



Office de la Propriété

Intellectuelle  
du Canada

Un organisme  
d'Industrie Canada

Canadian  
Intellectual Property  
Office

An agency of  
Industry Canada

CA 2616883 A1 2007/02/01

(21) **2 616 883**

**(12) DEMANDE DE BREVET CANADIEN  
CANADIAN PATENT APPLICATION**

**(13) A1**

(86) Date de dépôt PCT/PCT Filing Date: 2006/07/28  
(87) Date publication PCT/PCT Publication Date: 2007/02/01  
(85) Entrée phase nationale/National Entry: 2008/01/28  
(86) N° demande PCT/PCT Application No.: CA 2006/001258  
(87) N° publication PCT/PCT Publication No.: 2007/012197  
(30) Priorité/Priority: 2005/07/28 (CAPCTCA2005001166)

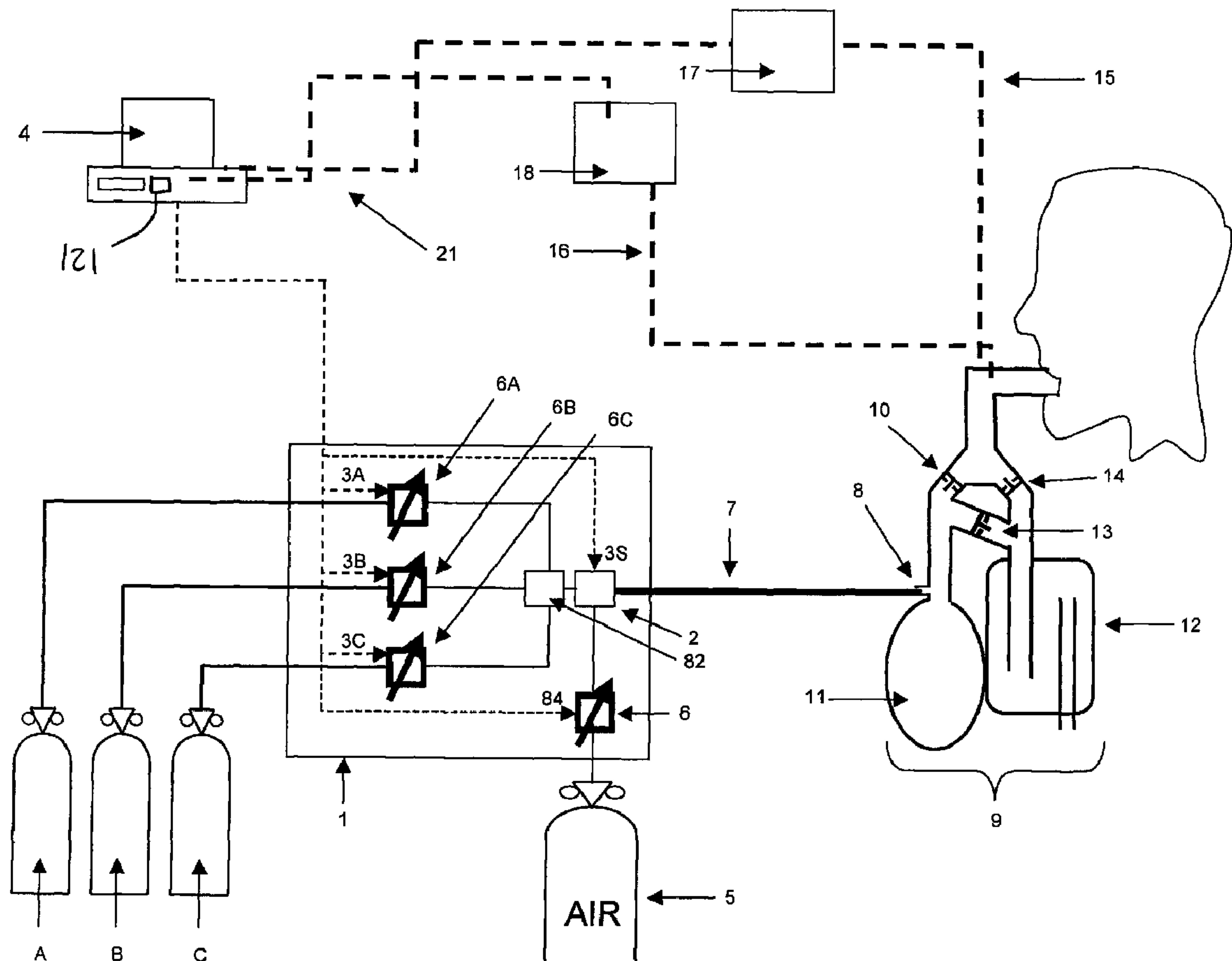
(51) Cl.Int./Int.Cl. *A61M 16/10* (2006.01),  
*A61B 5/026* (2006.01), *A61B 5/055* (2006.01),  
*A61B 8/06* (2006.01), *A61B 8/10* (2006.01),  
*A61M 16/00* (2006.01), *A61M 16/12* (2006.01)

(71) Demandeurs/Applicants:  
SLESSAREV, MARAT, CA;  
FISHER, JOE, CA; ...  
...

(72) Inventeurs/Inventors:  
SLESSAREV, MARAT, CA;  
FISHER, JOE, CA;  
VOLGYESI, GEORGE, CA; ...  
...

(74) Agent: HERMAN & MILLMAN

(54) Titre : PROCEDE ET APPAREIL PERMETTANT D'ATTEINDRE ET DE MAINTENIR DES CONCENTRATIONS  
CIBLES DE GAZ DE FIN D'EXPIRATION  
(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

(71) **Demandeurs(suite)/Applicants(continued):** VOLGYESI, GEORGE, CA; PRISMAN, EITAN, CA; MIKULUS, DAVID, CA; HUDSON, CHRIS, CA; ANSEL, CLIFF, CA

(72) **Inventeurs(suite)/Inventors(continued):** PRISMAN, EITAN, CA; MIKULUS, DAVID, CA; HUDSON, CHRIS, CA; ANSEL, CLIFF, CA

(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

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

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
1 February 2007 (01.02.2007)

PCT

(10) International Publication Number  
WO 2007/012197 A1

## (51) International Patent Classification:

*A61M 16/10* (2006.01) *A61B 5/026* (2006.01)  
*A61M 16/00* (2006.01) *A61B 8/06* (2006.01)  
*A61M 16/12* (2006.01) *A61B 8/10* (2006.01)  
*A61B 5/055* (2006.01)

## (71) Applicants and

**Inventors:** **SLESSAREV, Marat** [GB/CA]; C/o 200 Elizabeth Street, Suite 7-EN-242, Toronto, Ontario M5G 2C4 (CA). **FISHER, Joe** [CA/CA]; C/o 200 Elizabeth Street, Suite 7-EN-242, Toronto, Ontario M5G 2C4 (CA). **VOLGYESI, George** [CA/CA]; C/o 200 Elizabeth Street, Suite 7-EN-242, Toronto, Ontario M5G 2C4 (CA). **PRISMAN, Eitan** [CA/CA]; C/o 200 Elizabeth Street, Suite 7-EN-242, Toronto, Ontario M5G 2C4 (CA). **MIKULUS, David** [US/CA]; C/o 200 Elizabeth Street, Suite 7-EN-242, Toronto, Ontario M5G 2C4 (CA). **HUDSON, Chris** [CA/CA]; C/o 200 Elizabeth Street, Suite 7-EN-242, Toronto, Ontario M5G 2C4 (CA). **ANSEL, Cliff** [US/CA]; C/o 200 Elizabeth Street, Suite 7-EN-242, Toronto, Ontario M5G 2C4 (CA).

