

# Measurement of Functional Residual Capacity of the Lung by Partial CO<sub>2</sub> Rebreathing Method During Acute Lung Injury in Animals

Lara M Brewer MSc, Dinesh G Haryadi PhD, and Joseph A Orr PhD

**BACKGROUND:** Several techniques for measuring the functional residual capacity (FRC) of the lungs in mechanically ventilated patients have been proposed, each of which is based on either nitrogen wash-out or dilution of tracer gases. These methods are expensive, difficult, time-consuming, impractical, or require an intolerably large change in the fraction of inspired oxygen. We propose a CO<sub>2</sub> wash-in method that allows automatic and continual FRC measurement in mechanically ventilated patients. **METHODS:** We measured FRC with a CO<sub>2</sub> partial rebreathing technique, first in a mechanical lung analog, and then in mechanically ventilated animals, before, during, and subsequent to an acute lung injury induced with oleic acid. We compared FRC measurements from partial CO<sub>2</sub> rebreathing to measurements from a nitrogen wash-out reference method. Using an approved animal protocol, general anesthesia was induced and maintained with propofol in 6 swine (38.8–50.8 kg). A partial CO<sub>2</sub> rebreathing monitor was placed in the breathing circuit between the endotracheal tube and the Y-piece. The partial CO<sub>2</sub> rebreathing signal obtained from the monitor was used to calculate FRC. FRC was also measured with a nitrogen wash-out measurement technique. In the animal studies we collected data from healthy lungs, and then subsequent to a lung injury that simulated the conditions of acute lung injury/acute respiratory distress syndrome. The injury was created by intravenously infusing 0.09 mL/kg of oleic acid over a 15-min period. At each stage of the experiment, the positive end-expiratory pressure (PEEP) was set to 0, 5, 10, or 15 cm H<sub>2</sub>O. At each PEEP level we compared the average of 3 CO<sub>2</sub> rebreathing FRC measurements to the average of 3 nitrogen wash-out reference measurements. We also tested the FRC measurement system with a mechanical test lung in which the true FRC could be directly measured. **RESULTS:** The squared correlation for the linear regression between CO<sub>2</sub> rebreathing and nitrogen wash-out measurements in the animals was  $r^2 = 0.89$  ( $n = 50$ ). The average error of the CO<sub>2</sub> wash-out system was  $-87$  mL and the limits of agreement were  $\pm 263$  mL. In the mechanical test lung, the average error of the FRC measured via the CO<sub>2</sub> wash-in system was  $37$  mL, and the limits of agreement were  $\pm 103$  mL, which was equivalent to  $1.7\%$  of the true FRC. The squared correlation was  $r^2 = 0.96$ . **CONCLUSION:** These results indicate that FRC measurement via CO<sub>2</sub> rebreathing can reliably detect an FRC decrease during lung injury and can reflect the response of the FRC to treatment with PEEP. *Key words:* functional residual capacity, FRC, acute respiratory distress syndrome, acute lung injury, animal models, lung volumes, mechanical ventilation, carbon dioxide rebreathing, positive end-expiratory pressure. [Respir Care 2007;52(11):1480–1489. © 2007 Daedalus Enterprises]

---

Lara Brewer MSc and Joseph Orr PhD are affiliated with the Department of Anesthesiology, University of Utah, Salt Lake City, Utah. Dinesh Haryadi PhD is an employee of Respirionics, Wallingford, Connecticut.

Dr Orr receives royalties from Respirionics. Both Dr Orr and Ms Brewer work as consultants for Respirionics, which financially supported this research. The authors report no other conflicts of interest related to the content of this paper.

---

Ms Brewer presented a version of this report at the 51st International Respiratory Congress of the American Association for Respiratory Care, held December 3–6, 2005, in San Antonio, Texas.

Correspondence: Lara Brewer MSc, Department of Anesthesiology, University of Utah Health Sciences Center, 30 North 1900 East 3C444 SOM, Salt Lake City UT 84132.

## Introduction

Measurement of the functional residual capacity (FRC) of the lung via computed tomography is a sensitive indicator of decreased aeration and increased consolidation during the progression of acute respiratory distress syndrome (ARDS) and acute lung injury (ALI), as well as the reversal of the compromised state following appropriate ventilator treatment.<sup>1-2</sup> Suter et al<sup>2</sup> found that the highest FRC coincides with maximum oxygen transport and the highest static compliance at a specific positive end-expiratory pressure (PEEP). Hedenstierna<sup>3</sup> concluded that FRC measurement is critical for finding optimal ventilator settings.

As a surrogate for direct measurement of FRC in ventilated patients, some studies have pointed to the use of lung mechanics, including the static pressure-volume curves and the measurement of the upper and lower inflection points of the alveolar pressure-volume curve, to guide ventilator settings.<sup>4</sup> However, mechanics-based measurements have proven difficult to use for guiding ventilator settings,<sup>5</sup> because aeration of the injured lung is dynamic and heterogeneous.<sup>6</sup> Direct measurement of FRC could allow ventilation to be set by volume rather than by pressure.

