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(71) Applicant: **MAQUET CRITICAL CARE AB** [SE/SE];
P.O. Box 6108, 171 06 Solna (SE).(72) Inventor: **HALLBÄCK, Magnus**; Robertsviksvägen 8,
182 35 Danderyd (SE).(74) Agent: **ZACCO SWEDEN AB**; P.O. Box 5581, Val-
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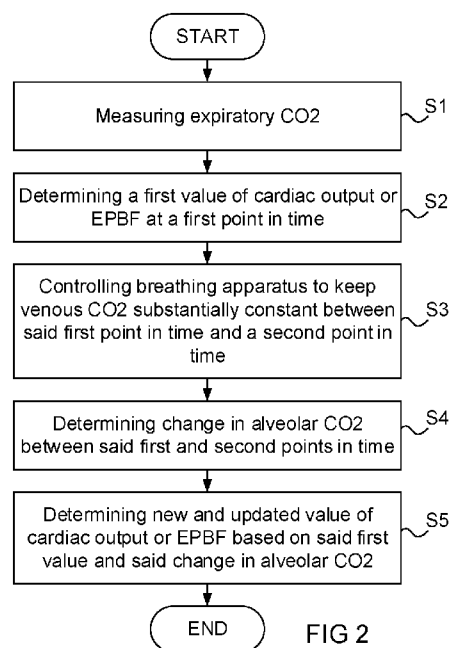


FIG 2

(57) Abstract: The present disclosure relates to a capnotracking method for continuous determination of cardiac output or EPBF of a mechanically ventilated subject (3), comprising the steps of measuring (S1) expiratory CO₂ of the subject and determining (S2) a first value of cardiac output or EPBF of the subject at a first point in time. The method further comprises the steps of controlling (S3) the mechanical ventilation of the subject to keep a level of venous CO₂ of the subject substantially constant between the first point in time and a second point in time, determining (S4) from the expiratory CO₂ measurements a change in alveolar CO₂ of the subject between the first and second points in time, and determining (S5) a second and updated value of cardiac output or EPBF of the subject based on the first value and the change in alveolar CO₂.

CAPNOTRACKING OF CARDIAC OUTPUT OR EFFECTIVE PULMONARY BLOOD FLOW DURING MECHANICAL VENTILATION

TECHNICAL FIELD

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The present disclosure relates to a method, a computer program and a breathing apparatus for determination of cardiac output or effective pulmonary blood flow of a mechanically ventilated subject.

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BACKGROUND

Monitoring of cardiac output and EPBF (effective pulmonary blood flow) is important when the cardiovascular stability of a subject is potentially threatened, e.g., during surgery or in critically ill patients. Therefore, it is often desired to monitor the cardiac output and/or the EPBF of mechanically ventilated patients.

Most non-invasive respiratory based methods for determination of cardiac output or EPBF are based on some form of the basic physiological principle known as the Fick principle. According to the Fick equation, the cardiac output of a patient may be determined using the following basic relationship:

$$Q = \frac{VCO_2}{(CvCO_2 - CaCO_2)} \quad \text{Eq. 1}$$

where Q is cardiac output, VCO₂ is the volume of carbon dioxide excreted from the body of a patient during respiration (carbon dioxide elimination), CvCO₂ is the carbon dioxide concentration in venous blood of the patient, and CaCO₂ is the carbon dioxide concentration in arterial blood of the patient.

As well known in the art, EPBF is directly derivable from the cardiac output as:

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$$Q \cdot (1 - fs) = EPBF \quad \text{Eq. 2}$$

where f_s is the pulmonary shunt fraction.

Most methods for cardiac output or EPBF determination employ differential Fick
5 techniques based on the premise that cardiac output and EPBF can be estimated
from measurable changes in CO_2 elimination (VCO_2) and partial pressure of CO_2 of
expired alveolar gas (PACO_2). The measurable changes in VCO_2 are normally
introduced by changing the effective ventilation of the patient, meaning that the
cardiac output or the EPBF of the mechanically ventilated subject is determined
10 from an analysed sequence of breaths during which the effective ventilation of the
patient is changed to cause a change in VCO_2 . The calculations for determination of
cardiac output or EPBF and the ventilation pattern employed to cause the change in
 VCO_2 may vary. Examples of calculations and ventilation patterns employed in prior
art are described in e.g., WO 2006/119546, US7135001, WO2013/141766,
15 EP2799008 and PCT/SE2015/051357.

Most of the above-identified Fick based methods allow for cardiac output or EPBF to
be determined continuously, i.e., on a breath by breath basis, as long as the patient
is ventilated using a cyclic ventilation pattern that is adapted to cause sufficient
20 changes in VCO_2 .

However, during mechanical ventilation, there is sometimes a need for changing the
effective ventilation of the patient in a manner that is not commensurate with the
ventilation pattern required for continuous Fick based determination of cardiac
25 output or EPBF, i.e., in a way that does not allow cardiac output or EPBF to be
determined from measured changes in VCO_2 . For example, interruption of the cyclic
ventilation pattern required for Fick based cardiac output or EPBF determination
may be required for the carrying out of blood gas withdrawal or other diagnostic or
therapeutic interventions on the ventilated patient. Alternatively, the measurement
30 signals used for the Fick based determination may, during certain circumstances, be
lost or deteriorated to an extent rendering cardiac output or EPBF determination
impossible. This may be the case, e.g., in a situation in which a surgeon affects the
breath-by-breath cardiac output of the ventilated patient in a manner making the
level of expired CO_2 fall outside the operating range of the Fick method.

To be able to estimate the cardiac output or EPBF of the patient also in situations where Fick based techniques cannot be used, various tracking techniques for tracking breath-to-breath changes in cardiac output or EPBF have been proposed.

- 5 Once a first (baseline) value of cardiac output or EPBF has been determined using, e.g., a Fick based method, the tracking techniques can be used to provide breath-by-breath estimates of cardiac output or EPBF even if the cyclic ventilation pattern is interrupted.
- 10 An example of such a tracking technique is disclosed in WO 2006/119546, wherein a baseline measure of cardiac output and a "continuity equation" for determining breath-by-breath changes in EPBF is used for continuous, non-invasive monitoring of cardiac output. This method is referred to as the "capnotracking method" as it uses CO₂ measurements in the cardiac output determination. A similar tracking
- 15 technique is disclosed in WO2009/062255. Yet other examples of tracking techniques for continuous determination of cardiac output or EPBF are discussed in US6217524 and EP1238631. In all of these tracking techniques, breath-by-breath changes in cardiac output or EPBF are calculated from measured changes in VCO₂.

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SUMMARY OF THE DISCLOSURE

- It is an object of this disclosure to provide an improved or at least alternative technique for continuous (breath-by-breath) determination of the cardiac output or
- 25 EPBF of a mechanically ventilated subject.

