiting for the full effects of the scarring action to take place, the patient is in danger of partial or full respiratory failure. Thus, hospitalization and close monitoring is required during this period.

What is needed, therefore, is a device for distributing sclerosing agents which reduces the risk of partial or full respiratory failure.

SUMMARY OF THE INVENTION

The present invention provides methods, materials and devices for treating pleural effusions. Other methods and compositions are also provided in U.S. patent applications entitled "Lung Device with Sealing Features" application no. 11/___,___ filed July 8, 2005 (Attorney Docket 30689-707.201); "Intra-Bronchial Lung Volume Reduction System," application no 11/153,235 filed June 14, 2005; "Targeting Damaged Lung Tissue Using Compositions," application no. 11/008,577, filed December 8, 2004; "Targeting Damaged Lung Tissue," application no. 11/008,092, filed December 8, 2004; "Targeting Sites of Damaged Lung Tissue Using Composition," application no. 11/008,094 filed December 8, 2004; "Targeting Sites of Damaged Lung Tissue," application no. 11/008,578, filed December 8, 2004; "Imaging Damaged Lung Tissue Using Compositions," application no. 11/008,649, filed December 8, 2004; "Imaging Damaged Lung Tissue," application no. 11/008,777, filed December 8, 2004; "Lung Volume Reduction Using Glue Compositions," application no. 11/008,093, filed December 8, 2004; "Glue Composition for Lung Volume Reduction," application no. 11/008,087 filed December 8, 2004; "Glue Composition for Lung Volume Reduction," application no. 11/008,580 filed December 8, 2004; and "Lung Volume Reduction Using Glue Composition," application no. 11/008,782 filed December 8, 2004.

One aspect of the invention provides a method of treating a patient for pleural effusion comprising percutaneously delivering an adhesive material to a pleural space of the patient. The delivering step can also comprise ejecting the adhesive material from a delivery device into the pleural space and further comprising mixing components of the adhesive material in the delivery device prior to the ejecting step. In some embodiments, while performing the method of the invention, the delivery device converts from a delivery configuration to an operational configuration. A further embodiment of the method can include percutaneously inserting a pleural space access member into the patient. Suction can be applied to the pleural space prior to delivering the adhesive material to the pleural space in performing the method of an embodiment of the invention. When suction is applied, the suction can be applied through the pleural space access member. Further, the delivering step of the method can comprise delivering the adhesive material through the pleural space access member. An embodiment of the method can also include delivering adhesive material to the pleural space without delivering a fibrosis inducing material to the pleural space. The adhesive material can be spread within the pleural space. The adhesive materials suitable for any of the embodiments of the methods of the invention have strength values up to 1.5 psi, or more; preferably having a strength value between 0.2-0.6 psi. In addition, the adhesive material suitable for any of the embodiments of the methods of the invention have viscosity levels of 1.1 centipoise and higher. Further, materials suitable for performing any of the methods of the invention can be selected from the group comprising hydrogels, proteins,

polymers and cross-linking agents. The hydrogel adhesive may include material selected from the group consisting of hyalurons, hyalyronic acid, alginates, chitins, chitosans, and derivatives thereof. The protein material comprises material that can be selected from the group consisting of albumins, porcine albumin, collagens and gelatins. The polymer material comprises material selected from the group consisting of poly(lactic acid) and poly(glycolide).The cross-linking agent material comprises material that may be selected from the group consisting of glutaraldehyde and stable polyaldehyde.

Another aspect of the invention includes a pleural effusion treatment apparatus comprising an adhesive material adapted to adhere pleural membranes defining a pleural space and a pleural space access member adapted to deliver the adhesive material to the pleural space. In an embodiment of the apparatus, the pleural space access member comprises an adhesive material delivery device. Further, the adhesive material delivery device can comprise a syringe. Adhesive materials suitable for the embodiments of the invention comprise two or more components, the delivery device comprising a mixing element adapted to mix the two components prior to injection of the adhesive material into the patient. The pleural space access member of an embodiment of the invention can comprise a chest tube. Additionally, an apparatus of the invention can comprise a suction apparatus. Where a suction apparatus is provided, the apparatus can be adapted to apply suction through the pleural space access member. A spreading element can also be provided that is adapted to spread adhesive material within the pleural space. For example, the pleural space access member can be a catheter. Various shapes of the pleural space access member can be employed including, but not limited to, a loop, an S shape, a V shape. Additionally, the shape can have an actuator forming a bend, a pull wire, and/or a memory element incorporated therein. Further, materials suitable for use in the adhesives suitable for the apparatus of the embodiments of the invention can be selected from the group comprising hydrogels, protein, and cross-linking agents. Polymer such as poly(lactic acid), poly(glycolide) can also be provided.

INCORPORATION BY REFERENCE

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

BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

FIG. 1 shows a lateral cross-sectional view of a lung and chest cavity of a patient showing a device according to one embodiment of the invention.

FIG. 2 shows a lateral cross-sectional view of a lung and chest cavity of a patient showing a device according to another embodiment of the invention.

FIG. 3 shows a lateral cross-sectional view of a lung and chest cavity of a patient showing a device according to yet another embodiment of the invention.

FIG. 4 shows a lateral cross-sectional view of a lung and chest cavity of a patient showing a device according to yet another embodiment of the invention having fiber reinforcement.

FIG. 5 shows an embodiment of an adhesive delivery catheter according to an embodiment of the invention.

FIG. 6 shows an embodiment of an adhesive delivery catheter according to another embodiment of the invention.

FIG. 7 shows an embodiment of an adhesive delivery catheter according to another embodiment of the invention.

FIG. 8 shows yet another embodiment of an adhesive delivery catheter according to an embodiment of the invention.

FIG. 10 shows an arrangement of holes on an adhesive delivery catheter.

FIG. 11 shows an alternate arrangement of holes on an adhesive delivery catheter.

FIG. 12 shows a delivery channel having a narrowed delivery port.

FIG. 13 shows a dual channel delivery channel.

FIG. 14 shows an adhesive delivery system according to an embodiment of the invention.

FIG. 15 shows an adhesive delivery catheter delivering adhesive to lung pleurae.

FIG. 16 shows an adhesive delivery device that provides percutaneous access to a pleural space.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides methods, materials and devices for treating a pleural effusion by gluing the pleura together using a suitable adhesive, such as glue, as a sealant to prevent the passage of liquid or gas. The materials used in the method include a fast-acting adhesive that cures in less than three days, more preferably less than two days, even more preferably less than one day, and most preferably less than one hour. A specific cure time may be tunable to allow for glue distribution before curing fully. Some glue formulations may require ancillary light sources, primers, catalysts, radiofrequency energy, electrical energy or radiation to cause the glue to cure.

Glue formulations for use with this invention may include solids, semi-solids, hydrogels, foams, agars, or sol-gels. Some glue formulations work in wet or dry tissue surface conditions. Some glue formulations may also stop active bleeding (*i.e.*, provide hemostasis). The glues are preferably biocompatible and can successfully fuse tissue in wet conditions. The glues adhere the pleura without causing fibrosis, inflammation or scarring of the pleural tissue. The glues are flexible and conformable to tissue geometry, and they possess high tensile strength. Solvents can be used to deliver the glue in order to drive the glue into the tissue.

One preferred embodiment is a glue formulation that crosslinks (chemically bonds) to the biological tissue it is applied to. More specifically, the adhesive either crosslinks to collagen or promotes the crosslinking of collagen at two adjoining tissue surfaces to be fused and allow for high adhesion.

Another preferred embodiment is a glue formulation that has a radiopaque component so that the glued boundary can be identified using x-ray-based imaging techniques during or after the procedure. Additives may include tantalum, platinum, bismuth, radiopaque metals, and polymers. Polymers can include, for example, poly(lactic acid) and poly(glycolide). Agents and drugs can also be added as primers.

Although many alternative glue formulations may be suitable to achieve these goals, one preferred glue formulation consists of a combination of a cross-linking agent, such as glutaraldehyde or stable polyaldehyde, and a protein, such as albumin, including porcine albumin and collagen, with or without additional additives. One such material suitable for pleural fusion is described in US Patent Application Publ. No. 2004/0081676. It works uniquely as a biologic glue that typically cures within a few minutes to fuse pleural layers without causing or requiring inflammation or heat. The glue's intrinsic viscosity can be tuned to allow for fast or slow spreading across target lung regions. The glue may be used for other purposes as well, such as anastomosis of blood vessels and bronchi/bronchioles and to seal pulmonary structures from air leaks, bleeding, or fluid leaks. Another adhesive that may be suitable is a cyanoacrylate adhesive.

Alternative glue formulations may be suitable to achieve these goals such as a combination of any one of the previously described components in combination with other additives that may include elastin, fibrin,

glycoprotein, liposomes, thrombin, calcium, neuroleptics, vitamins, growth factors, glucocorticosteroids, steroids, antibiotics, antibacterial compounds, bacteriocidal and bacteriostatic compounds, antiviral compounds, antifungal compounds, antiparasitic compounds, tumoricidal compounds, tumoristatic compounds, toxins, enzymes, enzyme inhibitors, proteins, peptides, minerals, neurotransmitters, lipoproteins, glycoproteins, immunomodulators, immunoglobulins and fragments thereof, dyes, radiolabels, radiopaque compounds, fluorescent compounds, fatty acids, polysaccharides, cell receptor binding molecules, anti-inflammatories, antiglaucomic compounds, mydriatic compounds, anesthetics, nucleic acids, and polynucleotides.

