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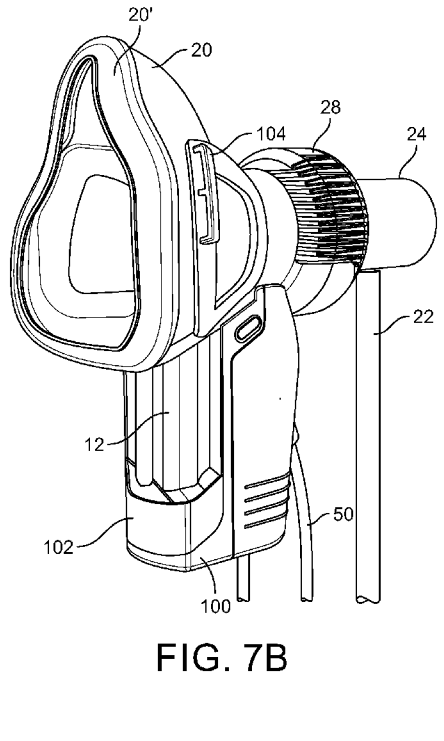

FIG. 7B

(57) Abstract: Disclosed is apparatus for use in obtaining a breath sample from a mammalian, preferably human, subject, the apparatus comprising: a headset which is attachable to the subject; a separate suction pump; and an umbilical connecting the suction pump to the headset so as to allow the suction pump to create a lower than ambient pressure within the headset; wherein the headset comprises: a mask piece which fits over the nostrils and mouth of the subject; at least one breath sample capture device, and at least one valve to regulate the passage of gas into the sample capture device.

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Title: Apparatus and Method for Obtaining a Breath Sample

Field of the Invention

The invention relates to a novel apparatus for use in obtaining a breath sample from a mammalian subject, and to a method of obtaining a breath sample using the novel apparatus.

Background of the Invention

There is increasing interest in the use of breath samples for the detection of biomarkers or other analytes of interest, especially for the detection and/or diagnosis of disease conditions in a subject.

Apparatus for obtaining a breath sample is disclosed, for example, in WO2017/187120 (Owlstone Medical Limited).

In broad terms, the apparatus disclosed in the prior art comprises a mask which fits closely over a subject's nose and mouth, so as to form a substantially air tight seal with the subject. The mask is attached to a housing which comprises a plurality of small pumps which can draw air exhaled from the subject into a selected one of a plurality of sample capture devices (typically industry-standard sorbent tubes).

The housing further comprises a CO_2 sensor and a pressure sensor, which monitor the subject's breathing frequency and adequacy, and an inlet for a scrubbed clean air supply to be inhaled by the subject. The housing further comprises a digital electronic controller for controlling the operation of the pumps and sensors.

The capture devices may be removed from the apparatus after sampling and subjected to analysis e.g. by FAIMS analysis.

The present invention aims to provide apparatus which, in preferred embodiments, provides certain advantages or benefits relative to the apparatus disclosed in WO2017/187120.

Summary of the Invention

In a first aspect, the present invention provides apparatus for use in obtaining a breath sample from a mammalian, preferably human, subject, the apparatus comprising: a headset which is attachable to the subject; a separate suction pump; and an umbilical connecting the suction pump to the headset so as to allow the suction pump to create a lower than ambient pressure within the headset; wherein the headset comprises: a mask piece which fits over the nostrils and mouth of the subject; at least one breath sample capture device, and at least one valve to regulate the passage of gas into the sample capture device.

By way of explanation, the present invention aims to provide certain improvements over the prior art apparatus disclosed in WO2017/187120. In particular, the applicant has found that the headset of the prior art apparatus, which includes one or more suction pumps, has a mass large enough to cause difficulty when sampling, especially during protracted sampling periods of more than about 10 minutes. Specifically, the applicant has found that the weight of the headset tends to cause the subject's head to tilt forward during sampling. This tends to occlude the subject's airways and can cause problems in obtaining sufficient sample flow rates and sample volumes. Accordingly, the present invention aims to provide a breath sampling apparatus having a headset with a lower weight than the prior art and, in particular, a headset with a lower turning moment exerted on a subject's head.

A further improvement of the apparatus of the present invention in preferred embodiments, is to facilitate the capture of larger sample volumes, since the applicant has found that, in some instances, the concentration of molecules or analytes of interest in the subject's exhaled breath is so low that samples obtained using the prior art apparatus do not contain enough mass of the molecule(s) or analytes to be reliably detected. In order to obtain larger sample volumes the apparatus must be suitable for use over prolonged sampling periods (i.e. more than 10 minutes).

In preferred embodiments, the apparatus of the present invention is intended for use in a secondary care context (i.e. typically in a hospital, clinic or other dedicated healthcare facility, and the operator may be a qualified healthcare professional such as a nurse or a clinician).

Headset

The headset advantageously comprises a headset chassis on which the rest of the headset components may be mounted.

The headset is typically provided with releasable attachment means for releasable attachment to the subject's head. The releasable attachment means conveniently comprises an elasticated head band, typically of adjustable length, which passes from one side of the headset around the back of the subject's head, and attaches to the other side of the headset.

The headset typically comprises a headset chassis, on which other components of the headset (e.g. mask portion and tube assembly, described below) can be mounted or to which they can be attached, preferably in a readily detachable manner. The mask piece and tube assembly are typically "single use" components, and are replaced each time the apparatus is used with a different subject.

The mask piece advantageously comprises a resiliently deformable material such as silicone rubber or other synthetic plastics material which, in use, can form a substantially air-tight seal with the subject's skin. In some embodiments, the majority of the mask piece is formed of a rigid synthetic plastics material, with a resiliently deformable surround or perimeter on that part of the mask which contacts the subject, so as to facilitate the formation of a substantially air-tight seal between the mask piece and the subject. Advantageously a substantially air-tight seal is formed around a perimeter of the mask, encompassing the subject's mouth and nostrils.

The mask piece is provided with an air inlet to allow the subject to inhale. In some simple embodiments the air inlet provides ambient air to the subject. In other embodiments the air inlet may provide a source of clean air to the subject which may, for example, be ambient air that has been passed through a scrubber to remove potentially contaminating organic molecules which might otherwise confuse and/or complicate the subsequent analysis if captured on the sample capture device. In particular the inlet may provide air from a “CASPER” clean air supply, described in greater detail below. The clean air may be supplemented with additional oxygen, if desired, and so the apparatus could be used with subjects who require ventilatory support.

The headset is desirably arranged and configured such that those components of it which are re-usable do not come into contact with any potential biological contamination from a subject (bacteria, fungi). To this end, a biological filter is preferably included in the headset. Conveniently this comprises a 0.22μm micropore sterilising filter, which is sufficient to exclude essentially all bacteria and fungi, but not viruses.

The mask piece cannot practically be protected from contamination by a subject and is therefore regarded as a “consumable” i.e. a fresh mask must be used for each new subject. For this reason, the mask piece is desirably designed to be readily detachable from the headset.

The headset also comprises at least one breath sample capture device. A preferred sample capture device is a sorbent tube. These are typically of industry standard design and composition – cylindrical glass-coated metal tubes (usually stainless steel) 3¼ inches (82.6mm) long with an internal bore of ¼ inch (6.4mm), packed with sorbent materials to adsorb volatile organic compounds from a subject’s exhaled breath. Preferred sorbents include a mixture of Tenax® GR and Carbograph® 5TD, but other sorbents are available and may be advantageous if a specific selected analyte or small number of analytes are of interest. The breath sample capture device is preferably provided as part of a component, described herein as a “tube assembly”, although the capture device is not necessarily a sorbent tube. The tube assembly is conveniently readily detachable from the headset, such that a fresh tube assembly can be inserted into the apparatus each time it is used with a new subject. The tube assembly will conveniently comprise other features, as described elsewhere below.

In preferred embodiments the headset comprises a plurality of breath sample capture devices. In preferred embodiments the headset may also comprise an empty sorbent tube (i.e. a tube substantially identical to the sample capture devices, but lacking any sorbent material), for reasons described in further detail below.

The headset also comprises at least one valve, to regulate flow of gas into the one or more sample tubes. The valve may comprise a plurality of outlets, control of the valve determining which of the valve outlets gas is directed to on leaving the valve body. For example, a single valve may have outlet connections to each of a plurality of sample capture devices, and the valve may be operated such that gas passing through the valve body is directed to a selected subset of the plurality of sample capture devices (the subset may be a single capture device, or a plurality of capture devices), or may be directed to all of the capture devices. Additionally, or alternatively, operation of the valve may control whether gas (e.g. containing exhaled air from the subject) is directed to a sample capture device or is vented to the external environment. In a preferred embodiment the headset comprises at least one 3 way valve, where one of the outlets from the valve is to an exhaust and one of the outlets is to a sample capture device.

The headset conveniently further comprises a digital electronic controller, such as a microprocessor or application-specific integrated circuit (ASIC), which may perform various functions, including controlling the actuation of the one or more headset valves, and may also have data inputs from one or more sensors mounted on the headset. The digital electronic controller may perform a data processing function. In addition, the headset may comprise a separate digital data storage component.

In particular, the headset may comprise one or more pressure sensors, which feed data to the digital electronic controller. The pressure sensor can be used to detect blockages or other problems. In addition, or alternatively, a pressure sensor may be used to identify particular phases of the subject's exhalation, and thus the controller can actuate the valve to collect exhaled air at selected phases of the subject's exhalation, thereby collecting a sample representative of, for example, the air from the subject's upper respiratory tract or from the lower respiratory tract, as the case may be. Further detail on the selective sampling of particular portions of a subject's exhaled breath is contained in WO2017/187141.

Another preferred feature of the headset is the inclusion of a movement sensor such as an accelerometer or an orientation sensor such as a gyroscopic sensor to detect improper positioning of the subject's head (e.g. slumping forward) which can partially obstruct the subject's airways and impede sample collection. Such a sensor may also feed data into the headset digital electronic controller.

More especially, in preferred embodiments the movement or orientation sensor detects angular displacement of the headset in at least one axis, preferably in at least two orthogonal axes, and most preferably in three orthogonal axes. In some embodiments the movement or orientation sensor detects only angular displacement, and not any other type of movement (such as translational movement). It will be appreciated that, since the mask portion is normally securely positioned on a subject's face, and should not normally move relative to the subject's face, so that detection of movement by the movement detection means typically indicates movement (i.e. at least angular displacement) of the subject's head.

In preferred embodiments the movement or orientation sensor comprises a gyroscope, more especially a microelectromechanical system (MEMS) gyroscopic sensor. Many different MEMS gyroscopic sensor devices are available, incorporated on integrated microcircuits which can be mounted on printed circuit boards and the like for attachment to the apparatus of the invention. Preferably the sensor takes the form of a gyroscopic sensor chip which is able to determine the position of the headset in three dimensions and in real time. Conveniently the gyroscopic sensor chip is mounted on a printed circuit board which forms an intrinsic part of the headset of the sampling apparatus. There are many different gyroscopic sensor chip devices which are commercially available and suitable for use in the apparatus of the invention. Examples of suitable chips are available online from Farnell (http://uk.farnell.com/mems-gyroscopes).

The chip is preferably positioned on a part of the headset that is distal to the subject's head, such that, for a given angle of head movement by the subject (especially forward and downward tilting movement of the head) the displacement of the gyroscopic sensor chip is maximised.

The apparatus of the invention preferably further includes an alarm signal generator. The alarm signal generator may cause the triggering of a visual alarm or an audible alarm, or may generate both a visual and an audible alarm. Desirably the alarm signal generator is also mounted on a PCB in the mask portion (typically the same PCB on which the movement or orientation sensor is preferably mounted), but the alarm *per se* (e.g. light and/or bell or buzzer) may be generated on the headset or on a remotely situated component of the apparatus, such as a computer monitor, laptop or tablet computer or the like, or a dedicated base station, as described below.

The alarm signal generator preferably generates an alarm signal when the information output from the movement or orientation sensor indicates that the subject's head has moved to a position which is outside a predetermined range of acceptable positions, which are stored in a digital electronic memory operably associated with the apparatus. Conveniently, for example, the apparatus comprises a preset or predetermined range of values for the subject's head orientation in three dimensions (X, Y, Z values), and these predetermined acceptable value ranges may be stored within the memory of the MEMS gyroscopic sensor device, or on a different memory component mounted on the PCB in the headset, or even on a remote memory component (e.g. a computer) operably associated with the headset (e.g. communicating therewith via a wired signal connection or wirelessly by Bluetooth™ or other wireless signalling connection).

Preferably the alarm signal is generated only if the subject's head stays outside the predetermined range of acceptable orientations for at least a measurable or predetermined time period. This is to stop the alarm from being triggered by momentary movements of the subject's head beyond the range of acceptable orientations. For example, the predetermined time period may be any of 3, 4, 5, 6, 7 or 8 seconds, preferably about 6 seconds. Alternatively the measurable time period may be, for example, the time taken for the subject to complete two breath cycles.

An audible alarm may comprise a bell, buzzer or beeper. A visual alarm may comprise one or more warning LEDs or an indication on an LCD or other electronic display screen. Howsoever the alarm is indicated, it prompts the user to require the subject to return their head to an acceptable orientation, or may prompt the subject to do so directly if they have previously been briefed as to the significance of the alarm. The movement or orientation sensor detects the corrective movement of the subject's head and once this has returned the subject's head to an orientation within the predetermined acceptable range of values for orthogonal X, Y and Z axes the alarm signal generation is cancelled and the alarm switched off.