Although computed tomography has been useful for determining the pathophysiology and progression of ARDS/ALI and for demonstrating the usefulness of the FRC measurement to actively control lung volume during mechanical ventilation, the method is regarded as risky and cumbersome to use regularly at the bedside for monitoring the evolution of lung injury and the effects of the ventilatory strategy. Several other techniques for FRC measurement in mechanically ventilated patients have been proposed during the past 2 decades, each of which is based on either nitrogen wash-out or dilution of tracer gases. The techniques include closed-circuit helium dilution,<sup>7,8</sup> open-circuit nitrogen wash-out,<sup>9-11</sup> and open-circuit sulfur hexafluoride wash-out.<sup>12,13</sup> Additionally, FRC has been estimated via electrical impedance tomography<sup>14</sup> and a single-breath-hold Fick method.<sup>15</sup> These methods are expensive, difficult and time consuming at the bedside, impractical for continual use, or require an intolerably large change in the fraction of inspired oxygen ( $F_{IO_2}$ ) to complete the measurement.

We propose here a  $CO_2$  wash-in method that allows automatic and continual measurement of FRC in mechanically ventilated subjects. The new method measures FRC using the “ $CO_2$  wash-in” signals during the onset of a partial  $CO_2$  rebreathing maneuver that is automatically initiated every 3 minutes by a  $CO_2$  rebreathing noninvasive cardiac output monitor (NICO2, Respironics, Wallingford, Connecticut). In an oleic acid model of ARDS/ALI in mechanically ventilated animals, we measured the

FRC before, during, and after lung injury, with 2 methods:  $CO_2$  wash-in and nitrogen wash-out. The aims of the study were to evaluate the new method in a mechanical lung model and to compare FRC measurements with the 2 methods in mechanically ventilated animals during induced lung injury. We demonstrate that the  $CO_2$ -based FRC measurement can be used to trend the effects of lung injury and track the response to treatment.

## Methods

### Nitrogen Wash-Out Method

We used a variation of the nitrogen wash-out FRC-measurement method published by Olegard et al<sup>16</sup> as the reference measurement. This method has been described in the literature but is not commercially available. In our implementation, the nitrogen wash-out method required a brief ( $< 5$  min) 0.2 step increase in  $F_{IO_2}$  (eg, from 0.4 to 0.6). The volume of released nitrogen and the change in nitrogen concentration following the change in  $F_{IO_2}$  were used to calculate FRC.

Oxygen was analyzed with a sidestream paramagnetic  $O_2$  analyzer (Datex, Helsinki, Finland).  $CO_2$  was measured with an infrared analyzer, and flow was measured with a differential pressure-type pneumotachometer, both of which are integrated in the NICO2 mainstream sensor (model 7300, Respironics-Novametrix, Wallingford, Connecticut). The gas analyzers were calibrated with calibration gas prior to the experiment. Each of the analyzers automatically re-zeros periodically to avoid baseline drift. Gas for the sidestream analyzer was sampled at the ventilator circuit Y-piece, and the mainstream sensor was placed between the gas sampling adaptor and the endotracheal tube. Both inspired and expired gases were measured continuously.

The raw data of flow and gas concentration measurements were sampled at 100 Hz and processed digitally using custom-written software to generate end-tidal and volumetric  $O_2$  and  $CO_2$  measurements and tidal volume ( $V_T$ ). We calculated oxygen consumption from the directly measured  $CO_2$  consumption ( $\dot{V}_{CO_2}$ ) and the minimum/maximum difference in the  $O_2$  signal. We assumed that since the waveform of the fast oxygen signal is an inverted, scaled version of the capnogram, oxygen consumption can be calculated as  $\dot{V}_{CO_2}$  multiplied by the minimum/maximum difference in the  $O_2$  divided by the minimum/maximum difference in  $CO_2$ .<sup>9,16</sup> We calculated end-tidal and mixed nitrogen fraction ( $F_{N_2}$ ) as the balance gas ( $F_{N_2} = 1 - F_{O_2} - F_{CO_2}$ ). Nitrogen excretion was calculated as the difference between expired volume multiplied by mixed expired  $N_2$  fraction and inspired volume multiplied by inspired  $N_2$  fraction. After at least 2 minutes of baseline data had been collected, the nitrogen wash-out FRC mea-

surement was initiated by increasing the  $F_{IO_2}$  by 0.2 for each measurement, within the range of 0.3 to 1.0. Typically, the successive step changes in  $F_{IO_2}$  for 3 measurements were 0.4 to 0.6, 0.6 to 0.8, and 0.8 to 1.0. The volume of excreted  $N_2$  ( $\dot{V}_{N_2}$ ) was recorded during wash-out. The wash-out at each step change of  $F_{IO_2}$  was allowed to continue to completion before the next measurement was begun.

