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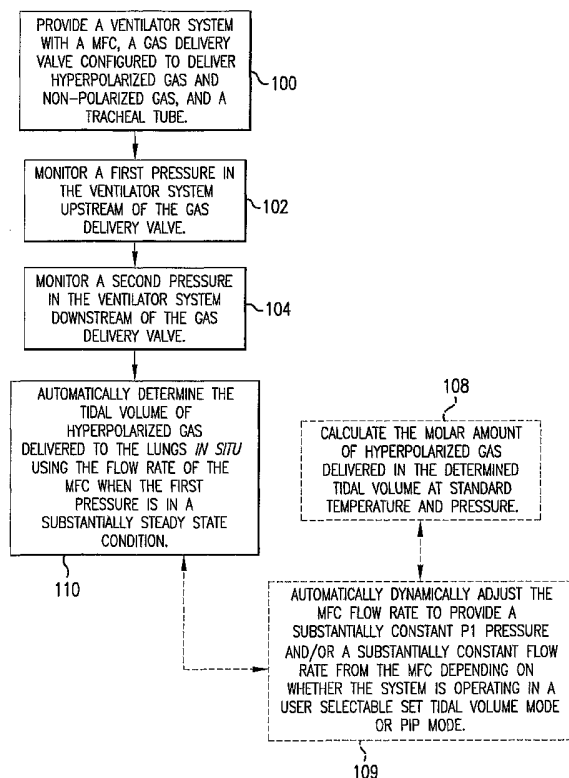
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(54) Title: MRI/NMR-COMPATIBLE, TIDAL VOLUME CONTROL AND MEASUREMENT SYSTEMS, METHODS, AND DEVICES FOR RESPIRATORY AND HYPERPOLARIZED GAS DELIVERY



(57) Abstract: Ventilator systems include: (a) a mass flow controller; (b) a gas delivery valve in communication with the mass flow controller and configured to selectively dispense a plurality of different gases to a subject; (c) a first gas source in fluid communication with the gas delivery valve; (d) a second gas source in fluid communication with the gas delivery valve; (e) a first pressure sensor located upstream of the gas delivery valve; (f) a second pressure sensor located downstream of the gas delivery valve; and (g) a controller operatively associated with the first and second pressure sensors and the mass flow controller, the controller comprising computer program code that monitors the pressures measured by the first and second pressure sensors and automatically dynamically adjusts the flow rate of the mass flow controller.



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**MRI/NMR-COMPATIBLE, TIDAL VOLUME CONTROL AND
MEASUREMENT SYSTEMS, METHODS, AND DEVICES FOR
RESPIRATORY AND HYPERPOLARIZED GAS DELIVERY**

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Field of the Invention

The present invention relates to the delivery of polarized noble gases to subjects for evaluations using NMR spectroscopy and/or magnetic resonance imaging ("MRI").

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Background of the Invention

Polarized inert noble gases can produce improved NMR signals in and/or MRI images of certain areas and regions of the body. Noble gases, such as polarized helium-3 (^3He) and xenon-129 (^{129}Xe), have been found to be particularly suited for this purpose. Unfortunately, the polarized state of the gases is sensitive to handling and environmental conditions and can, undesirably, decay from the polarized state relatively quickly.

Hyperpolarizers are used to produce and accumulate polarized noble gases. Hyperpolarizers artificially enhance the polarization of certain noble gas nuclei (such as ^{129}Xe or ^3He) over the natural or equilibrium levels, *i.e.*, the Boltzmann polarization. Such an increase is desirable because it enhances and increases the MRI signal intensity, allowing physicians to obtain better images of the substance in the body. *See* U. S. Patent Nos. 5,545,396; 5,642,625; 5,809,801; 6,079,213, and 6,295,834; the disclosures of these patents are hereby incorporated by reference herein as if recited in full herein.

In order to produce the hyperpolarized gas, the noble gas can be blended with optically pumped alkali metal vapors such as rubidium ("Rb"). These optically pumped metal vapors collide with the nuclei of the noble gas and hyperpolarize the noble gas through a phenomenon known as "spin-exchange." The "optical pumping" of the alkali metal vapor is produced by irradiating the alkali-metal vapor with circularly polarized light at the wavelength of the first principal resonance for the alkali metal (*e.g.*, 795 nm for Rb). Generally stated, the ground state atoms become excited, then subsequently decay back to the ground state. Under a modest magnetic field (10 Gauss), the cycling of atoms between the ground and excited states can yield

nearly 100% polarization of the atoms in a few microseconds. This polarization is generally carried by the lone valence electron characteristics of the alkali metal. In the presence of non-zero nuclear spin noble gases, the alkali-metal vapor atoms can collide with the noble gas atoms in a manner in which the polarization of the valence
5 electrons is transferred to the noble-gas nuclei through a mutual spin flip "spin-exchange." Alternative polarization enhancement techniques may also be used.

After the polarization process, the hyperpolarized gas is typically separated from the alkali metal (where spin-exchange techniques have been employed) prior to administration to a patient to form a non-toxic pharmaceutically acceptable product.
10 Unfortunately, during production and/or during and after collection, the hyperpolarized gas can deteriorate or decay relatively quickly (lose its hyperpolarized state) and therefore must be handled, collected, transported, and stored carefully.

In the past, several researchers have used hyperpolarized gas compatible ventilators for delivering polarized gas to subjects to image hyperpolarized noble
15 gases such as helium and xenon. For example, Hedlund et al., in *MR-compatible ventilator for small animals; computer controlled ventilation for proton and noble gas imaging*, 18 Magnetic Resonance Imaging, pp. 753-759 (2000), state that ventilators have been in routine use in their laboratory for a number of years. *See also*, Hedlund et al., *Three-dimensional MR microscopy of pulmonary dynamics*, Society of
20 Magnetic Resonance (New York, NY, 1996); and a poster presented by Hedlund et al. at the Amer. Thoracic Society 1998 International Meeting (Chicago, 1998), entitled *MRI of pulmonary airways with hyperpolarized helium; a computer-controlled ventilator for imaging synchronous gas delivery in animal studies* (describing ventilator technology). In addition, Black and co-workers have used a hyperpolarized
25 gas-compatible ventilator to generate what is believed to be the first ever *in vivo* images of hyperpolarized ^3He in guinea pig lungs. *See* Black et al., *In vivo He-3 MR images of guinea pig lungs*, Radiology, 199(3), pp. 867-870 (1996). One known commercial small animal ventilator that may have been modified to dispense hyperpolarized gas and other respiratory gases have been is believed to be available
30 from CWE Inc. (Ardmore, Pennsylvania) as Model SAR-830.

Unfortunately, conventional small animal ventilators used to deliver hyperpolarized gases do not provide a way to accurately determine the volume

delivered to the animal. Generally stated, conventional ventilators cannot adequately determine the volume delivered to the animal lungs separate from the volume delivered by the system itself. For example, certain conventional ventilators have proposed using flow meters with pressure transducers that control inspiration pressure and calculate an estimated volume by averaging the flow output to the subject over time. The variability in such an estimate may be undesirable, particularly when the amount of delivered polarized gas is small and the MRI/NMR signal depends on the amount, concentration and polarization level of polarized gas delivered, such as is the case for polarized gas investigations of small animals using millimole concentration ranges.

Thus, there remains a need for systems that can more accurately determine the amount of a gas and/or number of moles of gas delivered to an animal's lungs.

Summary of the Invention

Embodiments of the present invention can provide improved MRI compatible hyperpolarized gas delivery systems, methods, and computer program products that can calculate ventilation-dispensed polarized gas volumes based on (automated) measurements taken *in situ* at the animal delivery site to provide one or more of: (a) a known or calculated inspiration or tidal volume of gas; (b) automated controlled volumetric delivery; (c) *in situ* real-time or dynamic adjustment of flow rate based on pressure and volume parameters; and (d) controlled ventilation to provide blends or selectable respiratory gases, including at least one hyperpolarized gas.

Certain embodiments of the present invention include a feedback pressure or flow rate control system that can automatically monitor inlet and outlet pressures to adjust the flows to maintain a steady state condition during measurement/calculation (*i.e.*, flow in=flow out). Thus, embodiments of the present invention can maintain the system at a substantially constant pressure upstream of the gas delivery valve based on an automated *in situ* assessment of parameters associated with the system.

Particular embodiments of the present invention are configured with a tunable capacitance system to provide steady state pressure for controlled delivery of polarized gas or gas blends. The capacitance may be provided by a fluid-filled

syringe that acts as a tuning capacitor with fluid that is added or subtracted from the system flow path.

The inspiration pressure can be set and a known volume delivered and/or the inspiration volume can be set and a known pressure delivered.

5 Certain embodiments of the present invention are directed to ventilator systems having a ventilation flow path for ventilating a subject. The systems include: (a) a mass flow controller; (b) a gas delivery valve in communication with the mass flow controller and configured to selectively dispense a plurality of different gases to a subject; (c) a first gas source in fluid communication with the gas delivery valve; (d) 10 a second gas source in fluid communication with the gas delivery valve; (e) a first pressure sensor located upstream of the gas delivery valve; (f) a second pressure sensor located downstream of the gas delivery valve; and (g) a controller operatively associated with the first and second pressure sensors and the mass flow controller a controller operatively associated with the first and second pressure sensors and the 15 mass flow controller, the controller configured to monitor the pressures measured by the first and second pressure sensors and the flow rate of the mass flow controller and automatically determine a delivered tidal volume using a reading of the flow rate of the mass flow controller when the first pressure is at a substantially steady state condition.

20 The system can also include a tracheal tube and the controller can be configured to adjust the flow rate to generate a substantially constant pressure at the first pressure sensor during delivery of the polarized gas.

Other embodiments are directed to methods of delivering hyperpolarized gas to a subject. The methods include: (a) providing a ventilator system with a mass flow 25 controller, a tracheal tube and a gas delivery valve configured to deliver hyperpolarized gas and at least one non-polarized gas to a subject; (b) monitoring a first pressure in the ventilator system upstream of the gas delivery valve; (c) monitoring a second pressure in the ventilator system downstream of the gas delivery valve; (d) obtaining a reading of the mass flow controller when the first pressure is 30 substantially constant; and (e) automatically determining the tidal inspiration volume of hyperpolarized gas delivered to the subject *in situ* using the obtained mass flow controller reading.

Other embodiments are directed to a system for delivering hyperpolarized gas to a subject, including: (a) a gas delivery valve configured to deliver hyperpolarized gas and at least one non-polarized gas to a subject; (b) a mass flow controller disposed upstream of the gas delivery valve; (c) a tracheal tube disposed downstream of the gas delivery valve; (d) means for monitoring a first pressure in the ventilator system upstream of the gas delivery valve; (e) means for monitoring a second pressure in the ventilator system downstream of the gas delivery valve; (f) means for automatically obtaining readings of the mass flow controller; and (g) means for automatically determining the tidal inspiration volume of hyperpolarized gas delivered to the subject *in situ* using the monitored first pressure and the value of a reading of the mass flow controller obtained when the first pressure is substantially constant.

In certain embodiments, the ventilator system can include a variable mass flow controller disposed upstream of the gas handling valve and the method can be carried out to automatically dynamically adjust the flow rate of the mass flow controller to maintain a substantially constant first pressure during ventilation delivery of the hyperpolarized gas to the subject.

The system and/or method can also operate to accept user input to select a desired operational mode such as either a tidal volume operational mode with the desired tidal volume selected or a peak inspiration pressure operational mode with the desired peak inspiration pressure selected.

Still other embodiments are directed to ventilator systems having a ventilation flow path for ventilating a subject. The systems include: (a) a gas delivery valve configured to selectively dispense a plurality of different gases to a subject; (b) a mass flow controller disposed upstream of the gas delivery valve; (c) a first polarized source in fluid communication with the gas delivery valve; (d) a second gas source in fluid communication with the gas delivery valve; (e) a first pressure sensor located upstream of the gas delivery valve; (f) a second pressure sensor located downstream of the gas delivery valve; and (g) a manifold line having a fluidic tunable capacitance disposed upstream of the gas delivery valve. The fluidic capacitance has a volume that is at least about 10 times greater than the volume of the lungs of the subject.

The system can include at least one fixed volume reservoir (or line) that is configured to selectively engage the manifold to adjust the fluidic capacitance

responsive to pressure measurements obtained by the first and second pressure sensors. The system may include a syringe with a quantity of fluid therein with the syringe being in communication with the manifold line and configured to selectively add or remove fluid from the manifold.

5 All, or selected operations, features, functions and/or configurations of the embodiments described above may be carried out as methods, systems, computer program products, assemblies and/or devices as contemplated by the present invention.

The foregoing and other objects and aspects of the present invention are
10 explained in detail herein.

Brief Description of the Drawings

Figure 1 is a block diagram of operations that can be carried out according to embodiments of the present invention.

15 **Figures 2A-B** are a block diagram of operations that can be carried out according to additional embodiments of the present invention.

Figure 3A is a schematic illustration of a ventilator delivery system according to embodiments of the present invention.

Figure 3B is a schematic illustration of a portion of a ventilator system with a
20 tracheal tube and gas delivery valve that can be used to define a fixed volume according to embodiments of the present invention.

Figure 4 is a graph of pressure versus time illustrating volumetric changes to a ventilation system according to embodiments of the present invention.

Figure 5A is a graph of pressure versus time illustrating variable systemic
25 pressures in response to inspiration and/or expiration pressures.

Figure 5B is a graph of pressure versus time illustrating systemic and PIP pressures during ventilation according to embodiments of the present invention.

Figure 6 is a schematic illustration of a controller/interface module according to embodiments of the present invention.

30 **Figure 7** is a schematic illustration of an alternate ventilator delivery system according to embodiments of the present invention.

Figure 8 is a block diagram of a controller port configuration for a ventilator according to embodiments of the present invention.

Figure 9 is a schematic illustration of another alternative ventilator delivery system according to embodiments of the present invention.

5 **Figure 10A** is a schematic illustration of yet another ventilator delivery system according to embodiments of the present invention.

Figure 10B is a schematic illustration of an additional ventilator delivery system according to embodiments of the present invention.

10 **Figure 11** is a timing diagram of inspiration and expiration that can be used in conjunction with embodiments of the present invention.

Figure 12 is a timing diagram of a ventilation cycle with breath-hold and associated trigger regions that can be used in conjunction with embodiments of the present invention.

15 **Figure 13** is a timing diagram of inspiration stop in relation to the inspiration/expiration and breath-hold cycle according to embodiments of the present invention.

Figure 14 is a timing diagram of expiration stop in relation to inspiration/expiration and breath-hold cycle according to embodiments of the present invention.

20 **Figure 15** is a block diagram of an automated dynamic pressure feedback system for controlling tidal volume or inspiration pressure for delivering hyperpolarized gas using a ventilator system according to embodiments of the present invention.

25 **Figure 16** is a block diagram of operations that can be used to dispense a selected gas during ventilation of a subject according to embodiments of the present invention.

Figure 17 illustrates how Figures 17A-I are to be arranged so as to depict a schematic illustration of an automated ventilator system according to embodiments of the present invention.

30 **Figures 17A-I** depict portions of the schematic illustration to be assembled according to Figure 17.

Detailed Description of Embodiments of the Invention

The present invention will now be described more fully hereinafter with reference to the accompanying figures, in which preferred embodiments of the invention are shown. This invention may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein. Like numbers refer to like elements throughout. In the drawings, layers, regions, or components may be exaggerated for clarity. In the figures, broken lines indicate optional features unless described otherwise.

In the description of the present invention that follows, certain terms may be employed to refer to the positional relationship of certain structures relative to other structures. As used herein the term "forward" and derivatives thereof refer to the general direction the target gas or target gas mixture travels as it moves through the ventilator system; this term is meant to be synonymous with the term "downstream," which is often used in manufacturing environments to indicate that certain material being acted upon is farther along in the manufacturing process than other material. Conversely, the terms "rearward" and "upstream" and derivatives thereof refer to the directions opposite, respectively, the forward and downstream directions.

Also, as described herein, polarized gases are produced and collected and may, in particular embodiments, be frozen, thawed, used alone and/or combined with other constituents, for MRI and/or NMR spectroscopy applications. As also used herein, the term "polarized gas" includes at least one polarized gas of interest (such as, but not limited to, ^3He and/or ^{129}Xe) and may include one or more other constituents such as other carrier, blending or buffer gases. Further, the terms "polarize", "polarizer", "polarized", and the like are used interchangeably with the terms "hyperpolarize", "hyperpolarizer", "hyperpolarized" and the like.

The ventilator systems and gas delivery valves contemplated by the present invention can be used for any target subjects and are hyperpolarized gas-compatible for NMR and/or MRI procedures. Although described herein for ease of discussion as a single gas delivery valve for delivering selectable ventilation gases, a plurality of discrete valves may also be used. "Subjects", according to the present invention, can be any animal subject, and are preferably mammalian subjects (*e.g.*, humans, canines, felines, bovines, caprines, ovines, equines, rodents, porcines, and/or lagomorphs).

The term "small animals" includes mice, rats, guinea pigs, dogs, cats, monkeys, pigs, and rabbits.

Various techniques have been employed to accumulate and capture polarized gases. For example, U.S. Patent No. 5,642,625 to Cates et al. describes a high volume hyperpolarizer for spin-exchange polarized noble gas and U.S. Patent No. 5,809,801 to Cates et al. describes a cryogenic accumulator for spin-polarized ^{129}Xe . As used herein, the terms "hyperpolarize," "polarize," and the like, are used interchangeably and mean to artificially enhance the polarization of certain noble gas nuclei over the natural or equilibrium levels. Such an increase is desirable because it allows stronger imaging signals corresponding to better NMR spectroscopy and/or MRI images of the substance and a targeted area of the body. As is known by those of skill in the art, hyperpolarization can be induced by spin-exchange with an optically pumped alkali-metal vapor or alternatively by metastability exchange. See Albert et al., U.S. Patent No. 5,545,396.

In particular embodiments, the ventilated polarized gas may be a noble gas, such as ^{129}Xe or ^3He . Other gases and/or noble gases may also be used, alone or in combination. Buffer gas formulations may also be used as described in U. S. Patent No. 6,295,834, the contents of which are hereby incorporated by reference as if recited in full herein. In other embodiments, the polarized gas may comprise ^{13}C and/or ^{15}N compounds, such as organic molecules enriched in ^{13}C , which may be polarized using dynamic nuclear polarization (DNP) and/or para-hydrogen induced polarization.

Figure 1 illustrates operations that can be performed according to embodiments of the present invention. As shown, a ventilator system with a MFC ("mass flow controller"), tracheal tube and a gas delivery valve configured to (selectively) deliver hyperpolarized gas and a non-polarized gas is provided (**block 100**). A first pressure in the ventilator system upstream of the gas delivery valve is monitored (**block 102**). A second pressure in the ventilator system downstream of the gas delivery valve is monitored (**block 104**). The tidal volume of hyperpolarized gas delivered to the lungs can be automatically determined *in situ* using the flow rate of the MFC when the first pressure is in a substantially steady state condition (**block 110**). Steady state means that the pressure variation is within a desired tolerance such

that it neither increases nor decreases over time during a desired interval. In certain embodiments, the ventilator system automatically controls and adjusts the MFC flow rate dynamically so as to maintain a substantially constant first pressure during delivery of the hyperpolarized gas. The system may automatically dynamically adjust the MFC flow rate to selectively provide a substantially constant P1 pressure and/or a substantially constant flow rate from the MFC depending on whether the system is operating in a user-selectable set tidal volume mode or a PIP mode (**block 109**).

The molar amount of hyperpolarized gas delivered in one or more tidal volumes (the tidal volume can be described as the change in volume during each breath) can be calculated based on the determined tidal volume using the MFC data and adjusted to be at standard temperature and pressure (**block 108**). That is, the tidal volume can be measured at standard temperature and pressure and this value can be translated into moles at this volume at standard temperature and pressure to evaluate the number of moles of hyperpolarized gas delivered the subject's lungs is determined. The measured amount can be in the millimole range for small animal ventilation.

Figures 2A-B illustrate operations that can be carried out to operate a ventilator and deliver hyperpolarized gas according to other embodiments of the present invention. Similar to the embodiment discussed above, the ventilator delivery system can include an MFC, a tracheal tube and first and second spaced apart pressure sensors (one located upstream of the gas delivery valve and/or tracheal tube and one located downstream of the gas delivery valve and/or on or in the tracheal tube). The sensors can be configured to automatically measure respective first and second pressures, P1, P2, in the ventilator system during operation. A desired breathing cycle, rate and/or inspiration rate can be set (*i.e.*, breath per minute "BPM" and inspiration/expiration "I/E" ratio) (**block 153**). The tracheal tube can be positioned in the subject (before, during or after the operational mode is selected), in fluid communication with the lungs thereof (**block 157**). The MFC flow rate can be adjusted to provide a substantially constant P1 (**block 159**). When P1 is in steady state, the tidal volume of the ventilated subject can be calculated or determined at PIP (peak inspiration pressure) at standard temperature and pressure using flow rate/frequency = volume exhausted/cycle (typically in units of ml/cycle -- although

other units can be used) (**block 161**). The delivered amount of hyperpolarized gas can be output *in situ* using the calculated tidal volume (**block 165**).

A predetermined portion of the ventilation system gas flow path including the tracheal tube defines a first static geometric volume "V1" (**block 152**). In operation,
5 the first geometric volume "V1" can be subtracted from the calculated tidal volume V1' (**block 154**), which is the volume of gas exhausted during a (each) breath for a particular one or more PIP. The volumetric correction can provide a more representative or "truer" tidal volume delivered to small animals where small amounts can influence the results. The fixed geometry volume V1 can be calculated using
10 known or measured dimensions or dynamically determined when the first pressure stabilizes with the tracheal tube closed.