As well as a "tilt" alarm signal, the apparatus may comprise one or more further components to convey information to a user about the status of the apparatus. In simple embodiments these may comprise one or more LEDs for example. As an illustration, the device may comprise a green LED which lights when the apparatus is working normally, and/or a red LED which illuminates if the apparatus has a fault or breath sampling is not proceeding as expected. The green and/or red LED may be illuminated intermittently, e.g. in a flashing mode, to provide further indications to a user.

In addition to detecting movement of the subject's head to sub-optimal positions which may inhibit airflow in the patient's airways, the movement detection means may also optionally be used to identify if and when a subject coughs or sneezes. It is useful to identify such events because they can cause significant changes in pressure within the mask piece of the sampling apparatus. These can affect the readings taken by the apparatus and the operation of the breath sampling in undesirable ways. Accordingly data points in the data stream which correlate with events such as subject sneezes or coughs can be neglected, allowing more reliable and consistent breath sampling.

The sample capture devices are preferably provided as part of a component which may be readily detached from the rest of the headset. This component may be referred to, for simplicity, as the "tube assembly". The tube assembly preferably includes at least one filter (e.g. 0.22μm pore filter) downstream of the capture devices to prevent potential bacterial or fungal contamination of downstream components of the apparatus. In one embodiment each capture device may be associated with its own respective filter. In an alternative embodiment a single, common filter is located downstream and filters gas flow exiting from a plurality of the capture devices, possibly all thereof.

The tube assembly desirably connects to the headset in such a way that a substantially air tight seal is formed between at least the capture devices and the headset. This may conveniently be achieved by using conventional sealing means such as gaskets, sealing rings or the like, conveniently made of silicone rubber Viton® or other sealingly deformable material. The tube assembly advantageously attaches to the rest of the headset with a snap fit action, but other attachment options are possible, such as screw-threaded engagement or luer-type connection.

The tube assembly preferably further comprises a data transfer connection to a digital data storage and/or data processing component in the headset.

Alternatively, or in addition, the tube assembly component may itself comprise a digital data storage and/or data processing component.

In one embodiment the tube assembly component comprises a digital data storage component which stores data regarding the tube assembly. This data may be transferred to a digital data processing component on the headset via a data transfer connection established when the tube assembly is correctly docked on the headset chassis. Data stored in the data storage component on the tube assembly may include, for example, data concerning the type of sample capture device contained in the tube assembly, the type of analyte the capture device is suitable for capturing, expiry dates etc.

The data storage component on the tube assembly is preferably capable of being "written to" by a data processing component in the rest of the apparatus (typically by a component located on the headset chassis). The data transferred to the data storage component on the tube assembly may include information about the sampling conducted (e.g. a subject identifier; date and time of sampling; any error messages; the length of sampling; an operator identifier etc.).

The data storage component advantageously comprises an integral memory chip, which performs or permits one or more of the following: storage of test specific breath collection/fractionation parameters; recording of 32x16-bit numbers to characterise the breath samples; storage of patient identification number directly with breath sample data; and logging of any error codes associated with the breath sampling.

There are several possible memory chips suitable for this purpose, including, for example, the Maxim Integrated DS28E25 or Microchip ATSHA204A range. Both the aforementioned chips include 4kbit of memory, SHA256 hardware security features, and come in a variety of packages, including rectangular PCB mounted and integral self-contained versions with their own contact pads. Both also have so-called "1-wire" interfaces that need only two connections, but the applicant proposes to use a chip mounted on a PCB with electro-mechanical contacts, allowing 4 contacts (12C).

In a preferred embodiment, the tube assembly communicates with e.g. a digital electronic controller which controls the operation of the apparatus, such that there is provided a functional interlock which prevents the digital electronic controller from performing a breath sampling protocol which is inappropriate for the type and/or number of breath sample capture devices contained in the tube assembly. By way of explanation, it is envisaged that different types of sample capture device may be employed for different types of breath sampling protocols in which for instance, different protocols are employed to optimise the detection of different biomarkers or other compounds in the subject's exhaled breath. In particular, different sorbent materials may be desired for optional capture and/or subsequent analysis of different biomarkers.

As mentioned elsewhere above, in a preferred embodiment, the tube assembly comprises a ‘blank’ capture device (e.g. a sorbent tube not containing any sorbent material). This blank device is advantageously positioned upstream of a pressure sensor device. The pressure sensor may be in the tube assembly but more preferably is located in the headset, and is operably associated with the blank in the tube assembly via an air tight seal, which seal is formed when the tube assembly is docked on the headset chassis. In this way, the pressure sensor can be used to detect pressure (absolute and/or relative pressure) in the mask piece during sampling. The ‘blank’ allows the sensor to be sensitive and respond quickly to changes in pressure in the mask piece.

Conveniently the headset will comprise one or more sensors to sense the rate of flow of air through one or more parts of the headset. In a preferred embodiment at least one flow rate sensor is provided to measure the rate of flow through, or into, each of a plurality of sample capture devices, in order to permit calculation of the total breath sample volume collected.

Base Station

The apparatus comprises a vacuum pump or suction pump separate from the handset. The vacuum or suction pump is preferably provided as a component in a base station.

A typical suitable pump will have the capacity to pump about 3 litres/min and generate suction of about 0.5bar. Other desirable features include: chemically clean (no outgassing), non-pulsatile, and reliability with low maintenance requirements. Diaphragm or rotary vane pumps may be especially suitable.

A particularly suitable vacuum pump is the Thomas 142500 twin-head diaphragm pump, but other suitable pumps are commercially available.

In one embodiment, the vacuum pump operates substantially continuously during the breath sampling procedure, but preferably exhaled breath from the subject is drawn into the sample capture devices intermittently, as desired, by suitable actuation of the valve or valves located in the headset. Conveniently the at least one valve comprises a multiple outlet valve, in which one of the outlets makes a gas flow communication or connection with a breath sample capture device. If desired, the actuation of the valve may be controlled by an apparatus digital controller so as to sample exhaled breath only during a selected portion of the exhalation breathing pattern of the subject, over a plurality of exhalations, so as to capture a selected breath sample which is enriched with a particular fraction of exhaled air, e.g. representative of upper or lower respiratory tract, as desired. A suitable valve is the Burkett 621b type 3-way valve, but other suitable valves are readily available commercially. This particular valve is especially useful as it can switch between different outlets very quickly (about 5m/s operating time), which permits the possibility of capturing selected exhaled breath fractions.

In preferred embodiments, the vacuum pumping system is designed so that the vacuum pump runs substantially continuously during the sampling procedure. When breath is not being collected through a sorbent tube the flow is switched to suck ambient air via an alternative (or bypass) flow path. This means the vacuum system is always in steady state and when the breath sample collection valve is actuated suction (and hence sample collection) commences substantially instantaneously.

The bypass flow path ideally has a linear pressure versus flow characteristic to make it equivalent to an average sorbent tube, and has a very similar pressure drop to that across the sorbent tube.

Many manufacturers produce sintered stainless parts and can tune the properties to achieve desired characteristics. A suitable filter for the bypass flow path is the Swagelock cylindrical sintered filter (5mm diameter x 5mm high with 7μm pores) and has the required pressure loss characteristics.

As well as the vacuum or suction pump, the base station contains an electrical power supply. This may comprise a self-contained power supply (e.g. a battery, a fuel cell) and/or may comprise a connector to an external power supply (i.e. a mains power supply) together with an appropriate electrical connector, a transformer and/or rectifier etc. and an electrical outlet to supply electrical power from the base station to the headset.

The base station preferably comprises or further comprises a user interface. This will typically include a display screen or monitor. The display screen may conveniently be touch-sensitive. The user interface facilitates communication between the user and the apparatus: the user may input data, parameters and commands into the apparatus; and the apparatus can display information to the user (e.g. status; error messages; sampling progress indicator; etc.).

The base station preferably comprises or further comprises digital electronic control means such as a computer, microprocessor or the like to control the overall operation of the breath sampling system. The control means is preferably electronically programmable, and the base station may be provided with firmware or on-board software to operate the apparatus.

The base station preferably comprises or further comprises a CO_2 sensor, which can measure or monitor the absolute and/or relative amount of CO_2 in the breath exhaled from the subject. The primary purpose of the CO_2 sensor is to provide an estimate of the total lung volume of the subject - which may be used to calibrate the system and to adjust (scale) the volatile organic compound or other biomarker signals from the subsequent sample analysis. A suitable sensor is the PrimIR sensor, from Gas Sensing Solutions, although suitable sensors from other suppliers are available. The base station will typically also comprise at least one pressure sensor, at least one flow rate meter, and at least one timer means (e.g. a digital clock).

<u>Umbilical</u>

The umbilical conveys the suction, generated by the vacuum or suction pump in the base station, to the headset of the apparatus. As such the umbilical establishes an essentially air-tight gas flow conduit between the base station and the headset.

The umbilical is preferably flexible, so as to allow for a degree of relative movement between the headset and the base station. The umbilical typically comprises a flexible tube, hose or other flexible conduit or pipe. A suitable material comprises Tygon® or similar synthetic polymer material. A Tygon® tube with an inner diameter of about 3.2mm is especially suitable.

In addition to transferring suction, the umbilical preferably also transports electrical power from the base station to the headset. The umbilical thus conveniently further comprises insulated electrical flex or wiring to establish an electrical power connection between the base station and the headset.

Further, the umbilical advantageously comprises a data transfer or communication means to allow for data transfer or communication between the headset and the base station. Such communication is preferably two-way. The data transfer or communication means preferably comprises one or more electrical conductors. In one embodiment there are four such conductors – two for receiving data from the headset and two for transmitting data to the headset.

In some embodiments, the apparatus comprises a dedicated clean air supply ("CASPER"), which provides scrubbed air (optionally enhanced with oxygen or other gas) to the subject.

In such embodiments, the clean air supply is preferably provided to the headset via the umbilical. Again, a flexible air-tight tube, hose or other conduit is conveniently employed for this purpose. The material may be Tygon® or other similar synthetic polymer. An especially suitable material for the clean air supply is a Tygon® tube with an internal diameter of about 6.4mm.

Typically the umbilical will comprise an outer protective sheath, which wholly or substantially surrounds the various tubes, wires, hoses etc. provided in the umbilical. The outer sheath is preferably formed from a flexible material, such as a synthetic plastics material. At either end of the protective sheath the various wires, tubes and conduits separate and feed into respective connectors on the headset and base station, as appropriate.

Clean Air Supply

In those embodiments in which the apparatus includes a clean air supply to the subject, the clean air supply will preferably be provided via a “CASPER” unit. The CASPER unit may form an integral part of the base station, or may be provided as a separate unit. If the latter, then it is possible to pass the air exiting from the CASPER through the base station, to facilitate the monitoring of the air supplied to the subject, using suitable monitoring means located in the base station, but this is not essential. Parameters of the clean air supply that may conveniently be monitored include O_2 concentration, CO_2 concentration, pressure, and flow rate and suitable means for monitoring one or more of these may optionally be located on the base station, or optionally provided elsewhere in the system.

In a typical embodiment, the CASPER includes a pump to pump air to the subject, and a scrubber to clean the air by removing, for example, volatile organic compounds which might otherwise contaminate exhaled breath samples from the subject. The pump preferably has an output flow rate of at least 40 litres/minute.

In some embodiments, an additional auxiliary scrubber unit may be provided, between the CASPER and the headset, to provide even greater removal of volatile organic compounds from the air supplied to the subject.

The clean air supply is designed to provide a positive end expiratory pressure for the subject facilitating usage in patients with obstructive and restrictive lung disease. Furthermore, the CASPER can operate if this supply of clean air has additional oxygen added, up to and including 100% oxygen. This permits use of the device with subjects requiring ventilatory support and usage in exposure experiments with spiked gases inhaled by the subjects such as common in diffusion tests.

In a second aspect the invention provides a method of obtaining a breath sample, the method comprising use of the apparatus of the first aspect defined above. More especially the method comprises the steps of (i) contacting the mask piece of the apparatus with the subject; and (ii) either before or after step (i), activating the vacuum pump of the apparatus, such that when the mask piece is in place, at least some exhaled breath of the subject is drawn into the breath sample capture device.

General Principles

There are several general principles which the inventors have adopted in arriving at the present invention.

These include:

1. insofar as it reasonable, minimising the weight of the headset, so as to reduce user discomfort and facilitate maintenance of correct head position by the subject;

2. a need to collect larger sample volumes so as to detect analytes of interest which may be present in exhaled breath at very low concentrations;

3. a desire to reduce dead volume, where appropriate, so as to maximise responsiveness; and

4. a need to ensure that, in the relevant parts of the apparatus, the materials employed in the construction of the apparatus are not likely to "outgas" volatile organic compounds which could contaminate the collected breath samples in a way which might confuse or complicate the analysis thereof.

