(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)

(21) International Application Number:
PCT/CA2006/001258

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

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCTCA2005001166 28 July 2005 (28.07.2005) CA

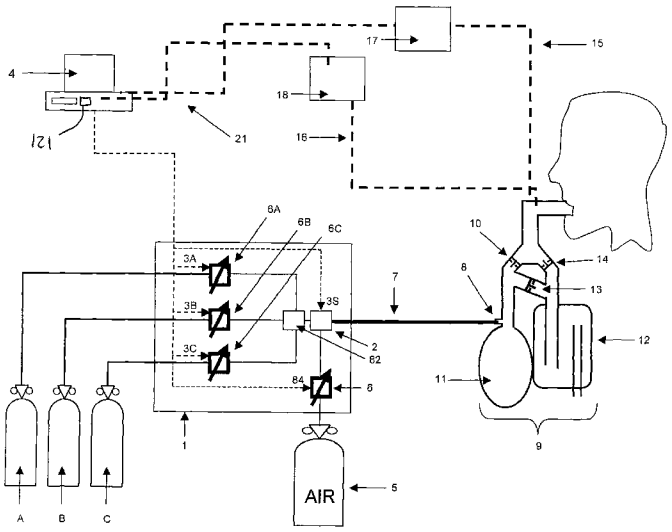
(71) Applicants and
(72) Inventors: **SLESSAREV, Marat** [GB/CA]; C/o 200 Elizabeth Street, Suite 7-EN-242, Toronto, Ontario M5G 2C4 (CA). **FISHER, Joe** [CA/CA]; C/o 200 Elizabeth Street, Suite 7-EN-242, Toronto, Ontario M5G 2C4 (CA). **VOLGYESI, George** [CA/CA]; C/o 200 Elizabeth Street, Suite 7-EN-242, 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).

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

(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

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.

(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, 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.

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

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

[0002] Ordinarily, when minute ventilation increases, the partial pressure of end tidal CO_2 ($P_{ET}CO_2$) decreases and partial pressure of end tidal O_2 ($P_{ET}O_2$) 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 $P_{ET}CO_2$ 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 $P_{ET}O_2$ 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_2 ($F_{T}ETCO_2$) and/or a target end tidal fractional concentration of O_2 ($F_{T}ETO_2$) for a given minute ventilation ($\dot{V}_E$), that is different from initial $F_{T}ETCO_2$ and $F_{T}ETO_2$.

[0003] Providing a level of control that permits attaining a target end tidal fractional concentration of CO_2 ($F_{T}ETCO_2$) and/or a target end tidal fractional concentration of O_2 ($F_{T}ETO_2$) for a given minute ventilation ($\dot{V}_E$), that is different from initial $F_{T}ETCO_2$ and $F_{T}ETO_2$. 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_2 and PO_2. The extent of the change in CBF in response to a stimulus is termed cerebrovascular reactivity

(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.

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

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

A: Breath-holding

[0006] One method for inducing changes in PCO_2 during Magnetic Resonance Imaging (MRI) is breath-holding. As there is a rapid drift in the baseline MRI signal, changes in MRI signal resulting from changes in brain blood flow can be detected only by rapidly alternating the stimulus between "control" and "test" values. With respect to PCO_2, this requires rapid step changes in PCO_2, preferably maintaining PO_2 constant. Cycle times of 3 min have been reported by Vesely et al (1) to be suitable, but shorter cycle times would be preferred. Breath-holding induces an increase in PCO_2 but it is not well suited to measuring CVR. The rise in blood PCO_2 during breath-holding is very slow as it is dependent on body CO_2 production ($\dot{V}CO_2$), which is small compared to body capacitance for CO_2. During breath holding, alveolar PO_2 declines progressively. As CO_2 production, CO_2 capacitance and the tolerable breath-holding time varies from subject to subject, so will the final blood PCO_2 and $P_{ET}O_2$. As there is no gas sampling during breath-holding the blood PCO_2 and PO_2 is unknown for the duration of the breath-hold so it is not possible to relate the MRI signal strength to PCO_2 or PO_2, a requirement for the calculation of CVR. The changes in lung and blood PCO_2 during breath-holding are an exponential function with time.

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

B: Inhaling CO_2

[0007] A second traditional method of changing PCO_2 is inspiring gas mixtures containing CO_2 via a facemask. This is known to result in a highly variable ventilatory response between subjects leading to a large variability in $P_{ET}CO_2$. Furthermore, inhaling CO_2 changes the minute ventilation ($\dot{V}E$) resulting also in variability in blood PO_2. Oxygen is a potent vasoconstrictor and confounds the interpretation of the relationship between PCO_2 and brain blood flow.

[0008] Therefore, neither breath-holding nor inhaling a gas mixture containing CO_2 provide suitable conditions for a consistent, repeatable quantitative test for CVR.

C: Gas forcing

[0009] Since the effects of inhaling a CO_2-containing gas mixture on increasing PCO_2 can be overcome by increasing minute ventilation, one can introduce a feedback loop to adjust the inhaled PCO_2 to effect a target $P_{ET}CO_2$. This is referred to as "gas forcing"(2) . Gas forcing has been shown to be effective in imposing target $P_{ET}O_2$ and target $P_{ET}CO_2$ 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_2. This necessitates very large flows of

gases and very precise flow controllers for each gas (such as N_2, O_2 and CO_2 if only these gases are controlled). This is very expensive and cumbersome, and an error which leads to presentation of pure N_2 or pure CO_2 could be deadly.

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

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

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

D: Sequential gas delivery method:

[0015] A more recent method introduced by Vesely et al.(1) solved some of these problems. They used O_2 flow to a sequential gas delivery (SGD) circuit to produce rapid changes in $P_{ET}CO_2$ 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^1) is provided first, and if the subject's breathing exceeds the available first gas, the balance of that breath is made up of the second gas (G^2). The second gas may be previously exhaled gas collected in a reservoir on the second limb.) To reduce PCO_2, they asked their subjects to hyperventilate while providing large O_2 flows into the SGD. To raise the PCO_2, they provided a bolus of CO_2 by briefly changing the composition of the gas entering the circuit and then maintained the raised PCO_2 by controlling the flow into the SGD. While this allowed transitions to a new $P_{ET}CO_2$, the lowering and raising of O_2 flows into the circuit to control $P_{ET}CO_2$ and the required changes in $\dot{V}_E$ cause alveolar, and thus end tidal, O_2 concentrations to change during the protocol despite near constant inspired O_2 concentration. For example, when O_2

flow is restricted in order to keep the $P_{ET}CO_2$ high, the $P_{ET}O_2$ tends to drift down (as O_2 consumption stays constant in the face of reduced O_2 delivery). When subjects hyperventilate to lower the $P_{ET}CO_2$, the increased O_2 flow into the circuit results in a rise of $P_{ET}O_2$ (as O_2 consumption stays constant and O_2 delivery is increased). The changes in blood PO_2 have an effect on the MRI signal independent of brain blood flow confounding the interpretation with respect to blood flow.

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

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

[0018] Not adequately following breathing instructions results in not meeting target PCO_2 values

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

[0020] The method of Vesely et al uses 2 gases and the manipulation of flow into the circuit to change end tidal CO_2 values. With this method, if the total flow is set, then

varying the inspired PCO_2 changes the inspired PO_2.