The series of measurements was completed within about 10 min, with the hope that absorption atelectasis caused by the higher  $F_{IO_2}$  would be minimized. Typical time to atelectasis with  $F_{IO_2}$  of 0.4 is 120 min, with  $F_{IO_2}$  of 0.8 is 60 min, and with  $F_{IO_2}$  of 1.0 is 50 min.<sup>17</sup>

FRC was calculated as the ratio of the volume of nitrogen excreted over a series of breaths divided by the change in end-tidal nitrogen fraction observed during the same series of breaths:

$$\dot{V}_{N_2} / (F_{etN_2\text{end}} - F_{etN_2\text{ini}}) \quad (1)$$

where  $\dot{V}_{N_2}$  is the volume of nitrogen leaving the lungs during the test,  $F_{etN_2\text{ini}}$  is the initial fraction of end-tidal nitrogen prior to the increase in  $F_{IO_2}$ , and  $F_{etN_2\text{end}}$  is the fraction of end-tidal nitrogen at the end of the test. It should be noted that this calculation ignores the excretion of  $N_2$  from the tissues. The effect of  $N_2$  excretion from the tissues on the FRC measurement should be small (< 100 mL) and consistent across the animals used in our study.<sup>18</sup> Because the published studies that describe the methods for estimating the volume of  $N_2$  excretion in response to increased  $F_{IO_2}$  assume human rather than porcine subjects, we elected to ignore the effect of  $N_2$  excretion in our calculations.<sup>18</sup>

The repeatability of the FRC measurements made during the successive  $F_{IO_2}$  increases was assessed by recording and comparing individual measurements. The average measured FRC with the nitrogen wash-out method was used as the reference value for comparison with the  $CO_2$ -based measurements.

### CO<sub>2</sub> Wash-In Method

FRC measurements with the  $CO_2$  wash-in method were made with an on-airway infrared  $CO_2$  analyzer, while airway flow was measured with an integrated differential pressure-type pneumotachometer, both of which are integrated in the NICO2 partial rebreathing cardiac output monitor. The monitor automatically actuates a pneumatic valve to commence partial  $CO_2$  rebreathing once every 3 min. The rebreathing period lasts 35 seconds and is used to measure pulmonary capillary blood flow. To calculate the FRC with the  $CO_2$  wash-in method, only the first breath of the rebreathing period is needed, wherein the changes in

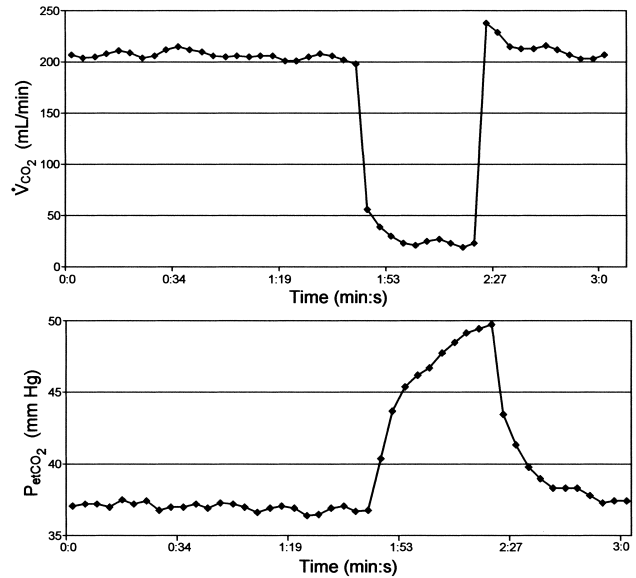


Fig. 1. Changes in end-tidal  $CO_2$  ( $P_{etCO_2}$ ) and corresponding changes in  $CO_2$  elimination ( $\dot{V}_{CO_2}$ ) with rebreathing during a 3-min period.

end-tidal and volumetric  $CO_2$  are recorded. Figure 1 depicts the typical  $CO_2$  rebreathing signals.

The calculations are as follows:

$$FRC \times F_{CO_2(n)} = FRC \times F_{CO_2(n-1)} + V_{bCO_2} - V_{eCO_2} \quad (2)$$

$$FRC \times [F_{CO_2(n)} - F_{CO_2(n-1)}] = V_{bCO_2} - V_{eCO_2} \quad (3)$$

where  $F_{CO_2(n)}$  is the fraction of end-tidal  $CO_2$  in the current breath (n),  $F_{CO_2(n-1)}$  is the fraction of end-tidal  $CO_2$  in the previous breath (n-1),  $V_{bCO_2}$  is the volume per breath of  $CO_2$  passing from the blood into the FRC, and  $V_{eCO_2}$  is the volume per breath of  $CO_2$  being excreted from the patient, measured at the mouth.

