

FLUID DELIVERY APPARATUS

Field of Invention

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This invention relates to fluid delivery apparatus for use with a system for containing or conveying fluid.

Background to the Invention

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The invention is applicable to apparatuses having various, different purposes, including the supply of a fluid to, and/or extraction of fluid from, a system. Typically, the fluid(s) to be delivered and the fluid(s) contained or conveyed by this system are in their liquid form. The invention is particularly applicable to coronary catheterization apparatus which may be used, for example, in Fractional Flow Reserve (FFR) analysis of a coronary artery stenosis. If the apparatus is to be used for coronary catheterization, then the system is the patient, and the fluid is blood.

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The coronary catheterisation procedure can involve first, inserting a guide wire into the patient's peripheral arteries, for example (via an incision in the wrist or groin), followed by passing a guide catheter over the wire. This can ease the initial placement of the catheter, allowing it to be guided through the patient's arterial network to the coronary arteries of interest.

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The guide wire may subsequently be replaced by either: a pressure wire, which is a similarly elongate, flexible wire, but that contains a miniature pressure sensor located at, or near, its distal tip; or a pressure catheter, which may be a rapid exchange microcatheter with a miniature pressure sensor located at, or near, its distal tip as described for example in US 2010/0241008. This subsequently introduced device can be advanced through the structures of the heart to measure the actual local blood pressure at different locations, for example downstream of an arterial stenosis. This local pressure can be compared to an aortic blood pressure measurement obtained using a proximal pressure sensor connected in a flow line at a point proximal of the guide catheter. This proximal sensor is supported, for example on a drip stand; and to avoid systematic errors arising from a hydrostatic head of pressure, is positioned at the same elevation as the patient's heart.

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The signals from both sensors are normally displayed in real-time on a pressure analyser/display unit. In addition to providing the cardiologist with instantaneous display of the patient's status, the unit may also calculate the ratio of the two pressures, which is used in FFR as a measure of the severity of a coronary stenosis.

The proximal pressure sensor provides an effective means of measuring aortic pressure when there is no flow of liquid along the guide catheter, so that the prevailing conditions at the tip of the guide catheter (i.e. the distal end) are replicated at the proximal sensor. However, the guide catheter is also used to supply drugs (in liquid form), such as adenosine to stimulate maximal blood flow in the coronary artery under investigation, or a contrast agent for facilitating the imaging of the coronary artery using, for example, an x-ray imager.

When a contrast agent or drug is being injected along the catheter, the proximal pressure sensor measurement would no longer bear a simple relationship to the aortic pressure and the proximal sensor is therefore typically isolated, normally by means of a valve, from the catheter during this part of the procedure.

This interruption in monitoring of aortic blood pressure can be disadvantageous. For example, if a vasodilator drug such as adenosine is being introduced, while the proximal sensor is in effect disabled, the exact time of maximal blood flow (hyperemia) through the stenosis may occur when the pressure measurements for FFR are not being taken. As a result, the resultant data may have been obtained in less than ideal circumstances.

The generally accepted view is that if a drug were to be supplied down the guide catheter while measurements were being taken by the proximal pressure sensor, there would need to be an additional lumen, such as a microcatheter introduced either parallel to or over the pressure wire, so as to provide a passage for the drug to be injected, whilst leaving an outer passage (the annulus between the microcatheter and the interior of the guide catheter) along which the pressure is transmitted to the proximal sensor. It is also known to use a similar arrangement having a microcatheter and a guide catheter where it is desired to measure blood flow rate in individual vessels by the principle of thermodilution, in which case the microcatheter

can used to introduce a liquid such as saline at the point of interest. However, such approaches significantly increase the complexity of the apparatus.

Against this background, it would be desirable to provide an improved apparatus and
5 method for monitoring the pressure of fluid in a system to which a fluid delivery system, for either the supply or extraction of fluids, is connected.

Summary of the Invention

10 According to a first aspect of the invention, there is provided fluid delivery apparatus for use with a system for containing or conveying fluid, the apparatus comprising a fluid delivery conduit, a fluid flow path extending at least in part through the fluid delivery conduit and having a distal end for connection to the system, pressure
15 monitoring means for monitoring the pressure of fluid at a proximal end of the fluid flow path, and compensation means for compensating for, or reducing the effect of, a flow of fluid through the flow path on the output of the pressure monitoring means, thereby to determine a fluid pressure in the system.

In use, the pressure monitoring means is in fluid communication with the system at
20 the distal end of the flow path, through the fluid in the flow path. The compensation means allows the apparatus to determine and monitor the fluid pressure within the system even while the fluid is travelling or flowing along the flow path. The pressure change caused by said fluid flow does not therefore prevent the correct measurement of pressure in the system.

25 The apparatus could be used to extract fluid, for example a sample, from the system, along the flow path (i.e. fluid delivery from the system). Alternatively, fluid may be supplied to the system along the flow path (i.e. fluid delivery to the system). In either case the apparatus preferably includes fluid displacement means for supplying or
30 extracting fluid to the system through the delivery conduit, thereby to cause fluid flow in the flow path. The delivery conduit may have a distal end for connection to the system.

Fluid supply is the more common use of the apparatus, but wherever this document
35 makes references to fluid delivery and the associated physical effects, it will be

understood by the reader that this could equally be supply or extraction and the corresponding physical effects.

5 Preferably the compensation means is operable to quantify an effect of the flow of fluid through the flow path and to use said quantity to compensate for, or reduce said effect of, the flow of fluid in the flow path on the output of the pressure monitoring means. Thus, the compensation means may be operable to quantify a parameter associated with the flow of fluid in the flow path and to use said parameter to compensate for the effect of the fluid flow through the flow path on the output of the pressure monitoring means, thereby to determine a fluid pressure in the system.

10 The compensation means may quantify the effect or determine the parameter by means of direct measurement of the effect or parameter. Alternatively, the compensation means may determine the quantity or parameter indirectly, for example from data on the relationship between the effect or parameter and the operation of the fluid displacement means.

15 Preferably the compensation means generates an output whose magnitude is nominally equal to the change in the output of the pressure monitoring means caused by the flow of said fluid along the flow path. In such a way the former output can be summed with the latter output to compensate for, or reduce the effect of, said fluid flow.

20 The reader will appreciate that “summing” is a mathematical function and so does not necessarily imply that the two output quantities have the same sign. For example, where the flow of fluid in the flow path is towards the system (i.e. fluid supply to the system), this will cause an increase in the output of the pressure monitoring means and so, to achieve the correct compensation, the output generated by the compensation means will be ascribed a negative value. Thus when the two outputs are summed, the output of the pressure monitoring means returns to being representative of the pressure in the system. Preferably, the two outputs are electrical signals. When there is no fluid flow in the flow path between the pressure monitoring means and the system, no compensation is required.

30 The fluid displacement means can be any passive or active device or arrangement that is capable of supplying fluid to the system through the conduit and/or extracting

fluid from the system through the conduit. For example, the fluid displacement means may be a manually-operated or automatic syringe, a gravity-fed or pressurised bag or reservoir, and so on. The fluid displacement means may be an injection means. More than one fluid displacement means may be connected to the conduit, directly or
5 through one or more valves, in which case two or more of the fluid displacement means may be capable of operating simultaneously. Preferably, the fluid displacement means comprises a pump, such an infusion pump or an extraction pump, for pumping fluid along the flow path and thereby through the conduit.

10 The compensation means may be operable or arranged to derive said quantity or quantify said parameter by a process of derivation from control signals or power supplied to the fluid displacement means, for example when the fluid displacement means comprises an automatically-controlled pump. In such a case, the compensation means does not need to measure the effect of the flow of fluid through
15 the flow path.

Alternatively, the compensation means may include sensor means for measuring said effect or parameter of the flow of fluid through the flow path or a related effect for example in fluid upstream (in the case of fluid supply to the system), or downstream
20 (in the case of fluid extraction from the system), of the conduit or the flow path. Thus the compensation means may include sensor means for quantifying the parameter associated with the flow of fluid by means of measurement.

In this case, when a fluid displacement means in the form of a pump is provided,
25 variations in the performance of the pump will not produce errors in the quantification of said effect or parameter.

The sensor means may be integral to the pump or other fluid displacement means, when present. Preferably, the sensor means is separate from the fluid displacement
30 means. Thus the sensor means may be connected distally (i.e. downstream in the case of fluid supply to the system, or upstream in the case of fluid extraction from the system) of the fluid displacement means. The sensor means may be disposed between the fluid displacement means and a distal end of the delivery conduit. Optionally, the sensor means is connected between the fluid displacement means
35 and the delivery conduit.

In such cases, the output of the sensor means may be particularly suitable for analysis by the rest of the compensation means as the supply of fluid to the flow path by routes other than via the pump or other single fluid displacement means will be taken into account in the output of the sensor means. An example of an apparatus in which fluid from more than one source may be supplied to the flow path is coronary catheterization apparatus for use in fractional flow reserve analysis. Such apparatus may include a pressurised saline bag connected to the flow path (in this case a coronary catheter) in parallel with an infusion pump for supplying a drug, such as adenosine, along the flow path. In addition, this type of apparatus may include an arrangement of a reservoir, valve(s) and a syringe for injecting a contrast agent along the flow path.

The pressure monitoring means may therefore comprise a proximal pressure sensor situated at a position spaced from the distal end of the fluid delivery conduit or flow path.

The proximal pressure sensor may be in fluid connection with the proximal end of the fluid flow path. A sensing element of the proximal pressure sensor may be directly exposed to fluid at the proximal end of the fluid flow path. Alternatively, the proximal pressure sensor may comprise fluid connection means, such as a fluid-filled port, a connecting passage, or a length of tubing, for fluidic connection of a sensing element of the proximal pressure sensor to the proximal end of the fluid flow path. It will be appreciated that, if the fluid in the connection means is not flowing, the proximal pressure sensor will measure the pressure at the point at which the connection means opens into the fluid flow path (i.e. the proximal end of the fluid flow path).

The proximal pressure sensor may be so arranged relative to the conduit, that, in use, fluid to be supplied to the system, or extracted from the system along the conduit also flows through or past the proximal pressure sensor.

It will be apparent that the height of the proximal pressure sensor relative to that of the system is not dictated by the position of the fluid delivery conduit since it is not necessarily co-located with the latter. The height of the proximal pressure sensor can thus be selected to be such that there is substantially no head of hydrostatic pressure as between the system and proximal pressure sensor. In the case of coronary catheterization apparatus, this equates to the proximal pressure sensor being

situated at substantially the same height as the patient's heart. The sensor means for measuring said effect of the flow of fluid preferably comprises sensor means which is sensitive to said flow.

- 5 The sensor means may comprise one or more flow sensors for measuring a flow rate of fluid. For example, the sensor means may comprise a thermal flow sensor. In such an arrangement, the sensor may comprise a heated element and means for measuring the temperature of the element and for regulating the input power to the element, such that it can be maintained at a constant temperature. The heated
10 element, which is typically miniaturized, is cooled by fluid passing across it within the fluid delivery conduit, and the increase in power required to maintain the element at a constant temperature thereby provides a measure of the flow rate in the conduit. In another example, the flow sensor comprises an ultrasound Doppler flow sensor. In this arrangement, the Doppler sensor determines the rate of flow of fluid along the
15 delivery conduit by means of the Doppler effect. In a further example, the flow sensor comprises an impellor.

- Preferably, the sensor means comprises pressure sensor means for determining a pressure difference associated with the flow of fluid in the fluid flow path. The
20 pressure sensor means may be arranged to measure the change in pressure of the fluid over a distance. The sensor means may comprise pressure change sensor means for measuring the pressure change in a fluid flowing through a passage.

- By measuring a pressure difference or pressure change in the fluid flow path, the
25 apparatus is able to automatically take into account the effect of variations which could affect the relationship between flow rate and its effect on the output of the pressure monitoring means. Examples of such variations are variations in temperature and/or fluid viscosity.

- 30 Preferably, the pressure sensor means comprises a first sensor coupled, in use, to fluid in the apparatus at a first position, and a second sensor coupled, in use, to fluid in the apparatus at a second position, spaced from said first position. The first and second positions may be spaced apart at the ends of or along a passage, and fluid flowing from one to the other of the positions may flow along at least part of the
35 passage.

Thus the difference in simultaneous measurements from the two sensors will be indicative of the pressure change along the distance between the sensors, for example along the passage or a portion of the passage, and this can be used to calculate the pressure change along the flow path.

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The first sensor or the second sensor may be the proximal pressure sensor, when present. In such cases, the proximal pressure sensor may be disposed proximally with respect to the other sensor, so that the other sensor is coupled to fluid in the fluid flow path between the proximal pressure sensor and the system. Alternatively,
10 the proximal pressure sensor may be disposed distally with respect to the other sensor, so that the other sensor is coupled to fluid outside the fluid flow path between the proximal pressure sensor and the system. For example, the other sensor may be disposed between a fluid displacement means and the proximal pressure sensor, so that the two sensors measure the pressure change associated with fluid flowing into
15 the proximal end of the fluid flow path (in the case of supply to the system) or out of the proximal end of the flow path (in the case of extraction from the system).

In another example, the pressure sensor means comprises a differential pressure sensor. The differential pressure sensor is preferably such that, in use, the difference
20 in pressure at two locations is measured without reference to any other common reference pressure such as atmosphere pressure.

Such a sensor preferably has a common pressure sensitive element having a first face coupled, in use, to fluid in the apparatus at a first position, and a second face
25 coupled, in use, to fluid in the apparatus at a second position spaced from the first position. The first and second positions may be spaced apart at the ends of or along a passage, and fluid flowing from one to the other of the positions may flow along at least part of the passage.

30 Preferably, said pressure sensitive element comprises a flexible diaphragm. One face of the diaphragm may be exposed, in use, to fluid at said first position, and the other face may be exposed, in use, to fluid at said second position.

Since the differential pressure sensor measures pressure difference, its output would
35 be substantially unaffected by the actual pressure of fluid on either side (i.e. upstream or downstream) of the sensor. The differential sensor can thus be designed

to have a high sensitivity, because it does not need to have a dynamic range large enough to match the range of actual pressures that might occur. In addition, errors arising from variations over time in sensitivities of separate sensors are avoided if a single differential pressure sensor is used.

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The passage disposed between the first and second positions may be of constant cross section. In the case of coronary catheterization apparatus, the passage may, for example, be constituted by an additional length or portion of catheter which mimics the pressure drop of fluid flowing along the coronary catheter.

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Preferably, however, the passage comprises a restriction disposed between the first and second positions. This restriction increases the pressure drop between the sensors for a given fluid flow rate and enables the pressure change sensor means to use a shorter passage than a constant cross-section flow path and thus to be of a relatively compact construction. Preferably, the restriction profile is such that the passage progressively tapers and then widens. Preferably, this is achieved by means of a restriction in the form of a Venturi. This facilitates laminar, non-turbulent flow so that the pressure change across the passage may be linearly related to the pressure change along the flow path, since ordinarily the flow therethrough will also be the laminar, non-turbulent flow. Preferably, said first position is upstream, of the restriction and said second position is downstream of the restriction, if the apparatus is being used to inject fluid into the system.

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In another arrangement, the apparatus further comprises an elongate insert for insertion into the fluid delivery conduit, and the insert comprises the sensor means, such as the pressure sensor means. The insert may be flexible, and may comprise a pressure wire, pressure catheter or guide wire. The sensor means is preferably disposed at least 100 mm from a distal end of the insert. In this way, the sensor means can remain within the fluid delivery conduit even when the distal end of the insert extends out of the distal end of the conduit, for example during a coronary catheterisation procedure. For example, the sensing means may be disposed at least 300 mm from the distal end of the insert.

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When the insert comprises first and second sensors, or a pressure sensitive element with first and second faces, that are coupled in use to the fluid at first and second positions, in use, the first and second positions may be spaced apart along the insert

by a distance of between 10 mm and 1000 mm, and more preferably by a distance of between 300 mm and 500 mm.

5 A tip pressure sensor may be located adjacent a distal end of the insert. The tip pressure sensor and the pressure sensor means may share common voltage supply conductors.

10 In a further arrangement, at least one pressure sensor of the pressure sensor means is situated in a bifurcated fitting for attachment to the proximal end of a fluid delivery conduit constituted by a guide catheter of the apparatus. The apparatus may comprise a device entry port for admitting a device to the system by way of the delivery conduit, and the sensor means may be located between the delivery conduit and the device entry port, such that the parameter associated with the flow of fluid is affected by any devices introduced to the system via the device entry gland and
15 delivery conduit.

Preferably, the compensation means further comprises analogue circuitry for combining the outputs of the proximal sensor and a pressure sensor, other than the proximal sensor, of the compensation means to give an output representative of fluid
20 pressure in the system. Preferably, the circuitry comprises a bridge circuit. Preferably, the bridge circuit comprises a Wheatstone bridge, or modified Wheatstone bridge circuit.

A bridge circuit is particularly suitable for coronary catheterization apparatus, since
25 the individual detecting elements of a proximal pressure sensor of a conventional arrangement of such apparatus are typically connected in the form of a Wheatstone bridge. Thus the use of a bridge circuit provides an output which provides the desired compensated pressure measurement, but which closely resembles existing apparatus and is thereby directly compatible with the instrumentation means to which
30 these are typically connected.

Preferably, the proximal pressure sensor includes piezo-resistive elements, each connected between a respective pair of junctions of the bridge. Additionally, a sensor of the pressure change sensor means, other than said proximal sensor, preferably
35 also has piezo-resistive elements, each connected between a respective pair of junctions of the bridge.

The sensor which is not the proximal sensor may be the second pressure sensor of the pressure change sensor means, if the pressure change sensor means is such that it includes the proximal and second pressure sensors. If the pressure change
5 sensor means has a differential pressure sensor, this may constitute the sensor which also has piezo-resistive elements connected to the bridge as described above.

Where the pressure change sensor means comprises said proximal pressure sensor and second pressure sensor, those two sensors preferably have differing sensitivities
10 such that, provided there is no change in system pressure, the voltage outputs of the two sensors are identical at any given rate of flow of fluid through the passage. With this arrangement, the pressure in the system is the only variable affecting the combined output of the sensors.

15 It will be appreciated that although the voltages are identical, they represent different pressures, by virtue of the difference in sensitivity.

If the sensors have a linear response, a simple summation or subtraction of the sensor outputs can produce a resultant output the only variable affecting which is the
20 pressure in the system (i.e. the pressure to be monitored).

Where the pressure change sensor means comprises a differential pressure sensor, the sensitivities of that sensor and the proximal pressure sensor and the relationship between the flow rate of fluid through the passage with the measured pressure
25 difference may be such that the pressure in the system may be the only variable affecting the combined output of the sensors.

Preferably, the apparatus is for use with a system for containing or conveying fluid when in its liquid state, the flow path functioning as a liquid flow path, the fluid
30 pressure to be monitored to being the pressure of liquid in the system.

Preferably, the apparatus comprises coronary or cardiac catheterization apparatus, for the delivery or extraction of blood, drugs or other liquids to or from the vascular systems of or around the human heart. Preferably the apparatus is for use in an FFR
35 procedure.

The apparatus may comprise a pressure analyser/display unit for displaying the pressure of fluid in the system. The compensation means may be at least partially contained within a casework enclosure of the analyser/display unit. Alternatively, the compensation means is external to the analyser/display unit.

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In a second aspect of the invention, there is provided a compensation means for use with fluid delivery apparatus in accordance with the first aspect of the invention. The compensation means is arranged to compensate for, or reduce the effect of, the flow of fluid through the flow path of the apparatus on the output of the pressure monitoring means of the apparatus. Thus, the compensation means may comprise sensor means for measuring a parameter associated with the fluid flow through the flow path.

The compensation means may be as described above with reference to the first aspect of the invention. In one example, the compensation means comprises an insert for insertion into the fluid delivery conduit of the apparatus, and the insert comprises the sensor means. In another example, the compensation means comprises a housing connectable in series with the fluid delivery conduit, and the sensor means is disposed in the housing. In this case, the housing may comprise a proximal end fitting, such as a bifurcated fitting, for the fluid delivery conduit. Alternatively, the housing may be connectable to a connecting tubing proximal of the fluid delivery conduit of the apparatus.

The compensation means may comprise a processor arranged to apply a compensation to the output of the pressure monitoring means.

In a third aspect, the present invention extends to a method of determining the pressure in a system by means of a proximal pressure sensor in fluid communication with the system via a fluid flow path including a fluid delivery conduit, the method comprising determining the pressure drop due to a flow of fluid along said fluid flow path, and using the determined pressure drop to compensate an output of the proximal pressure sensor for the effect of the flow of fluid in the fluid flow path.

The pressure drop may be determined by measurement. For example, the method may comprise measuring a pressure difference due to the flow of fluid, and determining the pressure drop in the fluid flow path using the measured pressure

difference. The pressure difference may be measured in any convenient way, for example by using first and second sensors or a differential pressure sensor. The measurement may be made with an insert device disposed within the fluid delivery conduit, by using the proximal pressure sensor and an additional pressure sensor, or
5 by using a dedicated pair of pressure sensors.

In a fourth aspect, the invention resides in a method for compensating for the effect of fluid flow in a delivery conduit on a measurement of fluid pressure in a system for conveying or containing fluid, wherein the system is fluidly connected to a distal end
10 of the fluid delivery conduit and wherein the measurement of fluid pressure is taken at a position proximal to the fluid delivery conduit. The method comprises determining at least one parameter associated with the fluid flow, determining a pressure drop compensation value from the at least one parameter associated with the fluid flow, and applying the pressure drop compensation value to the
15 measurement of fluid pressure.

The at least one parameter associated with the fluid flow may be determined by measurement using at least one sensor. The method may comprise measuring a pressure difference associated with the fluid flow, and determining the pressure drop
20 compensation value from the measured pressure difference. The method may for example comprise measuring the pressure difference using at least one sensor disposed within the delivery conduit, or measuring the pressure difference at a location proximal to the delivery conduit.

25 In a fifth aspect, the invention provides a method for simultaneous determination of blood pressure at a site in a patient and delivery or extraction of fluid at the site, the method comprising guiding a distal end of a catheter to the site, the catheter having a lumen for fluid flow during delivery or extraction of fluid, applying a fluid flow through the lumen for delivery or extraction of fluid, determining at least one parameter
30 associated with the fluid flow, measuring the pressure of fluid at a proximal position with respect to the catheter, determining a pressure drop compensation value from the at least one parameter associated with the fluid flow, and applying the pressure drop compensation value to the measurement of fluid pressure to determine the blood pressure at the site. The method may comprise measuring the at least one
35 parameter associated with the fluid flow. In one example, the method comprises

inserting an insert in the lumen, and the insert may comprise sensing means for measuring the at least one parameter associated with the fluid flow within the lumen.

