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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 July 2016 (21.07.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/115450 A1

(51) International Patent Classification:
A61B 10/04 (2006.01)

(21) International Application Number:
PCT/US2016/013576

(22) International Filing Date:
15 January 2016 (15.01.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/103,821 15 January 2015 (15.01.2015) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(54) Title: TRANSFEMORAL TRANSCAVAL LIVER ACCESS AND DEVICES

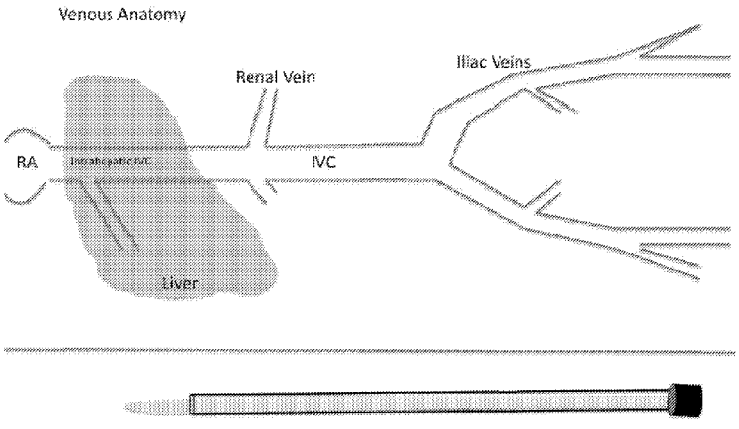

FIG. 1

(57) Abstract: Shaped liver biopsy sheaths and methods for transfemoral transcaval liver access are disclosed. The present invention provides methods of obtaining a tissue sample from the liver of a patient, the methods comprising inserting a hollow sheath, such as a stiffened sheath with an angled tip, through a femoral vein into a portion of the inferior vena cava (IVC) adjacent to the liver, wherein the sheath's tip is in the intrahepatic IVC and wherein the sheath has a shape that brings the tip of the sheath adjacent to the wall of the IVC at an angle that is optimal to allow penetration of the wall of the IVC by a biopsy needle, and inserting a biopsy needle through the sheath and through the wall of the IVC into the liver to obtain a tissue sample from the liver.

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TRANSFEMORAL TRANSCAVAL LIVER ACCESS AND DEVICES

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/103,821, filed on January 15, 2015, the content of which is herein incorporated by reference into the subject application.

BACKGROUND OF THE INVENTION

[0001] Throughout this application various publications are referred to in parentheses. Full citations for these references may be found at the end of the specification. The disclosures of these publications are hereby incorporated by reference in their entirety into the subject application to more fully describe the art to which the subject invention pertains.

[0002] Liver biopsy is the gold standard for the evaluation of acute and chronic liver disease. Percutaneous liver biopsy (PLB) remains the preferred approach in most situations; however, transjugular liver biopsy (TJLB) (1) can be performed where there are contraindications to a percutaneous approach, such as coagulopathy, thrombocytopenia or ascites where PLB may be prone to bleeding (2-4). TJLB is considered safer in these situations since any bleed will most likely be intravascular.

[0003] However, TJLBs can be difficult, and there are potential complications. TJLB requires hepatic vein cannulation through which the biopsy specimen is obtained. Difficulties include negotiating a stiffened cannula into acutely angled hepatic veins; maintaining a stiff cannula in the hepatic vein during movement caused by the patient's respiration while avoiding injury of the hepatic vein/liver junction, and the need for two operators - one to hold the cannula and one to remove the biopsy specimen from the needle.

[0004] Biopsies performed directly through the inferior vena cava (IVC) from a jugular approach have also been described in instances when a hepatic vein could not be cannulated (5). Difficulties with this approach can include difficult jugular access and the need to traverse and exit the right atrium (RA) into the IVC.

[0005] The present invention provides procedures and devices for a transfemoral transcaval (TFTC) approach for liver biopsies that is expected to be safer, easier and more reliable than a transjugular approach.