- In particular, it is an object of this disclosure to provide a technique for continuous determination of cardiac output or EPBF which can be used in situations where the ventilation pattern currently applied to the ventilated patient does not allow
- 30 conventional Fick based techniques to be used for cardiac output or EPBF determination.

These and other objects which will become apparent in view of the detailed description following hereinafter are achieved according to one aspect of the present

disclosure by a method for determination of cardiac output or EPBF during mechanical ventilation of a subject, comprising the steps of:

- measuring expiratory CO₂ of the subject, i.e., the CO₂ content of expiration gas expired by the subject;
- 5 - determining, at a first point in time, a first value of cardiac output or EPBF of the subject;
- controlling the mechanical ventilation of the subject to keep a level of venous CO₂ of the subject substantially constant between the first point in time and a second point in time;
- 10 - determining, from the expiratory CO₂ measurements, a change in alveolar CO₂ of the subject between the first and second points in time, and
- determining a second and updated value of cardiac output or EPBF of the subject based on the first value of cardiac output or EPBF and the change in alveolar CO₂.

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In accordance with certain embodiments of this disclosure, the level of venous CO₂ of the subject is kept substantially constant by determining the CO₂ elimination (VCO₂) of the subject and using VCO₂ as control parameter when controlling the mechanical ventilation of the subject. The VCO₂ of the subject may be determined
20 from the expiratory CO₂ measurements together with expiratory flow measurements. In some embodiments, expiratory flow measurements may also be used together with the expiratory CO₂ measurements in the determination of the change in alveolar CO₂.

- 25 If the metabolic production of CO₂ of the ventilated subject is constant during the relevant time period, the level of venous CO₂ will remain constant as long as the CO₂ elimination of the subject remains constant. Therefore, in embodiments in which the metabolic production of CO₂ is or is assumed to be constant, the level of venous CO₂ may be kept substantially constant by controlling the mechanical
30 ventilation of the subject to keep VCO₂ substantially constant between the first and second points in time.

In other embodiments of this disclosure, the method may be adapted to take variations in metabolic production of CO₂ of the ventilated subject into account. In

this scenario, the method may comprise the additional steps of measuring flow and oxygen content of respiration gases, and determining the O₂ consumption (VO₂) of the subject based on the measured flow and O₂ content. Preferably, but not necessarily, the O₂ consumption of the subject is determined from measurements of both inspiratory and expiratory flow and O₂ content. The level of venous CO₂ may then be kept substantially constant by controlling the mechanical ventilation of the subject in a manner causing VCO₂ to vary in proportion to VO₂ between the first and second points in time.

When changes in cardiac output or EPBF of the ventilated subject occur, e.g., due to changes in fluid status, ventilator settings, intrapulmonary shunt or due to surgical interventions in the subject, the transport of CO₂ from the blood to the lung of the subject becomes affected. This change in CO₂ transport in turn changes the level of alveolar CO₂ and the VCO₂ of the subject. While known techniques for capnotracking of cardiac output or EPBF use this change in VCO₂ to calculate changes in cardiac output or EPBF, the proposed technique uses a fundamentally different approach by keeping VCO₂ constant (or constant in relation to the oxygen consumption of the ventilated subject) through active control of the breathing apparatus mechanically ventilating the subject. This is advantageous in that changes in cardiac output or EPBF can be determined from changes in alveolar CO₂ alone. Another advantage of the proposed capnotracking technique is that that venous CO₂ content does not have to be determined on a breath-by-breath basis since the mechanical ventilation of the subject is controlled to prevent any changes therein.

Thus, according to the present disclosure, when changes in cardiac output or EPBF occur, the mechanical ventilation of the subject is changed to prevent changes in venous CO₂, thereby allowing the changes in cardiac output or EPBF to be quantified from changes in alveolar CO₂ alone.

The change in mechanical ventilation typically involves a change in the duration and/or volume of breaths delivered by the breathing apparatus to the subject, e.g., a change in respiratory rate (RR) or tidal volume (VTi). Consequently, in some embodiments, the method comprises the steps of measuring VCO₂ of the ventilated

subject and controlling the breathing apparatus to keep VCO₂ substantially constant, or constant in relation to a measured oxygen consumption of the subject, by adjusting any or both of the duration and volume of breaths delivered by the breathing apparatus.

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The first value of cardiac output or EPBF determined at the first point in time can be said to represent a baseline level of cardiac output or EPBF, serving as a starting point for determination of the new and updated value of cardiac output or EPBF. The proposed method thus presents a type of capnotracking technique for continuous
10 cardiac output or EPBF determination, which may be employed once a first “baseline value” of cardiac output or EPBF has been established.

The first value of cardiac output or EPBF may be determined using any known technique for cardiac output or EPBF determination. In accordance with certain
15 embodiments of this disclosure, the first value is determined using a non-invasive technique for cardiac output or EPBF since this makes the method completely non-invasive. In accordance with a particular embodiment, the first value of cardiac output or EPBF of the ventilated subject is determined from the expiratory flow and CO₂ measurements using a Fick based technique, such as a differential Fick
20 technique. For example, the first value of cardiac output or EPBF may be determined using the Fick based techniques disclosed in any of the above mentioned WO 2006/119546, US7135001, WO2013/141766, EP2799008 and PCT/SE2015/051357. For even more accurate cardiac output or EPBF determination taking relative variations in cardiac output or EPBF during the
25 sequence of analysed breaths into account, the first value may be determined using the Fick based technique disclosed in the unpublished, co-pending patent application PCT/SE2016/050402.

It is contemplated by the present disclosure that any of the above mentioned Fick
30 based techniques may be used for continuous (breath-by-breath) determination of the cardiac output or EPBF of a ventilated subject during periods of ventilation (hereinafter referred to as Fick phases) in which the subject can be ventilated using a ventilation pattern allowing cardiac output or EPBF to be determined using the Fick based technique, whereas the proposed capnotracking technique may be used

for determination of the cardiac output or EPBF of the ventilated subject in a capnotracking phase following one of the Fick phases using a value of cardiac output or EPBF determined during the Fick phase as a starting point or baseline value for capnotracking.

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The above described method is typically a computer-implemented method that is carried out through execution of a computer program. Thus, according to another aspect of the present disclosure there is provided a computer program for determination of cardiac output or EPBF of a mechanically ventilated subject. The computer program comprises computer program code segments which, when executed by a processing unit, i.e., a processor, of the above mentioned breathing apparatus, cause the breathing apparatus to:

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- measure expiratory CO₂ of the subject;
- determine, at a first point in time, a first value of cardiac output or EPBF of the subject;
- control the mechanical ventilation of the subject to keep a level of venous CO₂ substantially constant between the first point in time and a second point in time;
- determine, from the expiratory CO₂ measurements, a change in alveolar CO₂ of the subject between the first and second points in time, and
- determine a second and updated value of cardiac output or EPBF of the ventilated subject based on the first value and the change in alveolar CO₂.

