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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 October 2019 (10.10.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/193032 A1

(51) International Patent Classification:
A61M 5/00 (2006.01) *A61M 5/168* (2006.01)
A61M 5/145 (2006.01)

(21) International Application Number:
PCT/EP2019/058369

(22) International Filing Date:
03 April 2019 (03.04.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/651,723 03 April 2018 (03.04.2018) US

(71) Applicant: **KINEPICT HEALTH LTD.** [HU/HU]; Kelta köz 5, H-2092 Budakeszi (HU).

(72) Inventors: **ÓRIÁS, Viktor**; Török Ignác utca 20/d, H-8200 Veszprém (HU). **SZÖLLOSI, Dávid**; Béla utca 1/4, H-2461 Tárnok (HU). **KRISZTIÁN, Szigeti**; Leányka utca 7. 6. em. 37. a, H-1221 Budapest (HU). **OSVÁTH, Szabolcs**; c/o Kinepict Health Ltd, Kelta köz 5., H-2092 Budakeszi (HU).

(74) Agent: **BRANN AB**; P.O. Box 3690, SE-103 59 STOCKHOLM (SE).

(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, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, 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,

(54) Title: CONTRAST AGENT DELIVERY SYSTEM AND METHOD OF DELIVERING CONTRAST AGENT TO A PATIENT, COMPUTER PROGRAM AND NON-VOLATILE DATA CARRIER

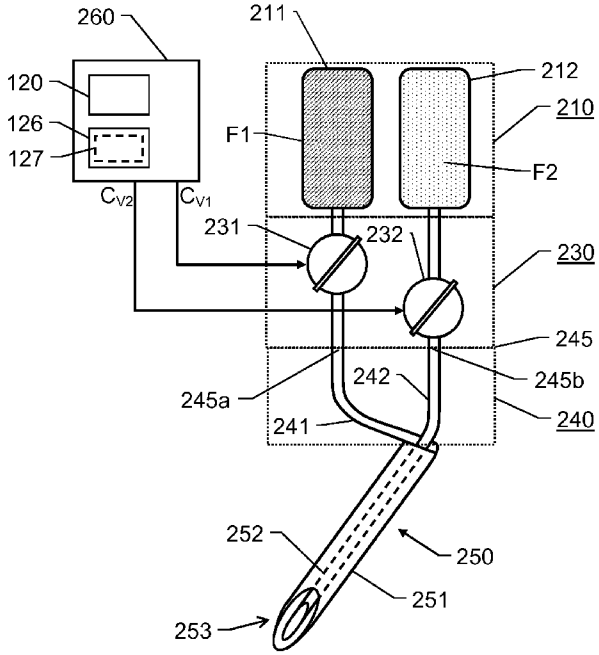

Fig. 5

(57) Abstract: First and second pressurized containers (211; 212) hold first and second fluids (F1; F2) in the form of a liquid contrast medium and a gas, e.g. CO_2, respectively. A valve assembly (230) causes the first and second fluids (F1; F2) to be ejected from the first and second containers (211; 212) in response to control signals (C_{V1}; C_{V2}). A tube assembly (240) forwards the first and second fluids (F1; F2) to a catheter (250) for delivery into a blood vessel of a patient. A control unit (260) controls the valve assembly (230) by generating a temporal sequence in the control signals(C_{V1}; C_{V2}) such that a composite arrangement of the first and second fluids (F1; F2) is formed in the blood vessel.The composite arrangement contains a bolus of the liquid contrast medium

WO 2019/193032 A1

[Continued on next page]

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))*

adjoining:a bubble of the gas downstream of the bolus, a bubble of the gas upstream of the bolus and/or a bubble of the gas enclosed by the bolus. Movement of the injected composite arrangement along the patient's blood vessels can be recorded at high quality on a series of X-ray images, which may then be digitally processed by a computer.

Contrast Agent Delivery System and Method of Delivering Contrast Agent to a Patient, Computer Program and Non-Volatile Data Carrier

TECHNICAL FIELD

The present invention relates generally to the use of contrast agents in medical imaging with the aim to improve image quality or use less contrast agent and obtain structural or functional information from digital image processing. In particular, the invention relates to a contrast agent delivery system for delivering contrast agent to a patient, and a corresponding method. The invention also relates to a computer program implementing the method and a non-volatile data carrier storing the computer program.

BACKGROUND

Minimally invasive diagnostic and therapeutic interventions for the treatment of vascular disease typically use a combination of catheter and wire-based devices. In performing a typical percutaneous vascular intervention, exemplary procedural elements may include the following: obtaining a clear image of the vasculature including a vessel obstruction, lesion, or other treatment site using X-ray angiography and injection of contrast imaging agents through the lumen of a guide catheter or sheath before, during, and/or after treatment; accessing and crossing the vessel obstruction or lesion using a combination of one or more guide wires, guide catheters, support catheters, and/or sheaths; and finally treatment of the obstruction or lesion using specialized catheter-based tools (for instance one or more angioplasty balloons, stent and stent delivery systems, atherectomy, drug delivery infusion catheters, and the like).

In a typical interventional vascular procedure, the steps may include introduction of a guide wire along a guide catheter or

sheath and across an obstruction using X-ray angiography, or fluoroscopic guidance. During this process, a contrast agent may be injected through the lumen of the guide catheter or sheath to provide an X-ray angiographic image that identifies the position of the radiopaque distal end of the guide wire relative to the vessel. This type of contrast imaging may be repeated at any point during the procedure in order to confirm the position of a treatment device such as a balloon catheter relative to the obstruction targeted for treatment. The balloon catheter is then advanced along the guide catheter and the guide wire until the balloon is positioned across or within the obstruction. The position of the balloon is then confirmed by injecting a contrast agent through the guide catheter or sheath to provide an angiographic image prior to the surgical or endovascular treatment. The obstruction is dilated by inflation of the balloon to restore blood flow, and the result is confirmed using conventional angiography. After treatment, the devices are removed from the patient.

X-ray angiography is an invasive medical diagnostic procedure that may visualize vessel anatomy and pathology to aid vascular interventions. Contrast agent injection into the vessels may be necessary to distinguish soft tissue from the blood flow inside the vessels. The contrast agent has an X-ray attenuation coefficient that is different from that of soft tissue or blood. The movement of the injected contrast agent along the blood vessels is recorded on a series of X-ray images, which may be digitally processed by a computer. The gold-standard image processing method is digital subtraction angiography (DSA). In DSA, a mask image is recorded without contrast agent and the mask is subtracted from all the other images in the series. As an alternative to DSA, kinetic imaging could also be used to analyze X-ray angiography image series. Kinetic imaging is an imaging modality that uses statistical calculations, and it may be used to visualize blood vessels through highlighting the motion of the contrast agent injected in the blood stream.

