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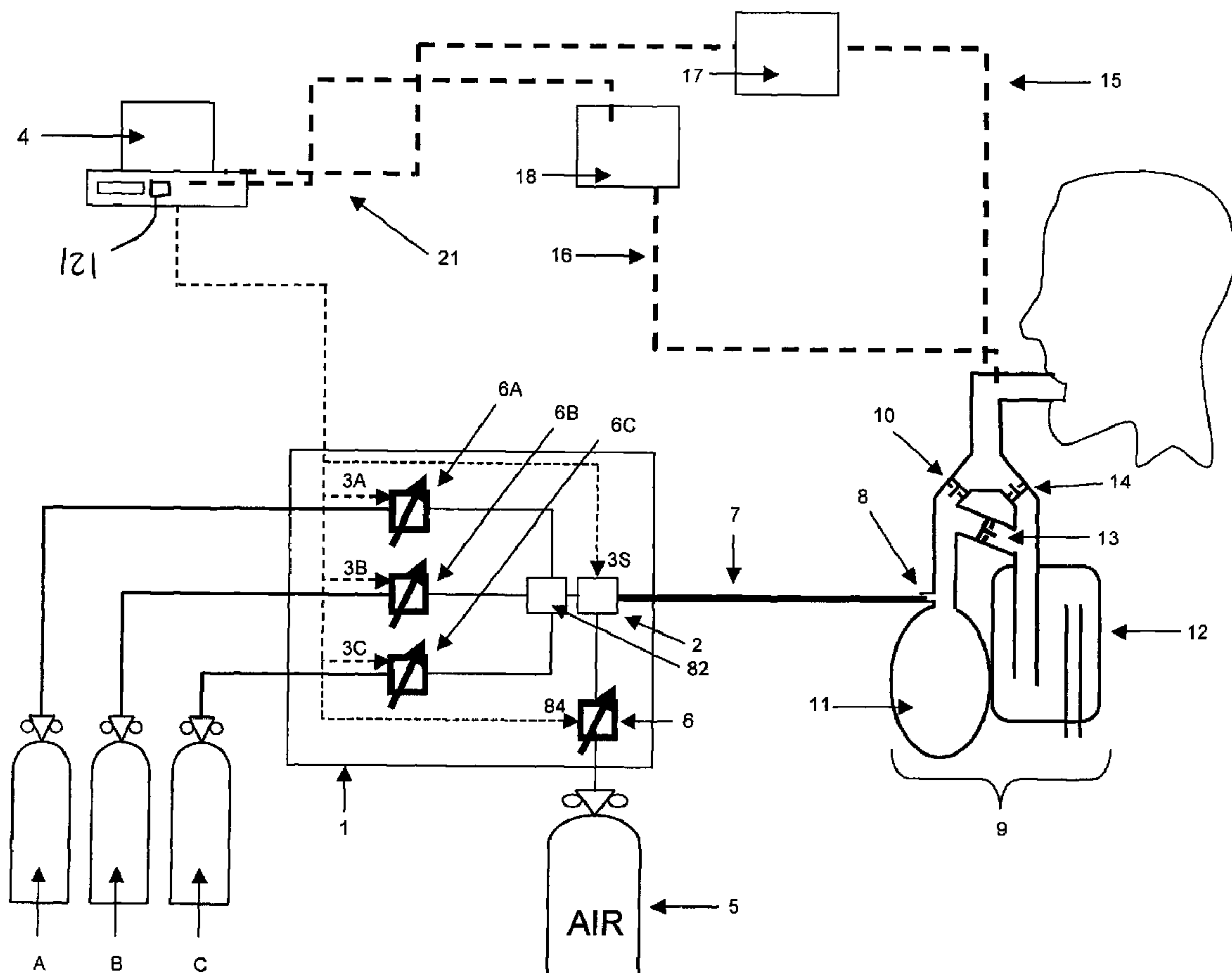
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(54) Title: A METHOD AND APPARATUS TO ATTAIN AND MAINTAIN TARGET END TIDAL GAS CONCENTRATIONS



(57) Abrégé/Abstract:

In a first aspect, the invention relates to an apparatus for inducing or maintaining a target end tidal concentration of a gas in a subject comprising a breathing circuit, a source of gas flow into the circuit, means for controlling the rate of the source of gas flow



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(57) **Abrégé(suite)/Abstract(continued):**

into the circuit and means for controlling the concentration of gases in the source gas flow independently from each other. In another aspect, the invention relates to a method of preparing an apparatus for inducing or maintaining a target end tidal concentration of a gas X in a subject comprising selecting a rate of a source gas flow into a breathing circuit, selecting the concentration of at least one constituent gas of a component gas making up the source gas to a level corresponding to the end tidal concentration of the gas X, whereby the apparatus is adapted to administer a source gas having a first gas composition

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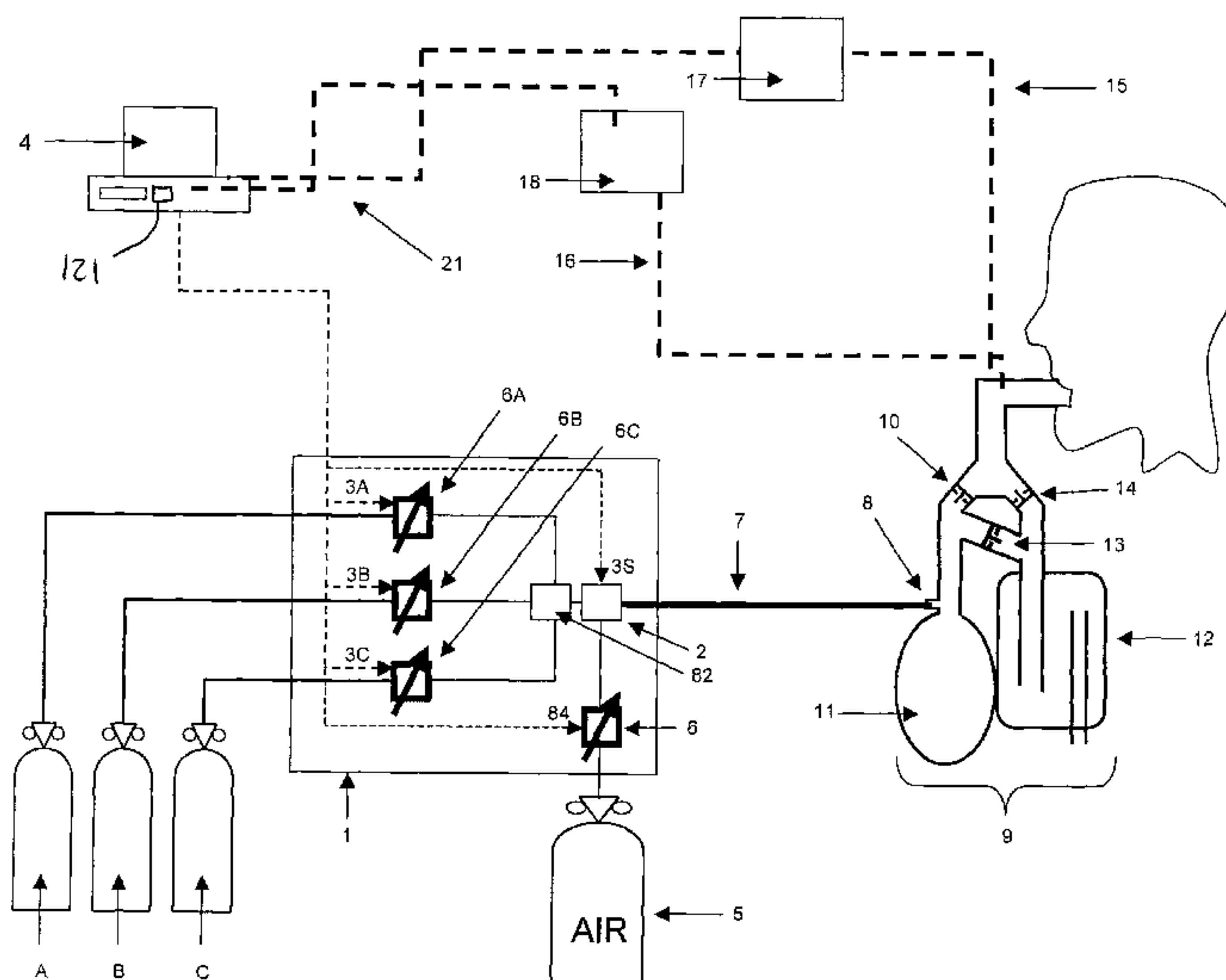
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(54) **Title:** A METHOD AND APPARATUS TO ATTAIN AND MAINTAIN TARGET END TIDAL GAS CONCENTRATIONS



(57) **Abstract:** In a first aspect, the invention relates to an apparatus for inducing or maintaining a target end tidal concentration of a gas in a subject comprising a breathing circuit, a source of gas flow into the circuit, means for controlling the rate of the source of gas flow into the circuit and means for controlling the concentration of gases in the source gas flow independently from each other. In another aspect, the invention relates to a method of preparing an apparatus for inducing or maintaining a target end tidal concentration of a gas X in a subject comprising selecting a rate of a source gas flow into a breathing circuit, selecting the concentration of at least one constituent gas of a component gas making up the source gas to a level corresponding to the end tidal concentration of the gas X, whereby the apparatus is adapted to administer a source gas having a first gas composition

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A METHOD AND APPARATUS TO ATTAIN AND MAINTAIN TARGET END TIDAL GAS CONCENTRATIONS

FIELD OF THE INVENTION

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[0001] The invention disclosed herein relates to the field of blood gas control.

BACKGROUND OF THE INVENTION

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[0002] Ordinarily, when minute ventilation increases, the partial pressure of end tidal CO₂ (PETCO₂) decreases and partial pressure of end tidal O₂ (PETO₂) increases. US Patent No. 6,622,725, (Fisher et al.), describes fixing fresh gas flowing into a partial rebreathing circuit, which in that instance was also a sequential gas delivery circuit, in order to maintain constant PETCO₂ in the face of increases in minute ventilation on the part of the subject. Canadian Patent Application 2,346,517 (Fisher et al.) also describes means of keeping PETO₂ constant at a given attained level despite increases in minute ventilation. None of these documents disclose means to set gas flows and gas concentrations into a circuit to attain a target end tidal fractional concentration of CO₂ (F_{TETCO₂}) and/or a target end tidal fractional concentration of O₂ (F_{TETO₂}) for a given minute ventilation (\dot{V}_E), that is different from initial F_{TETCO₂} and F_{TETO₂}.

[0003] Providing a level of control that permits attaining a target end tidal fractional concentration of CO₂ (F_{TETCO₂}) and/or a target end tidal fractional concentration of O₂ (F_{TETO₂}) for a given minute ventilation (\dot{V}_E), that is different from initial F_{TETCO₂} and F_{TETO₂}. can be used for a number of applications. For example, one such application is measuring cerebrovascular reactivity. Cerebral blood flow (CBF) is closely regulated by metabolic demands of the brain tissue. CBF also responds to changes in arterial PCO₂ and PO₂. The extent of the change in CBF in response to a stimulus is termed cerebrovascular reactivity

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(CVR). CVR may be a sensitive indicator of abnormal vessels such as vascular dysplasia or tissue abnormalities such as brain swelling and cancer. Quantitatively mapping CVR throughout the brain using imaging techniques such as magnetic resonance imaging (MRI) could identify areas of abnormal CVR.

5 **[0004]** Brain blood vessel diameter responds to changes in blood PO_2 as well as blood PCO_2 . Blood PO_2 and blood PCO_2 are strongly tied to end tidal concentrations of O_2 and CO_2 respectively. Present methods of inducing high $PETCO_2$ control $PETO_2$ poorly and do not control PCO_2 and PO_2 independently.

[0005] There are several current methods that are known for changing
10 blood PCO_2 and PO_2 via control of the gas concentrations in the lungs.

A: Breath-holding

[0006] One method for inducing changes in PCO_2 during Magnetic Resonance Imaging (MRI) is breath-holding. As there is a rapid drift in the baseline MRI signal, changes in MRI signal resulting from changes in brain blood
15 flow can be detected only by rapidly alternating the stimulus between "control" and "test" values. With respect to PCO_2 , this requires rapid step changes in PCO_2 , preferably maintaining PO_2 constant. Cycle times of 3 min have been reported by Vesely et al (1) to be suitable, but shorter cycle times would be preferred. Breath-holding induces an increase in PCO_2 but it is not well suited to
20 measuring CVR. The rise in blood PCO_2 during breath-holding is very slow as it is dependent on body CO_2 production ($\dot{V}CO_2$), which is small compared to body capacitance for CO_2 . During breath holding, alveolar PO_2 declines progressively. As CO_2 production, CO_2 capacitance and the tolerable breath-holding time varies from subject to subject, so will the final blood PCO_2 and $PETO_2$. As there is no
25 gas sampling during breath-holding the blood PCO_2 and PO_2 is unknown for the duration of the breath-hold so it is not possible to relate the MRI signal strength to PCO_2 or PO_2 , a requirement for the calculation of CVR. The changes in lung and blood PCO_2 during breath-holding are an exponential function with time.

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Therefore breath holding time is a poor variable to use to quantitate the strength of the stimulus.

