US009999372B2

(12) **United States Patent**
Clemensen et al.

(10) **Patent No.: US 9,999,372 B2**
(45) **Date of Patent: *Jun. 19, 2018**

(54) **COMBINATION OF INERT GAS REBREATHING AND MULTIPLE-BREATH WASH-OUT TECHNIQUES FOR DETERMINATION OF INDICES OF VENTILATION INHOMOGENEITY**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 230 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/982,066**

(22) Filed: **Dec. 29, 2015**

(65) **Prior Publication Data**

US 2016/0128609 A1 May 12, 2016

Related U.S. Application Data

(63) Continuation-in-part of application No. 12/904,543, filed on Oct. 14, 2010, now Pat. No. 9,265,444.

(30) **Foreign Application Priority Data**

Oct. 15, 2009 (EP) 09013044

(51) **Int. Cl.**
A61B 5/08 (2006.01)
A61B 5/087 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC ***A61B 5/0813*** (2013.01); ***A61B 5/087*** (2013.01); ***A61B 5/093*** (2013.01); ***A61B 5/7282*** (2013.01); *A61B 5/091* (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

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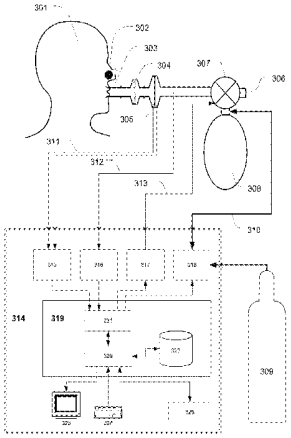
(74) *Attorney, Agent, or Firm* — Gearhart Law LLC

(57) **ABSTRACT**

The present invention discloses a method to determine the lung clearance index (LCI) or other indices of ventilation inhomogeneity of the lungs by combining two pulmonary gas exchange techniques; Inert gas rebreathing (IGR) is used for rapid wash-in of the inert tracer gas and this is followed by multiple-breath wash-out (MBW). The functional residual capacity (FRC) can either be determined from the tracer gas concentration and the gas flow inhaled and exhaled during multiple-breath wash-out or by gas analysis alone from the inert gas rebreathing. The cumulative expired volume (V_{CE}) required to clear the inert tracer gas from the lungs is determined from the multiple-breath wash-out, and LCI is calculated as the ratio between V_{CE} and FRC. The advantages of the method are i) significant reduction of required test time, ii) significant reduction of consumed gas mixture for wash-in of tracer gas, iii) potential for further reduction of the use of tracer gas, and iv) potential for more accurate determination of the FRC by gas dilution alone. Furthermore the present invention relates to a corresponding system and computer-readable medium.

17 Claims, 6 Drawing Sheets



(51) **Int. Cl.**

A61B 5/093	(2006.01)
A61B 5/00	(2006.01)
A61B 5/091	(2006.01)

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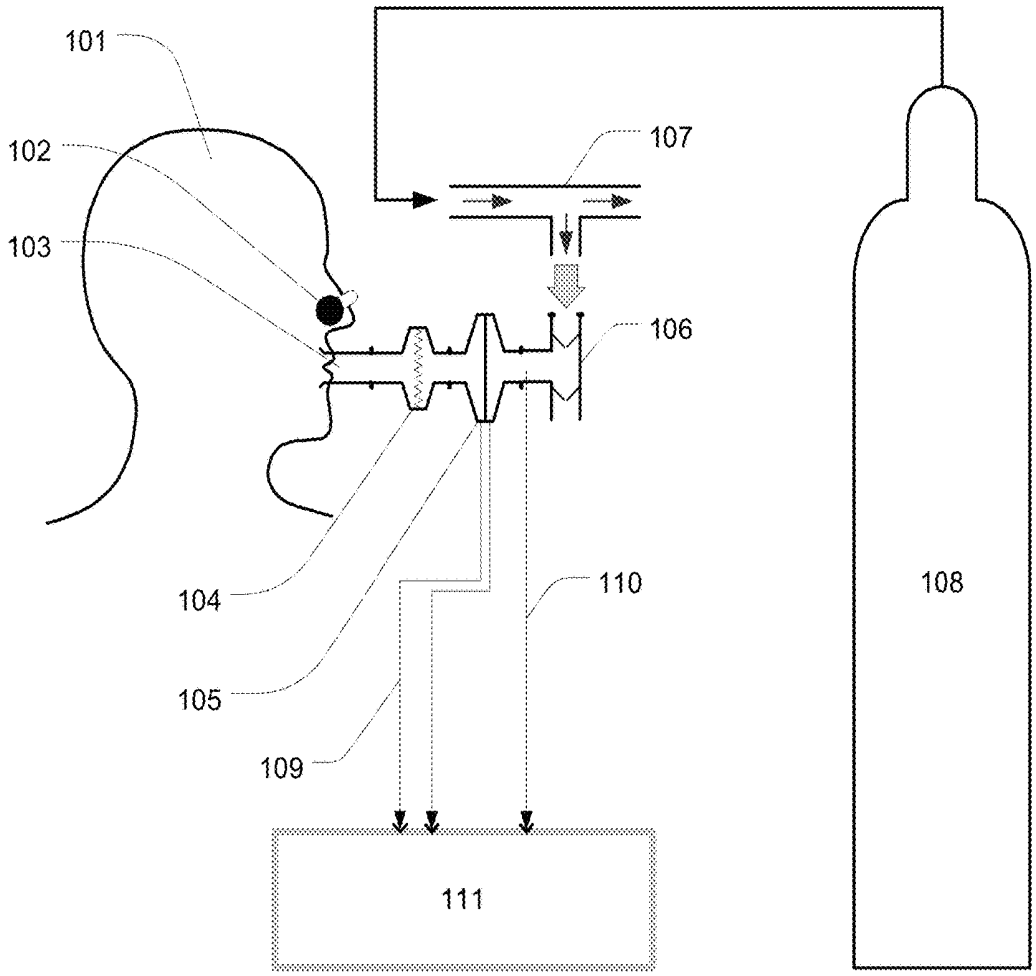