SUMMARY OF THE INVENTION

[0006] The present invention provides methods of obtaining a tissue sample from the liver of a patient, the methods comprising inserting a hollow sheath, such as a stiffened sheath with an angled tip, through a femoral vein into a portion of the inferior vena cava (IVC) adjacent to the liver, wherein the sheath's tip is in the intrahepatic IVC and wherein the sheath has a shape that brings the tip of the sheath adjacent to the wall of the IVC at an angle that is optimal to allow penetration of the wall of the IVC by a biopsy needle, and inserting a biopsy needle through the sheath and through the wall of the IVC into the liver to obtain a tissue sample from the liver.

[0007] The invention also provides kits for obtaining a tissue sample from the liver of a patient, the kits comprising an outer flexible vascular sheath having a length that extends from a femoral vein to the intrahepatic portion of the inferior vena cava (IVC) of the patient; a hollow sheath, such as a stiffened angled sheath, capable of passing through the outer flexible sheath, wherein the sheath is preshaped with one or more bends and/or is capable of being shaped *in vivo* to provide an angle between the tip of the sheath and the longitudinal axis of the sheath between >30 degrees to 90 degrees, and wherein the hollow sheath is longer than the outer flexible vascular sheath; and a flexible biopsy needle capable of passing through the hollow sheath to penetrate the wall of the IVC and pass into the liver to obtain a tissue sample from the liver, wherein the flexible biopsy needle is longer than the hollow sheath.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] Fig. 1. Schematic of venous anatomy and a vascular sheath (Item 1). The femoral veins are to the right of the venous diagram. IVC - inferior vena cava, RA - right atrium. Drawing not to scale.

[0009] Fig. 2. Illustration of an example of a schematic of an outer vascular sheath inserted through the femoral vein into the IVC to the level of the liver and of a preshaped rigid sheath (Item 2) that can be inserted through the outer vascular sheath. Drawing not to scale.

[0010] Fig. 3. Illustration of an example of a shapeable semirigid sheath (and dilator) that can be inserted over a guidewire into the IVC. The assembly is shown in the upper view of the figure. The guidewire and dilator can be removed from the sheath (middle view) and the sheath can be shaped *in vivo* into an optimal shape for a transcaval liver biopsy (lower view). Drawing not to scale.

[0011] Fig. 4. Illustration of an example of an inner sheath that has been advanced through an outer vascular sheath so that the tip of the inner sheath is positioned at a desired angle relative to the wall of the IVC. The inner sheath can be a preshaped rigid sheath or a shapeable semirigid sheath having a tip that can be shaped *in vivo*. A biopsy needle (not shown) can be advanced through the inner sheath to penetrate the wall of the IVC and obtain a tissue sample from the liver. Drawing not to scale.

DETAILED DESCRIPTION OF THE INVENTION

[0012] The present invention provides a method of obtaining a tissue sample from a liver of a patient, via a transfemoral transcaval route, the method comprising:

inserting a hollow sheath through a femoral vein into a portion of the inferior vena cava (IVC) adjacent to the liver, wherein the sheath's tip is in the intrahepatic IVC and wherein the sheath has a shape that brings the tip of the sheath adjacent to the wall of the IVC at an angle that is optimal to allow penetration of the wall of the IVC by a biopsy needle, and

inserting a biopsy needle through the sheath and through the wall of the IVC into the liver to obtain a tissue sample from the liver.

[0013] The sheath can be preshaped with one or more bends before the sheath is inserted into the patient. Alternatively, or in addition, the sheath can be shaped *in vivo* after the sheath is inserted into the IVC. The sheath may have, for example, one bend near the tip and a secondary bend in the longitudinal axis of the sheath farther from the tip.

[0014] The sheath can be inserted through an outer vascular sheath that has been inserted through the femoral vein into the IVC.

[0015] The sheath and/or outer vascular sheath can be inserted in the IVC with the aid of a guidewire.

[0016] The sheath has a main longitudinal body that can contain one or more bends to angle the tip of the sheath so that it is optimal to allow penetration of the wall of the IVC by a biopsy needle. The angle of the tip is indicated in reference to the longitudinal axis of the main body of the sheath (i.e., the main part of the sheath that is not bent). The angle between the tip of the sheath and the longitudinal axis of the sheath is preferably between >30 degrees to 90 degrees or 35-90 degrees or 40-90 degrees. In one embodiment, the angle between the tip of the sheath and the longitudinal axis of the sheath is between 40-80 degrees. In one embodiment, the angle between the tip of the sheath and the longitudinal axis of the sheath is between 50-70 degrees.