B: Inhaling CO₂

[0007] A second traditional method of changing PCO₂ is inspiring gas mixtures containing CO₂ via a facemask. This is known to result in a highly variable ventilatory response between subjects leading to a large variability in PETCO₂. Furthermore, inhaling CO₂ changes the minute ventilation (\dot{V}_E) resulting also in variability in blood PO₂. Oxygen is a potent vasoconstrictor and confounds the interpretation of the relationship between PCO₂ and brain blood flow.

[0008] Therefore, neither breath-holding nor inhaling a gas mixture containing CO₂ provide suitable conditions for a consistent, repeatable quantitative test for CVR.

C: Gas forcing

[0009] Since the effects of inhaling a CO₂-containing gas mixture on increasing PCO₂ can be overcome by increasing minute ventilation, one can introduce a feedback loop to adjust the inhaled PCO₂ to effect a target PETCO₂. This is referred to as "gas forcing"(2) . Gas forcing has been shown to be effective in imposing target PETO₂ and target PETCO₂ independent of minute ventilation. However, it does have some drawbacks with respect to measuring CVR:

[0010] Gas forcing depends on a feedback loop. Feedback loops can have inherent instability depending on the gain and time constant of the system, and are prone to drift and oscillation of end-tidal values.

[0011] Gas forcing is usually applied in a chamber or requires a hood over the head. As such, there is a large volume of gas that needs to be replaced rapidly for each change in inspired PCO₂. This necessitates very large flows of

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gases and very precise flow controllers for each gas (such as N₂, O₂ and CO₂ if only these gases are controlled). This is very expensive and cumbersome, and an error which leads to presentation of pure N₂ or pure CO₂ could be deadly.

[0012] Gas forcing requires the construction of a special chamber that is not available commercially and has been custom built for research purposes. This is available only in a few places in the world.

[0013] The requirement for specific air-tight chambers, large gas flow controllers, massive volumes of gases, and complex computer control algorithms makes gas forcing too cumbersome to be suitable for use in a radiology, MRI and ophthalmology suites.

[0014] The time constant for changes in alveolar gas concentrations is too long to be suitable for use with MRI.

D: Sequential gas delivery method:

[0015] A more recent method introduced by Vesely et al.(1) solved some of these problems. They used O₂ flow to a sequential gas delivery (SGD) circuit to produce rapid changes in PETCO₂ between two known levels (30-50 mmHg). (A SGD circuit provides (at least) two gases through two breathing circuit limbs. The gas from the first limb (G¹) is provided first, and if the subject's breathing exceeds the available first gas, the balance of that breath is made up of the second gas (G²). The second gas may be previously exhaled gas collected in a reservoir on the second limb.) To reduce PCO₂, they asked their subjects to hyperventilate while providing large O₂ flows into the SGD. To raise the PCO₂, they provided a bolus of CO₂ by briefly changing the composition of the gas entering the circuit and then maintained the raised PCO₂ by controlling the flow into the SGD. While this allowed transitions to a new PETCO₂, the lowering and raising of O₂ flows into the circuit to control PETCO₂ and the required changes in \dot{V}_E cause alveolar, and thus end tidal, O₂ concentrations to change during the protocol despite near constant inspired O₂ concentration. For example, when O₂

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flow is restricted in order to keep the PETCO₂ high, the PETO₂ tends to drift down (as O₂ consumption stays constant in the face of reduced O₂ delivery). When subjects hyperventilate to lower the PETCO₂, the increased O₂ flow into the circuit results in a rise of PETO₂ (as O₂ consumption stays constant and O₂ delivery is increased). The changes in blood PO₂ have an effect on the MRI signal independent of brain blood flow confounding the interpretation with respect to blood flow.

[0016] There are additional practical problems with this method:

[0017] Subjects must change their \dot{V}_E frequently during the protocol. It may be difficult for most people to comply adequately with this.

[0018] Not adequately following breathing instructions results in not meeting target PCO₂ values

[0019] Not responding to breathing instructions quickly enough invalidate the MRI data.

[0020] The method of Vesely et al uses 2 gases and the manipulation of flow into the circuit to change end tidal CO₂ values. With this method, if the total flow is set, then

varying the inspired PCO₂ changes the inspired PO₂.

PETO₂ cannot be determined independently of PETCO₂.

PETO₂ and PETCO₂ cannot be varied independently.

Reference List

- (1) Vesely A, Sasano H, Volgyesi G, Somogyi R, Tesler J, Fedorko L et al. MRI mapping of cerebrovascular reactivity using square wave changes in end-tidal PCO₂. Magn Reson Med 2001; 45(6):1011-1013.

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- (2) Robbins PA, Swanson GD, Howson MG. A prediction-correction scheme for forcing alveolar gases along certain time courses. J Appl Physiol 1982; 52(5):1353-1357.

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SUMMARY OF THE INVENTION

[0021] In one embodiment, the present invention relates to a method to control the end tidal CO₂ and end tidal O₂ independently of each other and
10 independently of minute ventilation.

[0022] In one aspect, the invention is directed to a method of inducing a target end tidal concentration, or maintaining the end tidal concentration at a target level, of a gas X in a subject comprising:

setting the source gas flow into a partial re-breathing circuit at a
15 rate equal to or less than the subject's minute ventilation;

setting the concentration of said gas X in the source gas to a predetermined level that will induce the end-tidal concentration of said gas X to be at the target end tidal concentration;

delivering the source gas to the subject through said circuit.

20 **[0023]** Throughout this disclosure, the term subject is intended to be interpreted broadly, and could include, for example, a human adult or child or an animal.

[0024] In a second aspect, the invention is directed to a method of inducing target end tidal concentrations, or maintaining end tidal concentrations
25 at a target level, of a plurality of gases in a subject comprising:

setting the source gas flow into a partial re-breathing circuit at a rate equal to or less than the subject's minute ventilation;

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setting the concentration in the source gas, of each gas whose target is being induced or maintained, to a predetermined level to attain the target end tidal concentration of that gas;

delivering the source gas to the subject through said circuit.

5 **[0025]** As further described herein, according to one embodiment of the invention, the concentration in the source gas, of each gas whose end tidal concentration in the subject is being set to or maintained at a target, may be set by using one or more pre-mixed gases as the source gas, the said pre-mixed gas having a minimal safe concentration of oxygen and otherwise concentrations of
10 target gases such as N₂ and CO₂ so as to provide the required target end tidal concentrations. Alternatively, the concentrations in the source of each gas whose end tidal concentration in the subject is being set to, or maintained at, a target, may be set by blending the source gas from a set of pure component gases, for example O₂, N₂, and CO₂.

15 **[0026]** Embodiments of the invention may be employed to simultaneously maintain or change the end tidal concentrations of two gases independently of one another. Alternatively, the invention may be employed to maintain the end tidal concentration of a first gas X, while the end tidal concentration of at least one second gas Y is changed from a first target to a second target, by altering
20 the composition of the source gas so that the concentration of the at least one second gas Y is changed.

[0027] According to one aspect of the invention the concentration of one or more gases in the source gas flowing into a partial rebreathing circuit may be controlled to achieve a particular target end tidal concentration of those gases
25 when such concentration of such gases in the source are predetermined and set based on one or more steps described herein. As described below, to achieve a target end tidal of a gas X that is physiologically produced by the subject's body, the concentration of said gas X is set using one formula:

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$$F_{G^1}X = F_{TET}X - \frac{\dot{V}X}{\dot{V}G^1}$$

where $F_{G^1}X$ is the concentration of gas X in the source gas G^1 , $\dot{V}X$ is the subject's minute production of the physiologically produced gas X, $F_{TET}X$ is the target end tidal concentration of said gas X, and $\dot{V}G^1$ is the flow rate of the
 5 source gas. An example of one such gas would be CO_2 .

[0028] The concentration in the source gas of gases that are physiologically consumed by the subject are set using the formula:

$$F_{G^1}X = F_{TET}X + \frac{\dot{V}X}{\dot{V}G^1}$$

where $F_{G^1}X$ is the concentration of gas X in the source gas G^1 ,
 10 $\dot{V}X$ is the subject's minute consumption of gas X, $F_{TET}X$ is the target end tidal concentration of gas X and $\dot{V}G^1$ is the flow rate of the source gas.

[0029] The above formulas are applicable in particular when the subject breathes into a partial rebreathing circuit and in particular a circuit such as that shown in Figure 1a, but is also applicable in any situation where the subject is
 15 breathing into a circuit with a flow of gas $G1$ and a flow of neutral gas $G2$ which is neutral with respect to the subject's end-tidal concentration of gas X.

[0030] The subject's minute production of a physiologically produced gas or minute consumption of a physiologically consumed gas may be estimated based on height and weight, or other parameters, or measured directly.

20 **[0031]** Whether the source gas can be, at any given time, made up of pre-mixed 'component' gases delivered individually or a blend of constituent gases, is a function of the capability of the apparatus (the apparatus may be adapted to accommodate one or both capabilities depending on its intended use) but is otherwise immaterial to the practice of the invention. In either case according to
 25 one preferred embodiment of the invention, the source gas flow into the

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breathing circuit preferably has a minimum safe concentration of O₂, for example 10%. Where the source gas is made up of blended component gases (examples of sets of components gases for providing a full array of target end tidal concentrations are described below), at least the most frequently used and
5 preferably each of the component gases comprises a minimum safe concentration of O₂.

[0032] In a broader aspect, to achieve one or more changes in the end tidal concentration of a given gas, the invention is directed to a method of changing an end tidal concentration of a gas X in a subject, comprising setting
10 the source gas flow into a partial rebreathing circuit at a rate equal to or less than the subject's minute ventilation and providing a first concentration of said gas X in the source gas and delivering the source gas to the subject through said circuit in order to effect a first end tidal concentration of said gas X.

[0033] In a preferred embodiment of the latter method, the further step of
15 providing at least one second different concentration of said gas X in the source gas and delivering the source gas to the subject through said circuit in order to effect a second end tidal concentration of said gas X conveniently enables a diagnostic assessment to be made by measuring a physiological parameter at two end tidal levels of said gas X.

20 **[0034]** In other aspects, the invention is directed to data acquisition and diagnostic methods employing any of the aforementioned methods of the invention and the various embodiments of those methods described herein and to apparatus adapted to carry out the method and components thereof, optionally including component gases, assembled to carry out the method.

25 **[0035]** Preferred embodiments of such data acquisition and diagnostic methods include:

[0036] A method to measure cerebrovascular reactivity comprising controlling the end tidal CO₂ and O₂ levels of a subject using one of the

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aforementioned methods and monitoring cerebral blood flow or oxygenation via some method such as a blood oxygen level dependent (BOLD) or ASL (arterial spin labeling) with functional Magnetic Resonance Imaging signal intensity, trans-cranial Doppler, carotid artery Doppler, Positron Emission imaging, Near
5 Infra-red Spectroscopy.

[0037] A method to measure oculovascular reactivity comprising controlling the end tidal CO₂ and O₂ levels of a subject using one of the aforementioned methods and monitoring oculovascular blood flow.

[0038] A method to measure a beneficial level of oxygenation to tissues for
10 the purpose of radiotherapy or chemotherapy, comprising controlling the end tidal CO₂ and O₂ levels of a subject using one of the aforementioned methods and monitoring oxygenation or blood flow in the skin, muscle, tumor or other tissue.

[0039] It will be appreciated that in the practice of the aforementioned diagnostic methods the end tidal CO₂ and O₂ levels are controlled independently
15 of each other. For example, the end tidal CO₂ levels may be changed while the end tidal O₂ levels are kept constant or the end tidal O₂ levels may be changed while the end tidal CO₂ levels are kept constant or the end tidal O₂ levels and the end tidal CO₂ levels may be changed simultaneously.

[0040] In yet another aspect, the invention is directed to a therapeutic
20 method comprising any of the aforementioned methods for controlling end tidal gas concentrations, for example a therapeutic method comprising using such a method to set the end tidal O₂ and CO₂ levels to pre-determined levels that provide a beneficial oxygenation level or blood flow level to tissues for the purpose of accelerating healing, or increasing sensitivity to ablation by
25 radiotherapy or chemotherapy.

[0041] In the practice of one embodiment of one of the aforementioned methods, the partial re-breathing circuit is a sequential gas delivery circuit and the apparatus includes

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means for controlling the rate of flow of the source gas into the circuit

and means for controlling the concentration of said gases in the source gas flow. Optionally, the apparatus further comprises means for monitoring pressure in the breathing circuit and optionally further comprises means for measuring the subject's end tidal gas concentrations.

[0042] Optionally, the method above may further comprise measuring the end tidal gas concentrations and using feedback control to increase or decrease the concentrations of a particular gas so as to minimize the difference between the current end tidal concentration and the target end tidal concentration, for example so as to effect a more rapid change in target end tidal levels.

[0043] Changes in end tidal CO₂ and/or O₂ can be used to determine vascular reactivity in cerebral, pulmonary, renal, or retinal vessels and other vascular beds as detected by various blood flow or blood flow surrogate sensors. Similarly, changes in end tidal CO₂ and/or O₂ can be used to determine changes on organ or tissue function by measuring such factors as blood pressure and heart rate variability, skin conductivity, capillary blood flow in the skin, hormone levels, organ temperature, finger or other limb plethysmography, and other measurements known to physiologists and others skilled in the art.