In particular embodiments, a distal portion of the tracheal tube (the end that will be the deepest in the subject) can be capped or otherwise closed *in situ*, prior to insertion into the subject (**block 155**). That is, V1' can be determined using the value
15 of the MFC when P1 is in steady state operation. Because the downstream geometric volume is constant (with the tube closed), V1 can be calculated from the change in pressure between PIP and atmospheric pressure. A selected gas can be delivered during the V1 fixed geometry evaluation at a known flow rate, when the first pressure and the peak inspiration pressure (measured at P2) stabilize or are in steady state
20 during PIP, then flow in will equal the flow out (*i.e.*, the flow during inspiration equals the flow during expiration) (**block 156**).

The first and second pressures can be monitored and the data used to automatically and dynamically adjust selected operational parameters of the system so that the desired peak inspiration pressure is reached and the first pressure is stable
25 (**block 160**). The dynamic adjustment(s) can be carried out to maintain a substantially constant first pressure during delivery of the polarized gas (**block 162**). The system can be operated on different selectable modes that can be set by the user; thus, the system can be operated via a set inspiration pressure mode, where the inspiration volume is determined, or measured, or a set tidal (inspiration) volume mode, where
30 the inspiration pressure is measured (**block 166**).

In any event, when the tidal volume is measured, the "total" tidal volume V1' is measured (primarily representing the volume downstream of the gas delivery

valve). The volumetric contribution of the tube V1 may be subtracted at a particular PIP. For medium or large animals the volumetric correction for the tube may not be required.

Figure 3A illustrates one embodiment of a ventilator system 10. As shown, the system 10 includes a controller 15, a variable mass flow controller (MFC) 18, a first pressure sensor 21 (shown as a pressure transducer PT1), a gas delivery valve 25, a second pressure sensor 27, and a tracheal tube 30. The gas delivery valve 25 is in fluid communication with a polarized gas source 43 and a non-polarized gas source 43. In certain embodiments, the gas delivery valve 25 may optionally be in communication with additional gas sources (designated herein at feature 47). The mass flow controller 18 can be a variable calibrated mass flow controller, such as a voltage controlled controller p/n DFC2600 available from AALBORG located in Orangeburg, NY.

Figure 3A also illustrates the direction of flow in and flow out of the subject (shown by the arrows), shown as an animal subject 50. During exhale or expiration the exhaust is directed out of the subject back through the tracheal tube 30 and out of the gas delivery valve 25 via vent port 25v. The vent port 25v may be in fluid communication with a gas sensor (not shown) that determines exhaled gas contents, concentration or ratios.

Generally described, in operation, a control feedback system is used to adjust the rate of flow of the mass flow controller 18 to control delivery of a desired volume to the subject. The feedback is based on monitored pressure readings of the first and second pressure sensors 21, 27. The first sensor 21 is disposed upstream of the gas delivery valve 25 proximate the mass flow controller 18. The second sensor 27 is located downstream of the gas delivery valve 25 proximate the animal 50. The sensor 27 can be a pressure transducer or other type of pressure sensor. In certain embodiments, the second pressure sensor 27 can be positioned in or on the endotracheal tube itself so as to be able to measure the pressure in the lungs by placing the sensor 27 as close to the source or target as possible. However, in certain particular embodiments, such as when the tracheal tube diameter is very small such as for use with mice and the like, the sensor 27 may be positioned upstream of the lungs.

A port can be added to the gas delivery valve that connects to the tracheal tube through the valve body.

The operational premise of “flow in=flow out” can be used in certain situations. Flow in means flow into the volume of the gas flow path upstream of the gas delivery valve from the MFC and flow out means flow out of the volume downstream of the gas delivery valve. If the pressure at the first sensor **21** continues to increase during ventilation, then the flow rate is too great and the controller **15** can dynamically reduce the flow. If the pressure at the first sensor **21** decreases during ventilation, then additional flow is needed and the controller **15** can dynamically increase the flow. If the pressure at the first and/or second sensors **21**, **27** reaches a steady state condition during a peak inspiration pressure calculation, then the proper flow is being used.

Readings of the mass flow controller **18** are based on a calibrated gas at standard pressure (1 ATM, 14.7 psia, 1033.51 cm H₂O) and temperature (70 degrees F). The temperature and pressure can be monitored and adjustments made (the readings normalized to the standard pressure and temperature) as suitable. For an initial or “first pass” operational set-up or evaluation, temperature effects can be assumed to be nominal. If the calibrated gas is not the gas used for output, a conversion constant can be applied to determine the flow set point. For example, if the mass flow controller **18** is calibrated for nitrogen but helium is used, then a conversion factor of 1.454 is used in the calculations. Table 1 lists examples of a conversion “K” factor for default settings (standard temperature and pressure) that can be used in calculating parameters used to operate the ventilator.

Table 1: K Factors

GAS	K Factor based on N ₂ calibration gas
Air	1.0000
AR	1.4573
He	1.4540
N ₂	1.0000
N ₂ O	0.7128
O ₂	1.0000

Figure 3B illustrates that a calibration pressure P_1 can be established when the tracheal tube **30** is capped (shown with an end cap **30c**) and disposed outside of the body of the subject with the tracheal tube **30** closed (via cap, valve or other means) to close the exit end of the tracheal tube **30** while attached to the system **10** defining a first fixed system volume " V_1 " that can also be described as a calibration volume V_c (and sometimes described as V_{cal} hereinafter). The calibration volume V_c is associated with a predetermined portion of the ventilator system gas flow path having a fixed geometry as shown in **Figure 3A**. Typically, the calibration volume V_c is that portion of the gas flow path has a length " L " that extends through a portion of the gas delivery valve **25** to the distal end **30d** of the tracheal tube **30**. The length may be about 12 inches. The endotracheal tube **30** may be formed of 1/16 inch inner diameter tubing that can releasably connect to the valve **25** via a male luer lock (not shown). **Figure 3B** illustrates one embodiment of a gas delivery valve **25** with a plurality of individually selectable gas valves **25₁**, **25₂**, **25₃**. The fixed volume V_1 in this embodiment is the volume indicated by the cross-hatched portion of the flow path, which includes the flow path extending downstream of or in advance of the valve **25₃** to the distal end **30d** of the tracheal tube **30** in the forward input flow direction and includes the connection to the pressure transducer **27** and, in the exhaust or output direction, from the tracheal tube to the valve **25₄** associated with vent port **25v**.

After the tracheal tube **30** is placed in operative position, in fluid communication with the lungs of the subject, the lungs have an associated tidal volume that changes during a breath, this volume is added to the first system volume V_1 to provide a total tidal volume V_1' . **Figure 4** graphically illustrates the addition of this volume to the ventilator system **10**. That is, absent the pressure feedback control system, the system **10** with the tracheal tube **30** open and in the lungs delivers to a larger reservoir volume at the same flow rate thereby causing the pressure to decrease (shown by the fall in pressure noted in **Figure 4** when V_2 is added). However, the flow rate can be increased to again bring (or keep) the system **10** at a desired substantially constant pressure, as shown in **Figure 4** as the pressure returns to

the P1 value and levels off with the lungs added to the system (when the tracheal tube is open and in position in the subject).

Figures 5A and 5B illustrate the pressure P1 at the first sensor **21** in relation to the pressure at the second sensor **27** over time (t) during operation with the tracheal tube **30** in position in the subject. The pressure P2 at the second sensor **27** is made in the subject's airway during operation and corresponds to the BPM and I/E ratio selected. The maximum P2 pressure is the peak inspiration pressure (PIP). **Figure 5A** illustrates pressure fluctuation in the first pressure that may cause measurement errors. **Figure 5B** illustrates the system **10** being controlled to provide a substantially constant operating or system pressure P1, with P1 being steady state or stable (not increasing or decreasing over time) and substantially equal to and/or greater than the PIP according to embodiments of the present invention. In certain embodiments, this P1 pressure stability can be carried out using a capacitance volume located upstream of the gas delivery valve as will be discussed further below. The size of the capacitance can be tuned to reduce the fluctuations of P1 shown in **Figure 5A** so that P1 behaves more like that shown in **Figure 5B**. It is noted that oversizing the capacitance may slow the responsiveness of the system.

Referring back to **Figure 3A**, in certain embodiments, the first sensor **21** can be a pressure transducer PT1 that is used to monitor the pressure in the system **10** between the mass flow controller **18** and the gas delivery valve **25** based on the flow into the gas delivery valve **25**. The second sensor **27** can also be a pressure transducer, PT2, and can be used to monitor the airway pressure from the subject (which can be an animal). The gas delivery valve **25** can be configured for either supplying the air to the subject and/or for allowing the subject to hold breath or exhale.

Figure 6 illustrates an alternative embodiment of a ventilator system **10'** using a flow meter **31** in-line with either a source of supply gas(es) (not shown) and/or a vent port **25v**. Other embodiments can use an independent flow meter and a proportional valve (not shown). Still other embodiments can employ manually adjustable flow valves (also not shown). Combinations of the above may also be used.

The lung volume can vary with PIP and BPM as lungs are typically somewhat elastic. Thus, an *a priori* evaluation of the animal expected lung physiological characteristics can be programmed to help establish flow rate adjustment increments and default operating parameters. For example, the ventilator system 10, 10' can be operatively associated with a reference library of animal characteristics, such as, but not limited to, estimated lung volume versus pressure, PIP, BPM, flow rates, and the like to help operate the feedback control system. An example of default parameters is listed in Table 2 below.

10

Table 2 Default Parameters

Animal	Tidal Volume	BPM	I/E
Mice	0.3 mL	110	30/70
Rats	1.5 mL	60	30/70
Guinea Pigs	4.0 mL	50	30/70
Rabbits	18.0 mL	35	30/70

Certain embodiments of the gas delivery valve 25 employ at least one spool or piston to actuate at least one gas flow path in a NMR/MRI compatible valve body. This configuration may be particularly suitable for small animal ventilators used during NMR spectroscopy and/or MRI imaging sessions. For additional description of a spool or shuttle valve, see U.S. Provisional Patent Application Serial No. 60/450,209 filed February 26, 2003, the contents of which are hereby incorporated by reference as if recited in full herein. Other valve configurations, such as but not limited to, diaphragm and/or pincher valves may also be used.

In any event, the gas delivery valve 25 can be configured to provide fast response times, which may be particularly suitable for use in situations where the subject is ventilated at a high BPM breathing rate with a low inhale/exhale or inspiration/expiration ratio (I/E). The I/E ratio is the inspiration time over the expiration time. "Inspiration" is the time during which the gas is provided to the animal (or other subject) while "expiration" is the time during which the animal (or other subject) is exhaling. Therefore, a high BPM, such as about 180 BPM, means that each breath lasts 333 ms. An I/E of 20/80 means that the device has 67 ms to

deliver the desired tidal volume to the animal (or other subject). The speed at which the valve opens can be important, as the faster the BPM, the smaller the I/E %, and the less time the valve has to open and supply the desired amount of gas to the animal (or other subject).

5 The I/E ratio is typically within about 30/70 to 60/40, but can vary outside of this range, depending on the desired result. The I/E ratio and BPM can be substantially fixed during "normal" (non-imaging) breathing. The BPM and I/E ratio can be adjusted to be different for imaging (hyperpolarized gas) breath runs, but once the image run is over, these operating parameters can return to "normal" breathing
10 parameters. See **Figures 11-14** for examples of breath cycles according to embodiments of the present invention.

Also, it is noted that 180 BPM may be an upper range for many small animal species and, in certain embodiments, the ventilators **10, 10'** may operate at a lower rate. The operating parameters are animal species/weight driven. For example, mice
15 use a faster BPM than a rabbit. The I/E ratio can change between animals but will typically stay within the range mentioned above. During NMR/MRI signal acquisition, the BPM may be about 30 BPM for a small animal such as a mouse.

In addition, the valve may be configured for an "on-off" operation of a single gas or different gases to deliver or hold back a single gas (typically hyperpolarized
20 gas) or different gases and/or to open and close the single or plurality of gas flow paths (not shown) for controlled inhalation delivery to a subject; the gas delivery valve **25** can also be configured to select between inhale, exhale, and/or breath-hold ventilation operations.

The valve body and polarized gas flow path (including the tracheal tube **30**)
25 and its internal components can be formed from and/or coated with a material or materials selected for the ability to inhibit depolarization of hyperpolarized gas (such as due to relaxation attributed to gas interaction therewith). Coatings such as sol-gel coatings, deuterated polymer coatings, metal film coatings and other coatings and non-magnetic materials that inhibit depolarization can also be used. See, e.g., U.S.
30 Patent Application No. 09/485,476 and U.S. Patent Nos. 5,612,103 and 6,423,387, the contents of which are hereby incorporated by reference as if recited in full herein. For example, the valve body and/or components may be formed of materials such as,

but not limited to, aluminum, TEDLAR, TEFLON, PTFE, DELRIN (acetal), and the like. Care should be taken to reduce the sources of friction by providing a smooth surface finish, and reducing the number of O-rings or selecting the O-ring material to reduce friction. In addition, the valve body can be fabricated to tolerances to provide
5 sufficient seals and yet provide reduced friction between the spool and valve body receptacle. Thus, the valve body bore finishes, the interface with the endotracheal tube, any O-ring compression, and lubricants may all be considered to reduce the sources of friction. The endotracheal tube can also be configured from medical grade biocompatible materials, which are also configured with material(s) or coatings that
10 inhibit hyperpolarized gas decay.

The valve 25 can be configured to automatically provide a selection of ventilation breath outputs and/or inputs according to embodiments of the present invention as directed by the controller 15. For discussion purposes, Gas A will be described as a hyperpolarized gas and Gas B as a non-polarized gas. In operation, a
15 reverse configuration can be used. The term "breath-hold" means that the gas or gases are held in the lungs for a breath-hold time to facilitate bio-uptake of the gas and/or allow a stronger hyperpolarized gas signal relative to normal respiration. The breath-hold duration may be between 5-30 seconds.

The valve 25 can be actuated to accommodate: (a) Gas "A" inhale; (b) Gas "B" inhale; (c) Gas "A" + Gas "B" inhale; (d) exhale; (e) partial exhale and breath hold; (f) Gas "A" inhale and breath hold; (g) Gas "B" inhale and hold; and (h) Gas "A" + Gas "B" inhale and breath hold. As noted above, the hyperpolarized gas may be a hyperpolarized noble gas such as ^3He and/or ^{129}Xe . The non-polarized gas may be a mixture of non-polarized gases. The non-polarized gas can be selected to inhibit
25 depolarization of the hyperpolarized gas, and may be also selected for biocompatibility. Examples of suitable non-polarized gases include, but are not limited to, nitrogen, xenon, and helium. The valve 25 may also be used to connect to an anesthetic vaporizer.

In addition, the valve 25 and polarized gas flow path in the ventilator system
30 can be configured to reduce any dead volume for the inhaled gas(es). The term "dead volume" means the volume from source to subject such as within the valve or downstream system that needs to be filled with gas before the gas will reach the

subject. The smaller the volume, the less gas that is “wasted”. Reducing the dead volume is particularly desirable when dispensing hyperpolarized gas because the hyperpolarized gas fills the volume of the flow path from source to subject and any polarized gas remaining in the dead volume may become unpolarized or decay to an undesirable polarization level, and must be displaced before suitably polarized gas can reach the subject on the next polarized breath.

In certain embodiments, the ventilator system **10, 10'** is configured to operate in an NMR/MRI suite having magnetic field strength up to about 5T. In other embodiments, the ventilator **10, 10'** can be configured to operate in a low magnetic field environment, typically under about 100 Gauss. The ventilator system **10, 10'** can be configured to operate in intermediate field strengths as well, such as, but not limited to, greater than about 100 Gauss and up to about 1.5T.

In certain embodiments, the ventilator system **10, 10'** can be configured to provide a tidal volume control of from about 0.2 mL to about 100 mL, in 0.1 mL increments. The system **10, 10'** may be configured to operate with a BPM range of from about 5-180, with about a 1 BPM adjustable increment. The system **10, 10'** may also be configured to allow selectable inspiration/expiration ratios from between about 5:1 to 1:5 with about a 1% increment adjustability and supply controlled PIP of from about 0-40 inches H₂O with about 1 inch H₂O increments. The tidal volume flow can range from about 0-5 liters/min. The ventilator **10, 10'** can be shielded so that EMI/RFI produced shall not unduly affect the polarization level of the gas or the operation of the MRI/NMR equipment.

Figure 7 illustrates one configuration of a controller **15** according to certain embodiments of the present invention. As shown, the controller **15** can include at least one RS232 communication port **210**, a body temperature monitoring port **212**, a plurality of analog to digital and/or digital to analog ports **214**, and a trigger input/output port **216** that can sequence or generate gated trigger signals to an NMR/MRI system during or prior to signal acquisition. The gated trigger signal can relate to a desired portion of a breath-hold cycle and/or an “R” trigger in a detected QRS cardiac rhythm. The controller **15** can also include a physiological monitor connection port **218** that accepts data regarding at least one of heart rate, ECG, blood

pressure, oxygen saturation levels, CO₂ during expiration, body temperature, and the like, as well as a pressure transducer input port(s) **219**.

The temperature monitor can monitor internal animal body temperature and direct heating and/or cooling of the animal to maintain the temperature within a
5 desired range. The temperature monitor may be independent of the controller **15**.

Figure 8 illustrates one embodiment of a controller **15** with an interface module having a plurality of different interface connections to remote, peripheral and/or integrated devices. As shown, the connections or ports include a control line to the mass flow controller **251**, a communication line between the first and second
10 sensors **252**, **253** and a control line to the gas delivery valve **254**. The controller **15** can also have a gas delivery valve control line **255** configured to control and direct the flow direction, *i.e.*, inspiration/expiration, a triggering event monitoring line **256**, and a physiological data collection communication line **257**. As shown, the controller **15** can also include a communication port to accept user input for operational parameters
15 **259** and can include a communication port or line **258** that engages an NMR/MRI device or system lines to record tidal volume/PIP or other information on NMR/MRI signal acquisitions or images.

Figure 9 illustrates another embodiment of a ventilator system **10''** according to the present invention. This embodiment may be particularly suitable to dispense
20 polarized gas or gas mixtures proximate in time (*i.e.*, just prior or during) to MRI/NMR imaging or signal acquisition in a specified tidal volume operational mode. As shown, the polarized gas source **43** comprises a compressible container **180b** inside a pressure vessel **180**. In this embodiment, a constant flow of nitrogen is fed into a variable flow pressure regulator that controls the flow of the nitrogen into
25 the vessel **180**. The nitrogen in the vessel **180** compresses the container **180b** that expels the hyperpolarized gas (Hp) to the gas delivery valve **25**. A pressure sensor **26** is located in the container and measures the pressure P_c used to compress the container **180b**. The PIP obtained from a normal breath (non-polarized gas) can be used as the pressure P_c adjusted by a constant or factor, as needed, based on the
30 properties of the gas used to squeeze the bag. That is, nitrogen and air have similar properties, so the normal breath pressure may be used. However, helium is less dense and a correction factor of air to helium can be used to provide the desired pressure

(e.g., X cc's of air = Y cc's of He). The tidal volume V_T can be the same value as that calculated in a normal breath cycle.

In operation, the system 10'' applies pressure to the bag 180b by pressurizing the chamber 180c in the vessel 180. The chamber 180c can be pressurized to a
5 pressure that is greater than the "current" PIP pressure (taken as a substantially real-time dynamic measurement). The pressure for the chamber 180c can be determined by multiplying the PIP times a constant adjustment factor to adjust for the difference in density and distance to the animal.

Figure 16 is a block diagram of operations that can be carried out to ventilate
10 a subject according to embodiments of the present invention. As shown, a ventilation system can be configured with a gas delivery valve and a tunable fluidic capacitance (block 400). The system can be configured with an adjustable capacitance volume that is at least about three times, typically at least about ten times, and more typically at least about 100 times greater than the size of the lungs of the target subject
15 undergoing evaluation (block 401). The capacitance size may be selected based on the average size of the lungs of the animal species undergoing evaluation. The system can be tuned by adjusting the volume of fluid held in the system manifold line upstream of the gas delivery valve (block 405).

The tuning can be carried out to maintain a substantially constant pressure
20 (block 406). The increase and/or decrease in fluid can be carried out by selectively engaging or disengaging one or more fixed volume lines or reservoirs (block 407) and/or by using a syringe that can inject and extract fluid from the system to adjust the capacitance.

Figure 10A illustrates one embodiment of a ventilator system 10a with a
25 variable mass flow tuning system having a tunable capacitance "C" that can reduce pressure variations and even out the operational pressure of the system 10a. As shown, the system 10a is configured with an increased fluid volume 301 and a syringe 300 or other input/output fluid adjustment mechanism that can add and/or remove a desired controlled amount of fluid to tune the system and create a substantially
30 constant pressure at the first sensor 21 (as shown in Figure 5B). The capacitance volume may be between about 50-1500ml. The system 10a can also include a pressure regulator 16 disposed upstream of the mass flow controller 18. The

capacitance is defined by a fluid volume **301** upstream of the gas delivery valve **25**. The capacitance can be at least ten times the volume of the lungs, and typically at least about 100 times greater than the volume of the lungs of the subject. Thus, for example, for a subject having a 3 ml lung capacity, the system **10a** can be configured
5 with a 300 ml fluid capacitance.