The glue can be packaged sterile, in a single part or in two liquid parts in an applicator. Upon delivery of a two-part formulation, liquid components can be mixed as they are delivered, by an applicator or stirring or mixing nozzle device. After application, the formulation may quickly or slowly solidify into a flexible solid glue. The glue can also be premixed and then applied. The glue may be formulated as a two part solution that can be applied independently. In doing so, the first part may be applied and allowed for spread time before the second is applied.

Devices for use with the invention preferably introduce or spread the glue evenly over the surfaces of the visceral and parietal pleurae. The pleural effusion glue may be applied in an aerosol form to cover large organ surfaces more effectively or as a liquid, via a syringe, a catheter (e.g., through the patient's chest tube), or other applicator.

FIG. 1 shows a lateral cross-sectional view of a patient's chest cavity. The pleural space ***10*** of lung ***8*** is defined by the visceral pleura ***12*** and the parietal pleura ***14***. A chest tube ***16*** has been inserted percutaneously into the pleural space. Suction applied from a suction source ***18*** may be used to draw excess fluid from the pleural space through holes ***21*** in chest tube ***16*** to suction line ***20*** and into fluid container ***22***.

A delivery catheter ***24*** having a plurality of holes ***26*** at its distal end is inserted through chest tube ***16*** into the pleural space. A two-part syringe ***28*** may be used to deliver an adhesive material through delivery catheter ***24*** into the pleural space. As described above, the adhesive material is preferably a glue that does not contain any fibrosis-inducing or inflammatory material. Curing of the glue causes pleurae ***14*** and ***12*** to adhere, thereby reducing the likelihood that the pleural space will again be filled with excess fluid.

To ensure adequate adhesion of the pleurae, more than one device may be used to introduce adhesive material to the pleural space. For example, a second syringe ***30*** and delivery catheter ***32*** may be used together with the device of **FIG. 1**, as shown in **FIG. 2**. Alternatively, a separate chest tube ***40*** may be used for the adhesive delivery catheter ***24***, as shown in **FIG. 3**. The glue ***42*** preferably spreads over substantially all of the pleural space ***10***, as shown in **FIG. 4**. The glue ***42*** also includes a fiber reinforcement component ***41*** which creates a composite of glue and fiber. Fiber reinforcement can include short or long fibers, glass, polymer, ceramic, metallic, and other suitable materials, as would be appreciated by those of skill in the art. The fiber acts as reinforcement and the sealant acts as a matrix material in the composite. This is beneficial where distances between surfaces, or gaps, is large.

FIGS. 5-9 show alternative embodiments of adhesive delivery catheters for use with the invention. In **FIG. 5**, delivery catheter ***50*** has one or more bends so that the catheter forms an S shape. In this embodiment, the shape shown in **FIG. 5** is the catheter's operational configuration. Prior to use, catheter ***50*** is preferably straightened to a delivery configuration and inserted percutaneously through a chest tube into a patient's pleural space, then allowed to form (or is caused to form) its operational configuration. Holes ***52*** in catheter ***50*** permit the delivery of glue or other adhesive under pressure, such as from a syringe. The shape of the catheter and distribution of the holes help ensure even distribution of the adhesive material. In addition, the catheter may be moved within the pleural space after introduction of the adhesive material to rake or spread the material within the pleural space. Catheter ***50*** is returned to its delivery configuration for removal from the patient.

FIG. 6 shows a delivery catheter *60* in an operational configuration in which the catheter has two branches *62* and *64* which split and meet to form an oval or heart shape. Catheter *60* may be straightened to a delivery configuration by moving branches *62* and *64* together for percutaneous delivery, then moved to its operational configuration by moving a pull wire or other actuator *66*. As in the other embodiments, holes *68* in catheter *60* permit the delivery of glue or other adhesive under pressure, such as from a syringe. The shape of the catheter and distribution of the holes help ensure even distribution of the adhesive material. In addition, the catheter may be moved within the pleural space after introduction of the adhesive material to rake or spread the material within the pleural space. Catheter *60* is returned to its delivery configuration by actuator *66* for removal from the patient.

FIG. 7 shows a delivery catheter *70* with two branches *72* and *74* separated into an operational configuration by spring elements *76* and *78* (made, e.g., from Nitinol or some other shape memory material). Catheter *70* may be straightened to a delivery configuration by moving branches *72* and *74* together against the action of the spring elements, then allowed to assume its operational configuration once inside the pleural space. Holes *79* in catheter *70* permit the delivery of glue or other adhesive under pressure, such as from a syringe. As in other embodiments, the shape of the catheter and distribution of the holes help ensure even distribution of the adhesive material. In addition, the catheter may be moved within the pleural space after introduction of the adhesive material to rake or spread the material within the pleural space. Catheter *70* is returned to its delivery configuration for removal from the patient, such as by inward camming action caused by pulling catheter *70* back into the distal end of a chest tube.

FIG. 8 shows a delivery catheter *80* with two branches *82* and *84* separated into an operational configuration by a spring element *86*. Catheter *80* may be straightened to a delivery configuration by moving branches *82* and *84* together against the action of the spring element, then allowed to assume its operational configuration once inside the pleural space. As in other embodiments, holes *88* in catheter *80* permit the delivery of glue or other adhesive under pressure, such as from a syringe; the shape of the catheter and distribution of the holes help ensure even distribution of the adhesive material. In addition, the catheter may be moved within the pleural space after introduction of the adhesive material to rake or spread the material within the pleural space. Catheter *80* is returned to its delivery configuration for removal from the patient, such as by inward camming action caused by pulling catheter *80* back into the distal end of a chest tube.

FIG. 9 shows a delivery catheter *90* similar to that of FIG. 8 but with four branches *91-94* and three spring elements *95-97* separating the branches into the operational configuration shown. Holes *98* in catheter *90* permit the delivery of glue or other adhesive under pressure, such as from a syringe; the shape of the catheter and distribution of the holes help ensure even distribution of the adhesive material. In addition, the catheter may be moved within the pleural space after introduction of the adhesive material to rake or spread the material within the pleural space. Catheter *90* is returned to its delivery configuration for removal from the patient, such as by inward camming action caused by pulling catheter *90* back into the distal end of a chest tube.

The arrangement of the holes in the delivery catheter may be modified to help provide even distribution of adhesive material within the pleural space. For example, FIG. 10 shows holes *102* in catheter *100* arranged along the outward facing side of a bend in catheter *100*, and FIG. 11 shows holes *112* spiraling around catheter *110*.

As an alternative to a delivery catheter with multiple adhesive material delivery holes, the delivery catheter may have a single delivery port. For example, the delivery catheter *120* shown in FIG. 12 has a delivery channel *122* leading through a narrowed portion *124* to a single delivery nozzle *126* configured to spray adhesive material *128* around the pleural space.

Some adhesives may be formed as two-part compositions. FIG. 13 shows a delivery catheter *130* with two channels, *132* and *134*. The two parts of a two-part adhesive composition may be delivered down the separate channels of catheter *130*, then allowed to mix in a mixing chamber *136* before being sprayed out of a nozzle or delivery port *138*.

FIG. 14 shows an alternative adhesive delivery system *140* in which the two parts of a two-part adhesive are delivered from separate syringe chambers *141* and *142* by moving plungers *143* and *144* tied together with a common actuator *145*. The adhesive components are injected from sealed tips *146* and *147* into a detachable mixing chamber *148*. Mixing chamber *148* may have prongs (not shown) that interact with tips *146* and *147* to break their seals when mixing chamber *148* is connected to the syringe. Baffles *149* or other mixing devices within mixing chamber *148* help ensure thorough mixing of the adhesive components. The mixing chamber *148* connects to a delivery catheter *152* which may be inserted into a patient's pleural space. The mixing chamber may have a porous plug or other filter *150* and an air bleed hole *151* at its distal end. Suitable plugs are microfiters available from Gen-Probe. The filter properties are such that air can be dispersed through the filter transverse to the axis of the glue while the glue will be forced axially through the filter.

FIG. 15 shows an adhesive delivery catheter *154* that has branches *155* and *156* that spread and wrap around anterior *158* and posterior *159* sides of the lung within the pleural space. Adhesive material may be delivered from syringe *157* to the pleural space via holes (not shown) in the branches *155* and *156* of catheter *154*.

FIG. 16 shows an adhesive delivery device *160* that provides percutaneous access to a pleural space *161* without the use of a chest tube. Device *160* has a sharp beveled distal end *162* that can pierce the patient's skin *163*. A plunger *164* may be moved within a syringe portion *165* of device *160* to move adhesive material *166* through a porous plug *167* or other filter and into the patient. An air bleed hole *168* may be provided to permit trapped air to escape.

As will be appreciated by those of skill in the art, the delivery device can be used by using a single tube to drain fluid within the pleural space and then deliver the adhesive material which acts as a sealant to prevent the passage of liquid or gas. Alternatively, the fluid can be left within the pleural space, the delivery device can be inserted between the pleural layers and then maneuvered into place before delivering the sealant. In this scenario, it may be desirable to drain the fluid from the pleural space before delivering the sealant. Suitable sealants will cure within, approximately, 20 seconds to 1 minute, to enable the curing process to proceed without being effected by movement of the lungs during breathing.