[0044] In yet another aspect, the invention is directed to a method of preparing an apparatus for the use of independently controlling the end tidal concentration of each constituent gas in the expired gas of a subject, comprising:

selecting a rate of a source gas flow into a breathing circuit, the rate projected to be not substantially more than the minute ventilation of the subject;

selecting the composition of said source gas by selecting the concentration of a constituent gas X in the source gas based on a selected end tidal concentration of the constituent gas X, whereby said apparatus is adapted to administer a source gas having a first gas composition. In one aspect, step b) includes

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mathematical computation of the selected concentration of the constituent gas X based on the selected end tidal concentration of the constituent gas X. In another aspect the invention is directed to the apparatus so prepared, such apparatus comprising at least one component gas inlet port, and conveniently 3 or 4 such
5 ports for controlling selected end tidal concentrations with a series of blended gases.

[0045] In yet another aspect, the inventions is directed to a system for independently controlling the end tidal concentration of each constituent gas in
10 the expired gas of a subject, the system comprising a source gas outlet, a plurality of component gas inlets, a flow controller for each component gas, an input device for inputting a selected end tidal concentration of a constituent gas X in the source gas and a processor unit programmable to derive the concentration of said constituent gas X in the source gas based on the end tidal concentration
15 of the constituent gas X in the expired gas, said processor unit operatively connected to each flow controller for setting the respective gas flow rate of said flow controller in order to achieve the derived concentration of said constituent gas X in the source gas.

[0046] In one embodiment, the selected concentration of the constituent
20 gas X in the source gas is mathematically computed based on the selected end tidal concentration of the constituent gas X in the expired gas. In another embodiment, the source gas is made up of at least three component gases.

[0047] In another embodiment, each component gas inlet is fluidly connected to a blended gas source comprising at least 10% O₂. In another
25 embodiment, a source gas outlet port is fluidly connected to a sequential gas delivery circuit, for example, a partial rebreathing circuit.

[0048] The system could be developed by preparing it for use with premixed gases of a selected composition such that the need for software to determine inlet concentrations of constituent gases and the need to have flow

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control on component gases is obviated. It is nonetheless considered within the scope of an embodiment of the present invention.

[0049] In yet another aspect, the invention is directed to a method of developing a system for independently controlling the end tidal concentration of
5 each constituent gas in the expired gas of a subject, comprising:

- a) making available for acquisition an apparatus having at least a source gas outlet, a plurality of component gas inlets, and a flow controller for each component gas; and
- 10 b) facilitating implementation of machine readable instructions to drive a processor unit programmable to derive the concentration of said constituent gas X in the source gas based on the end tidal concentration of the constituent gas X in the expired gas, said processor unit adapted to be operatively connected to each flow controller for setting the respective gas flow rate of said flow controller
15 in order to achieve the derived concentration of said constituent gas X in the source gas. The processor unit may be integrate within the housing of a gas blending apparatus or may have a data input interface for driving the flow controllers. Step b) may include carrying out one or more steps selected from:
 - developing of said machine readable instructions;
 - 20 out-sourcing development of said machine readable instructions;
 - making said machine readable instructions available for acquisition;
 - providing instructions for acquisition of said machine
25 readable instructions;
 - providing instructions for use of said machine readable instructions;
 - providing instructions for development of said machine readable instructions;

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5 providing instructions for acquisition of a processor unit
programmed with said machine readable instructions;
and
providing instructions for working, updating, upgrading,
trouble-shooting, substitution, repair or re-acquisition, of
said machine readable instructions or such processor
unit. The processor unit may be programmed or have
“hard-wired” such instructions.

[0050] It will be appreciated that a gas blending apparatus can be made
10 available for acquisition through direct sales or leasing or through collaborating
with a third party in the design, development, lease, marketing or sale of an
apparatus that is driven by a processor programmed by such machine readable
instructions.

[0051] The invention contemplates that the system and it method for
15 development can be used with particular gas mixtures that are derived,
especially by computation, using the formulas presented herein, thereby
obviating the need to calculate these on a case by case basis, and thereby
simplifying process control for the component gases. This obviates the need to
have individual flow controllers and attendant controls. Therefore in one aspect
20 the system comprises a much simplified apparatus by facilitating its use with
specialty gases. In this aspect of the invention the gases may be purchased for
use with the system and made be provided with the remainder of the system. In
either case instructions the developer facilitates use of the system with the
availability of instructions for the use of the specialty gases with a simplified
25 system.

[0052] Other aspects and features of the present invention will become
apparent, to those ordinarily skilled in the art, upon review of the following
description of the specific embodiments of the invention.

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BRIEF DESCRIPTION OF THE DRAWINGS

[0053] For a better understanding of the present invention, and to show more clearly how it may be carried into effect, reference will now be made, by way of example, to the accompanying drawings, which illustrate aspects of
 5 embodiments of the present invention and in which:

[0054] Figure 1A shows a rebreathing sequential gas delivery circuit.

[0055] Figure 1B shows a non-rebreathing sequential gas delivery circuit.

[0056] Figure 2 shows the preferred embodiment of the apparatus.

10 **[0057]** Figure 3 shows an alternate embodiment of the apparatus.

[0058] Figure 4 shows data from a subject using the apparatus and method, with constant $P_{ET}O_2$ and changes in levels of $P_{ET}CO_2$.

[0059] Figure 5 shows data from a subject using the apparatus and method, with constant $P_{ET}CO_2$ and changes in levels of $P_{ET}O_2$.

15 **[0060]** Figure 6 shows data from a subject using the apparatus and method, with simultaneous controlled changes in $P_{ET}CO_2$ and $P_{ET}O_2$.

DETAILED DESCRIPTION OF THE INVENTION

20 **[0061]** It should be noted that gas concentrations described herein may be referred to as partial pressures (e.g. PCO_2) or as fractional concentrations (e.g. FCO_2). Those skilled in the art will recognize the relationship between the two in that partial pressure = fractional concentration x ambient atmospheric pressure.

25 **Glossary of Terms**

Oxygen	O_2
Carbon dioxide	CO_2

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Nitrogen	N_2
Partial pressure of oxygen	PO_2
Partial pressure of carbon dioxide	PCO_2
Partial pressure of nitrogen	PN_2
Partial pressure of oxygen in end tidal gas	$PETO_2$
Partial pressure of carbon dioxide in end tidal gas	$PETCO_2$
O ₂ consumption	$\dot{V}O_2$
CO ₂ production	$\dot{V}CO_2$
Alveolar ventilation	\dot{V}_A
Minute ventilation	\dot{V}_E
Respiratory quotient	RQ
Target end tidal CO ₂	F_{TETCO_2}
Target end tidal O ₂	F_{TETO_2}
Minute ventilation	\dot{V}_E
Sequential gas delivery (breathing circuit)	SGD
Source gas, or gas inhaled first from an SGD	G^1
Reserve gas, or gas inhaled second from an SGD	G^2
Flow of fresh gas	$\dot{V}G^1$
Flow of reserve gas	$\dot{V}G^2$
Flow of Gas A	\dot{Q}_A
Flow of Gas B	\dot{Q}_B
Flow of Gas C	\dot{Q}_C
Target end tidal fractional concentration of CO ₂	F_{TETCO_2}
Target end tidal fractional concentration of O ₂	F_{TETO_2}
Fractional concentration of O ₂ in neutral component of G^1	$FG^1_nO_2$
Fractional concentration of CO ₂ in neutral component of G^1	$FG^1_nCO_2$
Fractional concentration of CO ₂ in G^1	FG^1CO_2
Fractional concentration of O ₂ in G^1	FG^1O_2

[0062] In the present invention the subject preferably breathes through a breathing valve manifold with breathing tubes (herein referred to as a breathing circuit) known as a partial rebreathing circuit. Preferably, the subject breathes on
5 a partial rebreathing circuit that is also a sequential gas delivery (SGD) circuit, whose functions will be reviewed briefly.

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[0063] The non-rebreathing sequential gas delivery circuit was taught by Fisher [US 6354292]. The rebreathing sequential gas delivery circuits were taught by Fisher [US 6622725, US 6612308]. Figure 1B illustrates the principles of a non-rebreathing sequential gas delivery circuit. During exhalation, the expiratory one-way valve (30) opens and gas is exhaled to atmosphere; meanwhile, the source gas enters the source gas port (32) and is stored in the source gas reservoir (33). Figure 1A illustrates the homologous circuit where exhaled gas is used as reserve gas. With this circuit, during exhalation, exhaled gas is directed into an exhaled gas reservoir (28) and made available to act as reserve gas. During inhalation, the one-way inspiratory valve (31) opens and source gas from the source gas port (32) and the source gas reservoir (33) are inhaled. In both of these circuits, when \dot{V}_E exceeds source gas flow, the difference between \dot{V}_E and source gas flow is made up of reserve gas which is presented through crossover valve (29) in the rebreathing circuit or via demand valve (35) in the non rebreathing circuit. Source gas and reserve gas are inhaled sequentially: at the beginning of inhalation, gas is inhaled from the fresh gas flow inlet and the fresh gas reservoir. Reserve gas in the non rebreathing circuit is comprised of gas that has similar properties to exhaled gas.

Description of Method to Independently Control End-Tidal Gases

[0064] The present invention describes a method for independent control of end tidal (end of exhalation) gas concentrations of a subject. The discussion herein describes the method particularly as it pertains to control of CO_2 and O_2 , although those skilled in the art will recognize that the method can be equally applied to control of other gases in the subject.

[0065] The method comprises:

[0066] determining or estimating the subject's $\dot{V}\text{CO}_2$ and $\dot{V}\text{O}_2$

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[0067] setting the initial flow rate of the source gas ($\dot{V}G^1$) into a partial rebreathing circuit, preferably a sequential gas delivery circuit, on which the subject is breathing, approximately equal to the subject's average \dot{V}_A (discussed further below). This may be accomplished by adjusting the source gas flow until
 5 the source gas reservoir of a sequential gas delivery circuit just empties on each breath, or alternatively, a flowmeter may be interposed between the subject and the circuit.

[0068] setting the O_2 and CO_2 concentrations in the source gas (FG^1O_2 and FG^1CO_2 respectively) to concentrations determined using the methods
 10 described below

[0069] A partial rebreathing circuit is required with the method since the end tidal concentrations when breathing on such a circuit become fixed (approximately fixed for most partial rebreathing circuits, and reliably fixed with sequential gas delivery circuits) and independent of minute ventilation (\dot{V}_E),
 15 provided the gas flow into the circuit is less than or equal to the \dot{V}_E . The end tidal concentrations become a function only of the gas concentrations of the source gas.

[0070] We will first describe the method for determining FG^1CO_2 . In order to carry out the method, one must first obtain values for the subject's CO_2
 20 production ($\dot{V}CO_2$), which can be done by direct measurement (for example by analyzing a timed collection of exhaled gas for FCO_2) or calculated from standard tables based on other anthropomorphic data such as weight and height.

[0071] The method makes use of the relationship known in the art that relates a rate of alveolar ventilation \dot{V}_A to the subject's fractional end tidal CO_2
 25 concentration:

$$F_{ET}CO_2 = \frac{\dot{V}CO_2}{\dot{V}_A} \quad \text{Equation (4)}$$

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[0072] This relationship states that for a given rate of alveolar ventilation, a particular end tidal concentration is produced. Lowering the alveolar ventilation raises $F_{ET}CO_2$ and raising it lowers $F_{ET}CO_2$.

[0073] As long as the subject's minute ventilation exceeds the $\dot{V}G^1$ the composition of G^1 determines the end-tidal concentrations of a gas. For example, consider a case where the subject has a resting \dot{V}_A with a corresponding resting end tidal PCO_2 . We may wish to increase the source gas flow $\dot{V}G^1$ to greater than the subject's resting \dot{V}_A to effect a more rapid transition in end-tidal PCO_2 or PO_2 . We instruct the subject to breathe at a rate $\geq \dot{V}G^1$ to assure that all of $\dot{V}G^1$ reaches the alveoli, then additional CO_2 in G^1 prevents a reduction in $P_{ET}CO_2$. To calculate the concentrations of constituent gases to G^1 is to mathematically split G^1 into a portion with a flow rate equal to the resting \dot{V}_A and a portion with the balance of the flow which is $(G^1 - \dot{V}_A)$. We call the portion that is equal to \dot{V}_A "fresh" gas flow because it contributes to gas exchange, $(\dot{V}G^1_f)$ by virtue of having no CO_2 . This gas flow therefore determines the end tidal concentration according to Equation (4). The second portion of G^1 consisting of the difference between the desired G^1 and the \dot{V}_A ($G^1 - \dot{V}_A$) requires a concentration of CO_2 that does not provide a gradient for gas exchange. Thus composed, it is considered a "neutral" gas flow ($\dot{V}G^1_n$). $FG^1_nCO_2$ equal to that of alveolar gas (as approximated by end tidal gas) by definition would be "neutral" with respect to gas exchange of CO_2 .