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

Figure 1 is a schematic representation of one embodiment of apparatus in accordance;

Figure 2 is a schematic view of one embodiment of the mask portion of apparatus in accordance with the invention, and showing its connections to other components of the apparatus;

Figure 3 is a perspective view of one embodiment of a tube assembly for use in the apparatus of the invention;

Figure 4 is a perspective view of one embodiment of a headset chassis for use in apparatus in accordance with the invention;

Figure 5 is a perspective view of the components illustrated in Figures 2-4 in their correct relative positions in apparatus in accordance with the invention;

Figure 6 is an exploded view of some of the components of a base station in one embodiment of apparatus in accordance with the invention;

Figures 7A and 7B are perspective views, from different angles, of one embodiment of a headset and associated components, of apparatus in accordance with the invention;

Figures 8A and 8B are schematic diagrams of one embodiment of a device in accordance with the invention: Figure 8A illustrates the headset component and Figure 8B illustrates the base station and clean air supply components; and

Figures 9A and 9B are schematic diagrams of a further embodiment of a device in accordance with the invention: Figure 9A illustrates *inter alia* the headset component, and Figure 9B illustrates the base station and clean air supply components.

<u>Detailed Description of Embodiments</u>

<u>Example</u> 1

Referring to Figure 1, one embodiment of breath sampling apparatus in accordance with the invention comprises a headset, indicated generally by reference numeral 2, a vacuum pump housed in a base station 4, an umbilical 6 providing air tight connections between the base station 4 and the headset 2, and a “CASPER” clean air supply unit 8.

The headset 2 comprises two consumable or disposable sub-components: a mask piece 10, and a tube assembly 12. These sub-components are consumables in the sense that a new mask piece 10 and tube assembly 12 must be used for each new subject.

The tube assembly 12 comprises a plurality of sorbent tubes which act as sample capture devices by capturing volatile organic compounds and analytes of interest present in exhaled breath from a subject.

In use, the headset is attached to the subject’s head by an elasticated band, so as to position the mask piece 10 over the subject’s nostrils and mouth and form a substantially air-tight seal with the subject.

The CASPER unit 8 contains an air inlet, which admits ambient air into the unit. The ambient air is cleaned by passage through a scrubber, which removes any volatile organic compounds which might be present in the ambient air and which might otherwise contaminate the captured breath samples. The scrubbed clean air is then pumped through the base station 4, via the umbilical 6, to the mask piece 10.

The subject inhales the clean air supplied to the mask and exhaled breath is fed, via the mask piece 10, to the tube assembly 12, where the compounds and other molecules present in the exhaled breath are captured, for subsequent analysis, preferably by FAIMS.

The base station 4 comprises a user interface which enables a user to input commands and data into the apparatus and to view data and other information generated by the apparatus. The base station includes a programmable digital electronic control means and a display. The base station also contains a source of electrical power (obtained from internal batteries or from connection to an external mains power supply) and this is fed, via the umbilical 6, to the headset 2.

The structure and operation of the various parts of the apparatus will now be described in further detail in relation to a particular embodiment.

With reference to Figure 2 there is shown, schematically, an embodiment of a mask portion of apparatus in accordance with the invention and its connections to other components. The mask piece comprises a face mask 20. This is a single-use item made of moulded synthetic plastics and having a flexible edge material to facilitate the formation of a substantially air-tight seal with the subject's face. A fresh face mask 20 is used for each new subject, and the face mask 20 is made available in a plurality of sizes, to fit subjects of different size and age.

The mask piece 10 is supplied with clean scrubbed air from the CASPER unit 8, which is fed via umbilical 6 (Figure 1) and tubing 22 to the mask 10. Tubing 22 is ¼ inch (6.4mm) internal diameter Tygon® tubing. The tubing is attached at its proximal end to a right-angled connector 24 of rigid moulded plastics, which also accommodates an exhaust valve 26. The air passes through a commercially available standard 0.22μm pore filter housed in filter unit 28 before reaching the face mask 20.

The mask piece 10 clips into the headset 2 and is readily removed and replaced with a fresh mask as required. The headset 2 comprises a further consumable (single-use), which is the tube assembly 12. An embodiment of the tube assembly 12 is shown in perspective view in Figure 3.

Referring to Figure 3, a tube assembly 12 is shown, which can be introduced into, and removed from, the headset 2 as a single sub-component. The tube assembly 12 comprises a plurality of sample capture devices, which take the form of sorbent tubes 30. These are of industry standard dimensions (82.6mm long and with an internal diameter of 6.4mm), and are glass-coated stainless steel tubes packed with a mixture of Tenax® GR and Carbograph® 5TD sorbent materials in a ratio of approximately 1:1. Two of the tubes 30 are packed with sorbent material. A third tube 30', is empty so as to allow ready flow of gas through the tube. A pressure sensor (not shown in the drawing) is located at a region below tube 30', which sensor monitors the pressure within the mask.

The three tubes 30, 30’ are seated in a common tube support block 32, which facilitates simultaneous removal of the tubes 30, 30’ from the headset 2. The support block 32 is formed of metal (e.g. aluminium or stainless steel) or rigid moulded synthetic plastics material. The tubes are sealingly attached to the support block 32 by air tight seals. Conveniently these seals are formed by silicone rubber sealing rings or gaskets. The support block 32 in turn forms an air tight connection to the headset 2. Again, sealing rings, gaskets or the like may typically be used to form such air tight seals. The support block 32 is at least partly hollow, and contains airways which marry up with the lower end of the tubes 30, 30’, so as to permit gas flow through the length of the tubes.

Mounted on, or otherwise attached to, the support block 32 is a small printed circuit board (PCB) 34 which incorporates a simple digital electronic memory chip (e.g. SOIC-8 or similar), and appropriate electromechanical contacts to connect with corresponding electrical contact pads on the headset chassis.

Referring to Figure 4, there is shown on embodiment of a headset chassis unit 40. The chassis unit 40 has three apertures 42, with corresponding respective sealing rings 44, which mate with the lower end of the support block 32 of the tube assembly 12, so that the tubes 30, 30’ of the tube assembly are in gas flow communication with the headset chassis 40.

A Tygon® tube of ⅛ inch (12.8mm) internal diameter, 46, enters the underside of the chassis 40 and communicates, via internal conduit or pipe formed within the chassis 40, with the apertures 44. The tube 46 is in gas flow communication, via umbilical 6, with the vacuum pump in the base station 4. In this way, the vacuum pump is able to draw exhaled breath from the subject into the sorbent tubes 30 of the tube assembly.

Also attached to the headset chassis 40 is a printed circuit board 48. The PCB 48 is about 6cm by 4cm and incorporates several components, including: a microprocessor (which communicates with the base station 4 and local sensors and valves located in the headset); a variety of active and passive electronic components including voltage regulators, valve drive circuits, capacitors etc.; an orientation sensor to detect poor positioning of the subject's head during sampling; an ambient pressure sensor (e.g. Bosch BMP280) to measure ambient pressure outside the headset; an electrical interface with a digital memory device located on the tube assembly 12; electrical connectors to valves in the headset; and electrical interfaces with the umbilical (including 6 wires – ground, power and 4 data transfer wires Tx^{+}, Tx^{-}, Rx^{+}, Rx^{-}).

Also shown in Figure 4 is the electrical power lead 50 from the base station 4 via umbilical 6 which plugs into a co-operating socket on the headset.

The aforementioned parts of the apparatus are shown together, in their correct relative positions, in Figure 5.

Figure 6 is an exploded view of some of the components of a base station in an embodiment of apparatus in accordance with the invention. The base station comprises a large PCB 60, on which is a microprocessor responsible for overall control of the breath sampling, and a second microprocessor which controls the user interface. The user interface includes a touch-sensitive display screen 62, a loudspeaker and alarm buzzer for audio alarms and providing audio feedback, and an on/off switch.

The base station further comprises: an inlet to accept a clean air supply tube 64 from the CASPER unit; an air outlet to supply air to the umbilical (e.g. a Luer ¼ inch connector); a vacuum connector (e.g. a Luer ⅛ inch connector) to the umbilical, to provide suction from the vacuum pump in the base station to the mask; a power cable socket (standard IEC connector) to accept a source of mains power, and electrical power handling components (e.g. transformer/rectifier); and an electrical connector to the umbilical (e.g. 6 wire Fischer Core Series Plastic 4032 connector with push/pull locking).

The CASPER unit employs, as a scrubber, a 600mm long x 54mm OD tube filled with 1100ml of Restek 20626 activated carbon, with an operating life of 916 hours at 40L/min airflow. A safety factor of 2 is allowed for, meaning that the scrubber is deemed exhausted after 900 breath sample collections, assumed to take a maximum of 30 minutes each.

This same volume of carbon could be packaged more compactly for closer integration with other parts of the system, e.g. for the purposes of illustration only, if the 600mm of tube were chopped up into nine sections arranged in a 3x3 grid it would take up a space 7cm high x 16cm x 16cm, neglecting the necessary connections between tube sections.

The vacuum pump may be, for example, a Thomas 142500 twin-head diaphragm pump. There may conveniently also be provided a CO_2 sensor (e.g. GSS PrimIR) and a pressure and temperature sensor which may be used to compensate CO_2 and flow rate measurements; a flow rate sensor; and exhaust filters and/or baffles to reduce the noise from the pump.

A further flow rate and/or pressure sensor may be provided to measure or monitor the flow rate and/or pressure of clean air supplied from the CASPER unit through the base station to the umbilical.

The base station will typically comprise a moulded synthetic plastics housing, which is cleanable, preferably to hospital hygiene standards. Conveniently the base station housing may be shaped with a suitable recessed portion in which the headset can be stored when not in use.

The clean air supply “CASPER” unit can be generally as described in PCT/GB2017/050094.

The umbilical has a protective outer sheath of synthetic plastics material. The clean air supply tube is a 6.4mm i.d. Tygon® tube with a Luer→barb adapter at each end; the barbs connect to the tube, and the Luer fittings connect to the base station and the mask connector 24 respectively. A similar arrangement is provided for the vacuum tube (a 3.2mm i.d. Tygon® tube). As described previously, the protective sheath also encompasses the electrical power and communications wires.

Figures 7A and 7B are perspective views of an embodiment of a headset for use in apparatus in accordance with the invention. The embodiment is similar to that depicted in Figure 2 and like components are indicated with common reference numerals.

The headset comprises a mask piece 10, a headset chassis unit contained within a moulded synthetic plastics housing 100, and a tube assembly 12, contained within a moulded synthetic plastics housing 102. The housing 102 snap fits onto housing 100, in such a way that the sample capture tubes within the assembly 12 are correctly positioned to mate with the airway apertures provided in the chassis unit, and also in the mask piece 10. Suction from the vacuum pump in the base station is provided via vacuum tubing 46, which enters the headset chassis via an opening provided on the underside of the housing 100. Similarly, electrical power from the base station is provided by power lead 50 which plugs into a socket provided in the housing 100.

The mask piece 10 comprises a rigid moulded synthetic plastics material face mask 20, which has a soft flexible edge portion 20’ around the perimeter of the face mask, which helps form a seal with the face of the subject. In use, an adjustable elasticated headband (omitted from the Figures) is provided through moulded slits provided on either side of the headset, one of which 104 is visible in the Figures.

Example 2

Figures 8A and 8B are schematic representations of one embodiment of a device in accordance with the invention. In Figures 8A and 8B, mechanical components are indicated by a rounded box with thin lines; electrical components are denoted by a rectangular box with thick lines; and software components are indicated by a box with discontinuous double lines. Air flow communication between components is indicated by a solid line with an arrow head, whilst electrical or data communication between components is indicated by a broken line with an arrow head. Referring to Figure 8A, a headset comprises two consumable or disposable sub-components: a mask piece 10 and a tube assembly 12. These sub-components are consumables in the sense that a new mask piece 10 and tube assembly 12 must be used for each new subject.

The mask piece 10 clips into the headset in such a way that the interior of the mask can communicate, via valves (not shown), with the tube assembly 12 and specifically with two sorbent capture tubes 30 and with empty sorbent tube 30'. Beneath each of the tubes 30, 30' is a biological filter 302 contained within the tube assembly 12. Each filter 302 comprises a 0.22μm pore filter.

The tube assembly 12 also comprises a PCB 34 which incorporates a simple digital electronic memory chip (e.g. SOIC-8 or similar) and appropriate electromechanical contacts to connect with co-operating electrical contact pads 402 on the headset chassis 40.

The headset chassis 40 has air flow communication with the air flowing through the sorbent tubes 30 and 30' in the tube assembly 12. In each instance, the air entering the chassis 40 first encounters a respective "last chance" filter 402. Air flow through the empty tube 30' then communicates with a mask pressure sensor 404. Air flowing through the two sorbent tubes 30 passes through, in sequence, a respective first pressure sensor 406, respective fractionation valves 408, a respective second pressure sensor 410, a respective orifice 412, and a respective third pressure sensor 414.

The airways then unite and emerge from the headset chassis 40 via an ⅛" Luer connector 416. It can be seen that the fractionation valves 408 are provided with a respective alternative "bypass" air flow channel 420, which allows air to enter the headset chassis 40 without first passing through the sorbent tubes 30 in the tube assembly 12. Each bypass airflow channel 420 is provided with a respective bypass filter 422. This bypass airflow channel allows suction to be continuously applied to the headset chassis 40 from a vacuum pump in the apparatus (see Figure 8B), without necessarily constantly drawing air through the capture sorbent tubes 30.

The headset chassis also includes an electrical socket 418 which accepts an electrical power lead 50 fed through the umbilical 6.

The headset end of umbilical 6 is indicated in Figure 8A. This comprises a push/pull electrical connector 602 to connect to the socket 418 on the headset chassis 40, and a ⅛" Luer to barb adapter to connect to the Luer connector 416 on the headset chassis 40.