There are multiple factors that can affect clear imaging or visualization of the vasculature and the target treatment site including, but not limited to the type of device or equipment used, concentration of the contrast agent used, amount or flow rate of injection, vessel condition (for instance vessel obstructions, side branches or collaterals, vessel tortuosity between the injection source and treatment site, total occlusion of the treatment site, etc.), patient profile or body habitus (for instance morbidly obese patients), distance between the injection source and the treatment site, patient clinical profile (i.e. low ejection fraction or presence of congestive heart failure), amongst other factors. Depending on specific factors that are present in a given patient, physician operators adjust the procedural approach and their choice of catheter-based devices in order to obtain diagnostic quality images, with the disadvantage that many of these approaches and devices provide an inefficient delivery of diagnostic contrast agents or solutions, which may result in a protracted procedure time, potential safety issues, and/or increased procedural costs.

Iodinated, or iodine-based, contrast agents act by attenuating the signal of an X-ray passed through the body of the patient. Iodinated contrast agents are available in either ionic (e.g. Hypaque 50, Isopaque 370, Hexabrix, etc.) or non-ionic (e.g. Isovue 370, Omnipaque 350, Ultravist 370, etc.) forms, and are commonly used due to their solubility and relatively benign interaction with the body. The contrast agent is introduced into the patient at a high concentration or volume to account for the dilution of contrast agent as it flows through the patient's vascular system and to compensate for losses due to flow through collateral or side-branch vessels (i.e. vessels that are not the subject of the target interventional procedure or surgery).

Acquiring images with sufficient image quality often necessitates the use of a higher concentration and/or a larger volume of contrast agent coupled with a longer X-ray exposure time due to the longer run off time to obtain images that are of sufficiently high

quality to aid in diagnosis and treatment.

The use of a higher volume of contrast agent can induce nephropathy (i.e. contrast agent-induced damage to the kidneys), which is especially relevant to a large cohort of the patient population that suffers from peripheral vascular disease (e.g. diabetics). Furthermore, the high, prolonged doses of radiation associated with these techniques are not beneficial and can be harmful to the patient and/or the treating physician and staff.

Gases may also be used as a contrast agent in various imaging methods. Because of its lack of renal toxicity and allergic potential, carbon-dioxide is a preferred contrast agent in patients with renal failure or contrast allergy, and particularly in patients who require large volumes of contrast medium for complex endovascular procedures.

In some cases, it is not possible to acquire images of high enough quality to complete the intervention or treatment. Even when the angiographic images are of sufficient quality to guide the procedure and the treatment of the lesion is successful, acquiring the follow-up angiogram can be challenging.

Multiple imaging methods may profit from engineering the bolus shape. Some methods may benefit from longer, more uniform bolus shapes, while other methods produce better image quality with more compact boluses. For example, the desired bolus shape for kinetic imaging may be a short bolus, with sudden rise and/or decrease of the contrast media concentration in the blood. In addition, for several applications it may be advantageous to use positive and negative contrast agents combined consecutively in a single bolus.

Theoretically, it is possible to control the shape of the injected bolus (e.g. the sharpness of the edges) at the proximity of the injection site. However, the prior art contains no power injector systems that can create a sharp bolus farther away. Blood flow distorts the shape of the injected contrast media bolus because the blood flow velocity is different throughout the cross section

of the vessels. In the case of laminar flow, this results in a parabolic velocity profile, meaning that the contrast media that is closer to the axis of the vessel travels at a higher velocity than the contrast media closer to the vessel wall, therefore the shape of the bolus changes as it flows in the vessel.

Products related to the pressure injection of fluids into a human subject are routinely used in the clinical practice. A number of these products are used for the intravascular introduction of imaging contrast media in patients during medical imaging procedures. Traditional angiographic applications of power injectors (e.g. digital subtraction angiography, CT angiography) usually consist of the injection of one type of contrast media (either positive contrast, or negative contrast) that may be combined with multiple other injections of the same type of contrast media and/or the injection of other, non-contrast-enhancing fluids. A set of parameters (including the flow rate, pressure, volume) can be controlled usually either by the user or in an automatic fashion to achieve optimal contrast enhancement at the region of interest while maintaining patient safety. The shape of the injected contrast media bolus can be optimized for different imaging applications.

US 2015/0174379 describes an apparatus and methods for delivering fluid into a body lumen. The apparatus may include a catheter including proximal and distal ends, a fluid delivery lumen extending from the proximal end to a transit port on a distal portion of the catheter, and an inflatable infusion element on the distal portion such that an interior of the inflatable infusion element communicates with the fluid delivery lumen. During use, a distal end of the catheter is introduced into a lumen or conduit with the inflatable infusion element in a collapsed condition, the inflatable infusion element is expanded to an expanded condition to partially or totally occlude the lumen or conduit, and fluid is infused from the catheter into the lumen or conduit proximally relative to the inflatable infusion element while the inflatable infusion element remains in the expanded condition.

US 6,635,030 discloses a design, wherein a contrast medium injector for injecting a patient with contrast medium for a CT scan is programmed to provide an injection protocol that is a representation of an ideally defined exponential curve with an initial injection rate decaying at an exponential rate. This has been found to produce a uniform vascular enhancement for the scanning of a patient's blood vessels. The particular exponential decay coefficient which has been found to be optimal is directly proportional to the cardiac output divided by the patient's weight and is approximated at 0.01 for a typical human.

US 2004/0242996 shows an injector system including a source of injection fluid, a pump device, a fluid path set disposed between the source of injection fluid and the pump device, and a fluid control device operatively associated with the fluid path set. The fluid control device is adapted to permit purging of air from the fluid path set and to stop flow of the injection fluid to a patient at substantially any pressure or flow rate generated by the pump device for delivering a sharp bolus of the injection fluid to the patient. The fluid control device is preferably part of the fluid path set between the source of injection fluid and the pump device.

US 7,623,903 reveals methods for confirming location of a catheter tip relative to a targeted location in a blood vessel of a subject and improving visualization of the blood vessels downstream of the catheter tip are provided. The methods comprise acquiring and displaying a first modified MR image of the subject's blood vessels between an insertion site for the catheter and the targeted location; acquiring and displaying a sequence of modified MR images of the blood vessels to monitor advancement of an inserted catheter from the insertion site to an intraluminal stop site at or near the targeted location; delivering a bolus of a magnetic resonance contrast agent through the tip of the catheter and to the intraluminal stop site, wherein the magnetic contrast agent alters the first modified MR image of the subject's blood vessels; acquiring and displaying an updated

second MR modified image of the blood vessels at and downstream of the tip of the catheter. Systems and computer readable medium storing computer executable instructions operable to perform computer executable aspects of the present methods are also provided.