$P_{ET}O_2$ cannot be determined independently of $P_{ET}CO_2$.

$P_{ET}O_2$ and $P_{ET}CO_2$ cannot be varied independently.

Reference List

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

(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.

SUMMARY OF THE INVENTION

[0021] In one embodiment, the present invention relates to a method to control the end tidal CO_2 and end tidal O_2 independently of each other and 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 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.

[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 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;

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.

[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 target gases such as N_2 and CO_2 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_2, N_2, and CO_2.

[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 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 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:

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

where $F_{G^1}X$ is the concentration of gas X in the source gas G^1, $\dot{V}X$ is the subject's minute production of the physiologically produced gas X, $F_{T}ETX$ 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:

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

where $F_{G^1}X$ is the concentration of gas X in the source gas G^1, $\dot{V}X$ is the subject's minute 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_2, 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 tidals concentrations are described below), at least the most frequently used and preferably each of the component gases comprises a minimum safe concentration of O_2.

[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 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 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.

[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.

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

[0036] A method to measure cerebrovascular reactivity comprising controlling the end tidal CO_2 and O_2 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 Infra-red Spectroscopy.

[0037] A method to measure occulovascular reactivity comprising controlling the end tidal CO_2 and O_2 levels of a subject using one of the aforementioned methods and monitoring occulovascular blood flow.

[0038] A method to measure a beneficial level of oxygenation to tissues for the purpose of radiotherapy or chemotherapy, comprising controlling the end tidal CO_2 and O_2 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_2 and O_2 levels are controlled independently of each other. For example, the end tidal CO_2 levels may be changed while the end tidal O_2 levels are kept constant or the end tidal O_2 levels may be changed while the end tidal CO_2 levels are kept constant or the end tidal O_2 levels and the end tidal CO_2 levels may be changed simultaneously.

[0040] In yet another aspect, the invention is directed to a therapeutic 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_2 and CO_2 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 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 monitoring pressure in the breathing circuit and optionally further comprises means for measuring the subject's end tidal gas concentrations.

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

[0043] Changes in end tidal CO_2 and/or O_2 can be used to determine vascular reactivity in cerebral, pulmonary, renal, or retinal vessels and other vascular beds as detected by various blood flow or blood flow surrogate sensors. Similarly, changes in end tidal CO_2 and/or O_2 can be used to determine changes on organ or tissue function by measuring such factors as blood pressure and heart rate variability, skin conductivity, capillary blood flow in the skin, hormone levels, organ temperature, finger or other limb plethysmography, and other measurements known to physiologists and others skilled in the art.

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

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

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

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 ports for controlling selected end tidal concentrations with a series of blended gases.

[0045] In yet another aspect, the inventions is directed to a system for independently controlling the end tidal concentration of each constituent gas in 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 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 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_2. In another 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

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 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

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 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;

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;

providing instructions for use of said machine readable instructions;

providing instructions for development of said machine readable instructions;

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

providing instructions for working, updating, upgrading, trouble-shooting, substitution, repair or re-acquisition, of said machine readable instructions or such processor unit. The processor unit may be programmed or have "hard-wired" such instructions.

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

[0051] The invention contemplates that the system and it method for 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 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 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.

BRIEF DESCRIPTION OF THE DRAWINGS

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

[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 $P_{ET}O_2$.

[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

[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.

Glossary of Terms

Oxygen	O_2
Carbon dioxide	CO_2

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	$F_{TET}CO_2$
Target end tidal O_2	$F_{TET}O_2$
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	$F_{TET}CO_2$
Target end tidal fractional concentration of O_2	$F_{TET}O_2$
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.

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

Description of Method to Independently Control End-Tidal Gases

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

[0065] The method comprises:

[0066] determining or estimating the subject's $\dot{V}CO_2$ and $\dot{V}O_2$

[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 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 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 ($\dot{V}_E$), 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 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 concentration:

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

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

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

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

$$\dot{V}G^1 \times F_{G^1}CO_2 = \dot{V}G^1{}_n \times F_{G^1{}_n}CO_2 \qquad \text{Equation (6)}$$

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

$$\dot{V}G^{1} \times FG^{1}CO_2 = \dot{V}G^{1}_{n} \times F_{T}ETCO_2 \qquad \text{Equation (7)}$$

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

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

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

$$\dot{V}G^{1} \times FG^{1}CO_2 = [\dot{V}G^{1} - \dot{V}_A] \times F_{T}ETCO_2 \qquad \text{Equation (7c)}$$

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

$$\dot{V}_A = \frac{\dot{V}CO_2}{F_{T}ETCO_2} \qquad \text{Equation (4)}$$

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

$$\dot{V}G^{1} \times FG^{1}CO_2 = [\dot{V}G^{1} - \frac{\dot{V}CO_2}{F_{T}ETCO_2}] \times F_{T}ETCO_2 \qquad \text{Equation (8)}$$

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

$$FG^{1}CO_2 = F_{T}ETCO_2 - \frac{\dot{V}CO_2}{\dot{V}G^{1}} \qquad \text{Equation (9)}$$

[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_2 targets below their resting levels. Additionally, having the subject breathe faster enables more rapid transitions between end tidal levels, particularly when moving from higher to lower CO_2 targets, since the breathing rate becomes the limiting factor when giving the lowest concentration (i.e. 0%) of CO_2 possible.

[0081] We now describe the method for determining $F_G{}^1O_2$. In order to carry out the method, we obtain values for the subject's O_2 consumption ($\dot{V}O_2$) , 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.

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

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

$$F_G{}^1O_2 = F_T ETO_2 + \frac{\dot{V}O_2}{\dot{V}G^1} \qquad \text{Equation (11)}$$

[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_2) or consumed (as is O_2) by the body. The general form of Equation 9 for inducing or maintaining a target end tidal concentration of a gas X that is

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

$$FG^1X = F_TETX - \frac{\dot{V}X}{\dot{V}G^1} \qquad \text{Equation (12)}$$

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

[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

$$FG^1X = F_TETX + \frac{\dot{V}X}{\dot{V}G^1} \qquad \text{Equation (13)}$$

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

[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_2, CO_2 and N_2. However, pure CO_2 and pure N_2 contain no O_2 and thus if the gas blending apparatus were to fail and the subject were to inhale just a few breaths of either of these two gases, it would lead to severe hypoxemia and possibly death. One aspect of the present invention is the use of source gases each of which has at least a minimum concentration of O_2 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.

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

[0088] To achieve a high signal / noise ratio for diagnostics, a wide range of $F_{ET}O_2$ and $F_{ET}CO_2$ values is desirable.

[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_2 than this and a low level of CO_2 to achieve the combination of low target $FTET O_2$ and low $F_{T}ETCO_2$.

[0090] The minimum oxygen concentration of one gas (call it gas "A") may be set so as to achieve the maximum $F_{ET}O_2$ desirable to give the subject.

[0091] One gas (call it Gas "B") may also contain at least a high enough CO_2 concentration so as to be able to achieve the maximum $F_{ET}CO_2$ desired. The concentration of CO_2 in Gas B is further constrained by the fact that, to get a high $F_{ET}O_2$ and high $F_{ET}CO_2$ simultaneously, a substantial amount of Gas A (high O_2 concentration) would be given, leaving less room for Gas B in the $\dot{V}G^1$. For example, to achieve a 7.5% $F_{ET}CO_2$ with a 90% $F_{ET}O_2$, Gas A would have over a 90% concentration of O_2 and Gas B would have at least a 60% concentration of CO_2 .