## (21) International Application Number:

PCT/CA2006/001258

(22) International Filing Date: 28 July 2006 (28.07.2006)

## (25) Filing Language:

English

(74) Agent: **HERMAN & MILLMAN**; 56 Sheppard Ave. W, Suite 200, Toronto, Ontario M2N 1M2 (CA).

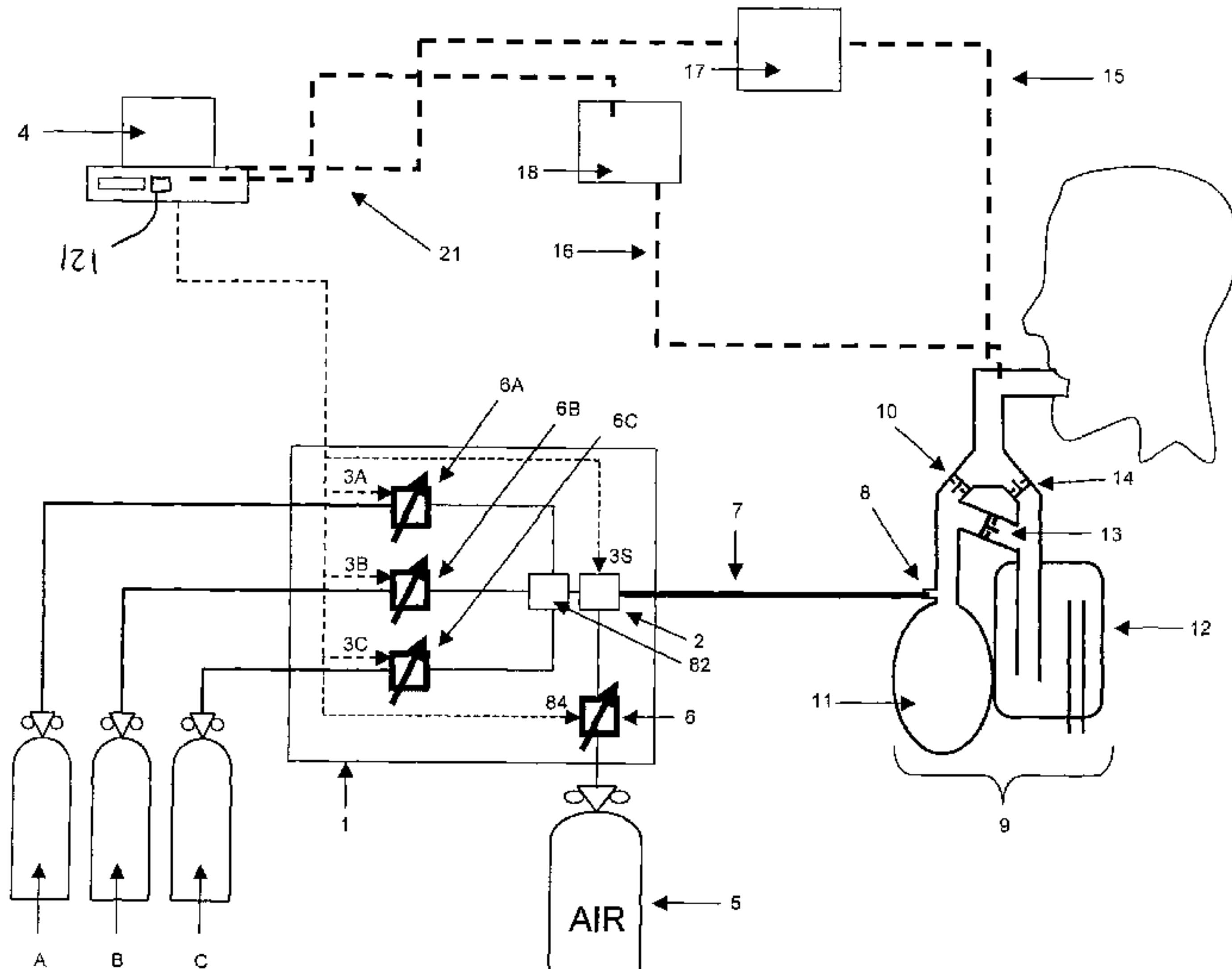
## (26) Publication Language:

English

**(81) Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA,

[Continued on next page]

## (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

WO 2007/012197 A1

WO 2007/012197 A1



NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

**(84) Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT,

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

## FIELD OF THE INVENTION

5

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

## BACKGROUND OF THE INVENTION

10

**[0002]** Ordinarily, when minute ventilation increases, the partial pressure of end tidal CO<sub>2</sub> (PETCO<sub>2</sub>) decreases and partial pressure of end tidal O<sub>2</sub> (PETO<sub>2</sub>) 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 PETCO<sub>2</sub> 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 PETO<sub>2</sub> 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 CO<sub>2</sub> (F<sub>T</sub>ETCO<sub>2</sub>) and/or a target end tidal fractional concentration of O<sub>2</sub> (F<sub>T</sub>ETO<sub>2</sub>) for a given minute ventilation (V̇<sub>E</sub>), that is different from initial F<sub>T</sub>ETCO<sub>2</sub> and F<sub>T</sub>ETO<sub>2</sub>.

**[0003]** Providing a level of control that permits attaining a target end tidal fractional concentration of CO<sub>2</sub> (F<sub>T</sub>ETCO<sub>2</sub>) and/or a target end tidal fractional concentration of O<sub>2</sub> (F<sub>T</sub>ETO<sub>2</sub>) for a given minute ventilation (V̇<sub>E</sub>), that is different from initial F<sub>T</sub>ETCO<sub>2</sub> and F<sub>T</sub>ETO<sub>2</sub>. 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 PCO<sub>2</sub> and PO<sub>2</sub>. The extent of the change in CBF in response to a stimulus is termed cerebrovascular reactivity

- 2 -

(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<sub>2</sub> as well as blood PCO<sub>2</sub>. Blood PO<sub>2</sub> and blood PCO<sub>2</sub> are strongly tied to end tidal concentrations of O<sub>2</sub> and CO<sub>2</sub> respectively. Present methods of inducing high PETCO<sub>2</sub> control PETO<sub>2</sub> poorly and do not control PCO<sub>2</sub> and PO<sub>2</sub> independently.

[0005] There are several current methods that are known for changing 10 blood PCO<sub>2</sub> and PO<sub>2</sub> via control of the gas concentrations in the lungs.

A: Breath-holding

[0006] One method for inducing changes in PCO<sub>2</sub> 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<sub>2</sub>, this requires rapid step changes in PCO<sub>2</sub>, preferably maintaining PO<sub>2</sub> 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<sub>2</sub> but it is not well suited to 20 measuring CVR. The rise in blood PCO<sub>2</sub> during breath-holding is very slow as it is dependent on body CO<sub>2</sub> production ( $\dot{V}CO_2$ ), which is small compared to body capacitance for CO<sub>2</sub>. During breath holding, alveolar PO<sub>2</sub> declines progressively. As CO<sub>2</sub> production, CO<sub>2</sub> capacitance and the tolerable breath-holding time varies from subject to subject, so will the final blood PCO<sub>2</sub> and PETO<sub>2</sub>. As there is no 25 gas sampling during breath-holding the blood PCO<sub>2</sub> and PO<sub>2</sub> is unknown for the duration of the breath-hold so it is not possible to relate the MRI signal strength to PCO<sub>2</sub> or PO<sub>2</sub>, a requirement for the calculation of CVR. The changes in lung and blood PCO<sub>2</sub> during breath-holding are an exponential function with time.