5 The invention also extends, in a sixth aspect, to apparatus for use in the simultaneous determination of blood pressure at a site in a patient and delivery or extraction of fluid at the site, comprising a catheter having a lumen for fluid flow during delivery or extraction of fluid, sensing means for measuring at least one parameter associated with the fluid flow, pressure sensing means for measuring the pressure of fluid at a proximal position with respect to the catheter when a distal end
10 of the catheter is positioned at the site, in use, and compensation means for determining a pressure drop compensation value from the at least one measured parameter associated with the fluid flow, and for applying the pressure drop compensation value to the measurement of fluid pressure to obtain a measurement of blood pressure at the site. The apparatus may further comprise an insert for
15 insertion in the lumen, and the insert may comprise the sensing means for measuring the at least one parameter associated with the fluid flow within the lumen.

According to a seventh aspect of the invention, there is provided a device for use with a fluid delivery apparatus, the fluid delivery apparatus comprising a fluid delivery
20 conduit, a fluid flow path extending at least in part through the fluid delivery conduit and having a distal end for connection with a system for conveying or containing fluid, a proximal pressure sensor for measuring a fluid pressure at a proximal end of the fluid flow path, and compensation means for determining a fluid pressure in the system based on an output of the proximal pressure sensor and a pressure drop
25 along the fluid flow path. The device comprises an elongate insert for insertion into the fluid delivery conduit. The insert comprises sensing means arranged to provide an output for use in determining the pressure drop along the fluid flow path. The fluid delivery apparatus may be in accordance with the first aspect of the invention and the insert may be as described above with reference to the first aspect.

30 With this device, the pressure in the system can be derived from the output of the proximal pressure sensor even when fluid is flowing along the fluid delivery conduit. Furthermore, because the sensing means is disposed on an insert that, in use, is positioned within the fluid delivery conduit, the sensing means can, if appropriate,
35 respond accurately to changes in fluid behavior in the conduit, such as changes in temperature or viscosity.

The insert may be flexible. Preferably, the device comprises a wire, preferably a pressure wire or guide wire, or a pressure catheter. The device may be particularly suitable for use in catheterisation apparatus, for example coronary or cardiac catheterisation apparatus. To this end, the fluid delivery apparatus may comprise catheterisation apparatus and the fluid delivery conduit may comprise a guide catheter, and the insert may be arranged to extend through the guide catheter in use. Fluids may be passed through the guide catheter when a suitable flow line is connected to its proximal end.

The sensing means may comprise one or more sensors. The sensing means may thus comprise a plurality of sensors.

The sensing means may comprise one or more flow sensors, as described above with reference to the first aspect of the invention. The resulting flow rate information can be used, together with knowledge of the effective internal diameter of the fluid delivery conduit and the flow conditions within the same, to determine the pressure drop along the length of the fluid delivery conduit. The effective internal diameter takes into account the effect of any other devices that may be inserted through the fluid delivery conduit alongside the insert. The flow conditions could comprise either laminar or turbulent flow conditions, a transition between the two, or combination of the two.

The sensing means may comprise one or more pressure sensors. In one example, in which the device is used with catheterisation apparatus of the kind having a proximal pressure sensor, the output(s) of the pressure sensor(s) (disposed inside the catheter in use) and the proximal pressure sensor may be analysed to yield information which is indicative of the pressure drop along the catheter and the associated flow path and which can be used to compensate for the effect of the pressure drop on the output of the proximal sensor.

Preferably, the sensing means comprises two or more pressure sensors situated at spaced apart positions along the insert. Thus pressure differences can be measured between the corresponding two or more locations along the insert, providing information from which the pressure drop along the length of the flow path can be determined. It will also be apparent that, if the flow path is of constant internal

diameter, knowledge of the internal diameter of the conduit, and of any other devices deployed in it alongside the insert, is not necessarily required to determine the pressure drop. Likewise, knowledge of the physical properties of the fluid in the conduit, such as its viscosity, is also unnecessary. Furthermore, by using multiple
5 sensors disposed in the conduit, in use, the measured pressure drop is not affected by changes in the position of the insert with respect to the conduit in use.

In long conduits with relatively slow moving fluids of moderate viscosity, the prevailing flow conditions are invariably fully developed laminar, and so the pressure
10 drop along the length of the delivery conduit is linear with respect to distance along the flow path. Preferably, therefore, the sensing means comprises two pressure sensor elements.

Accordingly, the sensing means may comprise first and second pressure sensors
15 arranged to measure the pressure of fluid in the fluid delivery conduit at first and second positions respectively, wherein the first and second positions are spaced apart along the insert.

In another embodiment, the sensing means comprises a differential pressure sensor.
20 The differential pressure sensor may comprise a common pressure sensitive element having first and second faces arranged to couple, in use, to the fluid in the fluid delivery conduit at first and second positions respectively, wherein the first and second positions are spaced apart along the insert. The first and second faces may be arranged to couple to the fluid in the fluid delivery conduit at the first and second
25 positions respectively by way of a coupling medium. The coupling medium may comprise fluid from the fluid delivery conduit and/or air. In another example, the coupling medium comprises a medium that is immobilised and yet can transmit pressure fluctuations, such as a gel.

In this and other aspects of the invention, the or each pressure sensor may employ
30 optical interferometry. For instance, established techniques such as Fabry-Pérot or low coherence interferometry may be used, such as that described in US Patent Application Publication No. US 2006/061768. In this case, the connection between the sensing element of the respective pressure sensor and the instrumentation
35 connected to the proximal end of the device is by means of an optical fibre.

The or each pressure sensor may comprise a piezo-resistive element. For example, the pressure sensors may include pressure sensor element(s) comprising silicon based piezo-resistive transducers of identical design. When two or more pressure sensors of this type are provided, the piezo-resistive elements may be connected
5 together in a Wheatstone bridge configuration. In this case, the pressure sensor element may together form a circuit with four interconnections.

Preferably, the insert comprises an outer sheath for housing the sensing means. The sheath may include opening means through which, in use, the sensing means are
10 coupled to fluid in the fluid delivery conduit. When the sensing means comprises a plurality of sensors, the opening means preferably comprises a respective aperture for each of the pressure sensors. When the sensing means comprises a differential pressure sensor having first and second faces, a respective aperture associated with each face may be provided.

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The device may further comprise a tip pressure sensor located adjacent a distal end of the insert. When the sensing means comprises one or more pressure sensors, the tip pressure sensor and the or each pressure sensor of the sensing means may share common voltage supply conductors. In embodiments in which the sensing
20 means comprises one or more pressure sensors, each of these elements of the sensing means constitutes a respective additional pressure sensor. Preferably, the tip pressure sensor operates using the same principles and shares common supply voltage conductors with the additional pressure sensors. In the case where two additional pressure sensors are provided, the pressure sensors of the sensing means
25 and the tip pressure sensor may together form a circuit with five interconnections.

Preferably, the device is a pressure wire or pressure catheter in which the tip pressure sensor is used for measuring pressure in the system. In one embodiment, for example, the device may comprise an elongate flexible insert with a pressure
30 sensor at or near its distal tip which, in use, can extend through and beyond the distal end of the fluid delivery conduit connected to the system, to enable the sensor to be exposed to fluid in the region of the system beyond said distal end of the conduit. The sensing means is preferably situated at a region of the insert proximal to the tip pressure sensor. Preferably the device is part of apparatus having a fluid delivery
35 conduit which is a coronary or cardiac catheter.

The compensation means may comprise a processor, such as a digital processor. The compensation means may instead comprise an analogue processor or analogue circuit. The compensation means may optionally be implemented as a dedicated device or in a suitably-programmed general purpose computer.

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The device of the seventh aspect of the invention may be used with other types of catheter, for example diagnostic catheters or microcatheters for purposes such as blood flow rate measurement by means of thermodilution such as is described in US Patent Application Publication No. US 2007/0078352.

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In a further aspect, the present invention resides in a combination of a device according to the seventh aspect of the invention, and a fluid delivery apparatus comprising a fluid delivery conduit, a fluid flow path extending at least in part through the fluid delivery conduit and having a distal end for connection with a system for conveying or containing fluid, a proximal pressure sensor for measuring a fluid pressure at a proximal end of the fluid flow path, compensation means for determining a fluid pressure in the system based on an output of the proximal pressure sensor and a pressure drop along the fluid flow path determined from the output of the sensing means.

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In another aspect, the invention resides in catheterisation apparatus for use in the field of cardiology having a catheter which acts as a fluid delivery conduit and a device according to the seventh aspect of the invention, the sensing means of the device being operable to determine a pressure drop caused by the flow of fluid along a flow path at least part of which is through the catheter, or to provide an output for use in compensating for an effect of said drop on a measurement of fluid pressure in the system which measurement is taken at a position proximal of the catheter.

30

In a still further aspect of the invention, a kit of parts is provided, comprising a fluid delivery conduit having a distal end for connection with a system for conveying or containing fluid, a proximal pressure sensor for fluid connection to the system by way of the fluid delivery conduit, and compensation means for determining a fluid pressure in the system based on an output of the proximal pressure sensor and a pressure drop along a fluid flow path. The kit may include a device according to the seventh aspect of the invention, or sensor means for use in determining the pressure drop along the fluid flow path.

35

As previously described, the devices, apparatus, combinations and methods of the invention may be suitable for use in cardiac catheterisation procedures, including, but not limited to, angioplasty. Aspects of the invention may be suitable for use in FFR procedures. Aspects of the invention are particularly suitable for use in a method of determining blood pressure and/or blood flow in a coronary artery.

Preferred and/or optional features of each aspect of the invention may be used, alone or in combination, with the other features of the invention also.

Brief Description of the Drawings

The invention will now be described, by way of example only, with reference to the accompanying drawings in which:

Figure 1 is a diagrammatic view of known coronary catheterization apparatus;

Figure 2 shows the apparatus in situ in a cardiology lab, and connected to a pressure analyser and display;

Figure 3 shows the circuitry of a pressure sensor of the known apparatus;

Figure 4 is a diagrammatic view of a first embodiment of fluid delivery apparatus in accordance with the invention; the apparatus taking the form of coronary catheterization apparatus;

Figure 5 is a corresponding view of a second embodiment of coronary catheterization apparatus in accordance with the invention;

Figures 6 and 7 are respective sectional side and exploded isometric views of a modified arrangement of pressure sensors for the apparatus shown in Figure 5, the Figure 7 view omitting a printed circuit board;

Figure 7A is a partially exploded view of the arrangement of Figures 6 and 7, including the circuit board;

Figure 8 schematically illustrates the pressure sensors of Figures 6 and 7 and Figures 11-13;

Figure 9 shows the circuitry for the pressure sensors of Figures 6-8 and 11-13;

5

Figure 10 illustrates the sensitivities of the pressure sensors of Figures 6-9 and Figures 11-13;

10 Figures 11-13 are respective isometric, sectional and exploded isometric views of an alternative arrangement of pressure sensors to that shown in Figures 6 and 7, the sensors of Figures 11-13 being incorporated into a bifurcated housing that constitutes a fitting to be connected directly to a guide catheter, and the circuit board of the arrangement being omitted from Figures 11 and 13;

15 Figure 13A is a partially exploded view of the arrangement of Figures 11-13, including the circuit board;

Figure 14 is a schematic view of the arrangement shown in Figures 11-13 when connected to a guide catheter;

20

Figures 15-17 are respective isometric, exploded isometric and side sectional views of a differential pressure sensor for use in a further embodiment of coronary catheterization apparatus in accordance with the invention;

25 Figure 18 is a schematic view of the sensor of Figures 15-17 in combination with a separate proximal sensor;

Figure 19 shows the sensor circuitry for the differential pressure sensor in combination with a separate proximal sensor;

30

Figures 20-22 are respective isometric, exploded isometric and sectional side views of an alternative type of differential pressure sensor, forming part of a further embodiment of apparatus in accordance with the invention, the differential pressure sensor in this case being incorporated into a bifurcated housing constituting a fitting
35 for direct connection a guide catheter;

Figure 23 is a schematic diagram of an alternative type of fitting which contains both the differential pressure and proximal pressure sensors;

5 Figure 24 shows a further embodiment of coronary catheterization apparatus, when in use, the apparatus having pressure change sensor means comprising the arrangements shown in Figures 6-8 or 15-17, with a separate proximal pressure sensor;

10 Figure 25 is similar to Figure 24, but shows an arrangement in which the pressure change sensor means is housed within a bifurcated fitting, such as either of the fittings shown in Figures 11-13 or 20-22, along with a separate proximal pressure sensor;

15 Figure 26 shows alternative circuitry for a pressure change sensor means which includes the proximal pressure sensor, the circuitry showing two pressure sensors each connected as a respective Wheatstone bridge;

20 Figure 27 shows analogue processing circuitry for combining the outputs of the circuitry shown in Figure 26;

Figure 28 is a diagrammatic view of a known pressure wire device;

25 Figure 29 is a diagrammatic representation of the miniaturised pressure sensors frequently used in known pressure wires;

Figure 30 illustrates the circuit within which the two sensing elements on the miniaturised pressure sensor are connected;

30 Figure 31 is a diagrammatic view of an insert device for use in the invention;

Figure 32 is an electrical wiring schematic diagram of the sensors in the device of Figure 31; and

35 Figure 33 shows the device of Figure 31 in use with coronary catheterisation equipment together with compensation means.

Detailed Description

The apparatus shown in Figure 1 comprises a guide catheter 1 in the form of a tube, typically of a diameter of about 2mm, having a distal, open end 2. The opposite end of the catheter 1, i.e. the proximal end, is connected to a bifurcated hub or fitting 4.

The end of the fitting 4, referenced 6, has a device entry gland (not shown) through which a pressure wire 8 or other devices can be passed into the catheter 1. The wire 8 extends through the lumen of the catheter 1 and has a tip 10 which can be extended, by a controlled distance, beyond the distal end 2 of the catheter 1. The tip of the wire 8 contains a miniature pressure sensor which can be advanced through the structures of the heart to measure the actual local blood pressure at different locations, for example downstream of an arterial stenosis.

The bifurcated fitting 4 includes a liquid inlet branch 12 which is itself connected to a tee-shaped housing 14 that has main and auxiliary inlet ports 16 and 18 and which contains a three-way valve controlled by a rotary manual control 20 to enable liquid to be injected into the catheter 1 through a selected one of either of the two ports 18 and 16, whilst the port which has not been selected is, in effect, isolated.

A length of tubing 22 connects the inlet port 16 to a two-valve manifold 24 which contains two three-way valves, each controlled by a respective one of two rotary controls 26 and 28 selectively to connect the inlet 16 to the contents of a pressurised saline bag 30 (by way of a pinch valve 31) or a contrast agent syringe 34. In addition, the valve operated by the control 28 can connect the contrast agent syringe 34 to a contrast agent reservoir 32, so that contrast agent may be drawn from the reservoir 32 into the syringe 34 (while the valve controlled by the control 26 isolates the reservoir 32 and syringe 34 from the inlet 16). When the controls 26 and 28 are set so that the bag 30 is isolated from the inlet 16, whilst the syringe 34 is in liquid communication with that inlet, contrast agent can then be injected using the syringe 34 along the tube 22 and into the lumen of the catheter 1 via the tee-shaped housing 14 and fitting 4.

The bag 30 is connected to the manifold 24 via a tube 36 which carries an inline proximal pressure sensor 38. The proximal pressure sensor 38 is of the type having

a silicon diaphragm having four piezo-resistive strain gauges applied to it. Each strain gauge constitutes a respective one of four piezo-resistive elements 40-43 connected together as a Wheatstone bridge circuit as shown in Figure 3, in which reference numeral 45 denotes a power supply line, and in which reference signs (a) and (b) denote outputs for a voltage signal which is amplified by differential amplifier 46. The piezo resistors can be formed by micro-machining or etching of the silicon diaphragm.

One face of the diaphragm is exposed to atmospheric pressure, whilst the other is in contact with the liquid in the tube 36 so that the differential voltage (i.e. the voltage difference between outputs (a) and (b)) may be used as a direct measure of the applied pressure so that this voltage, ΔV , increases with increasing liquid pressure. It will be understood that

$$\Delta V = a - b \quad (0)$$

Figure 2 shows the apparatus when in use in a cath lab on a patient denoted by reference numeral 48 supported on a table 50.

The catheter 1 has been inserted into the patient so that the distal end 2 is, in effect, connected to the blood in a coronary artery under investigation. The pressure sensor 38 and saline bag 30 are supported on a drip stand 52, with the pressure sensor 38 situated at precisely the same elevation as the patient's heart. This positioning of the sensor 38 prevents measurable errors in the measured blood pressure of the patient as a consequence of the difference in hydrostatic pressure between the proximal sensor 38 and the sensor on the tip of the pressure wire 8. It will be appreciated that the valves in the manifold 24 and the tee-shaped housing 14 can be set so that the sensor 38 is coupled to the environment in the region of the distal end 2 of the catheter 1 via the liquid in the catheter 1 and in the tubing 22 and 36. Since liquids are substantially incompressible, the proximal pressure sensor 38 provides an effective means of measuring aortic pressure while there is no flow of liquid in the catheter 1, since the prevailing conditions at the distal end of the catheter 1 will then be replicated at the sensor 38. However, the sensor 38 will be isolated from the distal end 2 if the valves in the manifold 24 are set so that the contrast agent may be injected along the catheter 1 using the syringe 34. The valve in the tee-shaped

housing 14 will also isolate the sensor 38 when a vaso-dilator drug, such as adenosine is injected into the catheter 1 through the inlet 18.

5 The output of the pressure sensor 38 is connected to a pressure analyser and display 54 which is also connected to the further pressure sensor at the tip of the wire 8 so that the analyser and display 54 can simultaneously show the aortic pressure measured by the sensor 38 and also the pressure (on the other side of a stenosis) measured by the sensor at the tip of the wire 8. These are real time signals that display pulsatile blood pressure and include details of important clinical significance, 10 such as the artefact known as the “dichrotic notch” associated with the closure of the aortic heart valve.

Isolating the sensor 38 during the introduction of the liquid along the catheter 1 is consistent with conventional thinking which is that in those circumstances the sensor 15 38 is no longer able accurately to measure aortic pressure, by virtue of the effect of the flow of liquid in the apparatus.

However, it would be highly beneficial to be able to continue to use the proximal pressure sensor accurately to monitor aortic pressure when various procedures, 20 involving the flow of liquid along the catheter, are being performed. Potentially, the most important time to be monitoring a patient could be precisely when such a procedure is under way, for example when a drug or other liquid is being infused or injected.

25 In that connection, it has been realised that, even though there might be flow of liquid along the catheter 1, the oscillating pressure pulses in the blood vessel where the catheter tip is located (such as the aorta) will still be transmitted through the catheter. Those pressure signals will be superimposed onto the pressures associated with any flowing liquid, and hence can still be “communicated” to a proximal sensor.

30 The clarity of the superimposed pressure signal may deteriorate if pressures within the liquid in the catheter are chaotic, such as during turbulent flow. However, the delivery of most liquids through typical catheters is generally such that prevailing flow conditions are laminar. In this case, the pressure pulse signal can be preserved.

35

Figure 4 shows a fluid delivery apparatus according to an embodiment of the invention, in which the flow of fluid in the system on the output of the proximal pressure sensor can be compensated for, so that pressure measurements can continue even during infusion or injection of a drug or other liquid or during extraction of a sample. The apparatus shown in Figure 4 has many features in common with the apparatus of Figures 1-3, and corresponding components are indicated by the reference numerals of Figures 1-3 raised by 100.

In the apparatus shown in Figure 4, the three-way valve attached to the bifurcated fitting 104 has been replaced by an open tee-shaped housing 156 which is located proximal and upstream of the two-valve manifold 124, and which, in effect, provides two inlets for one of the ports of the manifold 124. More specifically, the tee-shaped housing 156 connects the saline bag 130 and pressure sensor 138 to the manifold 124 in parallel with an infusion pump 158 which is operable to inject a drug into a patient via the lumen of the catheter 101 (and the manifold 124 and connecting tubing 122).

The effect of the fluid flow between the tee-shaped housing 156 and the proximal end 102 of the guide catheter 101 on the output of the proximal pressure sensor 138 can be determined using a knowledge of the flow rate at which liquid is being pumped by the infusion pump 158. In this embodiment, the infusion pump 158 has no need for flow rate sensors for measuring the rate at which liquid is being pumped by the pump 158 since its operating mechanism delivers liquid at a pre-determined rate (for example, as programmed by an operator through a user-interface resulting in the mechanism driving the plunger of a syringe at a fixed linear speed). This flow rate information is fed to a signal compensating processor 160, which also receives a signal from the proximal pressure sensor 138. The processor 160 analyses the two input signals so as to compensate for the effect of the flow of liquid along the catheter 101 on the relationship between the pressure measured by the sensor 138 and the actual aortic pressure at the distal end 102. As with the known arrangement, the proximal pressure sensor 138 is positioned at the same elevation as the patient's heart.

An example of the type of analysis that may be conducted by the compensating processor 160 is as follows:

At the typical flow rates involved, the flow conditions in the flow path from the tee-shaped housing 156 where the drug is injected up to and including the guide catheter 101 are predominantly laminar, in which case the pressure drop along the flow path will be directly proportional to the flow rate, Q.

5

$$\text{i.e.} \quad \Delta P_{\text{flow path}} \propto Q \quad (1)$$

The convention adopted in this document is that Q is positive for liquid being delivered to the patient (c.f. liquid sampling from the patient) and hence positive $\Delta P_{\text{flow path}}$ denotes an elevated pressure at the proximal end of the flow path (i.e. at the proximal pressure sensor 138).

10

The pressure detected at the proximal pressure sensor 138 (P_{proximal}) will be equal to the sum of the actual aortic blood pressure (BP) plus the flow path pressure drop.

15

$$\text{i.e.} \quad P_{\text{proximal}} = BP + \Delta P_{\text{flow path}} \quad (2)$$

Hence, in order to communicate the actual aortic pressure (BP) to the analyser/display, the processor 160 needs to generate an output signal, as follows:

20

$$BP = P_{\text{proximal}} - \Delta P_{\text{flow path}} \quad (3)$$

In order to derive $\Delta P_{\text{flow path}}$, the unit 160 needs to first read flow rate information from the pump 156, and then to convert this into a pressure-related signal, based on Equation (1) (which will have been empirically determined previously for the type of catheter and connecting tubing in use). Most modern infusion pumps are equipped with a serial data interface, such as RS232 or USB, and the unit 160 has a corresponding interface to input the necessary information. To perform the calculation of Equation (1), the unit 160 also has a processor to implement this as an algorithm. Many types of small processor could be used here, although the inventors have found a PIC microcontroller to be ideal for the purpose.

25

30

In this embodiment, the compensating unit 160 produces a voltage output, corresponding to the flowrate and with equivalent calibration as the sensor, and superimposes this onto the pressure signal from the sensor, ready to send to the

35

analyser/display 154. Since said pressure signal is the output from a Wheatstone bridge pressure sensor, it is of very small magnitude, and so the compensating signal is of similarly very small magnitude. The inventors have found that a suitable way to achieve this is to output a signal in the form of a pulse width modulated signal from the processor and to heavily attenuate this by means of an operational amplifier (so that the voltage level is compatible with the bridge output) and finally to add this to the bridge output by means of a summing amplifier.

