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(54) Title: METHOD AND APPARATUS FOR ENHANCING THE MATURATION RATE OF AN ARTERIOVENOUS FISTULA

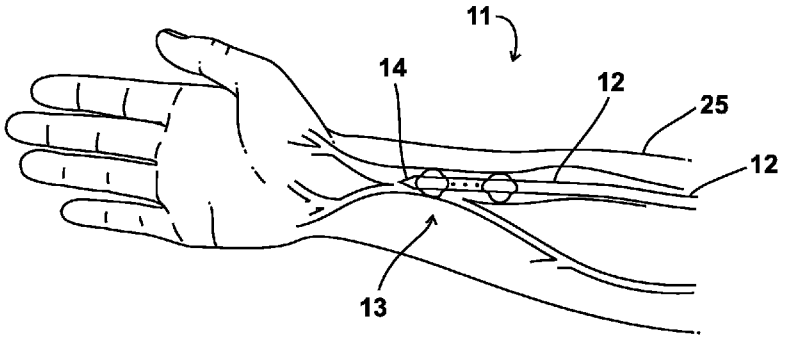


FIG. 2

(57) Abstract: A method and apparatus are aimed to improve arteriovenous fistula maturation rate by treating the fistula with a crosslink agent solution (fixative solution). The fixative solution will crosslink proteins and biomolecules, allowing formation of crosslinks that stabilize or stable tissue structure. The method and apparatus will address factors that contribute to arteriovenous fistula maturation failure by stopping the neointimal hyperplasia growth after vascular injury and stabilizing the venous wall to prevent the lumen from narrowing.

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TITLE OF THE INVENTION

METHOD AND APPARATUS FOR ENHANCING THE MATURATION RATE OF AN ARTERIOVENOUS FISTULA

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of US Provisional Patent Application Serial No. 62/372,109, filed 8 August 2016. Priority of US Provisional Patent Application Serial No. 62/372,109, filed 8 August 2016, incorporated herein by reference, is hereby claimed.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

Not applicable

REFERENCE TO A "MICROFICHE APPENDIX"

Not applicable

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a method and apparatus for enhancing or improving the arteriovenous fistula (AVF) maturation rate by treating the fistula with a crosslink agent solution (fixative solution) that will crosslink proteins and biomolecules thus enabling formation of crosslinks that stabilize the tissue structure.

2. General Background of the Invention

Arteriovenous fistulae are the preferred mode of dialysis vascular access due to low long-term rates of infection and stenosis. Patients with a functioning arteriovenous fistula or AVF live longer and cost less to treat as compared to patients dialyzing through a tunneled dialysis catheter (or TDC). Despite the many advantages of the native arteriovenous fistula, a number of studies have documented major problems with arteriovenous fistula maturation (failure to increase blood flow and diameter adequately to support dialysis) as a result of peri-anastomotic venous segment stenosis.

Recently a number of physicians have championed a more aggressive approach to arteriovenous fistula maturation failure in which repeated long segment angioplasty

procedures are used to sequentially dilate up the perianastomotic venous segment. Even though there are some successes with these procedures, there are also negative consequences with respect to pathology and pathogenesis of arteriovenous fistula maturation failure. At a biology level, an aggressive neointimal hyperplasia growth is most likely to migrate from the media or adventitia. At a pathologenetic level, it is likely that vascular injury is the initiator of neointimal hyperplasia and a lack of outward remodeling. Neointimal hyperplasia can be defined as an increase in the thickness of the lining of a blood vessel in response to injury or vascular reconstruction. It is an important cause of vein graft obstruction after coronary artery bypass surgery and in the premature closure of other vascular conduits, e.g., in dialysis access devices. It is characterized by the migration of smooth muscle cells into the graft, followed by the release of cytokines that damage the vessel wall and contribute to its degradation by inflammation.

Some patents have issued that relate generally to balloon treatment methods. The following possibly relevant U.S. Patent documents are incorporated herein by reference:

Patent Document No.	TITLE
8,911,468	Devices, Therapeutic Compositions and Corresponding Percutaneous Treatment Methods for Aortic Dissection
2015/0209558	Articulating Balloon Catheter and Method for Using the Same

BRIEF SUMMARY OF THE INVENTION

The present invention solves the problems confronted in the art in a simple and straightforward manner. The present invention provides a method and apparatus that is aimed to improve arteriovenous fistula (AVF) maturation rate by treating the fistula with a crosslink agent solution (fixative solution). The fixative solution will crosslink proteins and biomolecules, through the amine and/or carboxyl groups of collagen, allowing formation of crosslinks that stabilize tissue structure. The method and apparatus of the present invention will address factors that contribute to arteriovenous fistula maturation failure: (1) stop the neointimal hyperplasia growth after vascular injury and (2) stabilize the venous wall to prevent the lumen from narrowing.