Figure 1

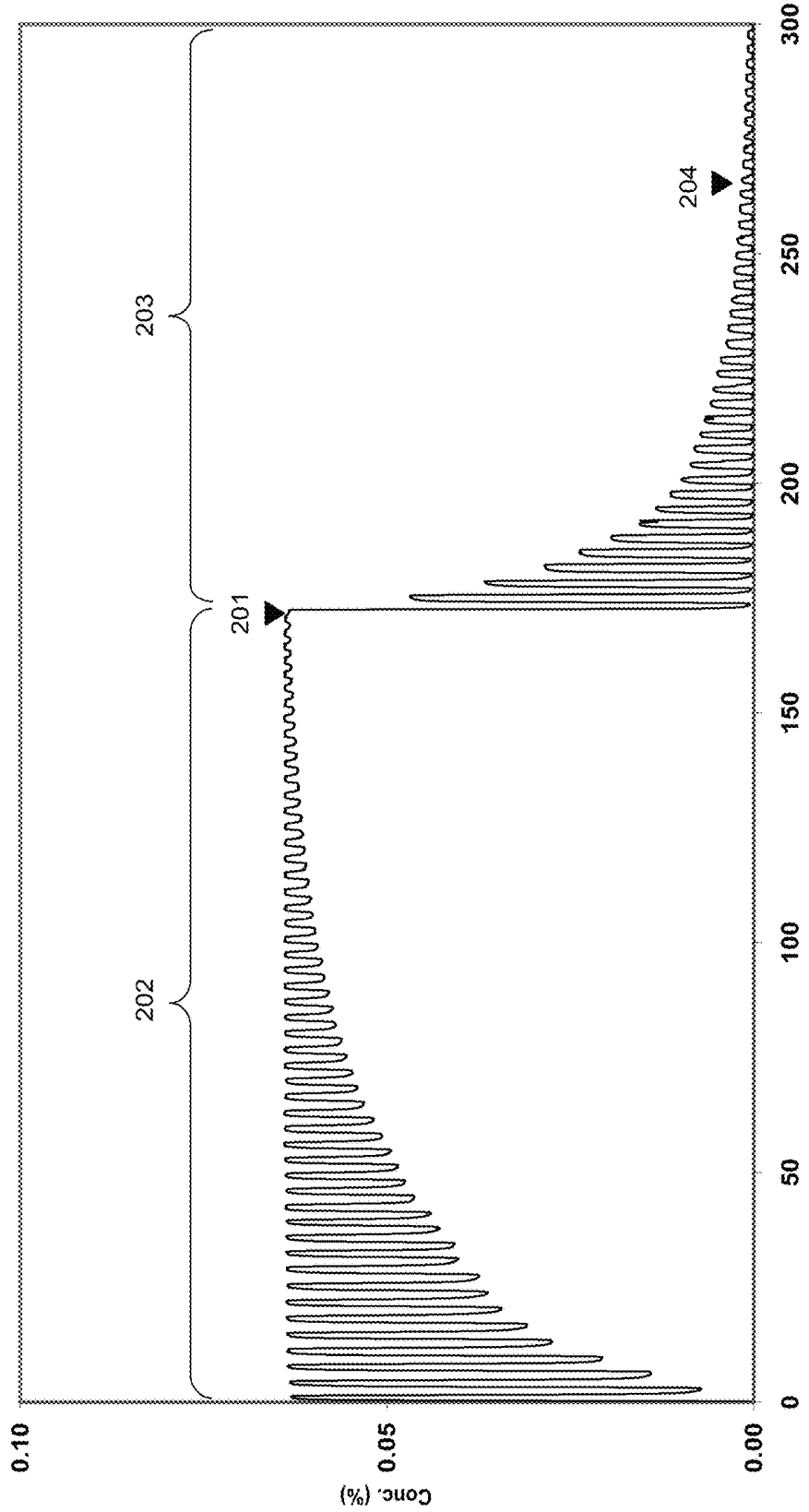

Figure 2

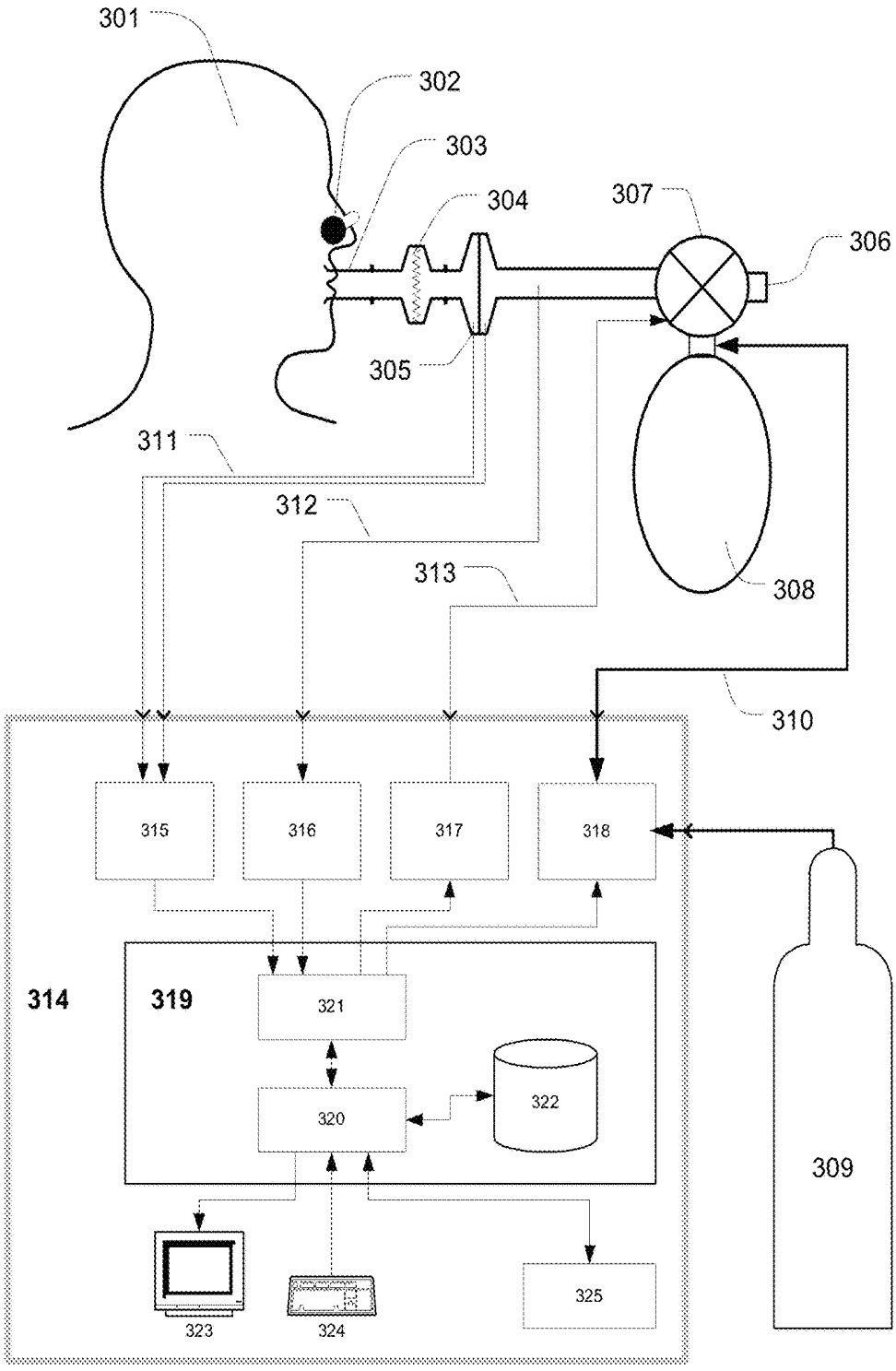
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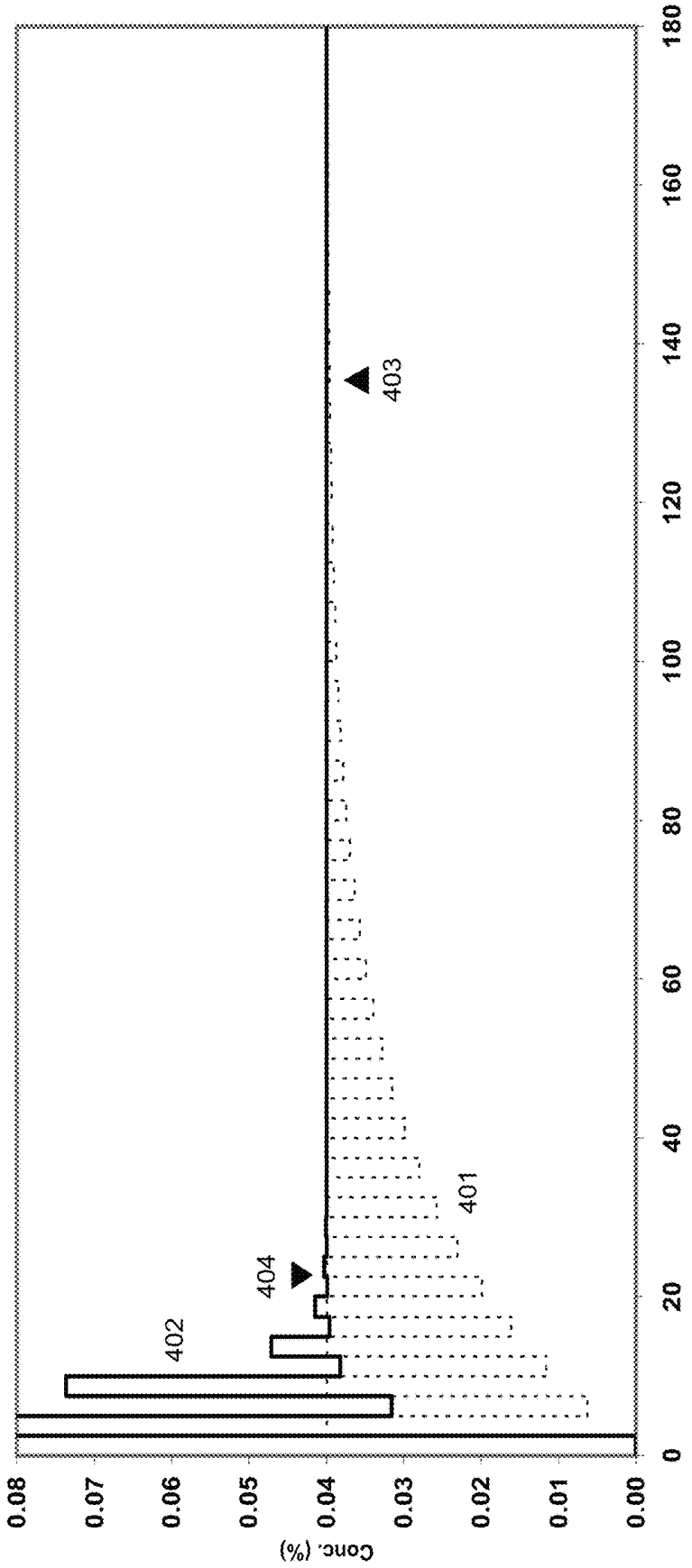
Figure 3