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

B: Inhaling CO<sub>2</sub>

[0007] A second traditional method of changing PCO<sub>2</sub> is inspiring gas mixtures containing CO<sub>2</sub> via a facemask. This is known to result in a highly variable ventilatory response between subjects leading to a large variability in PETCO<sub>2</sub>. Furthermore, inhaling CO<sub>2</sub> changes the minute ventilation (V<sub>E</sub>) resulting also in variability in blood PO<sub>2</sub>. Oxygen is a potent vasoconstrictor and confounds the interpretation of the relationship between PCO<sub>2</sub> and brain blood flow.

[0008] Therefore, neither breath-holding nor inhaling a gas mixture containing CO<sub>2</sub> provide suitable conditions for a consistent, repeatable quantitative test for CVR.

C: Gas forcing

[0009] Since the effects of inhaling a CO<sub>2</sub>-containing gas mixture on increasing PCO<sub>2</sub> can be overcome by increasing minute ventilation, one can introduce a feedback loop to adjust the inhaled PCO<sub>2</sub> to effect a target PETCO<sub>2</sub>. This is referred to as "gas forcing"(2) . Gas forcing has been shown to be effective in imposing target PETO<sub>2</sub> and target PETCO<sub>2</sub> 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 PCO<sub>2</sub>. This necessitates very large flows of

gases and very precise flow controllers for each gas (such as N<sub>2</sub>, O<sub>2</sub> and CO<sub>2</sub> if only these gases are controlled). This is very expensive and cumbersome, and an error which leads to presentation of pure N<sub>2</sub> or pure CO<sub>2</sub> could be deadly.

**[0012]** Gas forcing requires the construction of a special chamber that is  
5 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  
10 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  
15 of these problems. They used O<sub>2</sub> flow to a sequential gas delivery (SGD) circuit  
to produce rapid changes in PETCO<sub>2</sub> 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 (G<sup>1</sup>) is provided first, and if the subject's breathing  
exceeds the available first gas, the balance of that breath is made up of the  
20 second gas (G<sup>2</sup>). The second gas may be previously exhaled gas collected in a  
reservoir on the second limb.) To reduce PCO<sub>2</sub>, they asked their subjects to  
hyperventilate while providing large O<sub>2</sub> flows into the SGD. To raise the PCO<sub>2</sub>,  
they provided a bolus of CO<sub>2</sub> by briefly changing the composition of the gas  
entering the circuit and then maintained the raised PCO<sub>2</sub> by controlling the flow  
25 into the SGD. While this allowed transitions to a new PETCO<sub>2</sub>, the lowering and  
raising of O<sub>2</sub> flows into the circuit to control PETCO<sub>2</sub> and the required changes in  
VE cause alveolar, and thus end tidal, O<sub>2</sub> concentrations to change during the  
protocol despite near constant inspired O<sub>2</sub> concentration. For example, when O<sub>2</sub>

- 5 -

flow is restricted in order to keep the PETCO<sub>2</sub> high, the PETO<sub>2</sub> tends to drift down (as O<sub>2</sub> consumption stays constant in the face of reduced O<sub>2</sub> delivery). When subjects hyperventilate to lower the PETCO<sub>2</sub>, the increased O<sub>2</sub> flow into the circuit results in a rise of PETO<sub>2</sub> (as O<sub>2</sub> consumption stays constant and O<sub>2</sub> delivery is increased). The changes in blood PO<sub>2</sub> 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 10 may be difficult for most people to comply adequately with this.

[0018] Not adequately following breathing instructions results in not meeting target PCO<sub>2</sub> values

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

15 [0020] The method of Vesely et al uses 2 gases and the manipulation of flow into the circuit to change end tidal CO<sub>2</sub> values. With this method, if the total flow is set, then

varying the inspired PCO<sub>2</sub> changes the inspired PO<sub>2</sub>.

PETO<sub>2</sub> cannot be determined independently of PETCO<sub>2</sub>.

20 PETO<sub>2</sub> and PETCO<sub>2</sub> cannot be varied independently.

#### Reference List

25 (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 PCO<sub>2</sub>. Magn Reson Med 2001; 45(6):1011-1013.

- 6 -

(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.

5

### SUMMARY OF THE INVENTION

[0021] In one embodiment, the present invention relates to a method to control the end tidal CO<sub>2</sub> and end tidal O<sub>2</sub> 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;

- 7 -

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 N<sub>2</sub> and CO<sub>2</sub> 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 O<sub>2</sub>, N<sub>2</sub>, and CO<sub>2</sub>.

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:

$$FG^1X = F_T ETX - \frac{\dot{V}X}{\dot{V}G^1}$$

where  $FG^1X$  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,  $F_T ETX$  is the target end tidal concentration of said gas X, and  $\dot{V}G^1$  is the flow rate of the 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:

$$FG^1X = F_T ETX + \frac{\dot{V}X}{\dot{V}G^1}$$

where  $FG^1X$  is the concentration of gas X in the source gas  $G^1$ ,  $\dot{V}X$  is the subject's minute consumption of gas X,  $F_T ETX$  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 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.

**[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 one preferred embodiment of the invention, the source gas flow into the

breathing circuit preferably has a minimum safe concentration of O<sub>2</sub>, 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 O<sub>2</sub>.

**[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 CO<sub>2</sub> and O<sub>2</sub> levels of a subject using one of the

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 CO<sub>2</sub> and O<sub>2</sub> 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 CO<sub>2</sub> and O<sub>2</sub> 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 CO<sub>2</sub> and O<sub>2</sub> levels are controlled independently 15 of each other. For example, the end tidal CO<sub>2</sub> levels may be changed while the end tidal O<sub>2</sub> levels are kept constant or the end tidal O<sub>2</sub> levels may be changed while the end tidal CO<sub>2</sub> levels are kept constant or the end tidal O<sub>2</sub> levels and the end tidal CO<sub>2</sub> 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 O<sub>2</sub> and CO<sub>2</sub> 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

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 5 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 10 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 CO<sub>2</sub> and/or O<sub>2</sub> 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. 15 Similarly, changes in end tidal CO<sub>2</sub> and/or O<sub>2</sub> 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.

20 **[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;

25 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

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 invention 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% O<sub>2</sub>. 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

- 13 -

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 readable instructions;
  - 25 providing instructions for use of said machine readable instructions;
  - providing instructions for development of said machine readable instructions;

- 14 -

providing instructions for acquisition of a processor unit programmed with said machine readable instructions; and

5

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 its 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.

- 15 -

### **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 5 way of example, to the accompanying drawings, which illustrate aspects of 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	$CO_2$

- 16 -

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 a partial rebreathing circuit that is also a sequential gas delivery (SGD) circuit, whose functions will be reviewed briefly.