The present invention is aimed to develop a therapy treatment that uses a specially configured double seal (e.g., dual balloon, such as inflatable balloons) catheter delivery system and a crosslink agent or fixative solution, to improve arteriovenous fistula maturation rate. The catheter delivery system provides a shaft and dual (spaced apart) seals or balloons at the distal end portion of the catheter. The seals or balloons are located or spaced apart a distance which equals to the targeted treatment length (e.g., between about 10 and 300 mm.). With the distance between the seal or balloon locations, there are infusers or ports or holes that allow for infusion and aspiration of a fixative solution. Prior to the insertion of the catheter of the present invention, the veins are enlarged to a predetermined size using angioplasty. For example, this predetermined size is approximately 6 mm diameter. Following the angioplasty, the veins are stabilized further by infusing of fixative solution. The fixative solution can be for example the following: oxidizing agents, glutaraldehyde, neutral buffered formalin, paraformaldehyde, dimethyl suberimidate, dimethyl 3,3-dithiobispropionimidate, aceyl azie, lysyl oxidase and transglutaminase. For example, it could be DMS (dimethyl suberimidate dihydrochloride) Product number 20700, by Thermo Scientific. The fixative solution will react with various proteins, including any collagen that contains amine groups and/or carboxyl groups, allowing formation of crosslinks that stabilize the vein segment tissue structure. As a consequence, most of the vascular injury response from balloon angioplasty is discouraged. The vein segment vessel wall will become hardened due to the cross-linking of proteins.

The treatment can be applied either prior or post arteriovenous fistula creation. Initially, the vein segment can be subjected to multiple angioplasties for enlargement of the vessel lumen. The dual balloon catheter is then percutaneously delivered to the intended vein segment and inflated to block off blood flows in both directions. The residual blood within the lumen is aspirated and washed with saline to ensure that it is free of blood. The fixative solution is then infused into the vein lumen and incubated for a predetermined time to allow for cross-linking of proteins. The fixative solution is removed when the incubation time is expired. The incubation time is preferably dependent on the concentration of the cross-linking agent and the desired degree of the cross-linking within the vessel wall. Preferably this time ranges from about 5 minutes up to about 12 hours. The incubation time is typically shorter when the concentration of the fixative solution used is higher, and the incubation time is longer when the desired degree of crosslinking within the vessel wall is greater. One of ordinary skill in the art can determine the desired incubation time without undue experimentation.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

For a further understanding of the nature, objects, and advantages of the present invention, reference should be had to the following detailed description, read in conjunction with the following drawings, wherein like reference numerals denote like elements and wherein:

Figures 1 and 2 are schematic diagrams showing the method of the present invention and the preferred embodiment of the apparatus of the present invention;

Figures 3-5 are sequential views that illustrate the method and apparatus of the present invention;

Figures 6-7 are schematic diagrams of preferred embodiments of the apparatus of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Figures 1 and 2 are schematic diagrams showing a patient's arm 25 and an arteriovenous fistula 26, arteriovenous fistula maturation rate improvement apparatus 10 is placed in a targeted vein segment 11. The segment or vein 11 has a vein lumen 23 surrounded by a vein or vessel wall 24. A catheter 12 is configured to be inserted into vein segment 11 lumen 23 as shown in Figures 1 and 2. Catheter 12 has distal end portion 13 with tapered tip 14. Catheter 12 has lumen or bore 15 and ports or openings 19 that together with catheter bore 15 enable infusion of fluid to the vein segment 11 (see Figure 6).

A pair of seals, seal members or inflatable balloons 16, 17 are mounted on catheter 12. Seals 16, 17 are spaced apart a distance 21 (e.g., between about 10 and 300 mm). Catheter 12 has infusers, ports or openings 19 that enable transmission of a desired fixation solution 20 into the space 18 between seals 16, 17 and between catheter 12 and vessel wall 24. Alternatively, surgical clips could be used at the time of fistula creation to create the seal at either end.

Figures 3-5 show the method of the present invention. In Figure 3, a catheter 12 having spaced apart seals 16, 17 (e.g., inflatable or inflation balloons), distal end portion 13, tip 14 and catheter lumen 15 is inserted into a patient's vascular system as indicated by arrow 22 and placed next to or at the targeted vein segment 11.

In Figure 4, each seal 16, 17 is expanded radially wall 27 and circumferentially from catheter 12 to engage and seal against the vessel segment 11 wall 24. A space 18 is thus isolated between seals 16, 17 and between catheter 12 wall 27 and vein segment 11 wall 24. It is this space 18 that is filled with a selected fixation solution 20 as seen in Figure 5. The fixation solution 20 remains in space 18 for a selected incubation time sufficient to enable or

allow cross linking of collagen (between about 5 minutes and 12 hours). Fixation solution 20 can be a commercially available solution, such as from Thermo Scientific company and sold under the designation DMS (dimethyl suberimidate dihydrochloride).