Although many alternative sealant formulations may be suitable for this purpose, a preferred sealant would consist of primarily a combination of stable polyaldehyde, albumin and collagen with or without additional additives. The sealant can also have agents that initiate or accelerate the clotting cascade so the sealant can be used as a hemostatic agent. For example, a suitable material is described in US Patent Application Publ. No. **2004/0081676**. This sealant works as a biologic glue that cures within a few minutes to seal pleural layers without causing inflammation or heat. The glue's intrinsic viscosity can be tuned to allow for fast or slow delivery through a delivery system, such as those shown above and includes glue viscosity more than 1.1 centipoise. This glue formulation is appropriate for use with all lung tissue and structures within the pulmonary system as well as pulmonary vasculature. It can also be formulated and used for any adhesive or anti-adhesion purpose including anastomosis of blood vessels and bronchi/bronchioles and to seal pulmonary structures from air leaks, bleeding or fluid leaks. Ideally, the sealant will cure within a few minutes, works well in a damp or wet environment, and blocks air or fluid from entering the pleural cavity. Typically, the glues are composed of a condensation product of

glutaraldehyde that consists of cross-linked albumin, including porcine albumin. Adhesion values for the glue can be up to 1.5 psi, more preferably between 0.2-0.6 psi.

As described above, two-part sealants may be used with this invention. Sealant components for this application may include fibrin/thrombin, activated PEG/PEG-diamine, albumin/PEG, and albumin/glutaraldehyde sealants. The sealant is an implantable material that may contain hemostatic agents such as chitin derivatives including but not limited to carboxymethyl chitin and chitosan (1-100% deacetylated). The sealant components may also contain additives that affect viscosity, set time, adhesion, and biocompatibility. The albumin component may be formulated in weight to weight ratios of 10-50% where the remaining mass balance is aqueous solutions of salts, buffers, and additives or combinations thereof. The other component of the sealant is a cross-linker containing glutaraldehyde or derivatives thereof in weight to volume ratios of 1-25% where the remaining balance is an aqueous solution with or without additives, salts, or buffers or combinations thereof. These solutions may be applied from dispensers that deliver a ratio of 1 unit volume of protein solution per 1 unit volume of cross-linker solution (1:1 protein:cross-linker) and may be applied in ratios up to 10 unit volumes of protein solution per unit volume of cross-linker solution. Furthermore, mixing may occur by passing the solutions through a static mixing tip with helical or other geometrical devices that enhance the mixing efficiency. Sealants prepared from these solutions contain 5-45% protein and 0.5-14% crosslinker.

Other suitable sealants and other agents are described in US Pat. Appl. Publ. No. 2004/0052850; US Pat. Appl. Publ. No. 2004/0081676; USSN 11/008,577; USSN 11/008,092; USSN 11/008,094; USSN 11/008,578; USSN 11/008,649; USSN 11/008,777; USSN 11/008,087; USSN 11/008,093; USSN 11/008,580; and USSN 11/008,782.

Materials that solidify such as glue compositions form a structure that is typically stiffer than the intrinsic stiffness of lung tissue. Specifically, pull tests of lung parenchyma (comprised of alveolar sacks and collagen) sections show that the composite stiffness is very low. When agents are combined that form a stiffer structure than the underlying biomaterial or lung tissue, the modulus mismatch causes irritation, inflammation, tissue thickening, fibrosis, a remodeling cascade and adhesions that will promote and maintain lung volume reduction. Compositions that dry out or maintain viscosity levels above 2 centipoise (a measure of dynamic viscosity) generate shear and cause this stiffness mismatch to promote adhesions. Agents and hydrogel materials thicker than 10 centipoise work better. The glutaraldehyde glue technology employed can produce compositions that have 15 centipoise viscosity and higher levels up to and beyond 150 centipoise. By increasing the glue cross-linking properties, agents can be delivered that solidify to a gel or harder substance. Materials that gel to produce solids with a modulus greater than 10-20 centimeters of H_2O will produce this same effect. Materials that are stiffer in a range between 20 and 100 centimeter of H_2O are better. Materials that are stiffer than 100 cm H_2O are preferable. Implantable materials with viscosity enhancing agents to promote these effects can be manufactured.

Many of these agents cause tissue binding to form localized adhesions or a bio-response that will help maintain permanent pleurae bonding. Introduction of these materials instigates one or more elements of a tissue remodeling cascade process. The process includes tissue polymer decomposition and/or necrosis that leads to recruitment of cellular respondents that include one or more of the following: Neutrophils, white blood cells, macrophages, CD8+, MMP's, Interlukens, cytokins and protocylins. The tissue then remodels to initiate tissue formation and thickening that culminates in the formation of tissue adhesions.

Other materials that can initiate this effect are cadmium, smoke artifacts, tars, materials that irritate tissue such as alcohols, solvents, organic solvents, acids, materials that are basic and materials that are acidic. These materials include compounds or compositions that have pH levels between 1 and 6.9 with materials closest to 1

being a preferable acid material. Additionally, compounds or materials that have pH levels between 7.5 and 14 work very well; materials closest to 14 work best.

When applying an adhesive material of the present invention, such as an implantable hydrogel comprised of a biocompatible material, or an implantable liquid that undergoes a physical transition from a liquid to a gel or other solid such as solid adhesives, control of deposition is very important. Ways of controlling deposition include localized dispensing of the sealant through a suitable device containing a lumen, and also through the addition of agents that increase the viscosity of one or more components of the implantable material. Such agents include biocompatible materials with viscosities that are greater than those of water, and include glycerol, polymeric materials such as proteins, carbohydrate-based polymers and derivatives thereof, synthetic materials including polyethylene glycols (PEG), polyethylene oxides (PEO), polyvinyl pyrrolidone (PVP), polyvinyl alcohol and other components described in the "United States Pharmacopeia" and the "Handbook of Pharmaceutical Excipients", edited by A. H. Kibbe. Other materials for controlling viscosity include oils, lipids, and fatty acids, including oleic acid, and phosphocholines. Phase separation can be controlled with emulsifiers including poly sorbate. For sealants prepared by mixing two or more components, the viscosities of one or more of the components can be modified by adding an appropriate agent to control spreading after application. Viscosities of these components can range from 1 to 1000 centistokes (a measure of kinematic viscosity).

Deposition and control of spreading of sealants containing two or more components are also affected by the gel time, or set time, of the mixed sealant. Sealants with short set times are preferable to those with longer set times. Set time can be controlled by the addition of set time modifiers, including agents that reduce or increase the set time relative to the corresponding formulation lacking the set time modifier. An example of an agent that decreases the set time is carboxymethyl cellulose. An example of an agent that increases the set time is glycerol.

Glutaraldehyde, as currently processed and used in some commercial sealants, undergoes reversible reactions that cause reoccurring inflammation. These properties can be improved by chemical modification of the glutaraldehyde. One such modification includes glutaraldehyde condensation reactions, as described in "Bioconjugate Techniques" by G. T. Hermanson. This condensation involves the formation of derivatives of glutaraldehyde in aqueous solutions containing acid or base. This reaction can be monitored by ultraviolet spectroscopy at or near 280 and 234 nanometers. At 280 nanometers, pure glutaraldehyde has significant absorbance, and little or no absorbance at 234 nanometers when measured as an aqueous solution at 0.5% weight to volume. When glutaraldehyde is chemically modified, it has significant absorbance at 234 nanometers. These derivatives are effective cross-linking agents when used with nucleophilic substrates such as proteins, including albumins. Furthermore, sealants prepared from glutaraldehyde derivatives are adhesive *in vivo*, through chemical or mechanical means, or a combination of chemical and mechanical means.

Implantable materials are adhesives, glues and sealants. For the present invention implantable materials include agents administered into tissue, including sealants, which may be comprised of hydrogels, proteins, or other biocompatible materials, that can be implanted into compromised tissue to benefit the patient. Examples of hydrogels include those prepared from natural sources including carbohydrate-based materials. Such materials include hyaluronans, hyaluronic acid, alginates, chitins, chitosans, and derivatives thereof. Proteins that enable the present invention include albumins, including porcine albumins, collagens, gelatins, and other proteins that can be cross-linked or that form solutions with viscosities greater than water. Other implantable materials include those prepared by mixing two or more components so that a viscous solution, gel, or solid is formed. Such implantable materials are prepared from a protein substrate where the protein is derived from natural, synthetic, or semi-synthetic processes. The protein may also be derived from recombinant DNA technology and may be isolated from cell-

culture processes, as well as from transgenic plants and animals. Examples of proteins include albumins, collagens, and gelatins. Cross-linkers employed as part of the implantable material precursors include aldehydes, polyaldehydes, esters, and other chemical functionality suitable for cross-linking protein(s). Examples of homobifunctional cross-linking agents are described in "Bioconjugate Techniques" by G. T. Hermanson.

Materials of the invention, e.g., the cross-linked protein adhesives and heat-treated glutaraldehyde glues, when subjected to a swell test, have values in a percentile range lower than 100. To determine the swell test value, the material is placed in water and allowed to hydrate. The hydrated material is then weighed. Following the step of weighing the hydrated material, the hydrated material is then dried (e.g. by heating) and weighed again to determine a dry weight. The ratio of these two weights (hydrated vs. dry) comprises the result of the swell test and indicates how much moisture a material can take on in a percentage of its weight. Thus, for example, most non-glutaraldehyde glues typically have a swell test of 100-150%, which makes the glue come apart in a moist environment. Fibrin based glues have an even higher swell test value. Cross-linked albumin based glues of this invention have a lower swell test value which enables the glues to perform well in moist environments, with a swell test value ranging from -50% to 100%.