It is assumed that the  $CO_2$  excretion rate during the baseline period before rebreathing  $V_{CO_2\text{baseline}}$  is at a steady state and that the amount of  $CO_2$  eliminated per breath at the mouth is equal to the volume eliminated from the blood in the alveoli.

$$FRC = (V_{CO_2\text{baseline}} - V_{eCO_2(n)}) / (F_{CO_2(n)} - F_{CO_2(n-1)}) \quad (4)$$

The numerator of equation 4 reflects the amount of  $CO_2$  in excess of the amount delivered by the blood and retained in the FRC due to rebreathing. This equation is simply a 1-breath wash-in method using a soluble gas. Only the first breath is used because the increase (or decrease) in intra-alveolar  $CO_2$

quickly changes the rate of CO<sub>2</sub> delivery to the alveoli. Evaluating only a single breath minimizes that error.

The actual volume measured by this method includes not only the FRC but also the effective volume of the other stores of CO<sub>2</sub> in the lung, including the lung tissue and the blood. To compensate for these extra CO<sub>2</sub>-storing sites, the FRC is calculated as:

$$\text{FRC} = 0.45 \times (\text{V}_{\text{CO}_2\text{baseline}} - \text{V}_{\text{eCO}_2(n)}) / (\text{F}_{\text{CO}_2(n)} - \text{F}_{\text{CO}_2(n-1)}) \quad (5)$$

The factor of 0.45 was described by Gedeon et al<sup>15</sup> to account for the use of CO<sub>2</sub> in place of an insoluble gas.

A more precise calculation would include compensation for the effect of cardiac output and breath-to-breath changes in V<sub>T</sub>, but for the purposes of this study these assumptions provide reasonable estimates of FRC.

It should also be noted that the last breath of rebreathing could also be used instead of the first breath, provided that the CO<sub>2</sub> excretion rate had reached a steady state during rebreathing, such that the CO<sub>2</sub> excretion rate was equal to the rate of CO<sub>2</sub> elimination from the blood to the FRC. This would be called the CO<sub>2</sub> wash-out FRC, and calculated as:

$$\text{FRC} = 0.45 \times (\text{V}_{\text{CO}_2\text{steady}} - \text{V}_{\text{CO}_2(n)}) / (\text{F}_{\text{CO}_2(n-1)} - \text{F}_{\text{CO}_2(n)}) \quad (6)$$

where V<sub>CO<sub>2</sub>steady</sub> is the volume of CO<sub>2</sub> excreted in the last breath of rebreathing in the steady state, V<sub>CO<sub>2</sub>(n)</sub> is the CO<sub>2</sub> excreted in the first breath following rebreathing, F<sub>etCO<sub>2</sub>(n-1)</sub> is the fraction of end-tidal CO<sub>2</sub> in the first breath following rebreathing, and F<sub>etCO<sub>2</sub>(n)</sub> is the fraction of end-tidal CO<sub>2</sub> in the last breath of rebreathing. This method assumes that a steady state condition was achieved during rebreathing.

#### **Bench Validation of the CO<sub>2</sub> Wash-In Method With a Lung Model**

A training/test lung (Michigan Instruments, Grand Rapids, Michigan) was driven by a ventilator (900c, Siemens-Elcoma, Solna, Sweden) and infused with 250 mL/min CO<sub>2</sub>. A fan inside the lung completely mixed the gases. V̇<sub>CO<sub>2</sub></sub> and end-tidal CO<sub>2</sub> measurements were obtained from the NICO2 monitor. Partial rebreathing was automatically induced by the monitor for 35 seconds every 3 min. PEEP was changed from 0 cm H<sub>2</sub>O (FRC = 1.47 L) to 20 cm H<sub>2</sub>O in steps of 5 cm H<sub>2</sub>O, to increase the FRC to a maximum of 2.75 L. At each PEEP level, 2 CO<sub>2</sub>-wash-in-based FRC measurements were recorded, and the known volume of the mechanical lung was also recorded. At the end of the experiment, the PEEP was reduced back to zero, and the measurements were again re-

corded. The average CO<sub>2</sub> wash-in measurements at each PEEP step were compared via linear regression and Bland-Altman statistics to the known volumes.

#### **Bench Validation of the Nitrogen Wash-Out Method With a Lung Model**

The training/test lung was set up as described for the CO<sub>2</sub> validation. O<sub>2</sub> was measured using a paramagnetic fast oxygen sensor (Capnomac, Datex, Helsinki, Finland). Step changes in N<sub>2</sub> were imposed in the simulator by increasing F<sub>IO<sub>2</sub></sub> from 0.7 to 0.9. PEEP was applied at 4 different levels, from 0 cm H<sub>2</sub>O to 20 cm H<sub>2</sub>O. The PEEP was returned back to zero for the final measurement set. At each PEEP step, the known value of FRC was recorded and 2 nitrogen wash-out-based FRC measurements were recorded. The average measurements at each PEEP step were compared with linear regression and Bland-Altman statistics to the known volumes.