Conc. (%)
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0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
0
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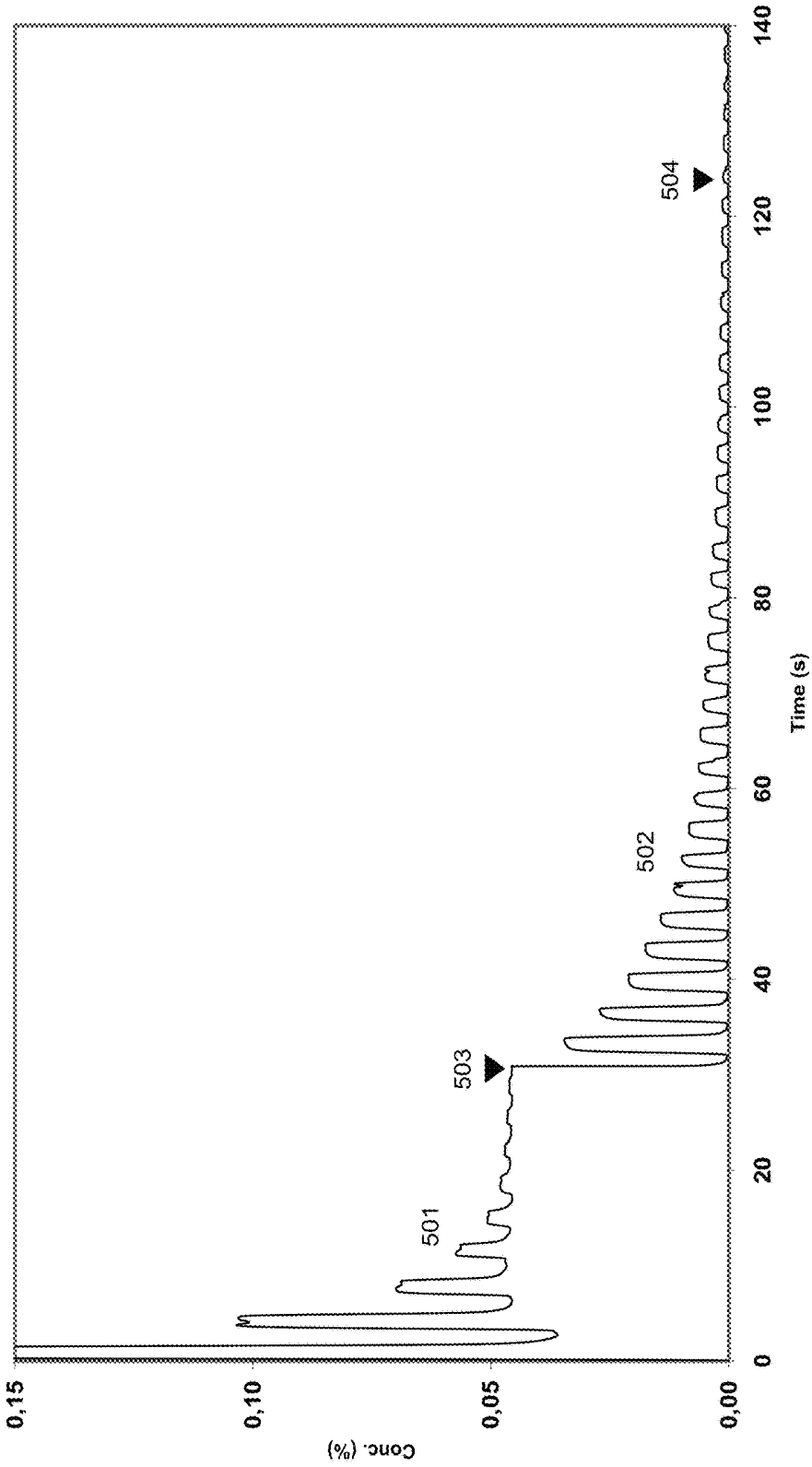
40
60
80
100
120
140
160
180
Time (s)
401
402
403
404

Figure 4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0,10
0,05
0,00
Conc. (%)
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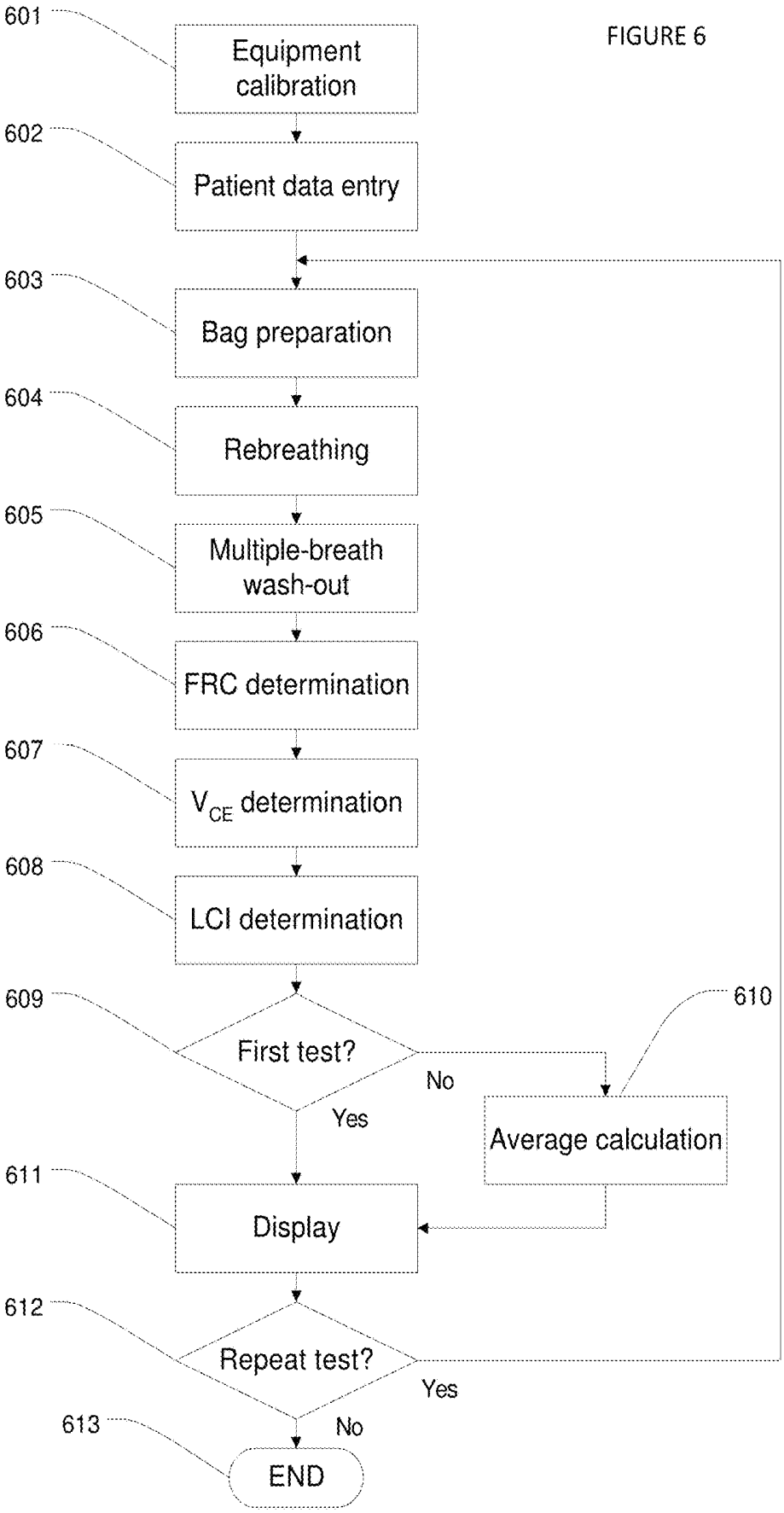
20
40
60
80
100
120
140
Time (s)
501
502
503
504

Figure 5

FIGURE 6


601
Equipment calibration
602
Patient data entry
603
Bag preparation
604
Rebreathing
605
Multiple-breath wash-out
606
FRC determination
607
V_{CE} determination
608
LCI determination
609
First test?
No
Yes
610
Average calculation
611
Display
612
Repeat test?
Yes
No
613
END

COMBINATION OF INERT GAS REBREATHING AND MULTIPLE-BREATH WASH-OUT TECHNIQUES FOR DETERMINATION OF INDICES OF VENTILATION INHOMOGENEITY

CLAIM OF PRIORITY

This application is a continuation in part application of U.S. patent application Ser. No. 12/904,543 filed Oct. 14, 2010 which claims priority to European Application No. 09013044.4 filed Oct. 15, 2009, the contents of the foregoing is incorporated by reference herein in their entirety for any purpose whatsoever.