In addition, the umbilical includes an air flow communication path 22 to connector 24. Air in the flow path 22 is provided from a scrubbed clean air supply (see Figure 8B) to the mask portion 10 via a commercial "off the shelf" ("COTS") biological filter 28. The connector 24 also has an air flow communication path to a COTS exhaust valve 26.

Referring to Figure 8B, the other parts of the apparatus co-operating with those parts detailed in Figure 8A, are shown. In particular the apparatus comprises the base station end of umbilical 6, a base station 4, and a "CASPER" clean air supply unit 8.

The base station end of the umbilical 6 comprises various connectors for making functional connections to the base station 4. These connectors include a circular push/pull electrical connector 602, which connects to a 6 wire strand cable 604 which provides electrical and data communication with the base station 4. The cable 604 plugs into socket 606 on the base station 4.

There is a Luer to barb adaptor 608 on the umbilical which connects, via tubing, to a Luer connector 610 on the base station. This connection provides an air flow path 612 for air drawn down the umbilical 6 by vacuum pump 614 in the base station 4. This air passes along flow path 612 into the base station and thence through a CO_2 sensor 616, a pressure sensor 618, and a flow rate sensor 620. Air pumped out by the vacuum pump 614 passes through a series of baffles (to reduce noise) and filters, jointly indicated as 622, to an exhaust outlet 624, where it is vented from the base station 4.

The base station end of umbilical 6 also includes a second, larger (¼ inch) Luer to barb adaptor, indicated by reference numeral 626. This connects, via tubing, to a co-operating Luer connector 628 on the base station, forming an air flow path 630, through which air output from the clean air supply unit 8 can be fed into the umbilical 6 and hence into the mask piece 10 (Figure 8A). The clean air supply unit 8 and the flow of air therefrom will be described further below.

The base station 4 also includes a touch-sensitive display screen 62, and a main PCB 60. Other components of the base station include a loudspeaker 632, a power switch 634, base station firmware 636, a power "brick" 638, an IEC power connector 640 for connection to an external mains electrical supply, and a "docking station" 642 for the chip/data 34 on the tube assembly 12 (Figure 8A). An optional feature is a diagnostics port 644, which can provide electrical or data communication with a laptop computer 646 and/or an interface 648.

Referring to the clean air supply unit 8, there is provided an IEC power connector 802 for connecting to an external mains electricity power supply and a switch 804 for switching on and off the pump 806. Ambient air enters the clean air supply unit 8 via the air inlet 808 and is forced by the pump 806 through scrubber unit 810 and particulate-removing filter 812 and exits the unit 8 via ¼" Luer connector 814 and passes via tubing 816 and Luer connector 818 into the base station 4. The clean, filtered air then passes through pressure and flow rate sensors, jointly indicated by reference numeral 820, via connector 628, along flow path 630, into the umbilical 6.

Example 3

Figures 9A and 9B are schematic representations of a further embodiment of a device in accordance with the invention. In general, the embodiment shown in Figures 9A/B is quite similar to that illustrated in Figures 8A/B, and like components are indicated with common reference numerals. The operation of the embodiment is also similar to that described for the embodiment in the preceding example and therefore, for the sake of brevity, will not be described in detail, but some description is appropriate in particular for those features which differ relative to the preceding example.

The headset also includes an inlet airway component 500, which connects to the mask piece 10 and comprises a barb connector 502 to accept an incoming clean air supply

504, and incorporates a one-way exhaust valve 506, so that the subject can exhale out of the mask when undergoing sampling and to permit the egress of excess clean air when the subject is not inhaling.

Also shown in Figure 9A is an auxiliary “mini-scrubber” 508, positioned in the air supply line between the main scrubber “CASPER” unit (shown in Figure 9B) and the mask piece. The auxiliary scrubber 508 serves to further remove volatile organic compounds (VOCs) from the air supplied to the subject. The components in the mini-scrubber include a one-way valve 510, a narrow pore membrane filter 512 (pore size 40µm), an activated carbon scrubber 514, a dust filter 516, and a barb connector 518.

Referring to Figure 9B, the apparatus includes a base station 4 and, separately, a clean air supply “CASPER” unit 8.

The base station 4 includes a vacuum pump 614, which creates the suction to draw exhaled air into the sorbent tubes in the mask portion. Air exits the base station via an exhaust 624, and is drawn into the base station via the vacuum connector 608. Between the connector 608 and the pump 614 is a pressure switch 650; a 40µm pore filter 652; two mass flow meters (one for redundancy) 620; a SprintIR 65 CO_2 sensor 616; pressure, humidity and temperature sensors 618; a restriction (narrow tube) 654 and a 100ml reservoir 656.

The restriction 654 and reservoir 656 act, in combination, as a flow damper to dampen most of the variation in flow rate caused by variation in the running of the vacuum pump.

The pressure, humidity and temperature sensors 618 allow calibration of the CO_2 sensor (which is affected by the parameters of pressure, humidity and temperature). In addition, the sensors 619 provide a crude “leak detection” indicator, as any significant variation from expected values in one or more of these parameters can be an indication that there is a leak in the air sampling/air flow system.

The mass flow meters 620 allow for calibration of the apparatus on start-up. The CO_2 sensor 616, by virtue of its 'downstream' position, necessarily gives a CO_2 signal which is somewhat time-delayed relative to the subject exhaling. Nevertheless, it is possible to extract useful information from the sensor output and, in particular, if the CO_2 level falls significantly below expected levels, this can be an indication that the mark portion has slipped and the subject's exhaled air is not being correctly sampled.

Figure 9B also illustrates the CASPER clean air supply unit 8, which is very similar to the embodiment illustrated in Figure 8B. However in the embodiment shown in Figure 9B, scrubbed clean air from the unit 8 does not pass to the base station 4, but instead passes directly into an umbilical and, via auxiliary scrubber 508 (shown in Figure 9A), into the mask portion. In addition, the clean air supply unit 8 includes an EEPROM 830. The function of the memory component 830 is to store how long the unit has been operating, which is important as the scrubber unit has a finite life and needs to be replaced periodically.

Claims

1. Apparatus for use in obtaining a breath sample from a mammalian, preferably human, subject, the apparatus comprising: a headset which is attachable to the subject; a separate suction pump; and an umbilical connecting the suction pump to the headset so as to allow the suction pump to create a lower than ambient pressure within the headset; wherein the headset comprises: a mask piece which fits over the nostrils and mouth of the subject; at least one breath sample capture device, and at least one valve to regulate the passage of gas into the sample capture device.

2. The apparatus of claim 1, wherein the mask piece is readily detachable from the headset.

3. The apparatus of claim 1 or claim 2, wherein the headset comprises a plurality of breath sample capture devices.

4. The apparatus of any one of the preceding claims, wherein the breath sample capture device comprises a sorbent tube.

5. The apparatus of any one of the preceding claims, wherein the headset comprises a readily detachable sub-assembly comprising a plurality of breath sample capture devices.

6. The apparatus of claim 5, wherein the sub-assembly comprises a digital electronic data storage means.

7. The apparatus of any one of the preceding claims, comprising at least one sterilising filter downstream of the mask piece.

8. The apparatus of any one of the preceding claims, comprising a movement and/or orientation sensor to detect an undesirable subject head position during sampling, and/or an alarm signal generator.

9. The apparatus according to any one of the preceding claims, comprising at least one multiple-outlet valve located in the headset, wherein at least one outlet from the valve makes a gas flow communication or connection with the breath sample capture device.

10. The apparatus according to any one of the preceding claims, wherein the umbilical comprises: tubing which connects a partial vacuum created by the vacuum pump to the headset; tubing supplying clean air to the mask piece; an electrical power connection from a base station to the headset; and electrical data communication between the base station and the headset.

11. The apparatus according to any one of the preceding claims, comprising a base station which includes a electronical digital control means, microprocessor, computer or the like which controls the operation of the apparatus.

12. The apparatus according to claim 11, wherein the base station further comprises a user interface.

13. The apparatus according to any one of the preceding claims, further comprising a clean air supply means, including a pump and a scrubber.

14. The apparatus according to any one of the preceding claims, further comprising at least one pressure sensor to measure the pressure in the mask piece.

15. The apparatus according to any one of the preceding claims, further comprising at least one flow rate sensor.

16. The apparatus according to any one of the preceding claims, further comprising at least one CO_2 sensor.

17. The apparatus according to claim 13 as dependent on any one of claims 1-12, further comprising a separate auxiliary scrubber unit.

18. The apparatus according to claim 10 as dependent on any one of claims 1-9, comprising a base station and a separate clean air supply means; wherein the base station comprises the vacuum pump.

19. The apparatus according to claim 18, wherein the clean air supply means supplies clean air to the mask without the said supply passing through the base station.

20. The apparatus according to any one of the preceding claims, comprising an alarm which gives a visual and/or audible alarm if sample collection is not, or may not be, proceeding correctly.

21. The apparatus according to claim 20, wherein the alarm is triggered by an alarm signal generator as defined in claim 8.

22. A method of obtaining a breath sample from a subject, comprising contacting the mask piece of apparatus according to any one of the preceding claims with a subject; and collecting exhaled breath from the subject on at least one sample capture device of the apparatus.

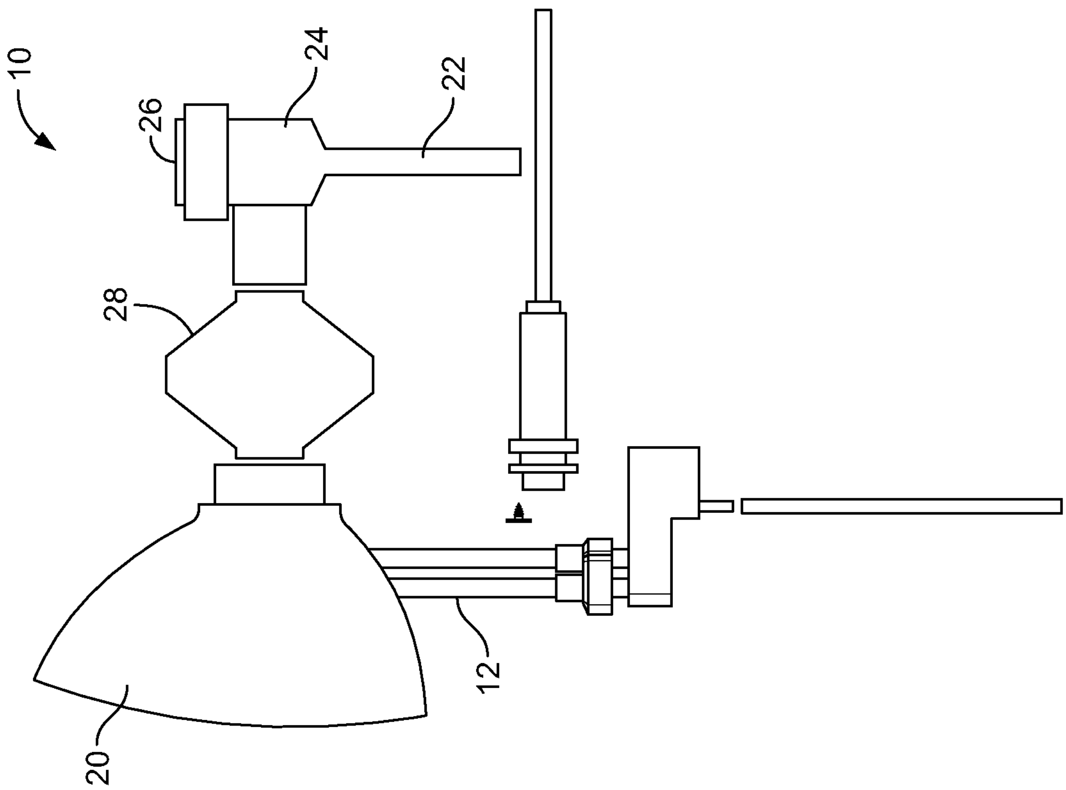
10
26
24
22
28
12
20

FIG. 2

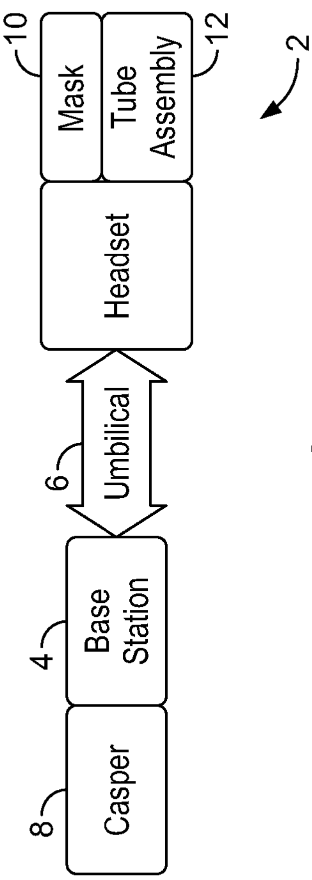
Mask
10
Tube Assembly
12
2
Headset
Umbilical
6
Base Station
4
Casper
8