There are multiple examples of injection systems designed to deliver a multitude of different liquids into a patient, for instance EP 2 477 677, US 9,011,377, US 9,457,140, US 9,649,436. These systems are typically used to deliver one or more boluses of liquid contrast agent and/or saline in a sequence. Pressure injectors designed for liquid delivery are typically not suitable for the delivery of gaseous substances. Similarly, pressure injectors designed for the delivery of gaseous substances are typically not suitable for the delivery of liquid contrast media. The documents US 2013/0204130, US 2017/0216515, CA 2,602, 107, US 2016/0213835 and EP 1 074 221 exemplify such pressure injectors.

There are also designs that may be suitable for the injection of both liquid and gaseous substances, for example as shown in WO 2013/079743, US 2011/0021905 and US5346470A. Here, however, the purpose is not to control the shape of the liquid contrast media bolus by the injection of a sequence of different phases (gaseous and liquid) of contrast media.

SUMMARY

The object of the present invention is to provide bolus injection that optimizes contrast media delivery to improve image quality.

According to one aspect of the invention, the object is achieved by a contrast agent delivery system for delivering contrast agent to a patient. The system includes a container assembly, a valve assembly, a tube assembly and a control unit. The container assembly comprises first and second pressurized containers, where the first container is configured to hold a first fluid in the form of a liquid contrast medium and the second container is con-

figured to hold a second fluid in the form of gas. The valve assembly is connected to a respective output from the first and second containers. The valve assembly is configured to cause the first and second fluids to be ejected from the container assembly in response to at least one first control signal. The tube assembly is connected to the valve assembly via an input interface. The tube assembly has a delivery output in the form of a catheter configured to be inserted into a blood vessel of the patient. The control unit is configured to control the valve assembly by generating a temporal sequence in the at least one first control signal, such that a composite arrangement of the first and second fluids is formed in the blood vessel. The composite arrangement comprises a bolus of the liquid contrast medium adjoining a bubble of the gas downstream of the bolus, a bubble of the gas upstream of the bolus and/or a bubble of the gas enclosed by the bolus.

This system is advantageous because the proposed composite arrangement of liquid contrast medium and gas bubbles enables control of the shape of the liquid contrast bolus. This, in turn, renders it possible to control the shape of the bolus edges, control the bolus length, combine different and allow synergistic combination of positive and negative contrast agent.

The introduction of gas bubbles near the leading edge (forerunner), the trailing edge (chaser), both edges, or inside of the injected contrast media reduces the bolus-distorting effect of blood flow. Thereby, it is possible to engineer more precisely the bolus shape at a farther distance from the injection site.

Introducing an alternating series of positive and negative contrast media may reduce image quality in image processing methods where the signal (the intensity of radiation after it passes through the subject) is averaged. In several image processing methods, however, the sequence of positive and negative contrast changes may improve image quality.

According to one embodiment of this aspect of the invention, the

contrast medium delivery system further contains a pump assembly configured receive at least one second control signal. In response thereto, the pump assembly is configured to apply a respective pressure level in the first and second containers, such that the first and second containers remain pressurized during delivery of the contrast agent to the patient. Hence, the first and second fluids can be adaptively controlled to have a desired pressure level throughout the delivery process.

According to another embodiment of this aspect of the invention, the catheter has a double-lumen section in which a first channel is configured to transport the first fluid and a second channel is configured to transport the second fluid. The first channel encloses the second channel, at least in a cannula portion of the double-lumen section. As a result, the composite arrangement of the first and second fluids can be formed directly in the blood vessel, i.e. in connection with said fluids being ejected from the catheter. In this embodiment, the tube assembly contains a first tube section interconnecting a first input of the input interface with the first channel, and a second tube section interconnecting a second input of the input interface with the second channel, so that the fluids can be transported to the catheter.

According to yet another embodiment of this aspect of the invention, the valve assembly includes a first valve connected to the first container and a second valve connected to the second container. The first valve is operable in response to a first control signal, and the second valve is operable in response to a second control signal. Consequently, the control unit may manipulate the valve assembly in such a manner that a desired composite arrangement of the first and second fluids is accomplished.

Alternatively, the valve assembly may include a dual-port valve having a first port connected to the first container and a second port connected to the second container. The dual-port valve is here operable in response to a third control signal from the control unit. Thus, a desired composite arrangement of the first and

second fluids may likewise be accomplished.

According to still another embodiment of this aspect of the invention, the catheter has a single-lumen section configured to transport the first and second fluids in agreement with the composite arrangement. Here, the tube assembly includes a tube intersection connecting a first tube section with a second tube section. The first tube section is arranged to transport the first fluid from a first input of the input interface to the tube intersection. Analogously, the second tube section is arranged to transport the second fluid from a second input of the input interface to the tube intersection. An output of the tube intersection is further connected to the catheter. Consequently, the composite arrangement of the first and second fluids can be formed already in the catheter, i.e. before said fluids are injected into the blood vessel.

According to another aspect of the invention, the object is achieved by a method of delivering contrast agent to a patient via a delivery system comprising a container assembly comprising first and second pressurized containers, where the first container is configured to hold a first fluid in the form of a liquid contrast medium and the second container is configured to hold a second fluid in the form of gas; a valve assembly connected to a respective output from the first and second containers, the valve assembly being configured to cause the first and second fluids to be ejected from the container assembly in response to at least one first control signal; and a tube assembly connected to the valve assembly via an input interface, where the tube assembly comprises a delivery output in the form of a catheter configured to be inserted into a blood vessel of the patient. The method involves controlling the valve assembly by generating a temporal sequence in the at least one first control signal such that a composite arrangement of the first and second fluids is formed in the blood vessel. The composite arrangement contains a bolus of the liquid contrast medium adjoining: a bubble of the gas downstream of the bolus, a bubble of the gas upstream of the bolus, and/or a bubble of the gas enclosed by the bolus. The advanta-

ges of this method, as well as the preferred embodiments thereof, are apparent from the discussion above with reference to the system.

According to a further aspect of the invention, the object is achieved by a computer program loadable into a non-volatile data carrier communicatively connected to a processing unit. The computer program includes software for executing the above method when the program is run on the processing unit.

According to another aspect of the invention, the object is achieved by a non-volatile data carrier containing the above computer program.

By preventing the spread of the contrast agent and providing a shorter and compact profile, the standard deviation of X-ray attenuation increases. Therefore, the signal-to-noise ratio of kinetic images also increases. The compacted bolus profile also aides the precise calculation of other time-derived parameters that could provide functional information about blood flow characteristics.

Further advantages, beneficial features and applications of the present invention will be apparent from the following description and the dependent claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is now to be explained more closely by means of preferred embodiments, which are disclosed as examples, and with reference to the attached drawings.