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The computer program may further comprise program code segments for determining the cardiac output or EPBF of the ventilated subject in accordance with any of the above described principles.

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According to yet another aspect of the present disclosure there is provided a non-volatile memory storing the computer program.

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According to yet another aspect of the present disclosure there is provided a breathing apparatus, such as a ventilator or an anaesthesia machine, configured to carry out the above described method for determination of cardiac output or EPBF of a mechanically ventilated subject.

To this end, the breathing apparatus comprises a CO₂ sensor for measuring expiratory CO₂ of the subject, and a control unit configured to determine, at a first point in time, a first value of cardiac output or EPBF of the subject, the control unit being configured to:

- 5 - control the mechanical ventilation of the subject to keep a level of venous CO₂ of the subject substantially constant between the first point in time and a second point in time;
- determine, from the expiratory CO₂ measurements, a change in alveolar CO₂ of the subject between the first and second points in time, and
- 10 - determine a second and updated value of cardiac output or EPBF of the subject based on the first value and the change in alveolar CO₂.

In accordance with certain embodiments of this disclosure, the control unit is configured to use a measure of CO₂ elimination (VCO₂) of the subject as control
15 parameter to keep the level of venous CO₂ substantially constant. To this end, the control unit may be configured to determine the VCO₂ of the subject from the expiratory CO₂ measurements together with expiratory flow measurements, which expiratory flow measurements, in some embodiments, are obtained by a flow sensor of the breathing apparatus. The expiratory flow measurements may also be used by
20 the control unit, together with the expiratory CO₂ measurements, in the determination of the change in alveolar CO₂.

In accordance with an embodiment of this disclosure, the control unit is configured to keep the level of venous CO₂ substantially constant by controlling the mechanical
25 ventilation to keep the VCO₂ of the subject substantially constant between the first and second points in time, or to keep the VCO₂ of the subject substantially constant in relation to a measured oxygen consumption of the subject.

More advantageous aspects of the proposed method, computer program and
30 breathing apparatus will be described in the detailed description of embodiments following hereinafter.

BRIEF DESCRIPTION OF THE DRAWINGS

Embodiments of this disclosure will become more fully understood from the detailed description provided hereinafter and the accompanying drawings which are given by way of illustration only. In the different drawings, same reference numerals correspond to the same element.

Fig. 1 illustrates a breathing apparatus according to an exemplary embodiment of the present disclosure, and

Fig. 2 is a flow chart illustrating a method for determination of cardiac output or EPBF of a mechanically ventilated subject, according to an exemplary embodiment of the present disclosure.

DETAILED DESCRIPTION

Fig. 1 illustrates a breathing apparatus 1 configured for determination of cardiac output or EPBF of a mechanically ventilated subject 3, hereinafter sometimes referred to as the patient, in accordance with a non-limiting, illustrating embodiment of the present disclosure. The breathing apparatus 1 may be a ventilator, an anaesthesia machine or any other breathing apparatus adapted for mechanical ventilation of a subject in need of respiratory support.

The breathing apparatus 1 is connected to the patient 3 via an inspiratory line 7 for supplying breathing gas to the patient 3, and an expiratory line 9 for conveying expiration gas away from the patient 3. The inspiratory line 7 and the expiratory line 9 are connected to a common line 11, via a so called Y-piece 12, which common line is connected to the patient 3 via a patient connector 13, such as a facemask or an endotracheal tube.

The breathing apparatus 1 further comprises a control unit 14, such as a control computer, for controlling the ventilation of the patient 3 based on preset parameters and/or measurements obtained by various sensors of the breathing apparatus. The

control unit 14 controls the ventilation of the patient 3 by controlling a pneumatic unit (i.e. a gas regulator) 15 of the breathing apparatus 1, which pneumatic unit 15 is connected, on one hand, to one or more gas sources 17, 19 and, on the other hand, to the inspiratory line 7 for regulating a flow and/or pressure of breathing gas delivered to the patient 3. To this end, the pneumatic unit 15 may comprise various gas mixing and regulating means well known in the art of ventilation, such as gas mixing chambers, controllable gas mixing valves and one or more controllable inspiration valves.

10 The control unit 14 comprises a processing unit 21 and a non-volatile memory device 23 storing a computer program for determining the cardiac output or EPBF of the patient 3 according to the principles described herein. Unless stated otherwise, actions and method steps described hereinafter are performed by, or caused by, the control unit 14 of the breathing apparatus 1 upon execution by the processing unit 15 21 of different code segments of the computer program stored in the memory 23.

The breathing apparatus 1 further comprises at least one flow sensor 27 for measuring at least an expiratory flow of expiration gas exhaled by the patient 3, and at least one CO₂ sensor 29 for measuring the CO₂ content of at least the expiration gas exhaled by the patient. The control unit 14 is configured to determine the cardiac output or EPBF of the patient 3 based on the CO₂ measurements obtained by the CO₂ sensor, as will be described in more detail below. Also the measurements of expiratory flow obtained by the flow sensor 27 may be used by the control unit 14 in the cardiac output or EPBF determination. Preferably, the flow and CO₂ sensors 27, 29 are configured to measure also inspiratory flow and CO₂ content.

In the illustrated embodiment, the flow sensor 27 and the CO₂ sensor 29 form parts of a capnograph 31 configured for volumetric capnography measurements. The capnograph 31 is arranged in the proximity of the airway opening of the patient 3, namely, in the common line 11 of the breathing circuit in which it is exposed to all gas exhaled and inhaled by the patient 3. The capnograph 31 is connected to the breathing apparatus 1 via a wired or wireless connection 33, and configured to communicate the result of the flow and CO₂ measurements to the breathing

apparatus for further processing by the processing unit 21. The breathing apparatus 1 may be configured to generate a volumetric capnogram 35 from the flow and CO₂ measurements received from the capnograph 31, and, additionally, to display the volumetric capnogram 35 on a display 37 of the breathing apparatus.

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Additionally, the breathing apparatus 1 may comprise an oxygen sensor 39 for measuring inspiratory O₂, i.e., the O₂ content of the breathing gas delivered to the patient 3 during inspiration, as well as expiratory O₂, i.e., the O₂ content of the expiration gas exhaled by the patient during expiration. The oxygen sensor 39 is
10 connected to the breathing apparatus 1 via a wired or wireless connection 41, and configured to communicate the result of the O₂ measurements to the breathing apparatus for further processing by the processing unit 21. In embodiments taking variations in the metabolic production of CO₂ into account, the processing unit 21 may be configured to use the O₂ measurements obtained by the O₂ sensor 39 to
15 determine the O₂ consumption of the patient 3, and to use the O₂ consumption in the determination of the cardiac output or EPBF of the patient 3, as will be described in more detail below.