#### **Animal Testing Protocol**

Using an approved animal research protocol, 6 healthy pigs, of mixed gender (38.8–50.8 kg), were fasted, with free access to water overnight before they were given an intramuscular bolus of Telazol (4 mg/kg). Following tracheal intubation, the animals were ventilated with a mechanical ventilator (Esprit, Respirationics, Carlsbad, California) with a V<sub>T</sub> of 10 mL/kg, F<sub>IO<sub>2</sub></sub> of 0.4, and an inspiratory-expiratory time ratio of 1:2. The respiratory rate was adjusted to maintain the nonbreathing end-tidal P<sub>CO<sub>2</sub></sub> near 35 mm Hg. An 18-gauge arterial cannula was inserted into the femoral artery to continuously measure blood pressure and to facilitate arterial blood gas samples. General anesthesia was maintained via continuous infusion of propofol (100–300 ug/kg/min), with a target mean blood pressure of 100 mm Hg. The animals were paralyzed with a continuous infusion of pancuronium (1 mg/kg/h). A flow-directed pulmonary artery catheter was inserted into the jugular vein and advanced until the tip rested in the pulmonary artery, as assessed by hemodynamic waveforms. Mixed venous blood gas samples were drawn from the catheter tip. Venous admixture (shunt fraction) was calculated with the measured arterial and venous blood gas data. Lactated ringers solution was given intravenously at 6 mL/kg/h throughout the experiment. The NICO2 monitor was placed in the breathing circuit between the endotracheal tube and the Y-piece. The partial CO<sub>2</sub> rebreathing signals obtained from that monitor were used to calculate FRC.

The protocol was divided into 2 phases: a healthy lung phase, and an oleic acid lung injury phase that simulated ARDS/ALI. In the healthy lung phase the



PEEP was set to 0, 5, 10, and 15 cm H<sub>2</sub>O. At each PEEP level we compared the average of 3 FRC measurements from CO<sub>2</sub> wash-in to the average of 3 nitrogen wash-out measurements. To ensure that the effects of each PEEP adjustment had stabilized, no FRC measurements were made in the first 20 min after each PEEP change. Then, partial rebreathing data (end-tidal CO<sub>2</sub> and CO<sub>2</sub> excretion in response to partial rebreathing) were collected for 12 min (4 rebreathing cycles, 3 min each) with the NICO2 monitor. Next, 3 reference nitrogen wash-out measurements were recorded. After collecting the nitrogen wash-out data, the PEEP was increased to the next level and the next measurement sequence was repeated. Arterial blood gas measurements were collected between the CO<sub>2</sub> wash-in and nitrogen wash-out measurements at each PEEP level. Average cardiac output (measured via bolus thermodilution), heart rate, arterial blood pressure, pulmonary artery blood pressure, and oxygen saturation, were also noted at each PEEP level.

Following FRC measurement at each of the 4 PEEP levels in healthy lungs, lung injury was created to simulate ARDS/ALI by infusing 0.09 mL/kg of oleic acid through the proximal port of the pulmonary artery catheter. A syringe pump was used to deliver the acid continuously over a 15-min period. We allowed 1 hour for the injury to develop before resuming comparison FRC data collection. Injury was confirmed by decreased static lung compliance and lung auscultation. After the lung injury had been created, we repeated the data collection procedure at each PEEP level: 0, 5, 10, and 15 cm H<sub>2</sub>O.

The average FRC measurements made with each of the methods at each PEEP level were compared via regression analysis and Bland-Altman statistics.

## Results

### Bench Validation Results: Comparison With the Known Lung Volume

In the bench validation, the average error in the FRC measured by the CO<sub>2</sub> wash-in system was 37 mL, with limits of agreement (LOA) of  $\pm 201$  mL, which was equivalent to 1.7% of the true FRC. The squared correlation was  $r^2 = 0.96$  (Fig. 2).

The average error in the FRC measured by the CO<sub>2</sub> wash-out system was 508 mL, with LOA of  $\pm 370$  mL, which was equivalent to 27% of the true FRC. The squared correlation was  $r^2 = 0.95$ . We observed that, because of the limitations of the physical lung model, the requirement of the CO<sub>2</sub> wash-out method that steady state end-tidal CO<sub>2</sub> be attained during rebreathing was not met.

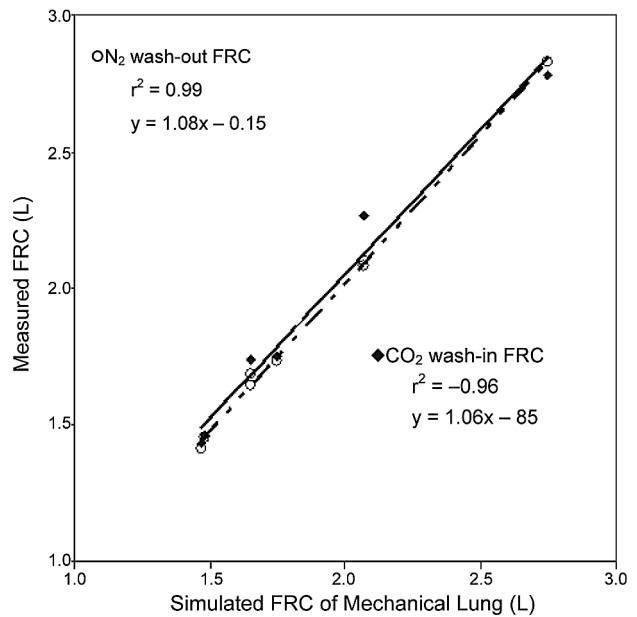


Fig. 2. Regression analyses of functional residual capacity (FRC) measurements with the CO<sub>2</sub> wash-in method and the nitrogen wash-out method, with the simulated FRC of the mechanical lung.