The apparatus shown in Figure 5 is similar in many respects to that shown in Figure 4 and corresponding components are therefore denoted by the reference numerals used in Figure 4, raised by 100. In the embodiment shown in Figure 5, the apparatus obtains flow information by means of measurement.

In this case, the proximal pressure sensor 238 is interposed between the open tee-shaped housing 256 and the manifold 224 to which the proximal sensor 238 is connected in series with a further pressure sensor 262 the output of which is also connected to the signal compensating processor 260. In this case, the infusion pump 258 is connected to the tee-shaped housing 256 via a three-way valve in a further tee-shaped housing 264.

The proximal pressure sensor 238 and the further pressure sensor 262 are substantially identical to each other, and are connected by a short length of connecting tubing 266. The tubing 266 defines a passage through which liquid being injected into the system from the infusion pump 258, the pressurised saline bag 230, or other source (not shown) connected to the auxiliary input 265 on the tee-shaped housing 264 flows from the sensor 238 to the sensor 262. It will be appreciated that the sensors 238 and 262 and connecting tubing 266 comprise pressure change sensor means or pressure change monitoring means that can be used to monitor the drop of pressure caused by liquid flowing along the tubing 266, from which the corresponding drop of pressure caused by the liquid flowing in the flow path from the proximal pressure sensor 238 to the distal end of the catheter 201 can be inferred. The sensor 238 is coupled to fluid at a first position, whilst the sensor 262 is coupled to fluid at a second position, wherein fluid flowing from sensor 238 to sensor 262 flows along the passage 266.

In use, liquid flowing through the pressure sensors 238, 262 from either the saline bag, infusion pump or auxiliary input in the tee-shaped housing 264 will cause a pressure drop in the flow path extending from the proximal pressure sensor 238 to the distal end of the catheter 201, by way of the connecting tubing 266 between the pressure sensors 238, 262, the manifold 224, the connecting tubing 222 between the manifold 224, and the bifurcated fitting 204. The output of the pressure sensors 238, 262 allows the pressure drop over the length of the connecting tubing 266 to be measured directly. and which in turn allows the the pressure drop or flowrate along the flow path to be determined or inferred, allowing the effect of fluid flow to be corrected for by the compensating circuit 260.

Similarly, if blood is sampled from the patient, for example by way of an extraction device connected to the auxiliary input 265 of the tee-shaped housing 264, there is a pressure drop in the opposite direction, and correction can also be made for this.

As described above, to avoid hydrostatic pressure errors, the proximal pressure sensor 238 is preferably located at the same elevation as the patient's heart. This can be achieved by locating it away from the surgical table as shown in Figure 2.

The pressure drop $\Delta P_{\text{flow path}}$ along the flow path inferred from the pressure change monitoring means output (i.e. from the output of both pressure sensors 238, 262) can be subtracted from the measured pressure signal at the proximal pressure sensor P_{proximal} to give the corrected aortic blood pressure (BP).

Hence:
$$BP = P_{\text{proximal}} - \Delta P_{\text{flow path}} \quad (4)$$

In a modification of the Figure 5 apparatus the proximal pressure sensor can be a separate third pressure sensor, with the first and second pressure sensors providing a dedicated pressure change monitoring means. As in the known arrangement, the proximal pressure sensor can be positioned at the same elevation as the patient's heart, thereby avoiding any potential hydrostatic pressure errors that could otherwise be introduced. It will also be appreciated that the proximal pressure sensor can be located proximal, and upstream of the tee-shaped housing 256 in the limb connecting to the saline bag 230.

An advantage of measuring the pressure drop across the passage 266 is that this measurement would be affected by changes in temperature or viscosity in the same way as the pressure drop along the catheter and in the remainder of the flow path. Thus effectively, the pressure change sensor means mimics the catheter and so
 5 responds in a similar way to extraneous changes.

Despite the assumption made above, the relationship between $\Delta P_{\text{flow path}}$ and the pressure drop along the passage 266 is not necessarily linear, but will depend on the prevailing flow conditions in the two at any point in time. The catheter is a long
 10 regular conduit and under many circumstances the Reynolds number is relatively low, so it provides opportunity for steady laminar flow to develop. Under laminar flow conditions, the pressure drop as a function of flow rate is governed by the Hagen-Poiseuille equation

$$15 \qquad \qquad \qquad \Delta P \qquad = 8\mu LQ/\pi r^4 \qquad \qquad \qquad (5)$$

where μ , L , Q and r are the liquid viscosity, length (of catheter), volumetric flowrate and radius respectively. Note that this is a linear relationship between pressure drop and flowrate.

20

If the passage 266 is of constant internal cross section, then it might take the form of a long tube (mimicking the flow path itself) in order to achieve laminar flow conditions.

25 However, the passage 266 can include a flow restriction (not shown) across which most of the pressure drop will occur so that the pressure drop along the passage will, in effect, be substantially the same as that across the restriction ($\Delta P_{\text{restriction}}$). This enables a shorter passage to be used.

30 If the passage were to have a flow restriction comprising a simple orifice, the flow regime through would be unlikely to be laminar (unless the viscosity is very high or the flowrate very low), and under these (i.e. turbulent or transition) flow conditions, the relationship between pressure drop and flowrate might no longer be a simple linear one (under many turbulent conditions it will follow a square law).

35

Thus, the restriction is such that the flow conditions through it are laminar, then both $\Delta P_{\text{flow path}}$ and $\Delta P_{\text{restriction}}$ will be linear relationships with flowrate and hence with each other. To that end the restriction in example could be a Venturi.

5 In which case:
$$\Delta P_{\text{flow path}} = k. \Delta P_{\text{restriction}} \quad (6)$$

And hence, when the proximal pressure sensor is proximal and upstream of the passage (as shown in Figure 5):

10
$$\begin{aligned} BP &= P_{\text{proximal}} - k. \Delta P_{\text{restriction}} - \Delta P_{\text{restriction}} \\ &= P_{\text{proximal}} - (1 + k) \Delta P_{\text{restriction}} \end{aligned} \quad (7)$$

Or if the proximal sensor were situated distal and downstream of the passage:

15
$$BP = P_{\text{proximal}} - k. \Delta P_{\text{restriction}} \quad (8)$$

Figures 6-8 show an arrangement of sensors which can be used as a dedicated pressure change sensor means or as a combined proximal pressure sensor and pressure change sensor means to be used in the arrangement of Figure 5 in place of the sensors 238 and 262 and connecting tubing 266. The arrangement comprises a tubular housing 268 formed as a single injection moulding of a suitable plastics material such as polypropylene or polycarbonate.

25 The housing 268 is formed with standard luer end connectors 270, 272 for connection to tubing so that the housing can be situated in series with the tubing for connection to the catheter. The moulding is formed with first and second square pockets 276, 274 which are axially spaced along, and at the same angular position on, the housing 278. At the base of each of the pockets 276, 274 there is provided a central, square aperture leading to the hollow interior of the housing 268, and surrounded by a respective square shoulder that provides a support for the components of a respective pressure sensor.

35 The pressure sensor which is situated in the first pocket 276 comprises a lower elastomeric sealing gasket 278, produced in a material such as EPDM, which sits on

the square shoulder of the base of the shoulder 276 and supports an etched silicon diaphragm or membrane 280 which carries piezo-resistive elements, and which is sandwiched between the gasket 278 (which acts as a sealing gasket) and an electrically conductive upper gasket 282. The upper gasket 282 could also be
5 manufactured in a material such as EPDM, but with localised areas impregnated with electrically conducting particles so that it forms selective electrical connections between the connection points on the silicon membrane and the external connection (see below).

10 The second pressure sensor, situated in the second pocket 274, is constituted by a similar arrangement of an etched silicone diaphragm or membrane 284 sandwiched between a lower sealing gasket 286 (which itself sits on the square shoulder at the base of the pocket 274) and an upper electrically conductive gasket 288.

15 The two pressure sensors are held in place in the pockets 274, 276 by means of an overlying PCB 287 attached to the housing by means of thermally deformed (heat staked) pegs 289 so as to retain the sensors in place and maintain a sealing contact between the elastomeric gaskets 278, 286 and the housing 268 and between the gaskets 278, 286 and the membranes 280, 284. The PCB can support a series of
20 printed resistive elements which can be laser machined during production, if necessary, to match the sensors to each other and to achieve a combined output having suitable performance characteristics (discussed below). The lower face of each membrane 280, 284 is exposed, in use, to liquid flowing through the housing, each upper face being exposed to atmospheric pressure.

25

Referring to Figures 6, 8 and 9, the housing 268 includes a restriction constituted by a throat in a form of a Venturi 290 situated downstream (relative to the flow of liquid through the housing in use) of one of the pockets 276, 274 and upstream of the other of the pockets 276, 274. The restriction is thus interposed between the positions at
30 which the pressure sensors are coupled to fluid in the fluid passage by the housing 268. If liquid is being injected into the system, the Venturi 290 will be downstream of the first pocket 276 and upstream of the second pocket 274. Extraction of liquid would involve flow of liquid through the fitting in the reverse direction so that the Venturi would then be downstream of the second pocket 274 and upstream of the
35 first pocket 276.

In Figure 8, the pressure sensor contained in the first pocket 276 is denoted by reference numeral 292 whilst the pressure sensor contained in the second pocket 274 is denoted by reference numeral 294.

5 If the assembly shown in Figures 6-8 is used in the apparatus of Figure 5 as described above, then the housing 268 is connected in series between the open tee-shaped housing 256 and the two-valve manifold 224. Once they are connected, the sensor 294 in the second pocket 274 is the lower of the two sensors (i.e. closest to the manifold 224), but may be used as the proximal pressure sensor 238. In such a
10 case, the apparatus is to be set up so that the sensor 294 is at the same level as the patient's heart. With this arrangement, in use, the sensor 294 obtains a measurement of aortic blood pressure, whilst the combined output of the sensors 294 and 292 is used to compensate for the effect of the flow of liquid along the flow path from the proximal pressure sensor into the patient.

15

When the sensor 294 in the second pocket 274 is employed as the proximal pressure sensor 238, the sensors 292 and 294 may be connected in a split bridge configuration as shown in Figure 9 in which the piezo-resistive elements of the sensor 294 in the bridge are shown at 296 and 298 whilst 300 and 302 denote the
20 piezo-resistive elements of the first sensor 292 in the other half of the bridge.

Hence the two sides of a conventional Wheatstone bridge circuit have been split between the two sensors 292, 294.

25 The two sensors 292, 294 may be from the 2xPC family manufactured by Honeywell, each of which includes a membrane 280, 284 having four piezo-resistive elements. In this case, only two of the four piezo-resistive elements in those devices would be electrically connected. By comparing Figures 3 and 9 it will be apparent to the reader which of the two elements are connected in the two sensors. A custom manufactured
30 silicon device with just two piezo-resistive elements would provide a number of benefits, such as reduced cost and the freedom to configure the precise sensitivity of the two sensors and the dimensions of the flow restriction as a specifically designed sub-system.

In the following, the measured pressure at the sensor 294 in the second pocket 274 is referred to as P_1 and the measured pressure at the sensor 292 in the first pocket 276 is referred to as P_2 .

- 5 Now, initially suppose that there is zero blood pressure (relative to atmospheric pressure) and that the sensitivity of the two sensors 292, 294 and the dimensions of the restriction 290 are designed such that, at any flowrate, the voltage output of the two sensors are identical. This is illustrated in Figure 10, in which the line 304 shows the response of sensor 294, whilst line 306 shows the response of the sensor 292.

10

Note that, in this specific situation, $P_1 = \Delta P_{\text{flow path}}$ and $P_2 - P_1 = \Delta P_{\text{restriction}}$

The voltage output from the two sensors in the condition of fluid flow, but zero BP (blood pressure) is:

15

$$\begin{aligned} c &= LP_1 \\ \text{and} \quad d &= MP_2 \end{aligned}$$

20

Where L is the gradient of line 304, and M is that of line 306, L and M can be designed such that:

$$\begin{aligned} c &= d \\ \text{hence} \quad LP_1 &= MP_2 \end{aligned}$$

25

If now blood pressure (BP) is re-introduced at the tip of the catheter, then the voltage output (corresponding to Figure 3 and Equation (0)) is:

30

$$\begin{aligned} \Delta V &= c - d \\ &= L(P_1 + BP) - M(P_2 + BP) \\ &= LP_1 - MP_2 + BP(L - M) \\ &= BP(L - M) \end{aligned} \tag{9}$$

Or, expressed using the terminology of Equation (0), the voltage output from the sensor system is:

$$\Delta V = BP (L-M) \quad (10)$$

5 Notice that this is a function of variable BP alone and that L and M can be selected so that the signal magnitude is equal to that of existing proximal sensors. Hence this arrangement successfully removes the effect of any flowrate in the catheter and can be used as a “drop-in” replacement for a conventional proximal pressure sensor to display true BP on the patient monitor.

10

Figures 11-13 show a similar arrangement of pressure sensors and a restriction within a housing, but in this case, the housing is a bifurcated fitting for direct connection to the guide catheter.

15 The housing 308 has a standard, distal luer fitting 310 which, in use, is inserted into the catheter. The opposite end of the housing 308 is provided with a known type of device entry gland 312 providing a central port 314 into which a pressure wire or other devices may be inserted. The housing may, for example, be formed by injection moulding of a suitable plastics material, and is provided with a liquid supply branch
20 316 via which liquid may be introduced into the fitting for injection into the patient along the catheter.

The underside of the housing 308 is provided with square pockets 318, 320 which are similar in form and function to the square pockets to the fitting shown in Figures 6
25 and 7, and which thus accommodate two pressure sensors 322, 324 which are of the same type as the pressure sensors 292, 294 described above with reference to Figures 6 and 7 (and thus comprise etched silicone membranes each of which is sandwiched between an elastomeric sealing gasket and a conductive gasket). For the proximal sensor 324, closest to the entry gland 312, reference numerals 326, 328
30 and 330 respectively denote the sealing gasket, the membrane and the conductive gasket. The arrangement of gaskets and membrane for the distal sensor 322, closest to the luer fitting 310, is identical. It will be appreciated that, since the pockets are on the underside of the housing 308, the uppermost gasket of each sensor is the elastomeric sealing gasket whilst the conductive gasket that connects the sensor to a
35 PCB 309 is the lowermost gasket, although in practice the housing 308 could be used in any convenient orientation. The PCB 309 is directly comparable to the PCB

287 of the Figure 6-8 arrangement, and is attached to the housing by means of thermally deformed (heat staked) pegs 311.

As can be seen from Figure 12, the sensors 324, 322 are positioned one on either side of a throat in the form of a Venturi 332, so that the Venturi 332 is interposed between the sensors 324, 322.

It will be appreciated that, if in this case the distal sensor 322 is to be used as the proximal pressure sensor, then the fitting should be maintained at the same elevation as the patient's heart. Alternatively, the pressure sensors 322 and 324 in the housing 308, together with the Venturi 332, could be used solely as means for measuring the pressure change across the restriction (which, for laminar flow through the restriction, will bear a simple relationship to the pressure change resulting from fluid flowing along the flow path) and using this in conjunction with a pressure reading taken from a separate proximal pressure sensor. Such an arrangement is shown in Figure 25, in which components corresponding to those shown in Figure 5 are indicated by the reference numerals of Figure 5 raised by 200. The bifurcated fitting is referenced 500 and is shown connected to the catheter 401, whilst the proximal pressure sensor 438 is supported on a drip stand 502 at the same height as the heart of the patient 504.

The schematic view shown in Figure 14 illustrates a guide catheter with a bifurcated fitting that includes pressure change sensor means in the form two pressure sensors (P_1 and P_2 positioned one either side of a restriction. The fitting only differs from the fitting shown in Figures 12 and 13 in that the pressure sensors are on top of the housing rather than the underside).

Figures 15-17 show another example of a dedicated pressure sensing means in which a differential pressure sensor is provided. This type of pressure sensing means would be used in conjunction with a separate proximal pressure sensor as illustrated in, for example, Figure 24 which corresponds in many respects to Figure 25 and in which corresponding components are therefore indicated by the same reference numerals as are used in Figure 25. In this case, however, the bifurcated fitting 500 is a standard fitting which therefore lacks any pressure sensors. Instead, the arrangement shown in Figures 15-17 is installed at 506.

The inline pressure sensing means shown in Figure 15-17 is a differential pressure sensor having a three-part housing 508 having a female luer connector 510 into which liquid flows into housing 508, through a passage (described below) and then out through an outlet comprising a male luer connector 512 on the opposite side of the housing 508.

The connectors 522 and 510 are provided on respective end plates 514 and 516 between which are sandwiched a mid-plate 518. The three plates 514, 516, 518 are bonded together by means of a suitable adhesive such as UV curing epoxy. Referring to Figure 16, the end plate 514 includes on its inner face a channel 520 along which liquid can flow. The channel 520 is aligned with a corresponding channel 522 in the opposite end plate 516, as shown in Figure 17. These two channels 520, 522 are, at their upper ends, aligned with a bore 524 in the mid-plate 518. The channels 520 and 522 and the bore 524 thus, between them, define a serpentine route for liquid flowing through the housing 508. The housing 508 could be injection moulded, for example from material such as polypropylene or polycarbonate.

It will be appreciated that the bore 524 is of a smaller cross-sectional area than the channels 520 and 522 and therefore constitutes a restriction and in addition, the bore is flared at both ends so that laminar flow of liquid through the bore 524 is promoted.

The mid-plate 518 includes a square aperture 526 which accommodates a pressure sensor generally referenced 528 similar in construction to the pressure sensors shown in Figures 6 and 7 and 11-13 (for example the pressure sensor 324). The pressure sensor 528 thus has an elastomeric gasket 530 and an electrically conductive gasket 532 between which is sandwiched an etched silicone membrane or diaphragm 534. The conductive gasket 532 abuts a square, intumed flange at the edge of the aperture 526 closest the plate 516. The gasket 532 is in contact with electrically conductive pins 538 which connect piezo-resistive elements of the diaphragm 534 to analysing circuitry. In use, both faces of the diaphragm 534 are exposed to liquid flowing through the housing 508. In the case of liquid delivery to the system, the liquid in contact with the face of the diaphragm 534 that is open to the channel 522 is upstream of the bore 524, whilst the liquid in contact with the opposite face of the diaphragm 534, i.e. the face open to the opposite channel 520, is downstream of the bore 524. The diaphragm 534 will thus flex in response to changes in the pressure drop across the bore 524, but will not be substantially

affected by the absolute pressure of liquid in the housing 508. Thus, if no liquid is flowing, then the pressure sensor 528 should give a zero reading whatever the absolute pressure of liquid.

5 Since only pressure change is being monitored in this arrangement, this type of pressure change sensor means is used with a separate proximal pressure sensor, as is shown at 540 in Figure 18. The sensors 528 and 540 can be connected together in a split bridge configuration as shown in Figure 19 in which reference numerals 542 and 544 denote the piezo-resistive elements of the differential pressure sensor 528,
10 and reference numerals 546 and 548 denote the piezoresistive elements of the proximal pressure sensor 540.

Use of a dedicated differential flow sensor, for example of the type shown in Figures 15 to 19, has several benefits:

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- even if the absolute pressure in the flowline is high, the differential pressure will remain moderately low, so it can be designed as a much more sensitive device

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- since flow is measured by a single device, any variances (e.g. from manufacturing) between individual devices are eliminated

- the voltage output from the bridge circuit associated with the sensor is a direct indication of flowrate.

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Thus, if the flow conditions through the restricted passage or orifice are laminar, the relationship is simplified to the following:

$$BP = P_{\text{proximal}} - (1 + k) P_{\text{diff}} \quad (11)$$

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where P_{diff} is the pressure difference measured by the differential pressure sensor. If the differential and proximal pressure sensors have sensitivity R and S , respectively, and the outputs of the split bridge circuit are e and f respectively as shown in Figure 19, then:

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$$e = R P_{\text{diff}}$$

and

$$f = S (BP + \Delta P_{\text{flow path}} + P_{\text{diff}})$$

5

$$= S (BP + (1 + k) P_{\text{diff}})$$

Hence:

$$f - e = S (BP + (1 + k) P_{\text{diff}}) - R P_{\text{diff}}$$

$$= S BP + (S(1+k) - R) P_{\text{diff}}$$

10

Now if R, S and k are selected so that $S (1 + k) = R$, then the voltage output (corresponding to Equation (9)) is:

$$f - e = S BP \quad (12)$$

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Or, expressed using the terminology of Equation (10), the voltage output from the sensor system is:

$$\Delta V = S BP \quad (13)$$

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This is a function of BP, i.e. blood pressure, alone (and not of flow) so if the value of S is chosen appropriately a combination of a differential pressure sensor 528 and a proximal pressure sensor 540 arranged as shown in Figures 18 and 19 can provide a “drop-in” replacement for existing BP proximal sensors.

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Figures 20-22 show a bifurcated catheter fitting similar to that shown in Figures 11-13, but in this case incorporating a differential pressure sensor.

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Thus the pressure change sensor means comprises a housing 550 provided at one end with a male luer connector 552 and at the other end with a gland 554 of a known type for receiving a pressure wire. The connector 552 is for connection to a guide catheter.

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The fitting also includes a liquid supply branch 556 through which liquid can be introduced into the guide catheter via the fitting. As can be seen from Figure 21, the

housing 550 is of a two-part construction having a main body part 557 the upper face of which includes an elongate slot 558 surrounded by an upstanding peripheral wall 560. The body part 557 and wall 560 also provide a square socket 562 for accommodating a pressure sensor 564 of the same type as the pressure sensor 528, thus including a silicon membrane or diaphragm 566 which is etched with piezo-resistive elements and is interposed between an upper, elastomeric sealing gasket 568 and a lower electrically conductive gasket 570 which is, in use, in contact with conductive pins 572 for connecting the sensor 564 to the circuitry for operating the sensor and analysing its output.

The other part of the housing 550 comprises the liquid supply branch 556, the underside of which is channeled so as to define, with the slot 558, part of the serpentine passage for liquid through the fitting. The channel in the body part 557 is shown at 574 in Figure 22. As can be seen from Figure 22, liquid supplied along the branch 556 will flow along the passage defined by the slot 558 and the channel 574, where the liquid will be in contact with one face of the diaphragm 566. The liquid will then pass into a main passage 576 of the housing 550, through a throat in the form of a Venturi 578, and past the opposite face of the diaphragm 566, before leaving the fitting. The sensor 564 thus acts as a differential pressure sensor in a similar fashion to the sensor 528 of the arrangement shown in Figures 15-17, with the Venturi 578 providing a flow restriction.

Figure 23 shows a slightly modified version of the fitting, in which there is also provided a proximal pressure sensor 580. The proximal pressure sensor 580 is disposed in a wall of the main passage 576 of the housing, to measure an absolute local pressure of the liquid in the main passage 576.

In either case, the output from the differential pressure sensor and the proximal pressure sensor (which may be in the fitting or separate) can be combined by means of a split bridge circuit in the way described above with reference to Figure 19.