- 17 -

**[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 5 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 10 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 15 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

20 **[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  $\text{CO}_2$  and  $\text{O}_2$ , although those skilled in the art will recognize that the method can be equally applied to control of other gases in the subject.

25 **[0065]** The method comprises:

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

- 18 -

[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 ( $F_G^1O_2$  and  $F_G^1CO_2$  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  $F_G^1CO_2$ . 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:

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

- 19 -

**[0072]** This relationship states that for a given rate of alveolar ventilation, a particular end tidal concentration is produced. Lowering the alveolar ventilation raises  $\text{FETCO}_2$  and raising it lowers  $\text{FETCO}_2$ .

**[0073]** As long as the subject's minute ventilation exceeds the  $\dot{V}G^1$  the 5 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  $\text{PCO}_2$ . 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  $\text{PCO}_2$  or  $\text{PO}_2$ . We instruct the subject to breathe at a rate  $\geq \dot{V}G^1$  to 10 assure that all of  $\dot{V}G^1$  reaches the alveoli, then additional  $\text{CO}_2$  in  $G^1$  prevents a reduction in  $\text{PETCO}_2$ . 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 15 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  $\text{CO}_2$ . 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 20 a concentration of  $\text{CO}_2$  that does not provide a gradient for gas exchange. Thus composed, it is considered a "neutral" gas flow ( $\dot{V}G^1_n$ ).  $\text{FG}^1_n\text{CO}_2$  equal to that of alveolar gas (as approximated by end tidal gas) by definition would be "neutral" with respect to gas exchange of  $\text{CO}_2$ .

**[0074]** Since there is no  $\text{CO}_2$  in  $\dot{V}G^1_f$ ,  $\dot{V}G^1_n$  is the source of all of the  $\text{CO}_2$  in  $G^1$  (Equation (6)).

$$\dot{V}G^1 \times \text{FG}^1\text{CO}_2 = \dot{V}G^1_n \times \text{FG}^1_n\text{CO}_2 \quad \text{Equation (6)}$$

25 **[0075]** In that case, the concentration in the neutral gas must be equal to the target  $\text{CO}_2$  concentration to maintain  $\text{PETCO}_2$  at the target value

- 20 -

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

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:

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

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:

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

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

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

20

- 21 -

**[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 CO<sub>2</sub> 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 CO<sub>2</sub> targets, since the breathing rate becomes the limiting factor when giving the lowest concentration (i.e. 0%) of CO<sub>2</sub> possible.

**[0081]** We now describe the method for determining F<sub>G<sup>1</sup></sub>O<sub>2</sub>. In order to carry out the method, we obtain values for the subject's O<sub>2</sub> 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 
$$\dot{V}O_2 = \frac{\dot{V}CO_2}{RQ} \quad \text{Equation (5)}$$

**[0082]** The method for determining F<sub>G<sup>1</sup></sub>O<sub>2</sub> is analogous to determining F<sub>G<sup>1</sup></sub>CO<sub>2</sub> with the exception that the sign on the  $\dot{V}O_2$  is reversed in Equation (9) reflecting the fact that O<sub>2</sub> is consumed by the body while CO<sub>2</sub> is produced by the body. Thus the analogous form for Equation (9) as is pertains to O<sub>2</sub> is as follows:

20 
$$F_{G^1}O_2 = F_{TETO_2} + \frac{\dot{V}O_2}{\dot{V}G^1} \quad \text{Equation (11)}$$

**[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 CO<sub>2</sub>) or consumed (as is O<sub>2</sub>) 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

- 22 -

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

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

where  $\dot{V}X$  is the subject's minute production of gas X,  $F_T ETX$  is the 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 as  $FG^1X$ ) using

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

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

**[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 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, for a given desired total flow, any combination of concentrations of  $CO_2$  and  $O_2$  in

the source gas may be achieved by mixing source gases consisting of pure O<sub>2</sub>, CO<sub>2</sub> and N<sub>2</sub>. However, pure CO<sub>2</sub> and pure N<sub>2</sub> contain no O<sub>2</sub> 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 5 death. One aspect of the present invention is the use of source gases each of which has at least a minimum concentration of O<sub>2</sub> 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<sub>ET</sub>O<sub>2</sub> and F<sub>ET</sub>CO<sub>2</sub> 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 O<sub>2</sub> than this and a low level of CO<sub>2</sub> to achieve the combination of low target F<sub>ET</sub>O<sub>2</sub> and low F<sub>TET</sub>CO<sub>2</sub>.

[0090] The minimum oxygen concentration of one gas (call it gas "A") may be set so as to achieve the maximum F<sub>ET</sub>O<sub>2</sub> desirable to give the subject.

20 [0091] One gas (call it Gas "B") may also contain at least a high enough CO<sub>2</sub> concentration so as to be able to achieve the maximum F<sub>ET</sub>CO<sub>2</sub> desired. The concentration of CO<sub>2</sub> in Gas B is further constrained by the fact that, to get a high F<sub>ET</sub>O<sub>2</sub> and high F<sub>ET</sub>CO<sub>2</sub> simultaneously, a substantial amount of Gas A (high O<sub>2</sub> concentration) would be given, leaving less room for Gas B in the  $\dot{V}G^1$ . For 25 example, to achieve a 7.5% F<sub>ET</sub>CO<sub>2</sub> with a 90% F<sub>ET</sub>O<sub>2</sub> , Gas A would have over a 90% concentration of O<sub>2</sub> and Gas B would have at least a 60% concentration of CO<sub>2</sub> .

- 24 -

**[0092]** The O<sub>2</sub> concentration of Gas "B" may be low enough to enable producing in the subject the highest desirable F<sub>ET</sub>CO<sub>2</sub> and the lowest desirable F<sub>ET</sub>O<sub>2</sub>.

**[0093]** Gas "A" may have a low CO<sub>2</sub> concentration since it contains a high O<sub>2</sub> concentration, and it may be desirable to have a high F<sub>ET</sub>O<sub>2</sub> and low F<sub>ET</sub>CO<sub>2</sub>, 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<sub>2</sub> and CO<sub>2</sub> in Gas A, Gas B and Gas C

	FO <sub>2</sub>	FCO <sub>2</sub>
Gas A	High (for greater range of maximum target end tidal O <sub>2</sub> – preferably 100%)	Low (maximum lower bound range for end tidal CO <sub>2</sub> – preferably 0%)
Gas B	The Safe Minimum O <sub>2</sub> concentration – preferably 10%	High (for greater range of maximum target end tidal CO <sub>2</sub> – preferably 20%-80%)
Gas C	The Safe Minimum O <sub>2</sub> concentration – preferably 10%	Low (maximum lower bound range for end tidal CO <sub>2</sub> – preferably 0%)

#### Blending Source Gases to Achieve the Required Total Gas Concentrations

15 of CO<sub>2</sub> and O<sub>2</sub>

**[0095]** For the present discussion, we assume that the FO<sub>2</sub> in Gas B and Gas C are set to achieve the lower bound of F<sub>ET</sub>O<sub>2</sub>, and FCO<sub>2</sub> in Gas A and Gas C are both set to achieve the lower bound F<sub>ET</sub>CO<sub>2</sub>. Hence, the greatest range of F<sub>ET</sub>O<sub>2</sub> and F<sub>ET</sub>CO<sub>2</sub> occurs when FBO<sub>2</sub> = FCO<sub>2</sub> and FACO<sub>2</sub> = FccCO<sub>2</sub>.