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

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

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

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

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

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

[0095] For the present discussion, we assume that the FO_2 in Gas B and Gas C are set to achieve the lower bound of F_TETO_2, and FCO_2 in Gas A and Gas C are both set to achieve the lower bound F_TETCO_2. Hence, the greatest range of F_TETO_2 and F_TETCO_2 occurs when $F_BO_2 = F_CO_2$ and $F_ACO_2 = F_CCO_2$.

Table 2 is used to defines terns used to designate the O_2 and CO_2 concentrations in Gas A, Gas B and Gas C.

Table 2: Definition of terms used to designate the O_2 and CO_2 concentrations in Gas A, Gas B and Gas C.

	Fractional concentration O_2	Fractional concentration CO_2
Gas A	F_AO_2	F_ACO_2
Gas B	F_BO_2	F_BCO_2
Gas C	F_BO_2	F_ACO_2

[0096] The method summarized by Equations 11 and 9 are used to determine fractional concentrations of CO_2 and O_2 that have to be supplied in G^1 to attain target $F_{TET}CO_2$ and $F_{TET}O_2$, 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^1 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_2 in the source gas is equal to the sum of the flows of O_2 from the individual gases. Therefore:

$$\dot{V}G^1 \times F_G{}^1O_2 = \dot{Q}_A \times F_AO_2 + \dot{Q}_B \times F_BO_2 + \dot{Q}_C \times F_CO_2$$

[0099] But since $F_CO_2 = F_BO_2$ this can be rewritten as

$$\dot{V}G^1 \times F_G{}^1O_2 = \dot{Q}_A \times F_AO_2 + (\dot{V}G^1 - \dot{Q}_A) \times F_BO_2$$

which simplifies to

$$\dot{Q}_A = \frac{\dot{V}G^1(F_G{}^1O_2 - F_BO_2)}{F_AO_2 - F_BO_2} \qquad \text{Equation (1)}$$

[00100] The flow of CO_2 in the source gas is equal to the sum of the flows in the individual gases. Therefore:

$$\dot{V}G^1 \times FG^1CO_2 = \dot{Q}_A \times FACO_2 + \dot{Q}_B \times FBCO_2 + \dot{Q}_C \times FCO_2$$

[00101] But since $FACO_2 = FCCO_2$ this can be rewritten as

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

[00102] This simplifies to

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

[00103] Finally,

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

[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_2 concentration of FG^1O_2 and CO_2 concentration FG^1CO_2. It should be appreciated by those skilled in the art that other gas combinations for component gases may be used, and the derivation above may be extended to the general case of any concentration for any gas in the component gas. The same method and approach that is described for O_2 can be applied to any other gas that is absorbed, including, but not limited to acetylene, carbon monoxide, nitrous oxide, anesthetic gases. It is recognized that by defining target PCO_2 and target PO_2, target PN_2 is also defined. In the same way, the target partial pressure of any inert gas can be defined, for example, but not limited to argon, helium, and xenon.

[00105] Another aspect of this invention is the use of the independent control of end tidal CO_2 and O_2 , N_2 or other gas levels to carry out diagnostic and therapeutic tests or carry out research in physiology. What follows are examples that are not meant to be an exhaustive list of applications for instituting targeted blood gases. For example, the CO_2 levels may be rapidly transitioned from low to high targets and back repeatedly while the subject's brain blood flow is measured using the Blood Oxygen Level Dependent (BOLD) MRI imaging technique. This produces a map of cerebrovascular reactivity. BOLD and transcranial Doppler, for example can be used to measure the physiology of brain and other tissue blood flow response to changes in blood concentrations of CO_2, O_2, with or without the presence of other gases or substances in the blood. Similarly, occulovascular reactivity may be measured by measuring blood flow in the retinal vessels with Doppler ultrasound, MRI or other devices known to those skilled in the art, at target concentrations of CO_2, O_2 and other gases, with and without the presence of other substances in the blood. Another test involves manipulating O_2 levels in tumors and measuring beneficial oxygenation levels in the tumor using BOLD MRI signal or other methods known to those skilled in the art. This would identify blood gasses providing beneficial levels of blood flow and oxygenation to tumors, sensitizing them to destruction by radiotherapy or 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_2 and PCO_2 allows the reproducibility of test conditions. This in turn allows the comparison of tests on one subject from one time to the next and between subjects. This reproducibility of the test enables the doctor, for the first time, to follow the progress of an

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

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

[00108] In summary, this invention provides the ability to provide standard, reproducible stimuli via the lung to vascular beds and other tissues. When combined with any of a long list of sensors, known to those skilled in the art, a 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

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

assume that a particular subject population has a small range of values for CO_2 production and O_2 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 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_2 O_2 , one might provide the following premixed gases each 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	$F_{TET}O_2$	$F_{TET}CO_2$
D (1.5% CO_2 , 52.5% O_2 , Bal. N_2)	50%	4.0%
E (3.7% CO_2 , 22.5% O_2 , Bal. N_2)	20%	6.2%
F (2.6% CO_2 , 72.5% O_2 , Bal. N_2)	70%	5.1%

End Tidal Control Apparatus

[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_2 and CO_2. With reference to 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

(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 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 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 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, 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 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.

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

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

Alternate Embodiment

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

[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_2, CO_2 and N_2 equal to those required in the G^1 gas during each phase of the sequence, are connected to gas blender (1). 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 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.

[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. 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.

[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_2. Where a component gas

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.

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

[00123] While the above description describes preferred embodiments, it 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:

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.

2. A method according to claim1, wherein the at least one component gas comprises a single constituent gas.

3. A method according to claim1 or 2, wherein the source gas comprises a single component gas.

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

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 ($F_{G^1}X$) is set according to $F_{G^1}X = F_TETX - \frac{\dot{V}X}{\dot{V}G^1}$, 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 ($F_{G^1}X$) is set according to

$F_{G^1}X = F_{T}ETX + \frac{\dot{V}X}{\dot{V}G^1}$, 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 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 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.
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 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.
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:

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

b) setting the concentration of said gas X in the source gas to a predetermined level corresponding to the target end tidal concentration of gas X

c) delivering the source gas to the patient through said circuit

18. The method of claim 17 wherein said gas X is a gas produced by the patient, and the concentration of said gas X ($F_{G^1}X$) is set according to

$F_{G^1}X = F_{T}ETX - \frac{\dot{V}X}{\dot{V}G^1}$, where $\dot{V}X$ 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 ($F_{G^1}X$) is set according to

$F_{G^1}X = F_{T}ETX + \frac{\dot{V}X}{\dot{V}G^1}$, where $\dot{V}X$ is the patient's minute consumption of gas

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

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

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

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

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

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

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.

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.

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.

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

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 minimum safe concentration of O_2 .

30. The method of Claims 27or 28 where the source gas flow into the breathing circuit has a minimum safe concentration of O_2 .

31. The method of Claims 29 or 30 where the minimum safe level of O_2 concentration is 10%.

32. The method of Claims 29 or 30 where the minimum safe level of O_2 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.