FIELD OF THE EMBODIMENTS

The present invention relates to a combination of techniques to determine the lung clearance index (LCI) or other indices of ventilation inhomogeneity of the lungs. Inert gas rebreathing (IGR) is used for rapid wash-in of the inert tracer gas and in one embodiment further provides means for accurate determination of the functional residual capacity (FRC) by gas analysis alone. This is followed by multiple-breath wash-out (MBW) for determination of the cumulative expired volume (V_{CE}) required to clear the inert tracer gas from the lungs and calculation of the LCI as the ratio between V_{CE} and FRC.

BACKGROUND OF THE EMBODIMENTS

Spirometry, i.e. the measurement of inspired and expired air flows and volumes at the airway opening of a test subject, is the commonest means of assessing lung function. Diseases causing obstruction of larger airways will eventually result in reduced expiratory flows and volumes as measured by spirometry. However, spirometry findings are often normal in the early stages of peripheral airway diseases, and therefore changes (obstruction or restriction) in the peripheral airways associated with early cystic fibrosis disease, early chronic obstructive pulmonary disease or mild asthma cannot be detected by spirometry until the disease has progressed considerably because the small airways only contribute to a very limited extent to the total airway resistance.

Peripheral airway diseases do, however, affect the way air mixes within the lungs and thus lead to increased ventilation inhomogeneity. Ventilation inhomogeneity may be assessed using the multiple-breath wash-out (MBW) test performed by washing out either a resident gas (e.g. nitrogen) from the lungs using e.g. pure oxygen or a previously washed-in non-resident inert tracer gas during tidal breathing of room air.

When using the MBW method to assess ventilation distribution in the lungs, several indices of overall ventilation inhomogeneity can be calculated as sensitive tracers of airway disease. They all reflect differences in specific ventilation between large and/or relatively small lung regions, resulting in delayed wash-out of the tracer gas from the poorly ventilated regions. Examples of indices of overall ventilation inhomogeneity that can be calculated from the MBW are mixing ratio (MR), which is calculated as the ratio between the actual and the estimated ideal number of breaths needed to lower the end-tidal tracer gas concentration to a certain fraction of the starting value, moment ratios of the wash-out curve and lung clearance index (LCI). The LCI can be calculated as the cumulative expired volume (V_{CE}) required to clear the gas from the lungs minus the number of wash-out breaths multiplied by external dead space outside the lips, divided by the subject's FRC (up to the lips). FRC is the amount of air that stays in the lungs after a normal expiration. In other words, LCI represents the number of lung volume turnovers (i.e. FRCs) that the subject must breathe to clear the lungs from the tracer gas (by convention, to an end-tidal concentration of 1/40 of the starting concentration over three subsequent breaths). Disregarding the correction for external dead space the equation is:

$$LCI = \frac{V_{CE}}{FRC} \quad (1)$$

The LCI is simple to calculate and intuitively understandable, and it is questionable whether any other index is more sensitive, reliable and clinically useful.

For the MBW test using a non-resident inert tracer gas there are several different gases with low solubility in blood and tissues that can be used, including helium (He) and sulfur hexafluoride (SF_6). Normally, a respiratory mass spectrometer is used for the gas analysis, and a flowmeter, e.g. a pneumotachometer, is used to record the inspiratory and expiratory flows at the mouth. The pressure gradient measured is directly related to flow thus allowing a computer to derive a flow-curve measured in L/minute. The test subject is breathing through a mouthpiece or a face mask connected to the flowmeter, and a gas sampling tube is connected to the breathing assembly for sidestream gas analysis. When performing MBW tests by use of a non-resident tracer gas, the tracer gas must first be washed in to obtain an even concentration in the lungs before the wash-out can start. A conventional breath-by-breath system for inert gas wash-out therefore further consists of a unit for delivering the wash-in gas mixture. This can be achieved by use of a bias flow of the gas mixture. A sufficiently long wash-in period is needed to allow the tracer gas to fully equilibrate in the lungs, which may take quite some time. Conventional wash-in by use of a bias flow also results in a significant consumption of gas because the bias flow must exceed the peak inspiratory flow of the test subject. Alternative setups, such as a demand valve, can be used but may lead to increased external dead space and resistance to breathing.

The wash-out phase is initiated by disconnecting the bias flow during expiration. The wash-out should continue until the end-tidal tracer gas concentration has fallen below 1/40 of the starting concentration over three successive breaths.

Guidelines on lung function testing recommend that the MBW test be repeated in order to obtain at least two tests in which the difference between two FRC values is less than 10% when comparing the higher to the lower FRC value.

In the conventional MBW test the FRC is calculated from the net volume of inert gas exhaled divided by the difference in end-tidal fractional concentration at the start and end of the wash-out:

$$FRC = \frac{\text{Net volume of inert gas exhaled}}{C_{ET,start} - C_{ET,end}} \quad (2)$$

The net volume of inert gas exhaled (numerator) is obtained by integration of the product of time aligned respiratory flow and fractional tracer gas concentration over time (i.e. expired minus re-inspired tracer gas volumes on a

breath-by-breath basis). Therefore, accurate determination of the FRC requires a rapid dynamic response and data acquisition rate of the gas analyzer. Proper alignment in time of the respiratory flow signal and fractional tracer gas concentration prior to the calculation is also critical. This makes demands on the performance of the gas analyzer and the calibration of the equipment.

SUMMARY OF THE EMBODIMENTS

The object of the present invention is to provide a method to avoid the main problems in the determination of the lung clearance index.

This is accomplished by using a method to determine the lung clearance index (LCI) of a test subject, said method comprising the steps of:

- in a closed rebreathing assembly, rebreathing an inert tracer gas mixture having a starting concentration of an inert tracer gas until a constant concentration of the inert tracer gas is reached to wash in the inert tracer gas, wherein the closed rebreathing assembly comprises a rebreathing bag filled with a volume of the inert tracer gas mixture corresponding to the resting tidal volume of the test subject;
- performing multiple-breath wash-out until end-tidal tracer gas concentration has fallen below a predetermined fraction of the starting concentration; and
- determining the lung clearance index (LCI) by:
  - determining via a processor, functional residual capacity (FRC);
  - determining via the processor, cumulative expired volume (V_{CE}) required to clear the inert tracer gas concentration from the lungs below a predetermined fraction of the starting concentration; and
  - calculating via the processor, the LCI as a ratio between V_{CE} and FRC.

The method combines two pulmonary gas exchange techniques; inert gas rebreathing (IGR) is used for rapid wash-in of an inert tracer gas, and multiple-breath wash-out (MBW) is used for determination of the cumulative expired volume (V_{CE}) required to clear the inert tracer gas from the lungs.

The rebreathing method is a more effective maneuver to obtain good mixing of the gases compared to multiple-breath wash-in.

In one embodiment the method uses a gas mixture containing the inert tracer gas, SF_6.

In one embodiment the method uses an oxygen enriched gas mixture comprising the inert tracer gas to avoid oxygen deficiency during the rebreathing maneuver.