- 25 -

Table 2 is used to defines terms used to designate the O<sub>2</sub> and CO<sub>2</sub> concentrations in Gas A, Gas B and Gas C.

*Table 2: Definition of terms used to designate the O<sub>2</sub> and CO<sub>2</sub> concentrations in 5 Gas A, Gas B and Gas C.*

	Fractional concentration O <sub>2</sub>	Fractional concentration CO <sub>2</sub>
Gas A	FAO <sub>2</sub>	FACO <sub>2</sub>
Gas B	FBO <sub>2</sub>	FBCO <sub>2</sub>
Gas C	FBO <sub>2</sub>	FACO <sub>2</sub>

**[0096]** The method summarized by Equations 11 and 9 are used to determine fractional concentrations of CO<sub>2</sub> and O<sub>2</sub> that have to be supplied in G<sup>1</sup> 10 to attain target F<sub>TETCO<sub>2</sub></sub> and F<sub>TETO<sub>2</sub></sub>, assuming the subject's or subject's  $\dot{V}CO_2$  and  $\dot{V}O_2$  are known.

**[0097]** The total flow of source gas G<sup>1</sup> 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 O<sub>2</sub> in the source gas is equal to the sum of the flows of O<sub>2</sub> 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 FCO<sub>2</sub> = FBO<sub>2</sub> 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

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

- 26 -

**[00100]** The flow of CO<sub>2</sub> in the source gas is equal to the sum of the flows in the individual gases. Therefore:

$$\dot{V}G^1 \times FG^1CO_2 = \dot{Q}_A \times FACO_2 + \dot{Q}_B \times FBCO_2 + \dot{Q}_C \times FcO_2$$

5 **[00101]** But since FACO<sub>2</sub> = FcCO<sub>2</sub> 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 O<sub>2</sub> concentration of FG<sup>1</sup>O<sub>2</sub> and CO<sub>2</sub> concentration FG<sup>1</sup>CO<sub>2</sub>. 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 O<sub>2</sub> can be applied to any other gas that is absorbed, including, but not limited to 15 acetylene, carbon monoxide, nitrous oxide, anesthetic gases. It is recognized that by defining target PCO<sub>2</sub> and target PO<sub>2</sub>, target PN<sub>2</sub> is also defined. In the same way, the target partial pressure of any inert gas can be defined, for 20 example, but not limited to argon, helium, and xenon.

**[00105]** Another aspect of this invention is the use of the independent control of end tidal CO<sub>2</sub> and O<sub>2</sub> , N<sub>2</sub> 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 targeted blood gases. For example, the CO<sub>2</sub> 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 brain and other tissue blood flow response to changes in blood concentrations of CO<sub>2</sub>, O<sub>2</sub>, 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<sub>2</sub>, O<sub>2</sub> and other gases, with and without the presence of other substances in the blood. Another test involves manipulating O<sub>2</sub> 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 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 vascular malformations.

**[00106]** Being able to achieve target end tidal PO<sub>2</sub> and PCO<sub>2</sub> 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

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<sub>2</sub>. Repeated standardized tests to the same target PCO<sub>2</sub> 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<sub>2</sub>. 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<sub>2</sub> or O<sub>2</sub>. 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<sub>2</sub> and PCO<sub>2</sub> 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<sub>2</sub> and O<sub>2</sub> in the source gas based on the target end tidal concentrations and the subject's rate of O<sub>2</sub> consumption and CO<sub>2</sub> production. It may be desirable for performance of certain diagnostic tests to

- 29 -

assume that a particular subject population has a small range of values for CO<sub>2</sub> production and O<sub>2</sub> 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 CO<sub>2</sub> O<sub>2</sub> , one might provide the following premixed gases each 10 of which corresponded to one pair of targets. These gases may be provided to 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 <sub>T</sub> ETO <sub>2</sub>	F <sub>T</sub> ETCO <sub>2</sub>
D (1.5% CO <sub>2</sub> , 52.5% O <sub>2</sub> , Bal. N <sub>2</sub> )	50%	4.0%
E (3.7% CO <sub>2</sub> , 22.5% O <sub>2</sub> , Bal. N <sub>2</sub> )	20%	6.2%
F (2.6% CO <sub>2</sub> , 72.5% O <sub>2</sub> , Bal. N <sub>2</sub> )	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 O<sub>2</sub> and CO<sub>2</sub>. 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

- 30 -

(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.

- 31 -

**[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  $F_{ET}CO_2$  and  $F_{ET}O_2$  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

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 5 non-rebreathing SGD, they are vented. Meanwhile, G<sup>1</sup> collects in the G<sup>1</sup> 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 10 (16) connected to an optional CO<sub>2</sub>/O<sub>2</sub> 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<sub>2</sub> and CO<sub>2</sub>. Data can be analyzed on- or off-line 15 and displayed on a computer screen that is optionally part of the processing unit and (4).

**[00116]** Optionally, if it is desired to give the subject air during a stand by 15 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 25 given pattern of transitions and steady states, individual concentrations of O<sub>2</sub> and CO<sub>2</sub> in the G<sup>1</sup> 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.

- 33 -

**[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 O<sub>2</sub>, CO<sub>2</sub> and N<sub>2</sub> equal to those required in the G<sup>1</sup> 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% O<sub>2</sub>. Where a component gas

- 34 -

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.

10 **[00123]** While the above description describes preferred embodiments, it 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.

**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 target end tidal concentration of gas X, whereby said apparatus is adapted to administer a source gas having a first gas composition.
- 10 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 20 X.
- 25 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,  $F_{TETX}$  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

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

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:

- setting the source gas flow into a partial rebreathing circuit at a rate equal to or less than the patient's minute ventilation
- 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
- 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

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

$F_T ETX$  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

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

$X$ ,  $F_{TETX}$  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:

5        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

10        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

15        concentration of said gas  $X$  in the source gas is set according to

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

$F_{TETX}$  is the target end tidal concentration of gas  $X$  and  $G^1$  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

20        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.

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

- 39 -

- 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

- 40 -

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 O<sub>2</sub> .
30. The method of Claims 27 or 28 where the source gas flow into the breathing circuit has a minimum safe concentration of O<sub>2</sub> .
31. The method of Claims 29 or 30 where the minimum safe level of O<sub>2</sub> concentration is 10%.
- 10 32. The method of Claims 29 or 30 where the minimum safe level of O<sub>2</sub> 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 O<sub>2</sub> .
36. The method of any of claims 17- 33 wherein the gas whose end tidal concentration target is being induced is CO<sub>2</sub> .
37. The method of Claim 33 where the component gases have the following 20 relative concentrations:
  - a) Gas A: High O<sub>2</sub> , Low CO<sub>2</sub>
  - b) Gas B: Low O<sub>2</sub> , High CO<sub>2</sub>
  - c) Gas C: Low O<sub>2</sub> , Low CO<sub>2</sub>
38. The method of Claim 16 where the source gases have the following 25 concentrations:
  - a) Gas A: 50-100% O<sub>2</sub> , 0-20% CO<sub>2</sub>
  - b) Gas B: 10-30% O<sub>2</sub> , 20-80% CO<sub>2</sub>
  - c) Gas C: 10-30% O<sub>2</sub> , 0-20% CO<sub>2</sub>