A further advantage of the embodiments shown in Figures 20-23 is derived from the fact that any additional devices, such as pressure wires, balloons, stents or micro-catheters, introduced to the patient's heart through the guide catheter, also pass through the flow restriction. Any said additional devices will cause a partial occlusion of the guide catheter resulting in increased pressure drop of any flowing liquid.

However, since the additional devices also pass through the restriction, it also will be affected in a similar way with a corresponding increase in pressure difference across it. Thus the embodiments of Figures 20-23 provide the capability to compensate for additional devices introduced to the patient's heart.

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It will be appreciated that, to realise this benefit, the flow restriction has to be located in the main passage 576 which is axially co-located with the guide catheter, whereas it could otherwise be located at any point in the route between the opposite faces of the sensor diaphragm, such as in the slot 558.

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The split bridge sensor systems described above offer simple and reliable design solutions, but under some circumstances it may be beneficial to modify the signal provided to the patient monitor, such as if either:

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- the flow through the restrictor cannot easily be controlled to laminar conditions, or
- it would be desirable to make the sensor configurable by the user, such as to be able to switch between catheters of different diameter.

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In such circumstances, the output signals from the full Wheatstone bridges connected to the sensors could be manipulated by one or more amplifiers. An example of such an arrangement is shown in Figure 26, in which P_1 represents the proximal pressure sensor and P_2 represents the pressure sensor on the other side of the restriction from the proximal pressure sensor P_1 .

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In electronic terms, the output needs to be compatible with the two wire system, with voltage signals to resemble the situation in Figure 3 (i.e. $\Delta V_{bp} = a - b$).

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If the sensors are configured with a restrictor as shown in Figure 8, the pressures measured at each sensor are as follows:

$$P_1 = BP + \Delta P_{\text{flow path}}$$

35 and

$$P_2 = P_1 + \Delta P_{\text{restriction}}$$

but if $\Delta P_{\text{flow path}} = k \Delta P_{\text{restriction}}$

then $BP = P_1 - k(P_2 - P_1)$

5

$$= (1 + k)P_1 - kP_2$$

If the voltages generated at the nodes of the two Wheatstone bridge circuits associated with P_1 and P_2 are a, b and c, d respectively, then the final voltage representing actual BP is given by:

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$$V = (1 + k)(a - b) - k(c - d)$$

However, to mimic the output of existing proximal sensors supplied to the pressure analyser, this needs to be in the form $\Delta V = a - b$. It can thus be rearranged to the following form:

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$$V = a - [(1+k)b - k(a-c+d)] \quad (14)$$

This is in a form that could be manipulated by a network of operational amplifiers or even a single summing differential amplifier as shown in Figure 27.

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In the summing differential amplifier the resistors can be selected so that the output voltage is of the correct form.

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Note also that a suitable amplifier circuit(s) could be arranged to provide the correct output if the sensors are configured with a restrictor as in Figure 9.

It will also be clear that any of these circuits could be configured to achieve different objectives. For example:

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- if it is preferable to use a simple orifice (for the restrictor) where the flow will almost inevitably be turbulent, the circuit output can be arranged to provide a matching non-linear output. This can be done in analogue electronics (with

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the use of MOSFET devices in the feedback loop) or by converting the signal

to digital format (using an A to D converter) and using a microprocessor to perform the necessary signal processing.

- if the system needs to be user-configurable for different size catheters, for example the gain of the amplifier(s) could be switchable to provide matching output. Alternatively, this might be easier to implement using digital electronics.

In the examples described with reference to Figures 5 to 27, the pressure drop along the flow path between the proximal pressure sensor and the patient is determined by measuring the pressure drop within a part of the system that is proximal with respect to the guide catheter (i.e. upstream of the guide catheter when fluid is being injected or infused into the system). However, in another embodiment of the invention, the pressure drop along the flow path can be determined by measuring the pressure drop within the guide catheter itself, as will now be described.

A known pressure wire device 601, as represented in Figure 28, is typically about 175 cm in length and 360 μ m in diameter. It generally consists of several regions providing a combination of different functions and different flexural stiffnesses to facilitate navigation into and around the arterial system. These regions are labeled A to E in Figure 28, and have the following primary purposes:

- A. Electrical connection rings 602 are provided at the proximal end of the wire. These make electrical connection to, either a cable system that is plugged into a pressure analyser/display unit, or wireless system that provides the same function.
- B. The longest region, typically occupying over 80% of the length of the pressure wire. This region has moderate stiffness since it does not protrude beyond the tip of the guide catheter and so does not need to bend around small radii within the arterial system. This region comprises a stainless steel tube or sheath 603 of about 360 μ m outside diameter and 300 μ m internal diameter. This tube has an external polymer coating 604, and internally, carries three insulated electrical conductors 605 each of about 30 μ m diameter.
- C. This region is about 30 cm in length and has increased flexibility to facilitate improved navigation. Its outer tube 606 is a medically compliant polyimide

material and internally it contains a solid stainless steel support wire 607 of about 100 μm diameter and the same three electrical conductors 605 referred to above.

5 D. This section is just a few mm in length, but contains the pressure sensor 608 which is mounted in, either a formed section of the end of the support wire, or a separate component, shaped in the form of a "boat" 609. This is enclosed in a very short length of tube 610 which protects the sensor, but also contains a small aperture 611 through which the face of the sensor is exposed to the external environment. The three electrical conductors 605 connecting to the
10 sensor pass between the boat 609 and the outer tube 610.

E. The extreme distal tip of the pressure wire includes a fine wire 612 of about 80 μm diameter formed into a helix around a central wire 613 of about the same diameter. The tip can be formed by the operator to impart a directional behaviour to the wire for navigational purposes. Furthermore, the wire 612 is
15 made from a material, such as platinum, that is radiopaque so that it is visible under x-ray during an interventional procedure.

The regions B, C, D and E together form an insert portion of the device 601, for insertion into a fluid delivery conduit as will be explained in more detail below.

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The miniaturised pressure sensor 608 used in this known device, as illustrated in Figure 29, is generally as described below.

The sensor 608 is manufactured from silicon using chemical etching or machining
25 techniques to form a thin membrane region 614. The membrane is bonded over an evacuated cavity 615 that remains so throughout the lifetime of the device. The vacuum so produced causes the membrane 614 to deflect in response to the pressure difference across its two faces, and hence to also deflect further in response to small changes in the applied external pressure. It also includes two
30 sensing elements. The first element 616 is located on the membrane 614 for sensing deflection of the membrane 614 caused by pressure changes; the second element 617 is located in the surrounding material, and is very similar to the first element 616 so that it responds to environmental changes such as temperature changes in the same way as the first element 616, but is immune to changes in pressure.

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It will be understood that the three-wire configuration of the sensor element shown in Figure 30, in which the two sensing elements 616, 617 are connected as shown, is suitable for connection to a Wheatstone bridge circuit in such a way that extraneous changes, such as temperature, are cancelled out.

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The pressure wire's external connecting cable (not shown) includes two further resistors that complete the Wheatstone bridge circuit and hence provides a four-wire configuration at its connector to the associated pressure analyser/display unit. One of the connectors on the cable may also include an EEPROM chip to provide each device with a unique identification number.

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Figure 31 provides a schematic illustration of a pressure wire or insert device 601 according to one embodiment of the present invention. The construction of this device follows generally similar principles to that described for the prior art device in Figure 28, and like reference numerals are used for like features. However, in addition to the tip pressure sensor 608, sensing means comprising two additional pressure sensors 618, 619 are disposed along the length of the shaft of the pressure wire in the region corresponding to region B described in Figure 28. The additional sensors are absolute pressure sensors that may be of the similar design and construction as the tip sensor 608 as described above with reference to Figure 30. Similarly, the individual sensing elements 616', 617', 616'', 617'' shown in Figure 32 correspond directly to those in the tip sensor 608, with the elements 616' and 617' being the elements of the sensor 618 and the references 616'', 617'' denoting the elements of the sensor 619. However, since the quantity of interest is the difference between the outputs of the two sensors, it will be appreciated that the temperature compensation function of the said second sensor elements 617', 617'' is not necessary since the said first sensing elements 616', 616'' can be connected in order to compensate for each other in this respect.

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The difference between the output signals of the two sensors 618, 619 can be used to provide a measure of the pressure drop along the guide catheter and associated flow line when the device 601 is inserted into the guide catheter in a coronary catheterisation procedure. A difference signal can be acquired by means of a first differential amplifier (not shown). The gain of the first amplifier can be arranged so that the difference signal has the same sensitivity (in terms of voltage per unit of pressure) as the output from the proximal pressure sensor. Once scaled

appropriately in this way, it can be added or subtracted to/from the output of the proximal sensor, by means of a second differential amplifier, in order to make the appropriate compensation for the pressure drop error caused by the flow of fluid.

- 5 In a similar fashion to the tip sensor 608, the two additional sensors 618, 619 are mounted within the stainless steel tube or sheath 603, but face the external environment through corresponding apertures 621, 622 in the stainless steel tube or sheath 603.
- 10 During assembly of the pressure wire, the additional sensors 618, 619 are bonded into two locations that are pre-formed into the support wire 607 at specific locations corresponding to the position of the two apertures 621, 622 in the side wall of the tube 603. The electrical conductors 605 are attached to the three devices according to the wiring schematic shown in Figure 32. Finally the assembly built onto the
- 15 support wire is assembled into the outer sheath tube 603 and locally bonded, with for example a UV curing adhesive, at the specific locations.

The design distance D between the locations of the additional sensors 618, 619 is selected so that they are sufficiently separated for there to be a measureable

20 pressure difference between them when fluid is flowing in the fluid delivery conduit. The inventors have found that a distance D of around 300-500 mm is optimal. The additional pressure sensors are sufficiently in-board of the ends of the pressure wire so that during normal use they are contained within the length of the delivery conduit.

- 25 To that end, both of the additional sensors are situated at region B of the wire, with the first additional sensor 618 being at least 10 cm from the tip E of the pressure wire.

The wiring schematic shown in Figure 32 illustrates that all three pressure sensors

30 share common +V and 0V conductors. It will be appreciated that the two additional sensors 618, 619 are wired so as to form a second Wheatstone bridge and hence that the output signals from these two sensors are suitable for direct connection to a differential amplifier. It will also be noted that, in this embodiment, the present invention is a five-wire device, and so five connection rings 602 can be seen in

35 Figure 31.

In an alternative embodiment (not shown), the two discrete additional pressure sensors 618, 619 are replaced by a single differential pressure sensor. The differential pressure sensor is located within the tube 603 at a position between the two apertures 621, 622. The differential pressure sensor does not include a vacuum cavity 615 but instead has a first face arranged to be fluidically coupled to fluid in the fluid delivery conduit at the first aperture position and a second face arranged to be fluidically coupled to fluid in the fluid delivery conduit at the second aperture position, in use.

To achieve fluidic coupling between the sensor faces and the fluid in the fluid delivery conduit, a coupling medium may be present within the tube 603 between the sensor faces and the respective apertures 621, 622. The coupling medium may be fluid from within the fluid delivery conduit or a combination of fluid from within the fluid delivery conduit and air, or alternatively may be a gel-like fluid injected into the cavity of the tube 603 during manufacture.

Figure 33 illustrates the device within the context of the coronary catheterisation environment together with compensation means. In this instance, the device 601 performs the role of a pressure wire, in that it has a pressure sensor 608 located at its tip for measuring the pressure downstream of coronary stenosis. A guide catheter 620 provides access, through an axial port 640, for the pressure wire 601 and other devices into the coronary arteries of the patient's heart. Through a side port 641, the guide catheter provides access for drug or other liquids to be injected into the patient's arterial system, for example from an infusion pump 631, a saline bag 644, an auxiliary input 645 and/or a contrast agent syringe 646. Fluid can also be extracted from the patient's arterial system through the side port 641, for example for sampling blood. The tubing 630 connected to the side port 622 also provides fluid communication, by way of a two-valve manifold 632, to the pressure monitoring means, which in this embodiment is a proximal pressure sensor 623. Liquid delivered to the patient by the apparatus flows along a flow path that includes the sensor 623, the tubing 630 and the guide catheter 620.

The electrical output signals 642, 643 from the distal tip sensor 608 and pressure drop sensing means 618, 619 of the pressure wire 601, together with the electrical output signal 624 from the proximal pressure sensor 623 are connected to a pressure analyser/display unit 626. In addition, a signal compensating processor 625 or

compensation means combines the pressure drop signal 640 with the proximal pressure signal 624 in order to compensate for the pressure drop along the path from the proximal sensor 623 to the distal end of the guide catheter 620. The compensating processor 625 can either be located within the casework 627 of the display unit 626, or be a discrete modular unit external to the display unit 626.

In use, the catheter 620 is inserted into the patient so that the distal end of the catheter 620 is, in effect, connected to the blood in a coronary artery under investigation. The proximal pressure sensor 623 and saline bag 644 are typically supported on a drip stand (not shown), with the proximal pressure sensor 623 situated at the same elevation as the patient's heart to prevent errors in the measured blood pressure of the patient as a consequence of a difference in hydrostatic pressure between the proximal sensor 623 and the sensor 608 on the tip of the device 601.

In use, the valves in the manifold 632 can be set so that the proximal pressure sensor 623 is coupled to the environment in the region of the distal end of the catheter 620 via the liquid in the catheter 620 and in the tubing 630.

When it is necessary to flow fluid through the catheter during the procedure, such as during the injection of contrast agent from the syringe 646, operation of the infusion pump 631 or when a vaso-dilator drug such as adenosine is injected into the catheter 620 through the auxiliary inlet 645, the device 601 provides an output that can be used to compensate for the effect of the flow of liquid in the fluid flow path between the proximal pressure sensor 623 and the patient.

Thus the device 601 allows continued use of the proximal pressure sensor 623 to monitor aortic pressure when various procedures, involving the flow of liquid along the catheter 620, are being performed.

Accordingly, in the apparatus of Figure 33, the proximal pressure sensor 623 remains in fluid communication with the catheter 620 even during fluid flow, and the first and second additional sensors 618, 619 of the device 601 are used to determine the pressure drop in the fluid flow path between the proximal pressure sensor 623 and the distal end of the catheter 620.

In this example, the first and second additional sensors 618, 619 of the device 601 provide a measurement of the pressure drop in the catheter 620 over the distance between the sensors 618, 619. The signal compensating means 625 analyses the output from the additional sensors 618, 619 to determine the effect of the flow of liquid along the catheter 620 on the relationship between the pressure measured by the proximal pressure sensor 623 and the actual aortic pressure at the distal end of the catheter 620.

To determine the pressure drop along the flow path between the proximal pressure sensor 623 and the distal end of the catheter 620, $\Delta P_{\text{flow path}}$, the processor 625 first determines the pressure difference ΔP_{sensor} between the first and second additional sensors 618, 619. Assuming laminar flow, both ΔP_{sensor} and $\Delta P_{\text{flow path}}$ vary linearly with flowrate, and hence with one another. The relationship between ΔP_{sensor} and $\Delta P_{\text{flow path}}$ can be determined empirically or otherwise in advance for the apparatus in use, so that the processor 625 can readily determine $\Delta P_{\text{flow path}}$ from the output of the sensors 618, 619. In this way, an output corresponding to the corrected aortic blood pressure BP can be calculated in accordance with Equation (4) above.

In a variant (not shown) of the device, the sensing means comprises a single additional pressure sensor. In this case, the pressure drop between the additional pressure sensor of the device and the proximal pressure sensor can be used to determine the pressure drop along the flow path, in a similar manner to the arrangement described above with reference to Figure 5.

The device 601 of Figure 31 is provided with sensing means in the form of one or more pressure sensors. However, it will be appreciated that other sensors could be used for the sensing means. For example, the sensing means could comprise one or more flow sensors to measure the flow rate in the catheter 620, instead of (or in addition to) the pressure drop. The relationship between the measured flow rate Q and the pressure drop along the flow path $\Delta P_{\text{flow path}}$, in accordance with Equation (1), can be empirically determined for the type of catheter in use and stored in the processor.

More generally, other types of sensor could be employed in the other embodiments of the invention. For example, a flow sensor could be used in place of the further pressure sensor 262 in the apparatus of Figure 5.

In the above examples, it will be appreciated that, in addition to the pressure drop that occurs along the catheter, pressure drops in other components (such as the side port 622, the tubing 630 and the manifold 632 in the example of Figure 33) may contribute to the overall pressure drop along the flow path between the proximal pressure sensor and the distal end of the catheter. The term $\Delta P_{\text{flow path}}$ in the above analyses therefore represents the overall pressure drop along the flow path. However, in some cases, the components connected to the catheter may contribute negligibly to the overall pressure drop along the flow path, in which case only the pressure drop along the catheter itself need be considered in the analysis.

In much of this document, the catheterisation configurations have been described within the context of FFR. However, many of the ideas and principles described could apply to other procedures (including non-medical procedures) where liquids (not limited to drugs) are delivered, or samples (not limited to blood samples) are taken whilst simultaneously measuring pressures at the tip of a catheter (or other conduit).

For example, it could be desirable in cardiac catheterisation procedures (in addition to FFR) for various agents to be delivered to, or samples taken from, the chambers of the heart or the arterial structure surrounding it, whilst simultaneously monitoring the patient's blood pressure.

Thus specific references made in this document could be applied more broadly (e.g. "guide catheter" can also apply to other cardiac catheters and catheters in general). Further modifications and variations of the above-described embodiments are also possible without departing from the scope of the invention as defined in the appended claims.

Claims

1. Fluid delivery apparatus for use with a system for containing or conveying
5 fluid, the apparatus comprising a fluid delivery conduit, a fluid flow path extending at least in part through the fluid delivery conduit and having a distal end for connection to the system, pressure monitoring means for monitoring the pressure of fluid at a proximal end of the fluid flow path, and compensation means for compensating for, or reducing the effect of, a flow of fluid through the flow path on an output of the
10 pressure monitoring means thereby to determine a fluid pressure in the system.
2. Apparatus according to claim 1, in which the compensation means is operable to quantify a parameter associated with the flow of fluid in the fluid flow path and to use said parameter to compensate for the effect of the fluid flow through the
15 flow path on the output of the pressure monitoring means.
3. Apparatus according to claim 2, in which the compensation means includes sensor means for quantifying the parameter by means of measurement.
- 20 4. Apparatus according to any preceding claim, further comprising fluid displacement means for supplying or extracting fluid to the system through the delivery conduit thereby to cause fluid flow in the fluid flow path.
5. Apparatus according to claim 4 when dependent on claim 3, wherein the
25 sensor means is separate from the fluid displacement means.
6. Apparatus according to claim 5, wherein the sensor means is disposed between the fluid displacement means and a distal end of the delivery conduit.
- 30 7. Apparatus according to claim 6, wherein the sensor means is connected between the fluid displacement means and the delivery conduit.
8. Apparatus according to any of claims 4 to 7, wherein the fluid displacement means comprises a pump.

9. Apparatus according to any preceding claim, comprising pressure sensor means for determining a pressure difference associated with the flow of fluid in the fluid flow path.

5 10. Apparatus according to claim 9, in which the pressure sensor means comprises a differential pressure sensor.

11. Apparatus according to claim 10, in which the differential pressure sensor comprises a common pressure sensitive element having a first face coupled, in use,
10 to fluid in the apparatus at a first position and a second face coupled, in use, to fluid in the apparatus at a second position spaced from the first position.

12. Apparatus according to claim 11, in which said pressure sensitive element comprises a flexible diaphragm.

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13. Apparatus according to claim 9, wherein the pressure sensor means comprises a first pressure sensor coupled, in use, to fluid in the apparatus at a first position and a second pressure sensor coupled, in use, to fluid in the apparatus at a second position spaced from the first position.

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14. Apparatus according to any of claims 11 to 13, comprising a restriction in a passage disposed between the first and second positions.

15. Apparatus according to claim 14, in which the restriction profile is such that
25 the passage progressively tapers and widens.

16. Apparatus according to claim 15, in which the restriction comprises a Venturi.

17. Apparatus according to any of claims 9 to 13, further comprising an elongate
30 insert for insertion into the fluid delivery conduit, wherein the insert comprises the pressure sensor means.

18. Apparatus according to claim 17, wherein the insert comprises a pressure wire, pressure catheter or guide wire.

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19. Apparatus according to claim 18, wherein the pressure sensor means is disposed at least 100 mm from a distal end of the insert.

20. Apparatus according to any of claims 17 to 19 when dependent on any of
5 claims 11 to 13, wherein the first and second positions are spaced apart along the insert by a distance of between 10 mm and 1000 mm.

21. Apparatus according to any of claims 17 to 20, further comprising a tip pressure sensor located adjacent a distal end of the insert.

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22. Apparatus according to claim 21, wherein the tip pressure sensor and the pressure sensor means share common voltage supply conductors.

23. Apparatus according to any of claims 17 to 22, wherein the insert is flexible.

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24. Apparatus according to any of claims 5 to 16, comprising a device entry port for admitting a device to the system by way of the delivery conduit, and wherein the sensor means is located between the delivery conduit and the device entry port, such that the parameter associated with the flow of fluid is affected by any devices
20 introduced to the system via the device entry gland and delivery conduit.

25. Apparatus according to any preceding claim, wherein the pressure monitoring means comprises a proximal pressure sensor situated at a position spaced from the distal end of the fluid delivery conduit or flow path.

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26. Apparatus according to claim 25 comprising first and second pressure sensors for determining a pressure difference associated with the flow of fluid in the fluid flow path, one of which is said proximal sensor.

27. Apparatus according to claim 25 or claim 26, in which the compensation means generates an electrical signal of magnitude equal to the effect on the output of the proximal pressure sensor of the flow of fluid through the flow path.

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28. Apparatus according to claim 27 in which said electrical signal is summed
35 with the output of the proximal pressure sensor to give a pressure representative of the fluid pressure in the system.

29. Apparatus according to claim 25 or claim 26, in which the compensation means further comprises analogue circuitry for combining the outputs of the proximal pressure sensor and a pressure sensor, other than the proximal pressure sensor, of the compensation means to give an output representative of fluid pressure in the system.

30. Apparatus according to claim 29, in which the circuitry comprises a bridge circuit, which incorporates the pressure sensors.

31. Apparatus according to claim 30, in which the bridge circuit comprises a Wheatstone bridge.

32. Apparatus according to claim 30 or claim 31, in which the proximal pressure sensor includes piezo-resistive elements, each connected between a respective pair of junctions of the bridge.

33. Apparatus according to claim 32, in which said sensor other than said proximal sensor, also has piezo-resistive elements, each connected between a respective pair of junctions of the bridge.

34. Apparatus according to claim 26, in which the proximal sensor and the first or second sensor have differing sensitivities such that the pressure in the system is the only variable affecting the combined output of the sensors.

35. Apparatus according to claim 25 comprising a differential pressure sensor for determining a pressure difference associated with the flow of fluid in the fluid flow path, in which the sensitivities of the differential pressure sensor and the proximal pressure sensor and the relationship between the flow rate of fluid through the passage with the measured pressure difference are such that the pressure in the system is the only variable affecting the combined output of the sensors.

36. Apparatus according to any preceding claim, in which the apparatus is for use with a system for containing or conveying fluid when in its liquid state, the flow path functioning as a liquid flow path, the fluid pressure to be determined being the pressure of liquid in the system.