A volume of the gas mixture corresponding to the test subject's resting tidal volume is filled into a rebreathing bag. The test subject is connected to the bag via a valve. At the end of an expiration the valve is opened and the subject then inhales the gas mixture from the bag and rebreathes the gas mixture in the closed rebreathing assembly until the inert gas is well mixed in the lungs (see FIG. **3** for setup for wash-in/wash-out tests using inert gas rebreathing).

Computer simulations have shown that rebreathing results in 5-10 times faster equilibration of the inert gas than open-circuit multiple-breath wash-in, and since the traditional open-circuit wash-in phase lasts longer than the subsequent wash-out phase, this means a reduction of total test time by typically more than 50%. See e.g. FIG. **4** which shows a comparison of inert gas rebreathing (used in the invention) and open-circuit multiple-breath wash-in (prior art) using data from computer simulations.

Use of rebreathing also reduces the total volume of gas mixture used. By rebreathing the volume is equal to the resting tidal volume (V_T) of the test subject, e.g. 0.6 liters in an adult. By multiple-breath wash-in the volume exceeds the peak inspiratory flow times the total wash-in time since the by-pass flow must exceed the peak inspiratory flow during the complete wash-in period. As an example, assuming that the peak inspiratory flow equals three times the tidal volume per each half breath cycle, the by-pass flow must exceed $V'peak=6\times V_T\times f_B$, where f_B is the respiratory rate (breaths/minute). For a total wash-in time of e.g. 2 minutes by open-circuit wash-in the consumption of gas mixture would be 12 $min\times V_T\times f_B$, or, for a breathing frequency of e.g. 15 breaths per minute this would equal $180\times V_T$. Thus, the gas consumption by rebreathing would be at least 180 times less than in the case of open-circuit wash-in. In case the gas mixture was inspired from a large non-diffusing bag in the open-circuit mode, the gas usage by rebreathing would be lower by a factor corresponding to the number of open-circuit wash-in breaths, i.e. the total wash-in time times the breathing frequency. Again, for a 2 minute open-circuit wash-in period and a breathing frequency of 15 breaths per minute, the gas consumption by rebreathing would be 30 times less than in the open-circuit mode.

Combining the inert gas rebreathing technique with the use of a sensitive gas analyzer (i.e. one with a high signal-to-noise ratio), for example based on photoacoustic spectroscopy (PAS) instead of a mass spectrometer as most frequently used in the known art, the consumption of gas would be minimized drastically. In one embodiment the inert gas rebreathing technique is combined with a sensitive SF_6 analyzer whereby the consumption of SF_6 would be minimized drastically. A PAS analyzer exists which has a unique sensitivity to SF_6 and is able to measure SF_6 accurately in the range 0-0.05% during wash-out. A typical concentration used in the inspired gas mixture for open-circuit wash-in when applying mass spectrometry for gas analysis is 4%. Thus, comparing inert gas rebreathing with e.g. 0.2% SF_6 as the initial concentration in the rebreathing bag and open-circuit multiple-breath wash-in using 4% SF_6 in the inspired gas mixture (i.e. a 20 times lower concentration) would result in >3,000 times less SF_6 consumed.

The fact that the open-circuit multiple-breath wash-in technique requires much more inert gas mixture than rebreathing makes the equipment more bulky and adds considerably to the overall cost of performing the procedure.

In one embodiment the method uses the conventional MBW calculation of FRC from the net volume of inert gas exhaled divided by the difference in end-tidal fractional concentration at the start and end of the wash-out period according to equation 2. The main advantage of using this calculation is that it is in line with recommendations given in the scientific literature.

In one embodiment the method uses the inert gas rebreathing method to calculate FRC by inert gas dilution alone according to the equation below:

$$FRC = V_{rb}\cdot\left(\frac{C_{rb,i}}{C_{eq,i}} - 1\right) \quad (3)$$

in which

V_{rb}=Initial rebreathing bag volume

$C_{rb,i}$=Initial fractional concentration of insoluble gas in the rebreathing bag

$C_{eq,i}$=Equilibrium fractional concentration of insoluble gas obtained after mixing

In the interest of brevity, dead spaces on each side of the valve are not accounted for, but these can easily be incorporated.

V_{CE} is determined by integrating the part of the wash-out flow curve which has a sign corresponding to expiration (e.g. all positive flow signals) over time. By integrating flow (l/s) over time (s) a volume (l) is obtained.

All mathematical expressions and illustrations throughout this document are made using fractional concentrations of dry inert gas. Fractional concentrations can be replaced by partial pressures using appropriate conversion factors as known in the art.

Volumes can be expressed at different gas conditions using appropriate conversion factors as known in the art.

The gas dilution technique by inert gas rebreathing may be more robust than the traditional wash-out technique for determination of FRC, because it is independent of the critical time alignment between gas analyzer and flowmeter signals. Further, it relaxes the requirements to rise time of the gas analyzer because only end-tidal concentrations are needed in determining the gas dilution, whereas in the open-circuit method a short rise time and accurate time alignment prior to integrating the product of flow and gas concentration signals are important in order to obtain accurate values of the flux of SF_6 in the rapid transitions during the beginning of expiration (phase II of the breath) and inspiration.

According to another aspect, the present invention also relates to a system adapted to determine the lung clearance index (LCI) of a test subject, said system comprising:

- a closed rebreathing setup configured to allow a test subject to rebreathe an inert tracer gas mixture having a starting concentration of an inert tracer gas until a constant concentration of the inert tracer gas is reached to wash-in the inert tracer gas during a rebreathing period, wherein the closed rebreathing setup comprises at least a rebreathing bag prefilled with a volume of the inert tracer gas mixture corresponding to the resting tidal volume of said test subject to rebreathe to and from during the rebreathing period;
- at least one gas analyzer for obtaining fractional concentration of said inert tracer gas inhaled and exhaled by said test subject;
- a flowmeter for monitoring gas flow inhaled and exhaled by said test subject;
- processing means for determining LCI of the lungs of said test subject by determining functional residual capacity (FRC) and using said gas flow to determine cumulative expired volume (V_{CE}) required to clear said inert tracer gas concentration from the lungs below a predetermined fraction of the starting concentration, wherein LCI is determined as the ratio between V_{CE} and FRC.

Hereby a system can be constructed that can achieve the same advantages as described above.

The gas analyzers could be any apparatus suitable for obtaining the fractional concentration of the inert gas. Such apparatus could for instance be a mass spectrometer or an infrared photoacoustic multi-gas analyzer, etc. In one embodiment of the invention the gas analysis is performed by a sensitive gas analyzer with a high signal-to-noise ratio for example based on photoacoustic spectroscopy (PAS). The gas analyzers can measure the end-tidal partial pressures or concentrations or a continuous partial pressure or concentration curve of the inert tracer gas.

The flowmeter could e.g. be a pneumotachometer, and is used to record the inspiratory and expiratory flows at the mouth. The pressure gradient measured is directly related to flow thus allowing a computer to derive a flow-curve measured in l/minute.

The processing means for determining LCI of the lungs of a test subject is comprised in the control system of the measuring system.

In one embodiment the system uses a gas mixture containing the inert tracer gas, SF_6, which has very low solubility in blood and tissues and which is a good choice when using infrared gas analysis techniques.

In one embodiment the system uses an oxygen enriched gas mixture comprising the inert tracer gas to avoid oxygen deficiency during the rebreathing maneuver.

In one embodiment the system comprises a carbon dioxide (CO_2) scrubber. When the test subject rebreathes in a closed system, an accumulation of CO_2 will take place in the system. This buildup of CO_2 can be experienced as uncomfortable by the test subject even though there is no lack of oxygen (O_2). This buildup of CO_2 can be reduced by implementing a CO_2 scrubber in the flow way e.g. close to the rebreathing port right above the rebreathing bag or by implementing a small circuit using recirculation of gas through the CO_2 scrubber to avoid adding extra dead space.

In one embodiment the system comprises a small cylinder for containing the inert tracer gas mixture. Since the system has incorporated a sensitive gas analyzer with a high signal-to-noise ratio and because rebreathing is the method of choice instead of open-circuit wash-in, a much smaller amount of inert gas is necessary for performing the test. The small cylinder contains approx. 150 ml of pressurized inert gas mixture which corresponds to 18 l of inert gas mixture at ambient pressure. In normal open-circuit wash-in the gas cylinder contains e.g. 1500 l of inert gas or more. The high concentration of inert gas inside the gas cylinder means that only approx. $1/10^{th}$ of the inhaled gas comes from the cylinder, the rest is atmospheric air or oxygen. The system can in one embodiment also comprise means to dilute the inert tracer gas mixture with air or oxygen. By using this dilution principle a much more compact system is obtained.