In a preferred embodiment, the control unit 14 is configured to determine a first
20 value, or baseline value, of cardiac output or EPBF of the patient 3 from the flow and CO₂ measurements obtained by the flow and CO₂ sensors 27, 29 using a non-invasive respiratory based method, preferably a Fick method.

Fick based determination of cardiac output or EPBF typically requires the level of
25 expired CO₂ to change with at least 0,2% and preferably around 0,5% or more during the analysed sequence of breaths. To this end, the control unit 14 is configured to introduce a change in the effective ventilation of the patient 3 by changing one or more breathing apparatus settings controlling the ventilation of the patient 3, and to determine the cardiac output or EPBF of the patient based on the
30 flow and CO₂ measurements obtained during an analysed sequence of breaths during which the change in effective ventilation occurs.

As in most Fick based methods for cardiac output determination, the analysed sequence of breaths may comprise any number of breaths but typically comprises 4

to 20 breaths, and preferably 4 to 12 breaths. The analysed sequence of breaths comprises at least one phase of increased ventilation and at least one phase of decreased ventilation, wherein each phase of increased and decreased ventilation comprises at least one breath, typically at least two breaths, and preferably two to six breaths. The transition from the phase of increased ventilation to the phase of decreased ventilation, and vice versa, is effectuated by the change in effective ventilation of the patient 3. The change in effective ventilation may be caused by the control unit 14 in any manner known in the art, e.g., by changing the duration and/or the tidal volume of the breaths delivered to the patient by the breathing apparatus.

10

Preferably, in order to determine cardiac output or EPBF continuously using a Fick based technique, the breathing apparatus 1 is configured to ventilate the patient 3 using a cyclic ventilation pattern comprising alternating phases of decreased and increased ventilation, wherein each phase of decreased ventilation is immediately followed by a phase on increased ventilation, and vice versa. Preferably but not necessarily, the number of breaths in each cycle of the cyclic ventilation pattern corresponds to the number of breaths in the analysed sequence of breaths.

Thus, the breathing apparatus 1 is preferably configured to ventilate the patient 3 using a cyclic ventilation pattern comprising alternating phases of increased and decreased ventilation, and to determine the cardiac output or EPBF of the patient 3 from expiratory flow and CO₂ measurements obtained during an analysed sequence of breaths, e.g., a sequence of ten breaths. For example, the control unit 14 may be configured to determine the cardiac output or EPBF of the patient 3 from the analysed sequence of breaths using any of the techniques described in WO 2006/119546, US7135001, WO2013/141766, EP2799008, PCT/SE2015/051357, or the co-pending application PCT/SE2016/050402. By replacing the measurements obtained during the oldest breath in the analysed sequence of breaths with measurements obtained during the most recent breath delivered by the breathing apparatus, an updated value of cardiac output or EPBF can be determined continuously, i.e., on a breath-by-breath basis.

If, due to the clinical situation at hand, the cyclic ventilation pattern can no longer be used or in the event the Fick based technique fails to determine or reliably

determine the cardiac output or EPBF of the ventilated patient 3, the control unit 14 of the breathing apparatus 1 is configured to switch from the above described Fick based determination of cardiac output or EPBF to a capnotracking technique for determination of cardiac output or EPBF in accordance with the principles of the present disclosure. Hereinafter, the phase during which cardiac output or EPBF is determined using the Fick based technique will be referred to as the Fick phase, whereas the following phase during which cardiac output or EPBF is determined using the proposed capnotracking technique will be referred to as the capnotracking phase.

10

In the capnotracking phase, the control unit 14 may be configured to use a value of cardiac output or EPBF determined during the preceding Fick phase as a baseline value of cardiac output or EPBF, which value serves as a starting point for the capnotracking. For example, the baseline value may be the most recent value of cardiac output or EPBF determined during the preceding Fick phase. In one embodiment, the Fick based determination of cardiac output or EPBF is made using any of the techniques disclosed in WO2013/141766 and PCT/SE2015/051357, which is advantageous in that these methods allow the effective lung volume (ELV) and the venous CO₂ content (CvCO₂) of the patient 3 to be determined at the same time as the cardiac output or EPBF. As will become apparent from the description following hereinafter, CvCO₂ will remain constant during the entire capnotracking phase and so does not need to be calculated again.

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When switching from the Fick phase to the capnotracking phase, the control unit 14 starts to control the breathing apparatus 1 to keep the level of venous CO₂ of the patient 3 substantially constant and equal to the level of venous CO₂ at the time of determination of the baseline value of cardiac output or EPBF. This is typically achieved by the control unit 14 by controlling the breathing apparatus 1 based on the CO₂ elimination (VCO₂) of the patient 3, as determined from the flow and CO₂ measurements obtained by the flow and CO₂ sensors 27 and 29.

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If the metabolic production of CO₂ of the patient is or can be assumed to be constant, the venous CO₂ content of the patient 3 will remain constant as long as VCO₂ remains constant, which allows the control unit 14 to keep the venous CO₂

content of the patient 3 at a substantially constant level by controlling the breathing apparatus 1 to keep measured VCO₂ substantially constant. In this scenario, the breathing apparatus 1 can be controlled based on expiratory flow and CO₂ measurements alone.

5

If, in this scenario, the cardiac output or EPBF of the patient 3 should change during capnotracking, the alveolar CO₂ of the patient will also change while VCO₂ is kept constant by adjusting the alveolar ventilation of the patient 3 through active control of the breathing apparatus 1, e.g., by adjusting the respiratory rate or the tidal volume of breaths delivered by the breathing apparatus. This allows the control unit 14 to determine a new and updated value of cardiac output or EPBF from the baseline value of cardiac output or EPBF and the change in alveolar CO₂ content, as determined from the CO₂ measurements obtained by the CO₂ sensor 29. The rationale behind this will be better understood in view of the following relationships.

15

First it should be noted that, given a constant level of CO₂ in the lungs of the patient 3, the respiratory based CO₂ elimination, VCO₂, balancing out the delivery of CO₂ from the blood to the lungs, depends on the difference between venous CO₂ content, CvCO₂, and pulmonary capillary CO₂ content, CcCO₂, according to:

20

$$VCO_2 = EPBF \cdot (CvCO_2 - CcCO_2) \quad Eq. 3$$

where $CvCO_2 - CcCO_2 (= \Delta CvcCO_2)$ is the difference between venous and pulmonary capillary CO₂ content.