35. The method of any of claims 17- 33 wherein the gas whose end tidal concentration target is being induced is O_2 .

36. The method of any of claims 17- 33 wherein the gas whose end tidal concentration target is being induced is CO_2 .

37. The method of Claim 33 where the component gases have the following relative concentrations:

a) Gas A: High O_2 , Low CO_2
b) Gas B: Low O_2 , High CO_2
c) Gas C: Low O_2 , Low CO_2

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

a) Gas A: 50-100% O_2 , 0-20% CO_2
b) Gas B: 10-30% O_2 , 20-80% CO_2
c) Gas C: 10-30% O_2 , 0-20% CO_2

39. The method of Claim 16 where the source gases have the following concentrations:
    a) Gas A: 100% O_2 , 0% CO_2
    b) Gas B: 10% O_2 , 20-80% CO_2
    c) Gas C: 10% O_2 , 0% CO_2
40. The method of Claim 16 where the source gases have the following concentrations:
    a) Gas A: 100% O_2 , 0% CO_2
    b) Gas B: 10% O_2 , 20-40% CO_2
    c) Gas C: 10% O_2 , 0% CO_2
41. The method of Claim 16 where the source gases have the following concentrations:
    a) Gas A: 100% O_2 , 0% CO_2
    b) Gas B: 10% O_2 , 40% CO_2
    c) Gas C: 10% O_2 , 0% CO_2
42. The method of Claim 16 where the source gases have the following concentrations:
    a) Gas A: 100% O_2 , 0% CO_2
    b) Gas B: 10% O_2 , 20% CO_2
    c) Gas C: 10% O_2 , 0% CO_2
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_2 and O_2 levels of a subject using the methods of claims 36 or 37.
    b) monitoring a blood oxygen level dependent (BOLD) MRI signal intensity
45. The method of Claim 44 where the end tidal CO_2 and O_2 levels are controlled independently of each other.
46. The method of Claim 44 or 45 where the end tidal CO_2 levels are changed while the end tidal O_2 levels are kept constant.

47. The method of Claim 44 or 45 where the end tidal PO_2 levels are changed while the end tidal PCO_2 levels are kept constant

48. The method of Claim 44 or 45 where the end tidal PO_2 levels and the end tidal PCO_2 levels are changed simultaneously

49. A method to measure occulovascular reactivity comprising:

a) controlling the end tidal CO_2 and O_2 levels of a subject using the methods of claims 36 or 37.

b) monitoring occulovascular blood flow

50. The method of Claim 49 where the end tidal CO_2 and O_2 levels are controlled independently of each other.

51. The method of Claim 49 or 50 where the end tidal CO_2 levels are changed while the end tidal O_2 levels are kept constant.

52. The method of Claim 49 or 50 where the end tidal PO_2 levels are changed while the end tidal PCO_2 levels are kept constant

53. The method of Claim 49 or 50 where the end tidal PO_2 levels and the end tidal PCO_2 levels are changed simultaneously.

54. A method to standardize measurement of occulovascular 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_2 and O_2 levels of a subject using the methods of claims 36 or 37.

b) monitoring oxygenation or blood flow in the tumor

56. The method of Claim 55 where the end tidal CO_2 and O_2 levels are controlled independently of each other.

57. The method of Claim 55 or 56 where the end tidal CO_2 levels are changed while the end tidal O_2 levels are kept constant.

58. The method of Claim 55 or 56 where the end tidal PO_2 levels are changed while the end tidal PCO_2 levels are kept constant

59. The method of Claim 55 or 56 where the end tidal PO_2 levels and the end tidal PCO_2 levels are changed simultaneously

60. A therapeutic method comprising any method according to claims 17 to 42.

61. A therapeutic method comprising:

a) using any of the methods of claims 55 to 60 to determine end tidal O_2 and CO_2 levels that provide a beneficial oxygenation or blood flow level to tissues for the purpose of radiotherapy or chemotherapy

b) using any of the methods of claims 17 to 42 to set the end tidal O_2 and CO_2 levels to said levels during radiotherapy or chemotherapy

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

d) means for controlling the concentration of said gases in the source gas flow independently of each other

63. The apparatus of Claim 62 further comprising means for monitoring end tidal CO_2 and O_2 concentrations

64. The apparatus of Claim 62 further comprising means for monitoring pressure 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 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

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 the following relative concentrations:

    a) Gas A: High O_2 , Low CO_2
    b) Gas B: Low O_2 , High CO_2
    c) Gas C: Low O_2 , Low CO_2

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

    a) Gas A: 50-100% O_2 , 0-20% CO_2
    b) Gas B: 10-30% O_2 , 20-80% CO_2
    c) Gas C: 10-30% O_2 , 0-20% CO_2

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

    a) Gas A: 100% O_2 , 0% CO_2
    b) Gas B: 10% O_2 , 20-80% CO_2
    c) Gas C: 10% O_2 , 0% CO_2

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

    a) Gas A: 100% O_2 , 0% CO_2
    b) Gas B: 10% O_2 , 20-40% CO_2
    c) Gas C: 10% O_2 , 0% CO_2

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

    a) Gas A: 100% O_2 , 0% CO_2
    b) Gas B: 10% O_2 , 40% CO_2
    c) Gas C: 10% O_2 , 0% CO_2

74. The apparatus of Claim 69 where the at least three component gases in the source gas have the following concentrations:
    a) Gas A: 100% O_2 , 0% CO_2
    b) Gas B: 10% O_2 , 20% CO_2
    c) Gas C: 10% O_2 , 0% CO_2
75. The method of claims 17 to 61 further comprising the steps of:
    a) monitoring the end tidal gas concentration of the patient for a particular gas
    b) increasing or decreasing the concentration of said gas so as to decrease 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 claim1, 2 or 3, wherein the at least one component gas is a blended gas.
77. A method according to claim1, 2 or 3 wherein the concentration of the at least 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:
    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 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.

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.

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

82. A method according to claim 78, wherein said gas X is a gas produced by the subject, and the concentration of said gas X (FG^1X) is computed according to $FG^1X = F_TETX - \frac{\dot{V}X}{\dot{V}G^1}$, 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.

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 according to $FG^1X = F_TETX + \frac{\dot{V}X}{\dot{V}G^1}$, 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.

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

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.

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

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 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 gas X.

90. A method according to claim 89, further comprising the step of measuring a physiological variable in a subject for at a least one time point within at least one time period in which the subject is exhaling a gas having said first end tidal concentration of gas X and for at a least one time point within at least 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 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 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.

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

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

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

98. A system according to claim 95, wherein said gas X is a gas produced by the subject, and the concentration of said gas X ($FG^{I}X$) is computed according to $FG^{I}X = F_{T}ETX - \frac{\dot{V}X}{\dot{V}G^{I}}$, where $\dot{V}X$ is the subject's minute production of gas X, $F_{T}ETX$ is the selected end tidal concentration of gas X, and $\dot{V}G^{I}$ is the flow rate of the source gas.

99. A system according to claim 94, wherein said gas X is a gas consumed by the subject, and the concentration of said gas X ($FG^{I}X$) is computed according to $FG^{I}X = F_{T}ETX + \frac{\dot{V}X}{\dot{V}G^{I}}$, where $\dot{V}X$ is the subject's minute consumption of gas X, $F_{T}ETX$ is the selected end tidal concentration of gas X and $\dot{V}G^{I}$ is the flow rate of the source gas.

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_2.