In one embodiment of the system, said processing means for determining LCI comprises processing means for determining FRC based on the conventional MBW calculation using the net volume of inert gas exhaled divided by the difference in end-tidal fractional concentration at the start and end of the wash-out period according to equation 2. Hereby the same advantages as described above are achieved.

In one embodiment of the system, said processing means for determining LCI comprises processing means for determining FRC based on gas analysis alone and processing means for determining V_{CE} required to clear the inert tracer gas concentration from the lungs below 1/40 of the starting concentration. Hereby the same advantages as described above are achieved. The processing means is comprised in the control system of the measuring system.

In one embodiment of the system, at least one gas analyzer for obtaining the fractional concentration of said inert tracer gas inhaled and exhaled by said test subject under the inert gas rebreathing comprises means for obtaining the partial pressure of said inert tracer gas.

One embodiment of a system comprises:

- a breathing assembly which can switch (manually or automatically) between an open circuit mode and a closed rebreathing mode (e.g. as illustrated in FIG. **3**).

a gas dose facility enabling filling of the rebreathing bag to a known volume with a gas mixture containing the inert tracer gas. Alternatively, the rebreathing bag can be prepared manually.

Consider a test sequence where the test subject is performing first one rebreathing test followed by a wash-out period as the test sequence sketched in FIG. **5**. The test periods do not have to be of equal length or of an equal number of breaths. The concentration of the inert tracer gas is monitored and when the concentration is constant (below a predetermined threshold value regarding the fluctuation of the concentration), the first time period called wash-in, is over. Hereafter the wash-out period begins where the concentration of the inert tracer gas is monitored until the concentration has reached 1/40 of the concentration in the beginning of the wash-out period.

According to one aspect, the multiple-breath wash-out (MBW) period is used both for determination of the functional residual capacity (FRC) and the cumulative expired volume (V_{CE}) required to clear the inert tracer gas from the lungs.

According to another aspect, the wash-in period is used for accurate determination of the functional residual capacity (FRC) and the multiple-breath wash-out (MBW) is used for determination of the cumulative expired volume (V_{CE}) required to clear the inert tracer gas from the lungs.

According to another aspect, the present invention also relates to the use of the method according to the above to determine the lung clearance index (LCI) of a test subject.

According to another aspect, the present invention relates to a non-transitory computer readable medium having stored therein instructions for causing a processing unit of a system switchable between an open circuit configuration and a closed rebreathing configuration to execute the determining of a lung clearance index (LCI) of a test subject through the following steps:

- initiating the flow of an inert tracer gas at a starting concentration in the closed rebreathing configuration for rebreathing wash-in of the inert tracer gas by a test subject until a constant concentration of the inert tracer gas is reached;
- determining when an end-tidal concentration of the inert tracer gas has fallen below a predetermined fraction of the starting concentration during multiple-breath wash-out in the open circuit configuration; and
- determining the lung clearance index (LCI) by:
  - determining, via the processing unit, functional residual capacity (FRC);
  - determining, via the processing unit, cumulative expired volume (V_{CE}) required to clear the inert tracer gas concentration from the lungs below a predetermined fraction of the starting concentration; and
  - calculating, via the processing unit, the LCI as a ratio between V_{CE} and FRC.

Hereby the same advantages as described above are achieved.

In one embodiment the steps for determining LCI further comprise controlling, via the processing unit, a respiration valve.

BRIEF DESCRIPTION OF THE DRAWINGS

In the following, preferred embodiments of the invention will be described referring to the figures, where;

FIG. **1** (prior art) is a schematic diagram illustrating a conventional setup for multiple-breath inert gas wash-in/wash-out tests for determination of FRC and ventilation distribution (e.g. LCI) as known in the art.

FIG. **2** (prior art) illustrates a curve from a conventional multiple-breath wash-in/wash-out test.

FIG. **3** is a schematic diagram illustrating a setup for wash-in/wash-out tests using inert gas rebreathing for wash-in of inert tracer gas as used in conjunction with the disclosed invention.

FIG. **4** is an example comparing the wash-in of an inert tracer gas by inert gas rebreathing as used in conjunction with the disclosed invention (solid curve) and by conventional wash-in as known in the art (dashed curve), respectively. The simulation in the example is performed using the following input values: FRC=3.0 l, dead space V_D=0.2 l, bag volume V_{RB} equal to tidal volume V_T=0.8 l. Ratio between wash-in breaths n_{MBW}/n_{RB}=6;

FIG. **5** is an example of a test sequence as used in conjunction with the disclosed invention comprising an inert gas rebreathing maneuver and a subsequent wash-out period.

FIG. **6** is an example of a flow chart illustrating a possible sequence of test preparations, measurements, calculations and displays used in the software of the processing means in conjunction with the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The preferred embodiments of the present invention will now be described with reference to the drawings. Identical elements in the various figures are identified with the same reference numerals.

Reference will now be made in detail to each embodiment of the present invention. Such embodiments are provided by way of explanation of the present invention, which is not intended to be limited thereto. In fact, those of ordinary skill in the art may appreciate upon reading the present specification and viewing the present drawings that various modifications and variations can be made thereto.

FIG. **1** (prior art) is a schematic diagram illustrating a conventional setup for multiple-breath inert gas wash-in/wash-out tests for determination of FRC and ventilation distribution (LCI) as known in the art. The setup includes a bias flow of a mixture containing a non-resident inert tracer gas for wash-in in the flowpast assembly **107**. A test subject **101** having the nose occluded with a nose clip **102** breathes through a mouthpiece **103**, a bacterial filter **104**, a respiratory flowmeter **105** and a non-rebreathing valve assembly **106**. The gas reservoir **108** is coupled to a flowpast assembly **107** via a gas line. Flowmeter connection(s) **109** and a gas sample line **110** are also part of the setup.

To perform a multiple-breath inert gas wash-in/wash-out test, the test subject **101** inspires the non-resident inert tracer gas from the flowpast assembly **107** through the non-rebreathing valve assembly **106**. The non-rebreathing valve assembly **106** is constructed by one-way valves allowing gas to flow in one direction only. Because of the construction of the valve **106**, the test subject does not breathe the non-resident inert tracer gas back to the flowpast assembly **107** during exhalation. Instead the test subject expires to the surrounding air. The test subject **101** may use a face mask instead of nose clip **102** and mouthpiece **103**. The analyzer unit **111** consists of a measuring apparatus comprising flowmeter electronics and at least one gas analyzer.

A typical test consists of a period where the test subject inspires from the flowpast and exhales to the surrounding air a number of times until the concentration of the tracer gas is

constant e.g. below a predetermined threshold fluctuation (wash-in period) followed by a period where the test subject is breathing fresh air (wash-out period). During the testing (both during the wash-in and the wash-out period) the concentration in the inhaled and/or exhaled air of the inert gas in the mixture is measured by a fast responding gas analyzer. Instead of gas concentration the gas analyzer may equally well measure the partial pressure of the gas. The partial pressure can be obtained from the fractional concentration of dry gas or any other measure of gas concentration or pressure using appropriate conversion factors as known in the art. Also the flow of the inhaled and/or exhaled air is measured by means of the flowmeter **105**. These measurements are made continuously.

FIG. **2** (prior art) outlines a curve from a conventional multiple-breath wash-in/wash-out test from where LCI can be determined. The insoluble gas, SF_6, has become the gas of choice for measurement of LCI. The concentration of SF_6 is monitored and when the concentration is constant (below a predetermined threshold fluctuation) **201**, the first time period called wash-in **202** is over. Hereafter the wash-out period **203** begins where the concentration of SF_6 is monitored until the concentration has reached 1/40 of the concentration in the beginning of the wash-out period **204**. The cumulative expired volume (V_{CE}) required to clear the lungs of the gas down to 1/40 of its start concentration can then be used in combination with the functional residual capacity (FRC) to determine the LCI of the test subject. In the conventional MBW test the FRC is calculated from the net volume of inert gas exhaled divided by the difference in end-tidal concentration at the start and end of the wash-out:

$$FRC = \frac{\text{Net volume of inert gas exhaled}}{C_{ET,start} - C_{ET,end}} \quad (2)$$

The net volume of inert gas exhaled (numerator) is obtained by integration of the product of time aligned respiratory flow and tracer gas concentration (i.e. expired minus re-inspired tracer gas volumes on a breath-by-breath basis). Therefore, accurate determination of the FRC requires a rapid dynamic response and data acquisition rate of the gas analyzer. Proper alignment in time of the respiratory flow signal and tracer gas concentration prior to the calculation is also critical. This makes demands on the performance of the gas analyzer and the calibration of the equipment.