Figures 1-4 schematically illustrate examples of how liquid boluses of contrast medium and gas bubbles may be arranged according to embodiments the invention;

Figure 5 shows a block diagram over the system according to a first embodiment of the invention;

Figure 6 shows a block diagram over the system according

to a second embodiment of the invention;

Figure 7 illustrates a dual-port valve according to one embodiment of the invention; and

Figure 8 illustrates, by means of a flow diagram, the general method according to the invention.

DETAILED DESCRIPTION

Figure 1 shows a first schematic illustration of how a liquid bolus 110 of a contrast medium is arranged relative to a pair of gas bubbles 120 and 130 respectively in a patient's blood vessel 100 according to one embodiment of the invention. Here, a forerunner gas bubble 120 is formed near a leading edge of the liquid bolus 110, and a chaser gas bubble 120 is formed near a trailing edge of the liquid bolus 110. The presence of the gas bubbles 120 and 130 disrupt a laminar flow of blood B that would otherwise have caused the liquid bolus 110 to be gradually dispersed as it travels along the blood vessel 100. Thus, the liquid bolus 110 may maintain a desired shape also at a relatively long distance from an injection site. This, in turn, enables high image quality in kinetic imaging, which requires short/compact boluses.

Figure 2 shows a second schematic illustration of how a liquid bolus 110 of the contrast medium is arranged relative to a forerunner gas bubble 120 near the leading edge of the liquid bolus 110 in the patient's blood vessel 100 according to one embodiment of the invention.

Figure 3 shows a third schematic illustration of how a liquid bolus 110 of the contrast medium is arranged relative to a chaser gas bubble 120 near the trailing edge of the liquid bolus 110 in the patient's blood vessel 100 according to one embodiment of the invention.

Figure 4 shows a fourth schematic illustration of how a liquid bolus 110 of a contrast medium is arranged relative to a gas bubble 125 enclosed in the liquid bolus 110 in the patient's blood

vessel 100 according to one embodiment of the invention.

The inventors have found that, similar to the embodiment of Figure 1, the gas bubbles 120, 130 and 125 respectively of the embodiments illustrated in Figures 2 to 4 disrupt the laminar flow of blood B in such a manner that the liquid bolus 110 is capable of maintaining a desired shape at long distances from the injection site. Hence, Figures 1 to 4 show alternative examples of composite arrangements of first and second fluids in the form of liquid contrast medium and gas bubbles, e.g. carbon-dioxide, that may be used for maintaining a desired compact bolus 110 having well-defined edges while travelling through a blood vessel 100. Of course, according to the invention, composite arrangements in the form of combinations of gas bubbles and boluses are conceivable, for instances longer sequences of liquid contrast medium and gas bubbles and/or sequences of one or more gas bubbles enclosed in each respective liquid bolus.

Figure 5 shows a block diagram over a contrast agent delivery system for delivering contrast agent to a patient according to a first embodiment of the invention. Here, the system includes a container assembly 210, a valve assembly 230, a tube assembly 240 and a control unit 260.

The container assembly 210 contains first and second pressurized containers 211 and 212 respectively. The first container 211 holds a first fluid F1 in the form of a liquid contrast medium. The first container 211 is pressurized and sealed, so that when the first fluid F1 is ejected there from, the pressure level in the first container 211 drops gradually. The second container 212 holds a second fluid F2 in the form of gas, preferably CO_2. Analogous to the first container 211, the second container 211 is pressurized and sealed. As a result, as the second fluid F2 is escapes there from, the pressure level in the second container 212 decreases gradually.

The valve assembly 230 is connected to a respective output from the first and second containers 211 and 212. The valve assembly 230 is configured to cause the first and second fluids F1 and F2 to be ejected from the container assembly 210 in response to first control signals C_{V1} and C_{V2} respectively generated by the control unit 260.

The tube assembly 240 is connected to the valve assembly 230 via an input interface 245. The tube assembly 240 has a delivery output in the form of a catheter 250 configured to be inserted into a blood vessel 100 of the patient for delivery of the contrast agent to a patient. The catheter may have a double-lumen section 250 (as illustrated in Figure 5), where a first channel 251 is configured to transport the first fluid F1, a second channel 252 is configured to transport the second fluid F2, and the first channel 251 encloses the second channel 252 in a cannula portion 253 of the double-lumen section 250.

In such a design, the tube assembly 240 preferably has a first tube section 241 interconnecting a first input 245a of the input interface 245 with the first channel 251, and a second tube section 242 interconnecting a second input 245b of the input interface 245 with the second channel 252. Thus, as the first and second valves 231 and 232 respectively are operated to open and close, the first and second fluids F1 and F2 are transported to the blood vessel 100 to form a composite arrangement of liquid contrast medium and bubbles of the gas therein.

The control unit 260 is configured to control the valve assembly 230 by generating a temporal sequence in the first control signals C_{V1} and C_{V2}, causing the first and second valves 231 and 232 to open and close, such that a composite arrangement of the first and second fluids F1 and F2 is formed in the blood vessel 100, for instance as illustrated in Figures 1 to 4. This means that the arrangement contains at least one bolus 110 of the liquid contrast medium adjoining a bubble of the gas. For example, the bolus 110 may adjoin a bubble of the gas downstream 120 of the

bolus 110, the bolus 110 may adjoin a bubble of the gas upstream 130 of the bolus 110 and/or the bolus 110 may adjoin a bubble of the gas 125 enclosed by the bolus 110. As mentioned above, longer and more complex sequences of composite arrangements may be formed according to the invention depending on the specific imaging scenario.

Using iodinated contrast agent as the first fluid F1 and carbon-dioxide as the second fluid F2 in the above-described embodiments results in image quality enhancement due to a shorter contrast agent bolus profile during X-ray angiography. A forerunner and/or chaser injection of carbon-dioxide prevents uncontrollable expansion of liquid iodinated contrast agent in the examined section of the vessel. Of course, the same is true also for alternative contrast agents and gases.

Figure 6 shows a block diagram over the system according to a second embodiment of the invention. Here, the valve assembly 230 has the same design as described above. However, the container assembly 210, the tube assembly 240 and the control unit 260 differ slightly from the first embodiment.

The container assembly 210 includes the first and second pressurized containers 211 and 212, which hold the first fluid F1 in the form of a liquid contrast medium and the second fluid F2 in the form of gas respectively. Here, the system further includes a pump assembly 220 that is configured receive second control signals C_{P1} and C_{P2}, and in response thereto, apply a respective pressure level in the first and second containers 211 and 212. Consequently, the first and second containers 211 and 212 can be controlled to remain pressurized at a relatively stable level during delivery of the contrast agent to the patient.

Also here, the tube assembly 240 is connected to the valve assembly 230 via an input interface 245. The tube assembly 240 likewise has a delivery output in the form of a catheter 350 configured to be inserted into the blood vessel 100 of the patient.