25

If VCO₂ is kept constant while the EPBF and the alveolar CO₂ content of the ventilated patient vary, equation 3 can be used to describe a relation between two different states between which the venous CO₂ content, CvCO₂, is also assumed to be kept constant and equal to a value CvCO_{2,0}, according to:

30

$$VCO_{2,0} = EPBF(t) \cdot (CvCO_{2,0} - CcCO_2(t)) = EPBF_0 \cdot (CvCO_{2,0} - CcCO_{2,0}) \quad Eq. 4$$

In equation 4, subscript "0" indicates values of the respective quantities at the point in time for determination of baseline value of EPBF, EPBF₀, i.e., the point in time for

the Fick based determination serving as starting point for capnotracking. $EPBF_0$ is typically the most recent EPBF value determined during the Fick phase, or the most recent sufficiently reliable EPBF value determined during the Fick phase.

- 5 The new and updated value of EPBF is the quantity denoted $EPBF(t)$ in equation 4. By rearranging equation 4, $EPBF(t)$ can be expressed in terms of quantities with subscript 0 and the varying pulmonary capillary CO₂ content, $CcCO_2(t)$, which can be determined breath by breath from the expiratory CO₂ measurements, in accordance with:

10

$$EPBF(t) = EPBF_0 \cdot \frac{CvCO_{2_0} - CcCO_{2_0}}{CvCO_{2_0} - CcCO_2(t)} \quad Eq. 5$$

By introducing $\Delta CvcCO_{2_0} = CvCO_{2_0} - CcCO_{2_0}$, equation 5 can be expressed as:

$$15 \quad EPBF(t) = EPBF_0 \cdot \frac{\Delta CvcCO_{2_0}}{\Delta CvcCO_{2_0} + CcCO_{2_0} - CcCO_2(t)} \quad Eq. 6$$

An advantage of this expression is that the pulmonary capillary CO₂ difference, $CcCO_{2_0} - CcCO_2(t)$, can be expressed in terms of partial pressure of pulmonary capillary CO₂ ($PcCO_2$) and a coefficient of CO₂ solubility in blood (S_{CO_2}):

20

$$EPBF(t) = EPBF_0 \cdot \frac{\Delta CvcCO_{2_0}}{\Delta CvcCO_{2_0} + S_{CO_2} \cdot (PcCO_{2_0} - PcCO_2(t))} \quad Eq. 7$$

- If it is assumed that alveolar CO₂ is in equilibrium with pulmonary capillary CO₂, a new and updated value of EPBF for breath n, $EPBF_n$, can be determined on a
25 breath-by-breath basis from measured variations in alveolar CO₂ ($PACO_2$) together with quantities that are obtainable at the point in time for determination of $EPBF_0$:

$$EPBF_n = EPBF_0 \cdot \frac{\Delta CvcCO_{2_0}}{\Delta CvcCO_{2_0} + S_{CO_2} \cdot (PACO_{2_0} - PACO_{2_n})} \quad Eq. 8$$

where $PACO2_0$ is the partial pressure of alveolar CO₂ at the time for determination of $EPBF_0$ and $PACO2_n$ is the partial pressure of alveolar CO₂ at breath n, directly derivable from the measurements of expiratory CO₂ obtained by the CO₂ sensor 29.

5

If the CO₂ level in the lungs of the patient 3 is in equilibrium at the time for determination of $EPBF_0$, and if a baseline level of CO₂ elimination ($VCO2_0$) is determined at the same time from the expiratory flow and CO₂ measurements, equation 1 can be used to calculate $\Delta CvcCO2_0$ as:

10

$$\Delta CvcCO2_0 = \frac{VCO2_0}{EPBF_0} \quad \text{Eq. 9}$$

Combining equations 8 and 9 yields the following relation which may be advantageously used by the control unit 14 of the breathing apparatus 1 to calculate a new and updated value of EPBF for any given breath n within the capnotracking phase following determination of a baseline value for EPBF, $EPBF_0$:

15

$$EPBF_n = EPBF_0 \cdot \frac{VCO2_0}{VCO2_0 + EPBF_0 \cdot S_{CO2} \cdot (PACO2_0 - PACO2_n)} \quad \text{Eq. 10}$$

20 Thus, according to one embodiment of the present disclosure, the control unit 14 may be configured to determine a first baseline value of EPBF, $EPBF_0$, at a first point in time using any known technique for EPBF determination, such as any of the above discussed Fick based techniques; control the mechanical ventilation of the patient 3 to keep the level of venous CO₂ in the patient substantially constant
25 between the first and a second point time, e.g., by adjusting the alveolar ventilation of the patient to keep $VCO2$ substantially constant; determining a change in alveolar CO₂ ($PACO2_0 - PACO2_n$) of the patient between the first and second points in time from the expiratory CO₂ measurements, and determining a new and updated value of EPBF, $EPBF_n$, based on the baseline value of EPBF, $EPBF_0$, and the change in
30 alveolar CO₂, e.g., by using equation 10.

If using equation 10, the control unit 14 would also need to use an estimate of the CO₂ solubility in blood in the determination of the new and updated EPBF value, EPBF_n. How to estimate S_{CO₂} is well-known in the art, and the control unit 14 may be configured to use any known constant estimate of S_{CO₂}, or to estimate S_{CO₂} from available data using any known technique for S_{CO₂} estimation. Constant S_{CO₂} estimates and techniques for estimating S_{CO₂} have been discussed, e.g., in Gedeon et al., A new method for noninvasive bedside determination of pulmonary blood flow, Med Biol Eng Comput 1980; 18:411-418, Capek et al., Noninvasive Measurement of Cardiac Output Using Partial CO₂ Rebreathing, IEEE Transactions on Biomedical Engineering, Vol. 35, No. 9, September 1988, and Cecchini et al., Non-invasive Estimation of Cardiac Output in Mechanically Ventilated Patients: A prolonged Expiration Method, Annals of Biomedical Engineering, August 2012, Volume 40, Issue 8, pp 1777-1789. Thus, it should be appreciated that the control unit 14 may be configured to estimate S_{CO₂} from available data, e.g., using any of the techniques discussed in the above mentioned publications, or to use a constant estimate of S_{CO₂}, e.g., an estimate that is manually input to the control unit 14 via a user interface of the breathing apparatus.