[0074] Since there is no CO_2 in $\dot{V}G^1_f$, $\dot{V}G^1_n$ is the source of all of the CO_2 in G^1 (Equation (6)).

$$\dot{V}G^1 \times FG^1CO_2 = \dot{V}G^1_n \times FG^1_nCO_2 \quad \text{Equation (6)}$$

[0075] In that case, the concentration in the neutral gas must be equal to the target CO_2 concentration to maintain $P_{ET}CO_2$ at the target value

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$$\dot{V}G^1 \times FG^1CO_2 = \dot{V}G^1_n \times F_{TET}CO_2 \quad \text{Equation (7)}$$

and the rate of flow of neutral gas is the difference between the rate of flow of the source gas and the rate of the subject's alveolar ventilation, or

5

$$\dot{V}G^1_n = [\dot{V}G^1 - \dot{V}_A] \quad \text{Equation (7b)}$$

[0076] This allows us to rewrite Equation (7) as:

$$\dot{V}G^1 \times FG^1CO_2 = [\dot{V}G^1 - \dot{V}_A] \times F_{TET}CO_2 \quad \text{Equation (7c)}$$

10

[0077] Also, the relationship between the subject's target end tidal and alveolar ventilation is known from Equation (4).

$$\dot{V}_A = \frac{\dot{V}CO_2}{F_{TET}CO_2} \quad \text{Equation (4)}$$

15

[0078] Therefore, substituting Equation (4) in equation (7c) we get:

$$\dot{V}G^1 \times FG^1CO_2 = \left[\dot{V}G^1 - \frac{\dot{V}CO_2}{F_{TET}CO_2} \right] \times F_{TET}CO_2 \quad \text{Equation (8)}$$

[0079] Dividing both sides by $\dot{V}G^1$ gives:

$$FG^1CO_2 = F_{TET}CO_2 - \frac{\dot{V}CO_2}{\dot{V}G^1} \quad \text{Equation (9)}$$

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[0080] This argument should hold generically for any gas that is absorbed by the body as well. In practice, it is preferable to have the subject breathing at a rate greater than their resting breathing rate in order to achieve end tidal CO₂ targets below their resting levels. Additionally, having the subject breathe faster
 5 enables more rapid transitions between end tidal levels, particularly when moving from higher to lower CO₂ targets, since the breathing rate becomes the limiting factor when giving the lowest concentration (i.e. 0%) of CO₂ possible.

[0081] We now describe the method for determining $F_{G^1}O_2$. In order to carry out the method, we obtain values for the subject's O₂ consumption ($\dot{V}O_2$),
 10 which can be done by direct measurement (for example by collecting exhaled gas in a bag and analyzing its concentration), calculated from standard tables based on other physiological data such as weight and height, or determined from $\dot{V}CO_2$ and the Respiratory Quotient (RQ) which relates $\dot{V}O_2$ to $\dot{V}CO_2$ and is usually estimated as having a value of 0.8 in most people.

$$15 \quad \dot{V}O_2 = \frac{\dot{V}CO_2}{RQ} \quad \text{Equation (5)}$$

[0082] The method for determining $F_{G^1}O_2$ is analogous to determining $F_{G^1}CO_2$ with the exception that the sign on the $\dot{V}O_2$ is reversed in Equation (9) reflecting the fact that O₂ is consumed by the body while CO₂ is produced by the body. Thus the analogous form for Equation (9) as it pertains to O₂ is as follows:

$$20 \quad F_{G^1}O_2 = F_{TET}O_2 + \frac{\dot{V}O_2}{\dot{V}_{G^1}} \quad \text{Equation (11)}$$

[0083] It will be appreciated by those skilled in the art that Equations 9 and 11 may respectively be generalized to any gas that is physiologically produced (as is CO₂) or consumed (as is O₂) by the body. The general form of Equation 9
 25 for inducing or maintaining a target end tidal concentration of a gas X that is

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physiologically produced by the body would thus be to set the concentration of gas X in the source gas (defined as FG^1X) using

$$FG^1X = F_{TETX} - \frac{\dot{V}X}{\dot{V}G^1} \quad \text{Equation (12)}$$

where $\dot{V}X$ is the subject's minute production of gas X, F_{TETX} is the
 5 target end tidal concentration of gas X, and $\dot{V}G^1$ is the flow rate of the source gas.

[0084] The general form of Equation 11 for inducing or maintaining a target end tidal concentration of a gas X that is physiologically consumed by the body would thus be to set the concentration of gas X in the source gas (defined
 10 as FG^1X) using

$$FG^1X = F_{TETX} + \frac{\dot{V}X}{\dot{V}G^1} \quad \text{Equation (13)}$$

where $\dot{V}X$ is the subject's minute production of gas X, F_{TETX} is the target end tidal concentration of gas X, and $\dot{V}G^1$ is the flow rate of the source gas.

15 **[0085]** Optionally, it will be appreciated by those skilled in the art that the method above may be used to target particular end tidal concentrations, however, the targeting may be fine tuned, or the target may be reached more quickly, by measuring the end tidal gas concentrations and using feedback control to increase or decrease the concentrations of a particular gas so as to
 20 minimize the difference between the current end tidal concentration and the target end tidal concentration.

Selection of Source Gases

[0086] Another aspect of the present invention is the selection of gases used to carry out the method. It will be appreciated by those skilled in the art that,
 25 for a given desired total flow, any combination of concentrations of CO_2 and O_2 in

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the source gas may be achieved by mixing source gases consisting of pure O₂, CO₂ and N₂. However, pure CO₂ and pure N₂ contain no O₂ and thus if the gas blending apparatus were to fail and the subject were to inhale just a few breaths of either of these two gases, it would lead to severe hypoxemia and possibly death. One aspect of the present invention is the use of source gases each of which has at least a minimum concentration of O₂ determined to be the safe minimum level. Preferably, this level is at least 10%, but under certain controlled and monitored conditions, levels less than 10% might still be used.

10 [0087] The gas concentrations are chosen subject to the following constraints:

[0088] To achieve a high signal / noise ratio for diagnostics, a wide range of F_{ET}O₂ and F_{ET}CO₂ values is desirable.

15 [0089] Each gas may have a minimum safe concentration of oxygen, such that if it is the only gas given, the subject will not be severely harmed. This is preferably about 10%. One gas (call it gas "C") may have no more O₂ than this and a low level of CO₂ to achieve the combination of low target F_{TET}O₂ and low F_{TET}CO₂.

[0090] The minimum oxygen concentration of one gas (call it gas "A") may be set so as to achieve the maximum F_{ET}O₂ desirable to give the subject.

20 [0091] One gas (call it Gas "B") may also contain at least a high enough CO₂ concentration so as to be able to achieve the maximum F_{ET}CO₂ desired. The concentration of CO₂ in Gas B is further constrained by the fact that, to get a high F_{ET}O₂ and high F_{ET}CO₂ simultaneously, a substantial amount of Gas A (high O₂ concentration) would be given, leaving less room for Gas B in the $\dot{V}G^1$. For example, to achieve a 7.5% F_{ET}CO₂ with a 90% F_{ET}O₂, Gas A would have over a 90% concentration of O₂ and Gas B would have at least a 60% concentration of CO₂.

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[0092] The O_2 concentration of Gas "B" may be low enough to enable producing in the subject the highest desirable $F_{ET}CO_2$ and the lowest desirable $F_{ET}O_2$.

[0093] Gas "A" may have a low CO_2 concentration since it contains a high O_2 concentration, and it may be desirable to have a high $F_{ET}O_2$ and low $F_{ET}CO_2$, which cannot be achieved any other way once the constraints on gases B and C above are considered.

[0094] Therefore, based on the above constraints, the preferred method includes using gases with relative concentrations as described in Table 1:

10

Table 1: Relative concentrations of O_2 and CO_2 in Gas A, Gas B and Gas C

	FO_2	FCO_2
Gas A	High (for greater range of maximum target end tidal O_2 – preferably 100%)	Low (maximum lower bound range for end tidal CO_2 – preferably 0%)
Gas B	The Safe Minimum O_2 concentration – preferably 10%	High (for greater range of maximum target end tidal CO_2 – preferably 20%-80%)
Gas C	The Safe Minimum O_2 concentration – preferably 10%	Low (maximum lower bound range for end tidal CO_2 – preferably 0%)

Blending Source Gases to Achieve the Required Total Gas Concentrations of CO_2 and O_2

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[0095] For the present discussion, we assume that the FO_2 in Gas B and Gas C are set to achieve the lower bound of $F_{TET}O_2$, and FCO_2 in Gas A and Gas C are both set to achieve the lower bound $F_{TET}CO_2$. Hence, the greatest range of $F_{TET}O_2$ and $F_{TET}CO_2$ occurs when $F_{BO_2} = F_{CO_2}$ and $F_{ACO_2} = F_{CCO_2}$.

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Table 2 is used to defines terns used to designate the O₂ and CO₂ concentrations in Gas A, Gas B and Gas C.

Table 2: Definition of terms used to designate the O₂ and CO₂ concentrations in Gas A, Gas B and Gas C.

	Fractional concentration O ₂	Fractional concentration CO ₂
Gas A	FAO ₂	FACO ₂
Gas B	FBO ₂	FBCO ₂
Gas C	FBO ₂	FACO ₂

[0096] The method summarized by Equations 11 and 9 are used to determine fractional concentrations of CO₂ and O₂ that have to be supplied in G¹ to attain target F_{TET}CO₂ and F_{TET}O₂, assuming the subject's or subject's \dot{V} CO₂ and \dot{V} O₂ are known.

[0097] The total flow of source gas G¹ into the apparatus is the sum of the flows of the individual gases A, B and C.

$$\dot{V}G^1 = \dot{Q}_A + \dot{Q}_B + \dot{Q}_C$$

[0098] The flow of O₂ in the source gas is equal to the sum of the flows of O₂ from the individual gases. Therefore:

$$\dot{V}G^1 \times FG^1O_2 = \dot{Q}_A \times FAO_2 + \dot{Q}_B \times FBO_2 + \dot{Q}_C \times FCO_2$$

[0099] But since FCO₂ = FBO₂ this can be rewritten as

$$\dot{V}G^1 \times FG^1O_2 = \dot{Q}_A \times FAO_2 + (\dot{V}G^1 - \dot{Q}_A) \times FBO_2$$

20 which simplifies to

$$\dot{Q}_A = \frac{\dot{V}G^1 (FG^1O_2 - FBO_2)}{FAO_2 - FBO_2} \quad \text{Equation (1)}$$

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[00100] The flow of CO₂ in the source gas is equal to the sum of the flows in the individual gases. Therefore:

$$\dot{V}G^1 \times FG^1CO_2 = \dot{Q}_A \times FACO_2 + \dot{Q}_B \times FBCO_2 + \dot{Q}_C \times FcCO_2$$

5 **[00101]** But since $FACO_2 = FcCO_2$ this can be rewritten as

$$\dot{V}G^1 \times FG^1CO_2 = \dot{Q}_B \times FBCO_2 + (\dot{V}G^1 - \dot{Q}_B) \times FACO_2$$

[00102] This simplifies to

$$\dot{Q}_B = \frac{\dot{V}G^1 (FG^1CO_2 - FACO_2)}{FBCO_2 - FACO_2} \quad \text{Equation (2)}$$

10 **[00103]** Finally,

$$\dot{Q}_C = \dot{V}G^1 - \dot{Q}_A - \dot{Q}_B \quad \text{Equation (3)}$$

[00104] Equations 1, 2 and 3 can be used to calculate flows required from each mixture to obtain a total flow ($\dot{V}G^1$) with O₂ concentration of FG^1O_2 and CO₂ concentration FG^1CO_2 . It should be appreciated by those skilled in the art that other gas combinations for component gases may be used, and the derivation above may be extended to the general case of any concentration for any gas in the component gas. The same method and approach that is described for O₂ can be applied to any other gas that is absorbed, including, but not limited to acetylene, carbon monoxide, nitrous oxide, anesthetic gases. It is recognized that by defining target PCO₂ and target PO₂, target PN₂ is also defined. In the same way, the target partial pressure of any inert gas can be defined, for example, but not limited to argon, helium, and xenon.

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[00105] Another aspect of this invention is the use of the independent control of end tidal CO_2 and O_2 , N_2 or other gas levels to carry out diagnostic and therapeutic tests or carry out research in physiology. What follows are examples that are not meant to be an exhaustive list of applications for instituting

5 targeted blood gases. For example, the CO_2 levels may be rapidly transitioned from low to high targets and back repeatedly while the subject's brain blood flow is measured using the Blood Oxygen Level Dependent (BOLD) MRI imaging technique. This produces a map of cerebrovascular reactivity. BOLD and transcranial Doppler, for example can be used to measure the physiology of

10 brain and other tissue blood flow response to changes in blood concentrations of CO_2 , O_2 , with or without the presence of other gases or substances in the blood. Similarly, oculovascular reactivity may be measured by measuring blood flow in the retinal vessels with Doppler ultrasound, MRI or other devices known to those skilled in the art, at target concentrations of CO_2 , O_2 and other gases, with and

15 without the presence of other substances in the blood. Another test involves manipulating O_2 levels in tumors and measuring beneficial oxygenation levels in the tumor using BOLD MRI signal or other methods known to those skilled in the art. This would identify blood gasses providing beneficial levels of blood flow and oxygenation to tumors, sensitizing them to destruction by radiotherapy or

20 chemotherapy. This may additionally be combined with using the method during radiotherapy so as to reproduce the determined level of oxygenation. It is obvious that similar studies may be performed in any of the other responsive vascular beds in the body including but not limited to the skin, kidney, heart, lung and various abnormal congenital and acquired conditions such as tumours and

25 vascular malformations.

[00106] Being able to achieve target end tidal PO_2 and PCO_2 allows the reproducibility of test conditions. This in turn allows the comparison of tests on one subject from one time to the next and between subjects. This reproducibility of the test enables the doctor, for the first time, to follow the progress of an

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abnormality, or a response to treatment. For example, in a subject with Moyamoya disease, an area of the brain develops abnormalities in blood vessels which can be identified by abnormal response to changes in PCO_2 . Repeated standardized tests to the same target PCO_2 allows the doctor to identify changes
5 in strength of response. In cranial artery stenosis, an area of the brain may lose its vascular reactivity as seen by response to BOLD imaging with MRI in response to changes in PCO_2 . The test can be repeated after surgery to identify the extent of recovery of vascular reactivity. If there are still areas of loss of reactivity, further surgery may be indicated.