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

- a) Gas A: 100% O<sub>2</sub> , 0% CO<sub>2</sub>
- b) Gas B: 10% O<sub>2</sub> , 20-80% CO<sub>2</sub>
- 5 c) Gas C: 10% O<sub>2</sub> , 0% CO<sub>2</sub>

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

- a) Gas A: 100% O<sub>2</sub> , 0% CO<sub>2</sub>
- b) Gas B: 10% O<sub>2</sub> , 20-40% CO<sub>2</sub>
- 10 c) Gas C: 10% O<sub>2</sub> , 0% CO<sub>2</sub>

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

- a) Gas A: 100% O<sub>2</sub> , 0% CO<sub>2</sub>
- b) Gas B: 10% O<sub>2</sub> , 40% CO<sub>2</sub>
- 15 c) Gas C: 10% O<sub>2</sub> , 0% CO<sub>2</sub>

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

- a) Gas A: 100% O<sub>2</sub> , 0% CO<sub>2</sub>
- b) Gas B: 10% O<sub>2</sub> , 20% CO<sub>2</sub>
- 20 c) Gas C: 10% O<sub>2</sub> , 0% CO<sub>2</sub>

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 CO<sub>2</sub> and O<sub>2</sub> 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 CO<sub>2</sub> and O<sub>2</sub> levels are controlled independently of each other.

46. The method of Claim 44 or 45 where the end tidal CO<sub>2</sub> levels are changed while the end tidal O<sub>2</sub> levels are kept constant.

- 42 -

47. The method of Claim 44 or 45 where the end tidal PO<sub>2</sub> levels are changed while the end tidal PCO<sub>2</sub> levels are kept constant
48. The method of Claim 44 or 45 where the end tidal PO<sub>2</sub> levels and the end tidal PCO<sub>2</sub> levels are changed simultaneously
- 5 49. A method to measure oculovascular reactivity comprising:
  - a) controlling the end tidal CO<sub>2</sub> and O<sub>2</sub> 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<sub>2</sub> and O<sub>2</sub> levels are controlled independently of each other.
- 10 51. The method of Claim 49 or 50 where the end tidal CO<sub>2</sub> levels are changed while the end tidal O<sub>2</sub> levels are kept constant.
52. The method of Claim 49 or 50 where the end tidal PO<sub>2</sub> levels are changed while the end tidal PCO<sub>2</sub> levels are kept constant
- 15 53. The method of Claim 49 or 50 where the end tidal PO<sub>2</sub> levels and the end tidal PCO<sub>2</sub> 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:
  - a) controlling the end tidal CO<sub>2</sub> and O<sub>2</sub> levels of a subject using the methods of claims 36 or 37.
  - b) monitoring oxygenation or blood flow in the tumor
- 20 56. The method of Claim 55 where the end tidal CO<sub>2</sub> and O<sub>2</sub> levels are controlled independently of each other.
- 25 57. The method of Claim 55 or 56 where the end tidal CO<sub>2</sub> levels are changed while the end tidal O<sub>2</sub> levels are kept constant.
58. The method of Claim 55 or 56 where the end tidal PO<sub>2</sub> levels are changed while the end tidal PCO<sub>2</sub> levels are kept constant

59. The method of Claim 55 or 56 where the end tidal PO<sub>2</sub> levels and the end tidal PCO<sub>2</sub> 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<sub>2</sub> and CO<sub>2</sub> 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<sub>2</sub> and CO<sub>2</sub> 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<sub>2</sub> and O<sub>2</sub> 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

- 44 -

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 O<sub>2</sub> , Low CO<sub>2</sub>
- b) Gas B: Low O<sub>2</sub> , High CO<sub>2</sub>
- c) Gas C: Low O<sub>2</sub> , Low CO<sub>2</sub>

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

10 the following concentrations:

- a) Gas A: 50-100% O<sub>2</sub> , 0-20% CO<sub>2</sub>
- b) Gas B: 10-30% O<sub>2</sub> , 20-80% CO<sub>2</sub>
- c) Gas C: 10-30% O<sub>2</sub> , 0-20% CO<sub>2</sub>

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

15 following concentrations:

- a) Gas A: 100% O<sub>2</sub> , 0% CO<sub>2</sub>
- b) Gas B: 10% O<sub>2</sub> , 20-80% CO<sub>2</sub>
- c) Gas C: 10% O<sub>2</sub> , 0% CO<sub>2</sub>

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

20 the following concentrations:

- a) Gas A: 100% O<sub>2</sub> , 0% CO<sub>2</sub>
- b) Gas B: 10% O<sub>2</sub> , 20-40% CO<sub>2</sub>
- c) Gas C: 10% O<sub>2</sub> , 0% CO<sub>2</sub>

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

25 the following concentrations:

- a) Gas A: 100% O<sub>2</sub> , 0% CO<sub>2</sub>
- b) Gas B: 10% O<sub>2</sub> , 40% CO<sub>2</sub>
- c) Gas C: 10% O<sub>2</sub> , 0% CO<sub>2</sub>

- 45 -

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

- 5 a) Gas A: 100% O<sub>2</sub> , 0% CO<sub>2</sub>
- b) Gas B: 10% O<sub>2</sub> , 20% CO<sub>2</sub>
- c) Gas C: 10% O<sub>2</sub> , 0% CO<sub>2</sub>

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

- 10 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 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.

- 46 -

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

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

15 according to  $FG^1X = F_{ET} + \frac{\dot{V}X}{\dot{V}G^1}$ , where  $\dot{V}X$  is the subject's minute consumption of gas X,  $F_{ET}$  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 .

- 47 -

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 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 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

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.

5

10 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.

15 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 ( $FG^1X$ ) is computed according to

20 
$$FG^1X = F_{TETX} - \frac{\dot{V}X}{\dot{V}G^1}$$
, 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  $\dot{V}G^1$  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 ( $FG^1X$ ) is computed according to

25 
$$FG^1X = F_{TETX} + \frac{\dot{V}X}{\dot{V}G^1}$$
, 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  $\dot{V}G^1$  is the flow rate of the source gas.

- 49 -

100. A system according to claim 95, wherein each component gas inlet is fluidly connected to a blended gas source comprising at least 10% O<sub>2</sub>.

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 acquisition 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;

- 50 -

- a. providing instructions for acquisition of said machine readable instructions;
- b. providing instructions for use of said machine readable instructions;
- 5 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

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.

20 108. 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.

- 51 -

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.