FIG. 1

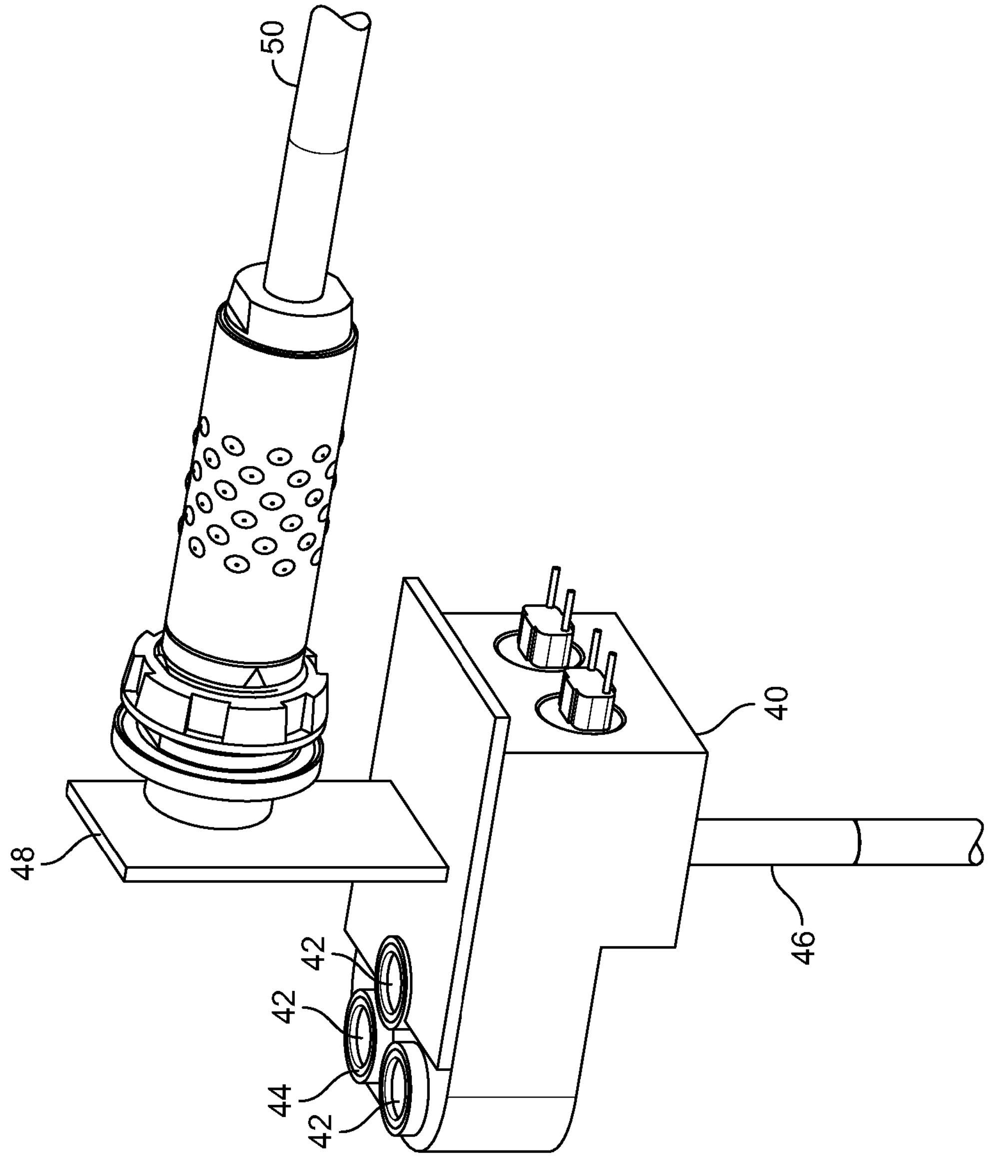

FIG. 4

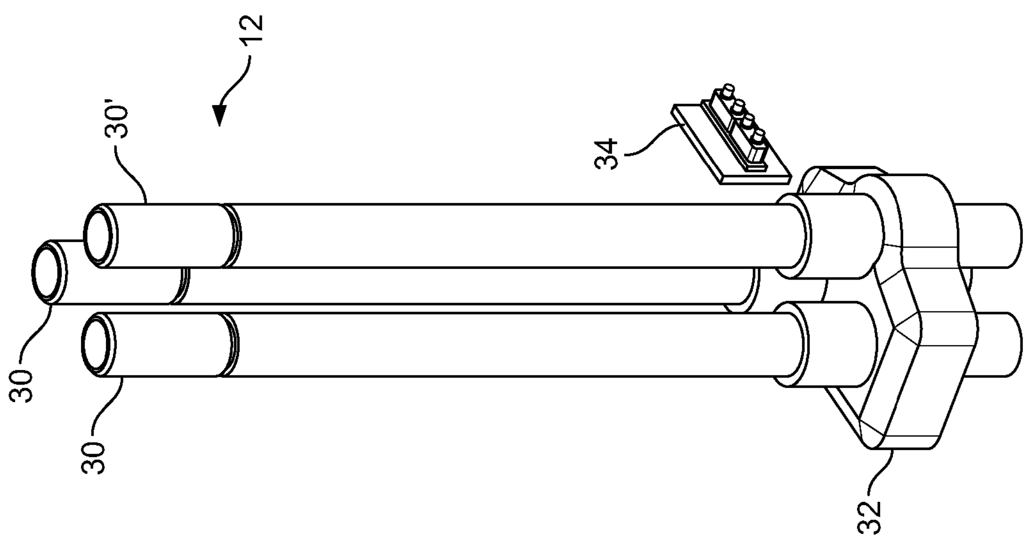

FIG. 3

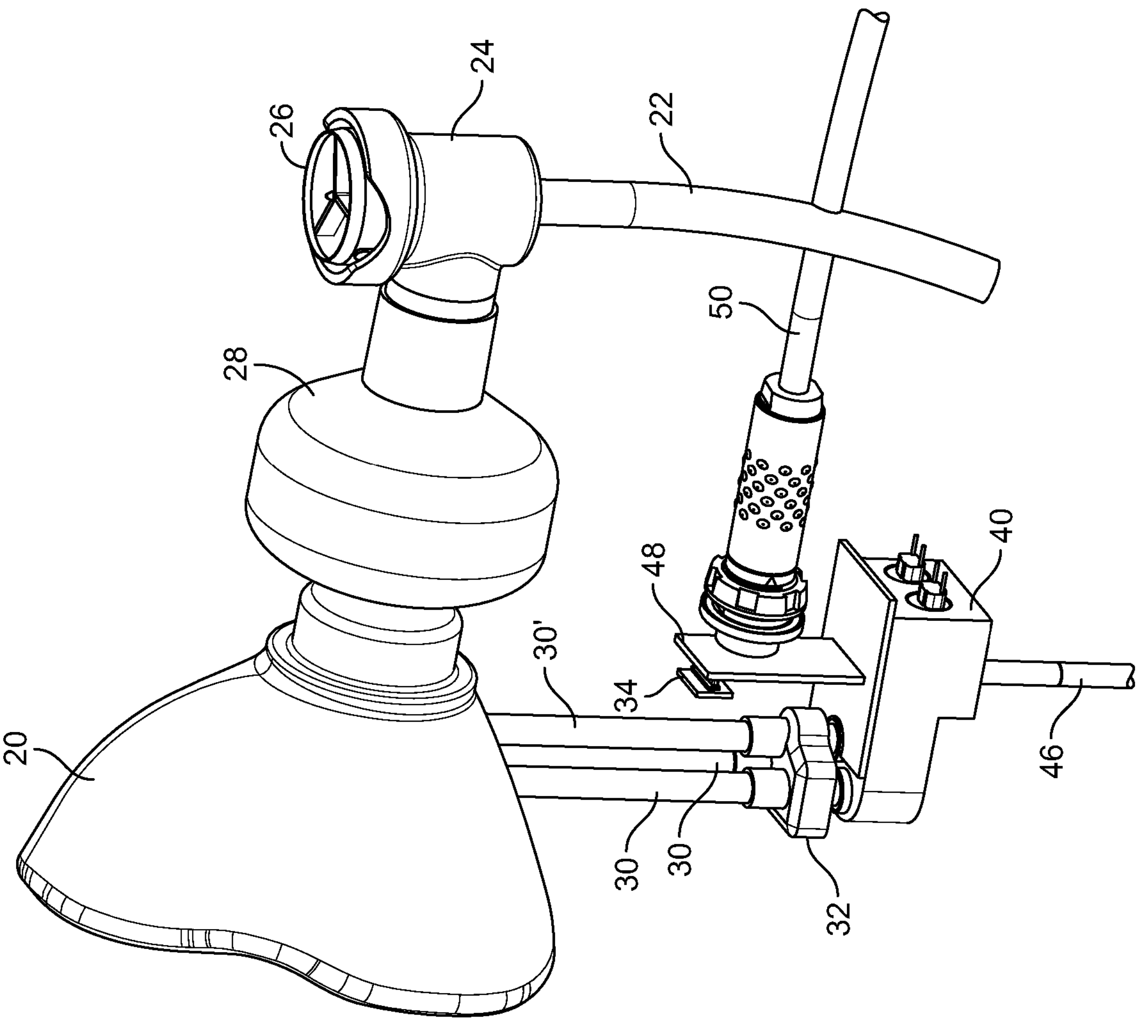

FIG. 5

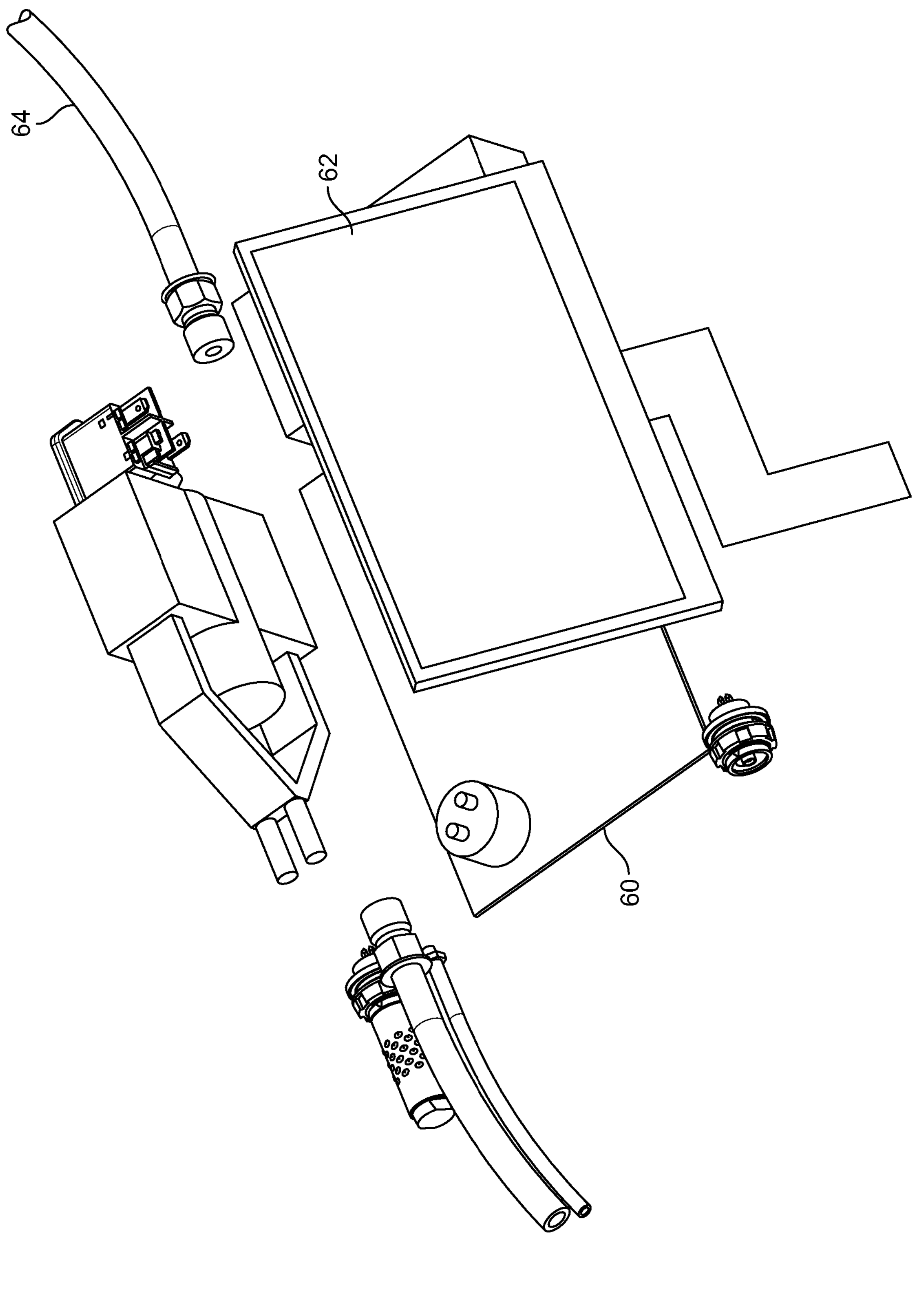

FIG. 6

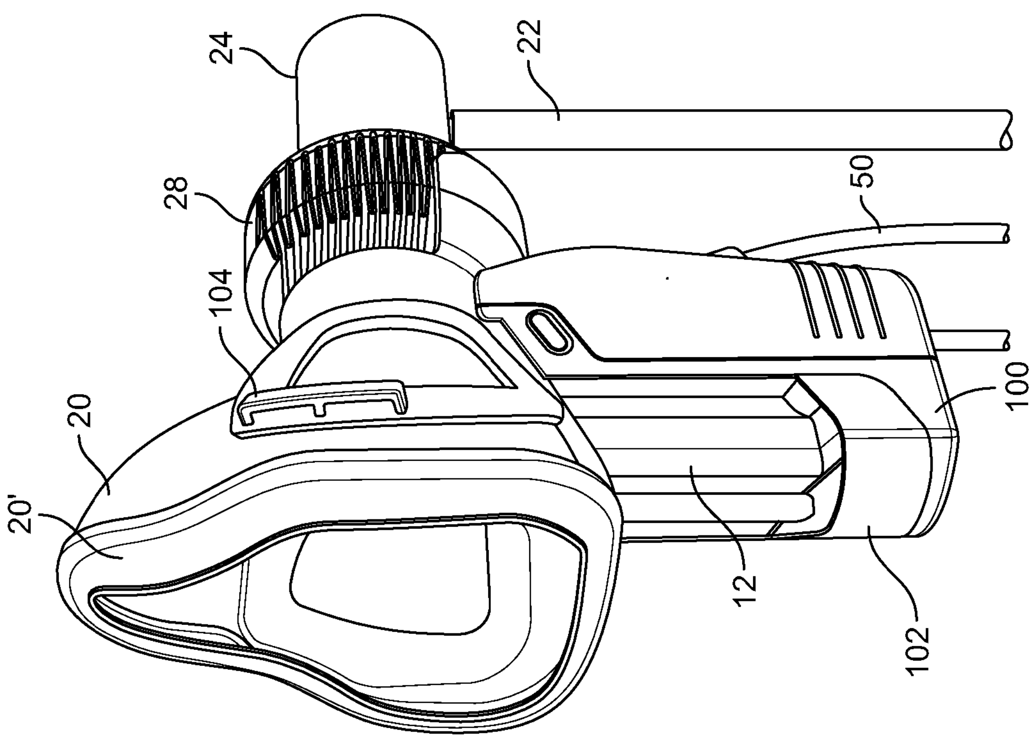

FIG. 7B

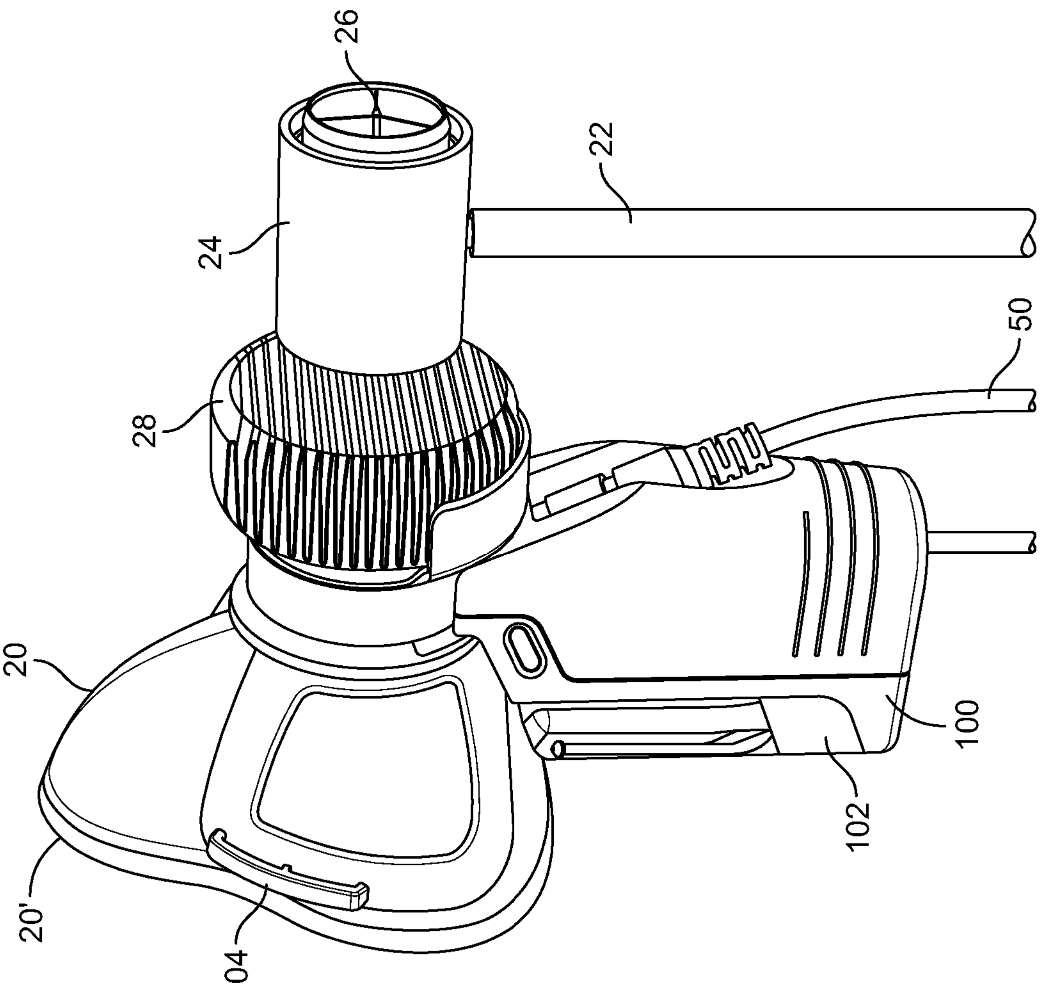

FIG. 7A

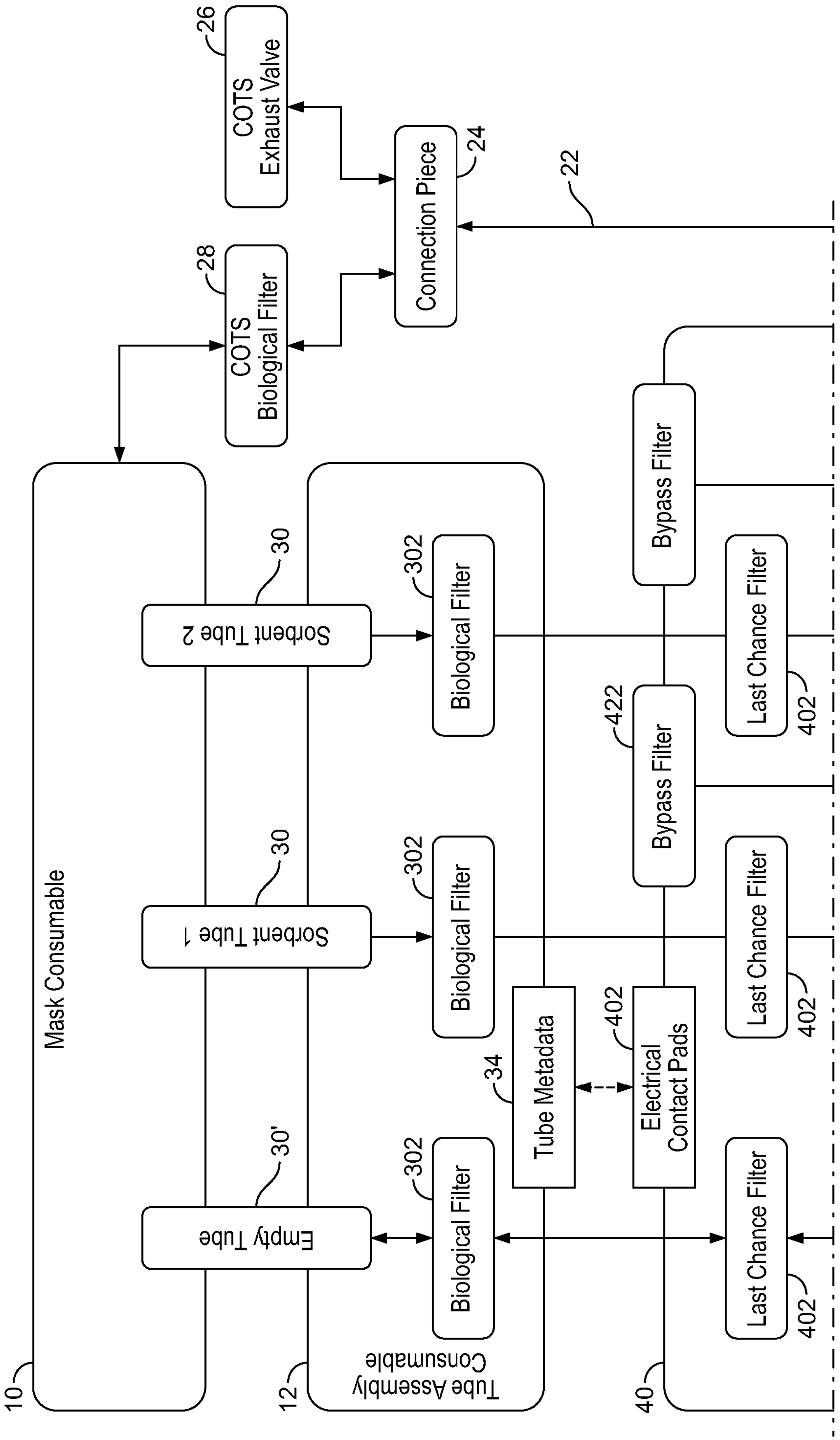
COTS
Exhaust Valve
26
COTS
Biological Filter
28