10 **[00107]** A standardized test allows the study of the normal physiology of control of blood flow to a tissue or organ that responds to CO_2 or O_2 . For example, trans cranial Doppler, BOLD MRI, spin labeling with MRI, Positron Emission Tomography or many other measurements known to those skilled in the art can be used to measure blood flow, oxygenation or metabolism of tissues
15 and organs in response to known, reproducible changes in PO_2 and PCO_2 or other gases with this method.

[00108] In summary, this invention provides the ability to provide standard, reproducible stimuli via the lung to vascular beds and other tissues. When combined with any of a long list of sensors, known to those skilled in the art, a
20 standard set of stimuli allows the comparison of results in a subject over time, between subjects in a group, of a group over time, and between groups being studied by different researchers. None of these advantages can be obtained from known methods that do not reliably provide reproducible stimuli.

Alternate Method Using Premixed Gases

25 **[00109]** Equations 9 and 11 above disclose the method for determining the fractional concentrations of CO_2 and O_2 in the source gas based on the target end tidal concentrations and the subject's rate of O_2 consumption and CO_2 production. It may be desirable for performance of certain diagnostic tests to

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assume that a particular subject population has a small range of values for CO₂ production and O₂ consumption, or to ignore the small variations that the differences in these values might make to the resulting end tidal concentrations. It would then be possible to use a plurality of gas mixtures with predetermined

5 concentrations of gas to achieve particular sets of targets. For example, assuming all subjects had a $\dot{V}O_2$ of 300 ml/min , $\dot{V}CO_2$ of 250 ml/min, and breathed at a rate of $\dot{V}_E = 10$ lpm, and given the following set of target end tidal concentrations of CO₂ O₂ , one might provide the following premixed gases each of which corresponded to one pair of targets. These gases may be provided to

10 the subject in a predetermined sequence to perform a diagnostic test, for example.

Table: Sample Premixed Gases to Achieve Desired set of Targets

Gas	F _{TET} O ₂	F _{TET} CO ₂
D (1.5% CO ₂ , 52.5% O ₂ , Bal. N ₂)	50%	4.0%
E (3.7% CO ₂ , 22.5% O ₂ , Bal. N ₂)	20%	6.2%
F (2.6% CO ₂ , 72.5% O ₂ , Bal. N ₂)	70%	5.1%

End Tidal Control Apparatus

15 **[00110]** Another aspect of the present invention is the apparatus used to carry out the method. The apparatus may include source gases chosen to provide the maximum range of combinations of targets for the end tidal gases, a gas blending device and a partial rebreathing circuit. In the preferred embodiment, the gases to be controlled are O₂ and CO₂. With reference to

20 Figure 2, three pressurized gases A, B and C (which may be referred to as component gases A, B, and C) are connected to the gas blending apparatus (1). When the method is conducted, gases A, B and C are delivered to the blender (1) at flows \dot{Q}_A , \dot{Q}_B and \dot{Q}_C that are regulated by flow controllers (6A), (6B) and (6C) via control inputs (3A), (3B) and (3C) respectively. These flow controllers

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(6a), (6B) and (6C) may be of many types known in the art, but are preferably mass flow controllers to enhance precision. The control inputs (3A), (3B) and (3C) may be provided via an operative connection between a processing unit (4) and the flow controllers (6A), (6B) and (6C). The processing unit (4) may derive
5 the appropriate control inputs (3A), (3B) and (3C) by looking up values from a database based on the target end tidal values for whatever gas or gases is/are selected to be controlled. The database values would be based on the formulas 9 and 11 discussed above. The processing unit (4) could alternatively calculate the data for the control inputs (3A), (3B) and (3C) directly based on the formulas
10 9 and 11 discussed above. The processing unit (4) may be any suitable type of processing unit, such as a computer, and may optionally include a screen and/or other output device. The processing unit (4) may be integral with other components, such as the gas blender (1), such that they are held in a common housing. Alternatively, the processing unit (4) may be a separate item that may
15 or may not be supplied with the rest of the system. For example, the processing unit (4) may be supplied by the customer.

[00111] Appropriate software 121 for use in controlling the flow controllers 6A, 6B and 6C as described above may be provided with the system. In embodiments wherein the processing unit (4) is provided as part of the system,
20 the software 121 may be provided pre-installed on the processing unit (4). In embodiments wherein the processing unit (4) is expected to be supplied by the customer, the software may accompany the system so that the customer can install the software on their own processing unit (4). Alternatively the software may be provided in some other way. For example, the software may be
25 downloadable remotely by the customer, for example, over the internet. In a situation where the software is supplied over the internet by means of permitting the customer to download the software, it is nonetheless to be considered as having been supplied as part of the system, whether or not the processing unit 4 is also included or is expected to be supplied by the customer.

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[00112] For clarity, the concept of controlling the flows of the component gases A, B and C comprises setting the flows of the gases A, B and C to achieve selectable concentrations for at least two of the constituent gases that are contained in the combined flow of the gases A, B and C. It is alternatively
5 possible to provide an apparatus with one or more gas inlets, wherein the one or more component gases connected to the one or more gas inlets already have a preselected concentration of gases in them, so that no flow control is needed on any individual component gas. For example, a single component gas could be used, which already contains a selected concentration of the gases to achieve a
10 particular desired end tidal concentrations. This may be applicable in certain diagnostic situations for example, where a subject is brought to a selected set of end tidal conditions that are consistent from subject to subject.

[00113] The concept of controlling the end tidal gas concentrations of a plurality of gases comprises selecting the end tidal gas concentrations for a
15 plurality of gases and setting the concentrations of gases in the source gas flow to achieve the selected end tidal conditions. It may be that one of the gases, for example, is selected to be maintained at constant concentration in the end tidal gas.

[00114] Flows of \dot{Q}_A , \dot{Q}_B and \dot{Q}_C are determined according to the present
20 method for target $FETCO_2$ and $FETO_2$ at each phase in the sequence. The blend of \dot{Q}_A , \dot{Q}_B and \dot{Q}_C results in $\dot{V}G^1$. The resulting mixture, G^1 , leaves the blender (1) via an output hose (7) and is delivered to the gas inlet (8) of the partial rebreathing circuit (9). In the preferred embodiment shown, the partial rebreathing circuit is a sequential gas delivery circuit. During inhalation,
25 inspiratory one-way valve (10) opens and the first part of the breath comes from the gas inlet (8) and G^1 reservoir (11). If \dot{V}_E exceeds $\dot{V}G^1$, the G^1 reservoir (11) collapses during the breath and the balance of the breath comes from the exhaled gas G^2 reservoir (12) via the crossover valve (13) or in the case of a

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non-rebreathing SGD from stored exogenous gas that approximates exhaled gas.

[00115] During exhalation, expiratory one-way valve (14) opens and expired gases are either collected in the exhaled gas reservoir (12), or in the case of a non-rebreathing SGD, they are vented. Meanwhile, G^1 collects in the G^1 source gas reservoir (11). Optional pressure sampling line (15) and pressure transducer (17) can be inserted at the subject-circuit interface to aid in synchronization of changes in gas flows with the breath. Optionally, gas may be sampled via line (16) connected to an optional CO_2/O_2 analyzer (18). Peak detection algorithm can use signals from pressure transducer (17) or gas analyzer to detect breaths and pick end-tidal values for O_2 and CO_2 . Data can be analyzed on- or off-line and displayed on a computer screen that is optionally part of the processing unit (4).

[00116] Optionally, if it is desired to give the subject air during a stand by phase, three-way solenoid valve (2) is electronically controlled by connection (3S) from machine intelligence (4) and is either open to air source (5) or to the manifold (82) collecting gas from gas sources A, B and C. When the apparatus is in the standby mode, the subject receives air flow which is regulated by flow controller (6) via control input (84).

20 **Alternate Embodiment**

[00117] If it is desired to "hardwire" a particular sequence of target end tidal concentrations, premixed gases with concentrations to achieve the desired targets can be used with an alternative apparatus described in Figure 3. For any given pattern of transitions and steady states, individual concentrations of O_2 and CO_2 in the G^1 gas measured among different subjects will depend on subject's $\dot{V}O_2$ and $\dot{V}CO_2$. In order to accommodate for these differences, apparatus described in Figure 3 allows precise control of $\dot{V}G^1$ according to the subject's $\dot{V}O_2$ and $\dot{V}CO_2$ or estimate thereof.

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[00118] With reference to Figure 3 a set of premixed gases (5 are shown, but one is needed for each set of target end tidal concentrations) D, E, F, G and H containing premixed mixtures of O₂, CO₂ and N₂ equal to those required in the G¹ gas during each phase of the sequence, are connected to gas blender (1).
5 Two-way solenoid valves (25D, 25E, 25F, 25G, 25H) control the flow of gases D, E, F, G and H. The two-way solenoid valves (25) are controlled by machine intelligence (4), which contains pre-programmed information about the order and duration of opening of each individual valve. Gas flow to the circuit (9) is regulated by a flow controller (26). Optional three-way solenoid valve (23) is
10 electronically controlled via machine intelligence (4) and may be open to optional air source (5) during an optional stand by phase or to the gases coming through solenoids (25). The rest of the apparatus may be the same as in Figure 2 .

[00119] Figures 4-6 show experimental data obtained from a subject whose end tidal values were controlled and set to target levels.

15 **[00120]** The term "selecting" in reference to "selecting" the rate of flow of the source gas does not necessarily imply that the apparatus is of a character where the rate must be adjustable. Strictly speaking the implication is that an operator need only prepare for use an apparatus with a rate of flow suitable to the task at hand, particularly where only a single rate of flow is acceptable.
20 Nevertheless, it will be appreciated that an adjustable rate of flow adds considerable flexibility to the way the apparatus can be used. For example, where a rapid change of one or more end tidal target gas concentrations is sought to be effected, setting the flow rate to be faster, with rapid breathing expected of the subject, permits more rapid alveolar gas exchange.

25 **[00121]** The term "source gas" is understood to mean the gas ultimately flowing to and inhaled by the subject. This gas may be made up of one or more "component gases", namely individual gases comprising one or more "constituent gases". Constituent gases are invariably understood to mean substantially "pure" gases in terms of their molecular make up eg. 100% O₂. Where a component gas

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comprises more than one constituent gas, this component gas is frequently referred to herein as a "mixed" or "blended" gas. However, in a particular context, a reference to a blended or mixed gas could possibly also be understood to refer to the source gas itself.

- 5 **[00122]** It will be understood that selecting the concentration of the at least one constituent gas of the at least one component gas may simply be accomplished by selecting the correct single component of a single component source gas.

- [00123]** While the above description describes preferred embodiments, it
10 will be appreciated that these embodiments are susceptible to modification and change without departing from the scope of the invention and the fair meaning of the accompanying claims.

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WE CLAIM:

1. A method of preparing an apparatus for inducing or maintaining a target end tidal concentration of a gas X in a subject comprising:
 - 5 a) selecting a rate of a source gas flow into a breathing circuit, the rate projected to be not substantially more than the minute ventilation of the subject;
 - b) selecting the concentration of an at least one constituent gas of an at least one component gas making up the source gas, to a level corresponding to the
 - 10 target end tidal concentration of gas X, whereby said apparatus is adapted to administer a source gas having a first gas composition.
2. A method according to claim 1, wherein the at least one component gas comprises a single constituent gas.
- 15 3. A method according to claim 1 or 2, wherein the source gas comprises a single component gas.
4. A method according to claim 3, wherein the at least one constituent gas is gas X, and wherein the concentration of gas X is selected to be at a predetermined level corresponding to the target end tidal concentration of gas X.
 - 20 X.
5. A method according to claim 4, wherein said gas X is a gas produced by the patient, and the concentration of said gas X (FG^1X) is set according to

$$FG^1X = F_{TETX} - \frac{\dot{V}X}{\dot{V}G^1},$$
 where $\dot{V}X$ is the patient's minute production of gas X,
 - 25 F_{TETX} is the target end tidal concentration of gas X, and $\dot{V}G^1$ is the flow rate of the source gas.
6. A method according to claim 4, wherein said gas X is a gas consumed by the patient, and the concentration of said gas X (FG^1X) is set according to

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$FG^1X = F_{TETX} + \frac{\dot{V}X}{\dot{V}G^1}$, where $\dot{V}X$ is the patient's minute consumption of gas

X, F_{TETX} is the target end tidal concentration of gas X and $\dot{V}G^1$ is the flow rate of the source gas.

7. A method according to claim 1, wherein the apparatus is fluidly connected to
5 a source of each of one or more component gases.
8. A method according to claim 7, further comprising the step of allowing a subject to inhale the source gas from the prepared apparatus, for a time period at least sufficient to attain the target end tidal concentration of gas X.
9. A method according to claim 8, wherein said at least sufficient time period is
10 no greater than 30 seconds of at a rate corresponding to a minute ventilation which is equal to or greater than the rate of flow of the source gas.
10. A method according to claim 9, wherein said at least sufficient time period is no greater than the duration of a single breadth and wherein the rate of flow of the source gas is between 5 and 20 litres per minute.
- 15 11. A method according to claim 8, further comprising the step of selecting a different concentration of at least one constituent gas in said source gas, the concentration of said at least one constituent gas selected to be at a predetermined level corresponding to a second different target end tidal concentration of gas X, whereby said apparatus is adapted to administer a
20 source gas having a second gas composition.
12. A method according to claim 11, further comprising the step of allowing a subject to inhale said source gas having said second composition from a correspondingly prepared apparatus for a time period at least sufficient to attain the second target end tidal concentration of gas X.
- 25 13. A method according to claim 12, further comprising the steps of measuring a physiological variable in a subject at a least one time point corresponding to a duration of retention of each of said first and second end tidal concentrations of gas X.