Figure 10B illustrates another embodiment of a system **10b**. In this embodiment, a three-way valve **114** can be positioned intermediate the mass flow controller **18** and polarized gas source **43**. The system **10b** can also include a pressure regulator **14** in communication with the three-way valve **114** and a pressure regulator
10 **16** upstream of the mass flow controller **18**. In operation, the three-way valve **114** is configured to temporarily disconnect the mass flow controller **18** when the system **10b** is in the tidal volume dispensing mode (operating to dispense a selected predetermined tidal volume of hyperpolarized gas). The nitrogen pressure can be controlled or set by the pressure regulator **14** and reservoir or lump capacitance **301**
15 (defined by one or more upstream reservoirs or fixed volumes (tied into the line in series or parallel) to keep the pressure substantially steady state during tidal volume dispensing of the polarized gas. The nitrogen at a controlled pressure is then directed into vessel **180** to compress the bag **180b** of hyperpolarized gas. Examples of suitable bags are described in U.S. Patent No. 6,423,387, the content of which is hereby
20 incorporated by reference as if recited in full herein.

Figure 11 illustrates the basic components of a breath cycle during ventilation. As shown, there is an inspiration and expiration duration that can be selected based on the I/E ratio. In the embodiment shown in **Figure 11**, there is also a region for input trigger delay **300t_i** (the trigger for obtaining an MRI/NMR signal) can be timed to
25 start a predetermined delay period from this time in the cycle. **Figure 12** illustrates the breath cycle with a hold-breath portion and three potential regions for output trigger delays: an output trigger delay from the start of inspiration **300t_{oi}**; an output trigger delay from the start of breath hold time **300t_{oh}**; and an output trigger delay from the start of expiration **300t_{oe}**.

30 **Figures 13 and 14** illustrate different portions of the breath cycle in which to initiate the breath-hold time of the polarized gas. **Figure 13** illustrates an inspiration stop and **Figure 14** illustrates an expiration stop.

Figure 17 and Figures 17A-I illustrate an example of an automated ventilator system **10d** according to certain embodiments of the present invention. As shown, the system **10d** includes a gas control module **500** that may be configured to reside in a desktop enclosure. The gas control module **500** includes a breathing gas control system **510**, a polarized gas control system **520**, and a gas delivery valve **25** control system **530**. The breathing gas control system **510** includes a first breathing gas input **500i** with associated pressures sensors, valves, and regulators, as well as the mass flow controller **18** and first pressure sensor **21**. As shown, the breathing gas control section **510** can also be in communication with an adjustable capacitance volume reservoir **301** (which can have a capacitance volume of between about 50-1500 ml, or even more, in certain embodiments). Optionally, the breathing gas control system **510** can also be in communication with an anesthetic vaporizer and/or scrubber. Small inner diameter conduit (typically about 1/8-1/16 of an inch) can be used to connect components. As is also shown, the breathing gas control system **510** can include an optional second breathing gas input **500i₂**.

The polarized gas control system **520** also includes pressure regulators, pressure sensors, and valves that are in communication with the polarized gas source **43**. The polarized gas source **43** is, in turn, in communication with the gas delivery valve **25** via small inner diameter polarization friendly tubing (shown as 1/16 inch i.d. tubing).

The gas delivery valve **25** control system **530** includes a pressure regulator and pressure transducer and a series of valves that control inhale, exhale and gas output to the subject. The configuration shown contemplates the use of a diaphragm valve **25**, but as noted above, other gas delivery valve **25** configurations can be used and the gas delivery valve control system **530** modified accordingly. In certain embodiments, such as where pressure transients may be undesirable and/or problematic, orifices can be added to the transducer lines (not shown).

The control module **500** can be configured to be in communication with various components and peripheral devices. As shown, the system **10d** can include a vital signs/power supply module **550** that may also be provided in the desktop enclosure housing the control module **500**. The vital signs/power supply module **550** can include a blood pressure sub-module **552** that communicate with a blood pressure

sensor **550s**, a cardiometer sub-module **553** that communicates with a heart monitoring sensor **550s**, and a gas pressure sub-module **551**. The system **10d** can also include a blanket-type heating pad **560** with temperature controller **570**. The system **10d** can also include an optional CO₂ analyzer **575₁** and/or scrubber **575₂** connected to vent port **25v** of the valve **25**. As shown by the designation **600** and software control box, the system **10d** can be software controlled for automated operation.

In certain embodiments, as shown in **Figure 17A**, the system can employ two mass flow controllers **18** and **18₂**. The mass flow controllers can be used to blend standard ventilation gases (such as oxygen and air) during non-polarized gas ventilation. The system can be configured to automatically control the operation of the supplemental mass flow controller to deliver a desired blend, mix or concentration of gases to the subject (such as to supply about 30% oxygen with 70% air).

It is noted that the features described above with respect to one embodiment of a ventilator described herein may be applied to other embodiments.

As will be appreciated by one of skill in the art, the present invention may be embodied as a method, data or signal processing system, or computer program product. Accordingly, the present invention may take the form of an entirely hardware embodiment, an entirely software embodiment or an embodiment combining software and hardware aspects. Furthermore, the present invention may take the form of a computer program product on a computer-usable storage medium having computer-usable program code means embodied in the medium. Any suitable computer readable medium may be utilized including hard disks, CD-ROMs, optical storage devices, or magnetic storage devices.

The computer-usable or computer-readable medium may be, for example but not limited to, an electronic, magnetic, optical, electromagnetic, infrared, or semiconductor system, apparatus, device, or propagation medium. More specific examples (a nonexhaustive list) of the computer-readable medium would include the following: an electrical connection having one or more wires, a portable computer diskette, a random access memory (RAM), a read-only memory (ROM), an erasable programmable read-only memory (EPROM or Flash memory), an optical fiber, and a portable compact disc read-only memory (CD-ROM). Note that the computer-usable or computer-readable medium could even be paper or another suitable medium upon

which the program is printed, as the program can be electronically captured, via, for instance, optical scanning of the paper or other medium, then compiled, interpreted or otherwise processed in a suitable manner if necessary, and then stored in a computer memory.

5 Computer program code for carrying out operations of the present invention may be written in an object oriented programming language such as Java7, Smalltalk, Python, or C++. However, the computer program code for carrying out operations of the present invention may also be written in conventional procedural programming languages, such as the "C" programming language or even assembly language. The
10 program code may execute entirely on the user's computer, partly on the user's computer, as a stand-alone software package, partly on the user's computer and partly on a remote computer or entirely on the remote computer. In the latter scenario, the remote computer may be connected to the user's computer through a local area network (LAN) or a wide area network (WAN), or the connection may be made to an
15 external computer (for example, through the Internet using an Internet Service Provider).

Figure 15 is a block diagram of exemplary embodiments of data processing systems that illustrates systems, methods, and computer program products in accordance with embodiments of the present invention. The processor **310**
20 communicates with the memory **314** via an address/data bus **348**. The processor **310** can be any commercially available or custom microprocessor. The memory **314** is representative of the overall hierarchy of memory devices containing the software and data used to implement the functionality of the data processing system **305**. The memory **314** can include, but is not limited to, the following types of devices: cache,
25 ROM, PROM, EPROM, EEPROM, flash memory, SRAM, and DRAM.

 As shown in **Figure 15**, the memory **314** may include several categories of software and data used in the data processing system **305**: the operating system **352**; the application programs **354**; the input/output (I/O) device drivers **358**; an automated dynamic pressure feedback flow adjustment module with selectable inspiration tidal
30 volume and PIP operational modes **350**; and the data **356**.

 The data **356** may include ventilation system operational data **362** which may be obtained from the ventilation system, patient physiological data, and/or may be

NMR/ MRI data from an NMR spectroscopy or MRI system **320**. As will be appreciated by those of skill in the art, the operating system **352** may be any operating system suitable for use with a data processing system, such as OS/2, AIX or OS/390 from International Business Machines Corporation, Armonk, NY, WindowsXP, WindowsCE, WindowsNT, Windows95, Windows98 or Windows2000 from Microsoft Corporation, Redmond, WA, PalmOS from Palm, Inc., MacOS from Apple Computer, UNIX, FreeBSD, or Linux, proprietary operating systems or dedicated operating systems, for example, for embedded data processing systems.

The I/O device drivers **358** typically include software routines accessed through the operating system **352** by the application programs **354** to communicate with devices such as I/O data port(s), data storage **356** and certain memory **314** components and/or the image acquisition system **320**. The application programs **354** are illustrative of the programs that implement the various features of the data processing system **305** and preferably include at least one application that supports operations according to embodiments of the present invention. Finally, the data **356** represents the static and dynamic data used by the application programs **354**, the operating system **352**, the I/O device drivers **358**, and other software programs that may reside in the memory **314**.

While the present invention is illustrated, for example, with reference to the Feedback Module **350** being an application program in **Figure 15**, as will be appreciated by those of skill in the art, other configurations may also be utilized while still benefiting from the teachings of the present invention. For example, the Pressure Feedback Module **350** may also be incorporated into the operating system **352**, the I/O device drivers **358** or other such logical division of the data processing system **305**. Thus, the present invention should not be construed as limited to the configuration of **Figure 15**, which is intended to encompass any configuration capable of carrying out the operations described herein.

In certain embodiments, the Pressure Feedback Module **350** includes computer program code for timing the delivery of the desired inhalation gas(es) and may include code for tracking polarization level data of the dispensed hyperpolarized gas. The Module **350** can direct initiation of operations that will automatically sequence the system to output at a desired breath per minute rate, a desired I/E ratio, a target

breath-hold time and may automatically adjust the pressure in the system based on sensed pressures.

The I/O data port can be used to trigger NMR/MRI signal acquisition and/or to transfer information between the data processing system **305** and the NMR/MRI data acquisition system **320** or another computer system, a network (*e.g.*, the Internet) or other device controlled by the processor. These components may be conventional components such as those used in many conventional data processing systems, which may be configured in accordance with the present invention to operate as described herein.

While the present invention is illustrated, for example, with reference to particular divisions of programs, functions and memories, the present invention should not be construed as limited to such logical divisions. Thus, the present invention should not be construed as limited to the configuration of **Figure 15** but is intended to encompass any configuration capable of carrying out the operations described herein.

The flowcharts and block diagrams of certain of the figures herein illustrate the architecture, functionality, and operation of possible implementations of probe cell estimation means according to the present invention. In this regard, each block in the flow charts or block diagrams represents a module, segment, or portion of code, which comprises one or more executable instructions for implementing the specified logical function(s). Certain of the flowcharts and block diagrams illustrate methods to operate hyperpolarizers or components thereof to yield polarized gas according to embodiments of the present invention. In this regard, each block in the flow charts or block diagrams represents a module, segment, or portion of code, which comprises one or more executable instructions for implementing the specified logical function(s). It should also be noted that in some alternative implementations, the functions noted in the blocks may occur out of the order noted in the figures. For example, two blocks shown in succession may in fact be executed substantially concurrently or the blocks may sometimes be executed in the reverse order, depending upon the functionality involved.

As noted above, the systems **10**, **10'**, **10''**, **10a**, **10b** can be configured to operate on the theory of flow into the system is equal to the flow out of the system.

The following non-limiting example is provided in further description of the present invention.

EXAMPLE

5

The following exemplary listing of sequence of operations can be used to deliver gas from the ventilator.

1.1) Fixed Volume Calculation:

10 1.1.1) The fixed volume of the system from the inhale port to the animal connection point including the pressure transducer is calculated. This calculation may be conducted either through an automate sequence using the mass flow controller and the pressure transducers or using volumetric calculations and the known tube lengths and diameters.

15 1.1.2) An automated sequence may comprise the following steps:

1.1.2.1) Prompting/instructing the user to cap off the tubing at the animal connection point.

1.1.2.2) Prompting the user for the type of subject (animal) to be ventilated.

1.1.2.3) Setting the inspiration/expiration ratio to 50%.

20 1.1.2.4) Setting the BPM and the PIP to the pre-programmed system defaults for the animal being ventilated.

1.1.2.5) Instructing the system to flow at the default flow rate for the animal selected.

25 1.1.2.6) Adjusting the flow rate until the pressure read by PT1 substantially matches the pressure read by PT2 within a predetermined tolerance.

1.2) Once a steady state pressure is achieved, the volume is determined as follows:

Fixed Volume = $V_{cal} = FR / (BPM ((PT8/1033.51 \text{ cmH}_2\text{O}) + 1 \text{ ATM}))$.

30 Where FR=Flow rate.

1.3) Normal Breathing Gas Delivery:

- 1.3.1) User enters the animal type into an input device associated with the ventilator system (computer touch screen, keyboard and the like)
- 1.3.2) User enters in either a desired PIP or Tidal Volume (V_T).
- 1.3.3) User enters in a desired inspiration/expiration ratio.
- 5 1.3.4) User enters in a desired BPM.
- Note, a default setting for each of the selectable parameters for a particular animal and/or size of animal can be programmed.
- 10 1.3.5) In PIP mode: (Note PIP is read at PT2)
- 1.3.5.1) The system calculates a starting Flow Rate (FR) based on the calibrated volume V_{cal} . This calculation can be based on $FR_{total} = FR_{cal} + FR_{animal}$; where FR_{cal} is the amount of flow used to raise the fixed volume from 1ATM to the desired PIP and FR_{animal} is the flow rate used to deliver the default
- 15 tidal volume to the animal at the desired PIP.
- 1.3.5.2) Initial flow rate can be established or estimated by:
- 1.3.5.2.1) $FR_{cal} = BPM * (((1 + (PIP_{desired} / 1033.51 \text{ cmH}_2\text{O})) * V_{cal}$
- 1.3.5.2.2) $FR_{animal} = BPM * V_{Tdefault}$.
- 20 1.3.5.2.3) $FR_{total} = FR_{cal} + FR_{animal}$.
- 1.3.5.3) Flow can then be initiated.
- 1.3.5.3.1) If the $PIP_{read} < PIP_{desired}$ then the FR can be (incrementally) increased until the desired PIP is reached.
- 25 1.3.5.3.2) PIP can be based on a plurality of cycles, typically an average of 5 contiguous cycles.
- 1.3.5.3.3) If $PIP_{read} > PIP_{desired}$ then FR can be incrementally decreased until the $PIP_{desired}$ is reached.
- 1.3.5.3.4) If $PIP_{desired}$ cannot be reached then an error can be indicated to the user.
- 30 1.3.5.4) After the PIP reading has stabilized:
- 1.3.5.4.1) PIP shall be the stabilized reading in cmH_2O .
- 1.3.5.4.2) The tidal volume shall then be calculated:

- 1.3.5.4.2.1) $V_T = V_{Total} - V_{fixed}$.
- 1.3.5.4.2.2) $V_{fixed} = V_{cal} * ((PIP_{read} / 1033.51 \text{ cmH}_2\text{O}) + 1)$.
- 1.3.5.4.2.3) $V_{Total} = FR/BPM * ((PIP_{read} / 1033.51 \text{ cmH}_2\text{O}) + 1)$.
- 1.3.5.4.3) Once the tidal volume has been calculated it can be tested to see if it is
 5 within the minimum (V_{Tmin}) and maximum (V_{Tmax}) range for the animal being ventilated.
- 1.3.5.4.4) If $V_T < V_{Tmin}$ then the $PIP_{desired}$ shall be increased and an error message can be sent to the user.
- 1.3.5.4.5) If $V_T > V_{Tmin}$ then the $PIP_{desired}$ shall be decreased and an error message
 10 can be sent to the user.
- 1.3.6) In V_T mode:
- 1.3.6.1) The system can calculate a starting FR based on the desired V_T entered by the user.
- 15 1.3.6.1.1) $FR_{total} = FR_{cal} + FR_{animal}$.
- 1.3.6.1.2) $FR_{animal} = BPM * V_{Tdesired}$.
- 1.3.6.1.3) $FR_{cal} = BPM * (((1 + (PIP_{default} / 1033.51 \text{ cmH}_2\text{O})) * V_{cal}$.
- 1.3.6.2) The V_T can be calculated each time the PIP stabilizes.
- 1.3.6.2.1) $V_T = V_{Total} - V_{fixed}$.
- 20 1.3.6.2.2) $V_{fixed} = V_{cal} * ((PIP_{read} / 1033.51 \text{ cmH}_2\text{O}) + 1)$.
- 1.3.6.2.3) $V_{Total} = FR/BPM * ((PIP_{read} / 1033.51 \text{ cmH}_2\text{O}) + 1)$.
- 1.3.6.3) If V_T is $< V_{Tdesired}$ then $PIP_{desired}$ can be increased.
- 1.3.6.4) If V_T is $> V_{Tdesired}$ then $PIP_{desired}$ can be decreased.
- 1.3.6.5) The PIP can be tested to see if it is outside the minimum PIP (PIP_{min}) and
 25 maximum PIP (PIP_{max}) for the animal being imaged.
- 1.3.6.5.1) If the $PIP_{min} \leq PIP_{read} \leq PIP_{max}$, then no fault message is generated and the new value can be utilized.
- 1.3.6.5.2) If the PIP_{read} is $< PIP_{min}$ then the PIP is raised and an error message can be displayed to the user.
- 30 1.3.6.5.3) If the $PIP_{read} > PIP_{max}$, then the PIP is lowered and an error message can be displayed to the user.

1.3.6.6) Changing the PIP value will cause the computer program or software to change the FR setpoint.

1.3.6.7) Once the desired V_T is reached the PIP will be PIP_{read} .

5 1.4) Imaging Gas Breathing:

1.4.1) The PIP from the normal breath analysis can be used as the pressure to squeeze the polarized gas source.

1.4.2) The T_V can be presumed to be the same as that calculated in the normal breath cycle.

10 1.4.3) The actual pressure to the bag can be adjusted by a constant factor based on the properties of the gas being used to squeeze the bag.

In summary, the ventilation systems of the present invention allow for computer control and adjustment of the tidal volume and peak inspiration pressure delivered to the animal. The systems can also be configured to allow for data feedback from both sides of the gas delivery valve(s) and utilizes this feedback to make automated adjustments during operation of the device. The systems can include a mass flow controller so that the mole concentration to the animal can be determined.

The foregoing is illustrative of the present invention and is not to be construed as limiting thereof. Although a few exemplary embodiments of this invention have been described, those skilled in the art will readily appreciate that many modifications are possible in the exemplary embodiments without materially departing from the novel teachings and advantages of this invention. Accordingly, all such modifications are intended to be included within the scope of this invention as defined in the claims. In the claims, means-plus-function clauses, where used, are intended to cover the structures described herein as performing the recited function and not only structural equivalents but also equivalent structures. Therefore, it is to be understood that the foregoing is illustrative of the present invention and is not to be construed as limited to the specific embodiments disclosed, and that modifications to the disclosed embodiments, as well as other embodiments, are intended to be included within the scope of the appended claims. The invention is defined by the following claims, with equivalents of the claims to be included therein.

THAT WHICH IS CLAIMED IS:

1. A ventilator system having a ventilation flow path for ventilating a subject, comprising:
 - 5 a mass flow controller;
 - a gas delivery valve disposed downstream of and in communication with the mass flow controller, the gas delivery valve being configured to selectively dispense a plurality of different gases to a subject;
 - a first gas source in fluid communication with the gas delivery valve;
 - 10 a second gas source in fluid communication with the gas delivery valve;
 - a first pressure sensor located upstream of the gas delivery valve;
 - a second pressure sensor located downstream of the gas delivery valve; and
 - a controller operatively associated with the first and second pressure sensors and the mass flow controller, the controller configured to monitor the pressures
 - 15 measured by the first and second pressure sensors and the flow rate of the mass flow controller and automatically determine a delivered tidal volume using a reading of the flow rate of the mass flow controller when the first pressure is at a substantially steady state condition.
- 20 2. A ventilator system according to Claim 1, wherein the controller is configured to automatically adjust the flow rate of the mass flow controller so that the pressure measured by the first pressure sensor is substantially constant during delivery of hyperpolarized gas.
- 25 3. A ventilator system according to Claim 2, wherein the first gas source is a polarized gas source and the second gas source is a non-polarized gas source, said system further comprising a tracheal tube in fluid communication with the gas delivery valve, wherein the gas delivery valve is configured with a vent port that allows expired breath to vent during expiration, and wherein the gas delivery valve is
- 30 configured to operate at a selectable breath per minute rate and inhale/exhale ratio with a breath-hold duration and to selectively deliver the polarized gas alone or with the non-polarized gas.

4. A ventilator system according to Claim 1, wherein the system is configured to be run in a user selectable set tidal volume mode or a set peak inspiration pressure mode.

5

5. A ventilator system according to Claim 1, wherein the mass flow controller has a variable mass flow rate, and wherein the controller is configured to dynamically monitor the first pressure and adjust the flow rate of the mass flow controller responsive thereto to deliver a user-selected predetermined fixed tidal volume.

10

6. A ventilator system according to Claim 3, wherein the controller is configured to calculate an adjusted delivered tidal volume *in situ* based on the difference between a the total tidal volume and a fixed geometric volume of the ventilator flow path that includes a portion of the ventilator flow path and the tracheal tube.

15

7. A ventilator system according to Claim 1, wherein the controller is configured to determine the delivered tidal volume using the mathematical relationship:

20

flow rate/frequency= volume exhausted per cycle (1),

where the flow rate is the flow rate of the mass flow controller taken when the first pressure is substantially stable or constant and frequency is the breath per minute rate.

25

8. A ventilator according to Claim 7, further comprising a temperature monitor in communication with the controller.

9. A ventilator according to Claim 8, wherein the temperature monitor is in communication with a thermal source that is configured to heat and/or cool a subject to a desired temperature during operation.

30

10. A ventilator system according to Claim 3, further comprising a tracheal tube end cap for closing off the tracheal tube, wherein said gas delivery valve comprises a plurality of gas actuation valves in communication with a plurality of gas flow paths for selecting at least one gas flow path therein, said system further
5 comprising computer program code for calculating a fixed volume "V1".

11. A ventilator system according to Claim 3, wherein the ventilator system is configured for small animals.

10 12. A ventilator system according to Claim 11, wherein the controller is configured to generate an estimated incremental decrease or increase of flow rate to provide a substantially constant pressure at the first sensor based on a selected breath per minute rate and an estimated volume of the animal's lungs.