The average error with N<sub>2</sub> wash-out was 6 mL, with LOA of  $\pm 83$  mL, which was  $-0.02\%$  of the true FRC. The squared correlation was  $r^2 = 0.99$  (see Fig. 2).

### Bench Validation CO<sub>2</sub> Measurement Repeatability

The average error in the FRC measured with the CO<sub>2</sub> wash-in system with duplicate measurements was 61 mL, with LOA of  $\pm 103$  mL. The squared correlation for duplicate measurements was  $r^2 = 0.97$ . The average error in the FRC measured with the CO<sub>2</sub> wash-out system with duplicate measurements was  $-10$  mL, with LOA of  $\pm 109$  mL. The squared correlation for duplicate CO<sub>2</sub> wash-out measurements was  $r^2 = 0.99$ .

### Animal Testing Results

In the healthy-lung phase of the experiment, the median P<sub>aO<sub>2</sub></sub>/F<sub>IO<sub>2</sub></sub> was 443 mm Hg (range 307–570 mm Hg) with an F<sub>IO<sub>2</sub></sub> of 0.3. Subsequent to the oleic-acid injury, the median P<sub>aO<sub>2</sub></sub>/F<sub>IO<sub>2</sub></sub> was 153 mm Hg (range 120–172 mm Hg). During the injury phase, the F<sub>IO<sub>2</sub></sub> was 0.4 in all animals except one, which had a P<sub>aO<sub>2</sub></sub>/F<sub>IO<sub>2</sub></sub> of 169 mm Hg with an F<sub>IO<sub>2</sub></sub> of 0.7.

Figure 3 shows the individual CO<sub>2</sub> wash-out FRC measurements from animal 3 and depicts the change in FRC during evolution of the oleic acid induced ALI, as well as recovery of FRC volume following PEEP therapy.

## MEASUREMENT OF FRC DURING ACUTE LUNG INJURY IN ANIMALS

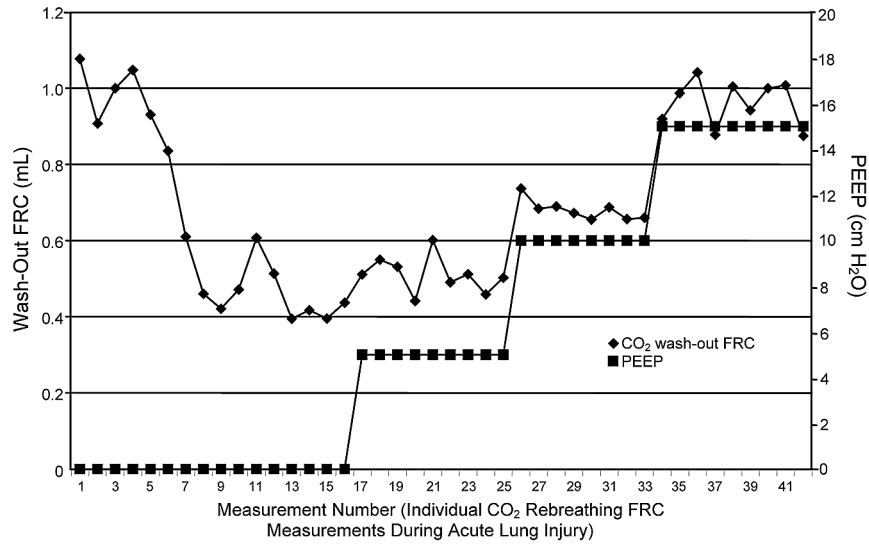


Fig. 3. Trend of CO<sub>2</sub>-wash-out functional residual capacity (FRC) measured during evolution of and ventilator treatment for acute lung injury. PEEP = positive end-expiratory pressure.