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14. A method according to claim 13, wherein said physiological variable is CVR as measured by MRI.
15. An apparatus for inducing or maintaining a target end tidal gas concentration of a gas X in a subject when prepared according to claim 1, said apparatus comprising a source gas outlet and at least one component gas inlet.
16. An apparatus for inducing or maintaining a target end tidal gas concentration of a gas X in a subject when prepared according to claim 1, said apparatus comprising a source gas outlet, a plurality of component gas inlets and a controller adapted to select the rate of flow of at least one component gas into a source gas conduit.
17. A method of inducing a target end tidal concentration of a gas X in a patient comprising:
- a) setting the source gas flow into a partial rebreathing circuit at a rate equal to or less than the patient's minute ventilation
 - b) setting the concentration of said gas X in the source gas to a predetermined level corresponding to the target end tidal concentration of gas X
 - c) delivering the source gas to the patient through said circuit
18. The method of claim 17 wherein said gas X is a gas produced by the patient, and the concentration of said gas X (FG^1X) is set according to
- $$FG^1X = F_{TETX} - \frac{\dot{V}X}{\dot{V}G^1}, \text{ where } \dot{V}X \text{ is the patient's minute production of gas X,}$$
- F_{TETX} is the target end tidal concentration of gas X, and $\dot{V}G^1$ is the flow rate of the source gas.
19. The method of claim 17 wherein said gas X is a gas consumed by the patient, and the concentration of said gas X (FG^1X) is set according to
- $$FG^1X = F_{TETX} + \frac{\dot{V}X}{\dot{V}G^1}, \text{ where } \dot{V}X \text{ is the patient's minute consumption of gas}$$

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X, F_{TETX} is the target end tidal concentration of gas X and $\dot{V}G^1$ is the flow rate of the source gas.

20. A method of simultaneously inducing target end tidal concentrations of a plurality of gases in patient, where said target end tidal concentrations are independent of each other, comprising:
- a) setting the source gas flow into a partial rebreathing circuit at a rate equal to or less than the patient's minute ventilation
 - b) setting the concentration of each gas in the source gas to attain the target end tidal concentration of that gas
 - c) delivering the source gas to the patient through said circuit

21. The method of claim 20 wherein at least one of the gases X whose end tidal concentration is being induced, is a gas produced by the patient, and the concentration of said gas X in the source gas is set according to

$FG^1X = F_{TETX} - \frac{\dot{V}X}{\dot{V}G^1}$, where $\dot{V}X$ is the patient's minute production of gas X, F_{TETX} is the target end tidal concentration of gas X and G^1 is the flow rate of the source gas.

22. The method of claim 20 wherein at least one of the gases X whose end tidal concentration is being induced, is a gas consumed by the patient, and the concentration said gas X is set according to $FG^1X = F_{TETX} + \frac{\dot{V}X}{\dot{V}G^1}$, where $\dot{V}X$ is the patient's minute consumption of gas X, F_{TETX} is the target end tidal concentration of gas X, and $\dot{V}G^1$ is the flow rate of the source gas.

23. A method of changing an end tidal concentration of a gas X in a patient comprising:

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- a) setting the source gas flow into a partial rebreathing circuit at a rate equal to or less than the patient's minute ventilation
 - b) providing a first concentration of said gas X in the source gas and delivering the source gas to the patient through said circuit in order to effect a first end tidal concentration of said gas X
 - c) providing a second concentration of said gas X in the source gas and delivering the source gas to the patient through said circuit in order to effect a second end tidal concentration of said gas X
- 10 24. A method of changing between target end tidal concentrations of a first gas X in a patient comprising inducing the first target end tidal concentration using any of the methods of Claim 17- 23, then inducing the second target end tidal concentration using any of the methods of Claim 17- 23.
- 15 25. The method of Claim 24 further comprising keeping end tidal concentration of a second gas Y at a fixed target level using any of the methods of Claim 17- 23.
- 20 26. The method of simultaneously changing between target end tidal concentrations of two or more gases in a patient comprising inducing the first target end tidal gas concentrations using any of methods of claims 17- 23, then inducing the second target end tidal gas concentrations using any of methods of claims 17- 23.
- 25 27. The methods of Claims 17- 26 where, for each set of target end tidal gas concentrations, the gas flow into the breathing circuit is comprised of a premixed gas
28. The methods of Claims 17- 26 where, for each set of target end tidal gas concentrations, the gas flow into the breathing circuit is comprised of a blend

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of at least two component gases, said component gases being blended to achieve the desired concentrations in the source gas flow of the gases whose end tidal concentrations are being targeted.

29. The method of Claims 27 or 28 where each of the component gases has a
5 minimum safe concentration of O₂ .
30. The method of Claims 27 or 28 where the source gas flow into the breathing circuit has a minimum safe concentration of O₂ .
31. The method of Claims 29 or 30 where the minimum safe level of O₂ concentration is 10%.
- 10 32. The method of Claims 29 or 30 where the minimum safe level of O₂ concentration is 10%.
33. The method of Claims 29 - 32 using 3 component gases.
34. The method of any of claims 17- 33 wherein the partial rebreathing circuit is a sequential gas delivery circuit.
- 15 35. The method of any of claims 17- 33 wherein the gas whose end tidal concentration target is being induced is O₂ .
36. The method of any of claims 17- 33 wherein the gas whose end tidal concentration target is being induced is CO₂ .
37. The method of Claim 33 where the component gases have the following
20 relative concentrations:
- a) Gas A: High O₂ , Low CO₂
 - b) Gas B: Low O₂ , High CO₂
 - c) Gas C: Low O₂ , Low CO₂
38. The method of Claim 16 where the source gases have the following
25 concentrations:
- a) Gas A: 50-100% O₂ , 0-20% CO₂
 - b) Gas B: 10-30% O₂ , 20-80% CO₂
 - c) Gas C: 10-30% O₂ , 0-20% CO₂

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39. The method of Claim 16 where the source gases have the following concentrations:

- a) Gas A: 100% O₂ , 0% CO₂
- b) Gas B: 10% O₂ , 20-80% CO₂
- 5 c) Gas C: 10% O₂ , 0% CO₂

40. The method of Claim 16 where the source gases have the following concentrations:

- a) Gas A: 100% O₂ , 0% CO₂
- b) Gas B: 10% O₂ , 20-40% CO₂
- 10 c) Gas C: 10% O₂ , 0% CO₂

41. The method of Claim 16 where the source gases have the following concentrations:

- a) Gas A: 100% O₂ , 0% CO₂
- b) Gas B: 10% O₂ , 40% CO₂
- 15 c) Gas C: 10% O₂ , 0% CO₂

42. The method of Claim 16 where the source gases have the following concentrations:

- a) Gas A: 100% O₂ , 0% CO₂
- b) Gas B: 10% O₂ , 20% CO₂
- 20 c) Gas C: 10% O₂ , 0% CO₂

43. A diagnostic method comprising any method according to claims 17 to 42.

44. A method to measure cerebrovascular reactivity comprising:

- a) controlling the end tidal CO₂ and O₂ levels of a subject using the methods of claims 36 or 37.
- 25 b) monitoring a blood oxygen level dependent (BOLD) MRI signal intensity

45. The method of Claim 44 where the end tidal CO₂ and O₂ levels are controlled independently of each other.

46. The method of Claim 44 or 45 where the end tidal CO₂ levels are changed while the end tidal O₂ levels are kept constant.

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47. The method of Claim 44 or 45 where the end tidal PO_2 levels are changed while the end tidal PCO_2 levels are kept constant
48. The method of Claim 44 or 45 where the end tidal PO_2 levels and the end tidal PCO_2 levels are changed simultaneously
- 5 49. A method to measure oculovascular reactivity comprising:
- a) controlling the end tidal CO_2 and O_2 levels of a subject using the methods of claims 36 or 37.
 - b) monitoring oculovascular blood flow
50. The method of Claim 49 where the end tidal CO_2 and O_2 levels are controlled
- 10 independently of each other.
51. The method of Claim 49 or 50 where the end tidal CO_2 levels are changed while the end tidal O_2 levels are kept constant.
52. The method of Claim 49 or 50 where the end tidal PO_2 levels are changed while the end tidal PCO_2 levels are kept constant
- 15 53. The method of Claim 49 or 50 where the end tidal PO_2 levels and the end tidal PCO_2 levels are changed simultaneously.
54. A method to standardize measurement of oculovascular reactivity.
55. A method to measure a beneficial level of oxygenation to tissues for the purpose of radiotherapy or chemotherapy, comprising:
- 20 a) controlling the end tidal CO_2 and O_2 levels of a subject using the methods of claims 36 or 37.
- b) monitoring oxygenation or blood flow in the tumor
56. The method of Claim 55 where the end tidal CO_2 and O_2 levels are controlled independently of each other.
- 25 57. The method of Claim 55 or 56 where the end tidal CO_2 levels are changed while the end tidal O_2 levels are kept constant.
58. The method of Claim 55 or 56 where the end tidal PO_2 levels are changed while the end tidal PCO_2 levels are kept constant

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59. The method of Claim 55 or 56 where the end tidal PO_2 levels and the end tidal PCO_2 levels are changed simultaneously
60. A therapeutic method comprising any method according to claims 17 to 42.
61. A therapeutic method comprising:
- 5 a) using any of the methods of claims 55 to 60 to determine end tidal O_2 and CO_2 levels that provide a beneficial oxygenation or blood flow level to tissues for the purpose of radiotherapy or chemotherapy
- b) using any of the methods of claims 17 to 42 to set the end tidal O_2 and CO_2 levels to said levels during radiotherapy or chemotherapy
- 10 62. An apparatus for inducing target end tidal gas concentrations in a patient simultaneously, and independently of each other comprising:
- a) a partial rebreathing circuit
- b) a source gas flow into said breathing circuit
- c) means for controlling the rate of said source gas flow into the circuit
- 15 d) means for controlling the concentration of said gases in the source gas flow independently of each other
63. The apparatus of Claim 62 further comprising means for monitoring end tidal CO_2 and O_2 concentrations
64. The apparatus of Claim 62 further comprising means for monitoring pressure
- 20 in the breathing circuit
65. The apparatus of Claim 62 where the breathing circuit is a sequential gas delivery circuit.
66. The apparatus of Claims 62 to 65 where, for each set of target end tidal gas concentrations, the gas flow into the breathing circuit is comprised of a
- 25 premixed gas
67. The apparatus of Claims 62 to 65 where, for each set of target end tidal gas concentrations, the gas flow into the breathing circuit is comprised of a blend of at least three component gases, said component gases being blended to

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achieve the desired concentrations in the source gas flow of the gases whose end tidal concentrations are being targeted.

68. The apparatus of Claims 62 to 67 with 3 component gases.

69. The apparatus of Claim 68 where the at least three component gases have

5 the following relative concentrations:

- a) Gas A: High O₂ , Low CO₂
- b) Gas B: Low O₂ , High CO₂
- c) Gas C: Low O₂ , Low CO₂

70. The apparatus of Claim 69 where the at least three component gases have

10 the following concentrations:

- a) Gas A: 50-100% O₂ , 0-20% CO₂
- b) Gas B: 10-30% O₂ , 20-80% CO₂
- c) Gas C: 10-30% O₂ , 0-20% CO₂

71. The apparatus of Claim 69 where the at least component gases have the

15 following concentrations:

- a) Gas A: 100% O₂ , 0% CO₂
- b) Gas B: 10% O₂ , 20-80% CO₂
- c) Gas C: 10% O₂ , 0% CO₂

72. The apparatus of Claim 69 where the at least three component gases have

20 the following concentrations:

- a) Gas A: 100% O₂ , 0% CO₂
- b) Gas B: 10% O₂ , 20-40% CO₂
- c) Gas C: 10% O₂ , 0% CO₂

73. The apparatus of Claim 69 where the at least three component gases have

25 the following concentrations:

- a) Gas A: 100% O₂ , 0% CO₂
- b) Gas B: 10% O₂ , 40% CO₂
- c) Gas C: 10% O₂ , 0% CO₂

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74. The apparatus of Claim 69 where the at least three component gases in the source gas have the following concentrations:

- a) Gas A: 100% O₂ , 0% CO₂
- b) Gas B: 10% O₂ , 20% CO₂
- 5 c) Gas C: 10% O₂ , 0% CO₂

75. The method of claims 17 to 61 further comprising the steps of:

- a) monitoring the end tidal gas concentration of the patient for a particular gas
- b) increasing or decreasing the concentration of said gas so as to decrease
10 the difference between the patient's end tidal concentration of said gas and the target end tidal concentration of said gas.

76. A method according to claim 1, 2 or 3, wherein the at least one component gas is a blended gas.

77. A method according to claim 1, 2 or 3 wherein the concentration of the at least
15 one constituent gas is selected to be at a predetermined level corresponding to the target end tidal concentration of gas X.