15 13. A ventilator system according to Claim 11, wherein the controller is operably associated with computer program code of a library of *a priori* values of predicted animal volumetric characteristics and/or animal volumetric changes at a plurality of different peak inspiration pressures.

20 14. A ventilator system according to Claim 11, wherein the ventilator system is configured to deliver a millimole amount of polarized ^{129}Xe gas and/or polarized ^3He .

25 15. A ventilator system according to Claim 11, wherein the ventilator is configured to operate with selectable breath per minute rates in the range of about 5-180.

30 16. A ventilator system according to Claim 1, wherein the polarized gas source comprises a pressure vessel holding a bag of polarized gas therein, wherein the bag of polarized gas is compressible by the controlled pressure of a non-polarized gas directed into the vessel, and wherein the system further comprises computer program

code that calculates and applies a calibration factor to define the pressure used to compress the bag to expel a desired amount of polarized gas.

17. A ventilator system according to Claim 16, wherein the ventilator is
5 configured to operate with selectable inspiration/expiration ratios from between about 5:1 to 1:5.

18. A ventilator system according to Claim 11, wherein the ventilator
system is configured to operate with a controllable peak inspiration pressure of
10 between about 0-40 inches of H₂O.

19. A ventilator system according to Claim 18, wherein the ventilator is
configured to provide a tidal volume flow of between about 0-5 liters/min.

20. A ventilator system according to Claim 11, wherein the ventilator
system is configured to operate with MRI/NMR systems having up to about 5T
magnetic fields.

21. A ventilator system according to Claim 11, wherein the ventilator
20 system is configured to operate with MRI/NMR systems having less than about 100 Gauss magnetic fields.

22. A ventilator system according to Claim 1, further comprising a
physiological monitor for monitoring heart rate and an ECG (electrocardiogram)
25 device.

23. A ventilator system according to Claim 3, wherein the gas delivery
valve is configured to provide gas flow paths for ventilation breath inhale inputs
and/or receive exhale outputs of at least: (a) hyperpolarized Gas A inhale; (b) exhale;
30 (c) hyperpolarized Gas A inhale and hold; and (d) non-polarized gas input.

24. A ventilator system according to Claim 23, wherein the gas delivery valve is configured to provide ventilation breath inhale inputs and/or receive exhale outputs of at least: (a) hyperpolarized Gas A inhale; (b) non-polarized Gas B inhale; (c) a combination of hyperpolarized Gas A and non-polarized Gas B inhale; (d) exhale; (e) partial exhale and hold; (f) hyperpolarized Gas A inhale and hold; (g) Gas B inhale and hold; and (h) a combination of hyperpolarized Gas A and Gas B inhale and hold.

25. A ventilator system according to Claim 24, wherein the gas delivery valve is fabricated from and/or coated with a material that inhibits depolarization of the hyperpolarized gas and is non-magnetic.

26. A ventilator system according to Claim 1, wherein the system has an associated fluid capacitance disposed intermediate the mass flow controller and the gas delivery valve.

27. A method of delivering hyperpolarized gas to a subject, comprising:
providing a ventilator system with a mass flow controller, a tracheal tube and a gas delivery valve configured to deliver hyperpolarized gas and at least one non-polarized gas to a subject;
monitoring a first pressure in the ventilator system upstream of the gas delivery valve;
monitoring a second pressure in the ventilator system downstream of the gas delivery valve;
obtaining a reading of the mass flow controller when the first pressure is substantially constant; and
automatically determining the tidal inspiration volume of hyperpolarized gas delivered to the subject *in situ* using the obtained mass flow controller reading.

28. A method according to Claim 27, wherein the ventilator system includes a variable flow rate mass flow controller disposed upstream of the gas delivery valve, said method further comprising automatically dynamically adjusting

the flow rate of the mass flow controller to maintain a substantially constant first pressure during ventilation delivery of the hyperpolarized gas to the subject.

29. A method according to Claim 27, further comprising accepting user
5 input to select a tidal volume operational mode with the desired tidal volume selected or a peak inspiration pressure operational mode with the desired peak inspiration pressure selected.

30. A method according to Claim 27, further comprising determining a
10 fixed geometric volume based on pressure measurements taken while a distal end portion of the tracheal tube is closed, and subtracting the fixed geometric volume from the determined tidal volume.

31. A method according to Claim 27, further comprising selecting a
15 desired ventilation delivery cycle with a breath per minute rate, a breath-hold duration and an inspiration/expiration ratio.

32. A method according to Claim 31, wherein the portion of the system
upstream of the gas delivery valve has an associated fluid capacitance volume that is
20 at least three times the volume of the lungs of the subject undergoing evaluation, said method further comprising controllably increasing and decreasing the fluid capacitance volume to stabilize the pressure upstream of the gas delivery valve to reduce the fluctuations in pressure between breaths.

25 33. A method according to Claim 32, further comprising triggering a MRI/NMR hyperpolarized gas signal acquisition sequence during a predetermined portion of the ventilation cycle when hyperpolarized gas is in the subject.

34. A method according to Claim 33, wherein the subject is a small
30 animal.

35. A method according to Claim 34, wherein the selected breath per minute cycle is about 30 BPM during MRI/NMR signal acquisition.

36. A method according to Claim 34, further comprising obtaining a
5 NMR/MRI signal having a signal strength and calibrating the NMR/MRI signal strength to the calculated tidal inspiration volume.

37. A method according to Claim 36, further comprising monitoring the temperature of the subject.

10

38. A method according to Claim 27, wherein the gas delivery valve is configured to selectively deliver hyperpolarized gas alone, non-polarized gas alone, and/or hyperpolarized gas combined with non-polarized gas, the method further comprising controlling the output of the first mass flow controller and a second mass
15 flow controller to automatically provide desired blends of selected ventilation gases to the subject during non-polarized gas ventilation.

39. A method according to Claim 34, wherein the monitoring steps are carried out during an NMR spectroscopy and/or MRI imaging session.

20

40. A method according to Claim 27, wherein the hyperpolarized gas comprises hyperpolarized ^{129}Xe .

41. A method according to Claim 27, wherein the hyperpolarized gas
25 comprises hyperpolarized ^3He .

42. A method according to Claim 27, wherein the gas delivery valve is configured to provide ventilation breath cycles of at least: (a) hyperpolarized Gas A inhale; (b) non-polarized Gas B inhale; (c) a combination of hyperpolarized Gas A and non-polarized Gas B inhale; (d) exhale; (e) partial exhale and hold; (f)
30 hyperpolarized Gas A inhale and hold; (g) Gas B inhale and hold; and (h) a combination of hyperpolarized Gas A and Gas B inhale and hold.

43. A method according to Claim 42, wherein the gas delivery valve receives exhaust gas from the subject and vents the exhaust gas from the gas delivery valve.

5

44. A method according to Claim 27, wherein the tidal volume determination is carried out by subtracting a known fixed calibration volume from the total determined tidal volume.

10

45. A method according to Claim 44, wherein the tidal volume is calculated using the relationship expressed by equation (1):

$$\text{flow rate} / \text{frequency} = \text{volume exhausted per cycle (1)}$$

where "flow rate" is the flow rate of the mass flow controller when the first pressure is substantially constant and frequency is a selected breath per minute rate.

15

46. A method according to Claim 27, wherein the gas delivery valve comprises a plurality of gas actuation valves for actuating selectable gas output flow paths therein.

20

47. A method according to Claim 27, further comprising generating an estimated incremental decrease or increase of output flow rate that can provide a substantially constant first pressure based on the selected breath per minute rate and an estimated delivered volume capacity associated with the type of animal undergoing analysis and adjusting the mass flow controller using the generated value.

25

48. A method according to Claim 27, further comprising generating a computer program library of *a priori* values of predicted animal volumetric characteristics and/or animal volumetric changes at a plurality of different peak inspiration pressures.

30

49. A method according to Claim 30, wherein the fixed geometric volume is determined for each size tracheal tubes used with the ventilator and/or for each species of subjects undergoing ventilation.

5 50. A system for delivering hyperpolarized gas to a subject, comprising:
a gas delivery valve configured to deliver hyperpolarized gas and at least one non-polarized gas to a subject;
a mass flow controller disposed upstream of the gas delivery valve;
a tracheal tube disposed downstream of the gas delivery valve;
10 means for monitoring a first pressure in the ventilator system upstream of the gas delivery valve;
means for monitoring a second pressure in the ventilator system downstream of the gas delivery valve;
means for automatically obtaining readings of the mass flow controller; and
15 means for automatically determining the tidal inspiration volume of hyperpolarized gas delivered to the subject *in situ* using the monitored first pressure and the value of a reading of the mass flow controller obtained when the first pressure is substantially constant.

20 51. A system according to Claim 50, wherein the ventilator system includes a variable flow rate mass flow controller disposed upstream of the gas delivery valve, said system further comprising means for automatically dynamically adjusting the flow rate of the mass flow controller to maintain a substantially constant pressure at the first pressure sensor during delivery of the hyperpolarized gas to the
25 subject.

52. A system according to Claim 50, further comprising:
means for accepting user input to select a tidal volume operational mode with the desired tidal volume selected or a peak inspiration pressure operational mode with
30 the desired peak inspiration pressure selected; and

a second mass flow controller, wherein the first and second mass flow controllers are used to automatically provide desired blends of selected ventilation gases to the subject.

5 53. A computer program product for delivering hyperpolarized gas using a ventilator with an associated gas delivery valve and tracheal tube, the computer program product comprising:

computer program code that monitors a first pressure in the ventilator system upstream of the gas delivery valve;

10 computer program code that monitors a second pressure in the ventilator system downstream of the gas delivery valve;

computer program code that obtains a reading of a mass flow controller when the first pressure stabilizes at a substantially constant pressure; and

15 computer program code that calculates a tidal volume using the reading of the mass flow controller when the first pressure is substantially constant.

54. A computer program product according to Claim 53, wherein the ventilator system includes a variable flow rate mass flow controller disposed upstream of the gas delivery valve, and wherein said computer program product further
20 comprises computer program code that automatically dynamically adjusts the flow rate of the mass flow controller to maintain a substantially constant first pressure during ventilation delivery of the hyperpolarized gas to the subject.

55. A computer program product according to Claim 54, further
25 comprising computer program code for accepting user input to select from predetermined operational modes: (a) a tidal volume operational mode with the desired tidal volume selected; and (b) a peak inspiration pressure operational mode with the desired peak inspiration pressure selected.

30 56. A computer program product according to Claim 53, further comprising computer program code that selectively configures the gas delivery valve for inhale, exhale, or breath-hold operation.

57. A computer program product according to Claim 56, further comprising computer program code that selectively operates the gas delivery valve to output hyperpolarized gas alone, non-polarized gas alone, and/or a blend of
5 hyperpolarized and non-polarized gas.

58. A computer program product according to Claim 53, further comprising computer program code that controllably actuates the gas delivery valve to select ventilation operation between at least: (a) hyperpolarized gas inhale; (b) non-
10 polarized gas inhale; (c) a combination of hyperpolarized gas and non-polarized gas inhale; (d) exhale; (e) partial exhale and hold; (f) hyperpolarized gas inhale and hold; (g) non-polarized gas inhale and hold; and (h) a combination of hyperpolarized gas and non-polarized gas inhale and hold.

59. A computer program product according to Claim 57, wherein the
15 hyperpolarized gas is a hyperpolarized noble gas, and wherein the non-polarized gas is a selected biocompatible non-polarized gas that inhibits depolarization of the hyperpolarized gas, and wherein the product further comprises computer program code that operates first and second mass flow controllers to automatically provide
20 desired blends of selected ventilation gases to the subject.

60. A ventilator system having a ventilation flow path for ventilating a subject, comprising:
a gas delivery valve configured to selectively dispense a plurality of different
25 gases to a subject;
a mass flow controller disposed upstream of the gas delivery valve;
a first polarized gas source in fluid communication with the gas delivery valve;
a second gas source in fluid communication with the gas delivery valve;
30 a first pressure sensor located upstream of the gas delivery valve;
a second pressure sensor located downstream of the gas delivery valve; and

a manifold line having a fluidic tunable capacitance disposed upstream of the gas delivery valve, wherein the fluidic capacitance has a volume that is at least about ten times greater than the volume of the lungs of the subject.

5 61. A ventilator system according to Claim 60, further comprising at least one fixed volume reservoir that is configured to selectively engage the manifold to adjust the fluidic capacitance responsive to pressure measurements obtained by the first and second pressure sensors.

10 62. A ventilator system according to Claim 60, further comprising a syringe with a quantity of fluid therein, the syringe being in communication with the manifold line and configured to selectively add or remove fluid from the manifold.

15 63. A ventilator system according to Claim 60, further comprising a second mass flow controller, wherein the first and second mass flow controllers are used to automatically provide desired blends of selected ventilation gases to the subject.

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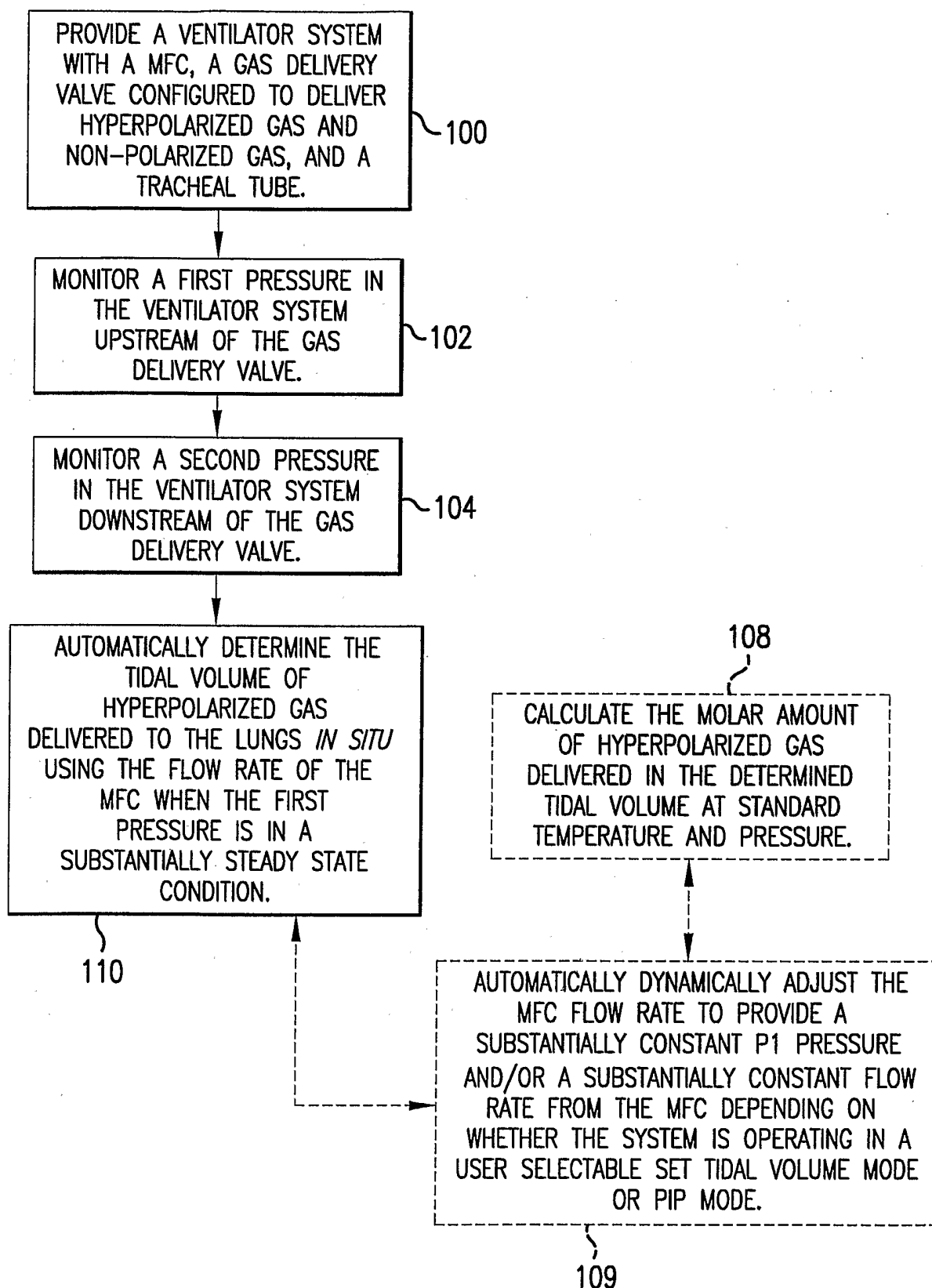
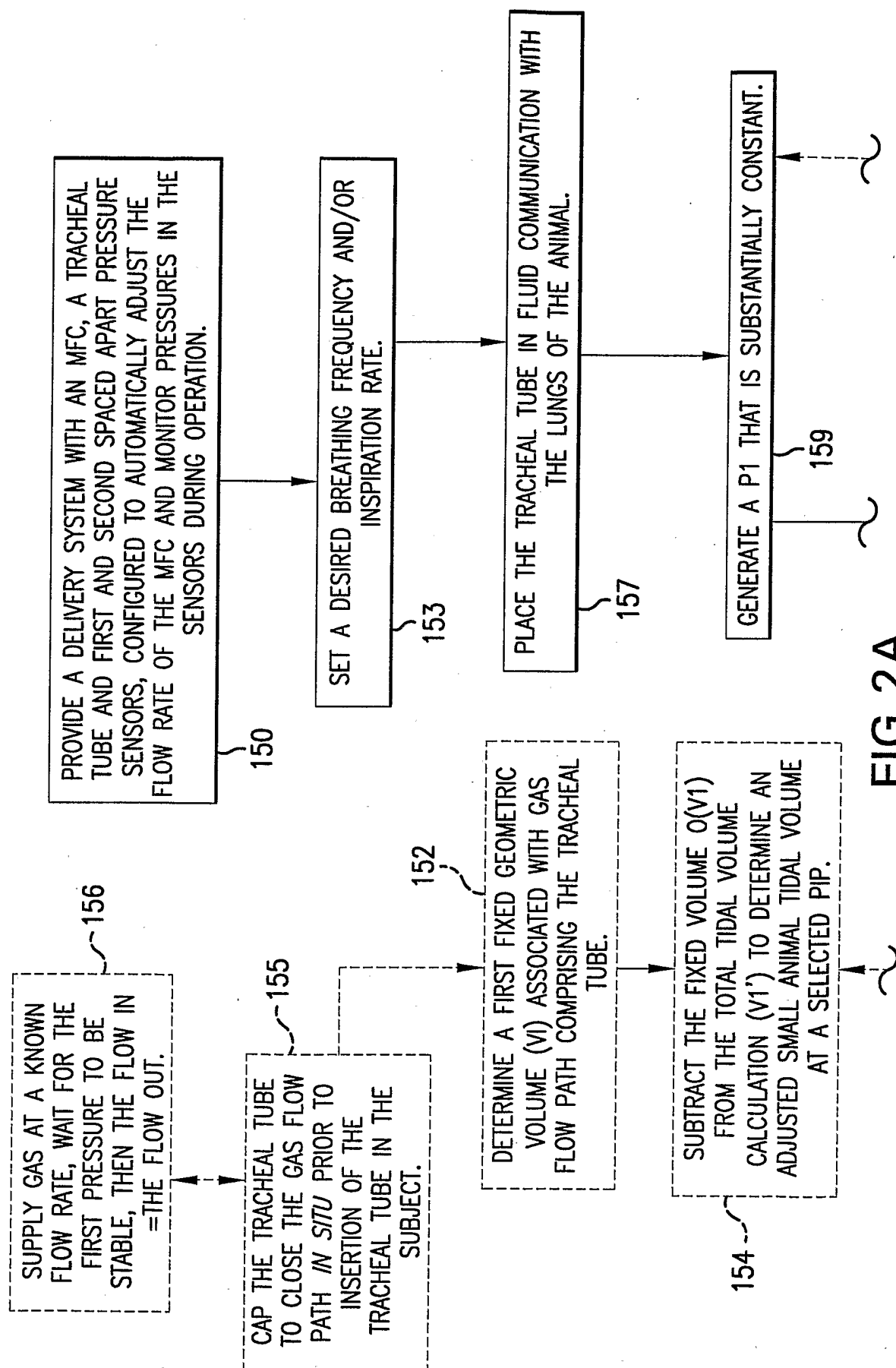