The control unit 14 may be configured to use any suitable control algorithm for keeping VCO₂ of the patient 3 substantially constant (in case of constant metabolic production of CO₂) during the capnotracking phase. In a basic implementation, the control unit 14 may be configured to control the mechanical ventilation of the patient 3 in proportion to VCO₂, according to:

$$VA_{n+1} = VA_n \cdot \frac{VCO_{2_0}}{VCO_{2_n}} \quad \text{Eq. 11}$$

where VCO_{2_0} is the CO₂ elimination of the patient 3 at the point in time for determination of EPBF₀, VA_n and VCO_{2_n} is the alveolar ventilation and the CO₂ elimination, respectively, of the patient 3 for a subsequent breath n, and VA_{n+1} is the alveolar ventilation to be provided to the patient by the breathing apparatus 1 in a breath n+1 following the subsequent breath n. This means that the mechanical ventilation may be controlled on a breath-by-breath basis during the capnotracking phase such that the alveolar ventilation of the patient 3 for any breath n+1 is based

on, and proportional to, the relationship between the baseline VCO₂ value, VCO_{2,0}, and the VCO₂ value, VCO_{2,n}, determined for the preceding breath n. As mentioned above, the alveolar ventilation of the patient 3 is preferably adjusted by the control unit 14 by adjusting the respiratory rate (RR) or the tidal volume (VTi) of breaths
5 delivered by the breathing apparatus 1. Most preferably, the respiratory rate is adjusted to achieve the desired alveolar ventilation.

The alveolar ventilation may, as well known in the art, be determined from the tidal volume and the airway deadspace of the patient 3. As also well known in the art, the
10 airway deadspace can be derived using volumetric capnography, and may thus be determined using the capnograph 31 of the breathing apparatus 1.

The above calculations are based on the assumption that the metabolic production of CO₂ of the ventilated patient 3 remains substantially constant during the
15 capnotracking phase. If, however, the metabolic CO₂ production varies, the venous CO₂ content of the patient 3 may vary in an unknown manner even if controlling the breathing apparatus 1 to keep VCO₂ substantially constant and equal to VCO₀.

Therefore, the proposed capnotracking technique may involve the steps of
20 measuring also the O₂ content of respiration gases, and taking the O₂ content into account to keep venous CO₂ substantially constant during the capnotracking phase.

To this end, the control unit 14 may be configured to determine the metabolic consumption of O₂ of the ventilated patient 3 from measured flow and O₂ content,
25 and to keep the venous CO₂ content of the patient 3 substantially constant during the capnotracking phase by controlling the mechanical ventilation of the patient 3 in a manner causing VCO₂ to vary in proportion to the metabolic O₂ consumption.

The metabolic production of CO₂ is proportional to the metabolic consumption of O₂
30 according to:

$$VCO_{2_{met}} = RQ \cdot VO_{2_{met}}$$

Eq. 12

where $VCO2_{met}$ is the metabolic production of CO₂ of the ventilated subject, $VO2_{met}$ is the oxygen consumption of the ventilated subject, and RQ is the so called respiratory quotient having a typical value in the range of 0.7-1.0, depending on the composition of the nutrition.

5

In order to keep the venous CO₂ content of the ventilated patient 3 substantially constant during the capnotracking phase, taking variations in the metabolic production of CO₂ into account, the control unit 14 may be configured to control the mechanical ventilation of the patient 3 to keep measured VCO₂ substantially equal to a variable target value that is calculated based on measured variations in O₂ consumption during the capnotracking phase, e.g., according to:

$$VCO2^{target}(t) = VCO2_0 \cdot \frac{VO2(t)}{VO2_0} \quad Eq. 13$$

where $VCO2^{target}(t)$ is the target value for CO₂ elimination at time t, $VO2(t)$ is the measured O₂ consumption at time t, and $VCO2_0$ and $VO2_0$ are the baseline values of VCO₂ and VO₂ at the time for determination of EPBF₀.

The new and updated value of EPBF may then be determined for any given breath n during the capnotracking phase by using the following relation, which corresponds to equation 10 with the exception that the term $VCO2_0$ in the numerator has been replaced with the VO₂ dependent target value of CO₂ elimination for breath n, $VCO2_n^{target}$:

$$EPBF_n = EPBF_0 \cdot \frac{VCO2_n^{target}}{VCO2_0 + EPBF_0 \cdot S_{CO2} \cdot (PACO2_0 - PACO2_n)} \quad Eq. 14$$

25

In other words, a new and updated value of EPBF, $EPBF_n$, may be derived from a baseline value of EPBF, $EPBF_0$, and a measured change in alveolar CO₂ ($PACO2_0 - PACO2_n$) using equation 14 which, assuming constant metabolic CO₂ production, may be simplified in accordance with equation 10.

30

Fig. 3 is a flow chart illustrating a method for determination of cardiac output or EPBF of a subject being mechanically ventilated by means of a breathing apparatus, according to an embodiment of the present disclosure.

- 5 In a first step, S1, expiratory CO₂ of the ventilated subject is measured. In the event VCO₂ is used as control parameter for controlling the mechanical ventilation of the subject (see step S3), or in the event expiratory flow is used together with expiratory CO₂ in determination of a change in alveolar CO₂ (see step S4), also expiratory flow may be measured. As mentioned above, expiratory flow and CO₂ may be
10 measured using a capnograph, or the like, such as the capnograph 31 schematically illustrated in Fig. 1, devised to measure flow and CO₂ content of expiration gases exhaled by the subject.

- In a second step, S2, a first value or baseline value of cardiac output or EPBF of the
15 subject is determined at a first point in time. As mentioned above, this baseline value may be determined using any known technique for cardiac output or EPBF determination, but is preferably determined at least partly from the expiratory flow and CO₂ measurements using a non-invasive Fick technique.

- 20 In a third step, S3, a capnotracking phase is initiated by starting to control the breathing apparatus to keep the venous CO₂ content of the subject at a substantially constant level. As discussed above, this is typically achieved by controlling the breathing apparatus based on measured VCO₂ by adjusting the respiratory rate and/or the tidal volume of breaths delivered by the breathing
25 apparatus to keep the measured VCO₂ constant, or proportional to measured oxygen consumption by the subject.

- In a fourth step, S4, a change in alveolar CO₂ content of the subject between the first and second points in time is determined from the expiratory CO₂ measurements
30 obtained in step S1. The change may, for example, be determined as a change in partial pressure of CO₂ of expired alveolar gas, e.g., measured by the capnograph 31. Expiratory flow measurements may also be used in addition to the expiratory CO₂ measurements in the determination of the change in alveolar CO₂ content.

In a fifth step, S5, a new and updated value of cardiac output or EPBF is determined based on the first or baseline value of cardiac output or EPBF and the change in alveolar CO₂ content. The new and updated value of cardiac output or EPBF may, for example, be calculated based on the relationship expressed by equation 14,
5 possibly simplified in accordance with equation 10.

In a subsequent step (not shown), the new and updated value of cardiac output or EPBF determined in step S5 may be compared with one or more threshold values, defining a recommended and pre-set range for cardiac output or EPBF, whereupon
10 an alarm signal may be generated in response to the comparison should the determined cardiac output or EPBF value fall outside the recommended range.

The method is typically a computer-implemented method, meaning that it is performed through execution of a computer program. As mentioned above, the
15 various method steps are typically performed by, or caused by, the control unit 14 of the breathing apparatus 1 upon execution by the processing unit 21 of different code segments of the computer program, which may be stored in the hardware memory device 23.