The catheter 350 contains a single-lumen section configured to transport the first and second fluids F1 and F2 in agreement with a desired composite arrangement. Depending on a physical extension of the single-lumen section relative to a temporal/physical extension of the composite arrangement, the latter may be entirely or partially formed already in the catheter 350 before entering into the blood vessel 100.

The tube assembly 240 contains a tube intersection 243 that connects a first tube section 241 with a second tube section 242. The first tube section 241 is arranged to transport the first fluid F1 from a first input 245a of the input interface 245 to the tube intersection 243. The second tube section 242 is arranged to transport the second fluid F2 from a second input 245b of the input interface 245 to the tube intersection 243. An output of the tube intersection 243 is connected to the catheter 350, so that the desired composite arrangement can be formed therein.

In this embodiment, the control unit 260 is configured to control the valve assembly 230 by generating a temporal sequence in the first control signals C_{V1} and C_{V2}. The control unit 260 is configured to control the pump assembly 220 to apply desired pressure levels in the first and second containers 211 and 212 by generating the second control signals C_{P1} and C_{P2}.

Naturally, in addition to the first and second fluids F1 and F2, a third fluid, e.g. containing saline solution, may be added to the above-described design in a straightforward manner by simply adding another fluid container to the container assembly 210 and adding another tube intersection to the tube assembly 240, plus corresponding control signaling from the control unit 260.

Figure 7 illustrates a dual-port valve 233 according to one embodiment of the invention, which may replace the first and second valves 241 and 242 in each of the embodiments described above with reference to Figures 5 and 6. The dual-port valve 233 has a first port 731 connected to the first container 211 and

a second port 732 connected to the second container 212. The dual-port valve 233 is operable in response to a third control signal C_V generated by the control unit 260. Preferably, the dual-port valve 233 is controllable to be set in one of three different positions depending on a value of the third control signal C_V, so that the first fluid F1, the second fluid F2 or no fluid passes there through.

Although the presented embodiments refer to X-ray angiography, the technology could also be used in computed tomography, ultrasound-, SPECT-, PET-, magnetic resonance-, infrared-imaging, visible-light imaging, ultraviolet-light imaging, opto-acoustic imaging, electron beam- or terahertz radiation imaging. In addition to blood vessels, the proposed technology may visualize other anatomic structures. Namely, apart from the flow of blood, the technology is capable of visualizing also other physiological movements.

The embodiments refer to an image processing algorithm called 'kinetic imaging' described in e.g. US 9,200,947. However, the technology is not restricted to this specific image processing algorithm.

Although the embodiments and the figures refer to several tools and devices to demonstrate possible delivery methods, the use of the technology is not restricted to any of these specific tools or delivery systems. The embodiments refer to, and figures depict, certain kinds of contrast agent delivery catheters. However, the technology of this disclosure is not restricted to these catheters, or these delivery methods.

Although the embodiments and the drawings mention carbon-dioxide as an example for gas state contrast agent, iodinated contrast agent as an example for liquid state contrast agent, and saline solution as an example for flush solution the technology is not restricted to these specific substances.

It is generally advantageous if the control unit 120 and the ca-

mera 110 are configured to effect the above-described procedure in an automatic manner by executing a computer program 127. Therefore, the control unit 120 may include a memory unit 126, i.e. non-volatile data carrier, storing the computer program 127, which, in turn, contains software for making processing circuitry in the form of at least one processor in the central control unit 120 execute the above-described actions when the computer program 127 is run on the at least one processor.

In order to sum up, and with reference to the flow diagram in Figure 8, we will now describe the general method according to the invention of delivering contrast agent to a patient via the proposed delivery system.

In a first step 810, first and second fluids in first and second fluid containers respectively are kept pressurized. This may be accomplished either by each container being pressurized and sealed, or via a pump assembly applying a respective pressure level in the first and second containers in response to one or more control signals.

In a subsequent step 820, a valve assembly, connected between the first and second fluid containers and a proximate interface of a tube assembly, is controlled such that a composite arrangement of the first and second fluids is formed in a patient's blood vessel after delivery through a catheter connected to a distal interface of the tube assembly.

The process described with reference to Figure 8 may be controlled by means of a programmed processor. Moreover, although the embodiments of the invention described above with reference to the drawings comprise processor and processes performed in at least one processor, the invention thus also extends to computer programs, particularly computer programs on or in a carrier, adapted for putting the invention into practice. The program may be in the form of source code, object code, a code intermediate source and object code such as in partially

compiled form, or in any other form suitable for use in the implementation of the process according to the invention. The program may either be a part of an operating system, or be a separate application. The carrier may be any entity or device capable of carrying the program. For example, the carrier may comprise a storage medium, such as a Flash memory, a ROM (Read Only Memory), for example a DVD (Digital Video/Versatile Disk), a CD (Compact Disc) or a semiconductor ROM, an EPROM (Erasable Programmable Read-Only Memory), an EEPROM (Electrically Erasable Programmable Read-Only Memory), or a magnetic recording medium, for example a floppy disc or hard disc. Further, the carrier may be a transmissible carrier such as an electrical or optical signal which may be conveyed via electrical or optical cable or by radio or by other means. When the program is embodied in a signal which may be conveyed directly by a cable or other device or means, the carrier may be constituted by such cable or device or means. Alternatively, the carrier may be an integrated circuit in which the program is embedded, the integrated circuit being adapted for performing, or for use in the performance of, the relevant processes.

The term “comprises/comprising” when used in this specification is taken to specify the presence of stated features, integers, steps or components. However, the term does not preclude the presence or addition of one or more additional features, integers, steps or components or groups thereof.

The invention is not restricted to the described embodiments in the figures, but may be varied freely within the scope of the claims.

Claims

1. A contrast agent delivery system for delivering contrast agent to a patient, the system comprising:

a container assembly (210) comprising first and second pressurized containers (211; 212), the first container (211) being configured to hold a first fluid (F1) in the form of a liquid contrast medium and the second container (212) being configured to hold a second fluid (F2) in the form of gas,

a valve assembly (230) connected to a respective output from the first and second containers (211; 212), the valve assembly (230) being configured to cause the first and second fluids (F1; F2) to be ejected from the container assembly (210) in response to at least one first control signal (C_{V1}; C_{V2}; C_V),

a tube assembly (240) connected to the valve assembly (230) via an input interface (245), the tube assembly (240) comprising a delivery output in the form of a catheter (250; 350) configured to be inserted into a blood vessel (100) of the patient, and

a control unit (260) configured to control the valve assembly (230) by generating a temporal sequence in the at least one first control signal (C_{V1}; C_{V2}; C_V) such that a composite arrangement of the first and second fluids (F1; F2) is formed in the blood vessel (100), which composite arrangement comprises a bolus (110) of the liquid contrast medium adjoining one or more of:

a bubble of the gas downstream (120) of the bolus (110),

a bubble of the gas upstream (130) of the bolus (110), and

a bubble of the gas (125) enclosed by the bolus (110).