FIG. 1

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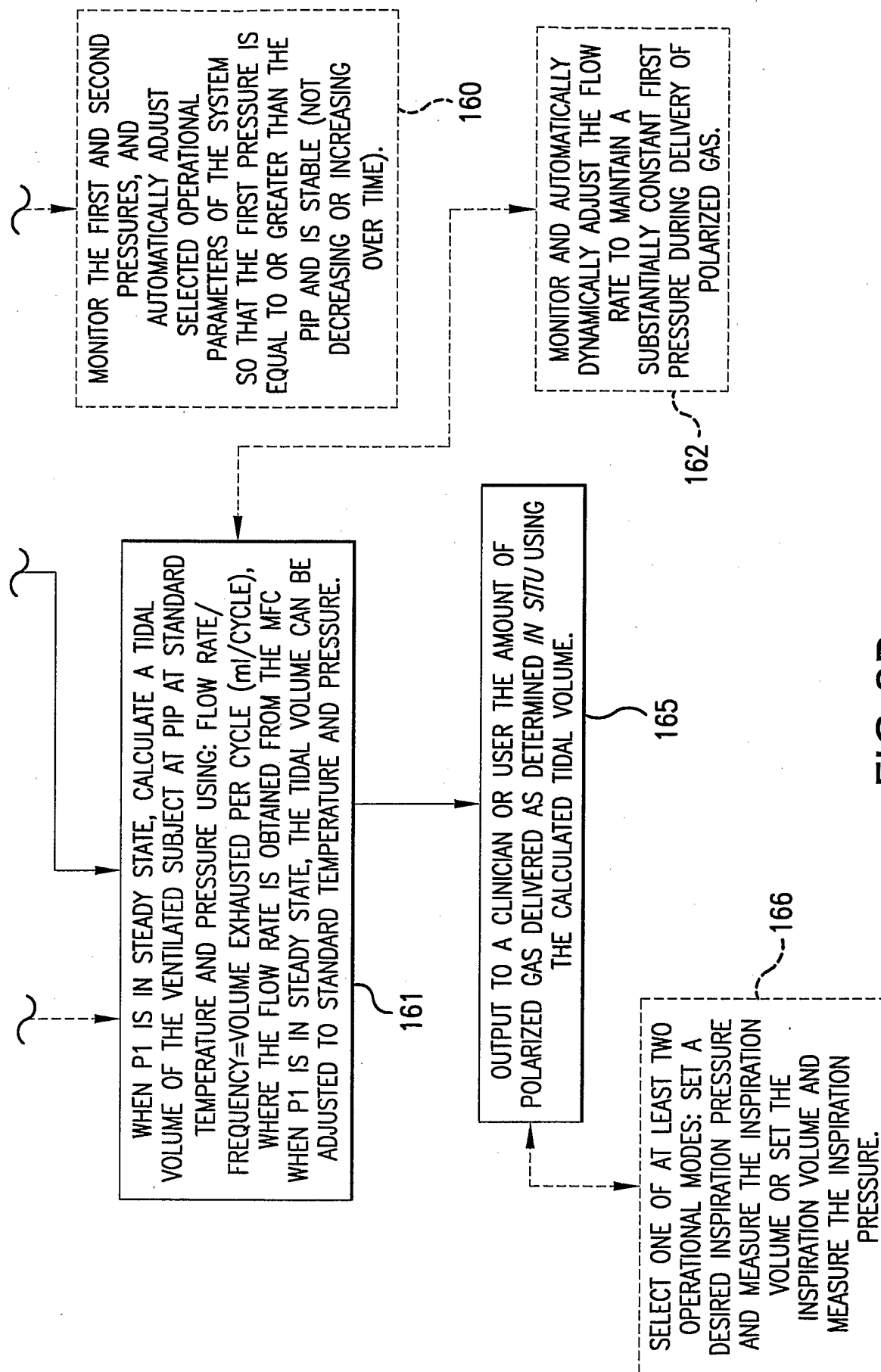


FIG. 2B

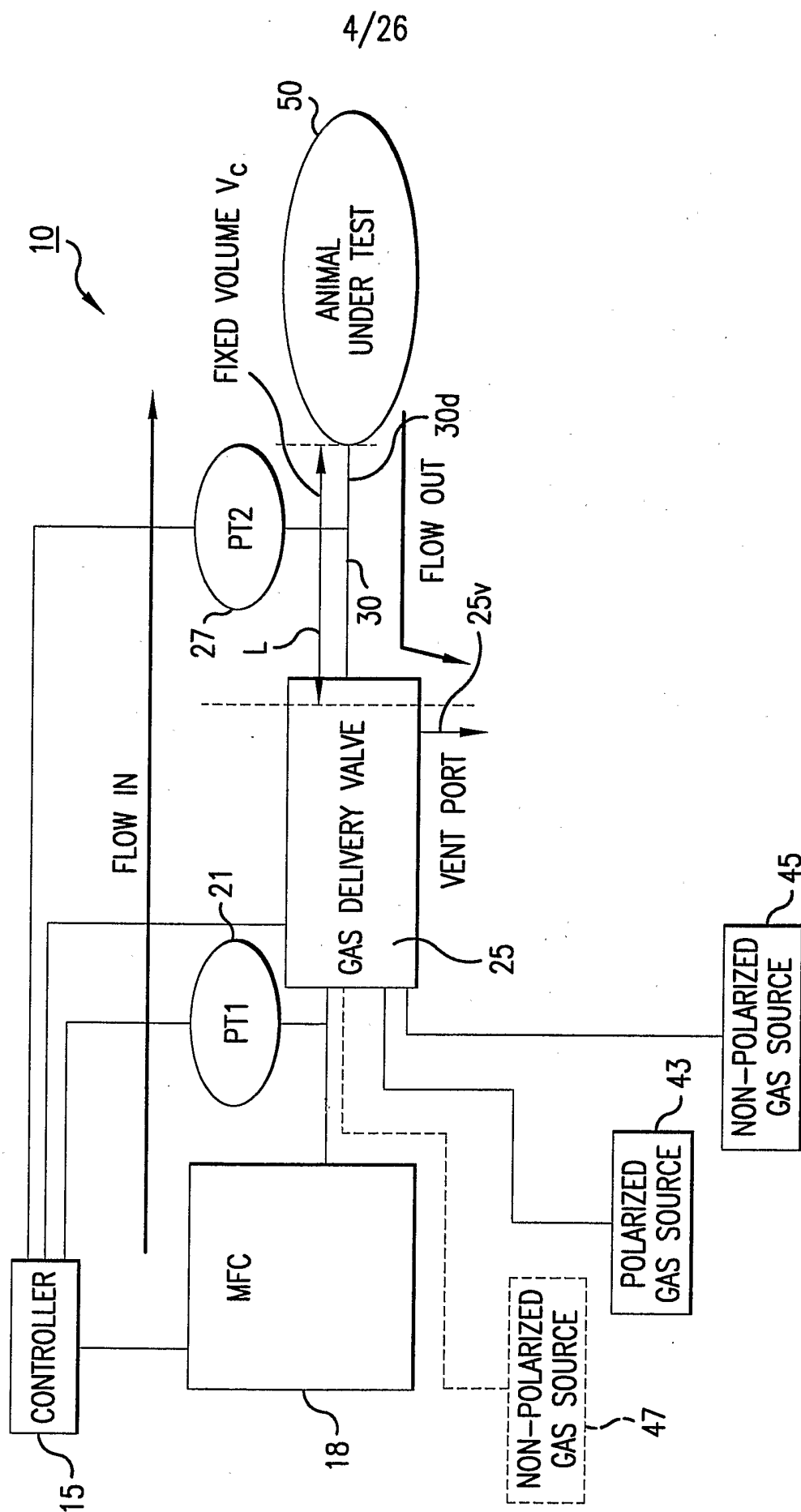


FIG. 3A

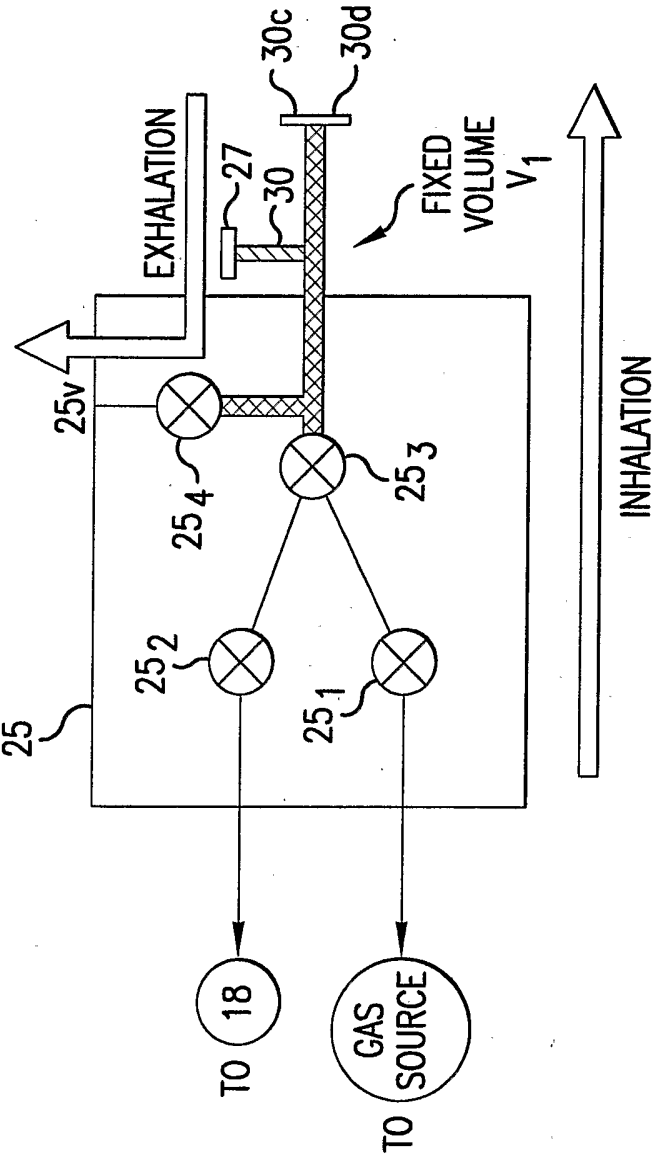


FIG.3B

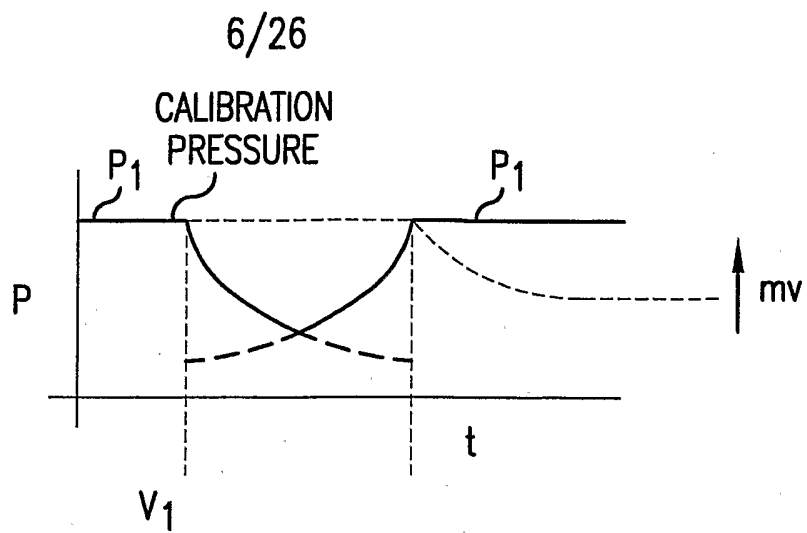


FIG. 4

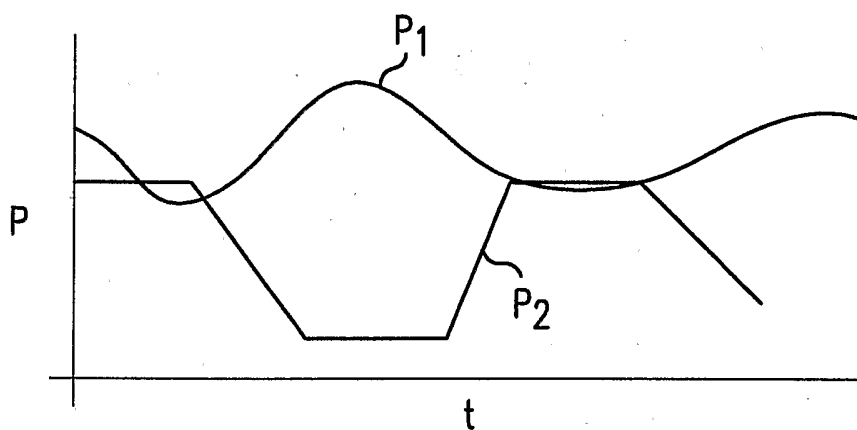


FIG. 5A

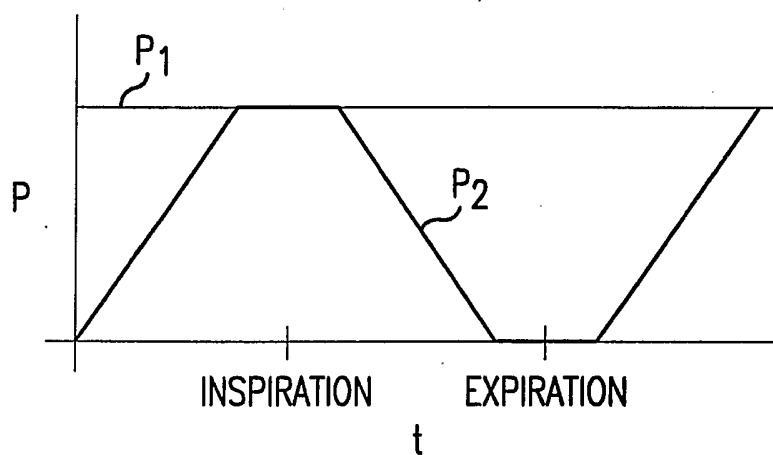


FIG. 5B

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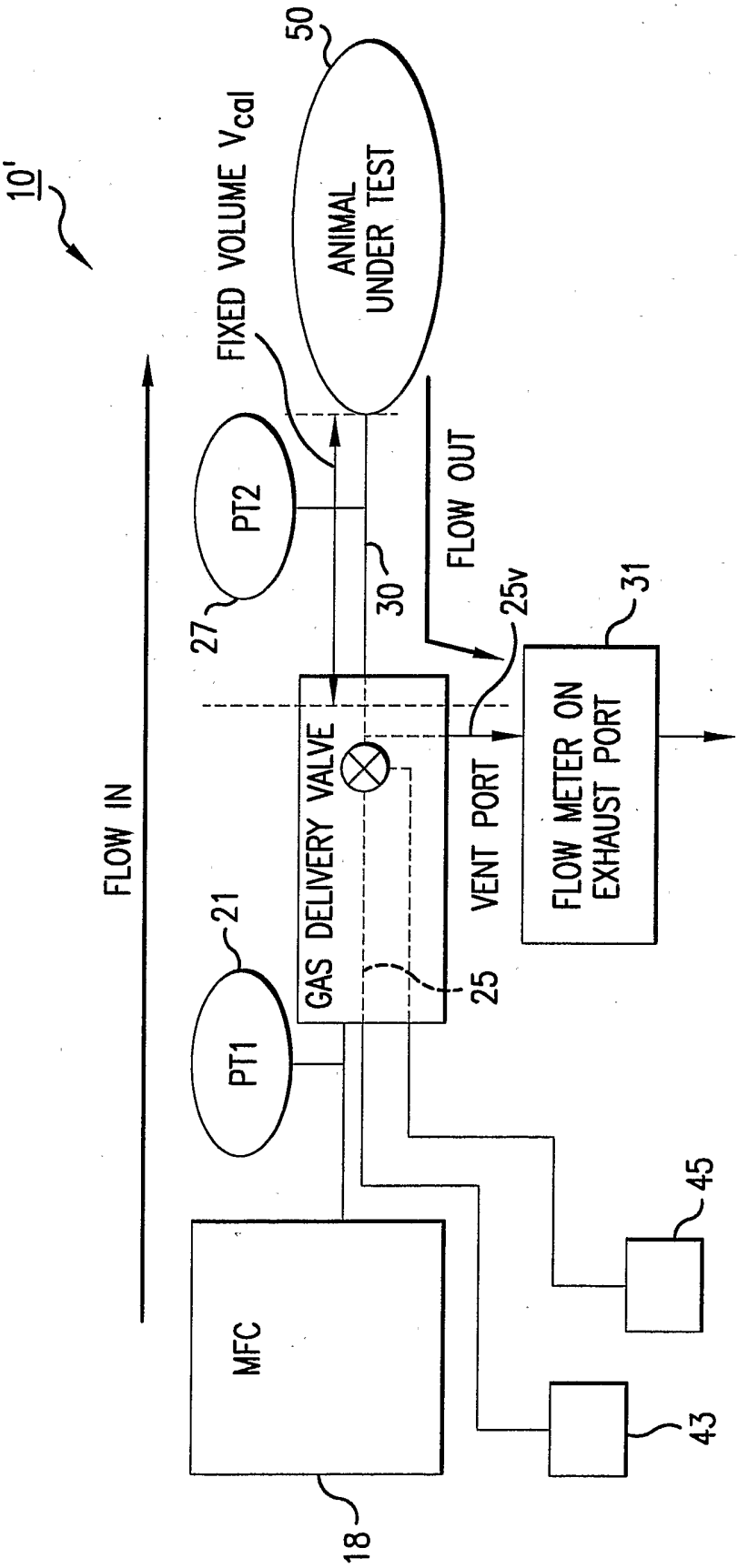


FIG.6

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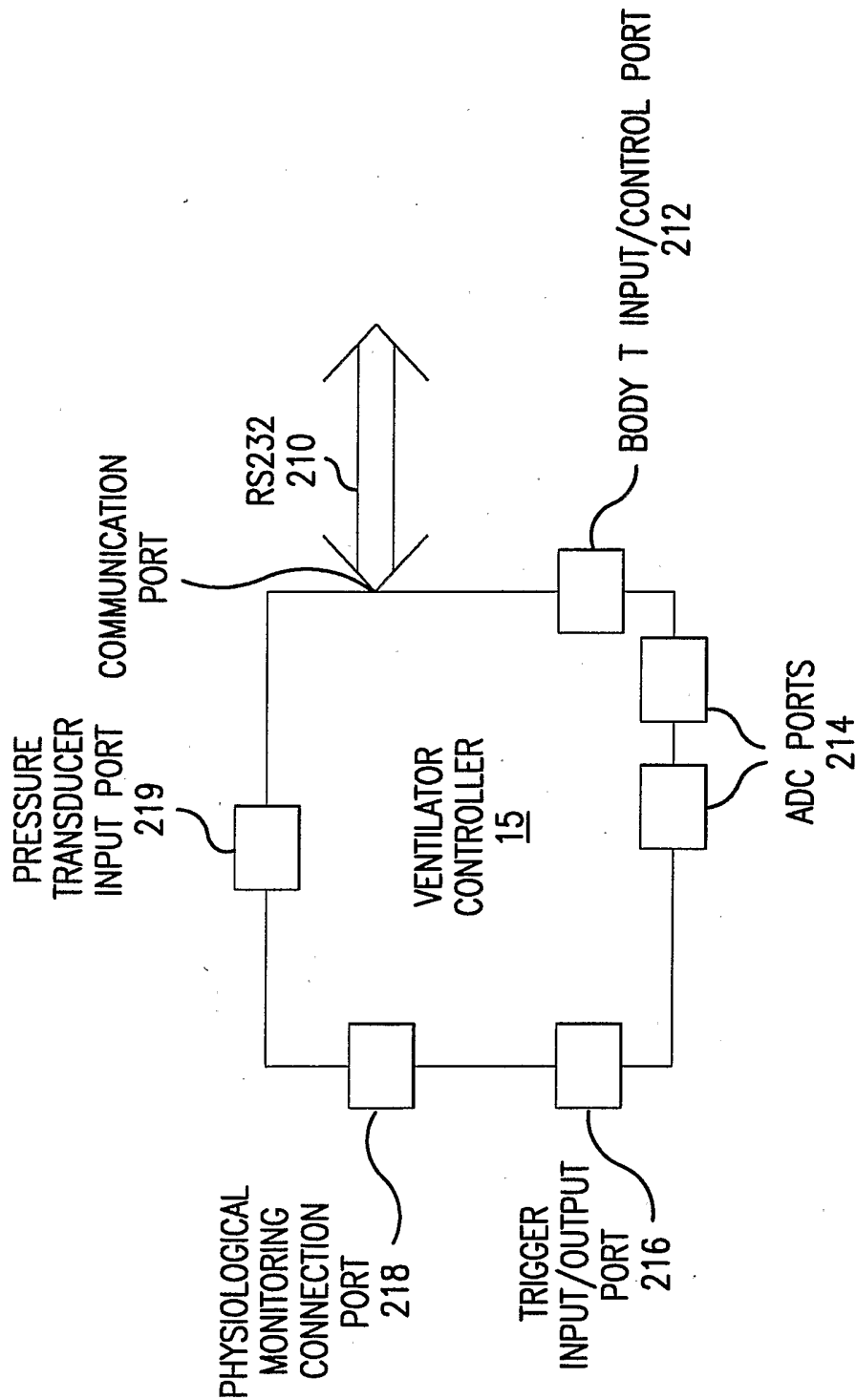