The implant components, including the cross-linking agent and the substrate, can be formulated at a pH in the range of 5-10 by adjusting the pH and/or by adding suitable buffers in the range of 1-500 mM. Examples of buffers include phosphate, carbonate, bicarbonate, borate, or imidazole, or mixtures thereof. Additionally, additives or stabilizers may be added to improve the stability of one or more of the components. Furthermore, imaging agents may be added to allow for detection of the material. Such agents include iodine, iodine compounds, metals such as gadolinium, radioisotopes, and other compounds for gamma scintigraphy, magnetic resonance imaging, fluoroscopy, CT, SPECT and other imaging modalities. Additionally, the material may be formulated such that the mechanical properties are suitable for applications in the specific tissue to which the implantable material is applied. Such properties include elasticity, modulus, stiffness, brittleness, strain, cohesion, adhesion, and stress. Agents for modifying the properties include fillers, plasticizers, and adhesion modifiers. Furthermore, the implant may induce a natural adhesive mechanism with or without the addition of chemical agents which may be added to the implant to induce a natural response. Such agents include particles in the range of 100 nm to 1 millimeter. Agents include chemical or biochemical agents (proteins or nucleic acids) that induce a natural response. Examples of such agents include bleomycin, cytokines and chemokines, and single stranded RNA molecules.

In some embodiments, it may be desirable to use bioabsorbable sealants that expand or swell in the presence of aqueous fluids such as biological fluids. A commonly used sealant of this type includes both natural and synthetic hydrogels. Synthetic hydrogels can be prepared from the following classes of polymers and these are generally considered to be non-biodegradable: poly (hydroxyalkyl methylacrylates) such as poly(glyceryl methacrylate)poly(acrylamide) and poly(methacrylamide) and derivativespoly(N-vinyl-2-pyrrolidone)anionic and cationic hydrogelspoly(vinyl alcohol)poly(ethylene glycol) diacrylate and derivatives from block copolymers composed of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) and poly(propylene oxide)-poly(ethylene oxide)-poly(propylene oxide) blocks, respectively. All of these materials can be cross-linked with agents such as ethylene glycol dimethacrylate or methylene-bis-acrylamide. Biodegradable synthetic hydrogels can be prepared from polymers such as those listed above by incorporating one or more of the following monomers: Glycolide, Lactide, e-Caprolactone, p-Dioxanone and Trimethylene Carbonateln addition. Exemplary hydrogels based on natural products include polypeptides such as gelatin and polysaccharide such as starch and dextran. These natural products can be further processed by cross-linking with formaldehyde, glutaraldehyde and various other dialdehydes.

The biologically compatible sealant of the present invention may also comprise a detectable label. The detectable labels suitable for use in the present invention include any composition detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. A wide variety of appropriate detectable labels are known in the art, which include luminescent labels, radioactive isotope labels, and enzymatic labels. In preferred embodiments, one will likely desire to employ a fluorescent dye or label. These exemplary labels may be incorporated by a number of means well known to those of skill in the art. For instance, the label can be mixed with the sealant. Alternatively, labels can be chemically conjugated to the sealant molecules.

The use of a detectable label is particularly desirable for imaging the pleural region. The specific imaging means will depend on the particular type of label being used. For instance, radioactive labels can be detected by X-ray imaging. Fluorescent labels can be detected by an array of fluoroscopic equipment commonly employed by artisans in the field.

Ideally the composition of the sealant enables it to perform in a wet tissue environment. As is known in the art and discussed above, fibrin glue alone does not operate well in a wet environment and has been abandoned for use in many medical applications because of its inability to perform in a wet environment. The sealants used herein, in combination with the devices and methods, provide high adhesion in a wet environment. The adhesion of the sealant is beyond a low threshold that fibrin provides in wet tissue.

In determining an appropriate sealant to use with the devices and methods, two pieces of thin collagen based tissue (e.g. 1 inch wide by 2 inches long) are submerged into water (H_2O) or saline. The glue or sealant to be tested is then applied to the surface of one of the pieces and the two pieces are placed together in the water bath. The testing environment and materials are maintained at 67-69°F. The glue or sealant joint between the two layers of collagen is formed within 2 minutes of removing the tissue from the fluid without benefit of drying. The test section is 1 square inch of overlapped tissue that is glued with the excess tissue extending out both ends so that the two pieces can be gripped independently. The ends are gripped and pulled in opposite directions to test the force to shear the 1 inch section apart. The result is measured as shear stress or shear pressure and is recorded as pounds force per unit area. Currently available fibrin glues tested using this method fail at approximately 0.0 – 0.2 pounds force per square inch. Sealants and glues with a composition suitable for this invention fail at levels above 0.2 to well above 3.0 depending on the formulation.

In determining an appropriate sealant to use in another embodiment, the sealant is tested for biocompatibility based on MEM Elusion tests and the Agar Overlay tests.

In the MEM Elusion test, solids with uniform surface area and thickness of around <0.5 mm: 120 cm^2, solids with uniform surface area and thickness > 0.5 mm: 60 cm^2, solids without uniform surface area of 4 grams, or liquids up to 10 mL are tested. The samples are extracted in a serum-supplemented mammalian cell culture media (MEM). Extractions may be performed in 0.9% saline or cell culture media without serum if desired. Samples are then extracted for 24-25 hours at 37 ± 1° C in 5 ± 1% CO_2. The extracts are then filtered and placed in contact with a monolayer of L-929 cells (mouse fibroblasts). The cells are incubated at 37 ± 2° C in 5 ± 1% CO2 for 48 ± 3 hours, 72 ± 3 hours or whatever incubation time is desired. The cells are then scored for cytopathic effect. The L929 cell line is the most commonly used for the test, however, as will be appreciated by those skilled in the art, other cell lines may be suitable as well.

Agar Overlay tests typically are used for solids of 300 mm^2 or 300 mg and liquids of 3 mL. In the Agar Overlay test, a layer of agarose mixed with cell culture media is placed on top of a monolayer of L929 cells (mouse fibroblasts). The samples are placed on top of the agar layer. The cells are incubated for a minimum of 24 hours at 37 ± 1° C in 5 ± 1% CO_2. The cells are scored for cytopathic effect. The L929 cell line is most commonly used for

testing. However, as will be appreciated by those skilled in the art, other cell lines can be used without departing from the scope of the invention.

Using either the MEM Elusion test or the Agar Overlay test result, the sealant should have a cytotoxicity, on a scale from 0-4, of 0 or 1, even if the sealant has glutaraldehyde to improve adhesion in the composition.

The amount of pharmacologically active ingredient administered and the dosing regimen used will, of course, be dependent on the particular drug selected, the age and general condition, or the pharmacological condition of the subject being treated, the severity of the subject's condition, and the judgment of the prescribing physician.

The above descriptions with reference to certain illustrated embodiments and certain exemplary practices are provided as a guide to a practitioner of ordinary skill in the art, and are not meant to be limiting in any way.

While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating a patient for pleural effusion comprising percutaneously delivering an adhesive material to a pleural space of the patient.

2. The method of claim 1 wherein the delivering step comprises ejecting the adhesive material from a delivery device into the pleural space.

3. The method of claim 2 further comprising mixing components of the adhesive material in the delivery device prior to the ejecting step.

4. The method of claim 3 further comprising moving the delivery device from a delivery configuration to an operational configuration.

5. The method of claim 1 further comprising percutaneously inserting a pleural space access member into the patient.

6. The method of claim 5 further comprising applying suction to the pleural space prior to delivering the adhesive material to the pleural space.

7. The method of claim 6 wherein the applying step comprises applying suction through the pleural space access member and the delivering step comprises delivering the adhesive material through the pleural space access member.

8. The method of claim 1 wherein the delivering step comprises delivering adhesive material to the pleural space without delivering a fibrosis inducing material to the pleural space.

9. The method of claim 1 further comprising spreading the adhesive material within the pleural space.

10. The method of claim 1 wherein the delivering step comprises delivering an adhesive material having an adhesive strength up to 1.5 psi.

11. The method of claim 1 wherein the delivering step comprises delivering an adhesive material having an adhesive strength of between 0.2-0.6 psi.

12. The method of claim 1 wherein the delivering step comprises delivering an adhesive material having viscosity levels of 1.1 centipoise and higher.

13. The method of claim 1, wherein the adhesive material comprises material selected from the group consisting of hydrogels, proteins, polymers and cross-linking agents.

14. The method of claim 13, wherein the hydrogel material comprises material selected from the group consisting of hyalurons, hyalyronic acid, alginates, chitins, chitosans, and derivatives thereof.

15. The method of claim 13, wherein the protein material comprises material selected from the group consisting of albumins, porcine albumin, collagens and gelatins.

16. The method of claim 13, wherein the polymer material comprises material selected from the group consisting of poly(lactic acid) and poly(glycolide).

17. The method of claim 13, wherein the cross-linking agent material comprises material selected from the group consisting of glutaraldehyde and stable polyaldehyde.

18. A pleural effusion treatment apparatus comprising an adhesive material adapted to adhere pleural membranes defining a pleural space and a pleural space access member adapted to deliver the adhesive material to the pleural space.

19. The apparatus of claim 18 wherein the pleural space access member comprises an adhesive material delivery device.

20. The apparatus of claim 19 wherein the adhesive material delivery device comprises a syringe.

21. The apparatus of claim 19 wherein the adhesive material comprises two components, the delivery device comprising a mixing element adapted to mix the two components prior to injection of the adhesive material into the patient.

22. The apparatus of claim 18 wherein the pleural space access member comprises a chest tube.

23. The apparatus of claim 18 further comprising a suction apparatus.

24. The apparatus of claim 23 wherein the suction apparatus is adapted to apply suction through the pleural space access member.

25. The apparatus of claim 18 further comprising a spreading element adapted to spread the adhesive material within the pleural space.

26. The apparatus of claim 25 wherein the pleural space access member comprises a catheter, the spreading element comprising a bend formed in catheter.

27. The apparatus of claim 26 wherein the bend comprises a loop.

28. The apparatus of claim 26 wherein the bend comprises an S shape.

29. The apparatus of claim 26 wherein the bend comprises a V shape.

30. The apparatus of claim 26 wherein the pleural space access member further comprises an actuator for forming the bend.