Connection Piece
24
22
Mask Consumable
10
Tube Assembly
Consumable
12
40
Sorbent Tube 2
Sorbent Tube 1
Empty Tube
30
30
30'
Biological Filter
Biological Filter
Biological Filter
302
302
302
Tube Metadata
34
Electrical
Contact Pads
402
Bypass Filter
Bypass Filter
422
Last Chance Filter
Last Chance Filter
Last Chance Filter
402
402
402

FIG. 8A

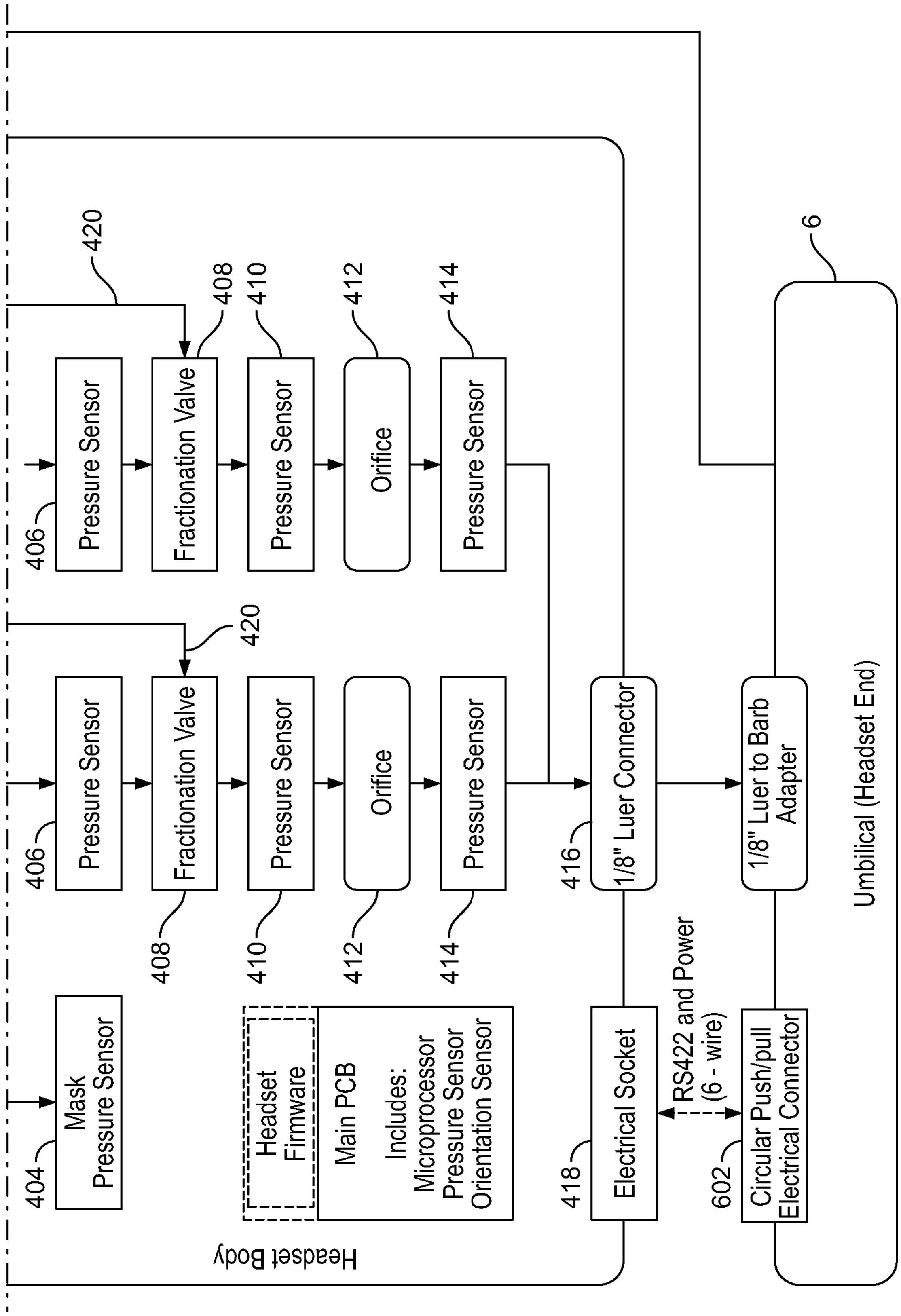

FIG. 8A (Continued)