2. The contrast medium delivery system according to claim 1, further comprising:

a pump assembly (220) configured receive at least one second control signal (C_{P1}; C_{P2}), and in response thereto, apply a respective pressure level in the first and second containers (211; 212) such that the first and second containers (211; 212) remain pressurized during delivery of the contrast agent to the patient.

3. The contrast medium delivery system according to any one of claims 1 or 2, wherein:

the catheter comprises a double-lumen section (250) in which a first channel (251) is configured to transport the first fluid (F1), a second channel (252) is configured to transport the second fluid (F2), the first channel (251) enclosing the second channel (252) in a cannula portion (253) of the double-lumen section (250) and

the tube assembly (240) comprises:

a first tube section (241) interconnecting a first input (245a) of the input interface (245) with the first channel (251), and

a second tube section (242) interconnecting a second input (245b) of the input interface (245) with the second channel (252).

4. The contrast medium delivery system according to claim 3, wherein

the valve assembly (230) comprises a first valve (231) connected to the first container (211) and a second valve (232) connected to the second container (212), the first valve (231) being operable in response to a first control signal (C_{V1}) of said at least one first control signal and the second valve (232) being operable in response to a second control signal (C_{V2}) of said at least one first control signal.

5. The contrast medium delivery system according to claim 3, wherein

the valve assembly (230) comprises a dual-port valve (233) having a first port (731) connected to the first container (211) and a second port (732) connected to the second container (212), the dual-port valve (233) being operable in response to a third control signal (C_V) of said at least one first control signal.

6. The contrast medium delivery system according to any one of claims 1 or 2, wherein:

the catheter (350) comprises a single-lumen section configured to transport the first and second fluid (F1, F2) in agreement with said composite arrangement, and

the tube assembly (240) comprises a tube intersection (243) connecting a first tube section (241) with a second tube section (242), the first tube section (241) being arranged to transport the first fluid (F1) from a first input (245a) of the input interface (245) to the tube intersection (243), the second tube section (242) being arranged to transport the second fluid (F2) from a second input (245b) of the input interface (245) to the tube intersection (243), and an output of the tube intersection (243) being connected to the catheter (350).

7. A method of delivering contrast agent to a patient via a delivery system comprising a container assembly (210) comprising first and second pressurized containers (211; 212), the first container (211) being configured to hold a first fluid (F1) in the form of a liquid contrast medium and the second container (212) being configured to hold a second fluid (F2) in the form of gas; a valve assembly (230) connected to a respective output from the first and second containers (211; 212), the valve assembly (230) being configured to cause the first and second fluids (F1; F2) to be ejected from the container assembly (210) in response to at least one first control signal (C_{V1}; C_{V2}; C_V); and a tube assembly (240) connected to the valve assembly (230) via an input interface (245), the tube assembly (240) comprising a delivery output in the form of a catheter (250; 350) configured to be inserted into a blood vessel (100) of the patient, the method comprising:

controlling the valve assembly (230) by generating a temporal sequence in the at least one first control signal (C_{V1}; C_{V2}; C_V) such that a composite arrangement of the first and second fluids (F1; F2) is formed in the blood vessel (100), which composite arrangement comprises a bolus (110) of the liquid contrast medium adjoining one or more of:

a bubble of the gas downstream (120) of the bolus (110),

a bubble of the gas upstream (130) of the bolus (110), and

a bubble of the gas (125) enclosed by the bolus (110).

8. A computer program (127) loadable into a non-volatile data carrier (126) communicatively connected to a processing unit (125), the computer program (127) comprising software for executing the method according any of the claims 9 to 16 when the computer program is run on the processing unit (125).