31. The apparatus of claim 30 wherein the actuator comprises a pull wire.

32. The apparatus of claim 29 wherein the actuator comprises a shape memory element.

33. The apparatus of claim 30 wherein the delivering step comprises delivering an adhesive material having an adhesive strength up to 1.5 psi.

34. The apparatus of claim 30 wherein the delivering step comprises delivering an adhesive material having an adhesive strength between 0.2-0.6 psi.

35. The apparatus of claim 29 wherein the delivering step comprises delivering an adhesive material having viscocity levels of 1.1 centipoise and higher.

36. The apparatus of claim 18, wherein the adhesive material comprises material selected from the group consisting of hydrogels, proteins, polymers and cross-linking agents.

37. The apparatus of claim 36, wherein the hydrogel material comprises material selected from the group consisting of hyalurons, hyalyronic acid, alginates, chitins, chitosans, and derivatives thereof.

38. The method of claim 36, wherein the protein material comprises material selected from the group consisting of albumins, porcine albumin, collagens and gelatins.

39. The method of claim 36, wherein the polymer material comprises material selected from the group consisting of poly(lactic acid) and poly(glycolide).

40. The method of claim 36, wherein the cross-linking agent material comprises material selected from the group consisting of glutaraldehyde and stable polyaldehyde.

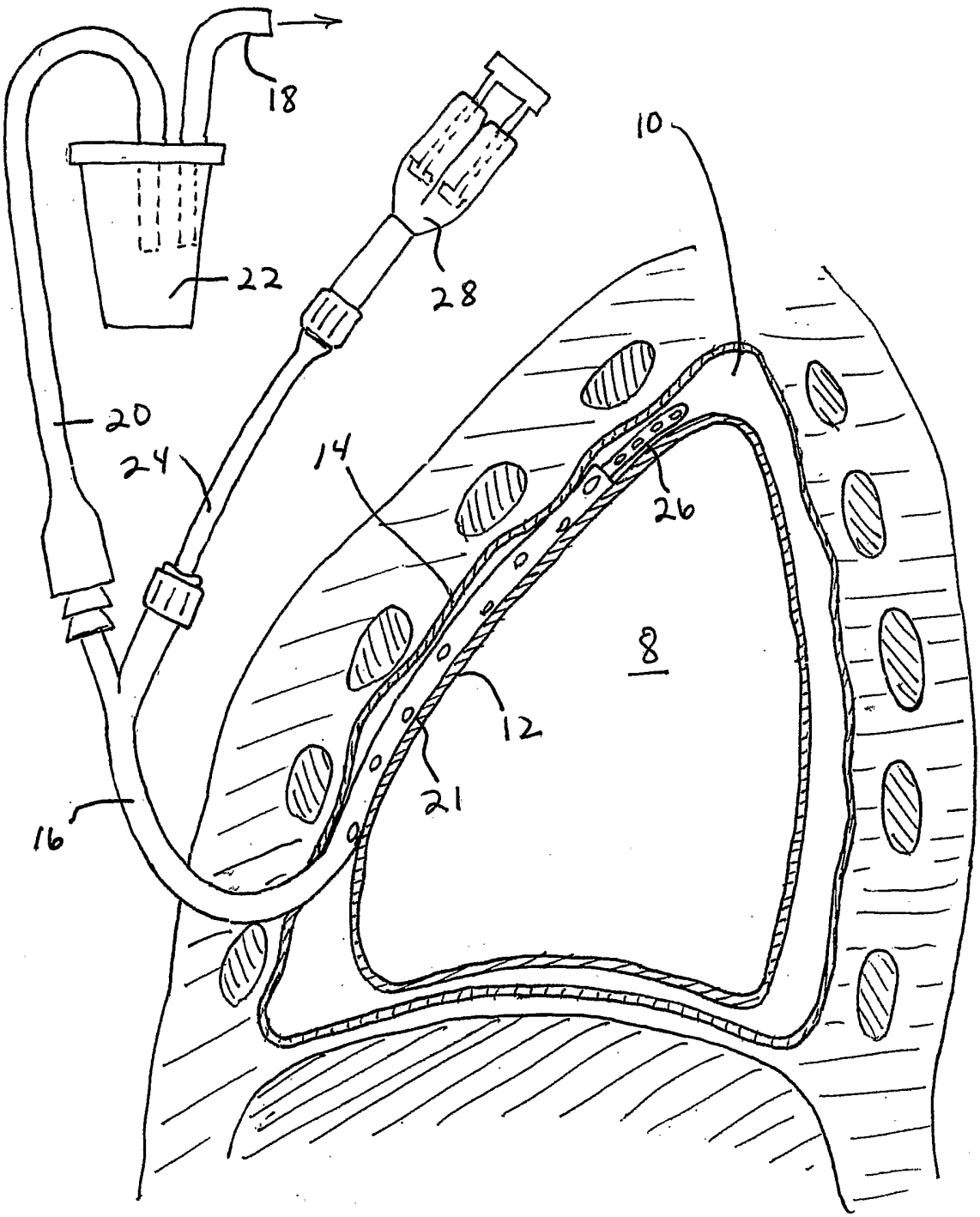


FIG. 1

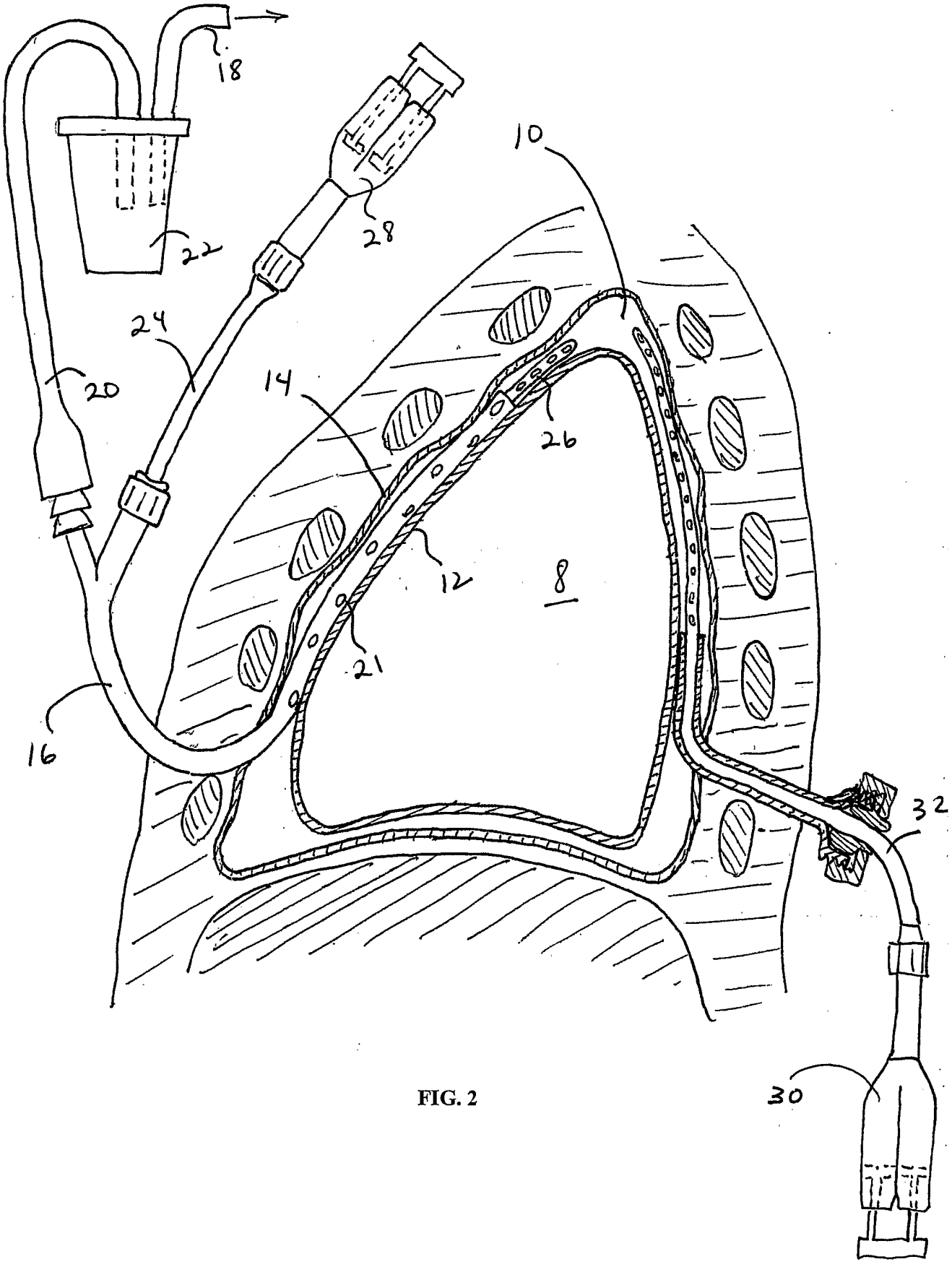


FIG. 2

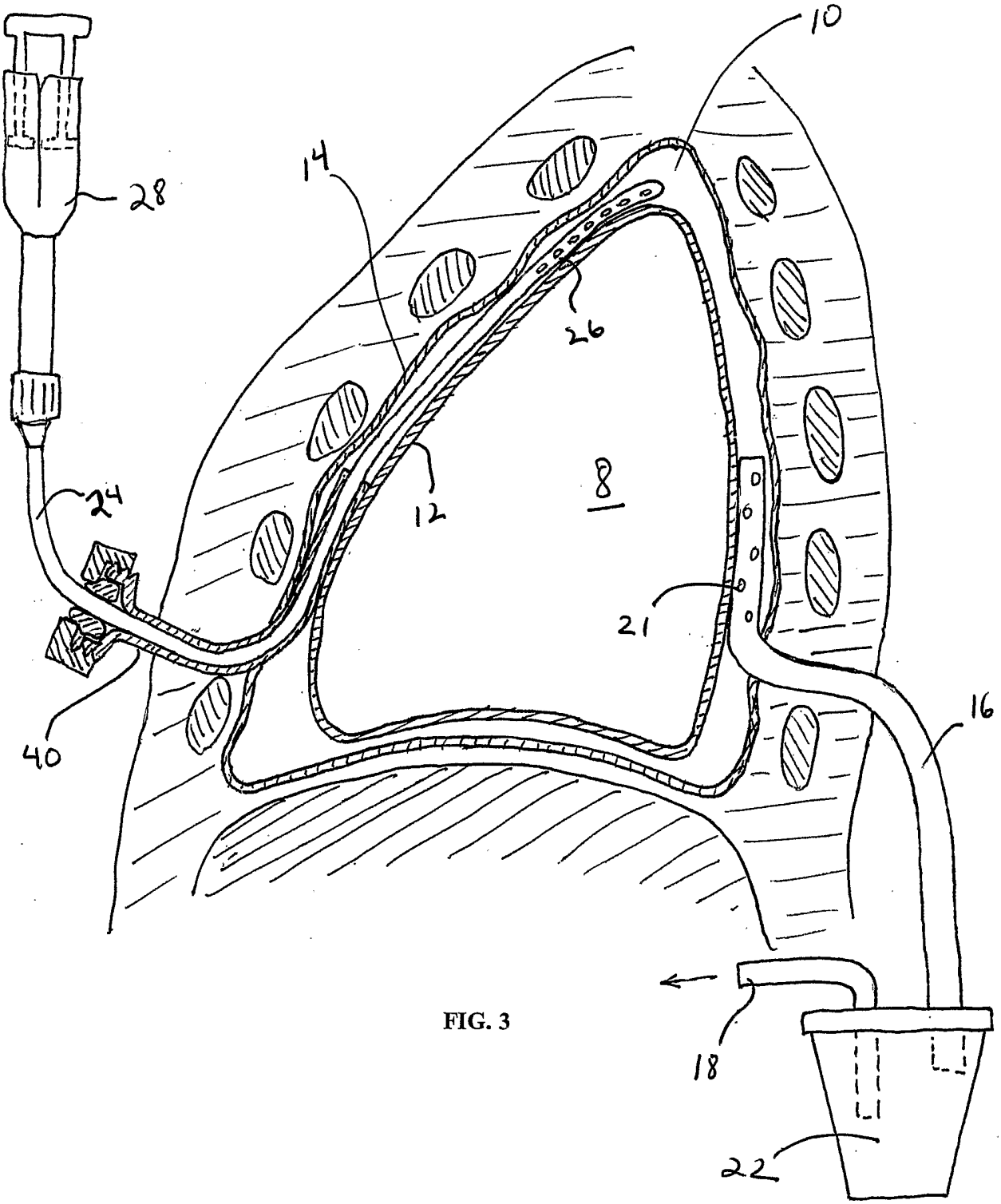
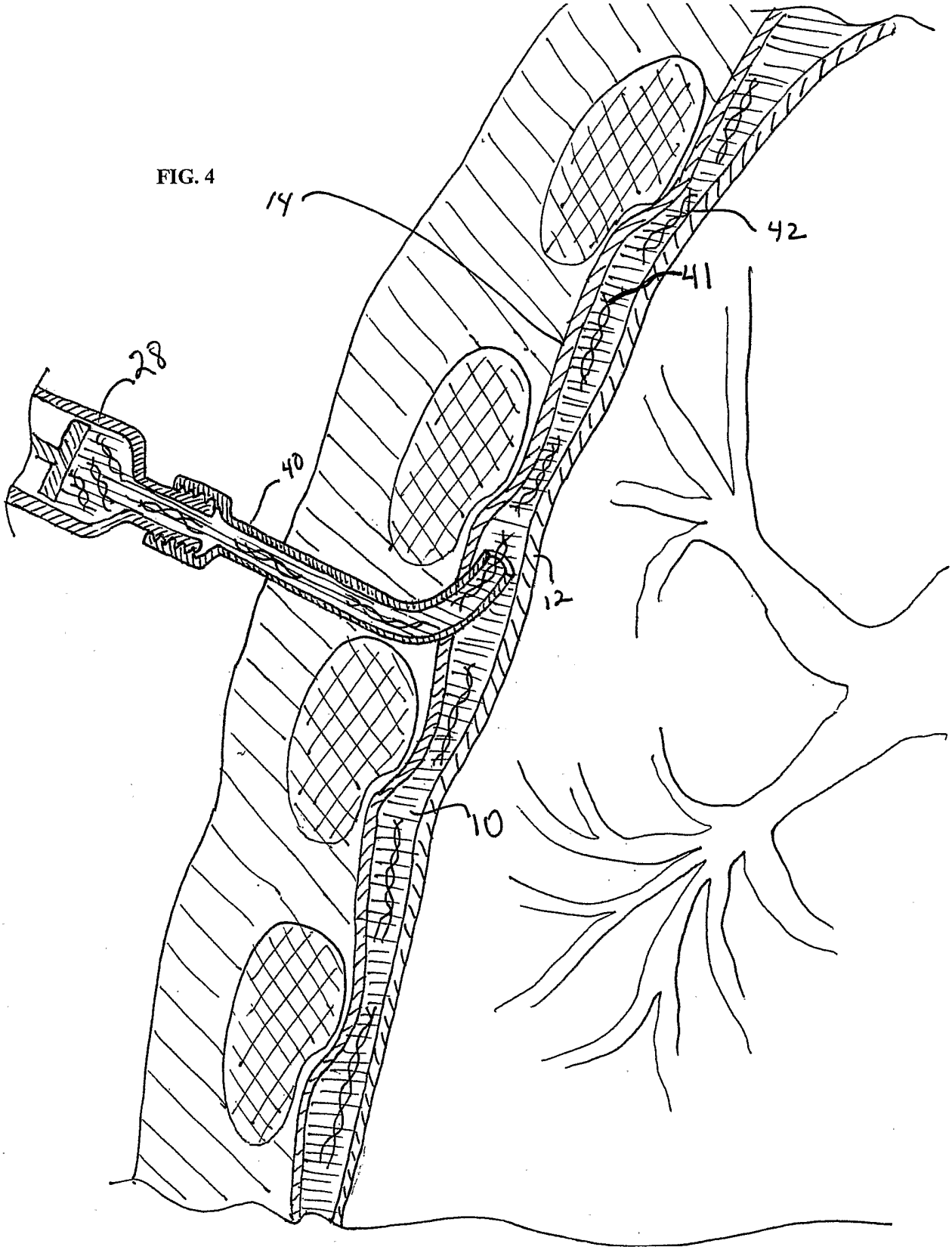