37. Apparatus according to claim 36, in which the apparatus comprises coronary or cardiac catheterization apparatus.

5 38. Apparatus according to claim 37, in which the apparatus is for use in an FFR procedure.

39. Apparatus according to claim 37 or claim 38 comprising pressure sensor means for determining a pressure drop associated with the flow of fluid in the fluid
10 flow path in which at least one pressure sensor of the pressure sensor means is situated in a bifurcated fitting for attachment to the proximal end of a flow path constituted by a guide catheter of the apparatus.

40. Apparatus according to any preceding claim, comprising a pressure
15 analyser/display unit for displaying the pressure of fluid in the system.

41. Apparatus according to claim 40, wherein the compensation means is at least partially contained within a casework enclosure of the analyser/display unit.

20 42. Apparatus according to claim 40, wherein the compensation means is external to the analyser/display unit.

43. Compensation means for use with fluid delivery apparatus in accordance with any of the preceding claims, the compensation means being arranged to compensate
25 for, or reduce the effect of, the flow of fluid through the flow path of the apparatus on the output of the pressure monitoring means of the apparatus.

44. Compensation means according to claim 43, comprising sensor means for measuring a parameter associated with the fluid flow through the flow path.

30

45. Compensation means according to claim 44, comprising an insert for insertion into the fluid delivery conduit of the apparatus, wherein the insert comprises the sensor means.

46. Compensation means according to claim 44, comprising a housing connectable in series with the fluid delivery conduit, and wherein the sensor means is disposed in the housing.

5 47. Compensation means according to claim 46, wherein the housing comprises a proximal end fitting for the fluid delivery conduit.

48. Compensation means according to claim 46, wherein the housing is connectable to a connecting tubing proximal of the fluid delivery conduit of the
10 apparatus.

49. Compensation means according to any of claims 43 to 48, comprising a processor arranged to apply a compensation to the output of the pressure monitoring means.

15

50. A method of determining the pressure in a system by means of a proximal pressure sensor in fluid communication with the system via a fluid flow path including a fluid delivery conduit, the method comprising determining the pressure drop due to a flow of fluid along said fluid flow path, and using the determined pressure drop to
20 compensate an output of the proximal pressure sensor for the effect of the flow of fluid in the fluid flow path.

51. A method according to claim 50, comprising determining the pressure drop by measurement.

25

52. A method according to claim 51, comprising measuring a pressure difference due to the flow of fluid, and determining the pressure drop in the fluid flow path using the measured pressure difference.

30 53. A method according to claim 52, comprising measuring the pressure difference using first and second pressure sensors or a differential pressure sensor.

54. A method according to claim 52 or claim 53, comprising measuring the pressure difference using an insert device disposed within the fluid delivery conduit.

35

55. A method according to claim 52, comprising measuring the pressure difference using the proximal pressure sensor and an additional pressure sensor.

56. A method for compensating for the effect of fluid flow in a delivery conduit on a measurement of fluid pressure in a system for conveying or containing fluid, wherein the system is fluidly connected to a distal end of the fluid delivery conduit and wherein the measurement of fluid pressure is taken at a position proximal to the fluid delivery conduit, the method comprising:

determining at least one parameter associated with the fluid flow;

determining a pressure drop compensation value from the at least one parameter associated with the fluid flow; and

applying the pressure drop compensation value to the measurement of fluid pressure.

57. A method according to claim 56, comprising determining the at least one parameter associated with the fluid flow by measurement using at least one sensor.

58. A method according to claim 57, comprising measuring a pressure difference associated with the fluid flow, and determining the pressure drop compensation value from the measured pressure difference.

59. A method according to claim 58, comprising measuring the pressure difference using at least one sensor disposed within the delivery conduit.

60. A method according to claim 58, comprising measuring the pressure difference at a location proximal to the delivery conduit.

61. A method for simultaneous determination of blood pressure at a site in a patient and supply or extraction of fluid to/from the site, the method comprising:

guiding a distal end of a catheter to the site, the catheter having a lumen for fluid flow during supply or extraction of fluid;

applying a fluid flow through the lumen for delivery or extraction of fluid;

determining at least one parameter associated with the fluid flow;

measuring the pressure of fluid at a proximal position with respect to the catheter;

determining a pressure drop compensation value from the at least one parameter associated with the fluid flow; and
applying the pressure drop compensation value to the measurement of fluid pressure to determine the blood pressure at the site.

5

62. A method according to claim 61, comprising measuring the at least one parameter associated with the fluid flow.

63. A method according to claim 62, comprising inserting an insert in the lumen,
10 the insert comprising sensing means for measuring the at least one parameter associated with the fluid flow within the lumen;

64. Apparatus for use in the simultaneous determination of blood pressure at a site in a patient and supply or extraction of fluid at the site, comprising:

15 a catheter having a lumen for fluid flow during supply or extraction of fluid;
sensing means for measuring at least one parameter associated with the fluid flow;

pressure sensing means for measuring the pressure of fluid at a proximal position with respect to the catheter when a distal end of the catheter is positioned at
20 the site, in use; and

compensation means for determining a pressure drop compensation value from the at least one measured parameter associated with the fluid flow, and for applying the pressure drop compensation value to the measurement of fluid pressure to obtain a measurement of blood pressure at the site.

25

65. Apparatus according to claim 64, further comprising an insert for insertion in the lumen, wherein the insert comprises sensing means for measuring the at least one parameter associated with the fluid flow within the lumen.

30

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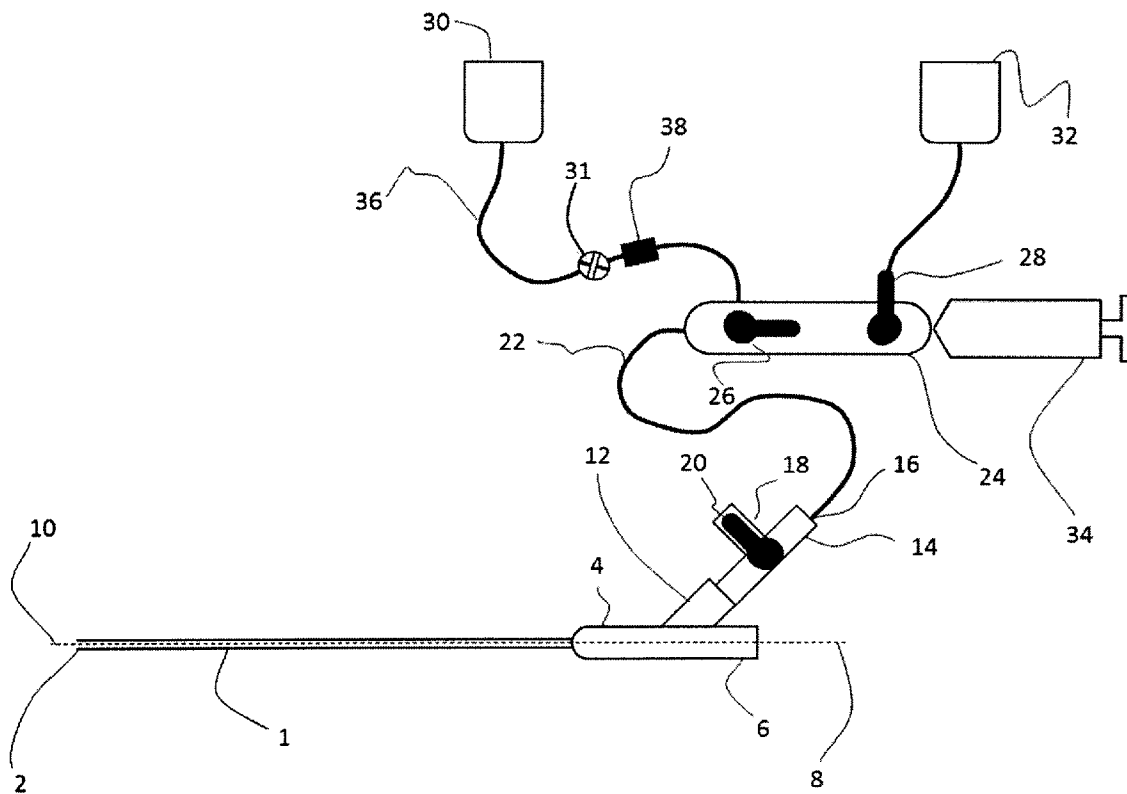


Figure 1
(prior art)

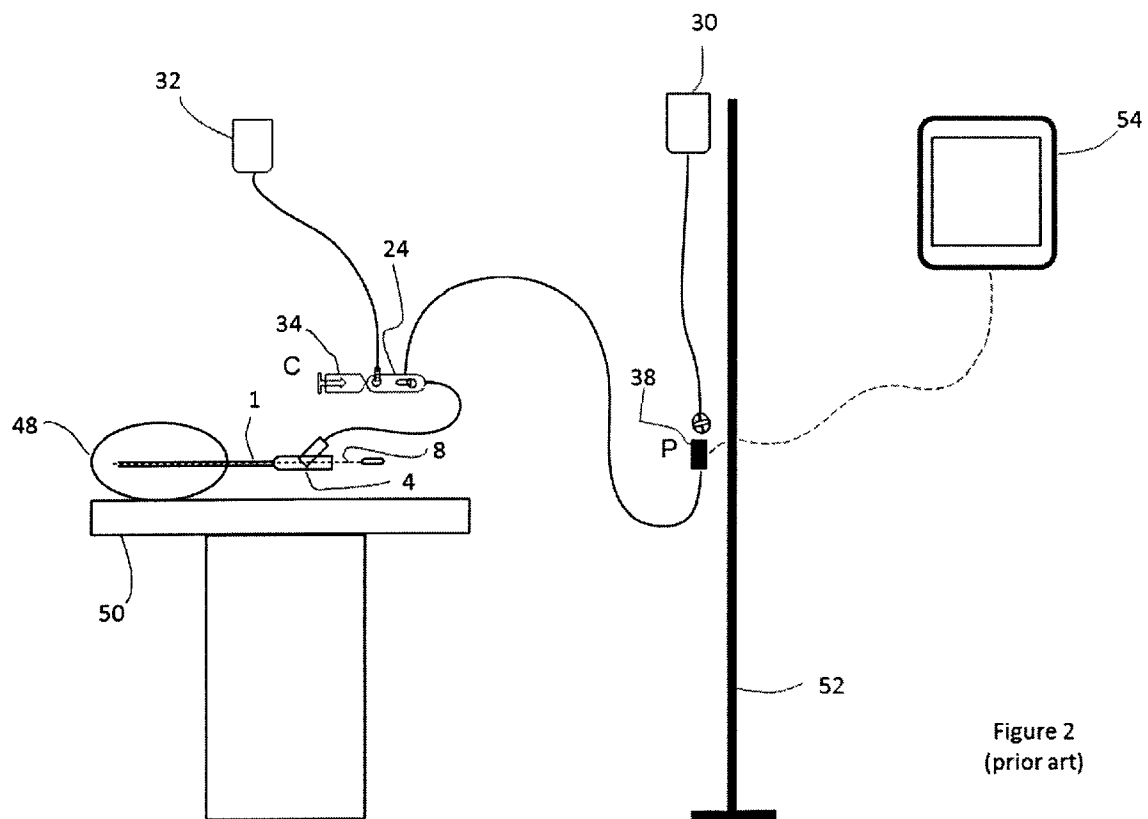


Figure 2
(prior art)

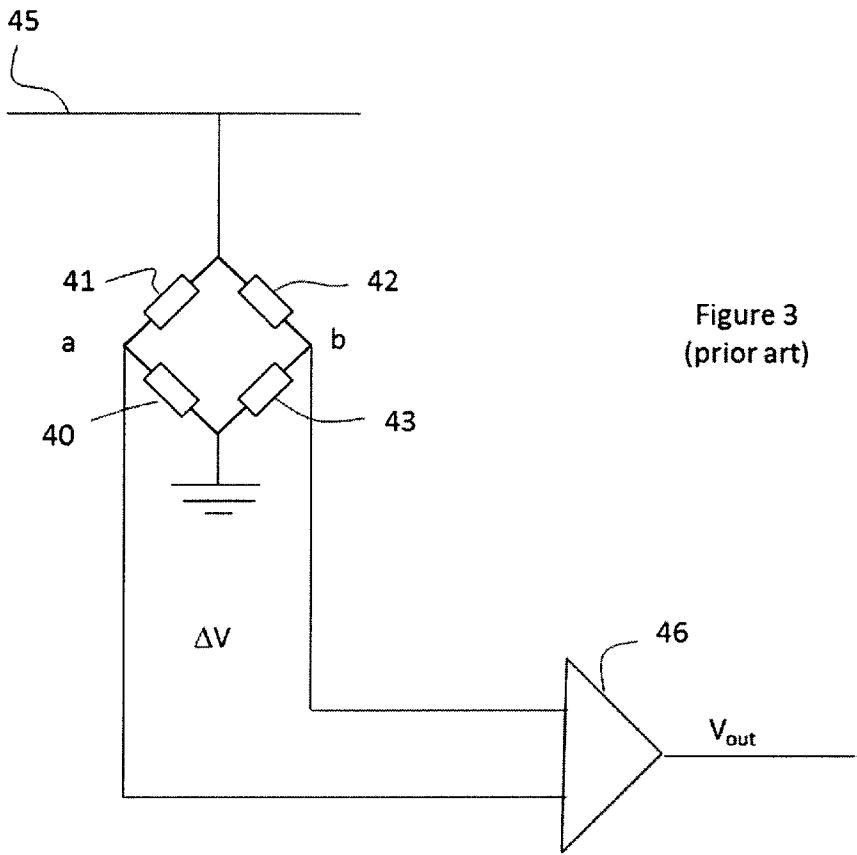


Figure 3
(prior art)

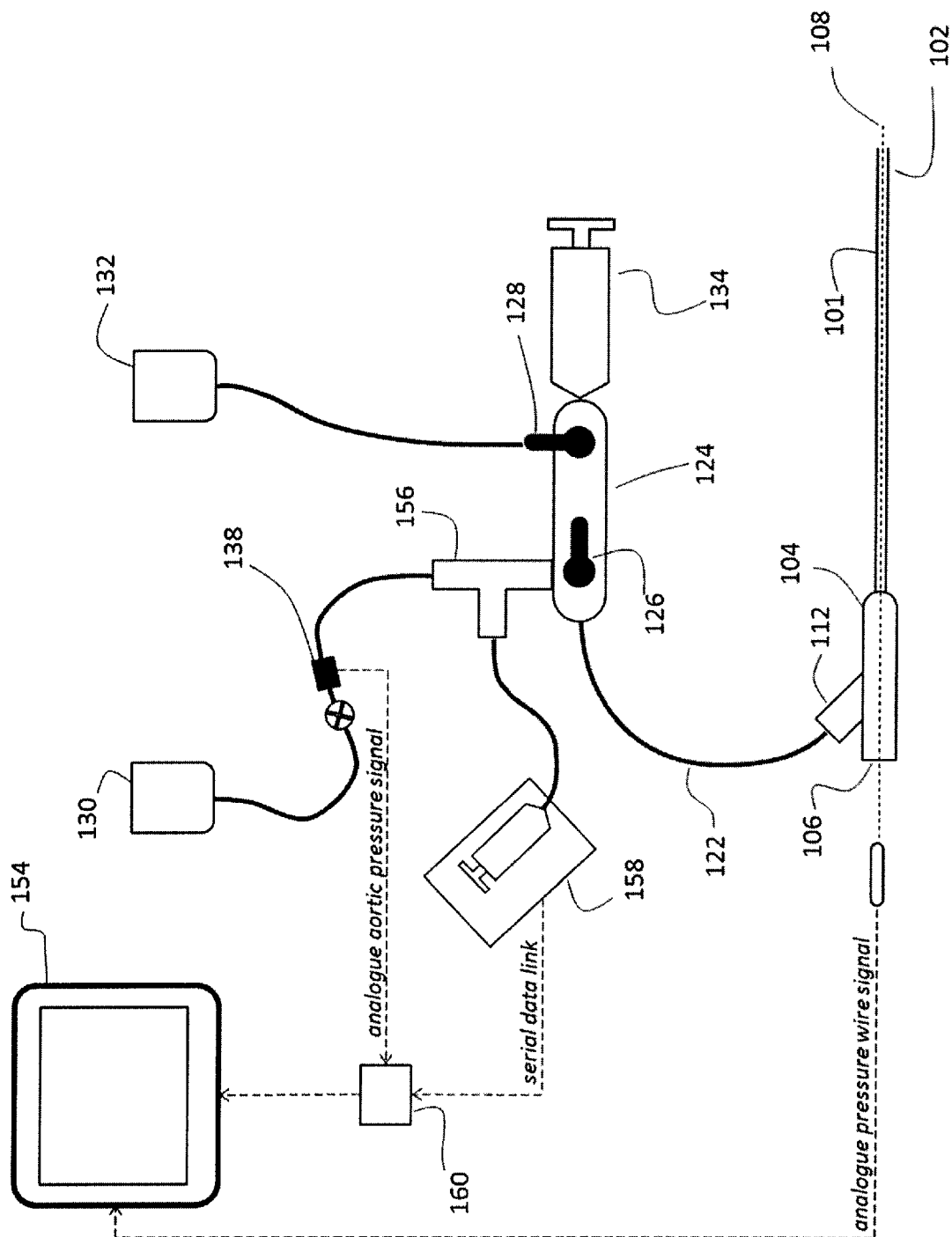
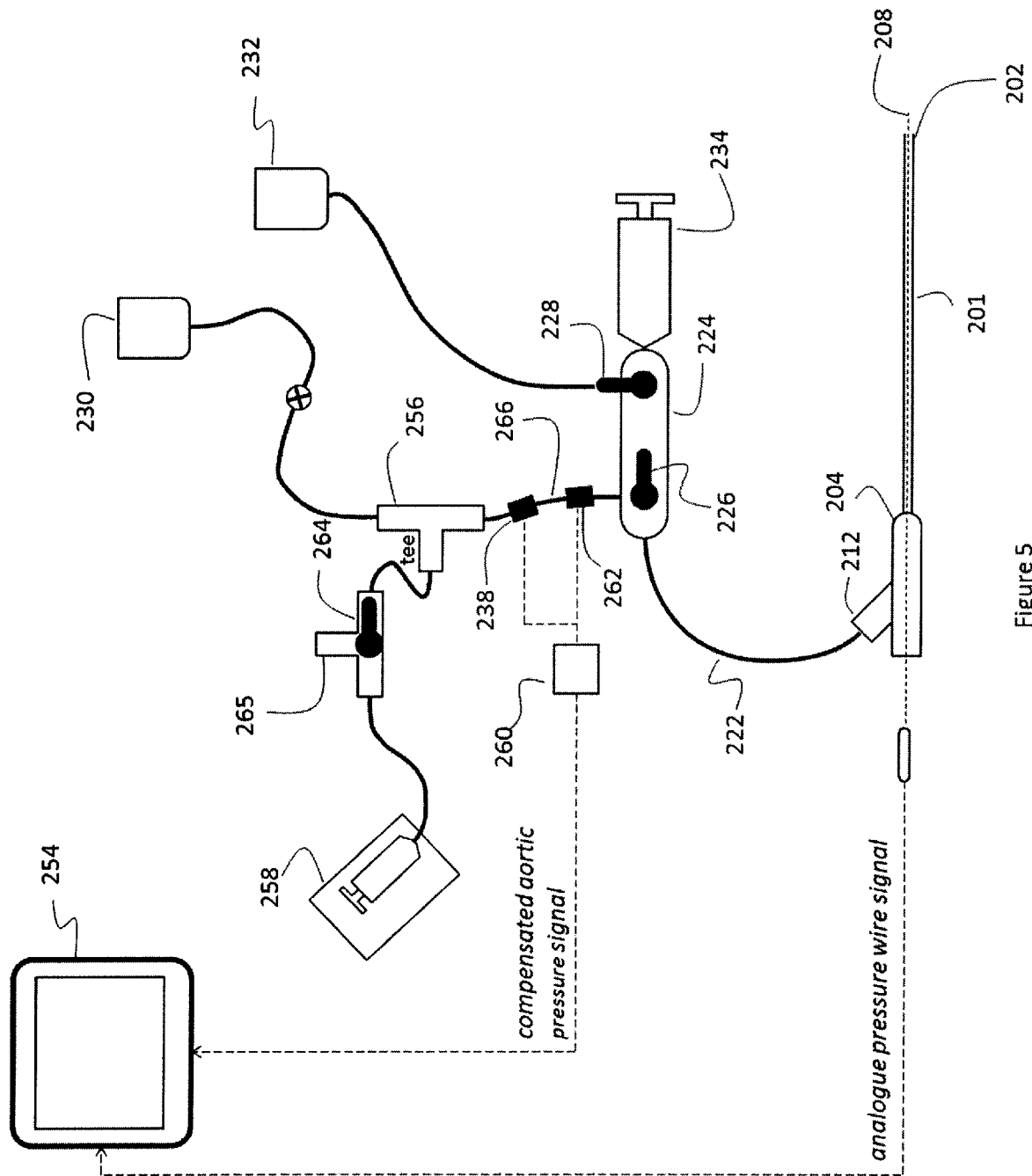


Figure 4

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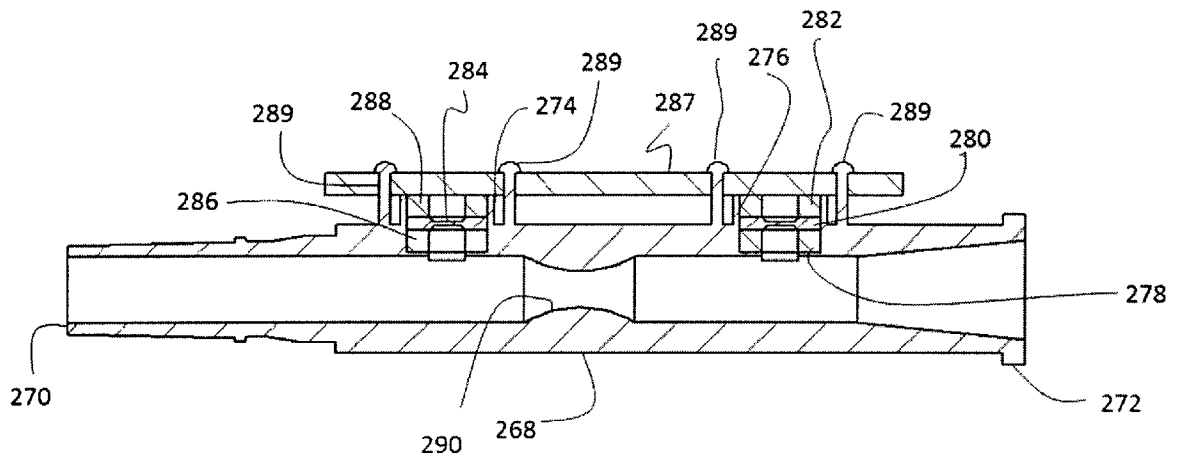