[0017] Preferred sheaths include those that are malleable to allow the introduction of secondary bends along the main body of the sheath.

[0018] The invention also provides a kit for obtaining a tissue sample from the liver of a patient, the kit comprising:

- an outer flexible vascular sheath having a length that extends from a femoral vein to an intrahepatic portion of the inferior vena cava (IVC) of the patient;
- a hollow sheath capable of passing through the outer flexible sheath, wherein the sheath is preshaped with one or more bends and/or is capable of being shaped *in vivo* to provide an angle between the tip of the sheath and the longitudinal axis of the sheath between >30 degrees to 90 degrees, and wherein the hollow sheath is longer than the outer flexible vascular sheath; and
-a flexible biopsy needle capable of passing through the hollow sheath to penetrate the wall of the IVC and pass into the liver to obtain a tissue sample from the liver, wherein the flexible biopsy needle is longer than the hollow sheath.

[0019] The kit can also include a guidewire to add insertion and placement of the outer flexible vascular sheath and/or hollow sheath in the IVC; and/or a dilator.

[0020] In different embodiments, the angle between the tip of the sheath and the longitudinal axis of the sheath is between 35-90 degrees, 40-90 degrees, 40-80 degrees or 50-70 degrees.

[0021] The kits disclosed herein can be used for obtaining a tissue sample from the liver of a patient.

[0022] The components of the present invention can be made from standard materials used in vascular surgery and biopsies. For example, the outer vascular sheath can be a 10-F sheath of 38.5 cm, such as provided, for example, by Cook, Inc., Bloomington, Indiana. The guidewire, if used, can be, for example, a 0.035-inch guide wire.

[0023] The preshaped sheath can be, for example, a 7-F stiffened cannula. Such cannulas can be provided by Argon Medical Devices, Inc., Athens, Texas. The preshaped sheath can have a precurved protective metallic insert or stiffener. The preshaped sheath needs to be preshaped with one or more bends to provide an angle of incidence of the tip of the sheath with respect to the wall of the IVC that is optimal to allow penetration of the wall of the IVC by a biopsy needle. Exisiting preshaped devices on the market are not meant to be resphaped, due to concerns about damaging the device. Accordingly, no preshaped device currently exists on the market that provides a tip angle suitable for a transfermoral

transcaval liver biopsy as disclosed herein. Alternatively, or in addition to, a preshaped sheath, the sheath can be shaped *in vivo* using, for example, a mechanical handle at the external end of the sheath. Catheters with ends that can be adjusted to change shape have been described, for example, in U.S. Patent No. 7,402,151 B2 (BioCardia, Inc., South San Francisco, CA), the contents of which are herein incorporated by reference. Whereas preshaped sheaths will typically be advanced into the IVC through a pre-positioned outer vascular sheath, flexible sheaths that can be shaped *in vivo* may not need to be advanced into the IVC through a pre-positioned outer vascular sheath due to the flexibility of the sheath. The length of the sheath needs to be sufficient to reach from the femoral vein to the intrahepatic IVC of the patient and can be, for example, about 70 cm long.

[0024] The flexible biopsy needle can be, for example, a 19-guage biopsy needle with a 20-mm throw, such as provided, for example, by Argon Medical Devices, Inc., Athens, Texas. Biopsy devices are described, for example, in U.S. Patent Nos. 6,419,641 B1, 7,078,694 B2 and 7,841,990 B2 (Promex Technologies, LLC, Franklin, IN), the contents of which are incorporated herein. The biopsy needle needs to be longer than the sheath so that the needle can penetrate the wall of the IVC and enter the liver.

[0025] Placement of the sheaths and biopsy needle can be monitored by real-time imaging of the patient.

[0026] Advantages of the transfemoral, transcaval approach disclosed herein include:

• no need for jugular access and its inherent complications,

• no need to cross the right atrium and its inherent complications (arrhythmias, tamponade, etc.),

• no need to advance a rigid cannula into a hepatic vein,

• multiple biopsies can be obtained without the need to hold the cannula in place,

• a single operator can perform the entire procedure – perform biopsy and remove the specimen from needle, and

• pressures (RA, IVC, HV and/or Wedge PV) can be easily obtained from the femoral route.