FIG. 3

FIG. 4



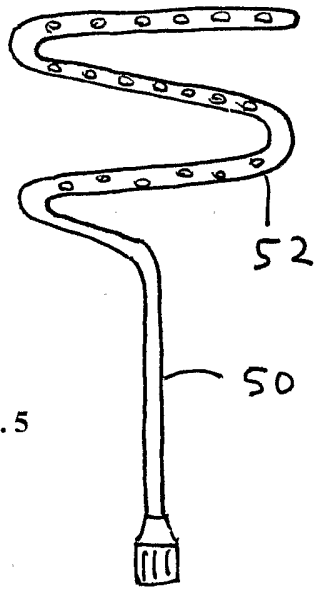


FIG. 5

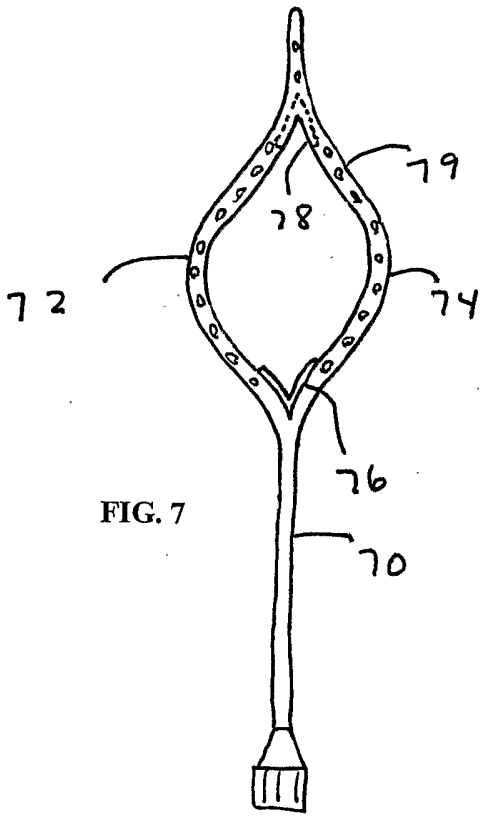


FIG. 7

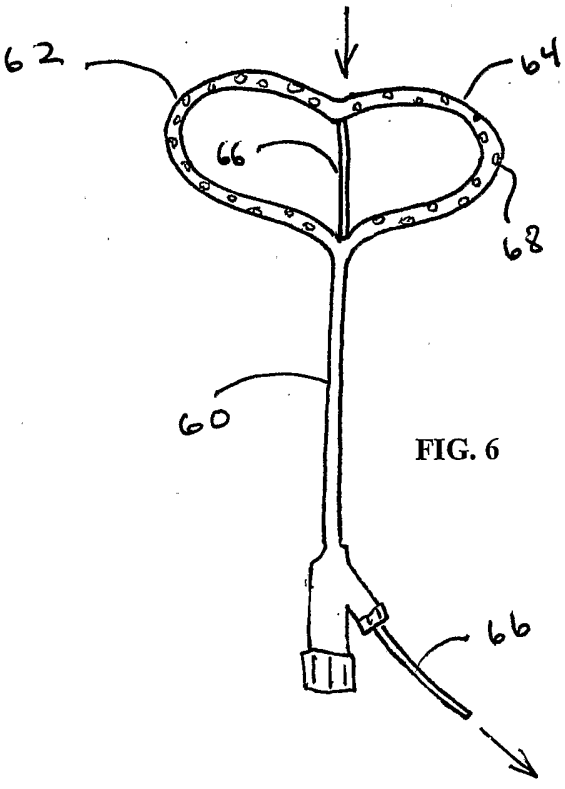


FIG. 6

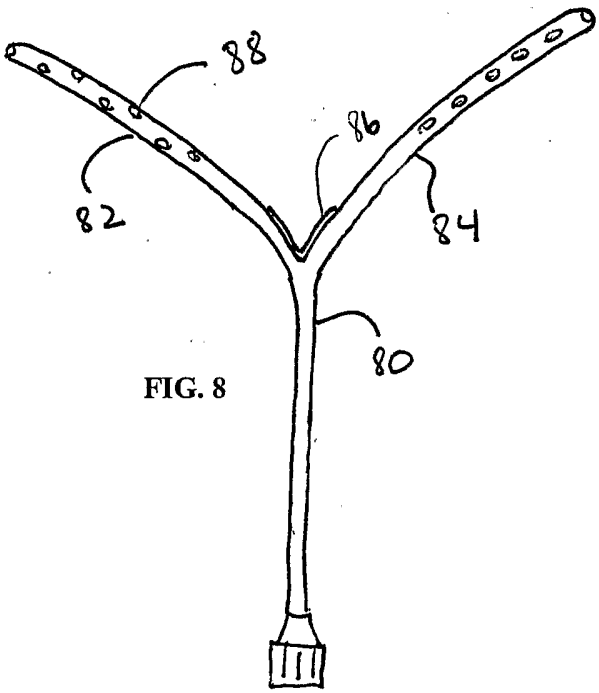


FIG. 8

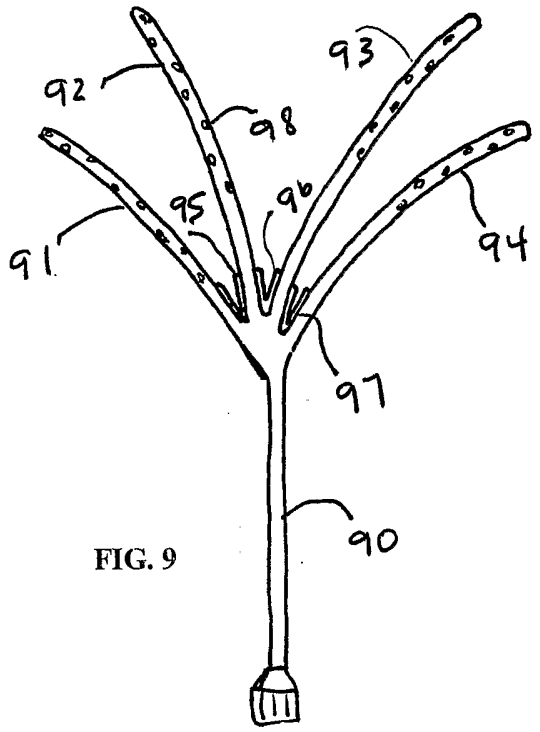


FIG. 9

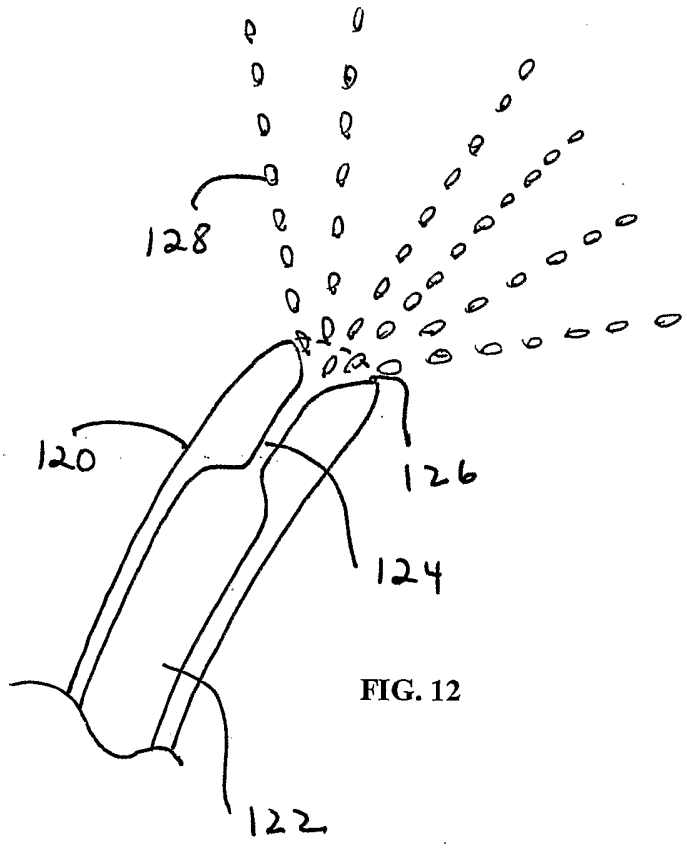