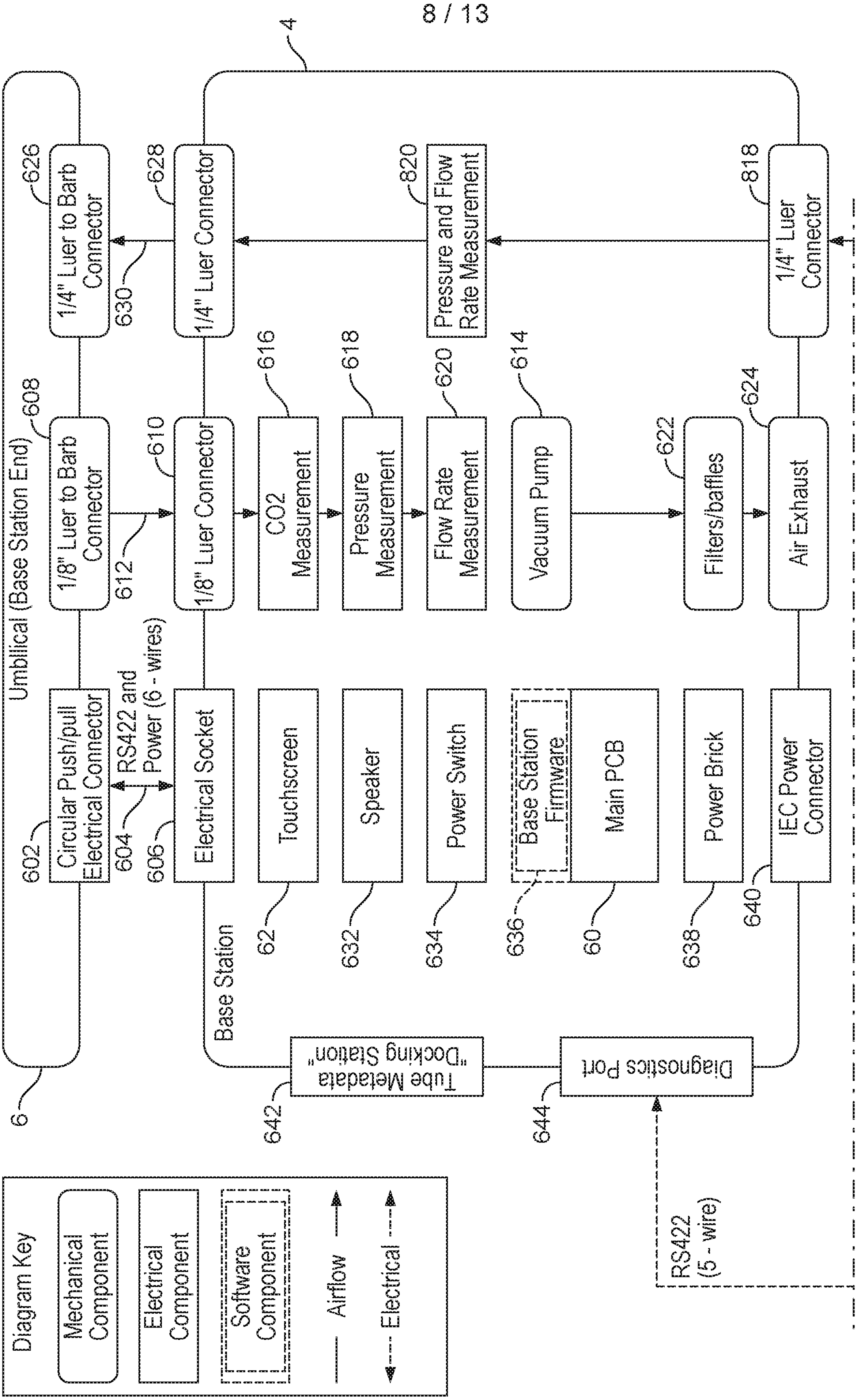
4
6
Umbilical (Base Station End)
602
Circular Push/pull Electrical Connector
604
RS422 and Power (6 - wires)
606
Electrical Socket
608
1/8" Luer to Barb Connector
612
610
1/8" Luer Connector
626
1/4" Luer to Barb Connector
630
628
1/4" Luer Connector
Base Station
62
Touchscreen
616
CO2 Measurement
618
Pressure Measurement
632
Speaker
634
Power Switch
620
Flow Rate Measurement
820
Pressure and Flow Rate Measurement
636
Base Station Firmware
60
Main PCB
614
Vacuum Pump
638
Power Brick
622
Filters/baffles
640
IEC Power Connector
624
Air Exhaust
818
1/4" Luer Connector
642
Tube Metadata "Docking Station"
644
Diagnostics Port
RS422 (5 - wire)
Diagram Key
Mechanical Component
Electrical Component
Software Component
Airflow
Electrical

FIG. 8B

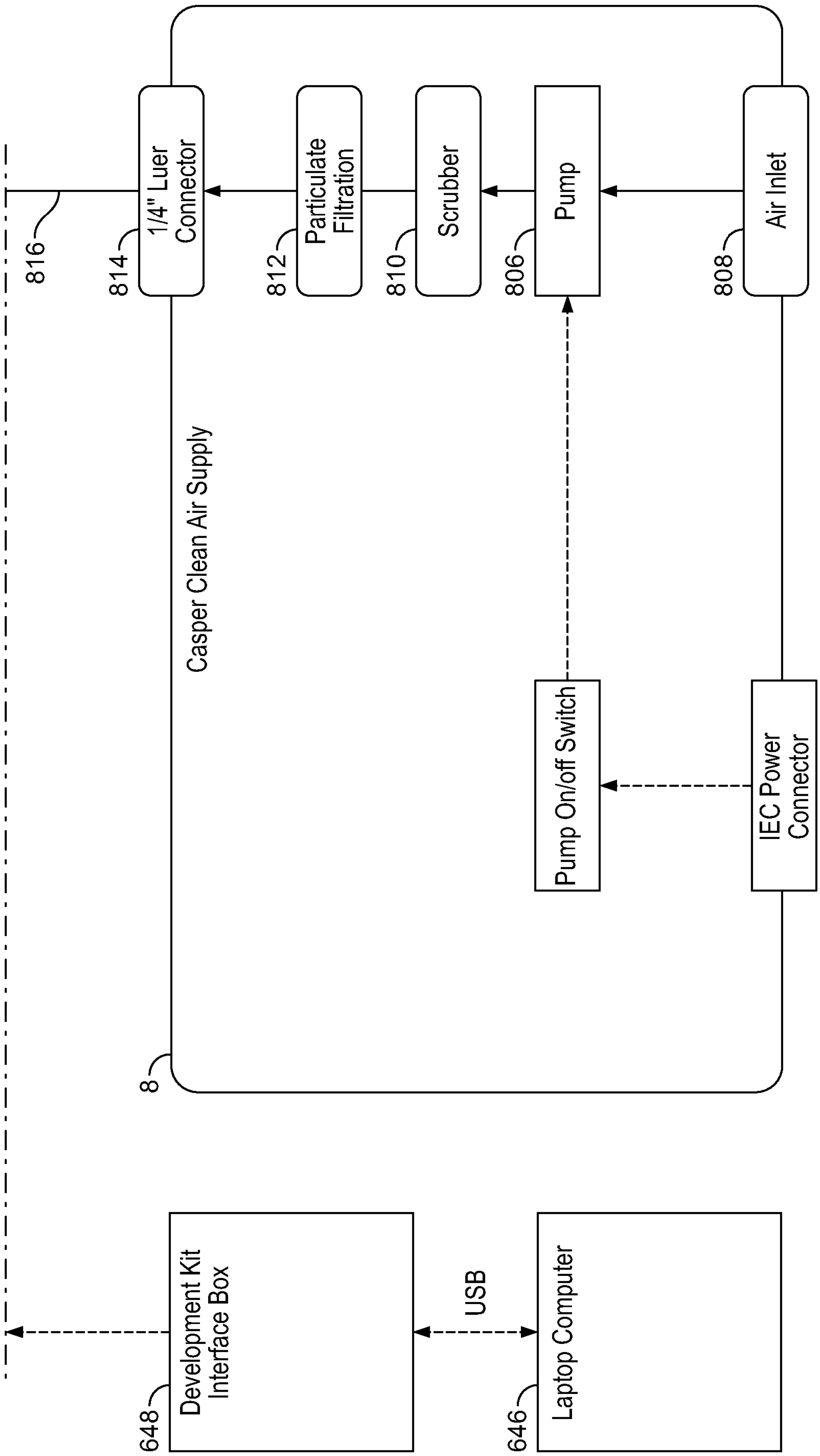

FIG. 8B (Continued)

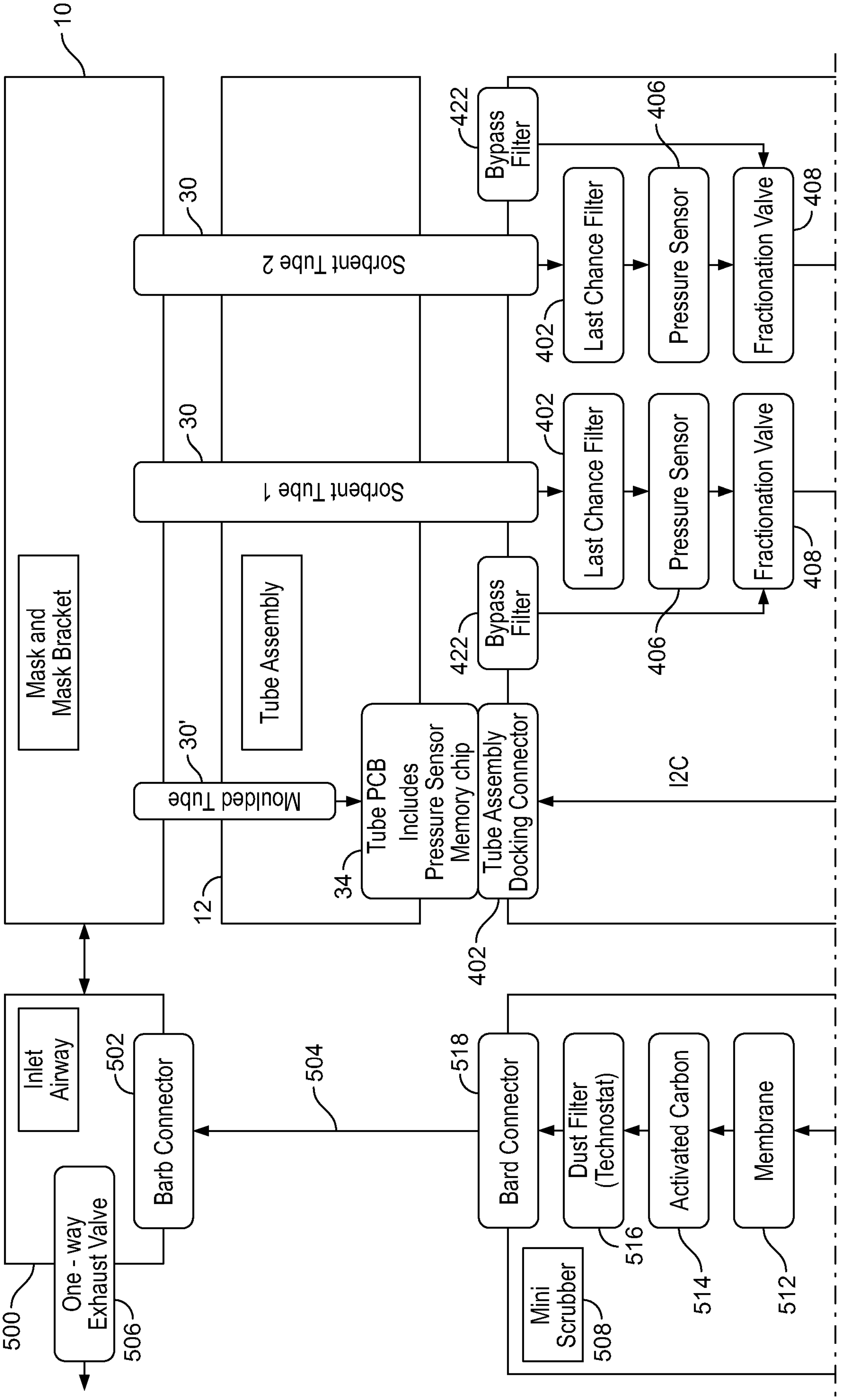
10
Mask and
Mask Bracket
Tube Assembly
12
30
30
30'
Sorbent Tube 2
Sorbent Tube 1
Moulded Tube
34
Tube PCB
Includes
Pressure Sensor
Memory chip
Tube Assembly
Docking Connector
402
422
Bypass
Filter
Last Chance Filter
Pressure Sensor
Fractionation Valve
402
406
408
422
406
408
I2C
500
One - way
Exhaust Valve
506
Inlet
Airway
502
Barb Connector
504
518
Bard Connector
Dust Filter
(Technostat)
516
Activated Carbon
514
Membrane
512
Mini
Scrubber
508