[0027] This invention will be better understood from the Experimental Details, which follow. However, one skilled in the art will readily appreciate that the specifics discussed are merely illustrative of the invention as described more fully in the claims that follow thereafter.

EXPERIMENTAL DETAILS

EXAMPLE I - Overview of obtaining hepatic tissue through the inferior vena cava through a femoral venous approach.

[0028] The invention involves inserting a sheath through a femoral vein into the inferior vena cava (IVC) to the level of the liver of a patient. The advancement and positioning the sheath can be monitored by real-time imaging of the patient. Examples of sheaths that can be used are illustrated in Figs. 1-4. A biopsy needle is then inserted through the sheath to penetrate the wall of the IVC and obtain a tissue sample from the liver. The sheath is positioned so that the angle of incidence of the tip of the sheath with respect to the wall of the IVC is optimal to allow penetration of the wall of the IVC by the biopsy needle.

[0029] Figs. 1 and 2 illustrate an example of a vascular sheath that is inserted through a femoral vein to the intrahepatic IVC. The sheath can be positioned in the vasculature using a guidewire. Fig. 4 illustrates an example of an inner sheath positioned though an outer vascular sheath so that the tip of the inner sheath is at a desired angle with respect to the wall of the IVC. The inner sheath can be preshaped prior to being inserted through the outer vascular sheath (e.g., Fig. 2, Item 2 - preshaped rigid sheath). Alternatively, the tip of the sheath can be shaped after the sheath is placed into the intrahepatic IVC (e.g., Fig. 3), in which case an outer vascular sheath may not be required.

EXAMPLE II - Obtaining hepatic tissue through the inferior vena cava through a femoral venous approach. This Example is summarized from Cynamon, J., *et al.* (9). See also (10).

Materials and Methods

[0030] The institutional review board approved this retrospective study. Sixty-six cases of transfemoral transcaval (TFTC) liver biopsies (65.2% male; mean age, 53.2 ±15.0 years) were reviewed. One patient underwent three TFTC biopsies; each was counted individually.

[0031] Abnormal coagulation parameters were defined by institutional laboratory thresholds. All patients with an international normalized ratio ≥ 1.8 or platelet count < 50,000/μL were transfused with fresh frozen plasma or platelets, respectively, immediately before the procedure, during the procedure, or both. Intravenous fentanyl and midazolam were administered for sedation at the operator's discretion. Patient oxygen saturation, hemodynamics, and electrocardiographic parameters were monitored during the case. After biopsy, patients were observed and vital signs were monitored for at least 4 hours.

Procedure-related complications were classified according to Society of Interventional Radiology (SIR) guidelines (6).

[0032] Right common femoral venous access was obtained using the Seldinger technique, and a 38.5-cm-long 10-F sheath (Flexor® Check-Flo® II; Cook, Inc., Bloomington, Indiana) was placed over a 0.035-inch guidewire into the inferior vena cava (IVC). The sheath dilator was then exchanged for a selective catheter such as a 5-F Cobra (Cook, Inc.) or 6-F Judkins Left 4 (Cook, Inc.). The catheter was used to select a hepatic vein to measure hepatic venous pressure.

[0033] Next, the catheter was exchanged for a physician-modified (with slight increase in curvature) precurved 7-F stiffened cannula (Argon Medical Devices, Plano, Texas), which was advanced through the long sheath over the guide wire and positioned in the intrahepatic IVC. This cannula was directed toward the lateral caval wall within the intrahepatic portion of the IVC at a level deemed favorable based on imaging.

[0034] Next, a 19-gauge biopsy needle (Flexcore, Argon Medical Devices) with a 20-mm throw was advanced through the caval wall, and the biopsy needle was fired under fluoroscopic observation. The stiffened cannula was repositioned slightly more inferiorly, and a second biopsy specimen was obtained in a similar fashion. Tissue samples were examined by the operator, and if deemed inadequate, additional samples were obtained. A venogram was then obtained through the sheath to document absence of caval injury before removal.

Results and Discussion

[0035] Hepatic tissue samples were obtained in 64 out of 66 cases (97%). Sufficient tissue for histopathologic diagnosis was obtained in 63 cases (95.5%). Complications after biopsy occurred in only two patients (3%), which were successfully treated. One of the two was a decrease in hemoglobin and the second was a self-limiting fever. No bleeding complications were observed.