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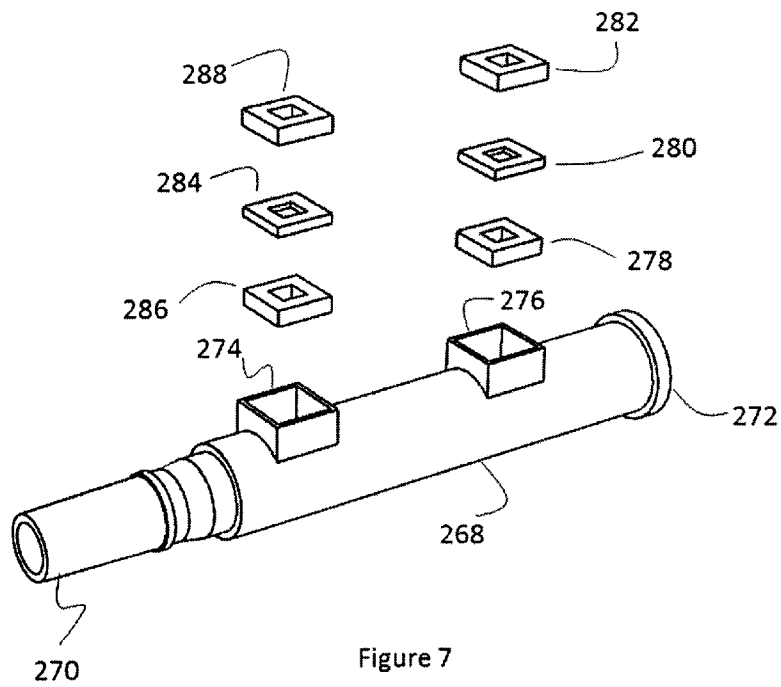


Figure 7

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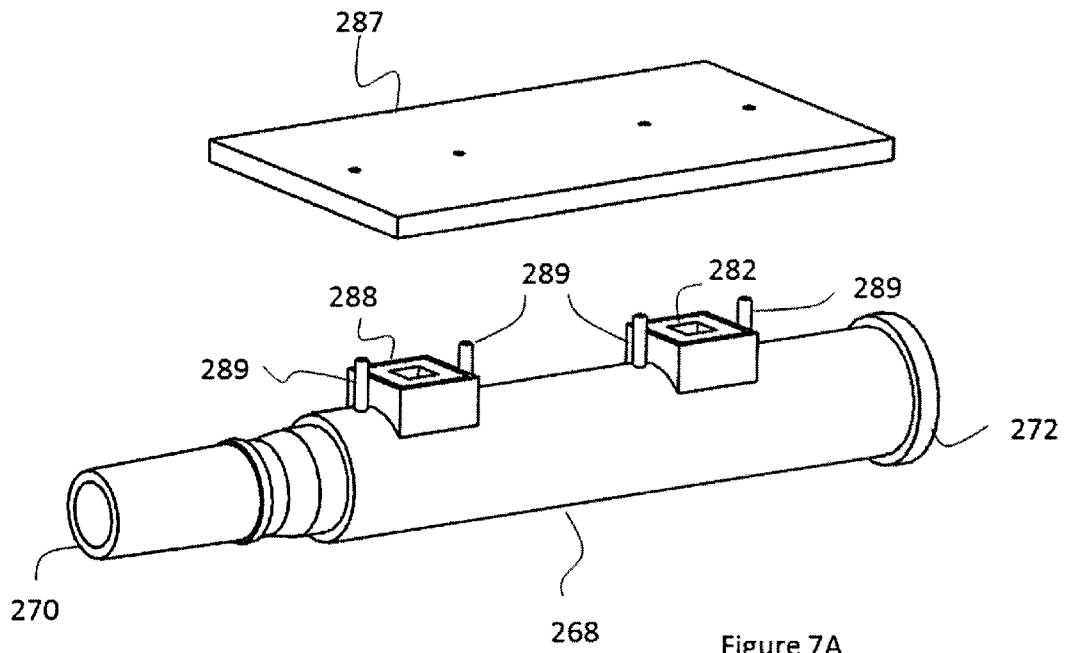


Figure 7A

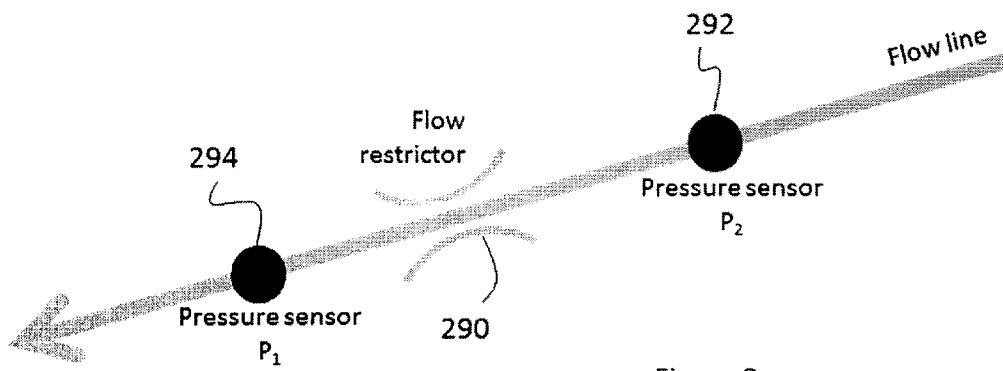


Figure 8

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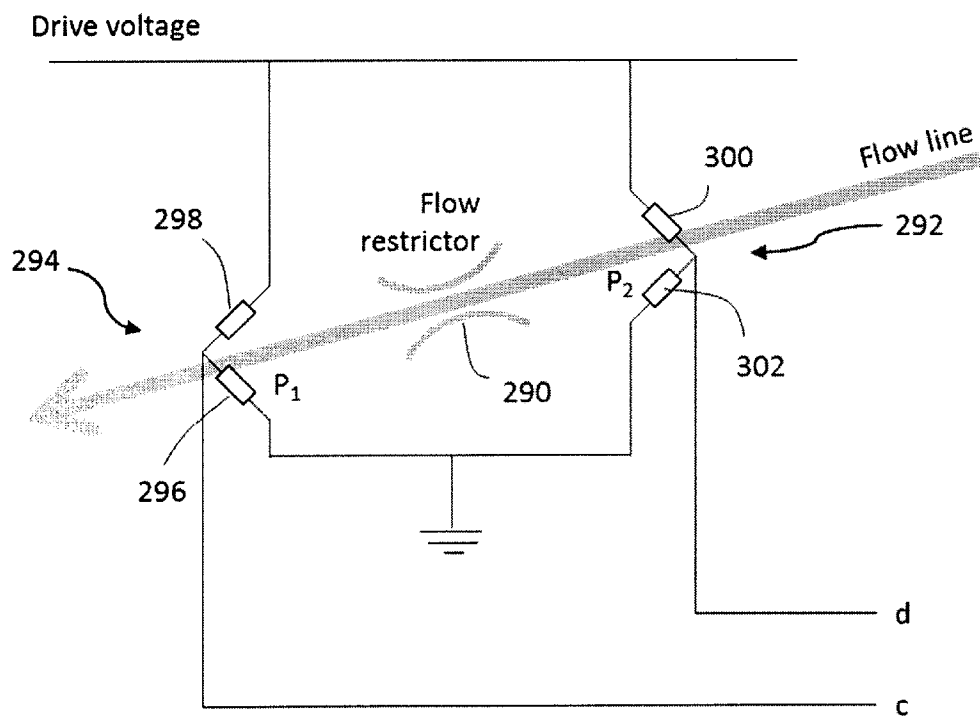


Figure 9

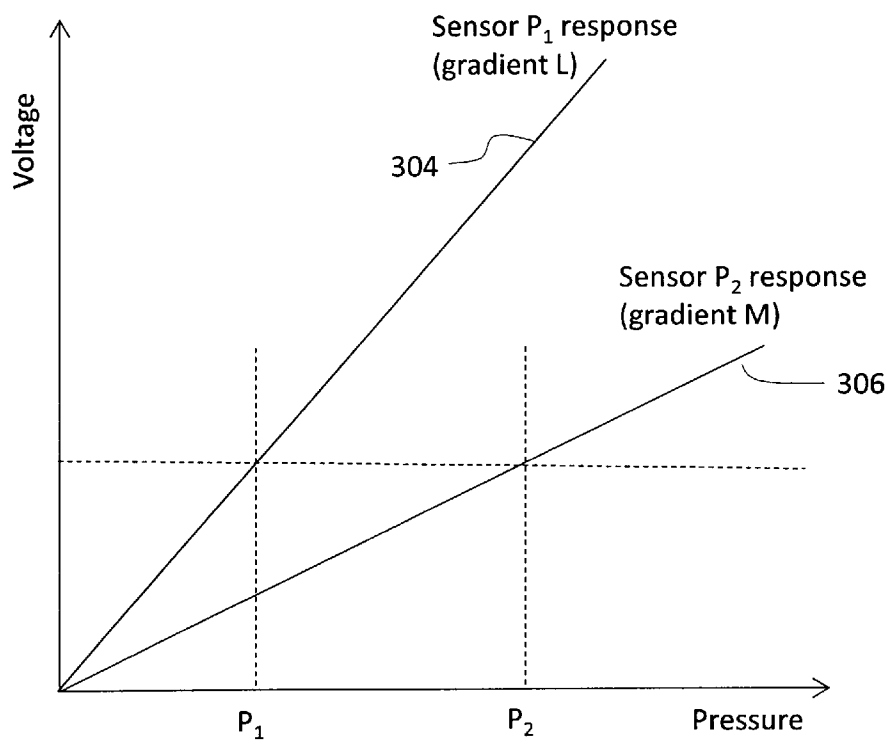


Figure 10

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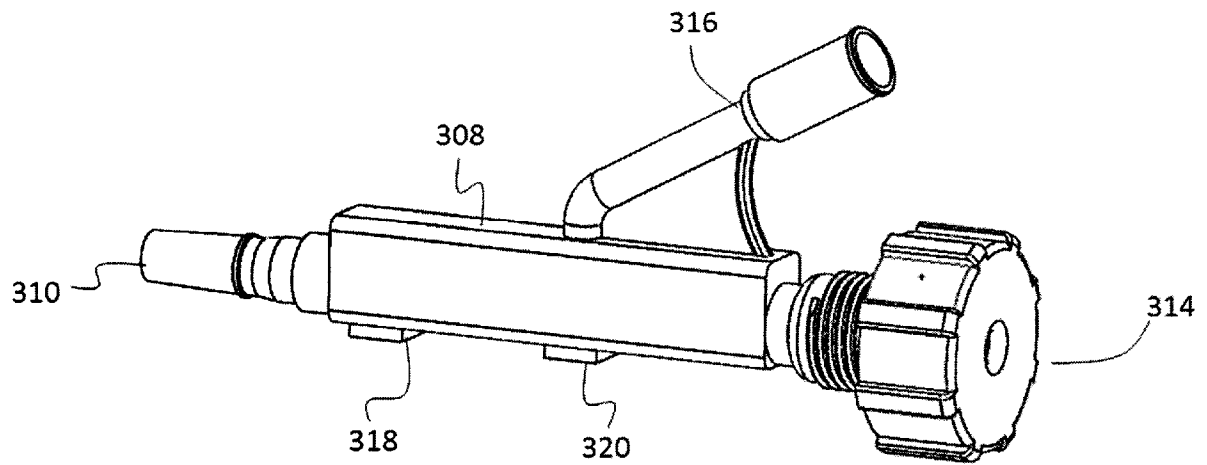


Figure 11

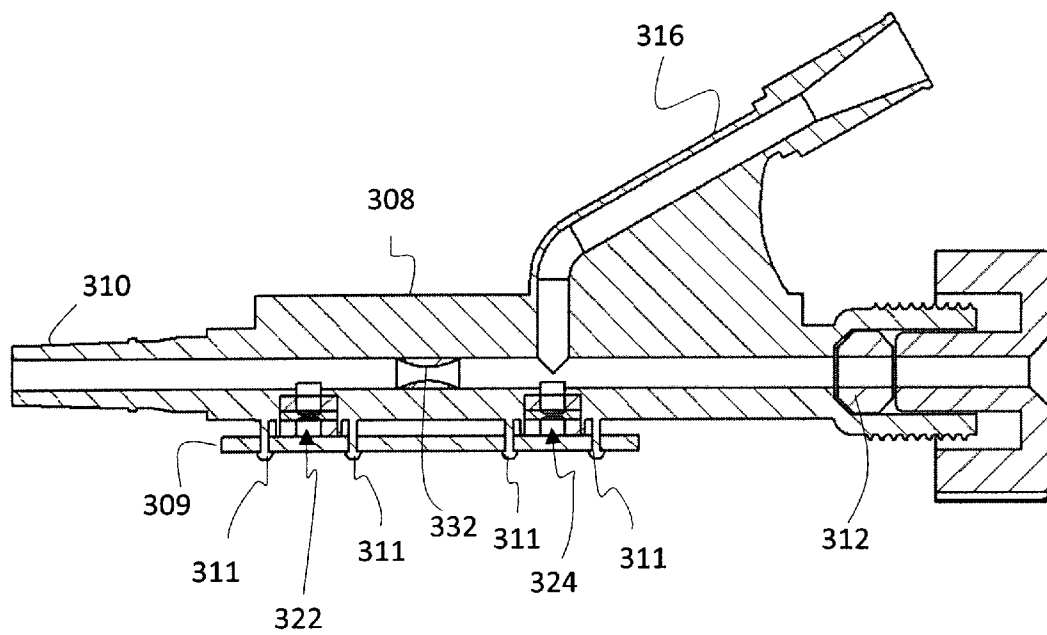


Figure 12

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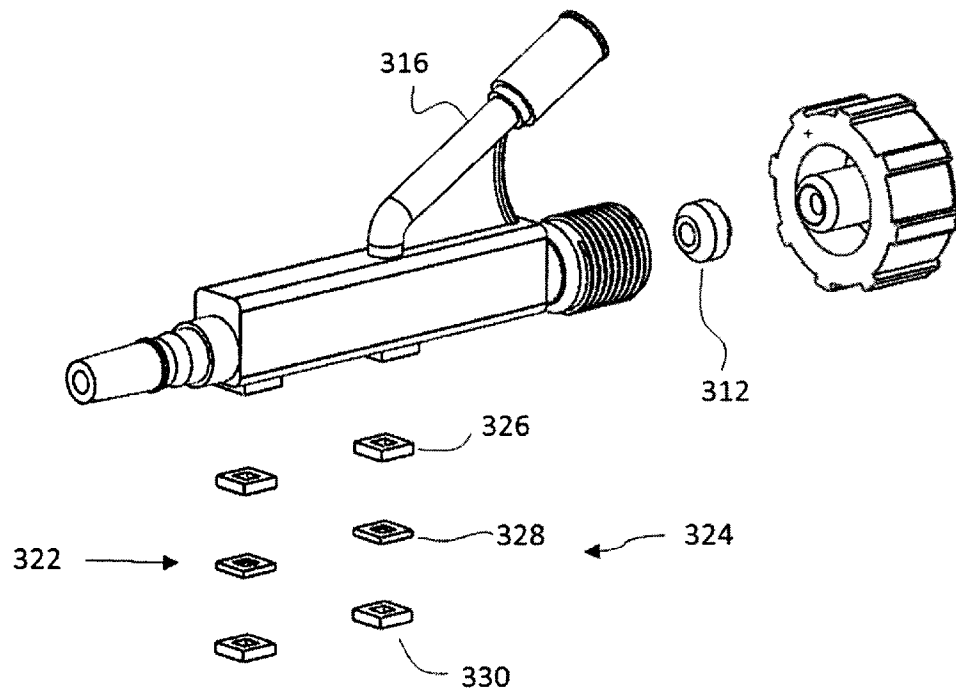


Figure 13

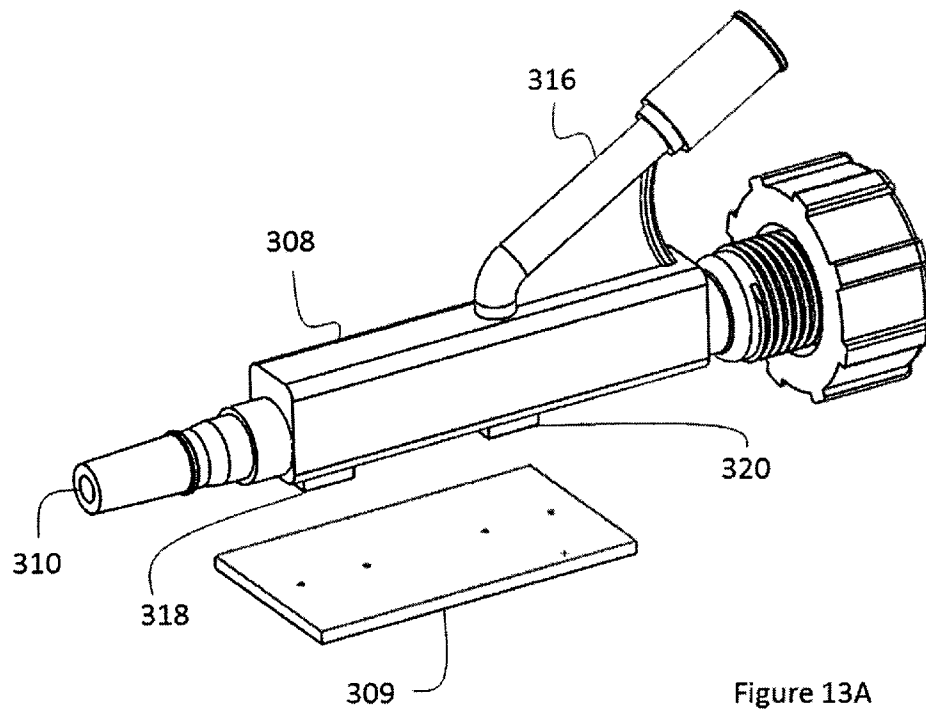


Figure 13A

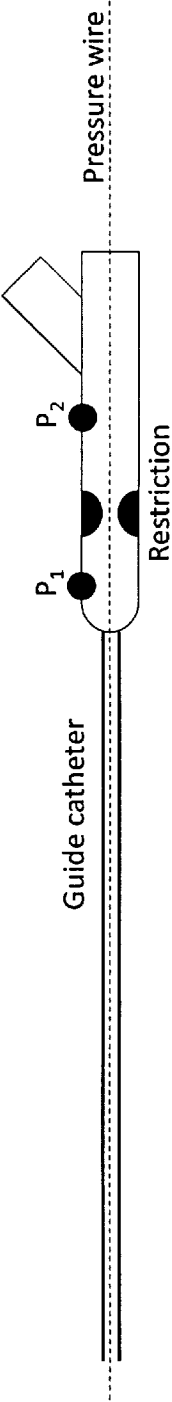


Figure 14

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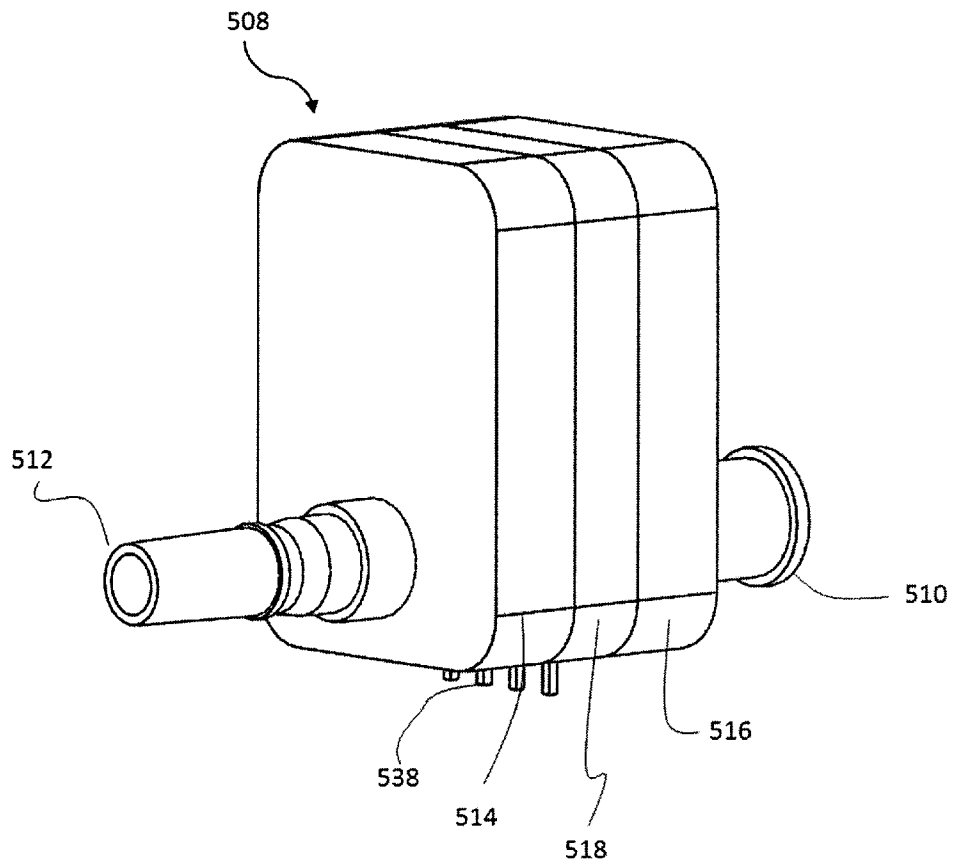