FIG. 12

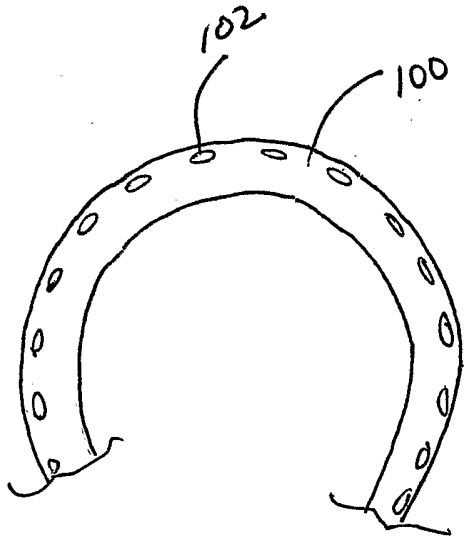


FIG. 10

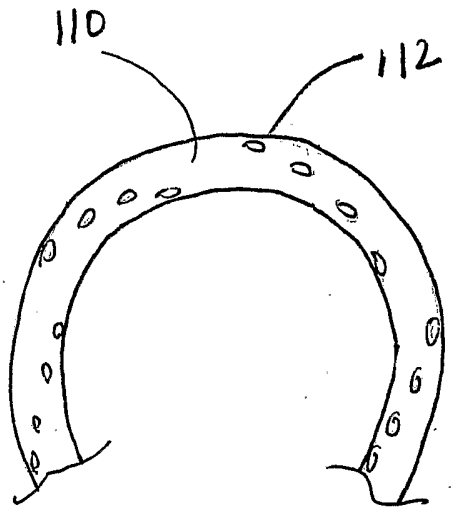


FIG. 11

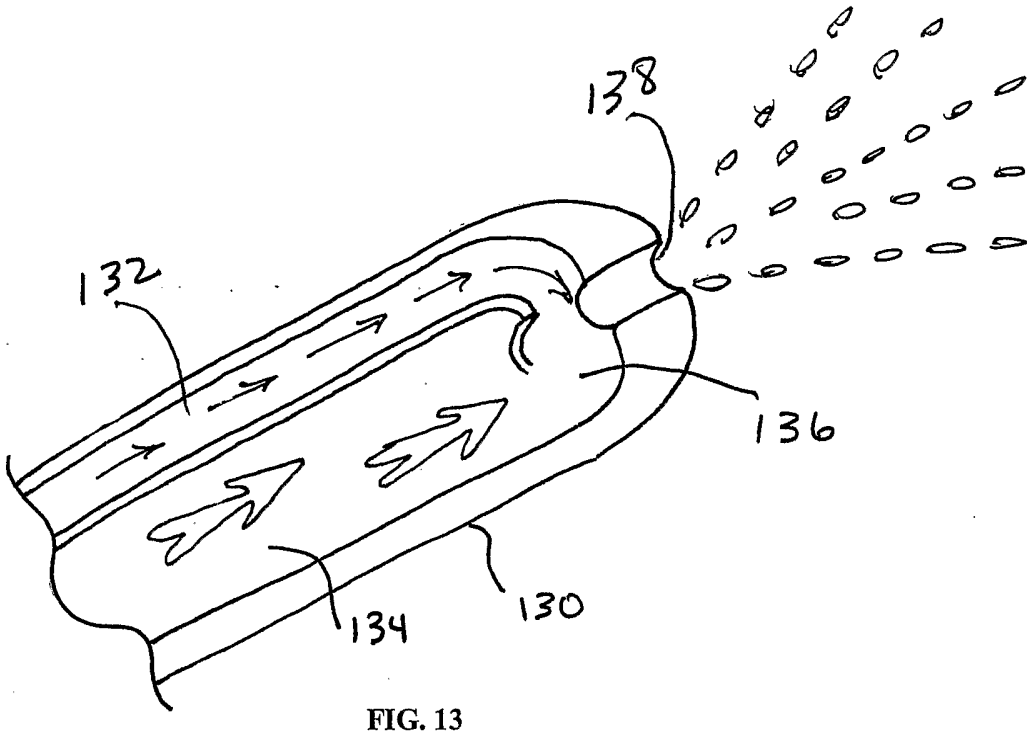
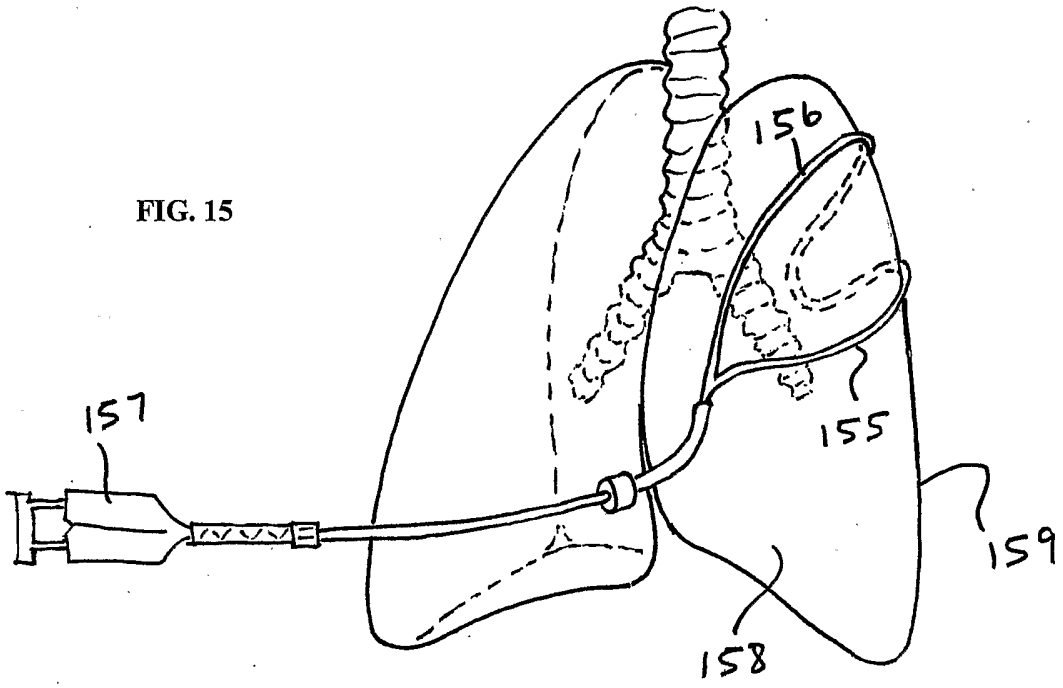


FIG. 13

FIG. 15



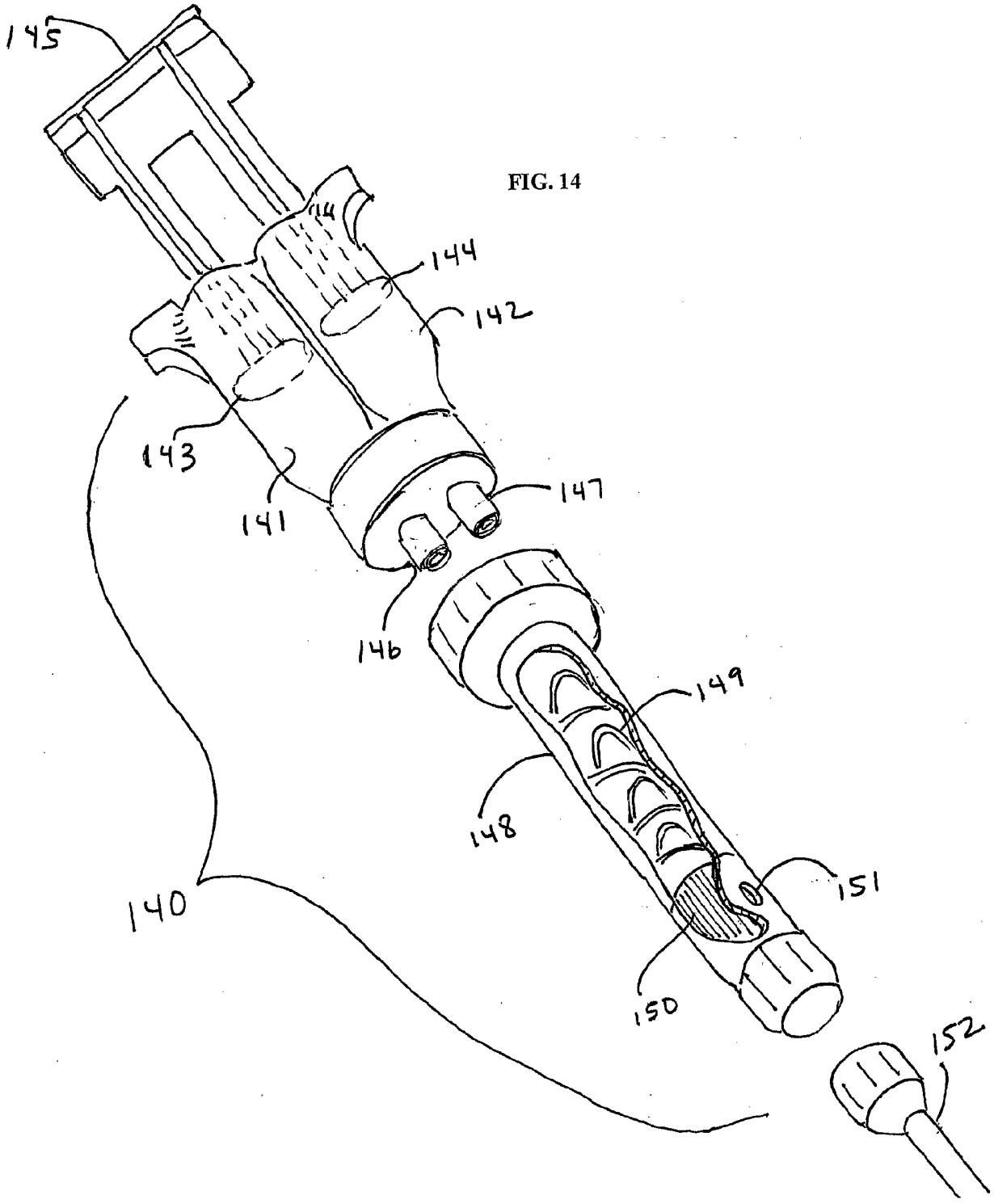


FIG. 14

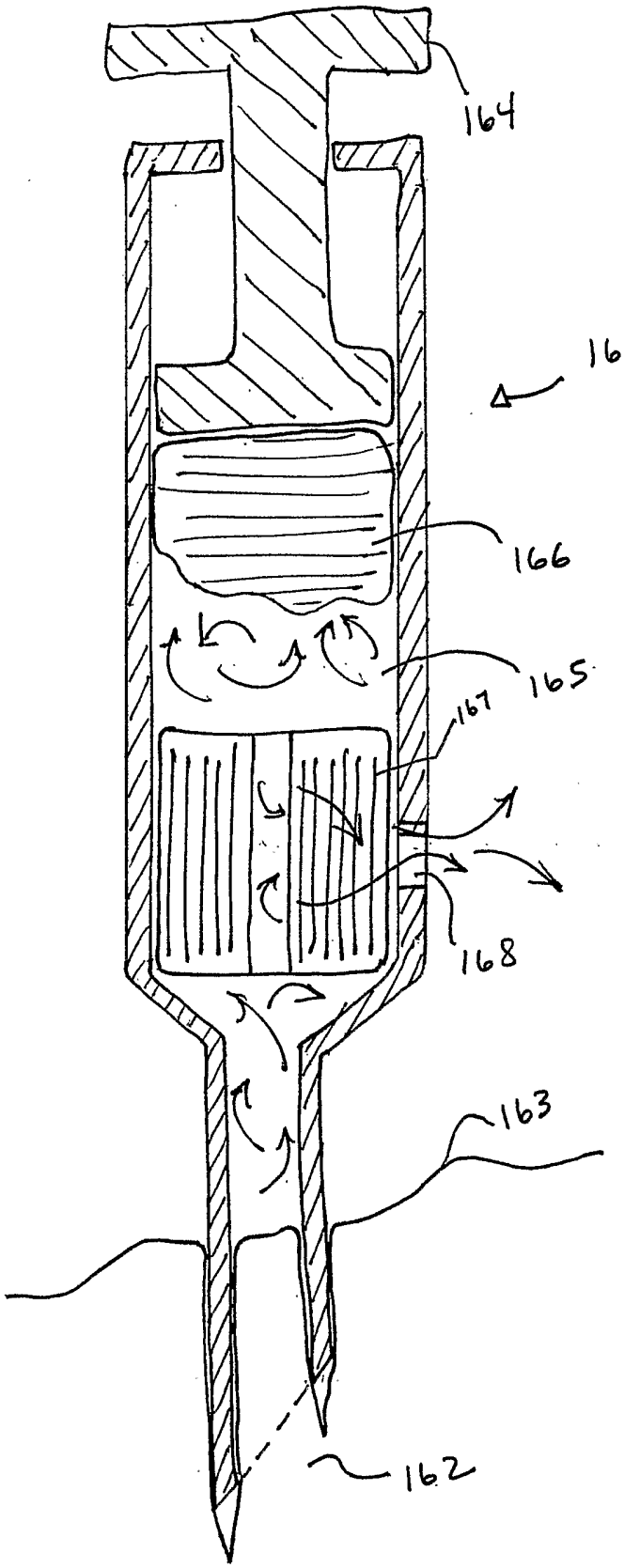


FIG. 16