FIG.7

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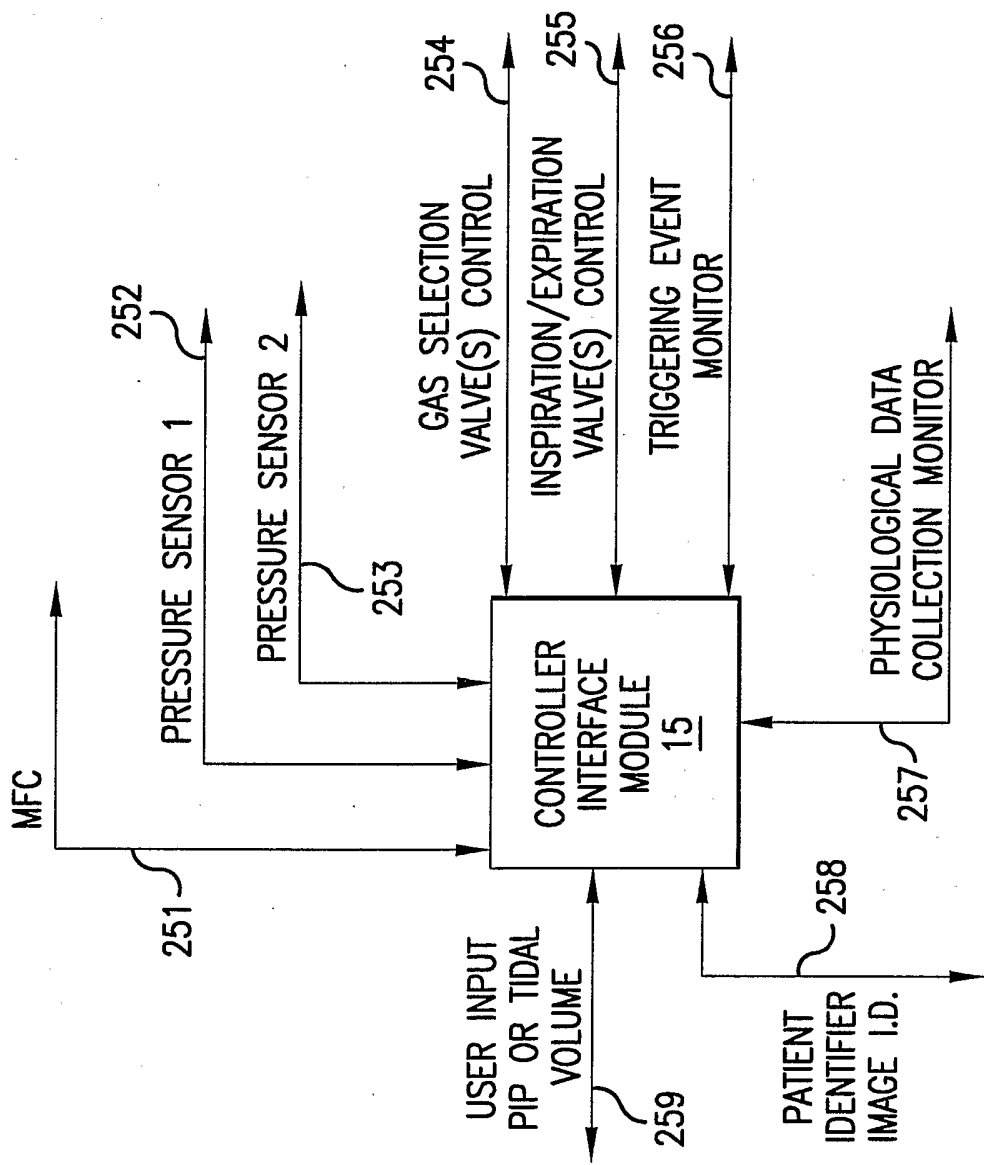


FIG. 8

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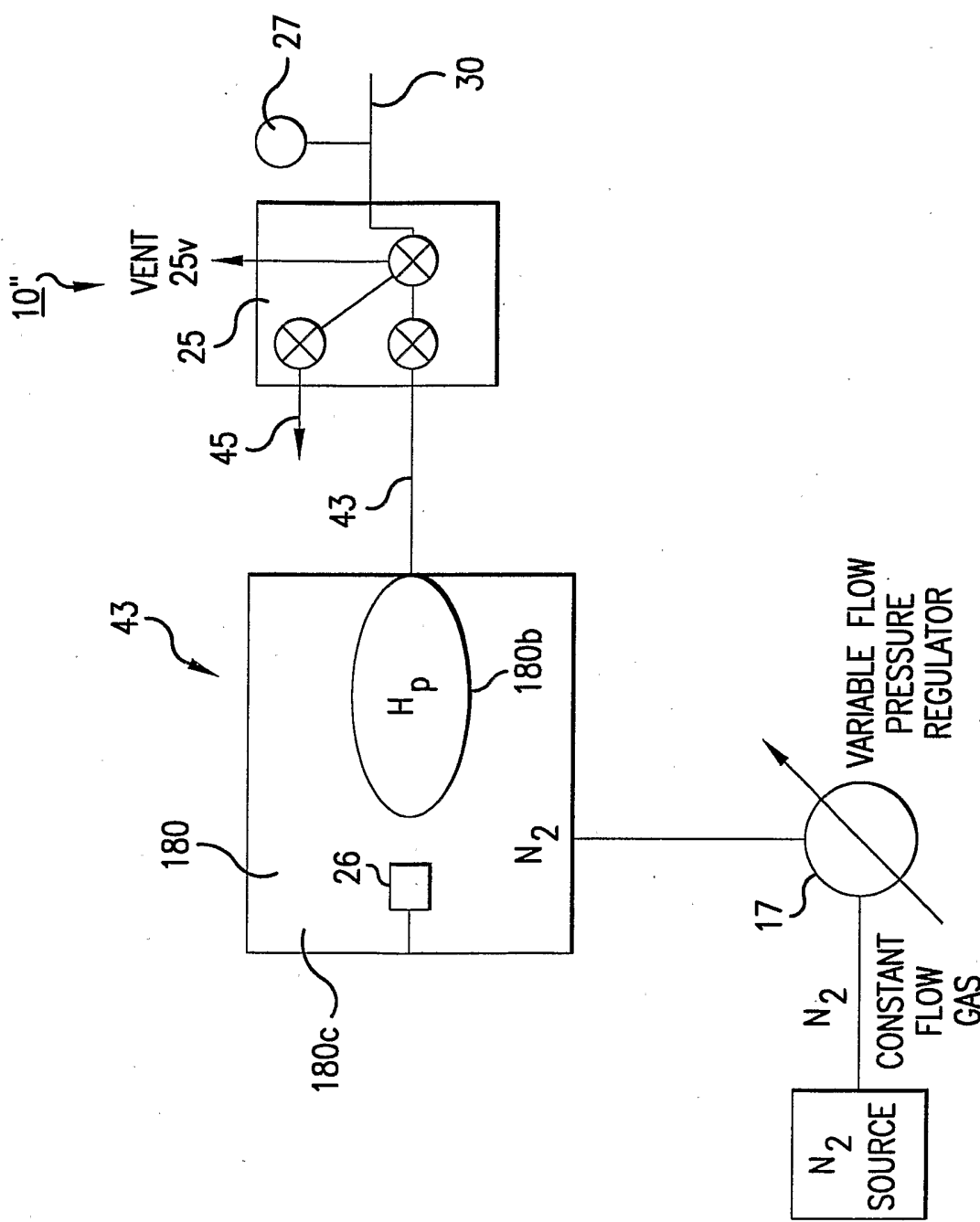


FIG. 9

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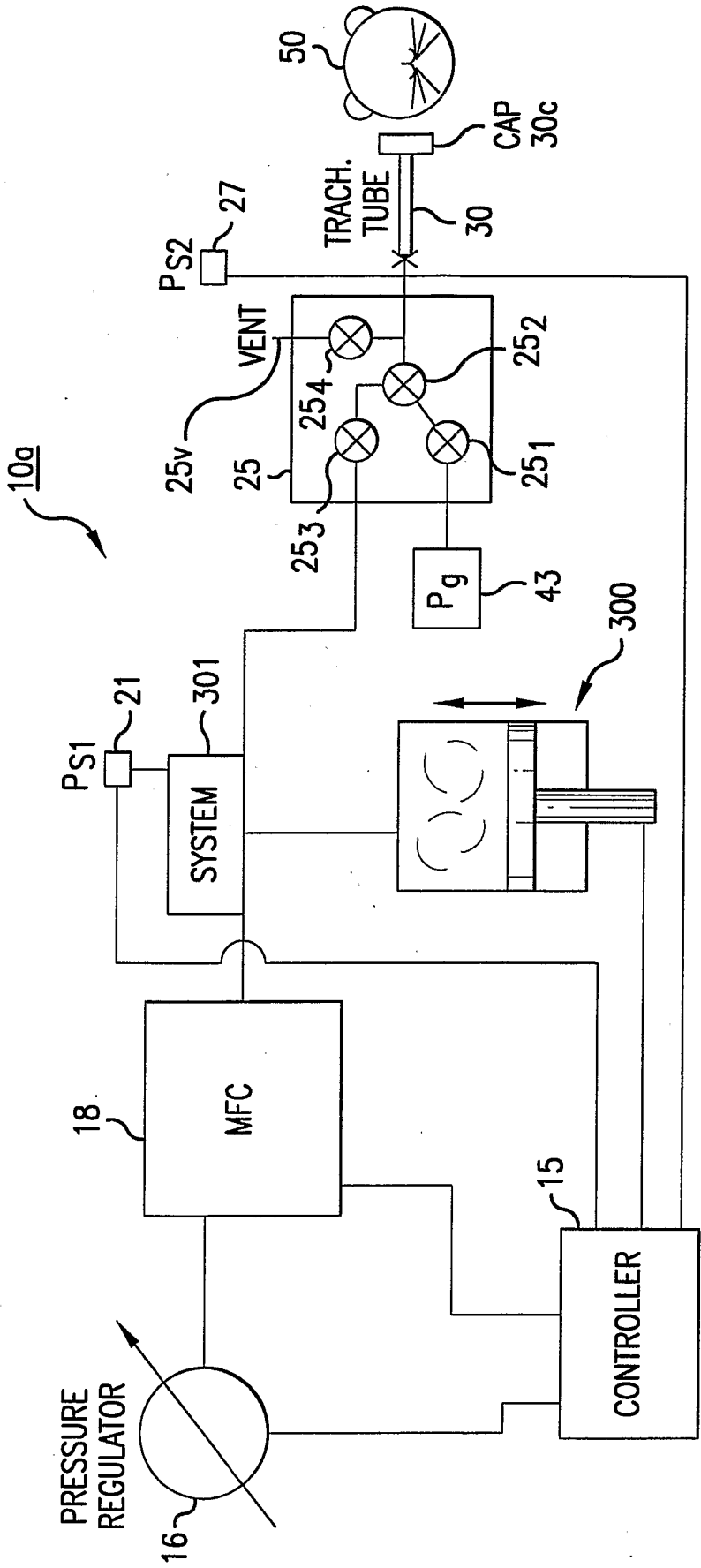


FIG. 10A

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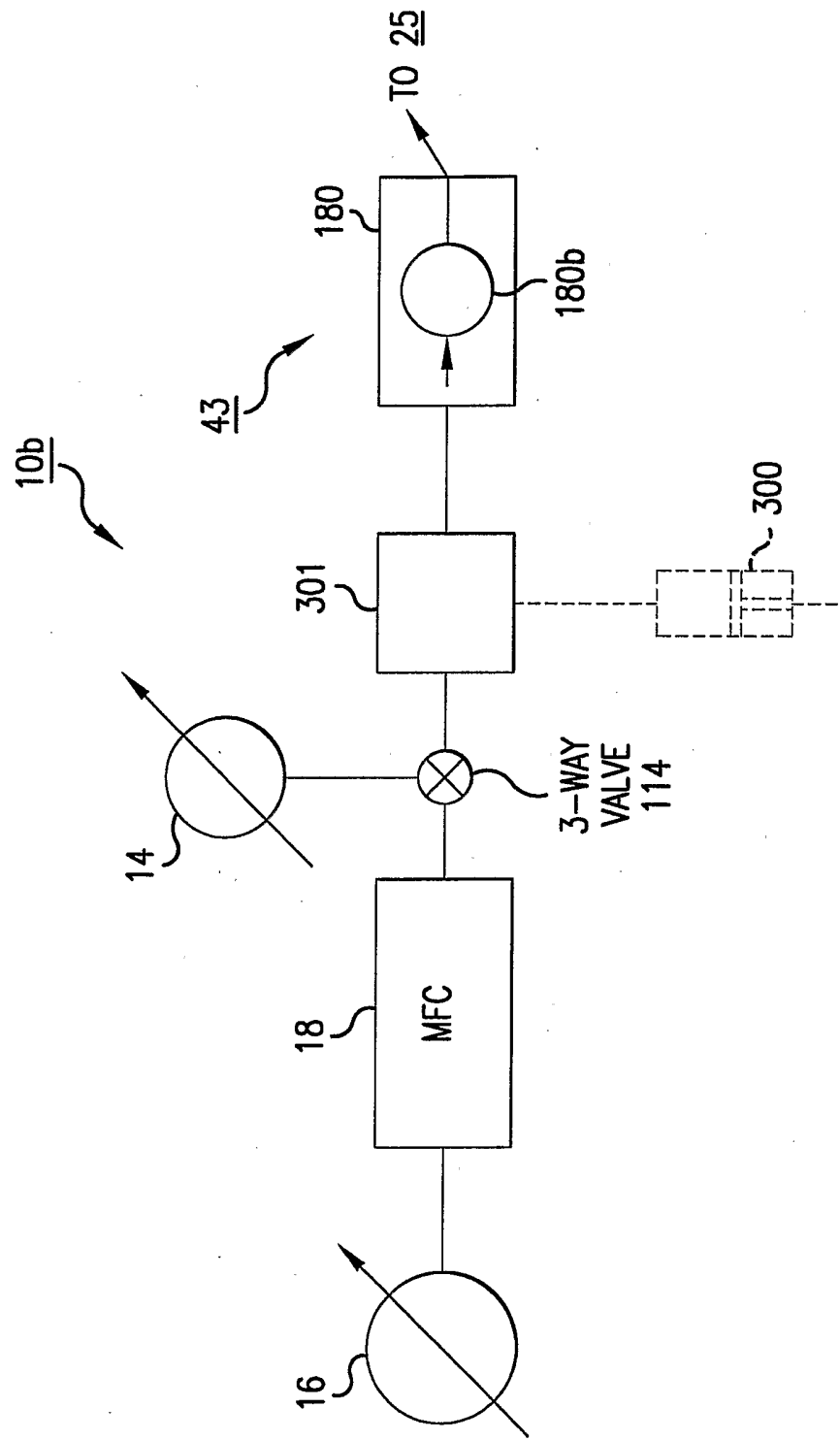


FIG.10B

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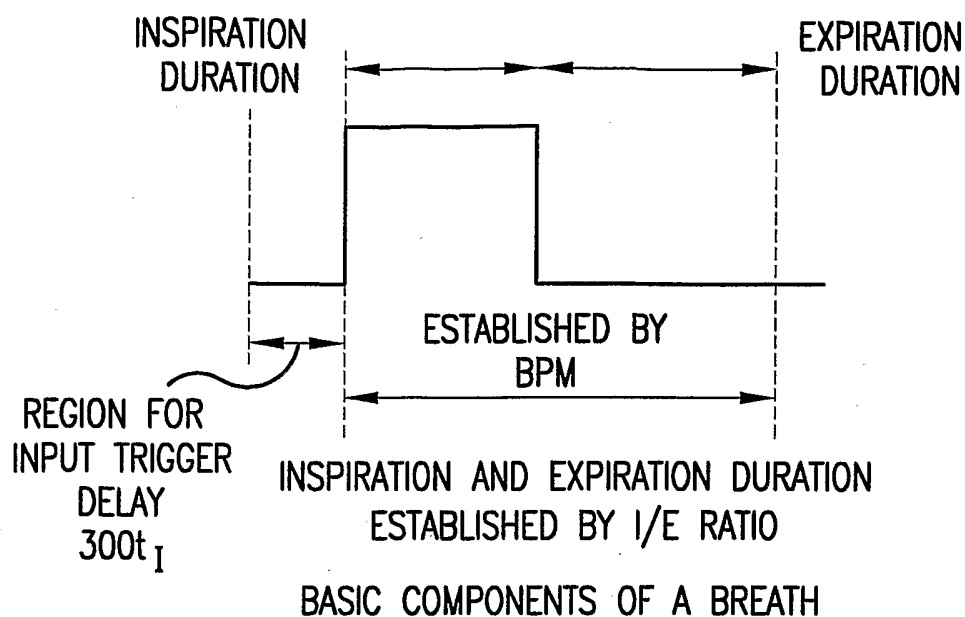
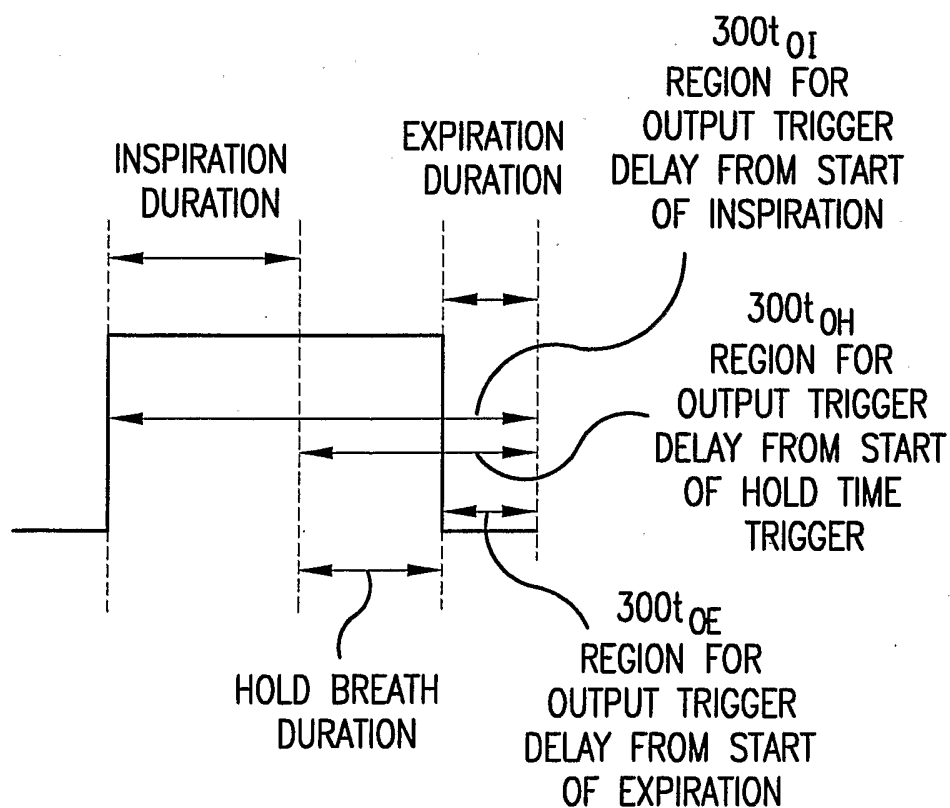


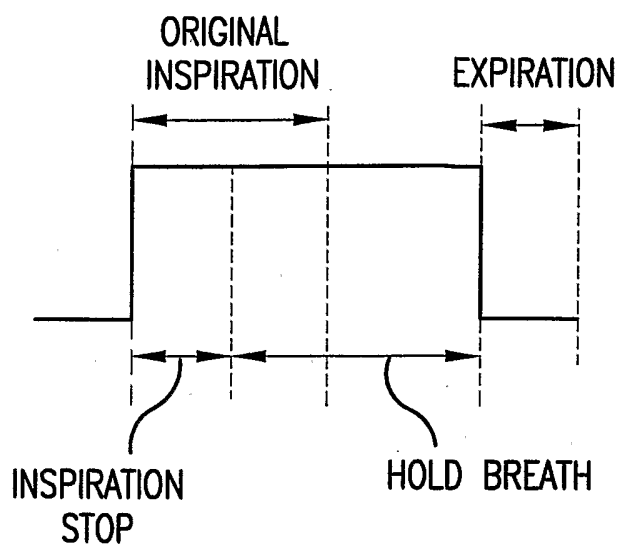
FIG.11



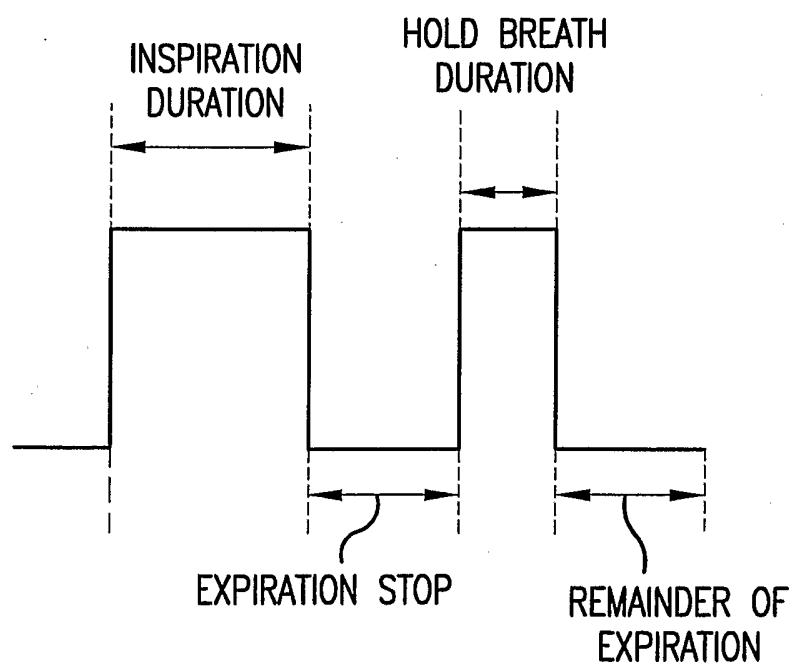
CYCLE WITH HOLD BREATH AND TRIGGERS

FIG.12

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INSPIRATION STOP

FIG.13

EXPIRATION STOP

FIG.14

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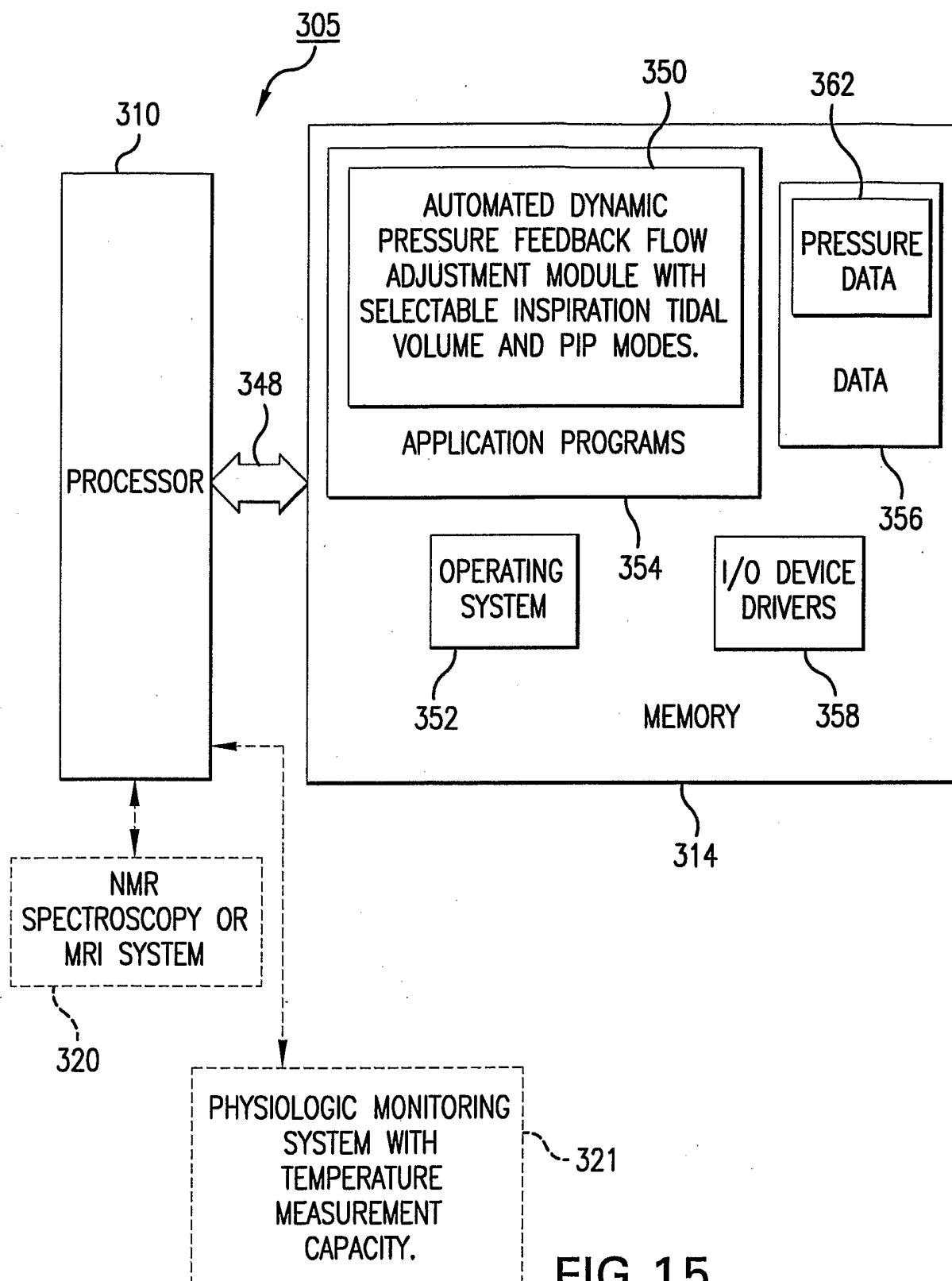