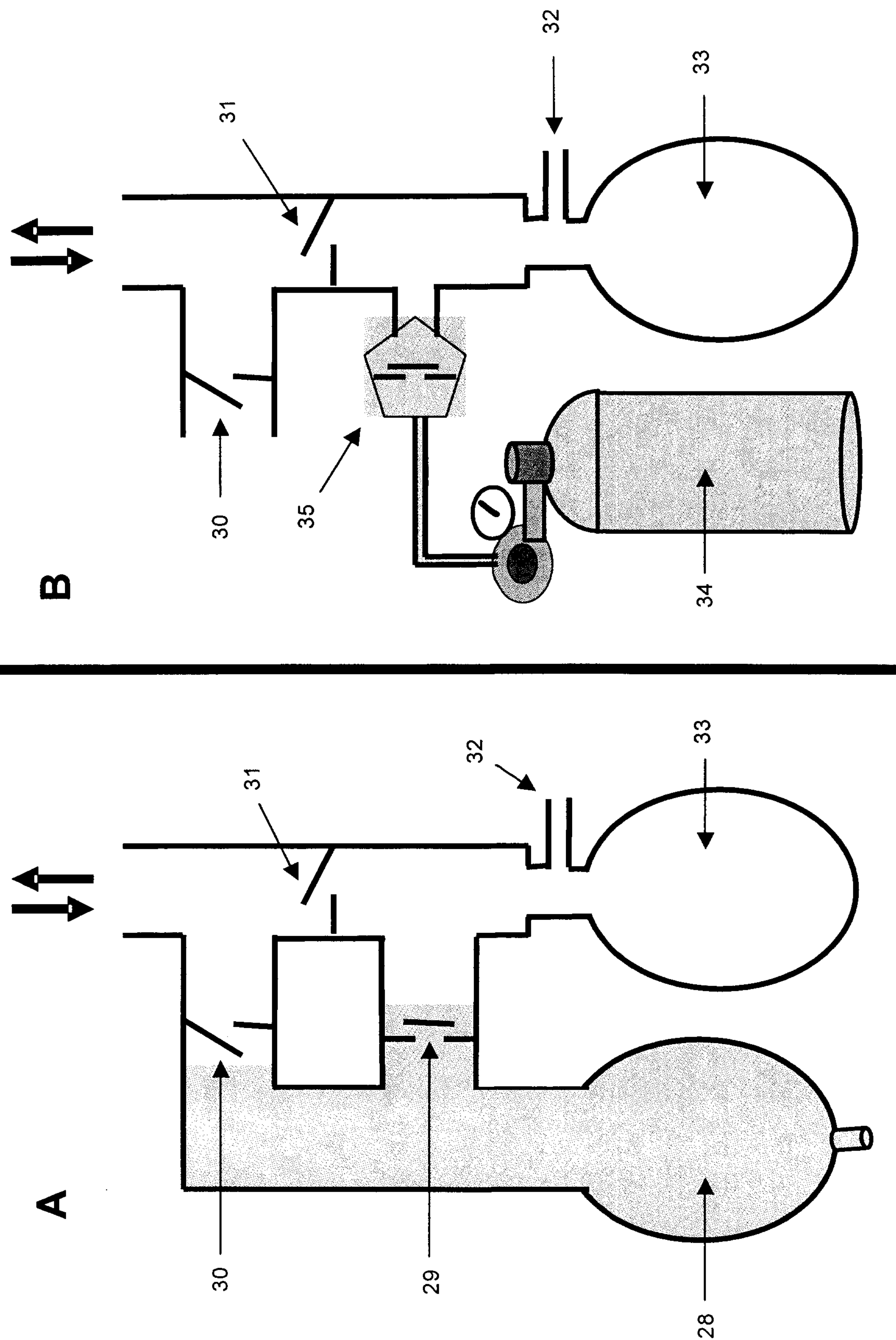

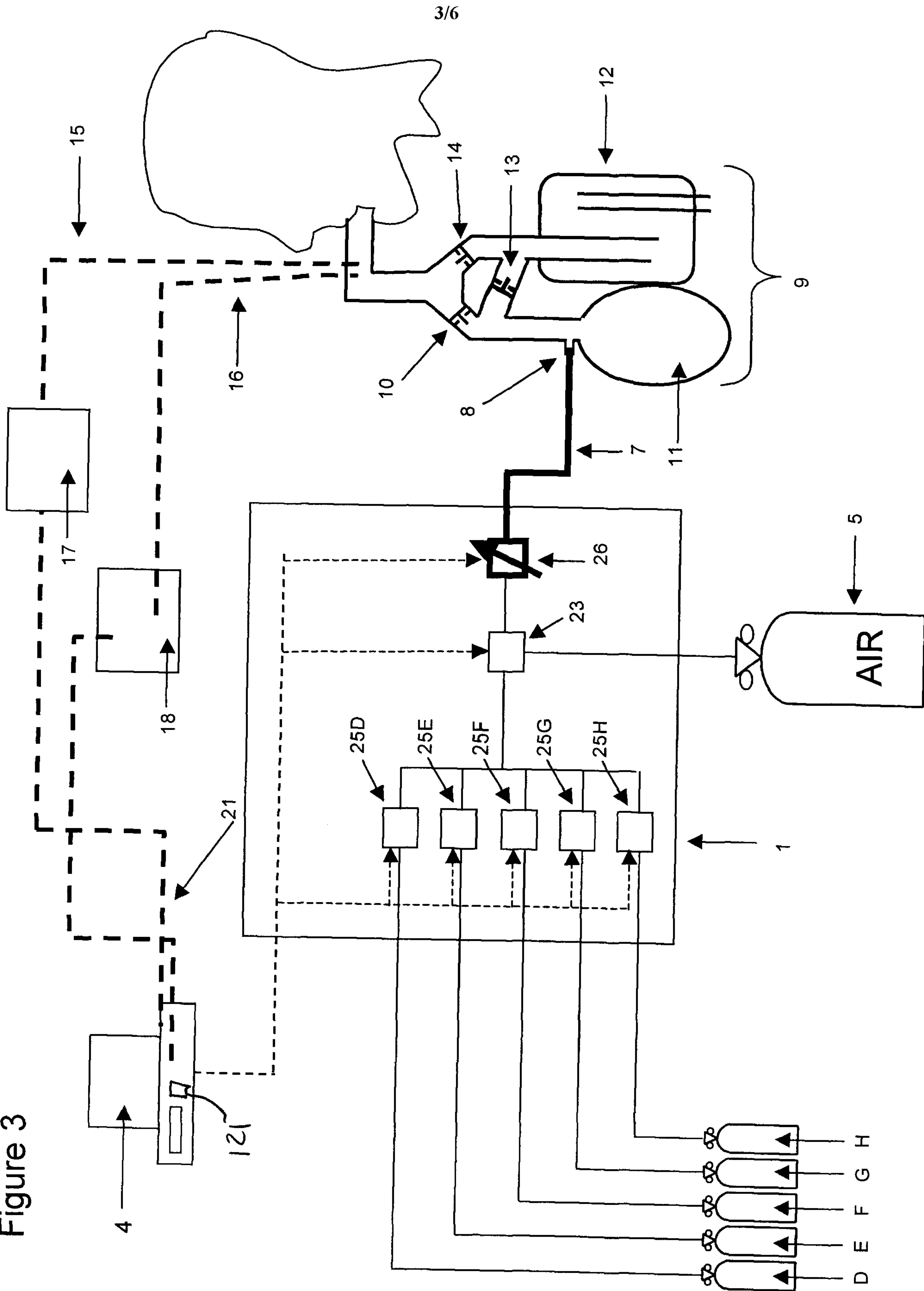


Figure 1



# Figure 3