78. A method of preparing an apparatus for the use of independently controlling the end tidal concentration of each constituent gas in the expired gas of a subject, comprising:

- 20 a) selecting a rate of a source gas flow into a breathing circuit, the rate projected to be not substantially more than the minute ventilation of the subject;
- b) selecting the composition of said source gas by selecting the concentration of a constituent gas X in the source gas based on a selected end tidal
25 concentration of the constituent gas X, whereby said apparatus is adapted to administer a source gas having a first gas composition.

79. A method according to claim 78, wherein step b) includes mathematical computation of the selected concentration of the constituent gas X based on the selected end tidal concentration of the constituent gas X.

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80. A method according to claim 78, wherein the source gas is made up of a plurality of component gases, each component gas containing at least one constituent gas.

5 81. A method according to claim 80, wherein each component gas is a blended gas.

82. A method according to claim 78, wherein said gas X is a gas produced by the subject, and the concentration of said gas X (FG^1X) is computed according to

$$FG^1X = F_{TETX} - \frac{\dot{V}X}{\dot{V}G^1}, \text{ where } \dot{V}X \text{ is the subject's minute production of gas X,}$$

10 F_{TETX} is the selected end tidal concentration of gas X, and $\dot{V}G^1$ is the flow rate of the source gas.

83. A method according to claim 78, wherein said gas X is a gas consumed by the subject, and the concentration of said gas X (FG^1X) is computed

$$\text{according to } FG^1X = F_{TETX} + \frac{\dot{V}X}{\dot{V}G^1}, \text{ where } \dot{V}X \text{ is the subject's minute}$$

15 consumption of gas X, F_{TETX} is the selected end tidal concentration of gas X and $\dot{V}G^1$ is the flow rate of the source gas.

84. A method according to claim 78, wherein the apparatus is fluidly connected to a source of each component gas.

20 85. A method according to claim 84, further comprising the step of allowing a subject to inhale the source gas from the prepared apparatus, for a time period at least sufficient to attain the target end tidal concentration of gas X.

86. A method according to claim 85, wherein said at least sufficient time period is no greater than 30 seconds at a rate corresponding to a minute ventilation which is equal to or greater than the rate of flow of the source gas.

25 87. A method according to claim 86, wherein the rate of flow of the source gas is between 10 and 15 liters per minute .

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88. A method according to claim 85, further comprising the step of selecting a different concentration of the constituent gas X in said source gas, the different concentration of said constituent gas X selected based on a second different selected end tidal concentration of the constituent gas X, whereby
5 said apparatus is adapted to administer a source gas having a second gas composition.
89. A method according to claim 88, further comprising the step of allowing a subject to inhale said source gas having said second composition for a time period at least sufficient to attain the second target end tidal concentration of
10 gas X.
90. A method according to claim 89, further comprising the step of measuring a physiological variable in a subject for at a least one time point within at least one time period in which the subject is exhaling a gas having said first end tidal concentration of gas X and for at a least one time point within at least
15 one time period in which the subject is exhaling a gas having said second end tidal concentration of gas X.
91. A method according to claim 90, wherein said physiological variable is cerebral blood flow.
92. An apparatus for independently controlling the end tidal concentration of each
20 constituent gas in the expired gas of a subject, when prepared for use according to claim 1, said apparatus comprising a source gas outlet and at least one component gas inlet.
93. An apparatus for independently controlling the end tidal concentration of each constituent gas in the expired gas of a subject when prepared for use
25 according to claim 1, said apparatus comprising a source gas outlet, a plurality of component gas inlets and a controller adapted to select the rate of flow of at least one component gas into a source gas conduit.
94. A system for independently controlling the end tidal concentration of each constituent gas in the expired gas of a subject, the system comprising a

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source gas outlet, a plurality of component gas inlets, a flow controller for each component gas, an input device for inputting a selected end tidal concentration of a constituent gas X in the source gas, a processor unit programmable to derive the concentration of said constituent gas X in the source gas based on the end tidal concentration of the constituent gas X in the expired gas, said processor unit operatively connected to each flow controller for setting the respective gas flow rate of said flow controller in order to achieve the derived concentration of said constituent gas X in the source gas.

95. A system according to claim 94, wherein the selected concentration of the constituent gas X in the source gas is mathematically computed based on the selected end tidal concentration of the constituent gas X in the expired gas.

96. A system according to claim 94, wherein the source gas is made up of at least three component gases.

97. A system according to claim 96, wherein each component gas is a blended gas.

98. A system according to claim 95, wherein said gas X is a gas produced by the subject, and the concentration of said gas X ($FG^I X$) is computed according to $FG^I X = F_{TETX} - \frac{\dot{V}X}{\dot{V}G^I}$, where $\dot{V}X$ is the subject's minute production of gas X, F_{TETX} is the selected end tidal concentration of gas X, and $\dot{V}G^I$ is the flow rate of the source gas.

99. A system according to claim 94, wherein said gas X is a gas consumed by the subject, and the concentration of said gas X ($FG^I X$) is computed according to $FG^I X = F_{TETX} + \frac{\dot{V}X}{\dot{V}G^I}$, where $\dot{V}X$ is the subject's minute consumption of gas X, F_{TETX} is the selected end tidal concentration of gas X and $\dot{V}G^I$ is the flow rate of the source gas.

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100. A system according to claim 95, wherein each component gas inlet is fluidly connected to a blended gas source comprising at least 10% O₂.
101. A system according to claim 95, wherein the source gas outlet is fluidly connected to a sequential gas delivery circuit.
- 5 102. A system according to claim 95, wherein the source gas outlet is fluidly connected to a partial rebreathing circuit.
103. A method of developing a system for independently controlling the end tidal concentration of each constituent gas in the expired gas of a subject, comprising the steps of :
- 10 a) making available for aquisition an apparatus having at least a source gas outlet, a plurality of component gas inlets, and a flow controller for each component gas;
- b) facilitating implementation of machine readable instructions to drive a processor unit programmable to derive the concentration of said
- 15 constituent gas X in the source gas based on the end tidal concentration of the constituent gas X in the expired gas, said processor unit adapted to be operatively connected to each flow controller for setting the respective gas flow rate of said flow controller in order to achieve the derived concentration of said constituent gas X in the source gas.
- 20 104. A method according to claim 103, wherein said apparatus said processor unit is included within a housing comprising said apparatus.
105. A method according to claim 103, wherein step b) includes carrying out one or more steps selected from:
- 25 a. developing of said machine readable instructions;
- b. out-sourcing development of said machine readable instructions;
- c. making said machine readable instructions available for acquisition;

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- a. providing instructions for acquisition of said machine readable instructions;
 - b. providing instructions for use of said machine readable instructions;
 - c. providing instructions for development of said machine readable instructions;
 - d. providing instructions for acquisition of a processor unit programmed with said machine readable instructions; and
 - 10 e. providing instructions for working, updating, upgrading, trouble-shooting, substitution, repair or re-acquisition, of said machine readable instructions or such processor unit.

15 106. The apparatus of Claim 68, wherein the at least three component gases have constituent gases with compositions in the following composition ranges:

- i) GAS A – 85-100% oxygen
- ii) Gas B – 85-100% carbon dioxide
- iii) Gas C - 85-100% nitrogen

20 107. An apparatus for inducing target end tidal gas concentrations in a patient simultaneously, and independently of each other comprising a partial rebreathing circuit, a source gas flow into said breathing circuit, means for controlling the rate of said source gas flow into the circuit and means for controlling the concentration of constituent gases in the source gas flow independently of each other.

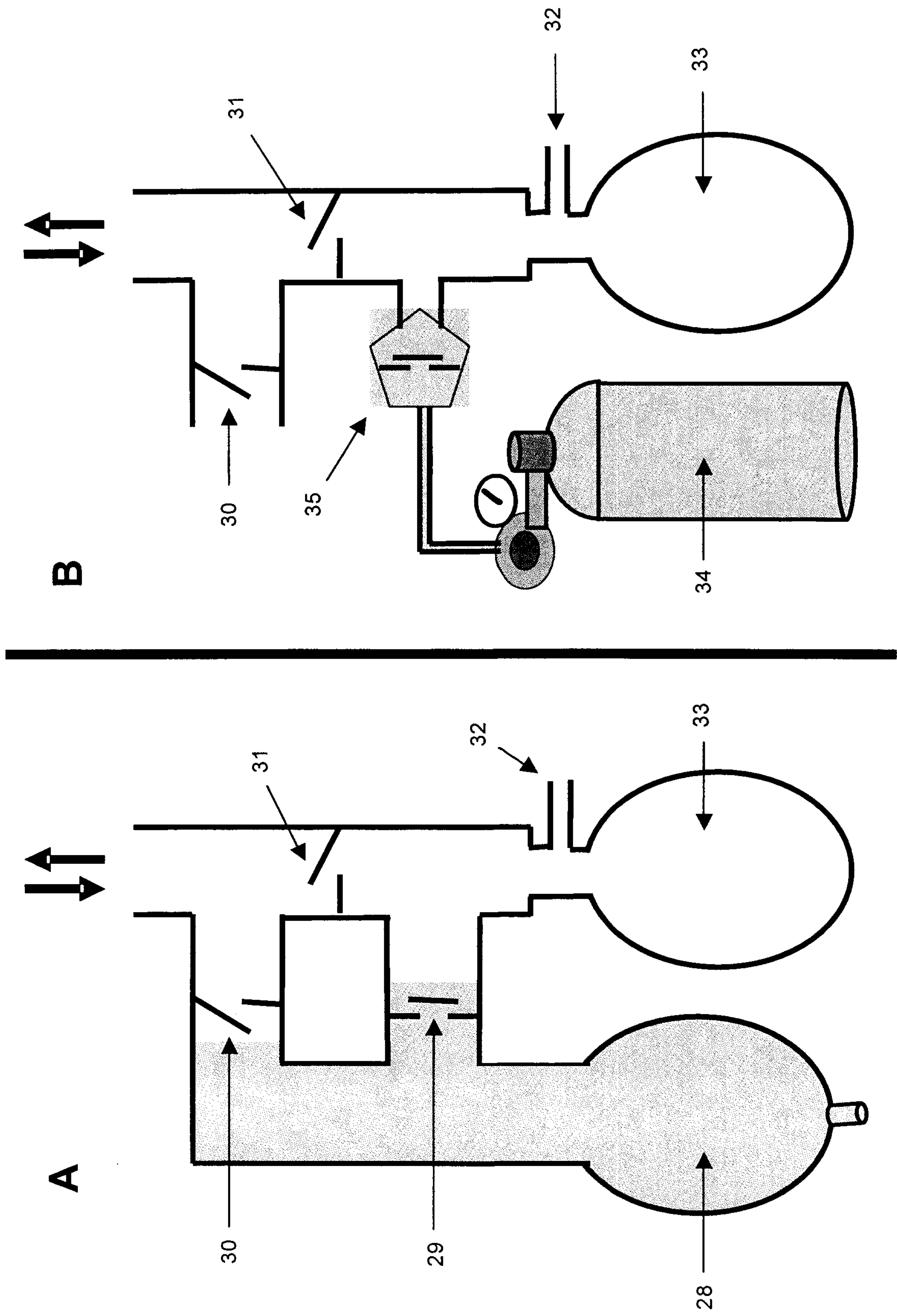
25 108. An apparatus according to claim 107, wherein the source gas flow is made up of at least three component gases.

109. An apparatus according to claim 107 or 108, wherein a flow controller is provided for each component gas in the source gas flow.

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110. An apparatus according to claim 109, wherein the flow controllers provided for each component gas in the source gas flow constitute the means for controlling the rate of source gas flow into the circuit.