FIG. 15

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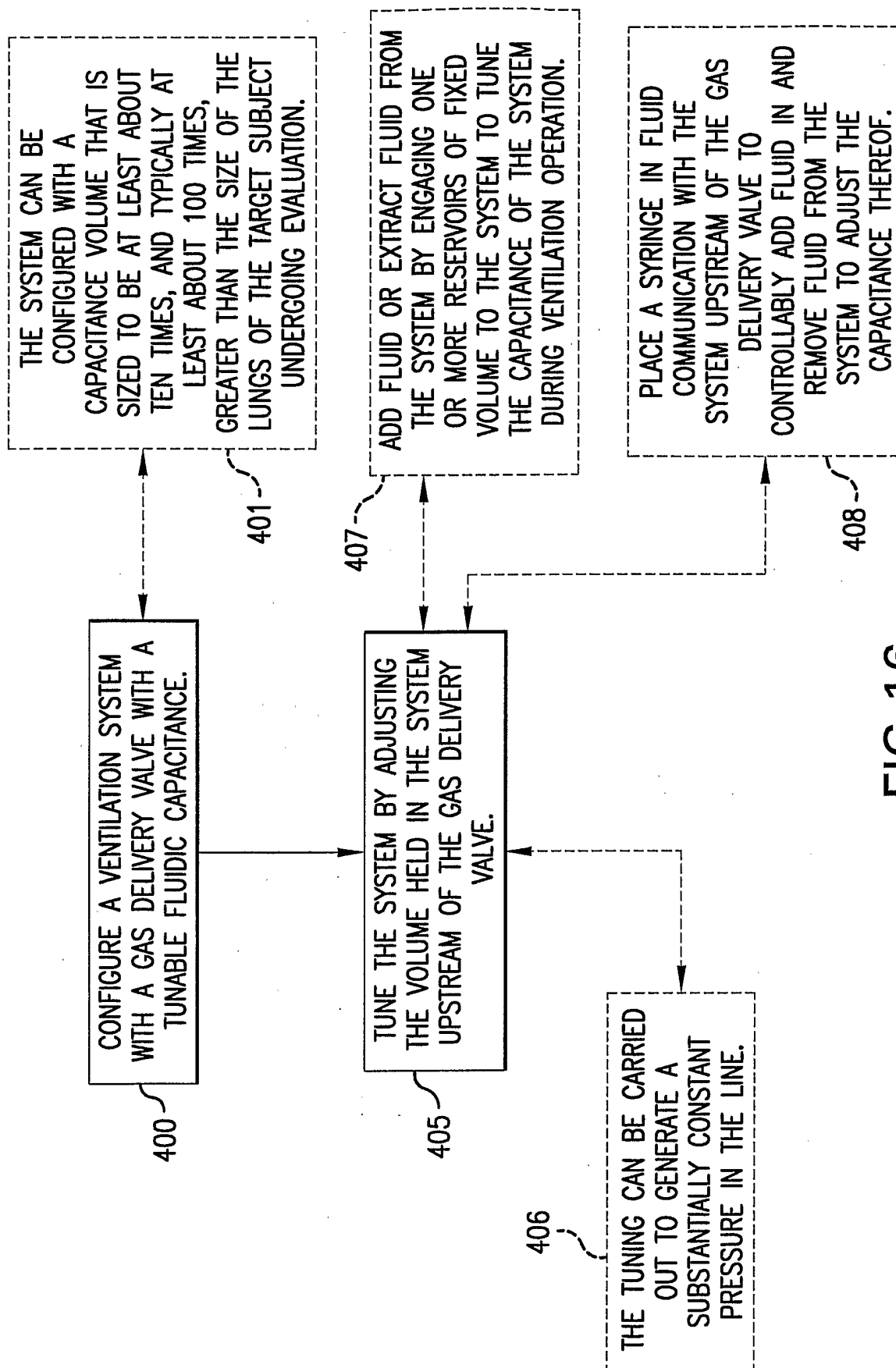