FIG. **3** is a schematic diagram illustrating a setup for wash-in/wash-out tests using inert gas rebreathing for rapid wash-in of the inert tracer gas as used in conjunction with the disclosed invention. A test subject **301** having the nose occluded with a nose clip **302** breathes through a mouthpiece **303**, a bacterial filter **304**, a respiratory flowmeter **305** and one port **306** of a rebreathing valve assembly **307**. A rebreathing bag **308** is connected to the valve assembly and evacuated and pre-filled with a gas mixture from a gas reservoir **309** via a gas line **310**. Flowmeter connection(s) **311** and a gas sample line **312** are also part of the setup.

To perform a rebreathing test the valve assembly **307** is switched (e.g. automatically by controlling line **313**) to allow the test subject **301** to inspire and rebreathe to and from the bag **308** for a certain amount of time until the valve assembly **307** is switched back again. The test subject **301** may use a face mask instead of nose clip **302** and mouthpiece **303**. The control system **314** of the measuring apparatus consists of flowmeter electronics **315**, at least one gas analyzer **316**, a valve control unit **317** (unless the valve assembly is manually driven) and a gas control unit **318** (unless the bag is prepared manually). A control unit **319** is also included, comprising a computing/processing unit (CPU) **320** with control interfaces **321**, one or more program and data storage devices **322** and user interfaces for example comprising a display **323** and a keyboard, touch screen or similar input device **324**. A data input/output module **325** may also be included.

The processing unit (CPU) can e.g. comprise processing means for determining LCI of the lungs of a test subject using the obtained fractional concentration of the inert tracer gas measured by the gas analyzer(s) and the gas flow measured by the flowmeter and associated flowmeter electronics. Also, the processing unit comprises processing means for determining FRC based on the gas concentrations and flow obtained during wash-out or on gas concentrations alone obtained during rebreathing. The processing unit also comprises processing means for determining V_{CE} required to clear the inert tracer gas concentration from the lungs below 1/40 of the starting concentration.

Prior to the rebreathing tests the rebreathing bag is filled with a known volume of an inert gas mixture. During the testing the test subject is breathing through the respiration valve, which allows switching from breathing air to rebreathing the inert gas mixture from the bag and switching back again.

A typical test consists of a period where the test subject is breathing to and from the bag (rebreathing period) followed by a period where the test subject is breathing fresh air (wash-out period). During the testing (both during the rebreathing and the wash-out period) the concentration in the inhaled and/or exhaled air of the inert gas in the mixture is measured by a fast responding gas analyzer **316**. Instead of gas concentration the gas analyzer may equally well measure the partial pressure of the gas. The partial pressure can be obtained from the fractional concentration of dry gas or any other measure of gas concentration or pressure using appropriate conversion factors as known in the art. Also the flow of the inhaled and/or exhaled air is measured by means of the flowmeter **315**. These measurements are made continuously.

FIG. **4** is an example comparing the wash-in curve of an inert tracer gas by conventional multiple-breath wash-in **401** (dotted line) with the wash-in curve of an inert tracer gas by rebreathing wash-in **402** (solid line) as used in conjunction with the disclosed invention, respectively. The simulation is based on the single compartment lung model and the example is performed using the following input values: FRC=3.0 l, deadspace V_D=0.2 l, and bag volume V_{RB} equal to tidal volume V_T=0.8 l. It can be seen that the rebreathing wash-in method **402** reaches equilibration **404** much faster, 5-10 times (ratio between wash-in breaths n_{MBW}/n_{RB}=6 in this example), than the conventional multiple-breath wash-in **401**, **403**, and since the conventional open-circuit wash-in phase lasts longer than the subsequent wash-out phase this means a reduction of total test time by typically more than 50%.

FIG. **5** is a typical example of a test sequence as used in conjunction with one embodiment of the disclosed invention comprising two pulmonary gas exchange techniques for determination of LCI. LCI represents the number of lung volume turnovers (i.e. FRCs) that the subject must breathe to clear the lungs from the tracer gas (by convention, to an end-tidal concentration of 1/40 of the starting concentration over three subsequent breaths). Disregarding the correction for external dead space the equation is:

$$LCI = \frac{V_{CE}}{FRC} \quad (1)$$

Inert gas rebreathing maneuver **501** is used for rapid wash-in of the inert tracer gas followed by a subsequent multiple-breath wash-out period **502**. The concentration of the inert tracer gas is monitored and when the concentration is constant **503** (below a predetermined threshold value regarding the fluctuation of the concentration), the first time period called wash-in **501**, is over. Hereafter the wash-out period **502** begins where the concentration of the inert tracer gas is monitored until the concentration has reached 1/40 of the concentration in the beginning of the wash-out period **504**.

In one embodiment the method uses the conventional wash-out calculation of functional residual capacity (FRC) from the net volume of inert gas exhaled divided by the difference in end-tidal fractional concentration at the start and end of the wash-out period according to equation 2. The main advantage of using this calculation is that it is in line with recommendations given in the scientific literature.

In another embodiment the wash-in period is used for accurate determination of the functional residual capacity (FRC) which is calculated by inert gas dilution alone according to the equation below:

$$FRC = V_{rb} \cdot \left(\frac{C_{rb,i}}{C_{eq,i}} - 1 \right) \quad (3)$$

in which

V_{rb}=Initial rebreathing bag volume

$C_{rb,i}$=Initial fractional concentration of insoluble gas in the rebreathing bag

$C_{eq,i}$=Equilibrium fractional concentration of insoluble gas obtained after mixing

In the interest of brevity dead spaces on each side of the valve are not accounted for, but these can easily be incorporated.

The gas dilution technique by inert gas rebreathing may be more robust than the traditional wash-out technique for determination of FRC, because it is independent of the critical time alignment between gas analyzer and flowmeter signals. Further, it relaxes the requirements to rise time of the gas analyzer because only end-tidal concentrations are needed in determining the gas dilution, whereas in the open-circuit method a short rise time and accurate time alignment prior to integrating the product of flow and gas concentration signals are important in order to obtain accurate values of the flux of SF_6 in the rapid transitions during the beginning of expiration (phase II of the breath) and inspiration.

The multiple-breath wash-out (MBW) is used for determination of the cumulative expired volume (V_{CE}) required to clear the inert tracer gas from the lungs prior to calculation of LCI. V_{CE} is determined by integrating the part of the wash-out flow curve which has a sign corresponding to expiration (e.g. all positive flow signals) over time. By integrating flow (l/s) over time (s), a volume (l) is obtained.

FIG. **6** is an example of a flow chart illustrating a possible test sequence used in the software of the processing means in conjunction with the present invention. Prior to the test the equipment may need to be calibrated **601** in order to measure flows, gas concentrations and flow-gas delay times accurately. When the equipment is ready the user can enter patient data **602** which may include data to be used for calculation of normative data for subsequent comparison with measured values. Thereafter, preparation of the rebreathing bag **603** begins with the patient being connected to the valve assembly via mouth piece or mask. The tidal breathing volume may be monitored to determine the volume to be filled into the bag for rebreathing. The software controls the equipment and initially prepares the filling of the bag and the opening and closing of the rebreathing valve assembly. During the test the patient may be asked to breathe as indicated or guided on the screen or it may be preferred to distract the patient by e.g. showing a video film on a second screen. Once the measurements are initiated, rebreathing **604** will start at the end of an expiration and continue until the software detects that gases are adequately mixed between bag and lungs and an equilibrium is obtained. Then the software controls the valve assembly to close the bag and wash-out begins **605**. The software detects when the end-tidal concentration of inert tracer gas has fallen to 1/40 of the starting (equilibrium) concentration and the test can stop. FRC, V_{CE} and LCI are then determined sequentially **606**, **607**, **608** as described above. If the test is the first test **609** performed on the patient the results are displayed **611**. The test may be repeated **612** to achieve two or more data sets, ideally where two sets have FRC values, which differ less than 10% when comparing the higher to the lower FRC value. If the test is repeated, average values of LCI and FRC are calculated **610** and displayed **611** as clinically more useful data. Once satisfactory results are obtained the test can be terminated **613**. The above test sequence may be described and explained in detail in the instructions for use accompanying the equipment. The software may run on an integrated computer, a separate computer or a wirelessly connected tablet computer or similar device.