9. A non-volatile data carrier (126) containing the computer program (127) of the claim 8.

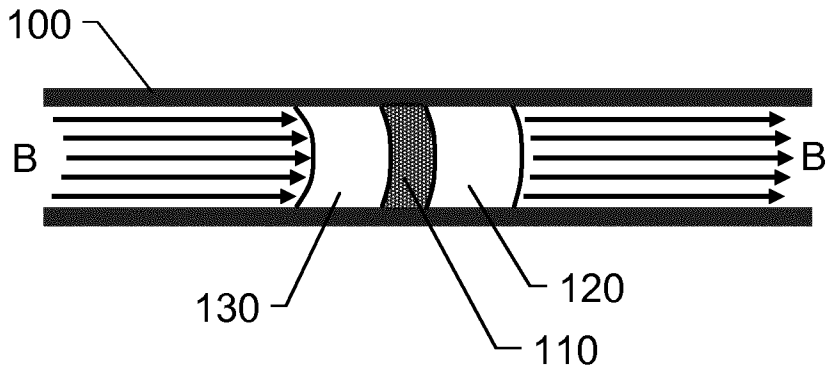

Fig. 1

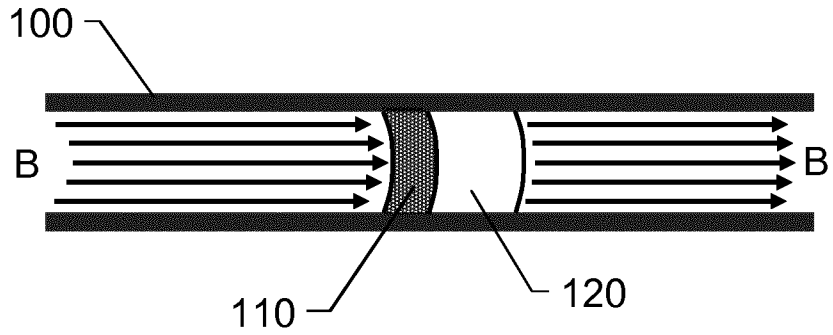

Fig. 2

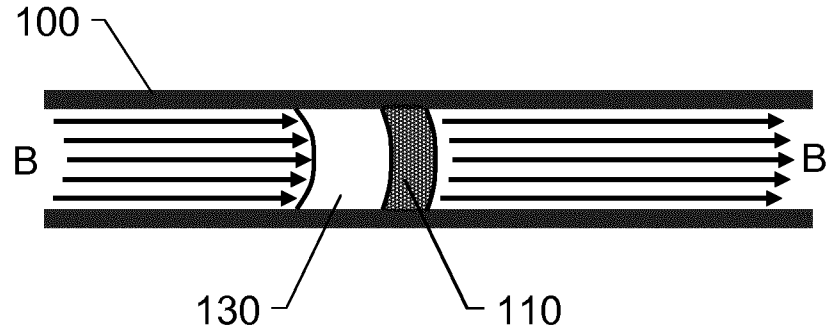

Fig. 3

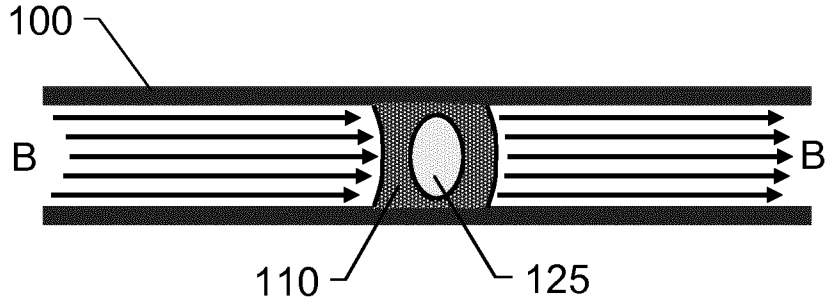

Fig. 4

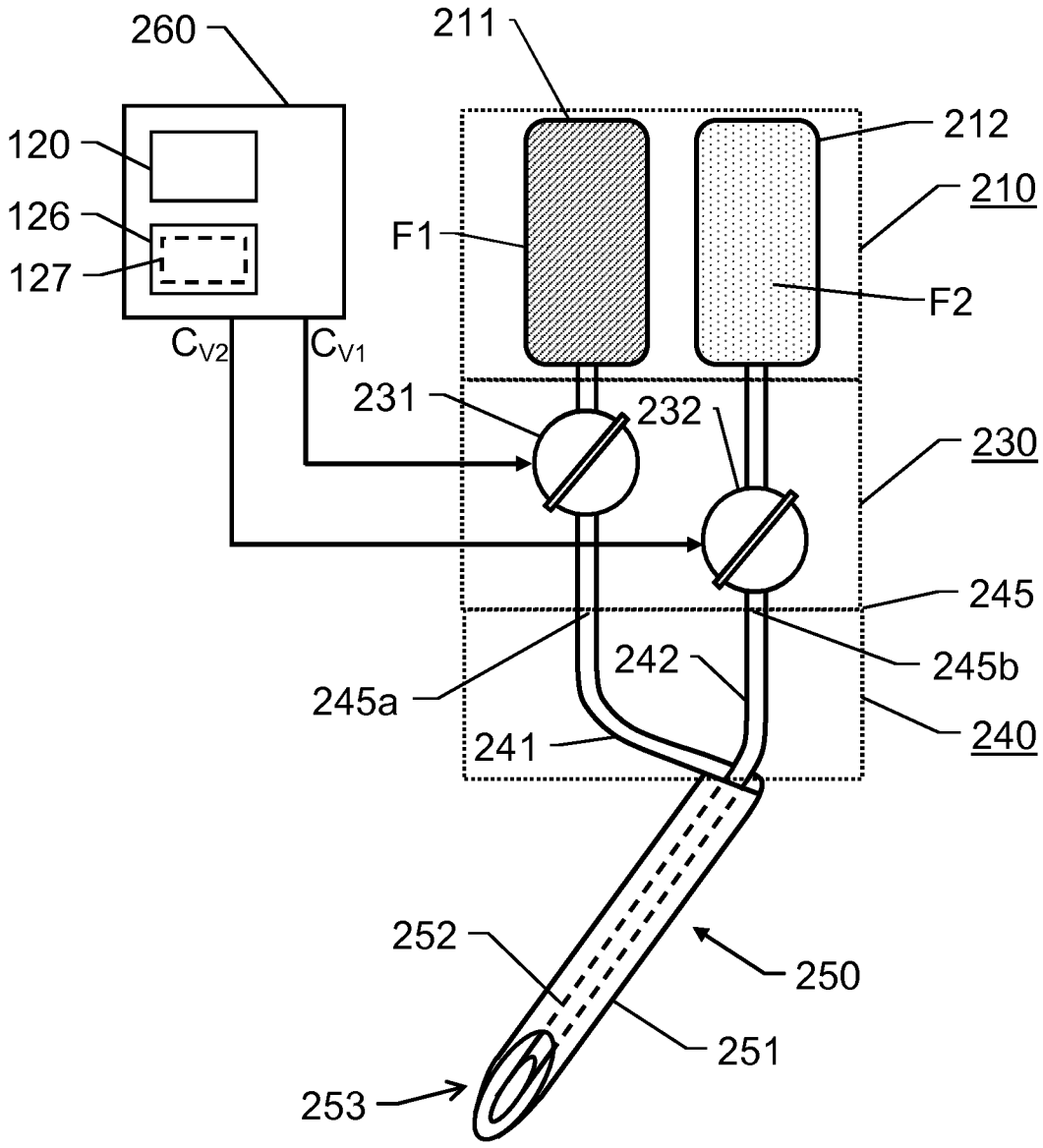
260
211
120
212
126
210
F1
127
F2
C_{V2}
C_{V1}
231
232
230
245
242
245b
245a
241
240
252
250
251
253

Fig. 5

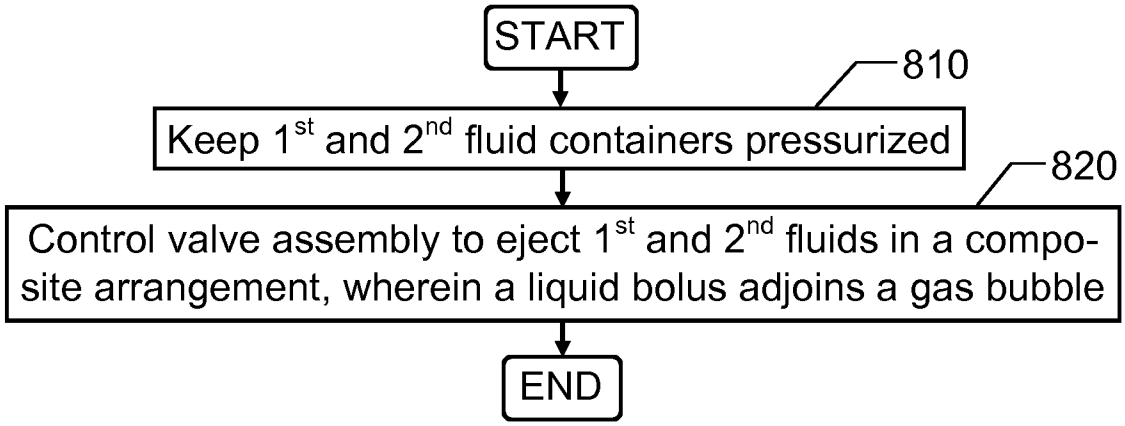
START
810
Keep 1st and 2nd fluid containers pressurized
820
Control valve assembly to eject 1st and 2nd fluids in a compo-site arrangement, wherein a liquid bolus adjoins a gas bubble
END