[0036] One advantage of the TFTC approach is that the procedure does not require traversing the right atrium, which occasionally may be difficult or lead to arrhythmias (2,7,8). This method also avoids the need to advance and maintain a stiff cannula in a hepatic vein, and obviates negotiating problematic hepatic venous anatomy. Performing the biopsy directly from the IVC also does not necessitate a lateral view to distinguish between the right and middle hepatic veins when the correct catheter position is in question (2,7), as is required for the TJLB procedure. Additionally, the biopsy needle is deployed within the

liver directly through the intrahepatic IVC away from central vessels so that arterial and capsular injuries may be avoided. Finally, positioning and maintaining the physician-modified cannula against the lateral caval wall during and between biopsies does not require more than one operator. The overall technical and histopathologic success rates in this study, which were 97.0% and 95.5%, respectively, are similar compared to prior large case series of TJLBs (2,3,7,8). TFTC liver biopsies are safe and have advantages over TJLB.

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What is claimed is:

1. A method of obtaining a tissue sample from a liver of a patient, the method comprising:

inserting a hollow sheath through a femoral vein into a portion of the inferior vena cava (IVC) adjacent to the liver, wherein the sheath has a tip in the intrahepatic IVC and wherein the sheath has a shape that brings the tip of the sheath adjacent to a wall of the IVC at an angle that is optimal to allow penetration of the wall of the IVC by a biopsy needle, and

inserting a biopsy needle through the sheath and through the wall of the IVC into the liver to obtain a tissue sample from the liver.

2. The method of claim 1, wherein the sheath is preshaped with one or more bends before the sheath is inserted into the patient.

3. The method of claim 1, wherein the sheath is shaped *in vivo* after the sheath is inserted into the IVC.

4. The method of any of claims 1-3 wherein the sheath is inserted through an outer vascular sheath that has been inserted through the femoral vein into the IVC.

5. The method of any of claims 1-4, wherein the sheath and/or outer vascular sheath is inserted in the IVC with the aid of a guidewire.

6. The method of any of claims 1-5, wherein the angle between the tip of the sheath and a longitudinal axis of the sheath is between >30 degrees to 90 degrees.

7. The method of any of claims 1-5, wherein the angle between the tip of the sheath and a longitudinal axis of the sheath is between 40-80 degrees.

8. The method of any of claims 1-5, wherein the angle between the tip of the sheath and a longitudinal axis of the sheath is between 50-70 degrees.

9. A kit for obtaining a tissue sample from the liver of a patient, the kit comprising:
- an outer flexible vascular sheath having a length that extends from a femoral vein to an intrahepatic portion of the inferior vena cava (IVC) of the patient;

a hollow sheath capable of passing through the outer flexible sheath, wherein the sheath is preshaped with one or more bends and/or is capable of being shaped *in vivo* to provide an angle between the tip of the sheath and a longitudinal axis of the sheath between >30 degrees to 90 degrees, and wherein the hollow sheath is longer than the outer flexible vascular sheath; and

a flexible biopsy needle capable of passing through the hollow sheath to penetrate the wall of the IVC and pass into the liver to obtain a tissue sample from the liver, wherein the flexible biopsy needle is longer than the hollow sheath.

10. The kit of claim 9, futher comprising
- a guidewire to add insertion and placement of the outer flexible vascular sheath and/or hollow sheath in the IVC; and/or
- a dilator.

11. The kit of claim 9 or 10, wherein the angle between the tip of the sheath and the longitudinal axis of the sheath is between 40-80 degrees.

12. The kit of claim 9 or 10, wherein the angle between the tip of the sheath and the longitudinal axis of the sheath is between 50-70 degrees.