FIG. 9A

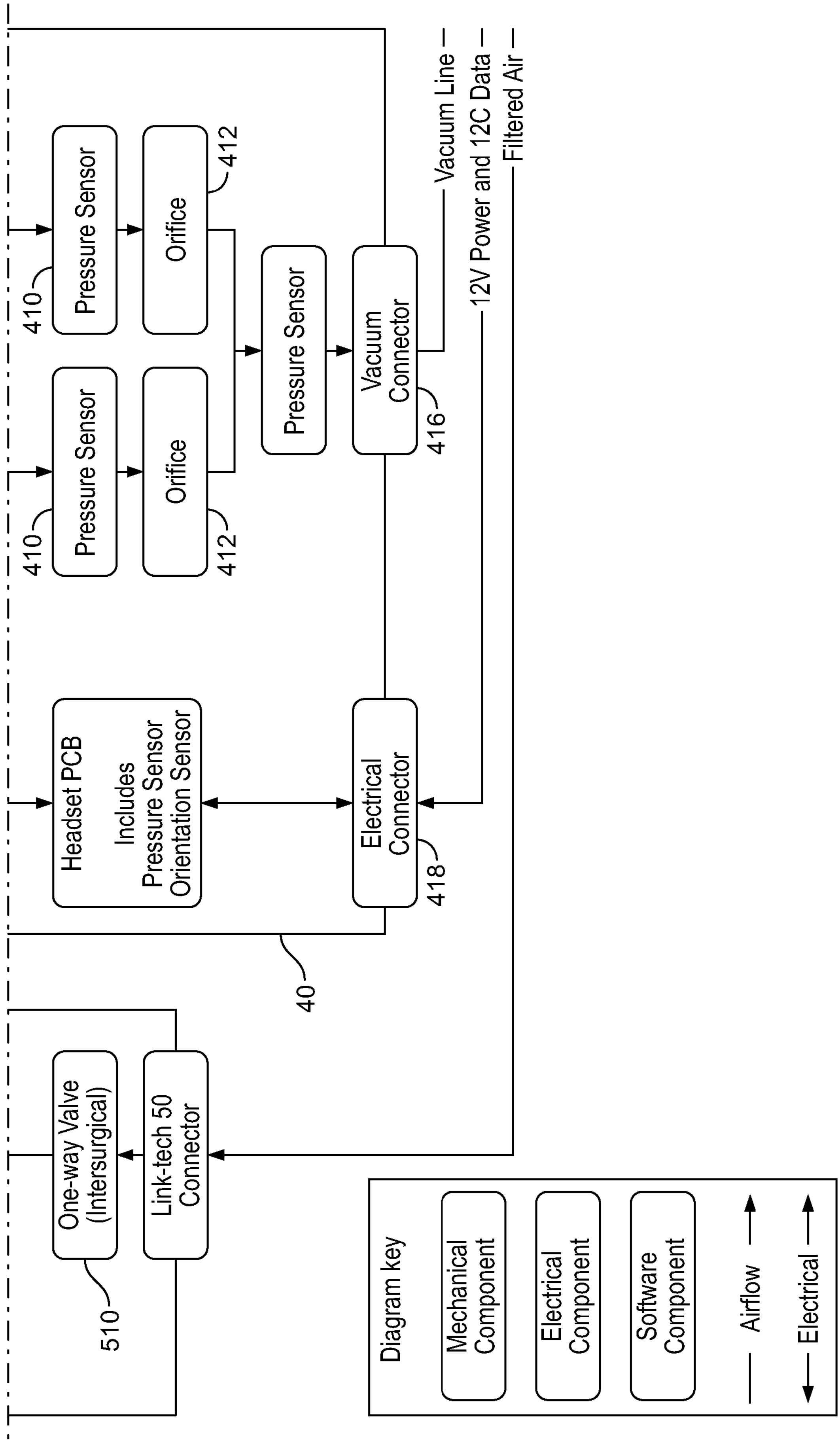

FIG. 9A (Continued)

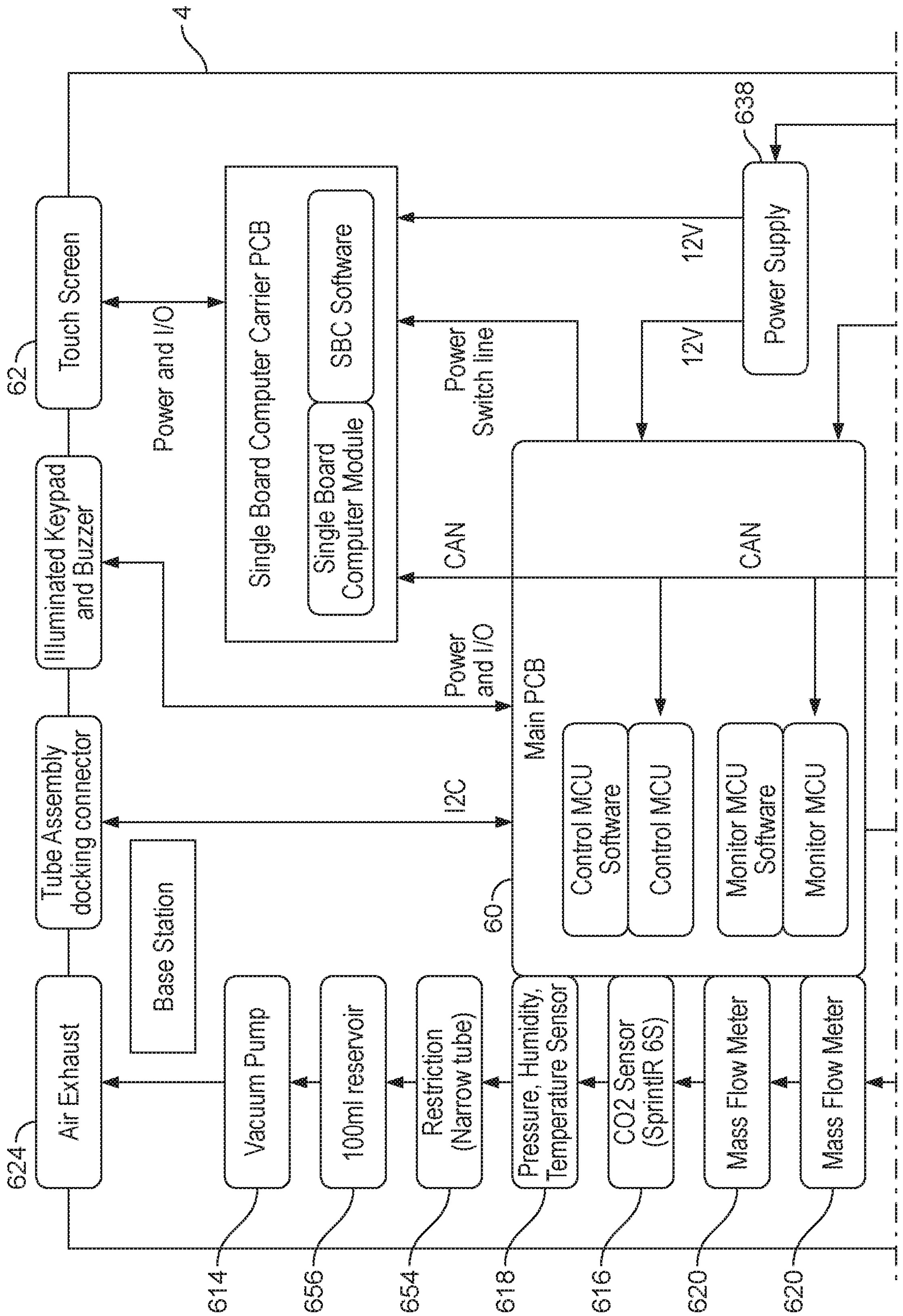
4
Touch Screen
62
Illuminated Keypad and Buzzer
Tube Assembly docking connector
Air Exhaust
624
Power and I/O
Single Board Computer Carrier PCB
SBC Software
Single Board Computer Module
638
Power Supply
12V
12V
Power Switch line
CAN
CAN
Power and I/O
Main PCB
I2C
Base Station
60
Control MCU Software
Control MCU
Monitor MCU Software
Monitor MCU
Vacuum Pump
100ml reservoir
Restriction (Narrow tube)
Pressure, Humidity, Temperature Sensor
CO2 Sensor (SprintIR 6S)
Mass Flow Meter
Mass Flow Meter
614
656
654
618
616
620
620

FIG. 9B

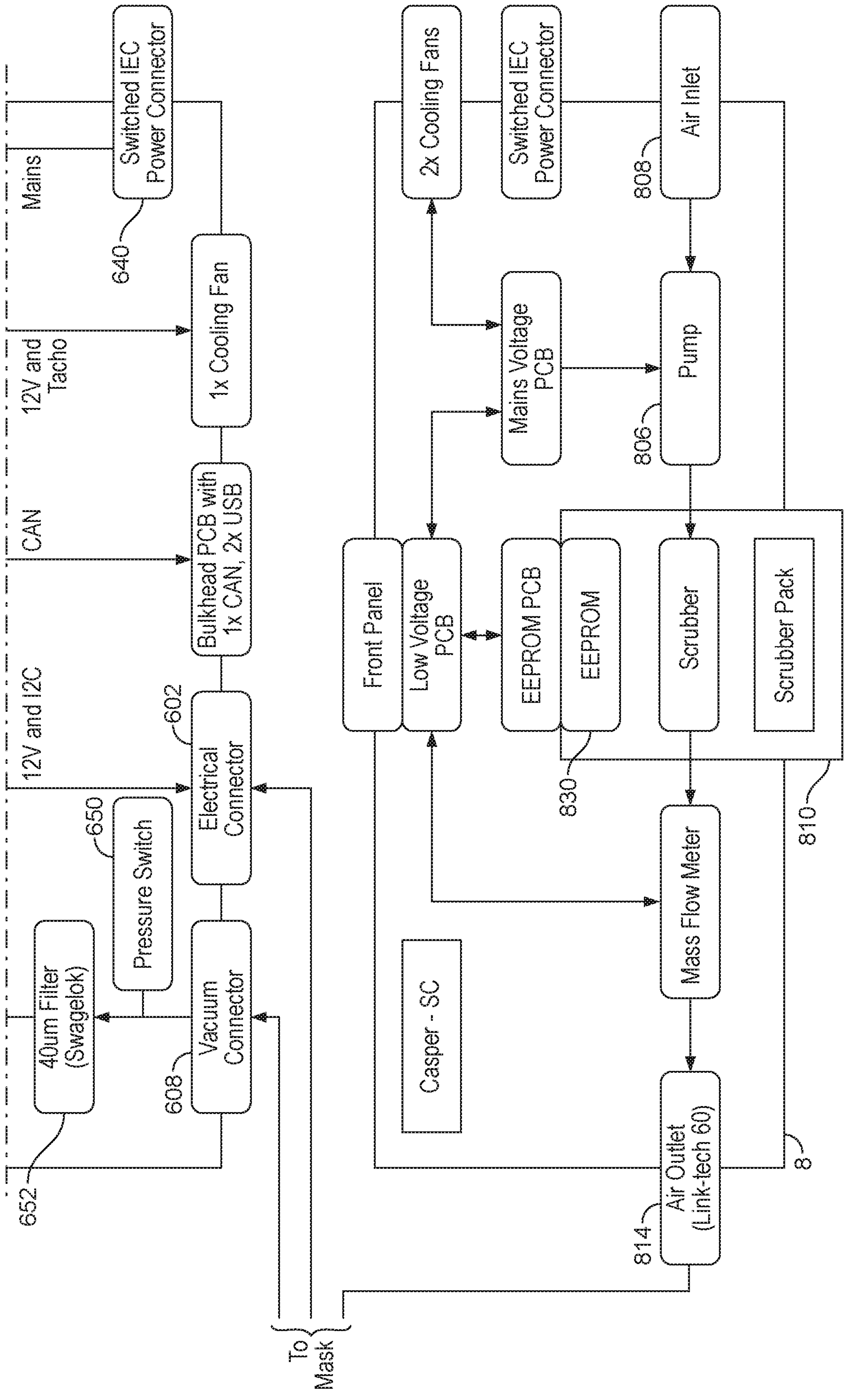

FIG. 9B (Continued)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference MJL/407.01/O	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/GB2019/050112	International filing date *(day/month/year)* 16 January 2019 (16-01-2019)	(Earliest) Priority Date *(day/month/year)* 24 January 2018 (24-01-2018)
Applicant OWLSTONE MEDICAL LIMITED		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into ______________________ , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. [ ] **Certain claims were found unsearchable** (See Box No. II)
3. [ ] **Unity of invention is lacking** (see Box No III)
4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:
5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority
6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. 7B
      [ ] as suggested by the applicant
      [X] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2019/050112

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/097
ADD. A61B5/083 A61B5/087 A61B5/11 A61B5/00

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

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

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

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2017/303822 A1 (ALLSWORTH MAX [GB] ET AL) 26 October 2017 (2017-10-26) figures 1, 2A, 2B, 8 paragraphs [0001], [0102], [0114] - [0117], [0126], [0131], [0138] -----	1-22
X	US 2012/294876 A1 (ZIMMERMAN PATRICK R [US]) 22 November 2012 (2012-11-22) figures 9, 13 paragraphs [0002], [0104], [0120], [0172], [0205], [0242] -----	1-22
X	US 2017/007795 A1 (PEDRO MICHAEL J [US] ET AL) 12 January 2017 (2017-01-12) figures 6, 12 paragraphs [0054], [0065] -----	1-22

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

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 March 2019	27/03/2019

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

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2019/050112

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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