The present invention will address two important factors that contribute to AVF maturation failure: (1) stop the neointimal hyperplasia growth after vascular injury and (2) stabilize the venous wall to prevent the lumen from narrowing.

This invention preferably includes a therapy treatment system, the treatment system comprises: (a) a dual balloon catheter delivery system 10, and (b) a crosslink agent solution 20, to improve AVF maturation rate. The catheter delivery system 10 preferably comprises a shaft 12 with two balloons 16, 17 at the distal end 13. The balloons 16, 17 are preferably spaced between 10 and 100 mm apart, which equals the targeted treatment length. Within the distance between the balloon locations, there are preferably infusers or holes 19 that allow for infusion and aspiration of the fixative solution 20. The fixative solution 20 can be one or more of the following: oxidizing agents, glutaraldehyde, neutral buffered formalin, paraformaldehyde, dimethyl suberimidate, dimethyl 3,3-dithiobispropionimidate, aceyl azie, lysyl oxidase and transglutaminase. For example, the fixative solution 20 could be DMS (dimethyl suberimidate dihydrochloride) Product number 20700, by Thermo Scientific. The fixative solution 20 will preferably react with various proteins, including any collagen that contains amine groups and/or carboxyl groups, allowing formation of crosslinks that stabilize the vein segment 11 tissue structure. The fixative solution 20 will preferably react with various proteins and other biomolecules, allowing formation of crosslinks that stabilize the tissue structure. As a consequence, most of the vascular injury response that may be caused by balloon angioplasty is discouraged. Additionally, the vessel wall 24 will harden due to the cross-linking of proteins.

The treatment system of the present invention can be applied either prior to or post AVF creation. Preferably, the vein segment 11 is first subjected to multiple angioplasties for enlargement of the lumen 23 to a determined size (for example, 6 mm diameter). Next, the dual balloon catheter 10 of the present invention is preferably percutaneously delivered to the intended vein segment 11 and preferably inflated to block off blood flow in both directions. Preferably, the residual blood within the lumen is aspirated and washed with saline to ensure the treatment area is free of blood. Then the fixative solution 20 is preferably infused into the vein lumen 23 and incubated for a predetermined time to allow for cross-linking of proteins. The fixative solution 20 is preferably removed when the incubation time is expired. The predetermined time can be between 5 minutes and 12 hours, for example. One with ordinary

skill in the art will be able to determine the proper incubation time based on the concentration of fixative solution and the level of stability desired of the vessel.

The present invention includes a method of improving arteriovenous fistula 26 maturation rate using the system of the present invention 10. The method comprises the steps of:

a) identifying an arteriovenous fistula vein segment 11 to be treated, said segment 11 having a vein segment wall 24 and a vein segment lumen 23;

b) placing a catheter 12 in the vein segment lumen 23, the catheter 12 having a catheter wall 27, an outer surface, an inner surface, a catheter bore 15, and one or more openings 19 in said wall 27;

c) wherein in step "b" the catheter 12 has spaced apart first 16 and second seals 17, each seal 16, 17 enabling a seal to be made between the vein segment wall 24 and the catheter outer surface;

d) transmitting a volume of a fixative solution 20 via the catheter bore 15 and catheter opening or openings 19 into a space that is in between the seals 16, 17 of step "c" and in between the catheter 12 and vein segment wall 24; and

e) retaining the fixative solution 20 in said space for an incubation time period sufficient to allow cross linking of proteins.

The incubation time of step "e" is preferably between about 5 minutes and 12 hours. More preferably, the incubation time of step "e" is at least 5 minutes.

Preferably, the incubation time of step "e" is dependent on the concentration of the fixative solution 20 used in step "d" and the desired degree of crosslinking within the vessel wall 24.

In a preferred embodiment, at least one of the seals 16, 17 of step "c" is an inflatable seal. More preferably, at least one of the seals 16, 17 of step "c" is an inflatable balloon. Preferably, both seals 16, 17 are inflatable balloons.

Preferably, the spacing the seals 16, 17 apart is between about 10 and 300 mm.

Preferably, the catheter 12 of step "b" has a bore 15 with a bore diameter of between about 0.1 and 2 mm.

In a preferred embodiment, the method further includes a preliminary step of subjecting the vein segment 11 to at least one angioplasty. More preferably, this preliminary step involves subjecting the vein segment 11 to multiple balloon angioplasties.

Preferably, the volume of fixative solution 20 in step "d" is between about 1 and 25 milliliters.