Figure 15

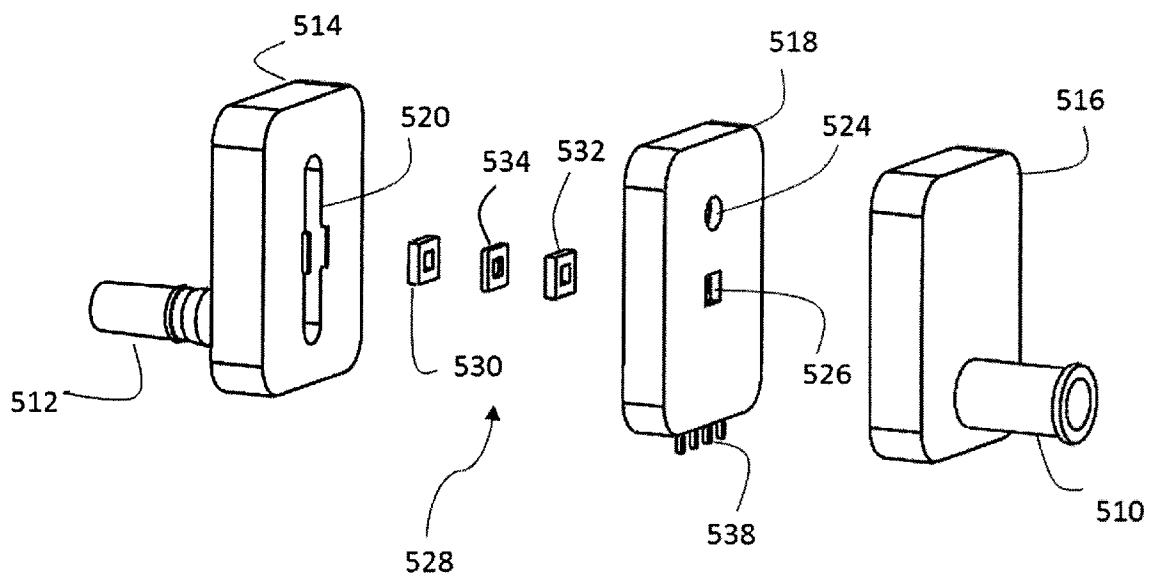


Figure 16

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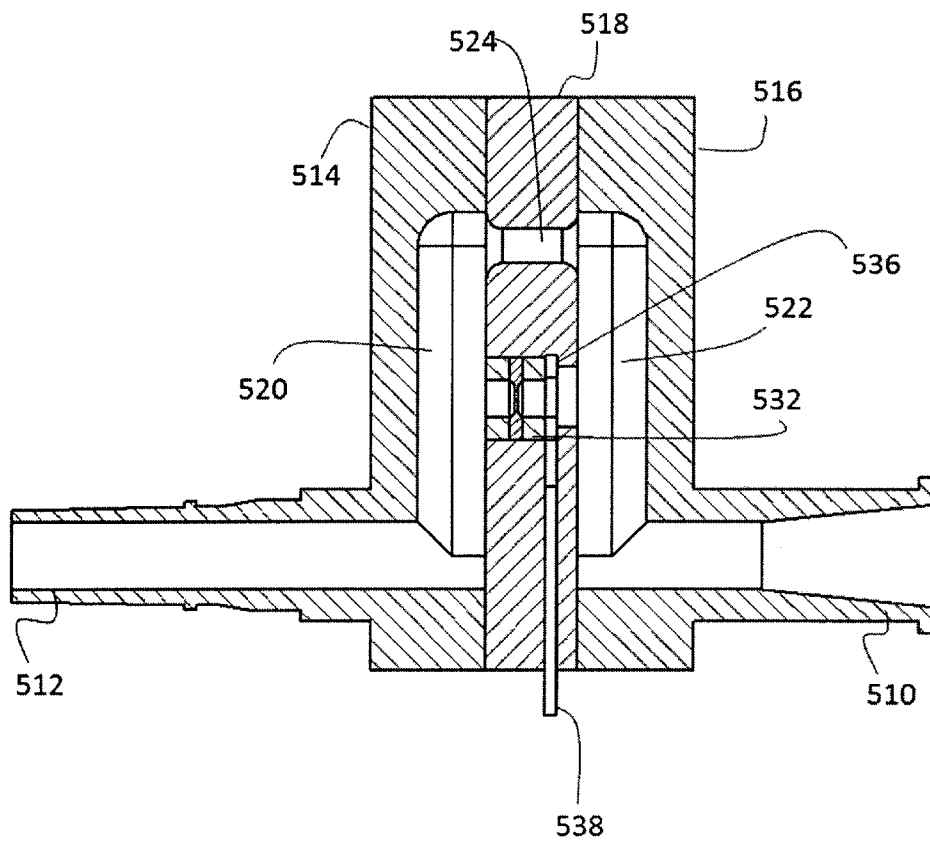


Figure 17

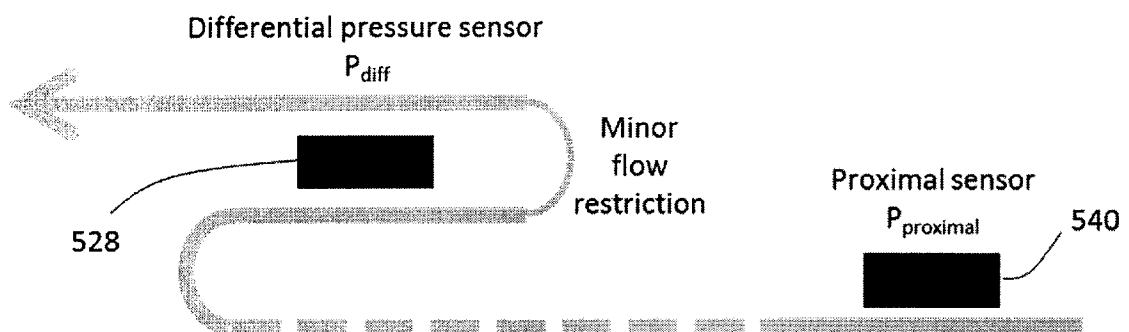


Figure 18

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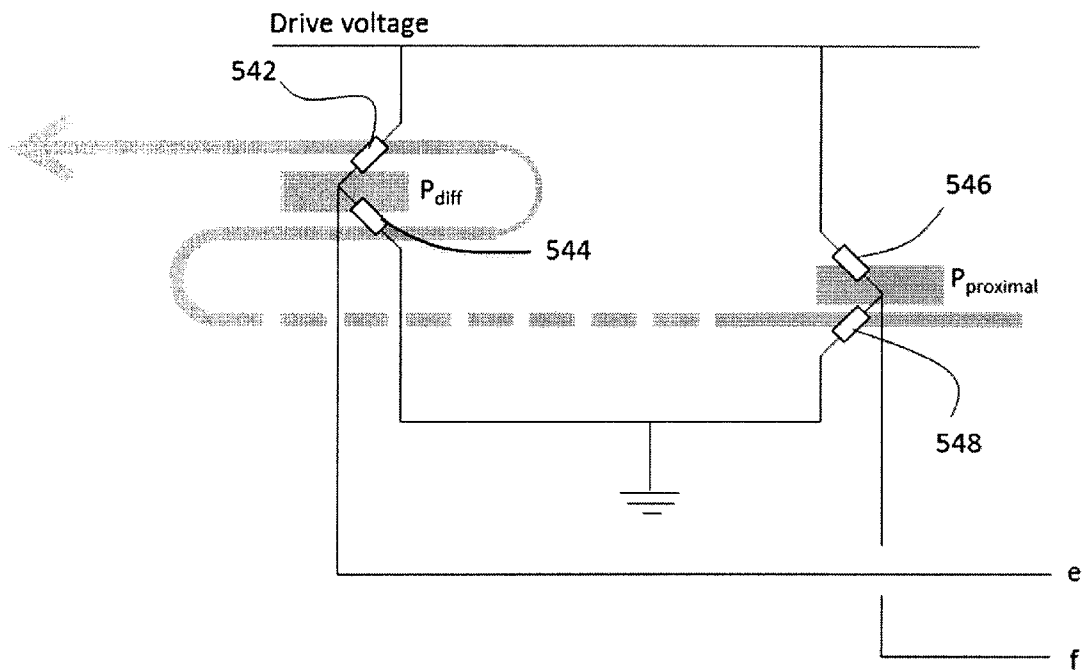


Figure 19

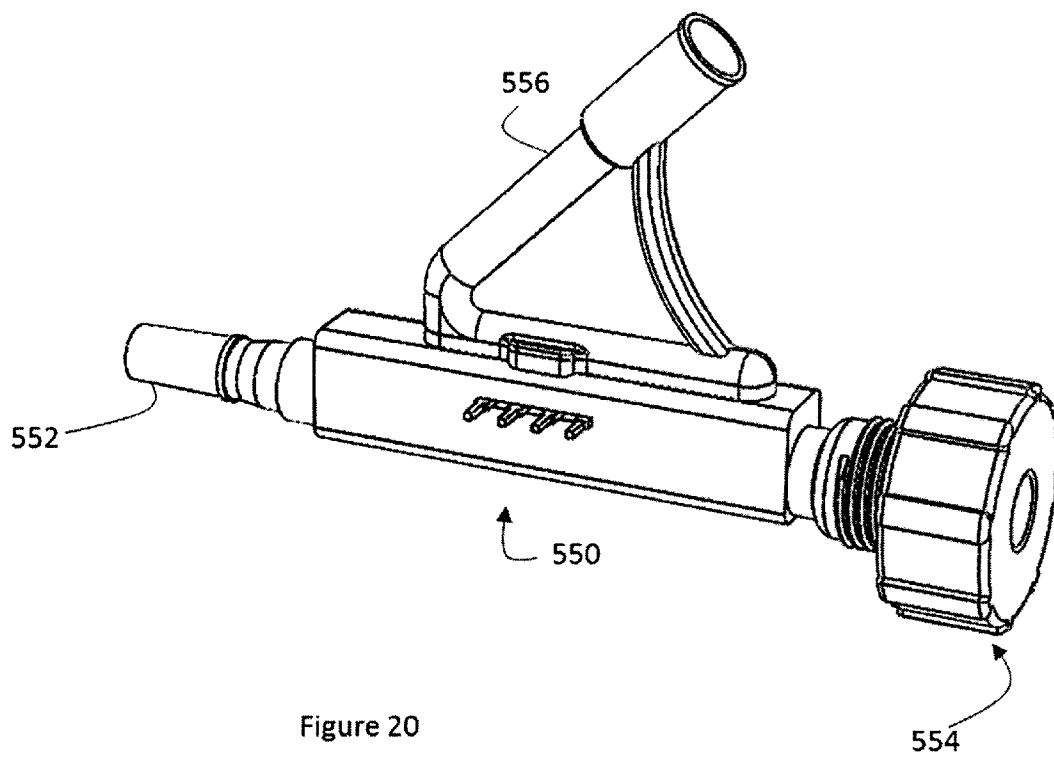


Figure 20

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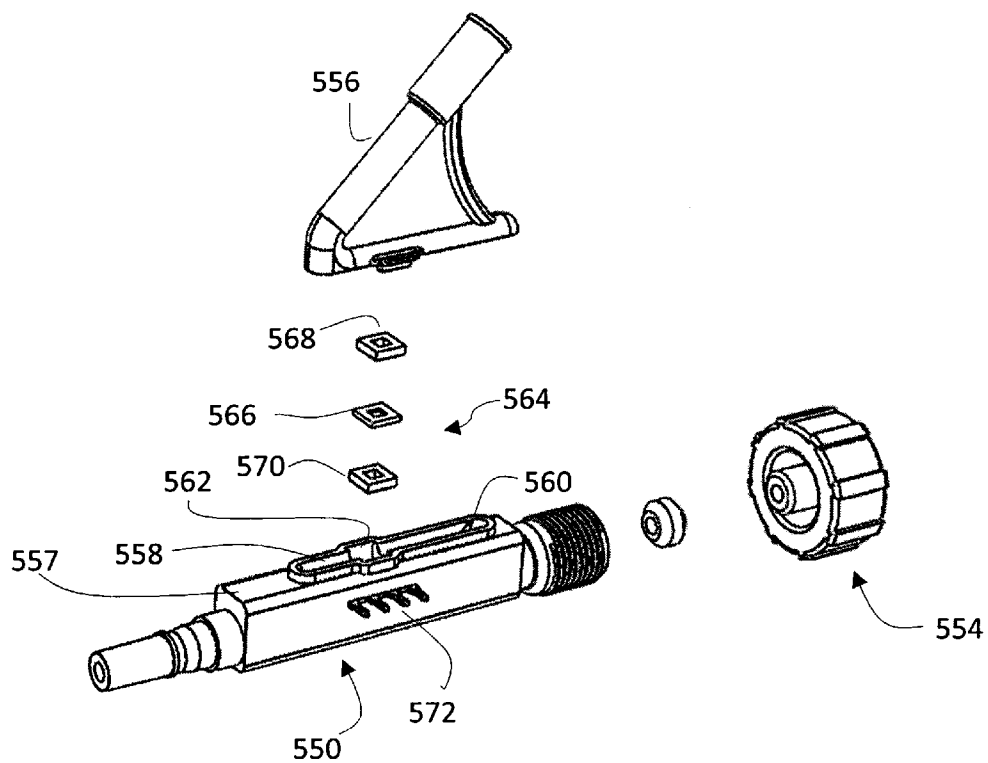