Fig. 8

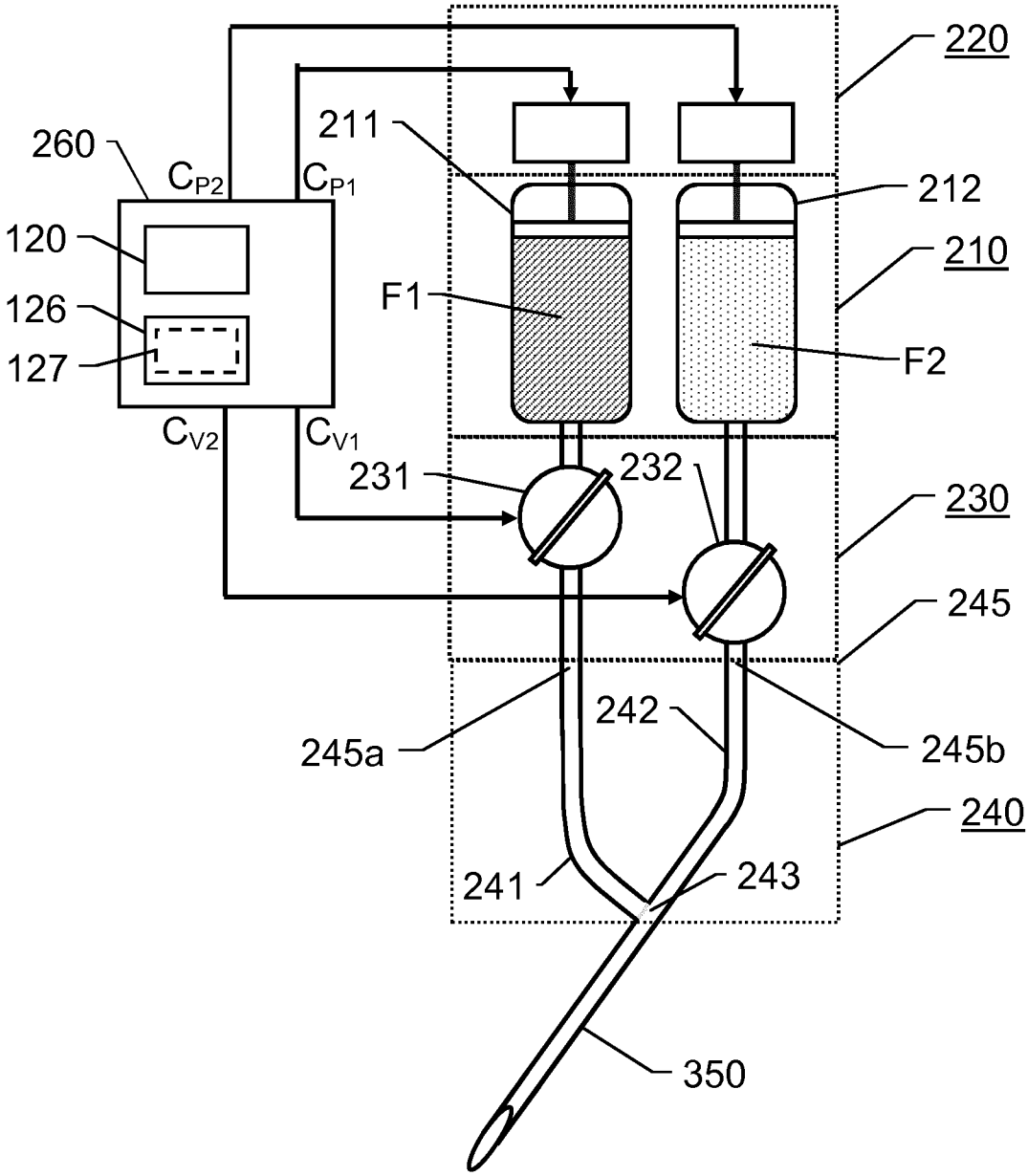
220
211
260
C_{P2}
C_{P1}
212
120
210
126
F1
127
F2
C_{V2}
C_{V1}
231
232
230
245
242
245a
245b
240
241
243
350

Fig. 6

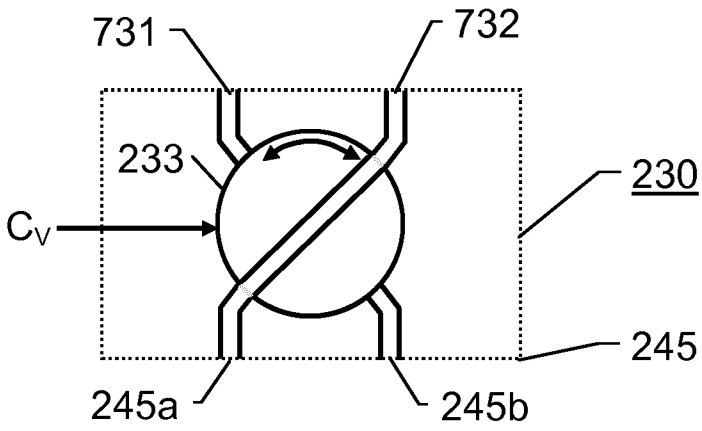
731
732
233
230
C_V
245
245a
245b

Fig. 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/058369

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61M5/00 A61M5/145 A61M5/168
ADD.

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)
A61M

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/253183 A1 (UBER ARTHUR E [US] ET AL) 16 December 2004 (2004-12-16) paragraphs [0056] - [0060] figure 2A	1-9
A	US 2014/046295 A1 (UBER III ARTHUR E [US] ET AL) 13 February 2014 (2014-02-13) paragraph [0067] figure 18	1-9
A	US 2013/211249 A1 (BARNETT BRADLEY POWERS [US] ET AL) 15 August 2013 (2013-08-15) paragraph [0192] figure 3	1-9

☐ 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
14 June 2019	01/07/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Walther, Manuel

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2019/058369

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2004253183 A1	16-12-2004	US 2004253183 A1	16-12-2004
		WO 2004069153 A2	19-08-2004
US 2014046295 A1	13-02-2014	CN 102119252 A	06-07-2011
		CN 104587552 A	06-05-2015
		EP 2315883 A1	04-05-2011
		HK 1210067 A1	15-04-2016
		JP 5726070 B2	27-05-2015
		JP 6325480 B2	16-05-2018
		JP 2011522623 A	04-08-2011
		JP 2015165893 A	24-09-2015
		US 2011209764 A1	01-09-2011
		US 2014046295 A1	13-02-2014
		WO 2009149367 A1	10-12-2009
US 2013211249 A1	15-08-2013	US 2013211249 A1	15-08-2013
		WO 2012012772 A2	26-01-2012