FIG. 16

FIG.17A	FIG.17D	FIG.17G
FIG.17B	FIG.17E	FIG.17H
FIG.17C	FIG.17F	FIG.17I

FIG.17

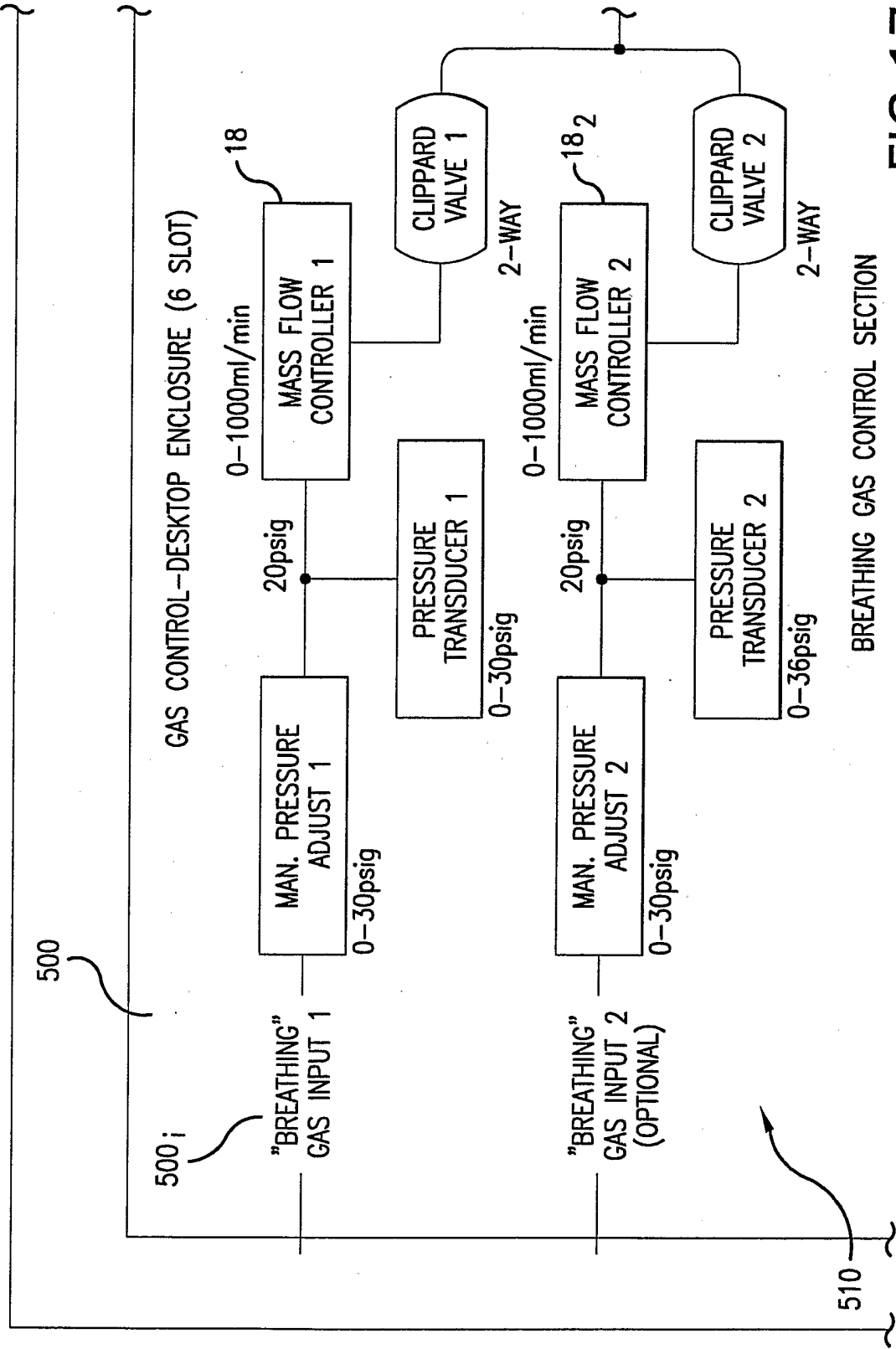


FIG.17A

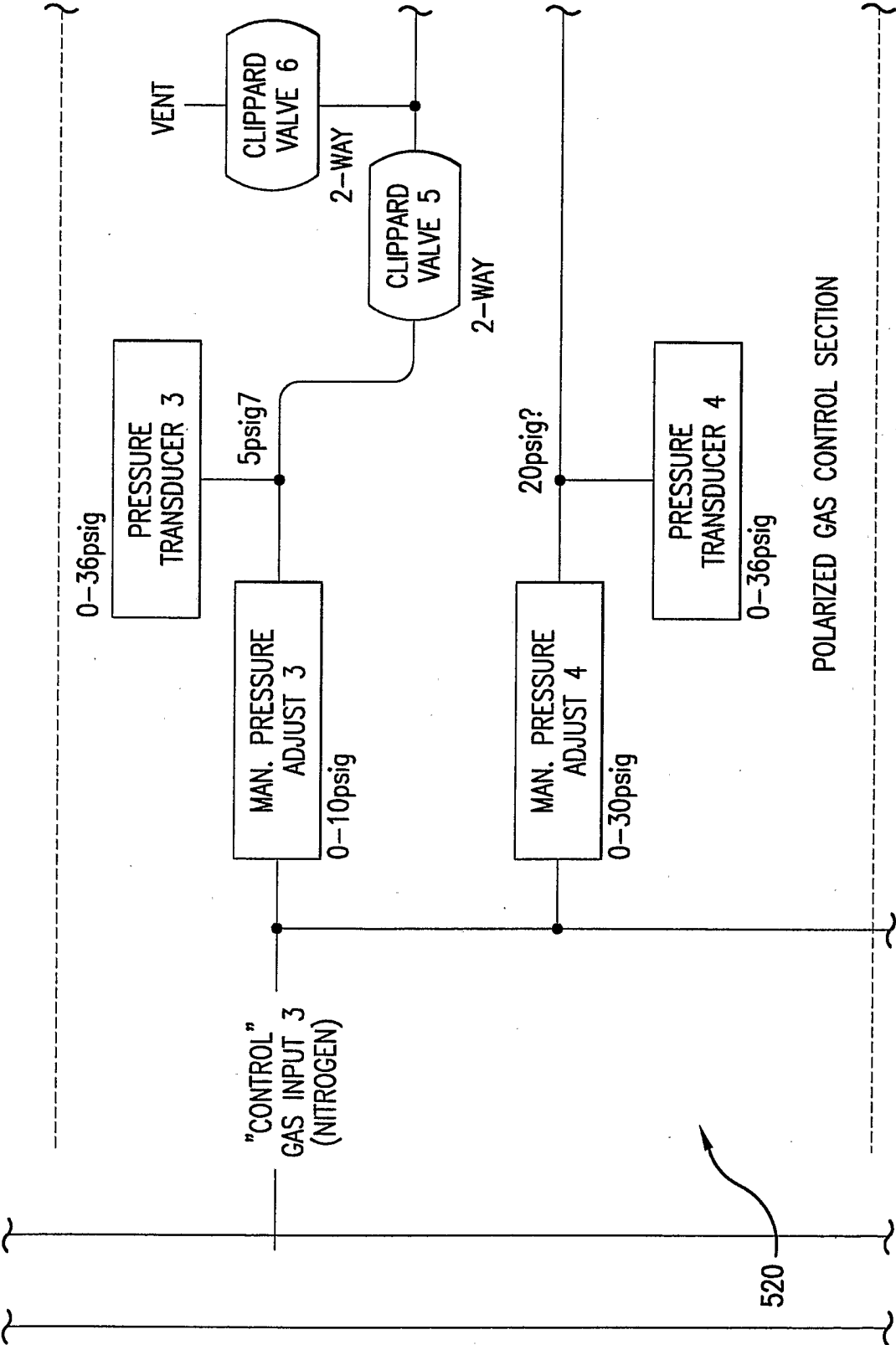


FIG.17B

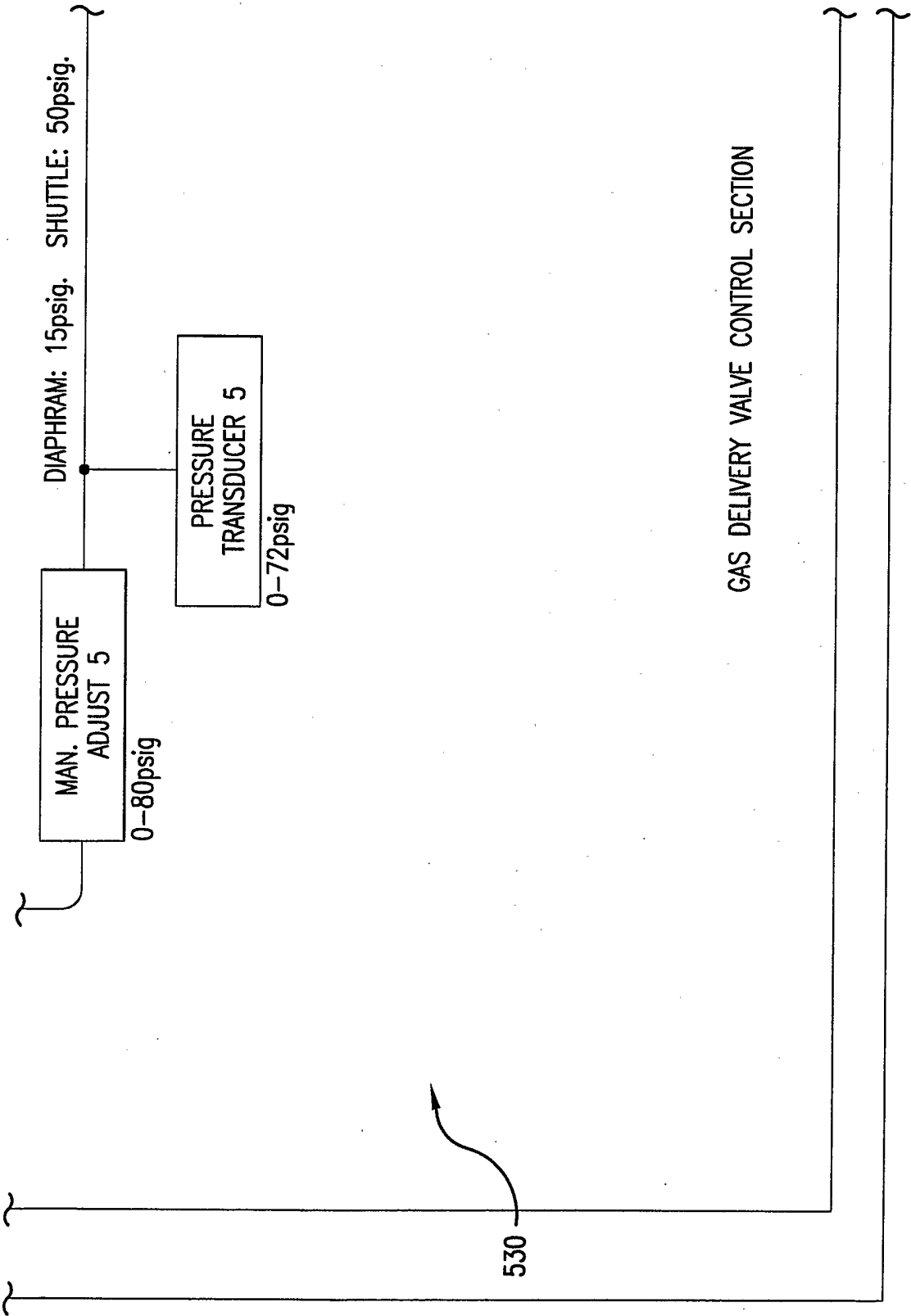


FIG.17C

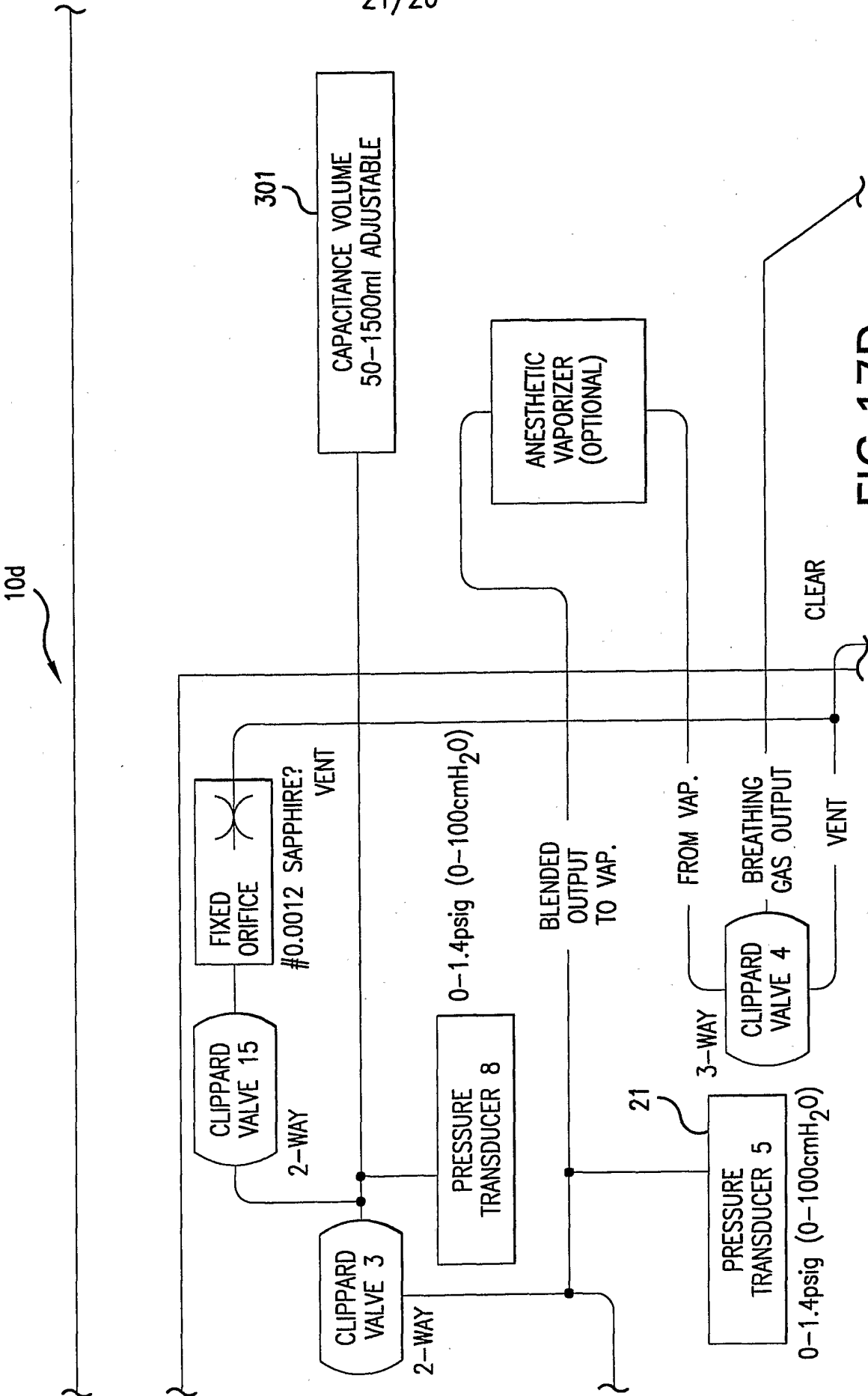


FIG.17D

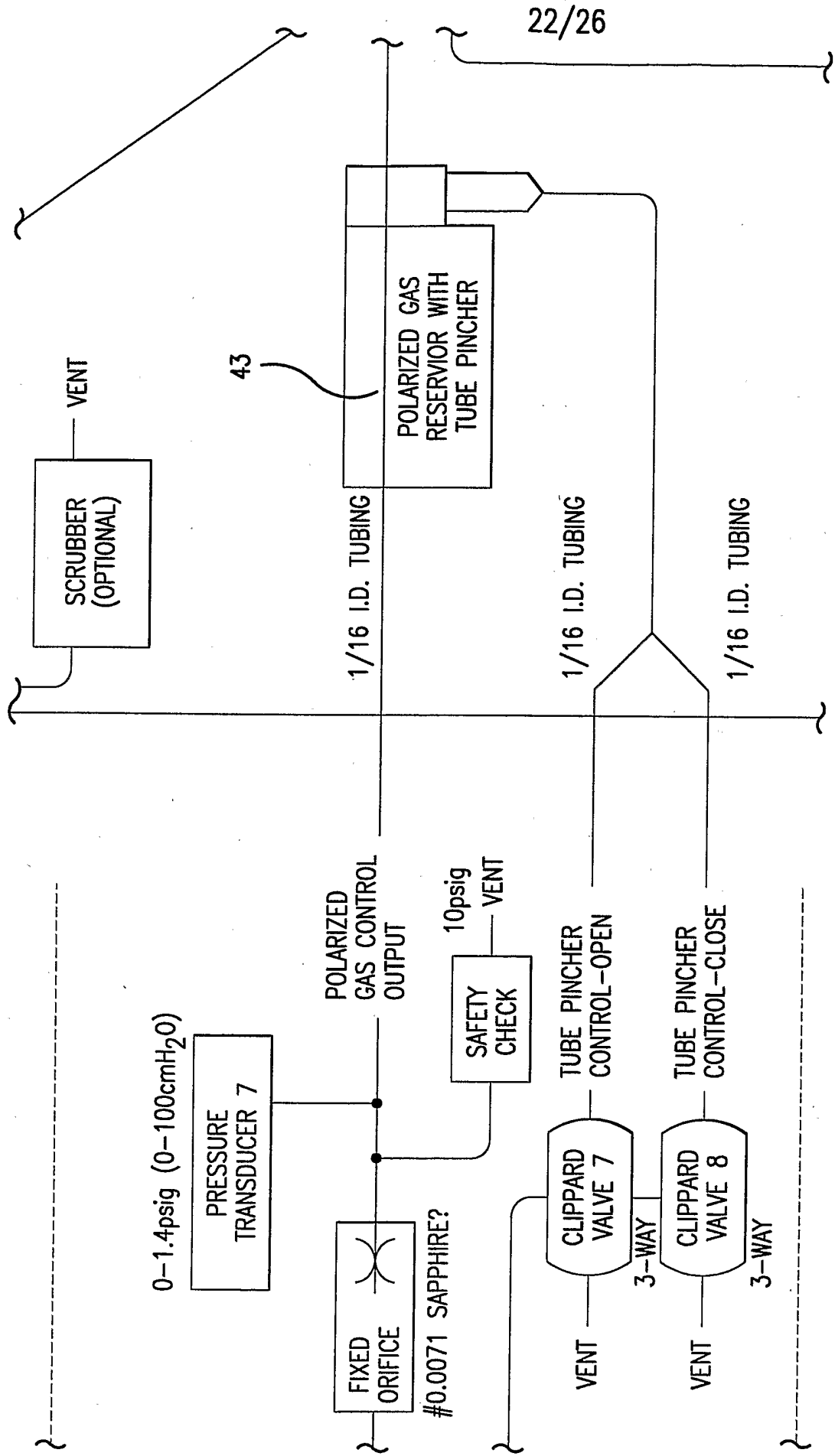


FIG.17E

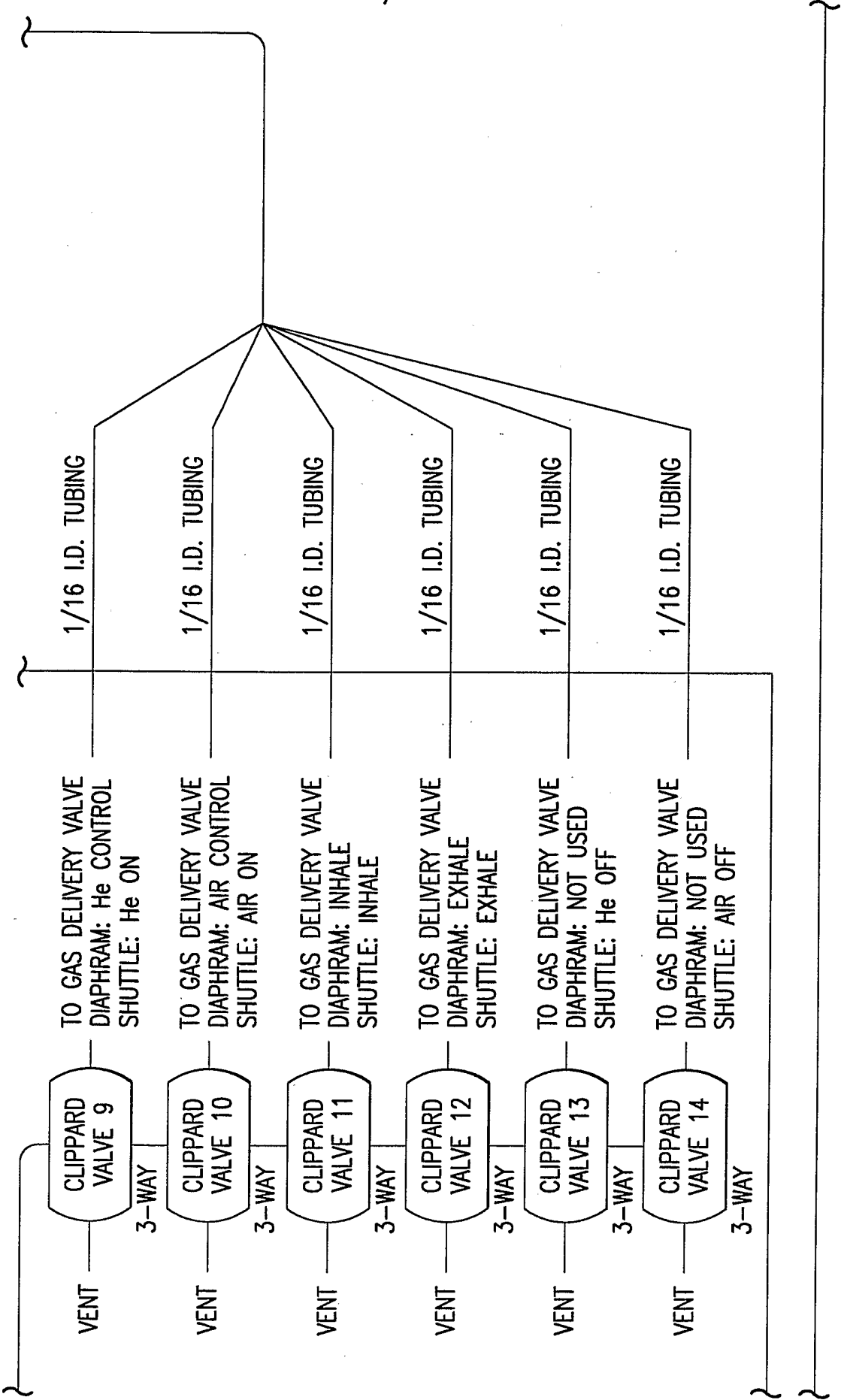


FIG.17F

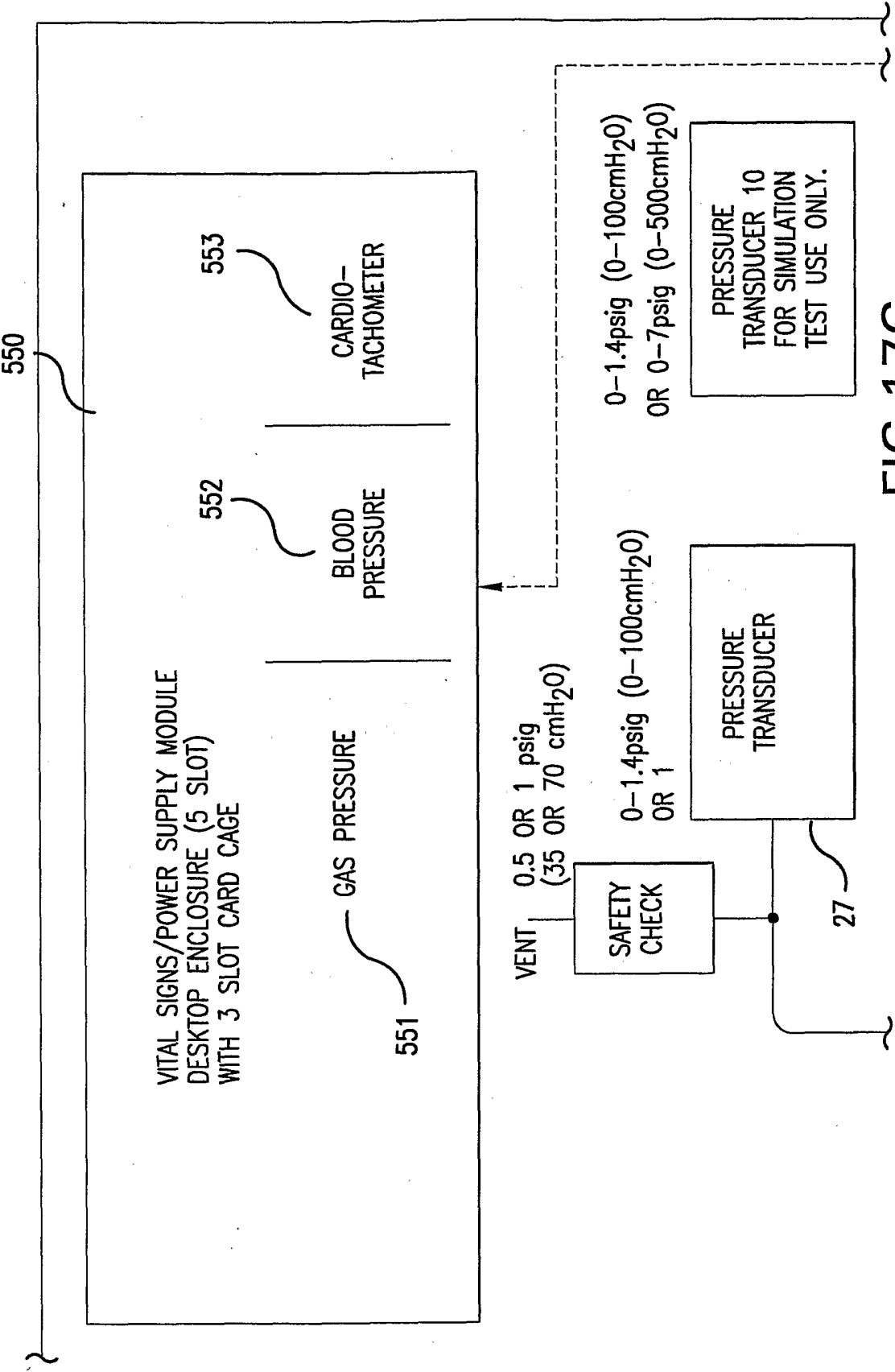


FIG.17G

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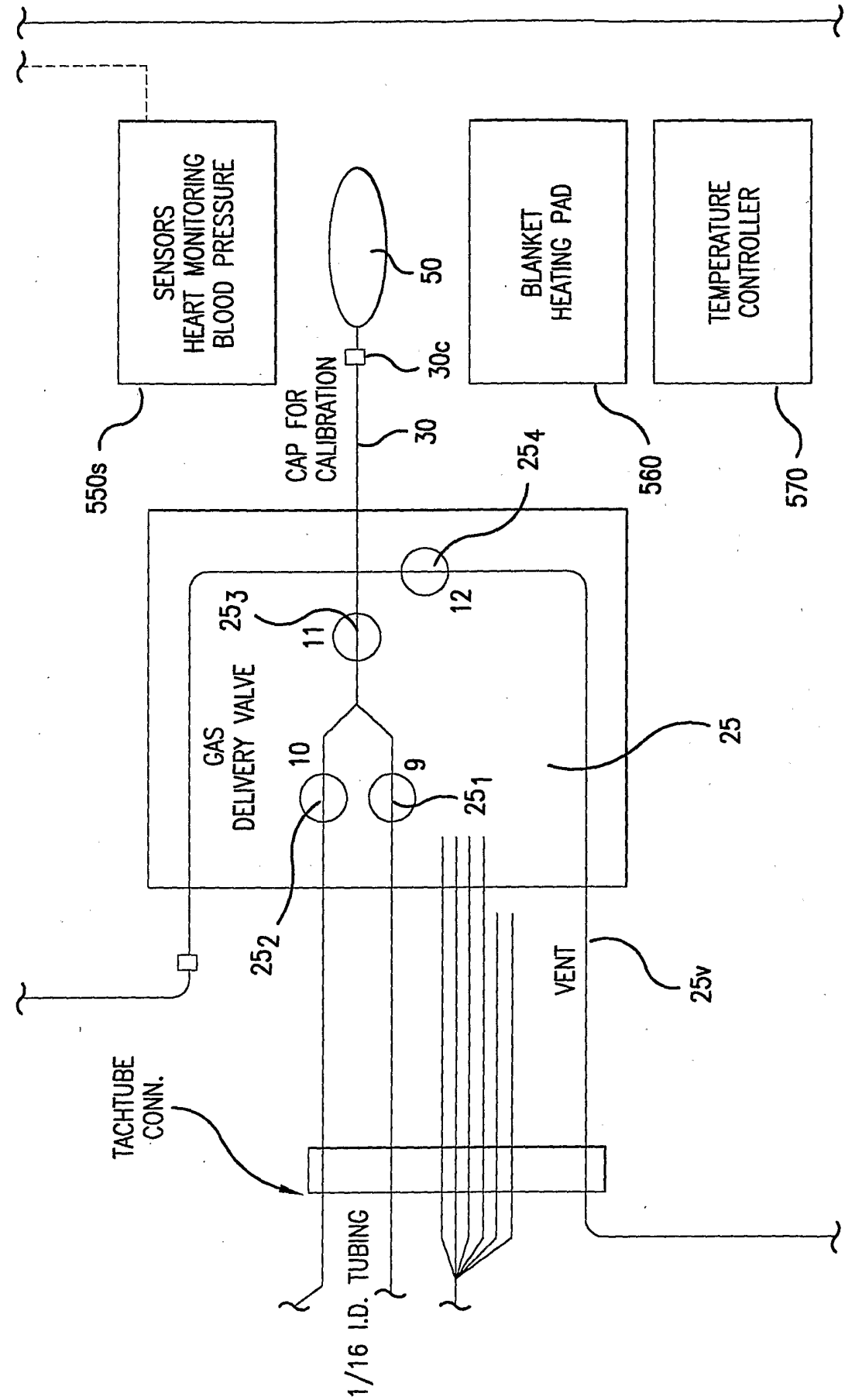


FIG. 17H

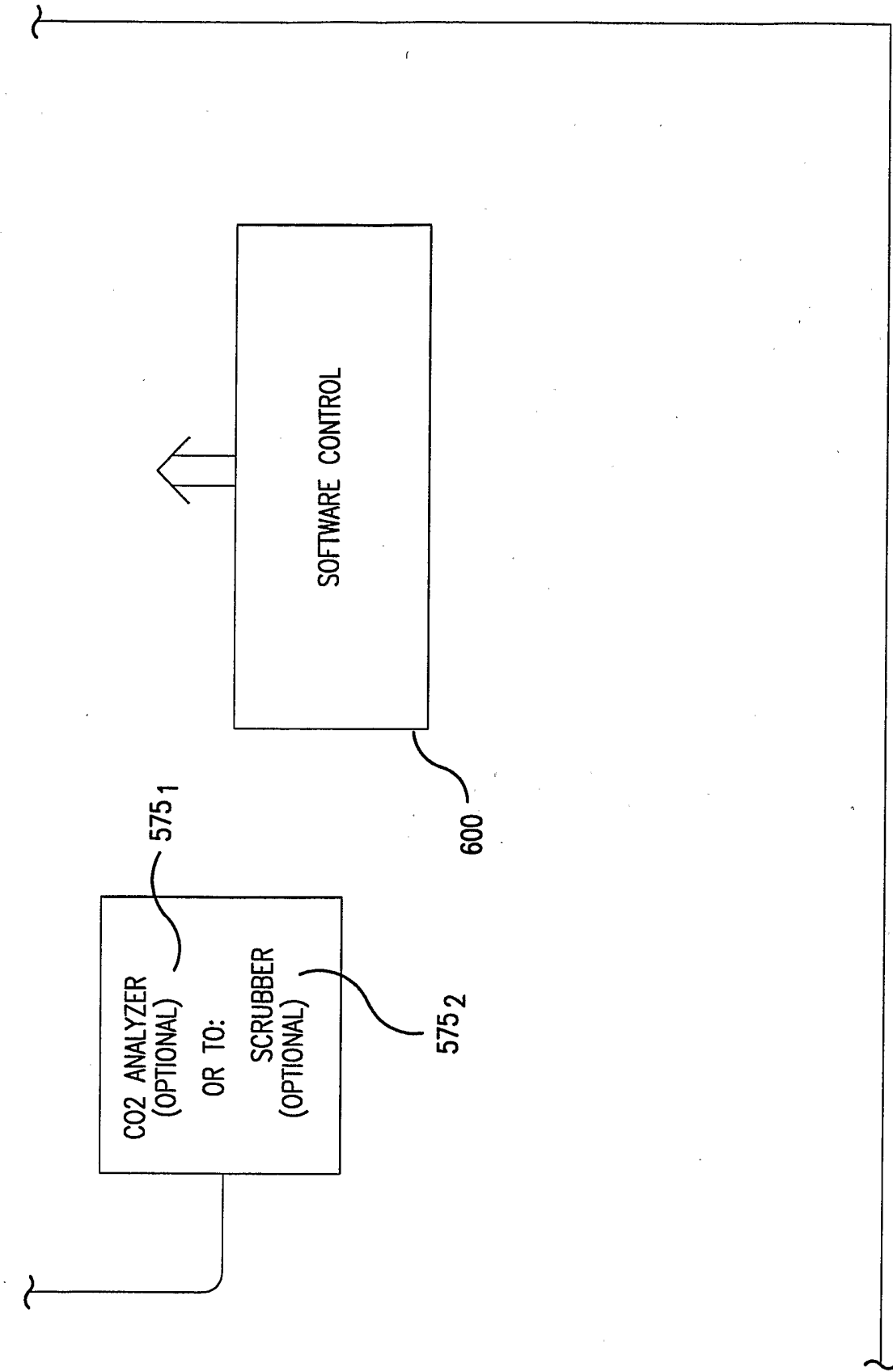


FIG.17I

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/012237

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61M16/12

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61M A61K

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 practical, 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.
A	HEDLUND L W ET AL: "MR-COMPATIBLE VENTILATOR FOR SMALL ANIMALS: COMPUTER-CONTROLLED VENTILATION FOR PROTIN AND NOBLE GAS IMAGING" MAGNETIC RESONANCE IMAGING, TARRYTOWN, NY, US, vol. 18, no. 6, 2000, pages 753-759, XP001029472 ISSN: 0730-725X the whole document	1-26, 50-63
A	US 6 085 743 A (CHUPP TIMOTHY ET AL) 11 July 2000 (2000-07-11) abstract; figure 1	1-26, 50-63
A	US 6 467 479 B1 (ALBERT MITCHELL S ET AL) 22 October 2002 (2002-10-22) column 3, line 7 - line 41; figures 1-3	1
-/--		

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

☒ Patent family members are listed in 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 document 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.

G document member of the same patent family

Date of the actual completion of the international search

7 October 2004

Date of mailing of the international search report

14/10/2004

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2004/012237

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KWANT G ET AL: "GAS MIXING FOR BIOMEDICAL APPLICATION USING MASS FLOW CONTROLLERS" MEDICAL AND BIOLOGICAL ENGINEERING AND COMPUTING, PETER PEREGRINUS LTD. STEVENAGE, GB, vol. 27, no. 6, 1 November 1989 (1989-11-01), pages 634-636, XP000095064 ISSN: 0140-0118 the whole document	1
P,A	WO 2004/010045 A (MEDI PHYSICS INC) 29 January 2004 (2004-01-29) the whole document	1
P,A	US 6 581 599 B1 (STENZLER ALEX) 24 June 2003 (2003-06-24) abstract	1

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US2004/012237

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 27-49
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/012237

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6085743	A	11-07-2000	NONE	
US 6467479	B1	22-10-2002	AU 6418399 A WO 0021601 A1	01-05-2000 20-04-2000
WO 2004010045	A	29-01-2004	WO 2004010045 A1 US 2004016768 A1	29-01-2004 29-01-2004
US 6581599	B1	24-06-2003	US 2003131848 A1	17-07-2003