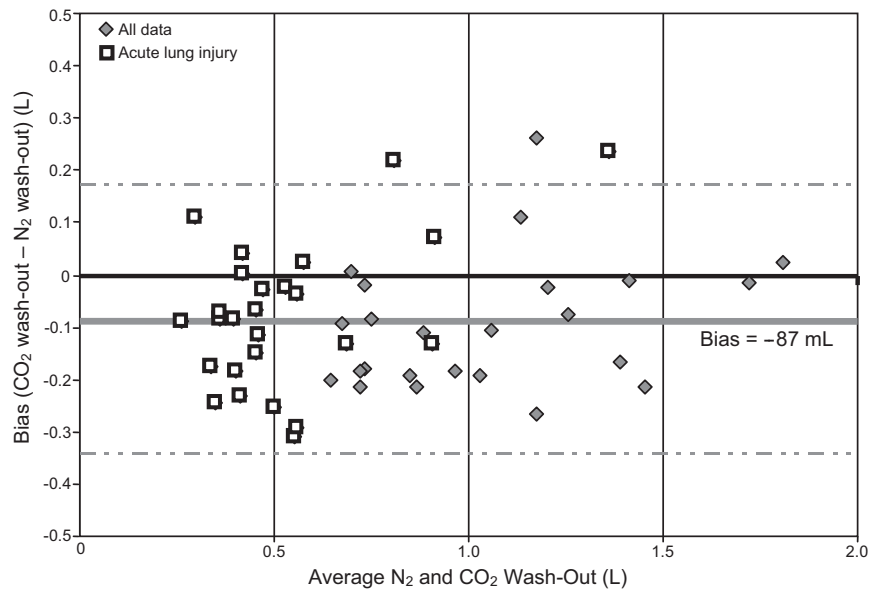


Fig. 4. Bland-Altman comparison of CO<sub>2</sub>-wash-out and nitrogen-wash-out functional residual capacity (FRC) measurement techniques.

### Comparison of CO<sub>2</sub> Methods With Nitrogen Wash-Out FRC Measurements

When compared with nitrogen wash-out, the average error in the FRC measured with the CO<sub>2</sub> wash-out system was  $-87$  mL, with LOA of  $\pm 258$  mL (Fig. 4). The correlation coefficient was  $r^2 = 0.89$  ( $n = 50$ ) and the slope was 1.018. For the ALI phase alone,  $r^2$  was 0.75, the slope was 1.13, and the bias was  $-77$  mL, with LOA of  $\pm 276$  mL ( $n = 26$ ).

When CO<sub>2</sub> wash-in data were compared with nitrogen wash-out, the average error was  $-3$  mL, with LOA of

$\pm 346$  mL. The correlation coefficient was  $r^2 = 0.75$  ( $n = 43$ ).

### CO<sub>2</sub> Wash-Out and Wash-In FRC Measurement Technique Repeatability

Regression of duplicate CO<sub>2</sub> wash-out measurements at each PEEP resulted in an  $r^2 = 0.98$  for all data combined and  $r^2 = 0.96$  for just the ALI phase. The average error at each PEEP in the FRC for duplicate CO<sub>2</sub> wash-out measurements was 2.9 mL, with LOA of  $\pm 124$  mL for all the

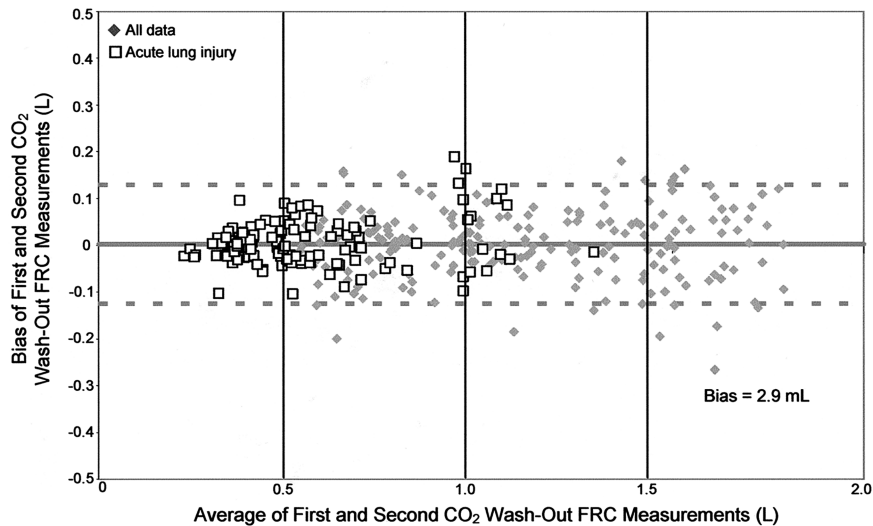


Fig. 5. Bland-Altman comparison of the first and second CO<sub>2</sub>-wash-out functional residual capacity (FRC) measurements during the healthy lung and injured lung phases.

data ( $n = 357$ ) (Fig. 5) and 3.8 mL, with LOA of  $\pm 95$  mL for the ALI phase ( $n = 140$ ).

Regression of duplicate CO<sub>2</sub> wash-in FRC measurements resulted in an  $r^2 = 0.93$  for all data combined, and  $r^2 = 0.87$  for just the ALI phase. The CO<sub>2</sub> wash-in repeatability bias for all data together was 1 mL, with LOA of  $\pm 183$  mL ( $n = 360$ ). For the ALI phase only, the wash-in repeatability bias was 7 mL, with LOA of  $\pm 161$  mL ( $n = 147$ ).