The present invention includes an arteriovenous fistula vein segment maturation rate improvement apparatus. The apparatus comprises (a) a catheter 12 having proximal and distal 13 portions, a catheter wall 27, a catheter bore 15, and one or more flow ports 19 through said catheter wall 27; (b) first and second seals 16, 17 mounted to the catheter 12 at spaced apart 21 positions; (c) the catheter 12 and seals 16, 17 being configured to be positioned within the lumen 23 of a vein segment 11 to be treated; (d) the seals 16, 17 being movable between a first position that enables insertion into the vein segment lumen and a second position that forms a seal between the catheter wall 27 and the vein segment 11; (e) a volume of a fixation solution 20 that occupies a space 18 that is in between the seals 16, 17 when in the second position and in between the catheter 12 and the vein segment wall 24; (f) wherein the fixative solution 20 promotes cross linking of proteins of the vein segment 11; and (g) wherein one or both of the seals 16, 17 has a first diameter when in said first position and a second diameter that is longer than said first diameter when in said second position.

Preferably, at least one of said seals 16, 17 is an inflatable seal. More preferably, both of said seals 16, 17 is an inflatable seal. More preferably, each of the seals 16, 17 is an inflatable balloon. Most preferably, each of the seals 16, 17 is an inflatable balloon.

Preferably, the seals 16, 17 are spaced apart 21 between about 10 and 300 mm.

Preferably, the volume of fixation solution 20 is between about 1 and 25 milliliters (ml).

Preferably, the catheter 12 has a diameter of between about 0.33 and 5 mm.

Preferably, the catheter bore 15 has a diameter of between about 0.1 and 1 mm.

The present invention includes an arteriovenous fistula maturation rate improvement apparatus, comprising: (a) a catheter 12 having proximal and distal 13 portions, a catheter wall 27, a catheter bore 15, and one or more flow ports 19 through said catheter wall 27; (b) first and second seals 16, 17 mounted to the catheter 12 at spaced apart positions a distance 21; (c) the catheter 12 and seals 16, 17 being configured to be positioned within the lumen 23 of a vein segment 11 to be treated; (d) the seals 16, 17 being movable between a first and collapsed position that enables insertion into the vein segment lumen 23 and a second and expanded position that forms a seal between the catheter wall 27 and the vein segment 11; (e) a volume of a fixation solution 20 that occupies a space 18 that is in between the seals 16, 17 when in the second position and in between the catheter 12 and the vein segment wall 24; (f) wherein the fixation solution 20 promotes cross linking of proteins of the vein segment 11; (g) wherein one or both of the seals 16, 17 has a first diameter when in said first position and a second diameter that is greater than said first diameter when in said second position; and (h)

wherein in said second position the seals 16, 17 each have an extended diameter of between 2 and 10 mm and the catheter wall 27 between said seals 16, 17 has a diameter that is less than said extended diameter.

Preferably, the incubation time of step "e" is shorter when the concentration of the fixative solution 20 used in step "d" is higher, and the incubation time of step "e" is longer when the desired degree of crosslinking within the vessel wall 24 is greater.

The following is a list of parts and materials suitable for use in the present invention:

PARTS LIST:

PART NUMBER	DESCRIPTION
10	arteriovenous fistula maturation rate enhancement system
11	vein segment/vein
12	catheter
13	distal end/distal end portion
14	tapered tip
15	catheter lumen /catheter bore
16	first seal member/first balloon
17	second seal member/second balloon
18	space
19	infusers/apertures/openings
20	fixation solution
21	distance/spacing
22	arrow
23	vein lumen
24	vein wall/vessel wall
25	arm
26	arteriovenous fistula
27	catheter wall

All measurements disclosed herein are at standard temperature and pressure, at sea level on Earth, unless indicated otherwise. All materials used or intended to be used in a human being are biocompatible, unless indicated otherwise.

The foregoing embodiments are presented by way of example only; the scope of the present invention is to be limited only by the following claims.

CLAIMS

1. A method of improving arteriovenous fistula maturation rate, comprising the steps of:

a) identifying an arteriovenous fistula vein segment to be treated, said segment having a vein segment wall and a vein segment lumen;

b) placing a catheter in the vein segment lumen, the catheter having a catheter wall, an outer surface, an inner surface, a catheter bore, and one or more openings in said wall;

c) wherein in step "b" the catheter has spaced apart first and second seals, each seal enabling a seal to be made between the vein segment wall and the catheter outer surface;

d) transmitting a volume of a fixative solution via the catheter bore and catheter opening or openings into a space that is in between the seals of step "c" and in between the catheter and vein segment wall; and

e) retaining the fixative solution in said space for an incubation time period sufficient to allow cross linking of proteins.

2. The method of claim 1 wherein the incubation time of step "e" is between about 5 minutes and 12 hours.

3. The method of claim 1 wherein the incubation time of step "e" is at least 5 minutes.

4. The method of claim 1 wherein at least one of the seals of step "c' is an inflatable seal.

5. The method of claim 1 wherein at least one of the seals of step "c' is an inflatable balloon.

6. The method of claim 1 further comprising the step of spacing the seals apart between about 10 and 300 mm.

7. The method of claim 1 wherein the catheter of step "b" has a bore with a bore diameter of between about 0.1 and 2 mm.

8. The method of claim 1 further comprising the step of preliminary subjecting the vein segment to at least one angioplasty.