101. A system according to claim 95, wherein the source gas outlet is fluidly connected to a sequential gas delivery circuit.

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 :

a) making available for aquisition an apparatus having at least a source gas outlet, a plurality of component gas inlets, and a flow controller for each component gas;

b) facilitating implementation of machine readable instructions to drive a processor unit programmable to derive the concentration of said 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.

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:

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;

a. providing instructions for acquisition of said machine readable instructions;

b. providing instructions for use of said machine readable instructions;

c. providing instructions for development of said machine readable instructions;

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

e. providing instructions for working, updating, upgrading, trouble-shooting, substitution, repair or re-acquisition, of said machine readable instructions or such processor unit.

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.

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.

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.

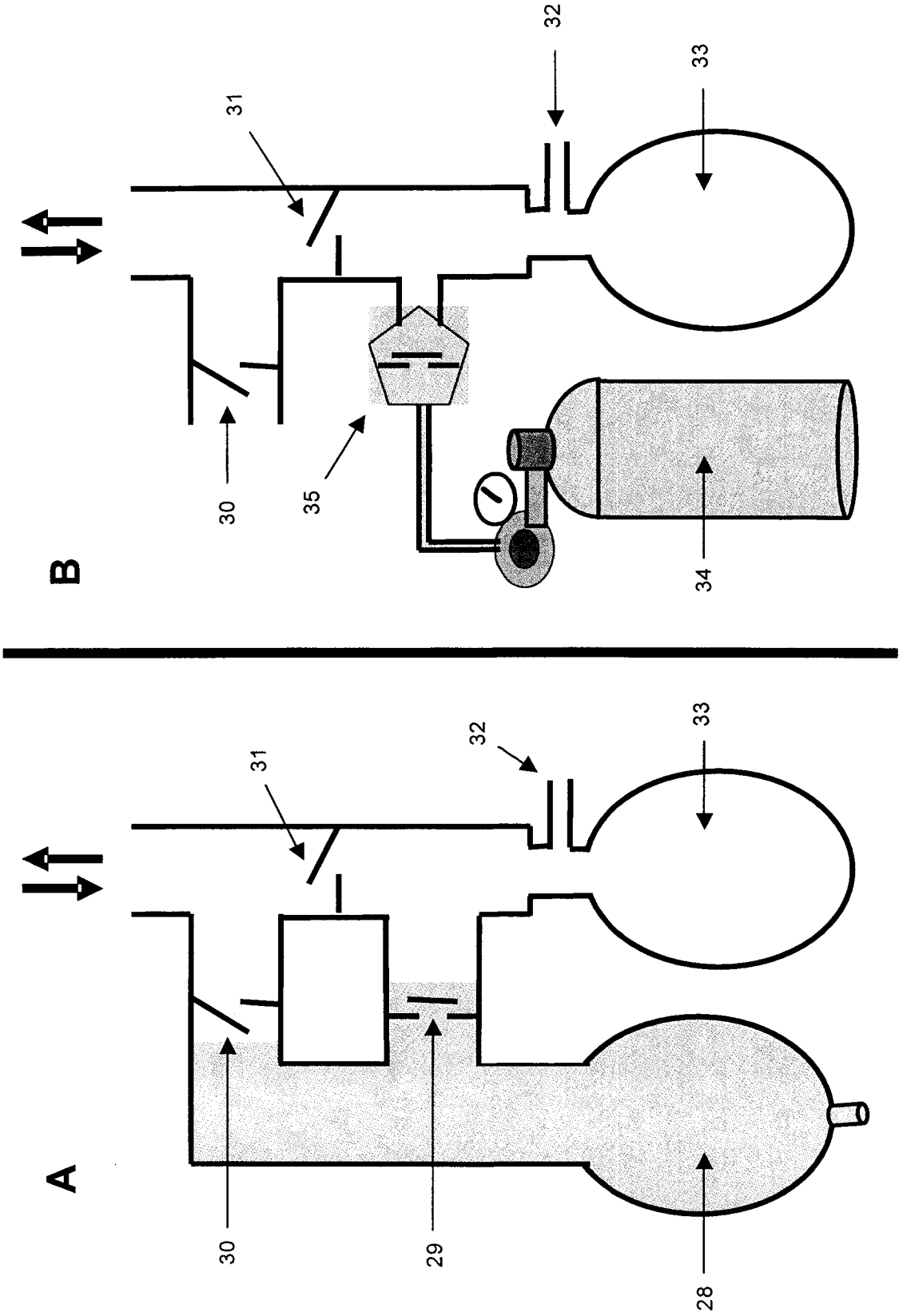


Figure 1

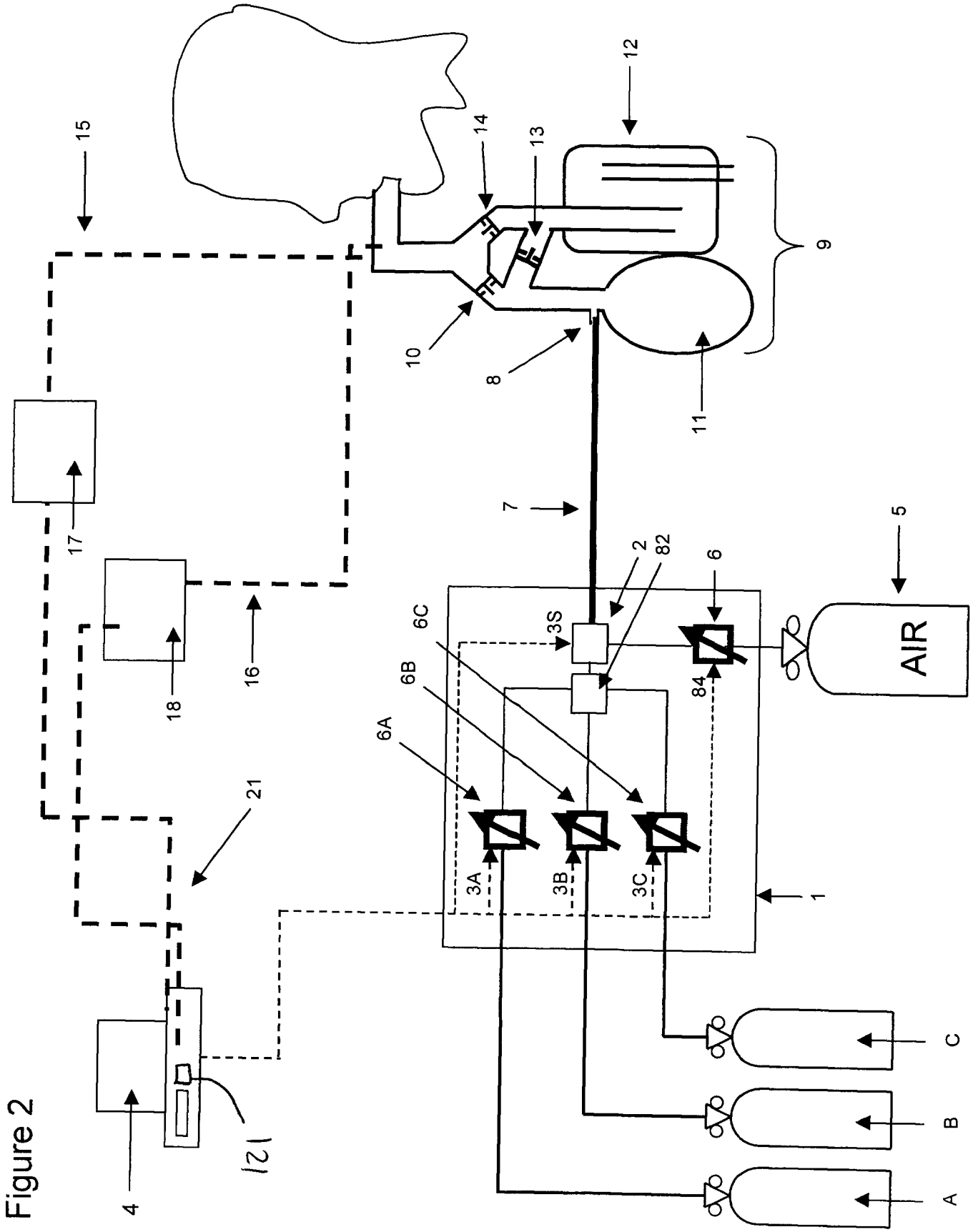

15
14
13
12
9
10
8
11
17
7
5
2
82
6
6C
3S
AIR
6B
84
6A
18
16
21
3A
3B
3C
1
4
121
C
B
A

Figure 2

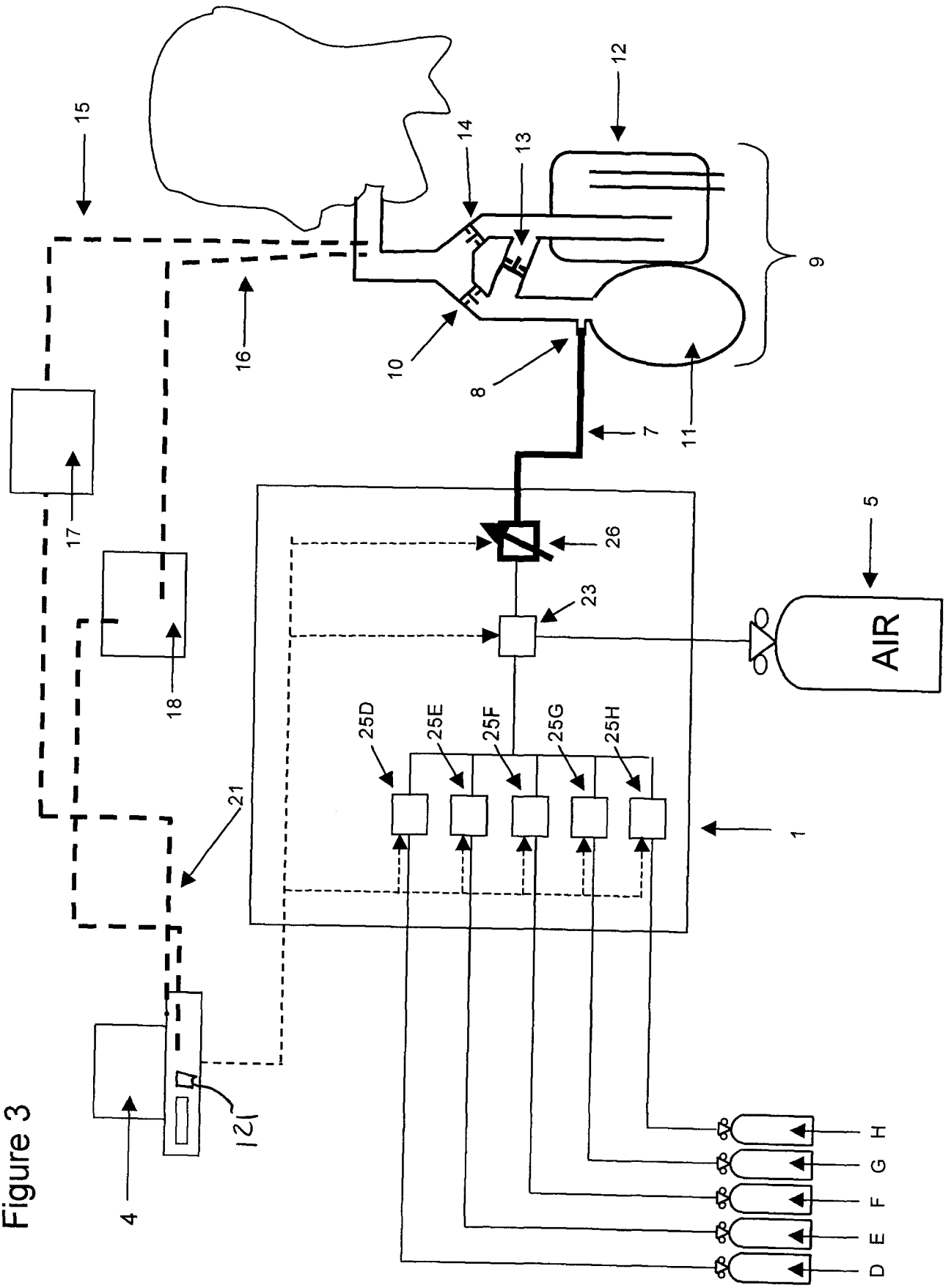

15
14
13
12
9
16
10
8
11
7
17
26
23
5
AIR
18
25D
25E
25F
25G
25H
21
1
121
4
D E F G H

Figure 3

Figure 4

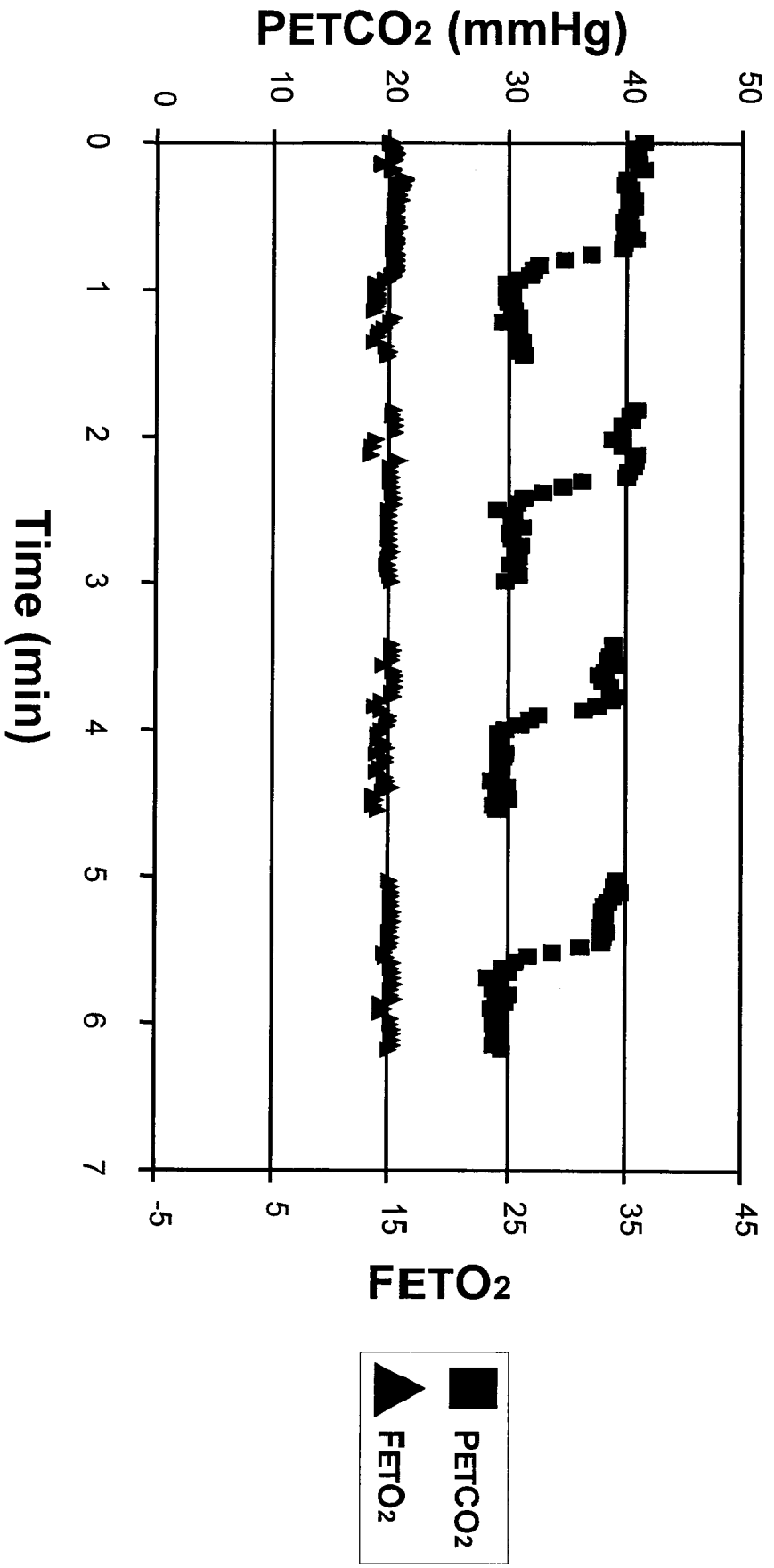

CO2 steps at normoxia
PETCO2 (mmHg)
0
10
20
30
40
50
Time (min)
0
1
2
3
4
5
6
7
FETO2
-5
5
15
25
35
45
PETCO2
FETO2

Figure 5

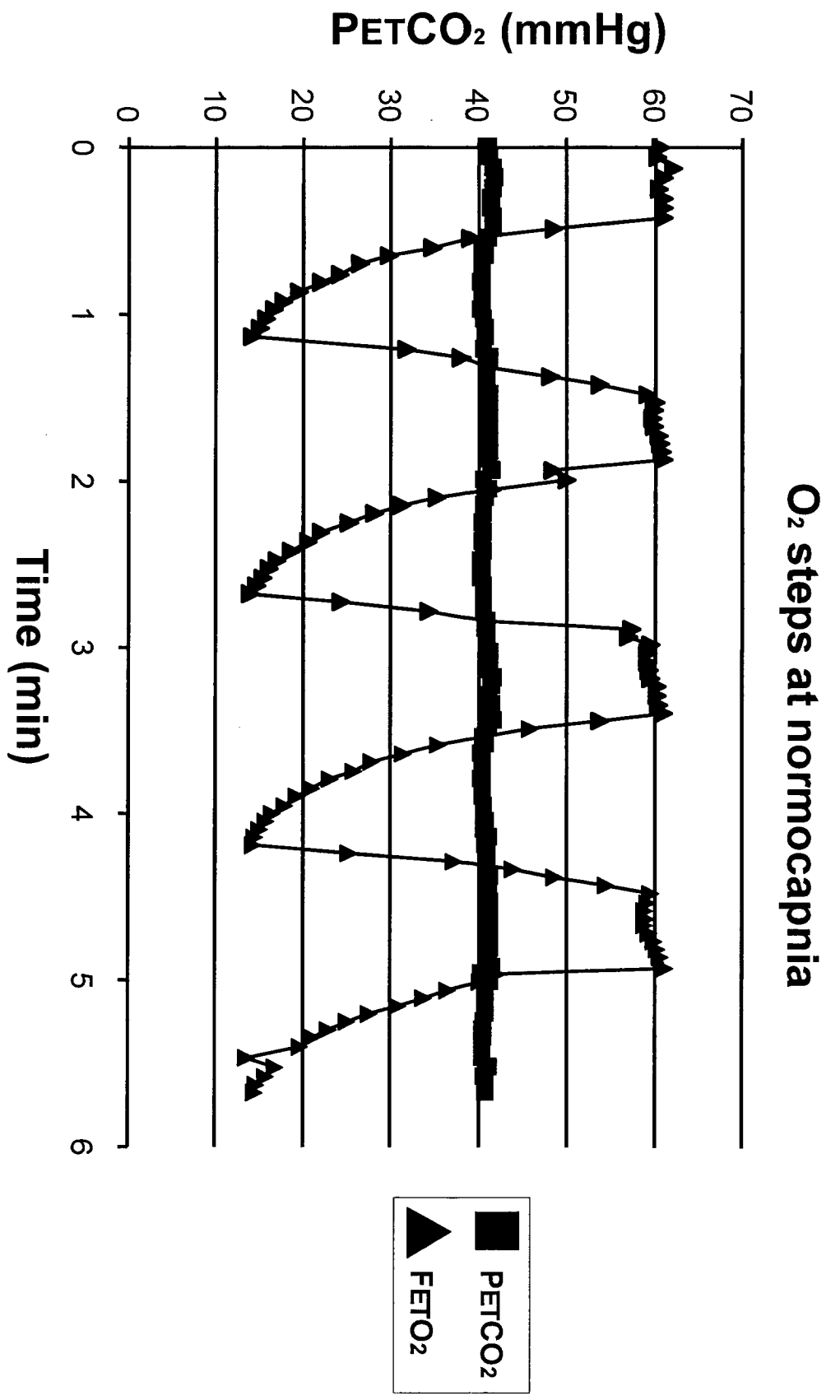
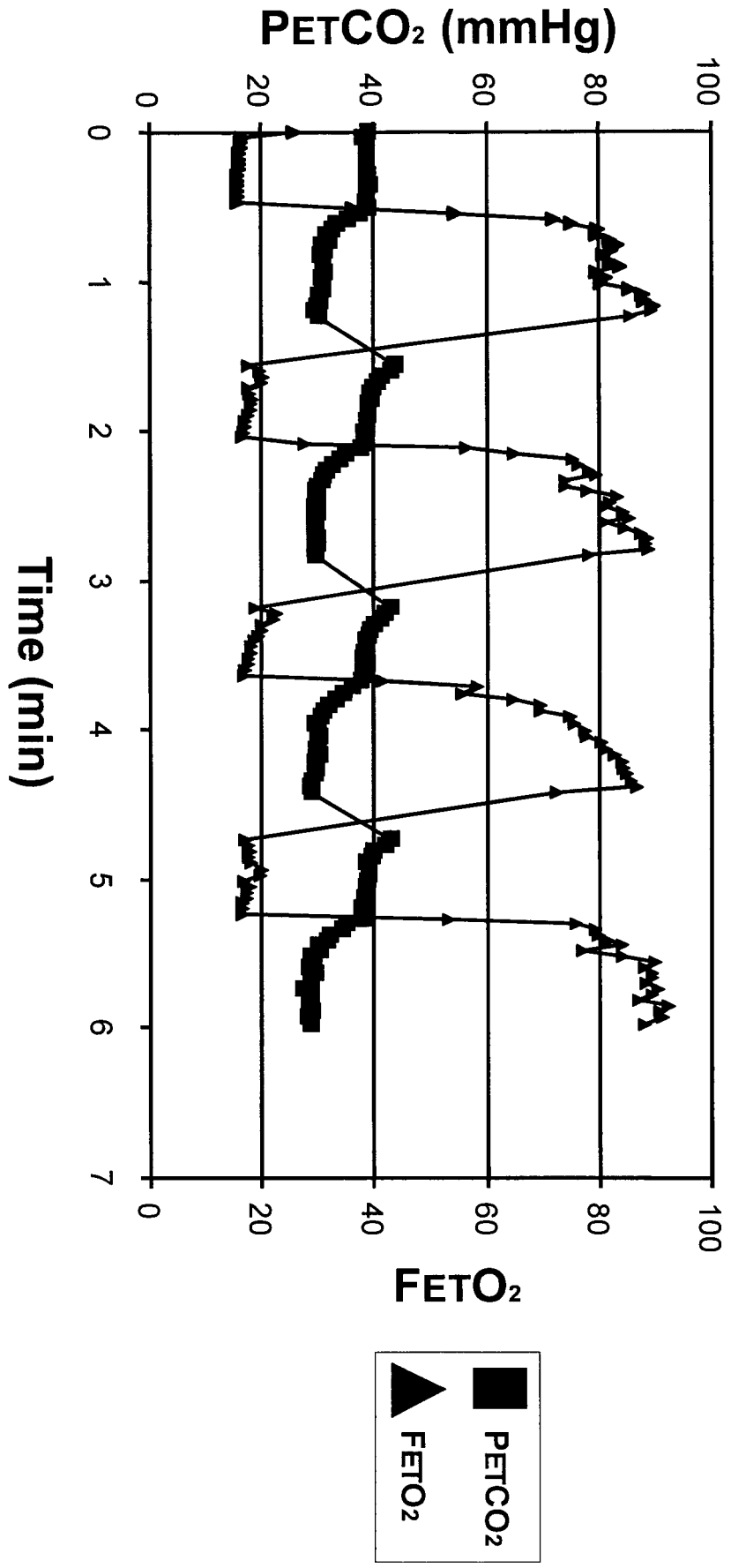