20 Although the proposed capnotracking technique has been described above in conjunction with a Fick based technique for determination of the baseline value of cardiac output or EPBF, it should be emphasized that any known technique for cardiac output or EPBF determination can be used to generate the baseline value. In alternative embodiments, the baseline value may, for example, originate from
25 invasive techniques for cardiac output monitoring, such as invasive pulse contour analysis. Furthermore, the baseline value may be determined automatically by the control unit 14 of the breathing apparatus 1 based on available data, or it may be determined by the control unit 14 based on user input that is input to the control unit 14 by a user or operator via a user interface of the breathing apparatus. Thus, in yet
30 alternative embodiments, the control unit 14 may be configured to receive user input indicating a value of cardiac output or EPBF, and to use this value as a baseline value for cardiac output or EPBF during a subsequent phase of capnotracking of cardiac output or EPBF according to the principles described herein.

Furthermore, although the above calculations have been performed for capnotracking of EPBF, it should be noted that the cardiac output of the ventilated subject can be continuously determined using the same principles. In accordance with equation 2, cardiac output is directly proportional to EPBF in case of constant shunt. The above equations for calculation of EPBF may hence be readily adapted for calculation of cardiac output, taking the pulmonary shunt fraction, f_s , into account. The shunt fraction may be estimated by the control unit 14 in any manner known in the art, or an estimate of the shunt fraction may be provided to the control unit 14 by an external device to which the breathing apparatus is connectable, or by a user or operator via a user interface of the breathing apparatus. The shunt fraction may either be assumed to remain constant during the period of capnotracking, or the equations for calculation of a new and updated value of cardiac output may be adapted to take variations in shunt fraction during the capnotracking phase into account in order to further increase the accuracy in cardiac output determination.

CLAIMS

1. A method for determination of cardiac output or EPBF of a mechanically ventilated subject (3), comprising the steps of:
 - measuring (S1) expiratory CO₂ of the subject, and
 - determining (S2), at a first point in time, a first value of cardiac output or EPBF of the subject,

characterised by the steps of:

 - controlling (S3) the mechanical ventilation of the subject to keep a level of venous CO₂ of the subject substantially constant between the first point in time and a second point in time;
 - determining (S4), from the expiratory CO₂ measurements, a change in alveolar CO₂ of the subject between the first and second points in time, and
 - determining (S5) a second and updated value of cardiac output or EPBF of the subject based on the first value and the change in alveolar CO₂.
2. The method of claim 1, wherein a measure of CO₂ elimination of the subject is used as control parameter to keep the level of venous CO₂ substantially constant.
3. The method of claim 2, wherein the level of venous CO₂ is kept substantially constant by controlling the mechanical ventilation to keep the CO₂ elimination of the subject substantially constant between the first and second points in time, or to keep the CO₂ elimination of the subject substantially proportional to a measured oxygen consumption of the subject.
4. The method of any of the preceding claims, wherein the first value of cardiac output or EPBF is a first value of EPBF and the second and updated value of cardiac output or EPBF is a second and updated value of EPBF, which second value is calculated based on the following relationship:

$$EPBF_n = EPBF_0 \cdot \frac{VCO2_n^{target}}{VCO2_0 + EPBF_0 \cdot S_{CO2} \cdot (PACO2_0 - PACO2_n)}$$

where EPBF_n is the second and updated value of EPBF, EPBF₀ is the first value of EPBF, VCO₂₀ and PACO₂₀ are the CO₂ elimination and partial pressure of

alveolar CO₂, respectively, of the ventilated subject at the first point in time, PACO_{2n} is the partial pressure of alveolar CO₂ of the ventilated subject at the second point in time, S_{CO₂} is the coefficient of CO₂ solubility in blood, and VCO_{2n}^{target} is a target value for VCO₂ at the second point in time.

5

5. The method of claim 4, wherein VCO_{2n}^{target} is set to VCO_{2o}, assuming constant metabolic production of CO₂ of the ventilated subject, or calculated based on a measured change in oxygen consumption of the ventilated subject between the first and second points in time.

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6. A computer program for determination of cardiac output or EPBF of a mechanically ventilated subject (3), comprising program code segments which, when executed by a processing unit (21) of a breathing apparatus (1), cause the breathing apparatus (1) to:

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- measure (S1) expiratory CO₂ of the subject, and
- determine (S2), at a first point in time, a first value of cardiac output or EPBF of the subject (3),

characterised in that the computer program further causes the breathing apparatus (1) to:

20

- control (S3) the mechanical ventilation of the subject to keep a level of venous CO₂ of the subject substantially constant between the first point in time and a second point in time;

- determine (S4), from the expiratory CO₂ measurements, a change in alveolar CO₂ of the subject between the first and second points in time, and

25

- determine (S5) a second and updated value of cardiac output or EPBF of the subject based on the first value and the change in alveolar CO₂.

7. A computer program product comprising a non-volatile memory (23) storing a computer program according to claim 6.

30

8. A breathing apparatus (1) operable to determine cardiac output or EPBF of a mechanically ventilated subject (3), comprising:

- a CO₂ sensor (29) configured to measure expiratory CO₂ of the subject, and

- a control unit (14) configured to determine, at a first point in time, a first value of cardiac output or EPBF of the subject,

characterised in that the control unit (14) is configured to:

- control the mechanical ventilation of the subject (3) to keep a level of venous CO₂ of the subject substantially constant between the first point in time and a second point in time;
- determine, from the expiratory CO₂ measurements, a change in alveolar CO₂ of the subject between the first and second points in time, and
- determine a second and updated value of cardiac output or EPBF of the subject (3) based on the first value and the change in alveolar CO₂.

9. The breathing apparatus (1) of claim 8, wherein the control unit (14) is configured to use a measure of CO₂ elimination as a control parameter to keep the level of venous CO₂ substantially constant.

10. The breathing apparatus (1) of claim 9, wherein the control unit (14) is configured to keep the level of venous CO₂ substantially constant by controlling the mechanical ventilation of the subject to keep the CO₂ elimination of the subject substantially constant between the first and second points in time, or to keep the CO₂ elimination of the subject substantially proportional to a measured oxygen consumption of the subject.