13. The kit of any of claims 9-12 for use in obtaining a tissue sample from the liver of a patient.

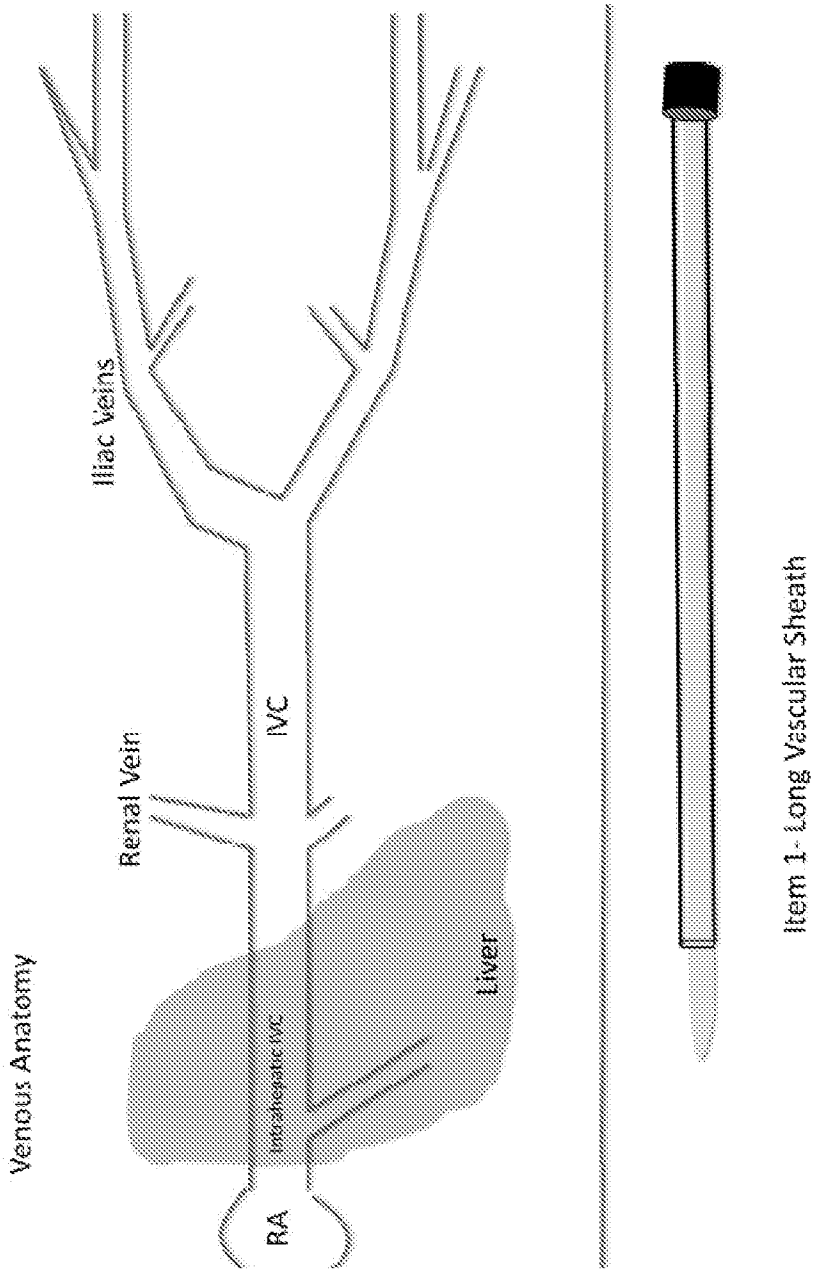
Venous Anatomy
Iliac Veins
Renal Vein
IVC
Liver
RA
Item 1- Long Vascular Sheath