9. The method of claim 1 further comprising the step of preliminary subjecting the vein segment to multiple balloon angioplasties.

10. The method of claim 1 wherein in step "d" the volume is between about 1 and 25 milliliters.

11. An arteriovenous fistula vein segment maturation rate improvement apparatus, comprising:

a) a catheter having proximal and distal portions, a catheter wall, a catheter bore, and one or more flow ports through said catheter wall;

b) first and second seals mounted to the catheter at spaced apart positions;

c) the catheter and seals being configured to be positioned within the lumen of a vein segment to be treated;

d) the seals being movable between a first position that enables insertion into the vein segment lumen and a second position that forms a seal between the catheter wall and the vein segment;

e) a volume of a fixation solution that occupies a space that is in between the seals when in the second position and in between the catheter and vein segment wall;

f) wherein the fixation solution promotes cross linking of proteins of the vein segment; and

g) wherein one or both of the seals has a first diameter when in said first position and a second diameter that is longer than said first diameter when in said second position.

12. The apparatus of claim 11 wherein at least one of said seals is an inflatable seal.

13. The apparatus of claim 11 wherein each of said seals is an inflatable seal.

14. The apparatus of claim 11 wherein each of the seals is an inflatable balloon.

15. The apparatus of claim 13 wherein each of the seals is an inflatable balloon.

16. The apparatus of claim 11 wherein the seals are spaced apart between about 10 and 300 mm.

17. The apparatus of claim 11 wherein the volume of fixation solution is between about 1 and 25 milliliters.

18. The apparatus of claim 11 wherein the catheter has a diameter of between about 0.33 and 5 mm.

19. The apparatus of claim 11 wherein the catheter bore has a diameter of between about 0.1 and 1 mm.

20. An arteriovenous fistula maturation rate improvement apparatus, comprising:

a) a catheter having proximal and distal portions, a catheter wall, a catheter bore, and one or more flow ports through said catheter wall;

b) first and second seals mounted to the catheter at spaced apart positions;

c) the catheter and seals being configured to be positioned within the lumen of a vein segment to be treated, the vein segment having a lumen and a wall;

d) the seals being movable between a first and collapsed position that enables insertion into the vein segment lumen and a second and expanded position that forms a seal between the catheter wall and the vein segment;

e) a volume of a fixation solution that occupies a space that is in between the seals when in the second position and in between the catheter and the vein segment wall;

f) wherein the fixation solution promotes cross linking of proteins of the vein segment;

g) wherein one or each of the seals has a first diameter when in said first position and a second diameter that is greater than said first diameter when in said second position; and

h) wherein in said second position the seals each have an extended diameter of between 2 and 10 mm and the catheter wall between said seals has a diameter that is less than said extended diameter.

21. The method of claim 1 wherein the incubation time of step “e” is dependent on the concentration of the fixative solution used in step “d” and the desired degree of crosslinking within the vessel wall.

22. The method of claim 21 wherein the incubation time of step “e” is shorter when the concentration of the fixative solution used in step “d” is higher, and the incubation time of step “e” is longer when the desired degree of crosslinking within the vessel wall is greater.