11. The breathing apparatus (1) of any of the claims 8 to 10, wherein the first value of cardiac output or EPBF is a first value of EPBF and the second and updated value of cardiac output or EPBF is a second and updated value of EPBF, the control unit (14) being configured to calculate the second value based on the following relationship:

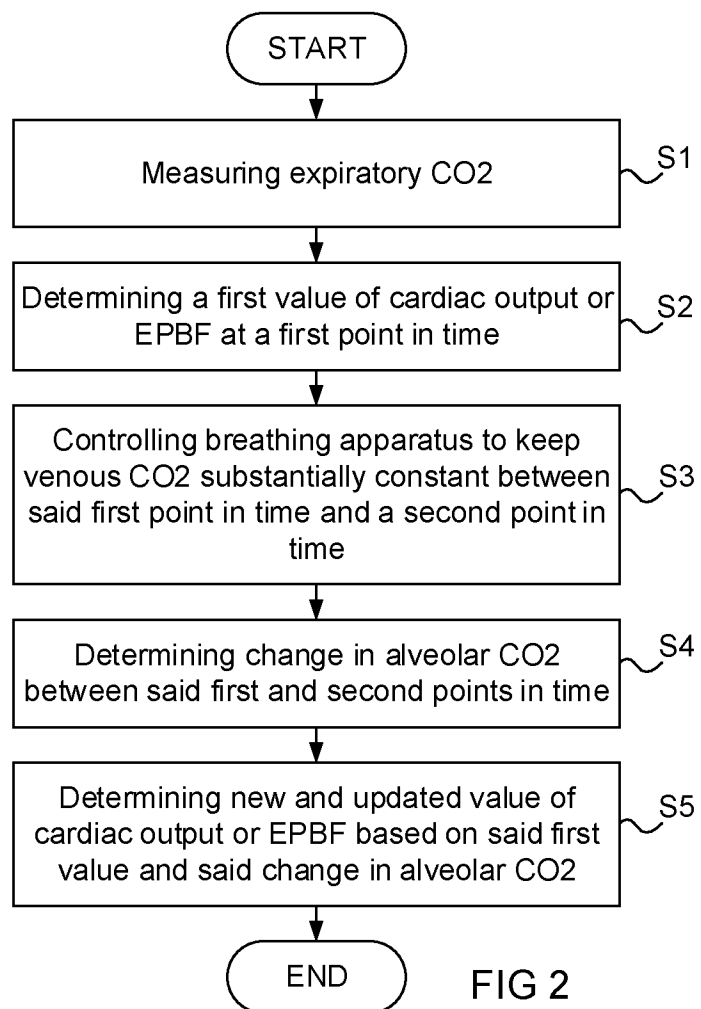
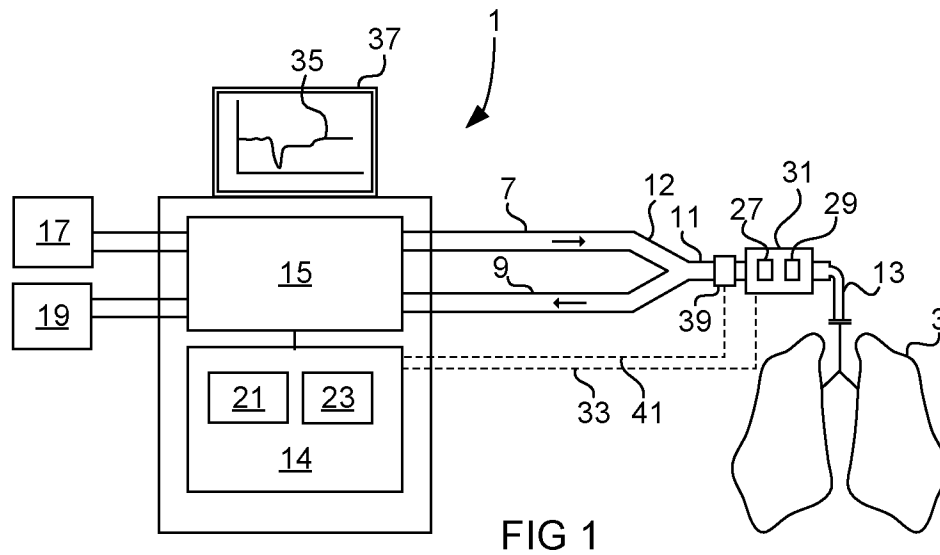
$$EPBF_n = EPBF_0 \cdot \frac{VCO2_n^{target}}{VCO2_0 + EPBF_0 \cdot S_{CO2} \cdot (PACO2_0 - PACO2_n)}$$

where EPBF_n is the second and updated value of EPBF, EPBF₀ is the first value of EPBF, VCO₂₀ and PACO₂₀ are the CO₂ elimination and partial pressure of alveolar CO₂, respectively, of the ventilated subject at the first point in time, PACO_{2n} is the partial pressure of alveolar CO₂ of the ventilated subject at the

second point in time, S_{CO_2} is the coefficient of CO₂ solubility in blood, and VCO_{2n}^{target} is a target value for VCO₂ at the second point in time.

12. The breathing apparatus of claim 11, wherein the control unit (14) is configured
5 to set VCO_{2n}^{target} to VCO_{20} , assuming constant metabolic production of CO₂ of the ventilated subject, or to calculate VCO_{2n}^{target} based on a measured change in oxygen consumption of the ventilated subject between the first and second points in time.

1/1



INTERNATIONAL SEARCH REPORT

International application No
PCT/SE2016/050405

A. CLASSIFICATION OF SUBJECT MATTER		
INV. A61B5/083	A61B5/029	A61B5/087 A61B5/00 A61B5/08
ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) A61B		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data, COMPENDEX, EMBASE, INSPEC		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 238 631 A1 (INSTRUMENTARIUM CORP [FI]) 11 September 2002 (2002-09-11) cited in the application abstract; figures paragraph [0024] - paragraph [0032] paragraph [0036] - paragraph [0044] paragraph [0049] - paragraph [0050] paragraph [0063] - paragraph [0083]; claim 1	6-12
A	EP 2 641 536 A1 (MAQUET CRITICAL CARE AB [SE]) 25 September 2013 (2013-09-25) abstract; figures paragraph [0006] paragraph [0018] - paragraph [0020] paragraph [0032] - paragraph [0034] paragraph [0050] - paragraph [0051] paragraph [0071] - paragraph [0072] ----- -/-	6-12
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 13 January 2017		Date of mailing of the international search report 20/01/2017
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Juárez Colera, M

INTERNATIONAL SEARCH REPORT

International application No

PCT/SE2016/050405

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 210 342 B1 (KUECK KAI [DE] ET AL) 3 April 2001 (2001-04-03) the whole document -----	6-12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2016/050405

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

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

1. ☒ Claims Nos.: 1-5
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery and therapy
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest 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/SE2016/050405

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1238631	A1	11-09-2002	AT 418914 T 15-01-2009
			EP 1238631 A1 11-09-2002
			US 2002169385 A1 14-11-2002

EP 2641536	A1	25-09-2013	CN 103315730 A 25-09-2013
			EP 2641536 A1 25-09-2013
			EP 2799008 A1 05-11-2014
			US 2013253359 A1 26-09-2013
			WO 2013141766 A1 26-09-2013

US 6210342	B1	03-04-2001	NONE