FIG. 1

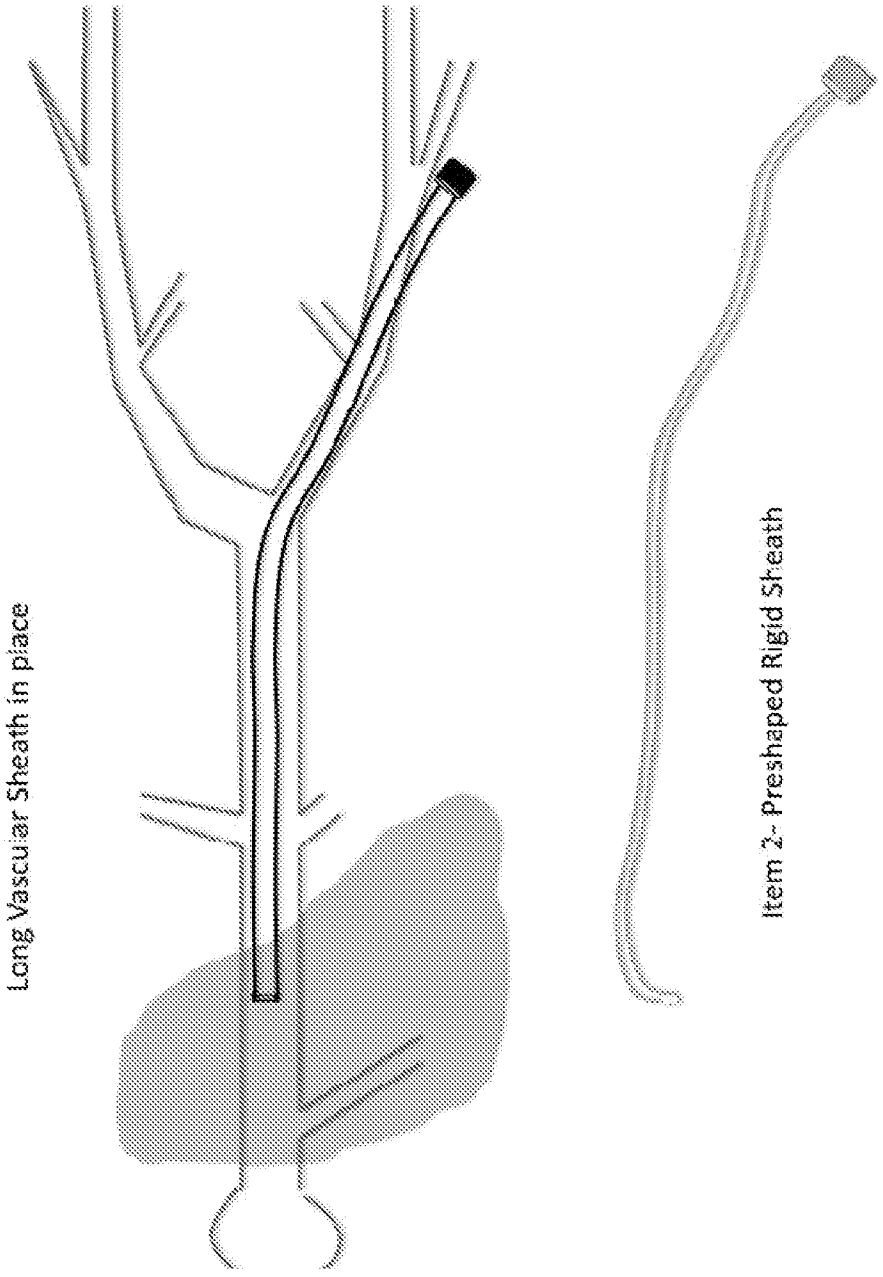
Long Vascular Sheath in place
Item 2- Preshaped Rigid Sheath