Figure 21

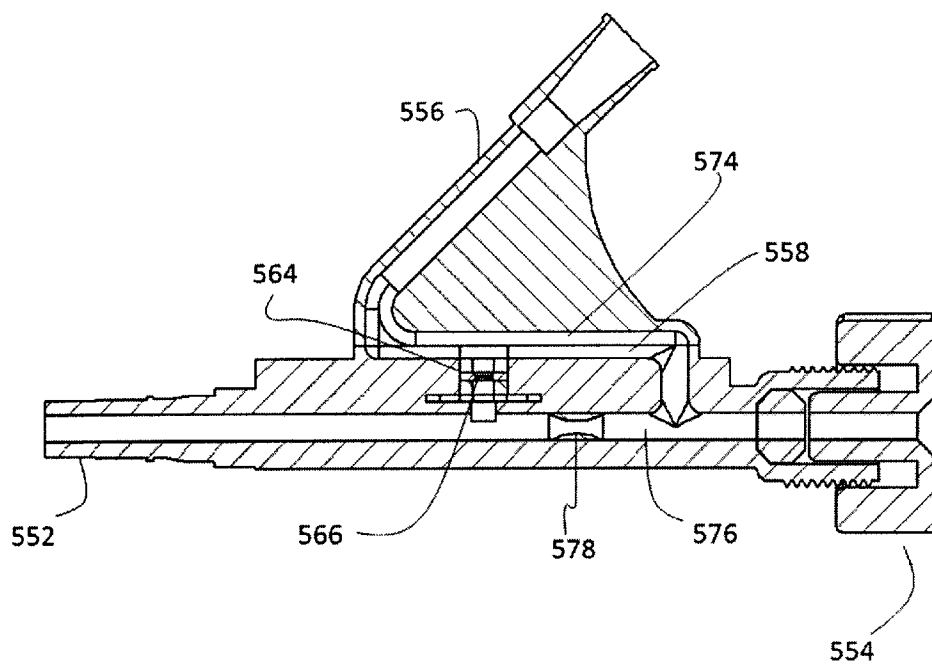


Figure 22

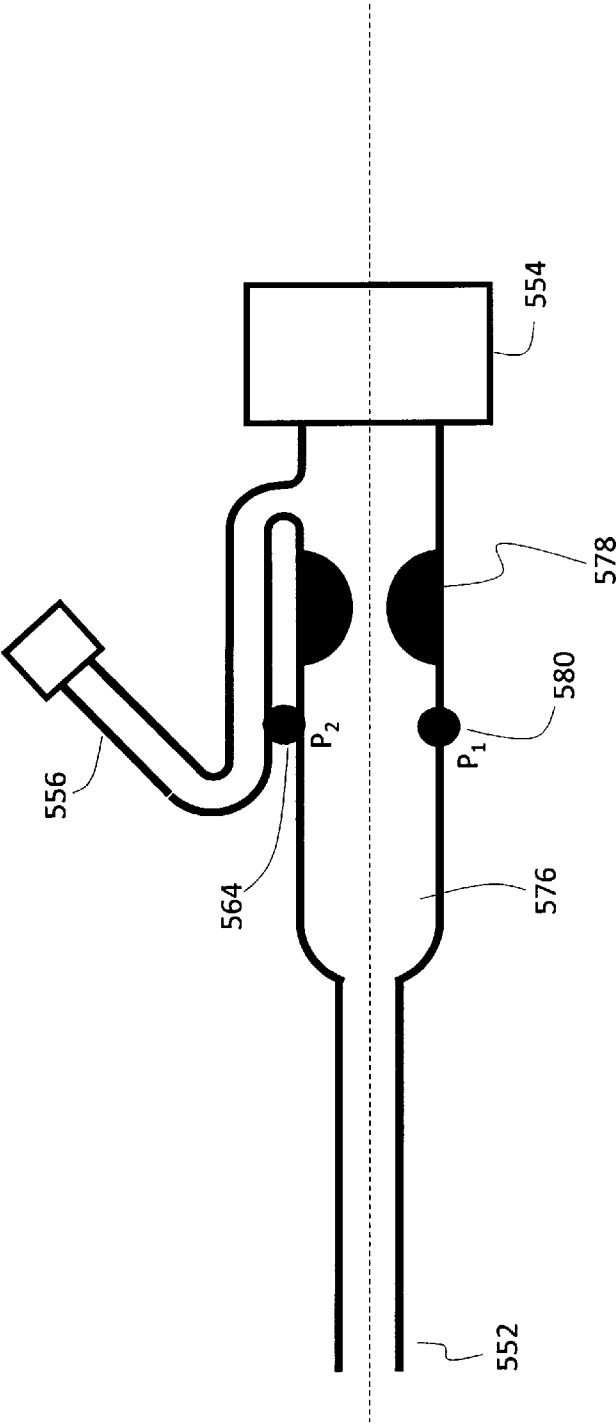


Figure 23

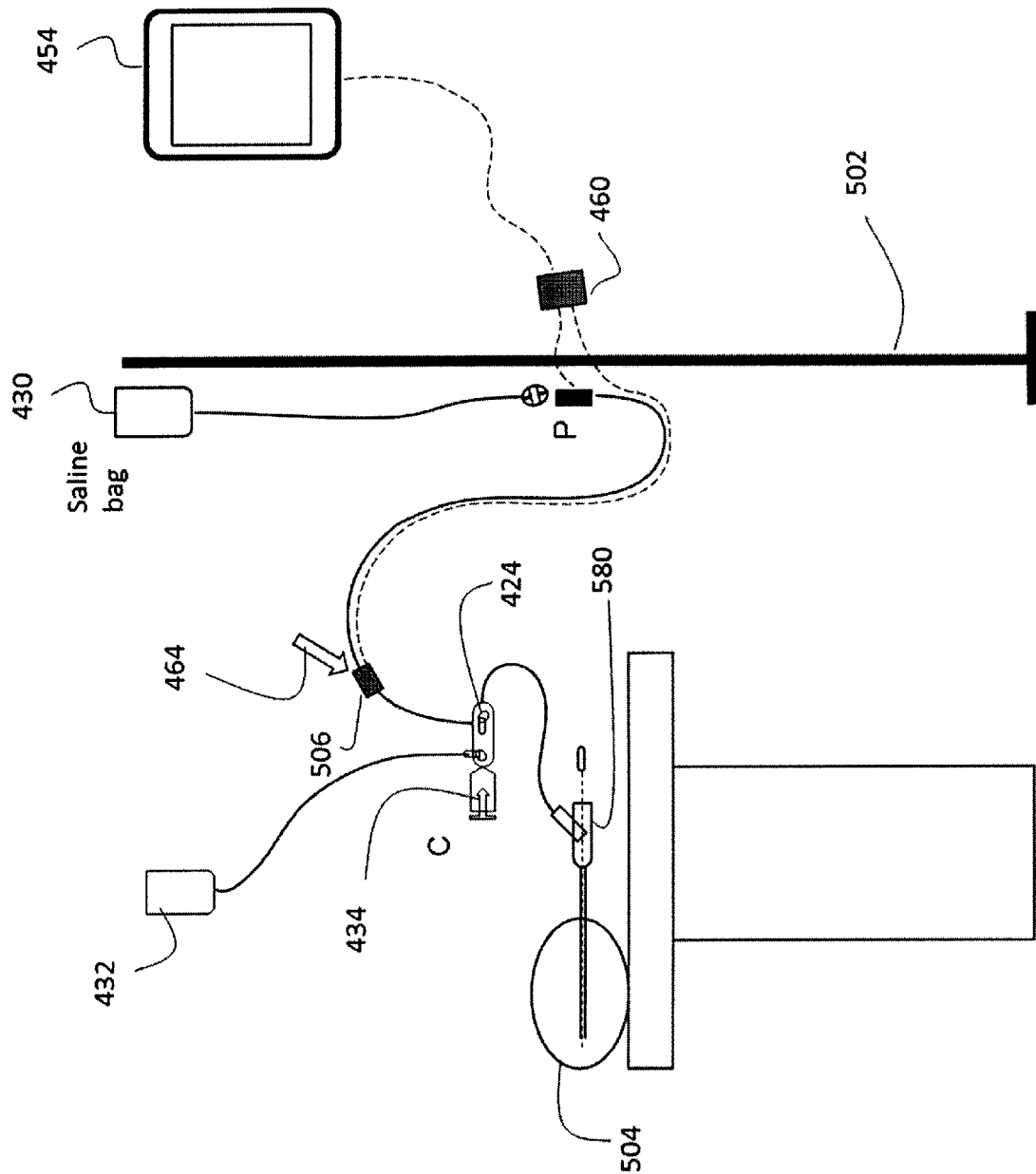


Figure 24

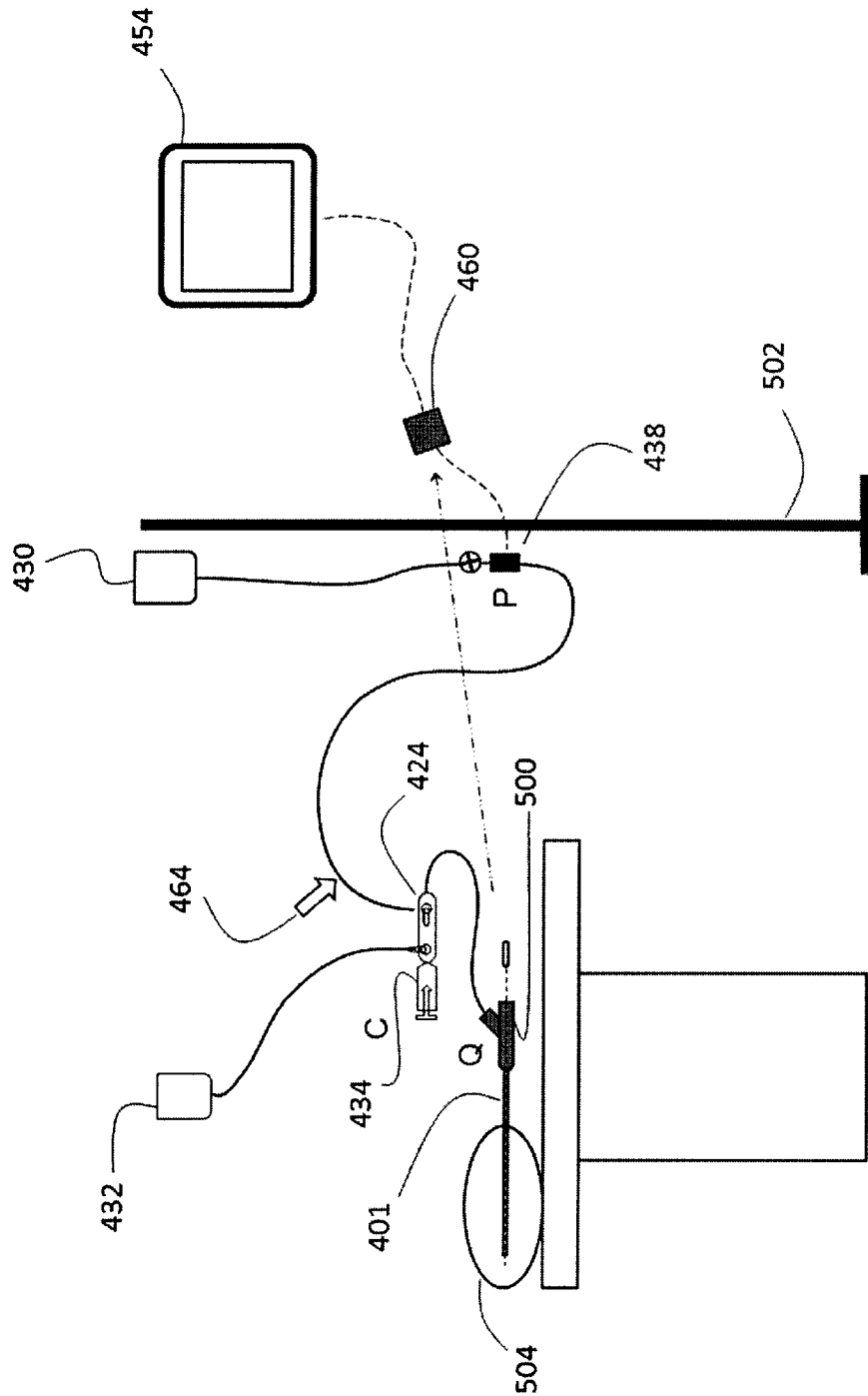


Figure 25

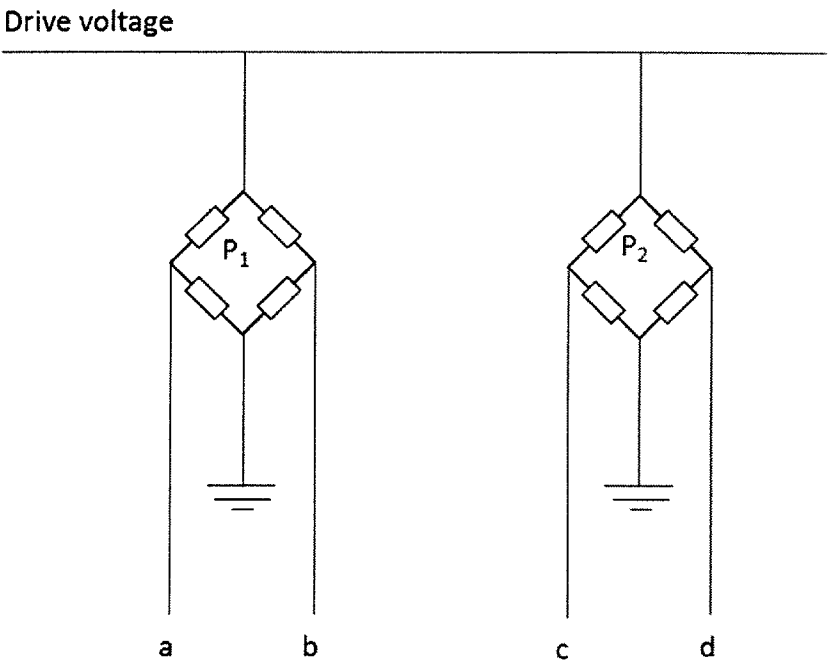


Figure 26

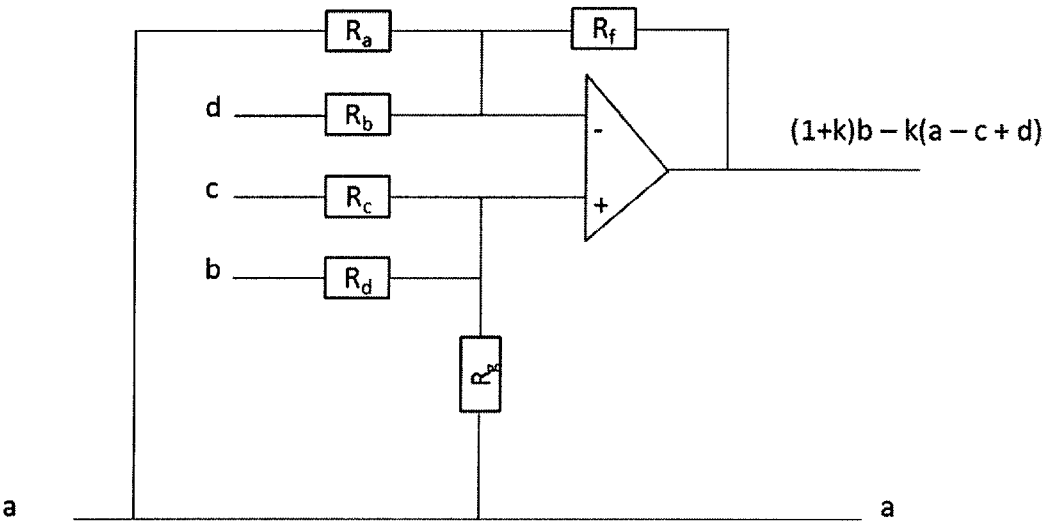


Figure 27

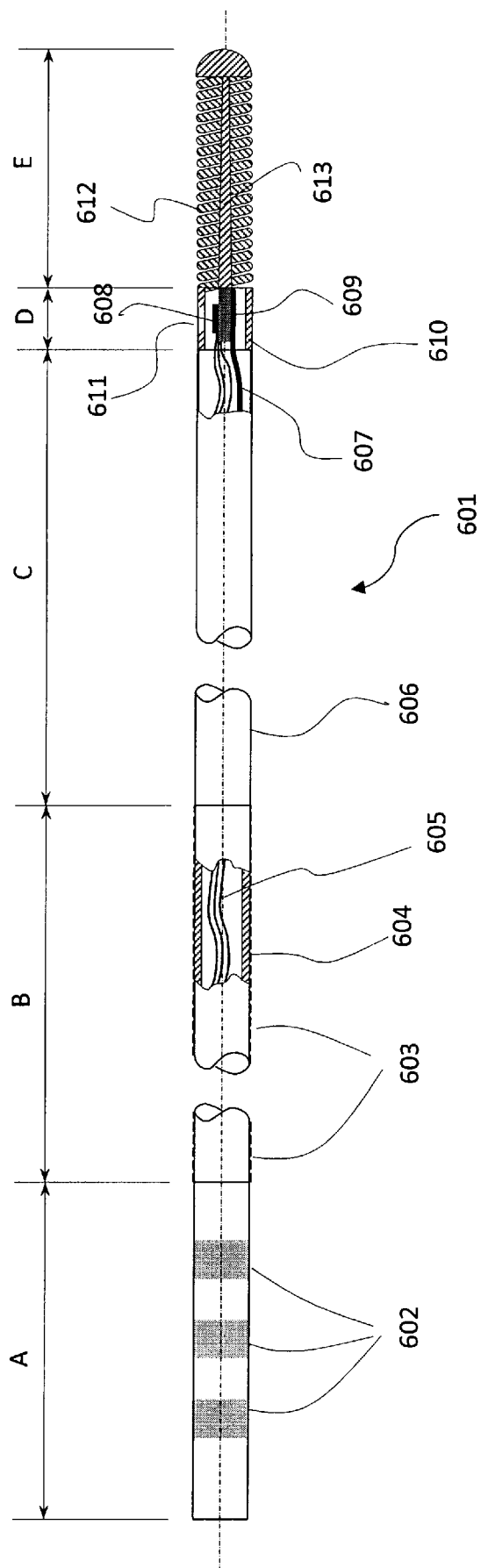


Figure 28

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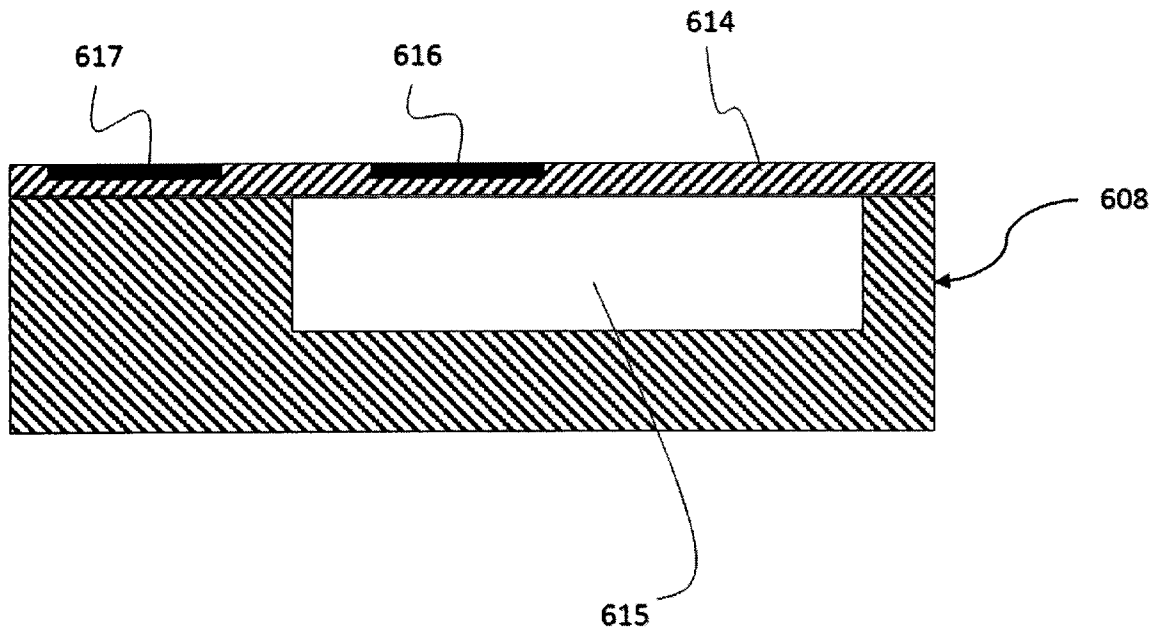


Figure 29

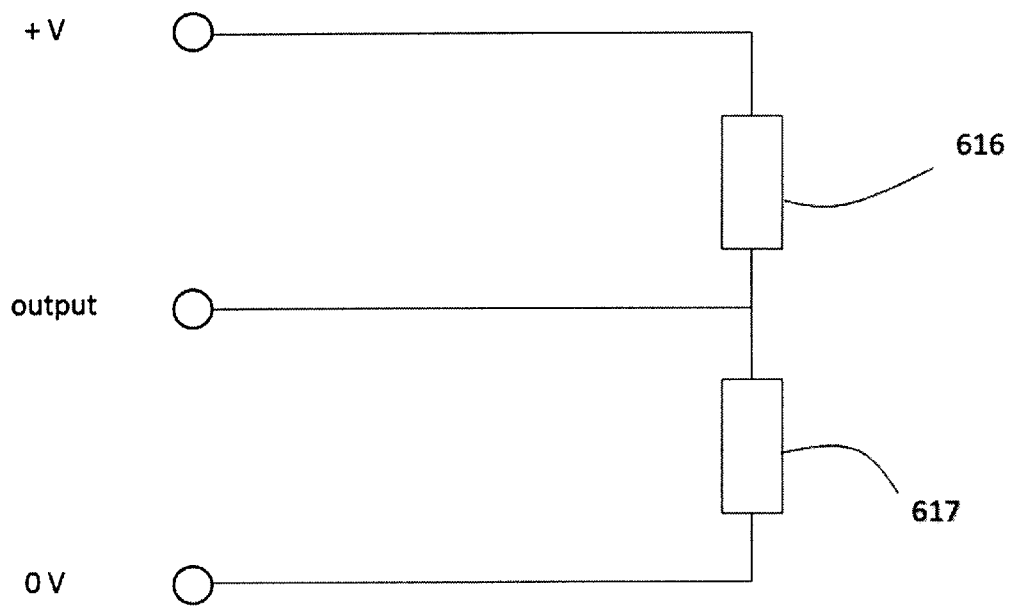


Figure 30

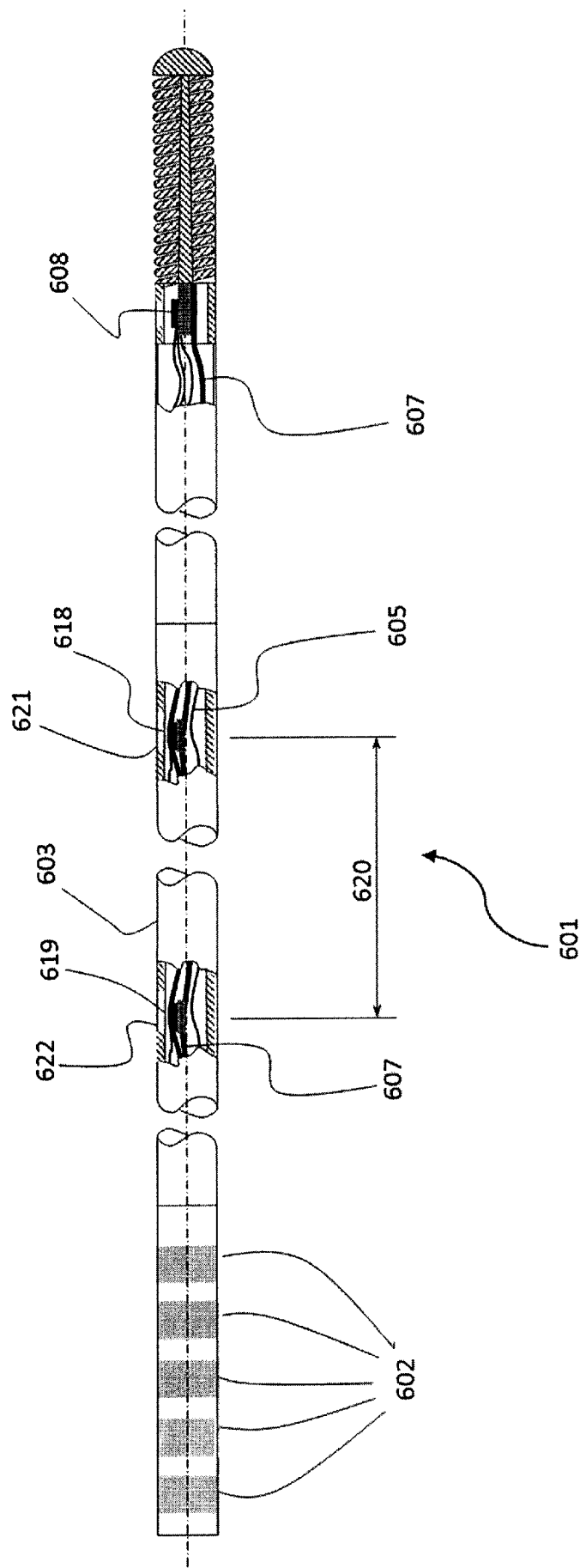


Figure 31

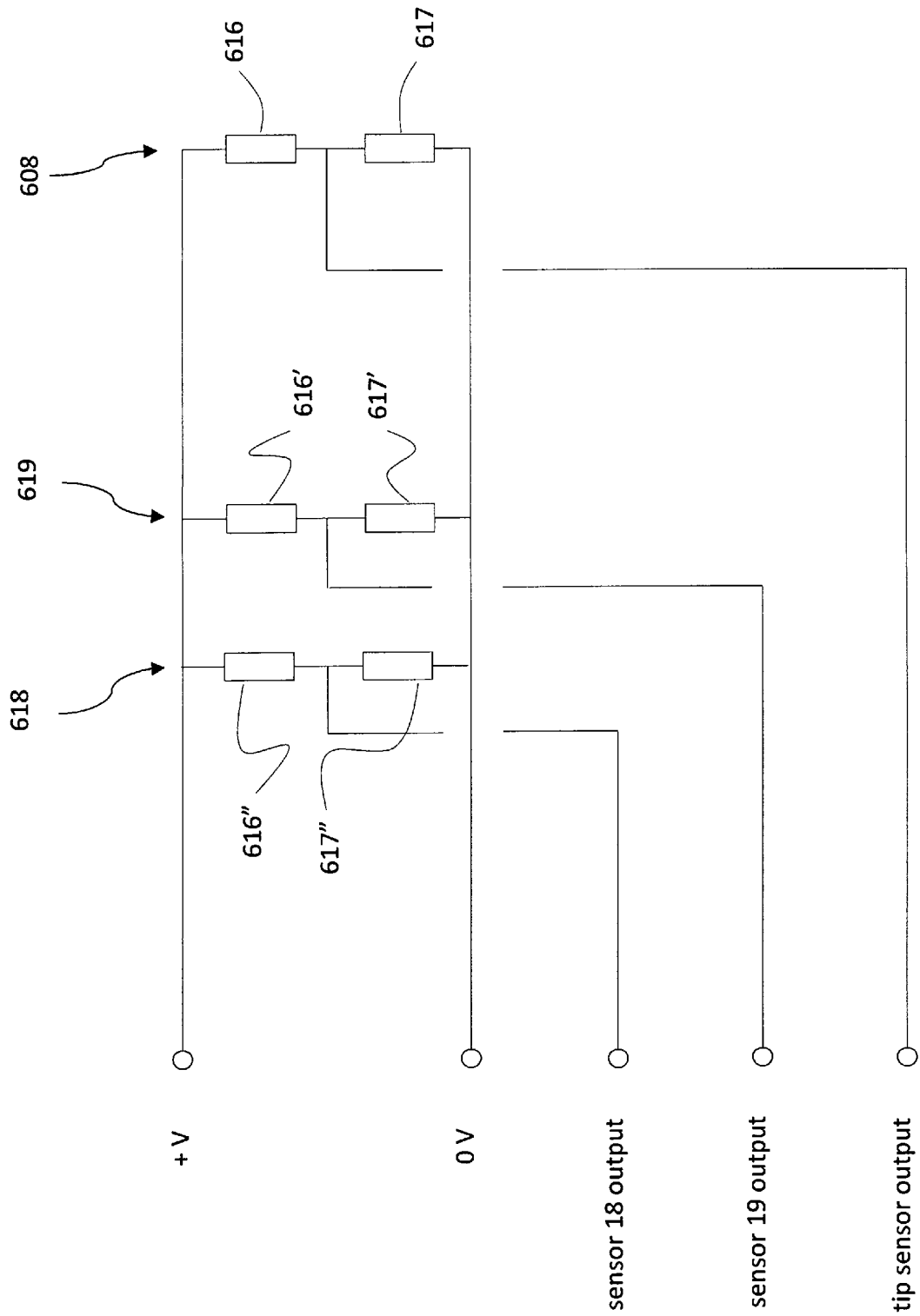


Figure 32

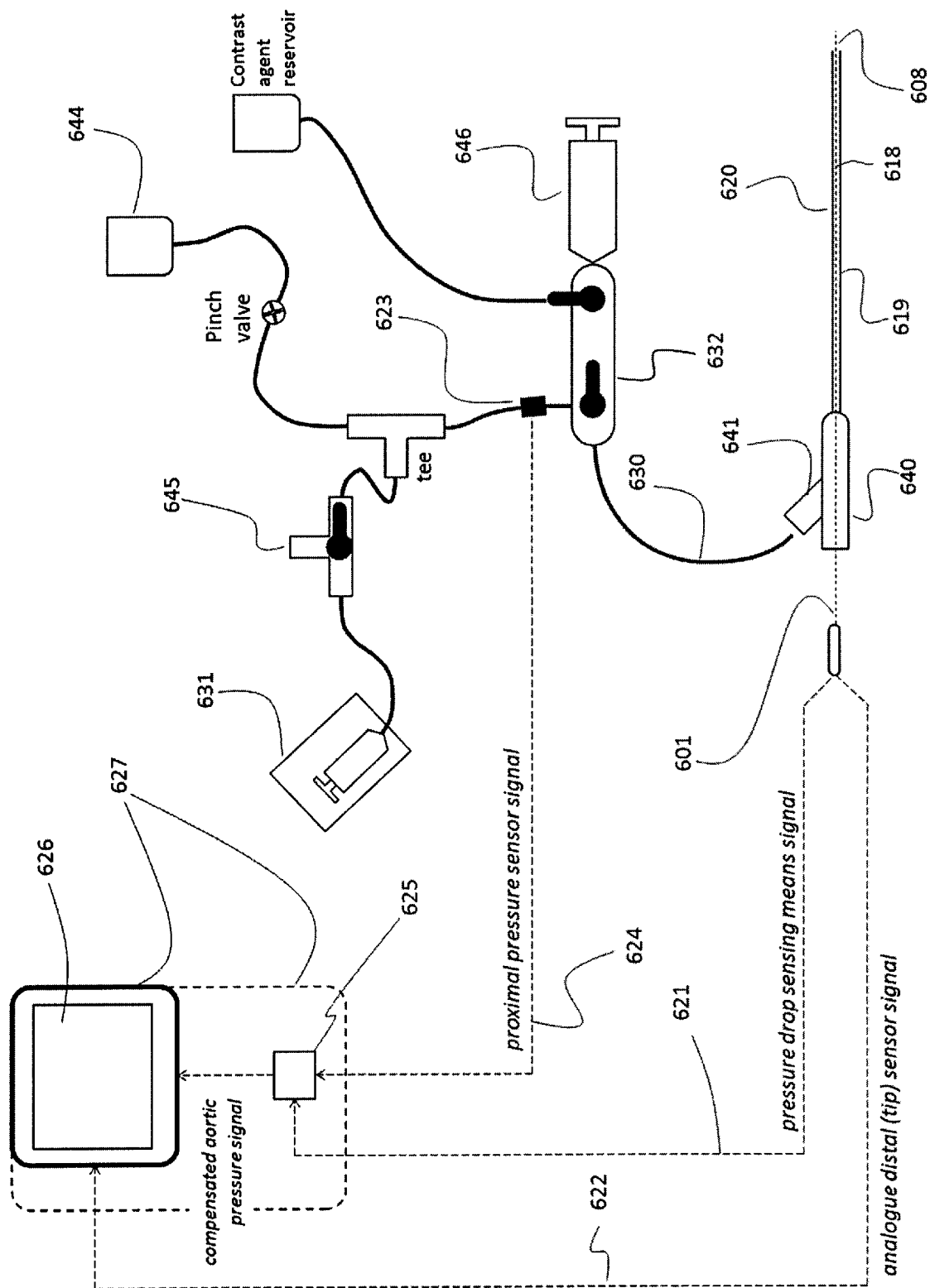


Figure 33

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2016/052162

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61B5/0215
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)

A61B 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)

EP0-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	EP 0 529 902 A2 (SMITH & NEPHEW DYONICS [US]) 3 March 1993 (1993-03-03)	1-8,25, 27,28, 36, 40-44, 49-51, 56,57, 61,62,64
Y	page 3, lines 30-40 page 4, line 1 - page 5, line 9 figures ----- -/--	9-24,26, 29-35, 37-39, 45-48, 52-55, 58-60, 63,65

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search

16 November 2016

Date of mailing of the international search report

22/11/2016

Name and mailing address of the ISA/

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Authorized officer

Bataille, Frédéric

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2016/052162

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	US 5 275 169 A (AFROMOWITZ MARTIN A [US] ET AL) 4 January 1994 (1994-01-04) column 6, line 63 - column 7, line 31 column 12, lines 27-41 figures 2A-2C -----	1-8,25, 27,28, 36,43, 44,50, 51,56, 57,61, 62,64
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International application No

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