Figure 1



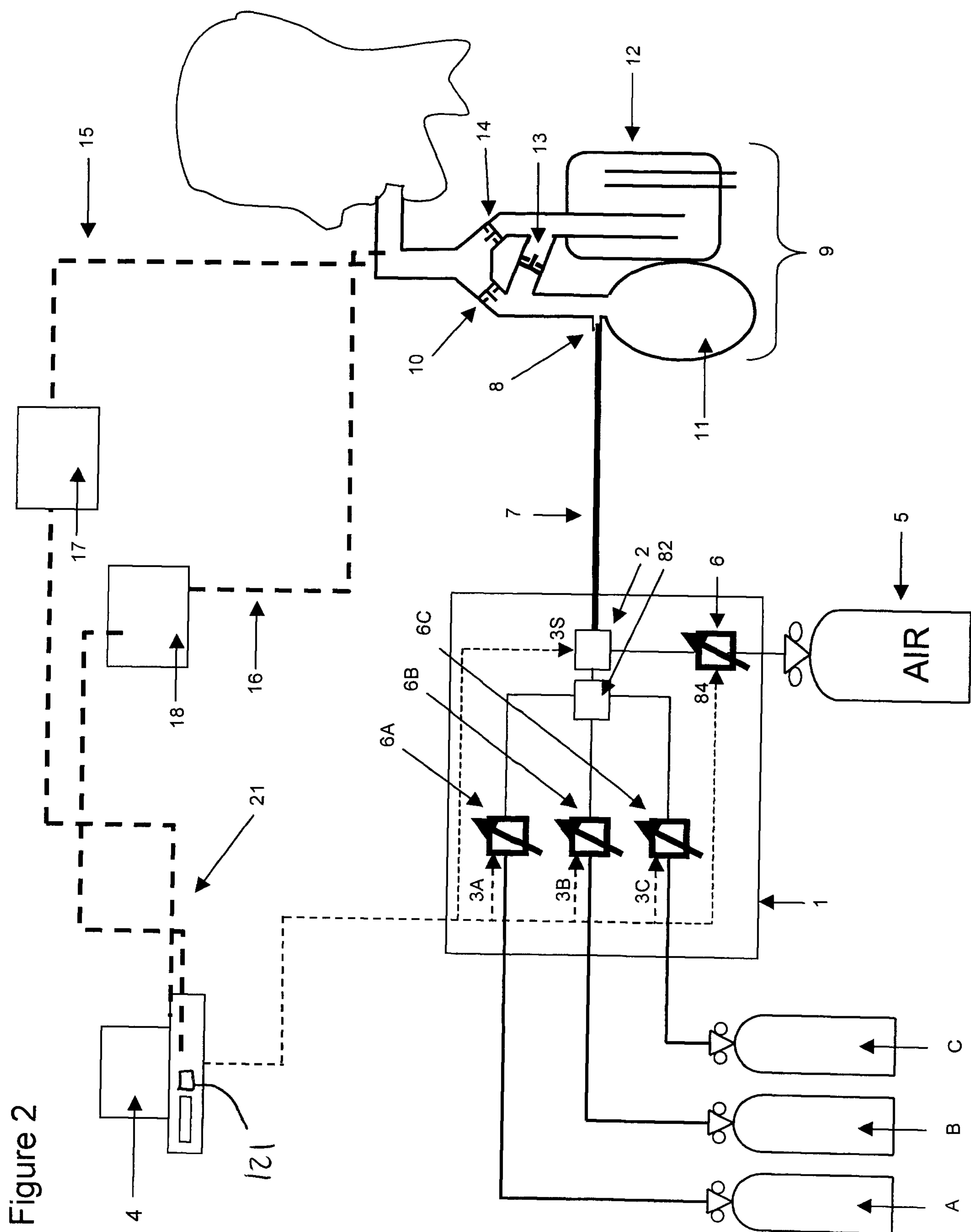


Figure 3

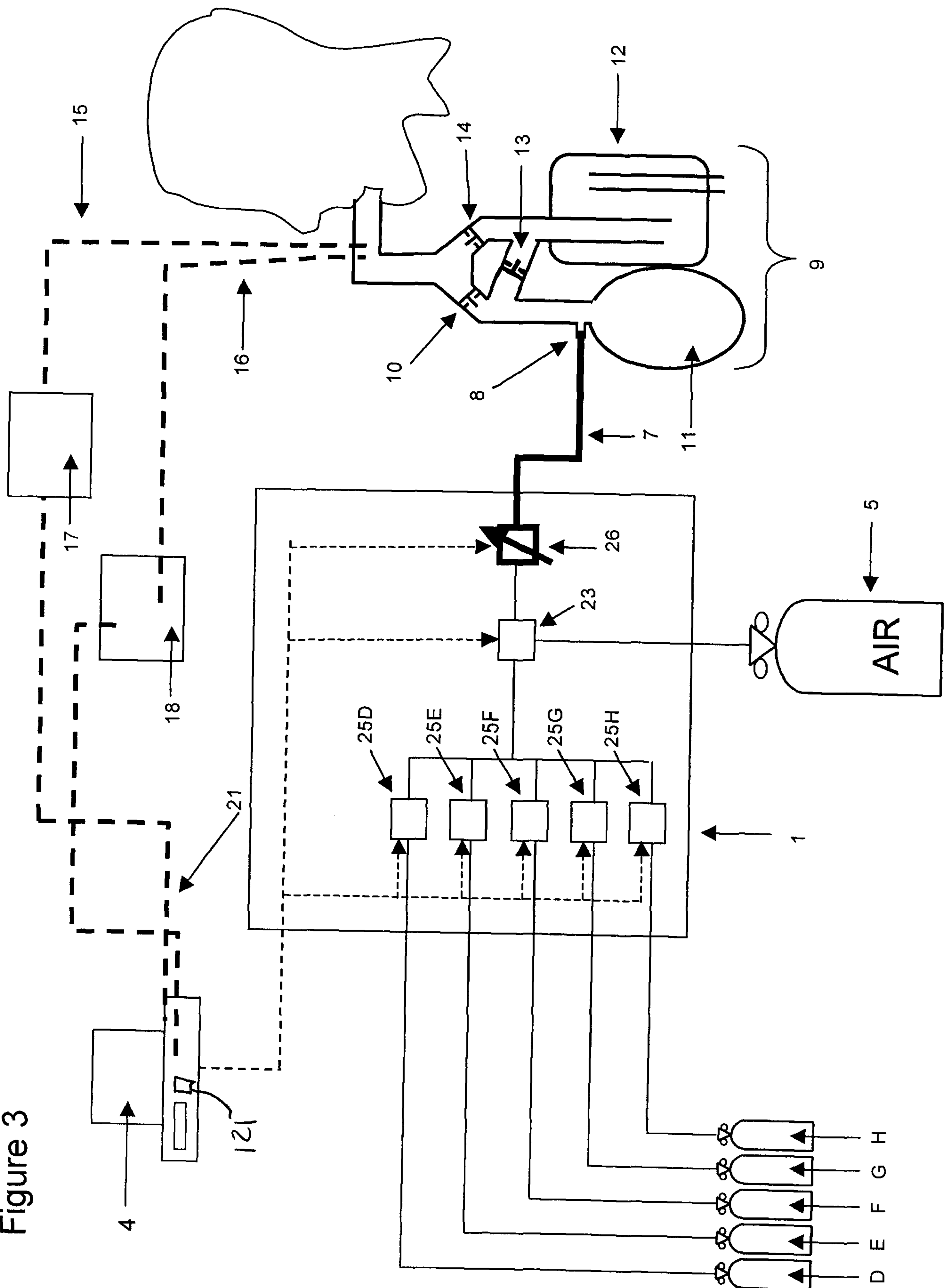


Figure 4

CO₂ steps at normoxia

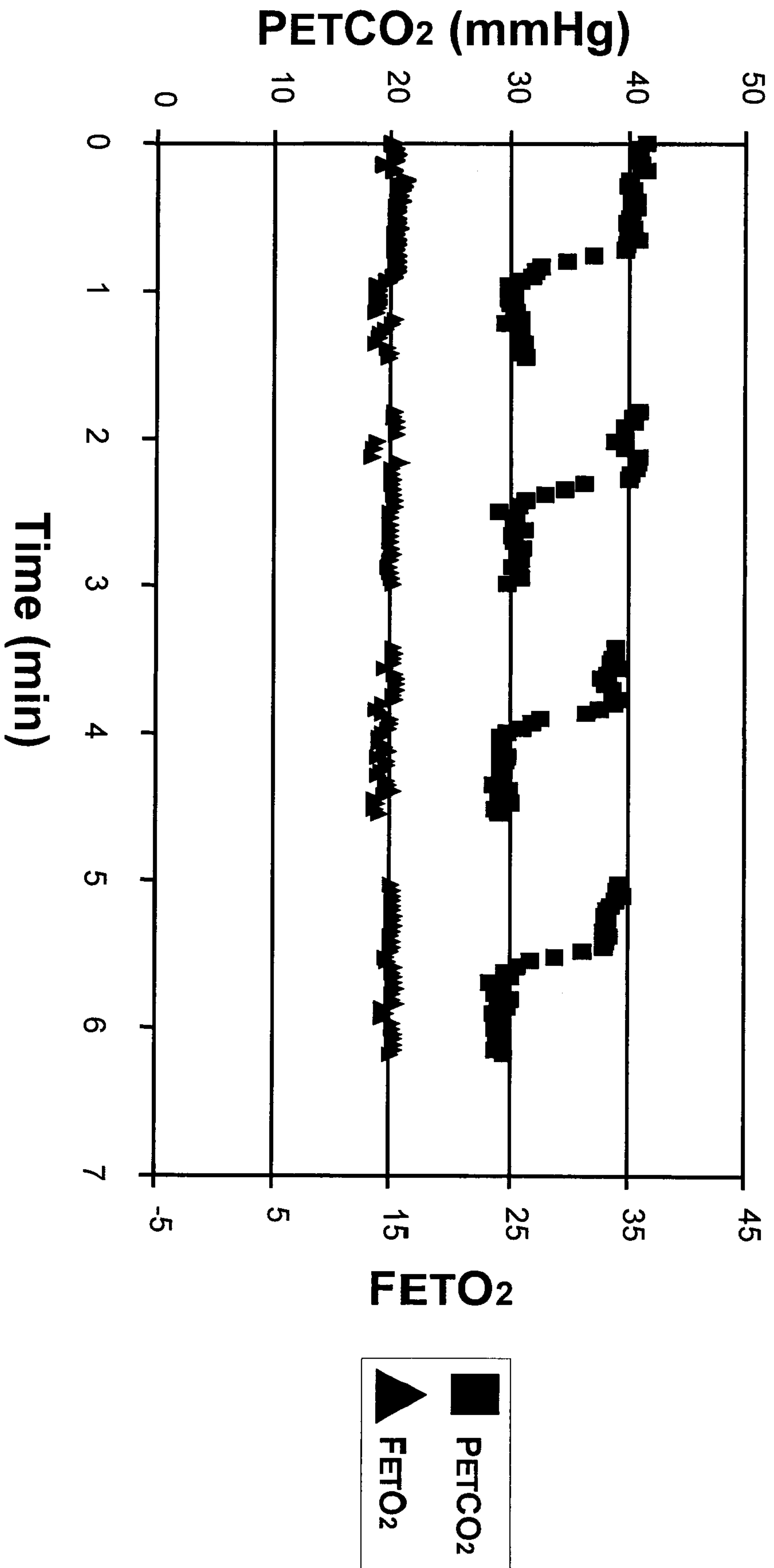


Figure 5

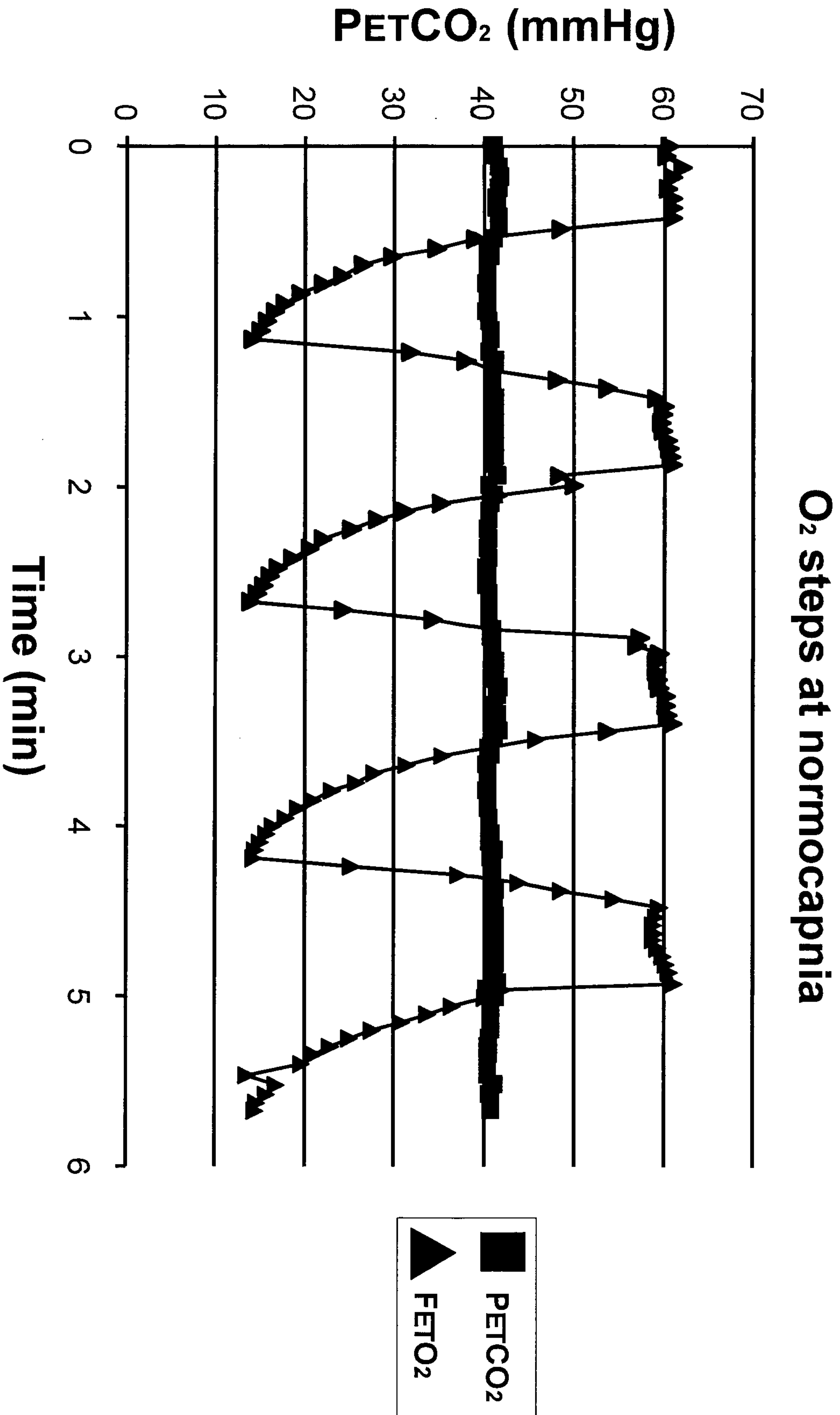


Figure 6