23. The invention(s) substantially as shown and/or described herein.

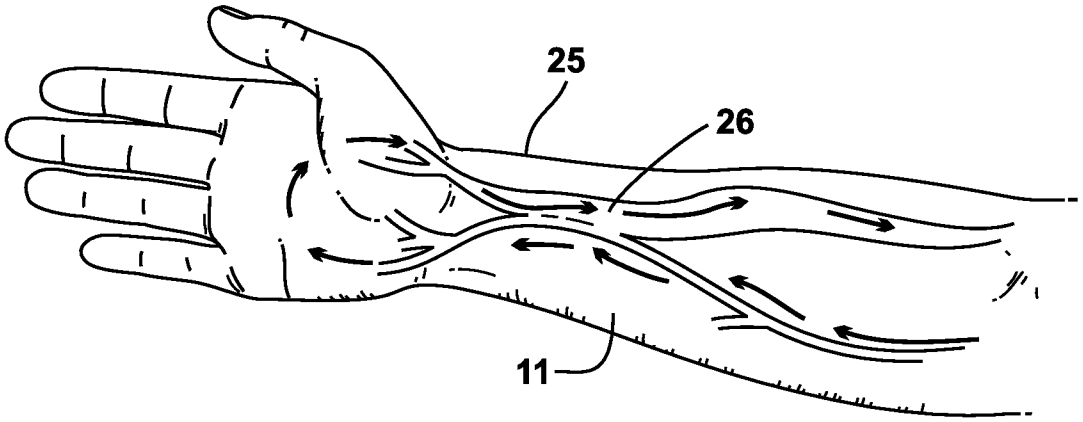


FIG. 1

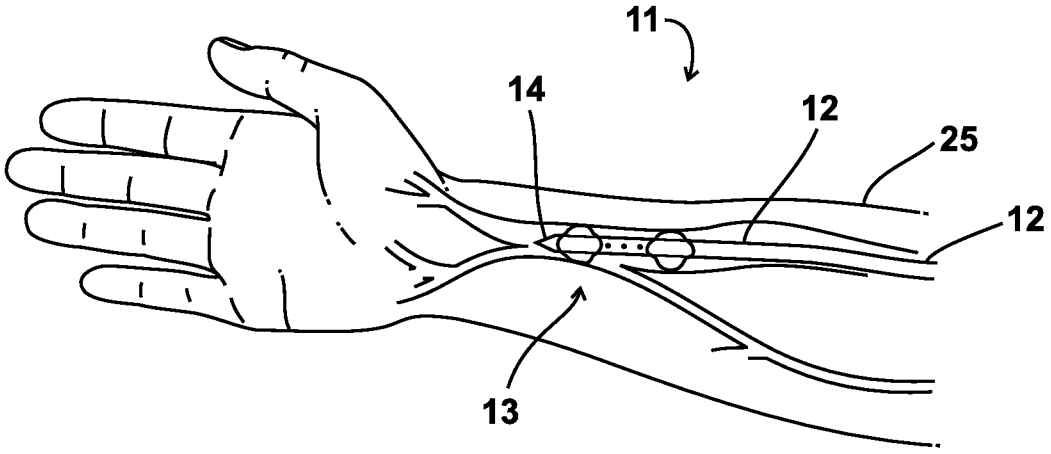


FIG. 2

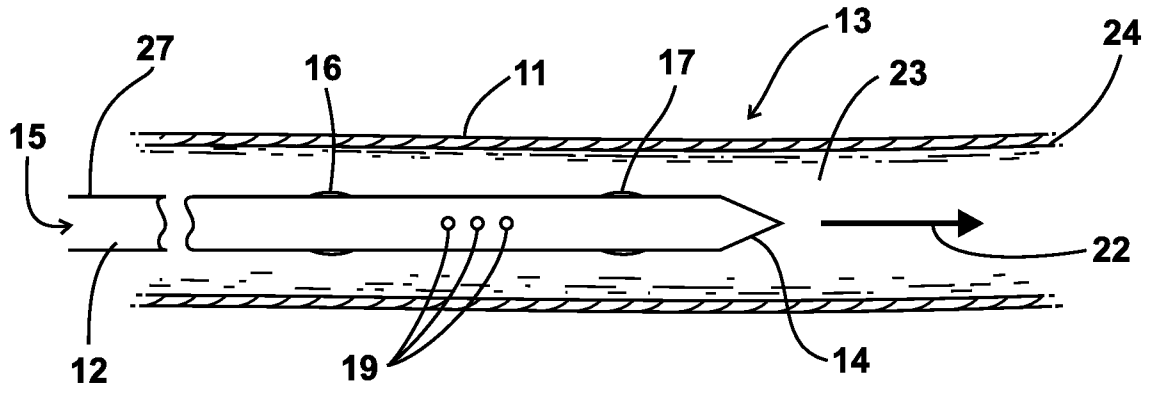


FIG. 3

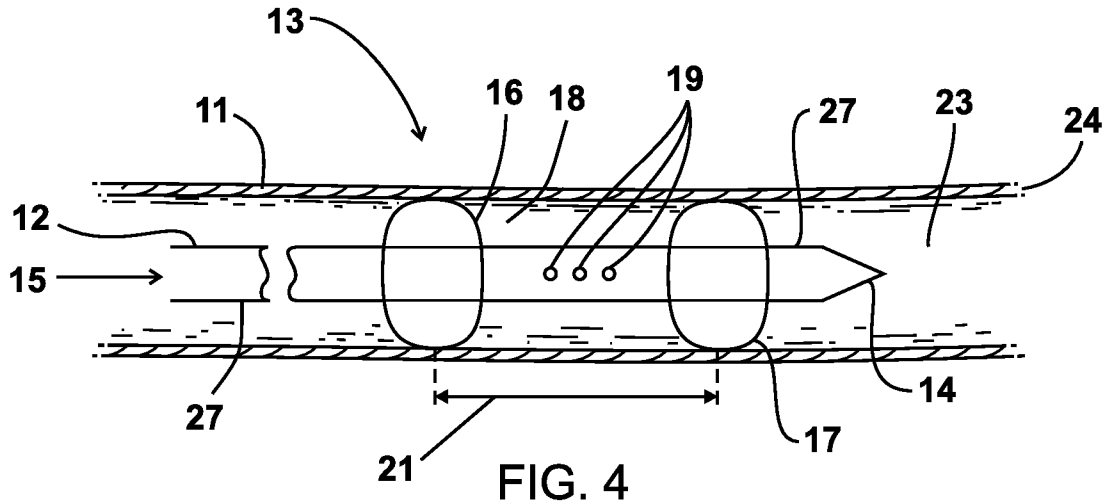


FIG. 4

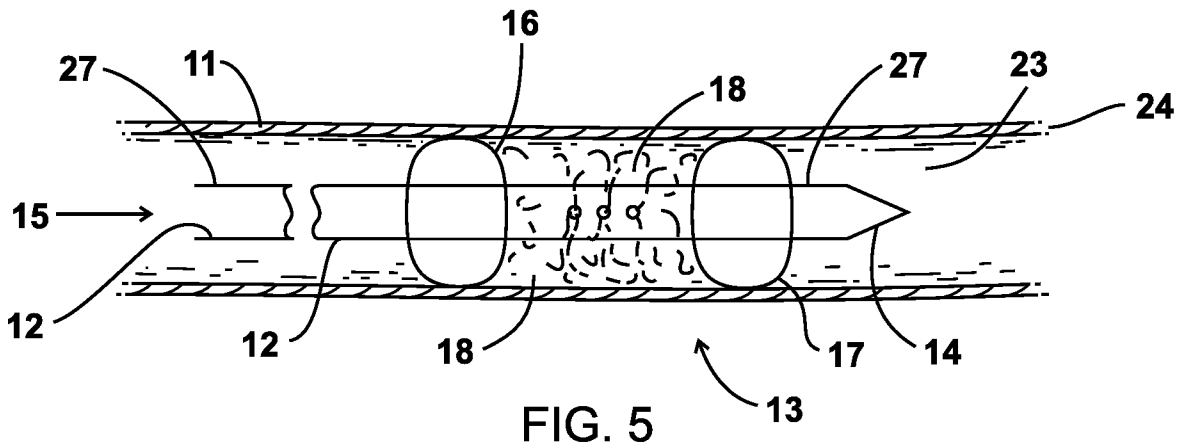


FIG. 5

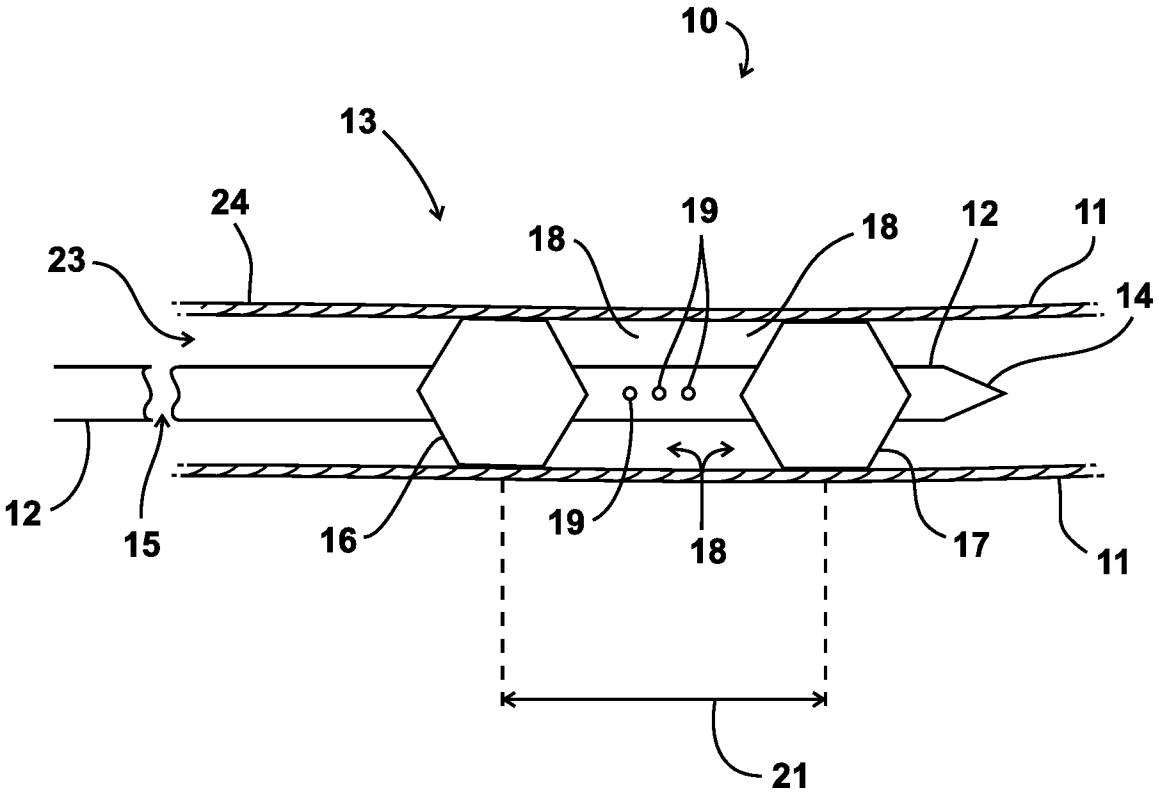


FIG. 6

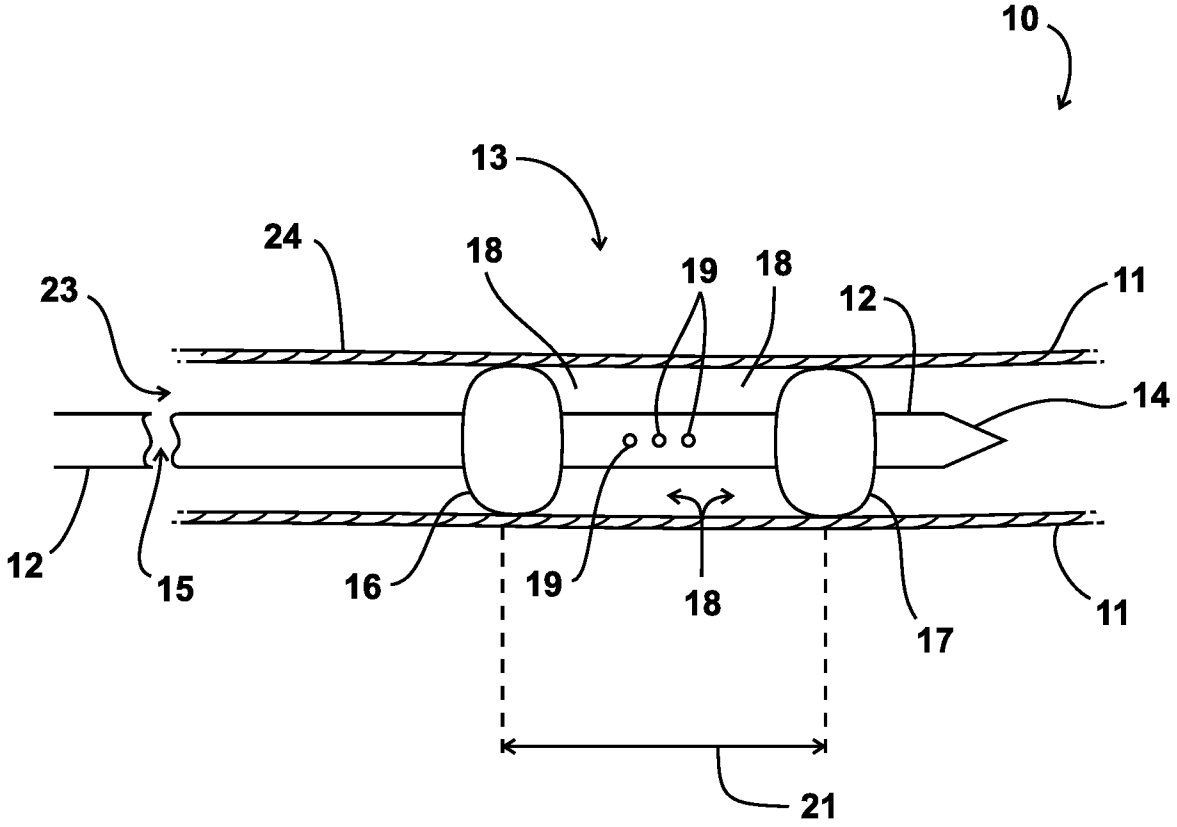


FIG. 7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/45958

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61M 25/10 (2017.01)
CPC - A61M 2025/1052, A61M 2025/1043, A61M 2025/1015, A61M 2025/1013, A61M 25/1011

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,575,815 A (SLEPIAN et al.) 19 November 1996 (19.11.1996) Entire document, especially Abstract, col 4, ln 23-27, col 5, ln 8-47, col 11, ln 29- col 12, ln 21 and FIGS. 1-3.	1-15
X	US 2011/0218517 A1 (OGLE et al.) 08 September 2011 (08.09.2011) Entire document, especially Abstract, para[0026]-[0027], [0042]-[0044], [0069]-[0070] and FIGS. 1-2.	11-22
A	US 6,808,518 B2 (WELLMAN et al.) 26 October 2004 (26.10.2004) Entire document.	1-22
A	US 2015/0032087 A1 (TERUMO KABUSHIKI HAISHA) 29 January 2015 (29.01.2015) Entire document.	1-22
A	US 2015/0134049 A1 (THE GENERAL HOSPITAL CORPORATION) 14 May 2015 (14.05.2015) Entire document.	1-22
A	US 8,486,155 B2 (MCALISTER et al.) 16 July 2013 (16.07.2013) Entire document.	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 October 2017	21 NOV 2017
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/45958

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 23
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim 23 is an omnibus claim. It is indefinite because it is unclear what is included or excluded by the claim language. This claim is not drafted in accordance with PCT Rule 6.2(a).

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.