It should be noted that the above-mentioned means of implementation illustrate rather than limit the invention, and that those skilled in the art will be able to suggest many alternative means of implementation without departing from the scope of the appended claims. Rather, the words used in the specification are words of description rather than limitation, and it is understood that various changes may be made without departing from the scope of the invention. The word 'comprising' does not exclude the presence of other elements or steps than those listed in a claim. The invention can be implemented by means of hardware and software comprising several distinct elements, and by means of a suitably programmed computer. In a device claim enumerating several means, several of these means can be implemented by one and the same item of hardware or software. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage.

While this disclosure refers to exemplary embodiments, it will be understood by those skilled in the art that various changes may be made and equivalents may be substituted for elements thereof without departing from the scope of the disclosure. In addition, many modifications will be appreciated by those skilled in the art to adapt a particular instrument, situation or material to the teachings of the disclosure without departing from the spirit thereof. Therefore, it is intended that the disclosure not be limited to the particular embodiments disclosed.

When introducing elements of the present disclosure or the embodiment(s) thereof, the articles "a," "an," and "the" are intended to mean that there are one or more of the

elements. Similarly, the adjective "another," when used to introduce an element, is intended to mean one or more elements. The terms "including" and "having" are intended to be inclusive such that there may be additional elements other than the listed elements. Therefore, it is intended that the disclosure not be limited to the particular embodiments disclosed.

What is claimed is:

1. A method of determining a lung clearance index (LCI) of a test subject, said method comprising the steps of:

in a closed rebreathing assembly, rebreathing an inert tracer gas mixture having a starting concentration of an inert tracer gas until a constant concentration of the inert tracer gas is reached to wash-in the inert tracer gas, wherein the closed rebreathing assembly comprises a rebreathing bag filled with a volume of the inert tracer gas mixture corresponding to the resting tidal volume of the test subject;

performing multiple-breath wash-out until end-tidal tracer gas concentration has fallen below a predetermined fraction of the starting concentration, where the concentrations are measured by a gas analysis; and

determining the lung clearance index (LCI) by:

determining, via a processor, functional residual capacity (FRC);

determining, via the processor, cumulative expired volume (V_{CE}) required to clear the inert tracer gas concentration from the lungs below the predetermined fraction of the starting concentration; and

calculating, via the processor, the LCI as a ratio between V_{CE} and FRC.

2. The method according to claim **1**, wherein the inert tracer gas is SF_6.

3. The method according to claim **1**, wherein the inert tracer gas mixture is an oxygen enriched gas mixture.

4. The method according to claim **1**, wherein the gas analysis is performed by a photoacoustic spectroscopy (PAS) sensitive gas analyzer.

5. The method according to claim **1**, wherein the FRC is determined from the tracer gas concentration and a gas flow inhaled and exhaled during multiple-breath wash-out.

6. A system adapted to determine a lung clearance index (LCI) of the lungs of a test subject, said system comprising:

a closed rebreathing setup configured to allow a test subject to rebreathe an inert tracer gas mixture having a starting concentration of an inert tracer gas until a constant concentration of the inert tracer gas is reached to wash-in the inert tracer gas during a rebreathing period, wherein the closed rebreathing setup comprises at least a rebreathing bag prefilled with a volume of the inert tracer gas mixture corresponding to the resting tidal volume of said test subject to rebreathe to and from during the rebreathing period;

at least one gas analyzer for obtaining fractional concentration of said inert tracer gas inhaled and exhaled by said test subject;

a flowmeter for monitoring gas flow inhaled and exhaled by said test subject; and

a non-transitory computer readable medium having stored therein instructions for causing a processing unit of the system to execute said instructions, comprising:

determining, via said processing unit, the LCI of the lungs of the test subject by determining functional residual capacity (FRC) and using said gas flow to determine, via said processing unit, cumulative expired volume (V_{CE}) required to clear said inert tracer gas concentration from the lungs below a predetermined fraction of the starting concentration, wherein LCI is determined as a ratio between V_{CE} and FRC.

7. The system according to claim **6**, wherein the inert tracer gas is SF_6.

8. The system according to claim **6**, wherein the inert tracer gas mixture is an oxygen enriched gas mixture.

9. The system according to claim **6**, wherein the at least one gas analyzer comprises a photoacoustic spectroscopy (PAS) sensitive gas analyzer.

10. The system according to claim **6**, wherein the FRC is determined from the tracer gas concentration and the gas flow inhaled and exhaled during multiple-breath wash-out.

11. The system according to claim **6**, wherein the FRC is determined by gas analysis alone from the inert gas rebreathing.

12. The system according to claim **6**, wherein the closed rebreathing setup further comprises a CO_2 scrubber.

13. The system according to claim **6**, wherein the closed rebreathing setup further comprises a cylinder for containing a pressurized inert tracer gas mixture.

14. The system according to claim **6**, wherein the at least one gas analyzer for obtaining the fractional concentration of said inert tracer gas inhaled and exhaled by said test subject comprises means for obtaining the partial pressure of said inert tracer gas.

15. The system according to claim **6**, wherein the closed rebreathing setup further comprises a respiration valve assembly which allows switching from breathing air to rebreathing the inert tracer gas mixture.

16. A non-transitory computer readable medium having stored therein instructions for causing a processing unit of a system switchable between an open circuit configuration and a closed rebreathing configuration to execute the determining of a lung clearance index (LCI) of a test subject through the following steps:

initiating the flow of an inert tracer gas at a starting concentration in the closed rebreathing configuration for rebreathing wash-in of the inert tracer gas by a test subject until a constant concentration of the inert tracer gas is reached;

determining when an end-tidal concentration of the inert tracer gas has fallen below a predetermined fraction of the starting concentration during multiple-breath wash-out in the open circuit configuration; and

determining the lung clearance index (LCI) by:

determining, via the processing unit, functional residual capacity (FRC);

determining, via the processing unit, cumulative expired volume (V_{CE}) required to clear the inert tracer gas concentration from the lungs below the predetermined fraction of the starting concentration; and

calculating, via the processing unit, the LCI as a ratio between V_{CE} and FRC.

17. The non-transitory computer readable medium according to claim **16**, wherein the steps for determining LCI further comprise: controlling, via the processing unit, a respiration valve.

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专利名称(译)	结合惰性气体再呼吸和多次呼出冲洗技术确定通气不均匀性指标		
公开(公告)号	US9999372	公开(公告)日	2018-06-19
申请号	US14/982066	申请日	2015-12-29
[标]申请(专利权)人(译)	知识产权控股APS		
申请(专利权)人(译)	IPR HOLDING APS		
当前申请(专利权)人(译)	IPR HOLDING APS		
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IPC分类号	A61B5/08 A61B5/087 A61B5/00 A61B5/093 A61B5/091		
CPC分类号	A61B5/0813 A61B5/087 A61B5/7282 A61B5/093 A61B5/091		
优先权	2009013044 2009-10-15 EP		
其他公开文献	US20160128609A1		
外部链接	Espacenet USPTO		

摘要(译)

本发明公开了一种通过结合两种肺气体交换技术来确定肺清除指数（LCI）或肺通气不均匀性的其他指标的方法;惰性气体再呼吸（IGR）用于惰性示踪气体的快速洗涤，然后进行多次呼出冲洗（MBW）。功能残余容量（FRC）可以由示踪气体浓度和在多次呼出冲洗期间吸入和呼出的气流或仅通过惰性气体再呼吸的气体分析来确定。从多次呼出冲洗中确定从肺部清除惰性示踪气体所需的累积呼气量（V CE ），并且LCI计算为V CE 和FRC。该方法的优点是：i）显着减少所需的测试时间，ii）显着减少用于示踪气体洗涤的消耗的气体混合物，iii）进一步减少示踪气体的使用的可能性，以及iv）可能的更多仅通过气体稀释精确测定FRC。此外，本发明涉及相应的系统和计算机可读介质。