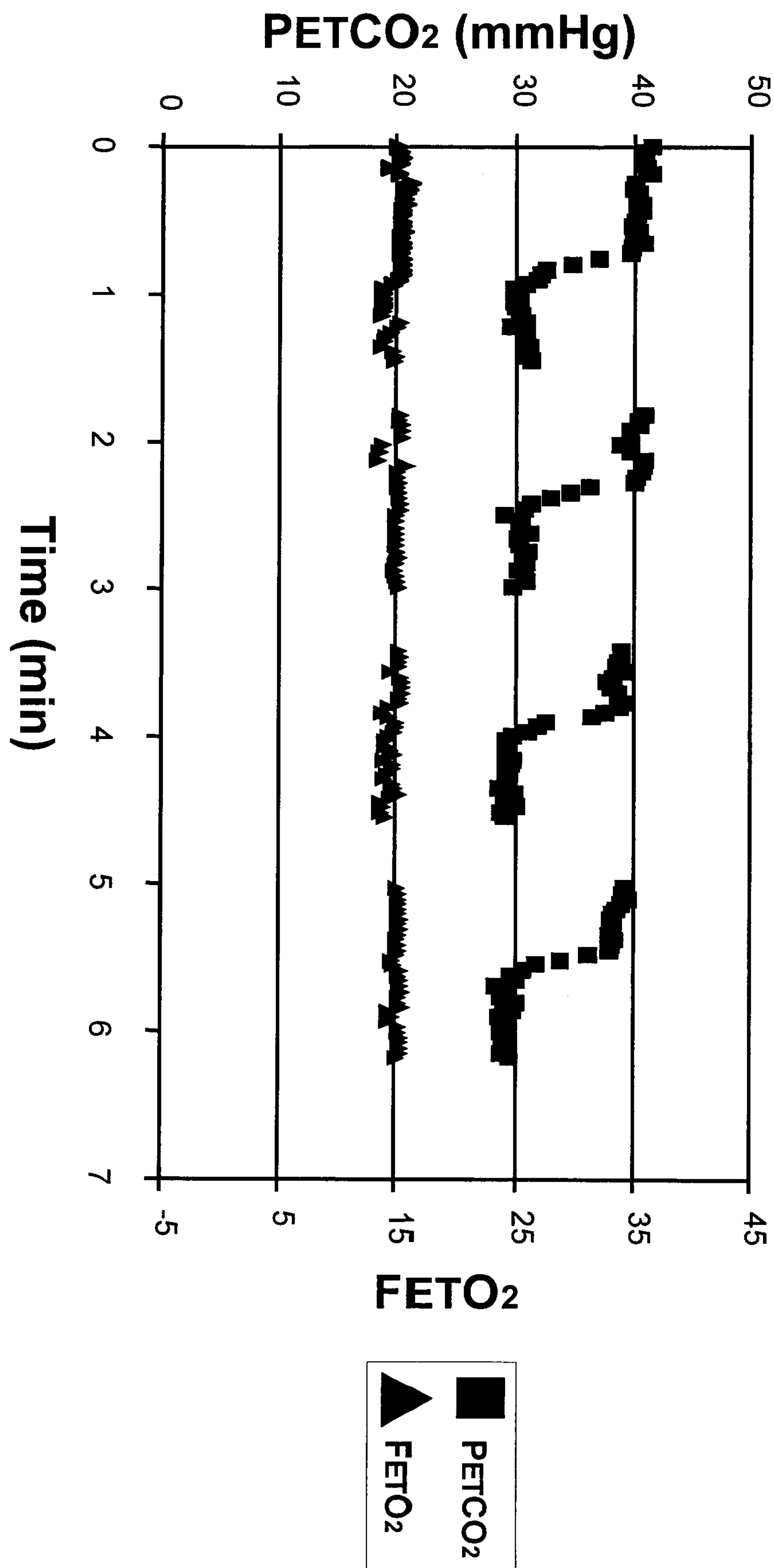


Figure 4

CO<sub>2</sub> steps at normoxia

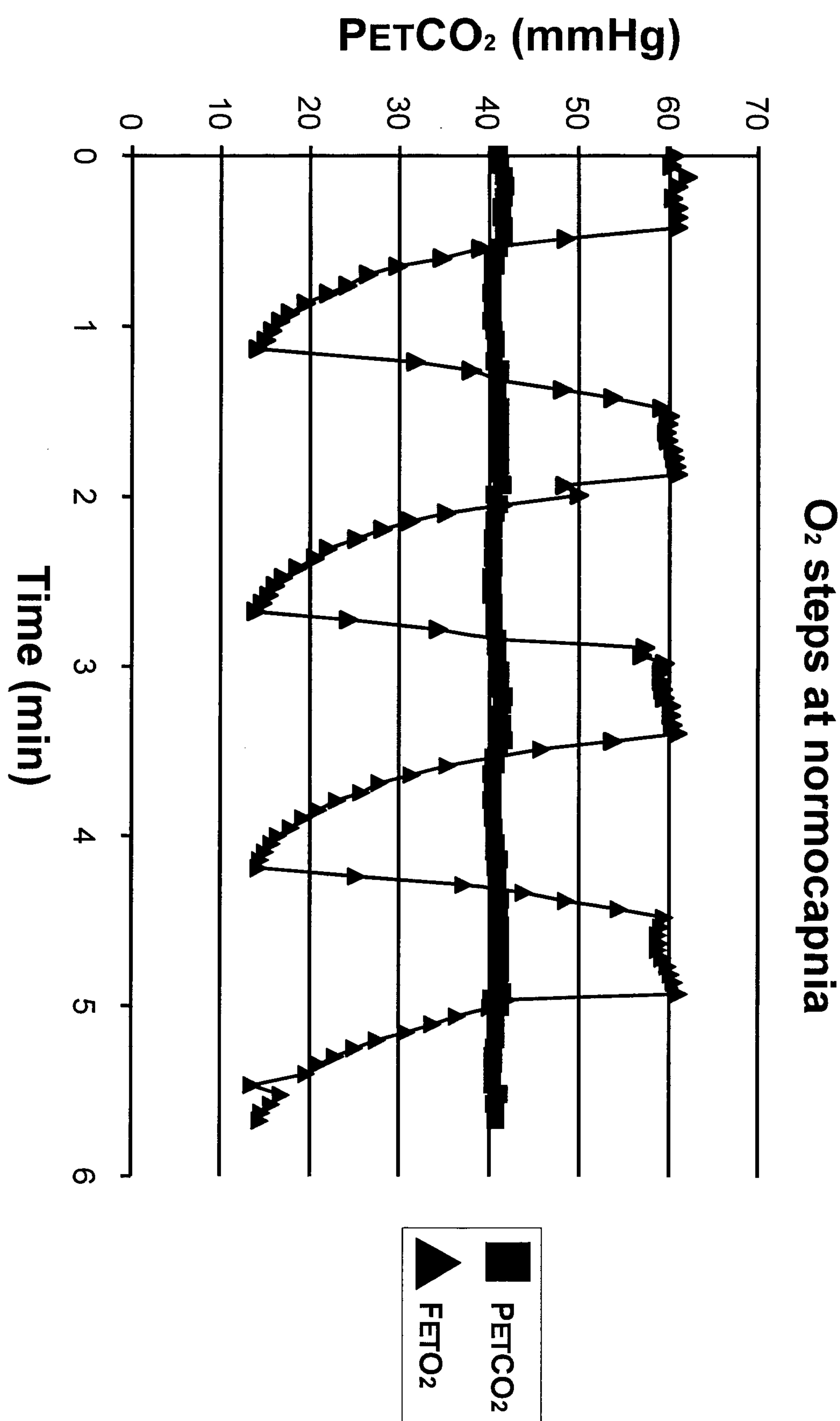


Figure 5

Figure 6