PETCO2 (mmHg)
0
10
20
30
40
50
60
70
Time (min)
0
1
2
3
4
5
6
O2 steps at normocapnia
PETCO2
FETO2

Figure 6


Simultaneous changes in O2 and CO2
PETCO2 (mmHg)
0
20
40
60
80
100
Time (min)
0
1
2
3
4
5
6
7
FETO2
PETCO2
FETO2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/001258

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***A61M 16/10*** (2006.01) , ***A61M 16/00*** (2006.01) , ***A61M 16/12*** (2006.01) , *A61B 5/055* (2006.01) , *A61B 5/026* (2006.01) , *A61B 8/06* (2006.01) , *A61B 8/10* (2006.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC: *A61M 16/*-- (2006.01) , *A61B 5/*-- (2006.01) , *A61B 8/*-- (2006.01); ECLA: A61M16/00C;
ICO: K16:10A10, 10A10C, 10A10D; US Classes: 128/204.22, 128/205.17

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Delphion, Qweb, USPTO, Canadian Patent Database, Esp@cenet, PubMed, Internet and keywords: target, end, tidal, concentration, gas, re-breathing or rebreathing, minute ventilation, constituent or component, source, induc*, maintain*, cerebrovascular reactivity, O2 and

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2004/0206354 A1 (Fisher et al.) 21 Oct. 2004 (21-10-2004) Entire document	1-4, 7, 15, 16, 62-74, 76-81, 84, 92-97, 100-110
Y	*MRI mapping of cerebrovascular reactivity using square wave changes in end-tidal PCO_2*, Vesley et al., Magnetic Resonance in Medicine, Volume 45, Issue 6 , Pages 1011 - 1013, Published Online: 23 May 2001	1-4, 7, 15, 16, 62-74, 76-81, 84, 92-97, 100-110
Y	US 5 320 093 (Raemer) 14 June 1994 (14-06-1994) Entire document	63
Y	US 2004/0060560 A1 (Stenzler et al.) 1 Apr. 2004 (01-04-2004) paragraphs 7 and 8 and figures 1 to 3	65, 101
Y	US 5 957 129 (Tham et al.) 28 Sep. 1999 (28-09-1999) col. 5, line 56 to col. 7, line 30 and figure 1	67-74, 96, 100, 106, 108-110
A	US 2004/0144383 A1 (Thomas et al.) 29 July 2004 (29-07-2004) Entire document	1, 62, 78, 94, 103, 107
A	US 2004/0230113 A1 (Bolam et al.) 18 Nov. 2004 (18-11-2004) Entire document	1, 62, 78, 94, 103, 107

[ ] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 December 2006 (06-12-2006)	13 December 2006 (13-12-2006)

Name and mailing address of the ISA/CA	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	Eric Lafontaine 819- 956-9965

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/001258

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. [X] Claim Nos. : 8-14, 17-53*, 55-61, 75 and 85-91
because they relate to subject matter not required to be searched by this Authority, namely :

The claims are directed to a method for treatment of the human or animal body by surgery or therapy, are not required to be searched nor is a written opinion required by this Authority.
*if claims 38-42 are dependent on claim 37 instead of claim 16 (similar to dependency of claims 71 to 74 on claim 70)

2. [X] Claim Nos. : 54
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

The claim is directed to the desired result rather than to the combination necessary to achieve that result as described in the description.

3. [ ] Claim Nos. :
because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2006/001258

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
US2004206354	21-10-2004	AU4626601 A	15-10-2001
		CA2304292 A1	30-09-2001
		CA2340511 A1	30-09-2001
		CA2346517 A1	04-11-2002
		EP1267978 A1	02-01-2003
		EP1370319 A1	17-12-2003
		EP1383565 A2	28-01-2004
		US6612308 B2	02-09-2003
		US6622725 B1	23-09-2003
		US6799570 B2	05-10-2004
		US7100606 B2	05-09-2006
		WO0174433 A1	11-10-2001
		WO02072185 A1	19-09-2002
		WO02089888 A2	14-11-2002
US5320093	14-06-1994	AU9167591 A	22-07-1992
		WO9211052 A1	09-07-1992
US2004060560	01-04-2004	AT311921T T	15-12-2005
		DE60302622D D1	12-01-2006
		DE60302622T T2	03-08-2006
		EP1402915 A1	31-03-2004
		US2004084048 A1	06-05-2004
US5957129	28-09-1999	DE69827997D D1	13-01-2005
		DE69827997T T2	08-12-2005
		EP0894506 A2	03-02-1999
US2004144383	29-07-2004	AU2003291817 A1	30-08-2004
		CA2514481 A1	19-08-2004
		EP1590029 A1	02-11-2005
		JP2006513004T T	20-04-2006
		MXPA05008071 A	17-03-2006
		WO2004069317 A1	19-08-2004
US2004230113	18-11-2004	CA2520248 A1	11-11-2004
		CN1777454 A	24-05-2006
		EP1620154 A1	01-02-2006
		WO2004096333 A1	11-11-2004