FIG. 2

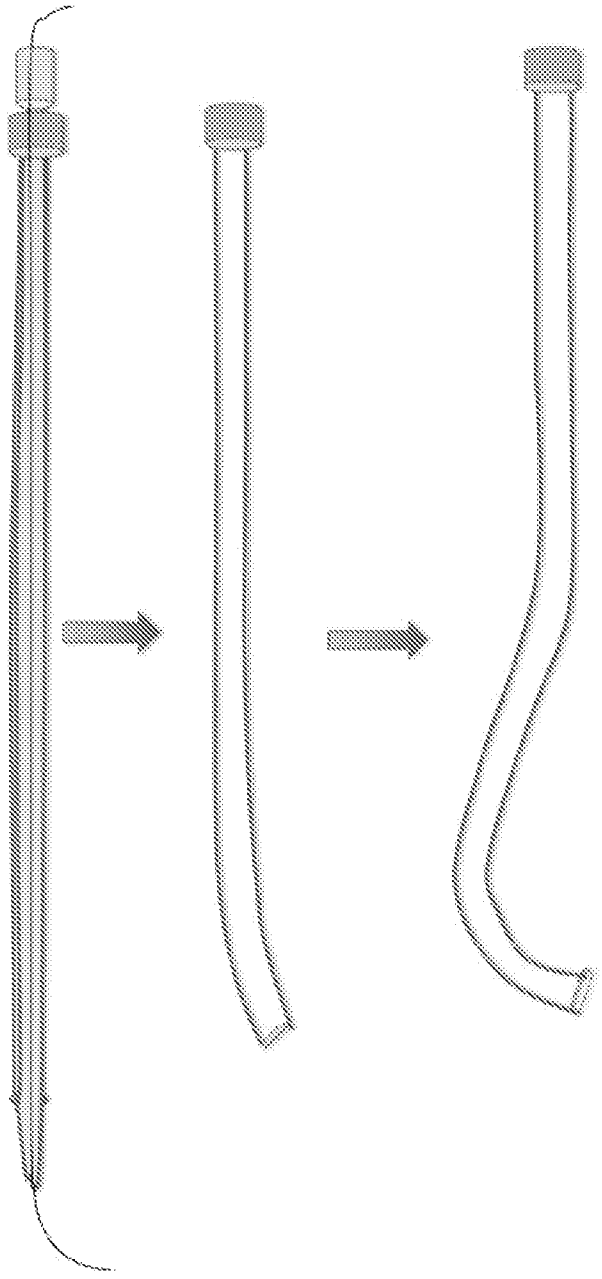

FIG. 3

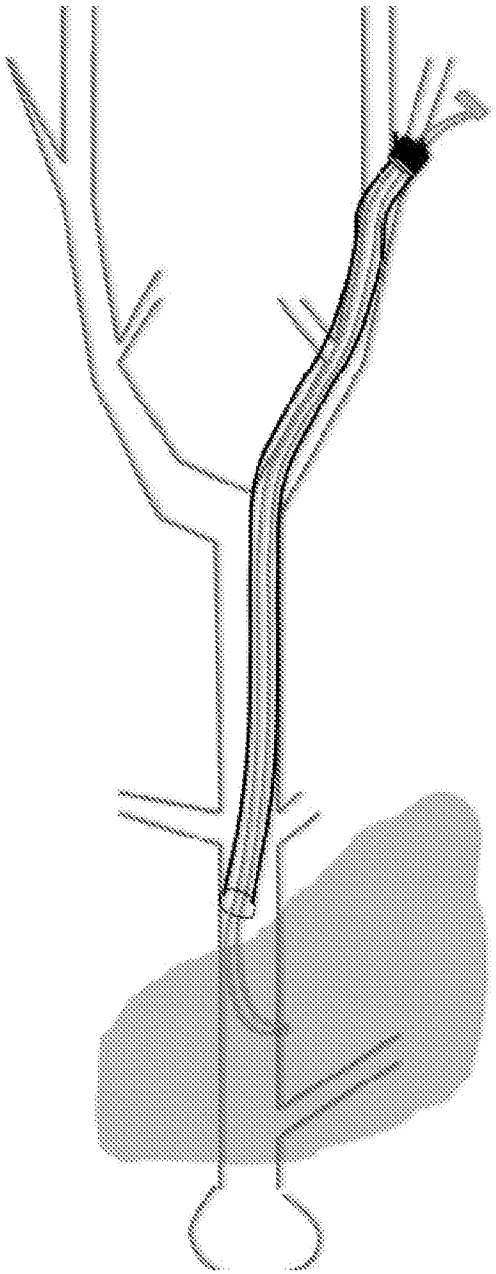

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/013576

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61B 10/04 (2016.01)
CPC - A61B 10/0266 (2016.02)
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)
IPC(8) - A61B 10/0275, 19/00, 17/34, 17/00, 10/04, 10/02; A61M 25/00 (2016.01)
CPC - A61B 2017/003, 2017/00292, 2017/00238, 10/0275, 10/0266, 5/4244 (2016.02)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 600/567, 564, 562; 606/185, 170 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Patbase, Google Patents , GoogleScholar
Search terms used: liver biopsy femoral vein inferior vena cava steer bend hepatic intrahepatic guidewire dilator

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,273,051 A (WILK) 28 December 1993 (28.12.1993) entire document	1-4, 9-12
A	US 2009/0156995 A1 (MARTIN et al) 18 June 2009 (18.06.2009) entire document	1-4, 9-12
A	US 2003/0125725 A1 (WOODARD et al) 03 July 2003 (03.07.2003) entire document	1-4, 9-12

☐ 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
02 March 2016	16 MAR 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver 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/US2016/013576

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.:
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:

3. ☒ Claims Nos.: 5-8, 13
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.