### Nitrogen Wash-Out Repeatability

Regression of duplicate nitrogen wash-out measurements resulted in an  $r^2 = 0.98$  for all data combined and  $r^2 = 0.93$  for just the ALI phase. The average error at each PEEP in the FRC from one nitrogen wash-out to the next was 13 mL, with LOA of  $\pm 119$  mL for all data together, and was 11 mL, with LOA of  $\pm 111$  mL for the ALI phase.

### Discussion

We found good repeatability and clinically acceptable limits of agreement and bias between the proposed CO<sub>2</sub> technique and the nitrogen wash-out method for FRC measurement. The CO<sub>2</sub> technique allows automated, continual measurements of lung volume in mechanically ventilated subjects with ALI. An update in the measurement can occur in less than 3 minutes, which is rapid enough to be of clinical use. The method does not require a change in the ventilator settings and therefore could run independently and provide a trend of FRC measurements without clinician intervention. Since the method is repeatable, the clinician could also obtain early feedback from individual

measurements regarding the physiologic response to changes made in PEEP and other ventilator settings.

CO<sub>2</sub> wash-out showed better LOA for both the comparison of accuracy and the comparison of repeatability than CO<sub>2</sub> wash-in did in these subjects. This is probably because the signal-to-noise ratio of the first wash-out breath is slightly better, as long as steady state has been reached during the partial rebreathing period before the step change to nonrebreathing is actuated. Further testing is needed to determine whether CO<sub>2</sub> wash-in or wash-out (or a combination of the two) is the best approach. The CO<sub>2</sub> wash-in measurement makes use of the first breath of rebreathing, whereas the wash-out measurement is based on the last breath of rebreathing. The wash-out measurement requires the assumption that steady state has been reached during the rebreathing period.

We observed no systematic difference between the CO<sub>2</sub> wash-out and the nitrogen wash-out techniques. Each method responded similarly to the loss of aeration during the evolution of lung injury and to an increase in PEEP. This was expected, since both methods measure the communicating gas (ie, the gas that flows into and out of the lung during tidal ventilation) rather than the whole enclosed gas volume. The nitrogen wash-out method had a better signal-to-noise ratio than either CO<sub>2</sub> method at larger FRCs. The repeatability of our implementation of the nitrogen wash-out was similar to what Olegard et al<sup>16</sup> reported. They found a bias of  $-5$  mL, with limits of agreement of approximately  $-380$  mL to 375 mL.

Subsequent FRC measurements taken according to our protocol of successive, stepwise increases in F<sub>IO<sub>2</sub></sub> for a period of about 10 min did not show a decrease in FRC with each increase in F<sub>IO<sub>2</sub></sub>. If we had observed a decrease

with each subsequent measurement, we might have assumed that increasing the  $F_{IO_2}$  had lead to absorption atelectasis. We observed no systematic difference between the first FRC measurement, which was taken at a lower  $F_{IO_2}$ , and the subsequent measurement, which was taken at a higher  $F_{IO_2}$ . The average squared correlation between subsequent measurement pairs was  $r^2 = 0.97$ , with an average difference of 12 mL. This implies that the method is insensitive to differences in  $F_{IO_2}$  and that increases in  $F_{IO_2}$  did not create a change in FRC due to absorption atelectasis or a similar effect.

One limitation of FRC measurement with the  $CO_2$  method is the requirement that breath-to-breath  $V_T$  be fairly consistent. Since changes in  $V_T$  create variation in end-tidal  $CO_2$ , and the  $CO_2$  method uses changes in end-tidal  $CO_2$  for the calculation, any respiratory pattern in which breath-to-breath volumes are inconsistent may be unsuitable for  $CO_2$  FRC measurements. Also, since the  $CO_2$  methods use a single breath for the calculation, lung volumes that are not well ventilated may not be represented in the measurement.

Current practice involves monitoring of improvements in  $O_2$  saturation or dynamic compliance as a measure of a successful recruitment maneuver.<sup>19–26</sup> However, the improvement in  $O_2$  saturation following a recruitment maneuver is transient,<sup>27</sup> whereas the measurement of FRC remains a sensitive indicator of the aeration of the lung. Compliance change in early ALI/ARDS is a measure of aerated tissue, which leads to baby lung, rather than a stiff lung as previously thought.<sup>28</sup> Rylander et al<sup>1</sup> found that FRC was a more sensitive indicator of decreased aeration and increased consolidation than is lung compliance, and he concluded that FRC might be a useful adjunct to  $P_{aO_2}$  monitoring at the bedside.

It has been shown<sup>29</sup> that when PEEP is added to lungs that exhibit repetitive alveolar collapse and expansion, the alveoli are stabilized and protected from ventilator-induced lung injury. If continual monitoring of FRC could facilitate faster detection of the early phase of ARDS/ALI, which is characterized by deterioration in FRC due to collapse and flooding, rather than by fibrosis,<sup>1</sup> perhaps ventilator treatment aimed at maintaining alveolar stabilization could be initiated sooner. Additionally, direct FRC measurements may aid in detection of de-recruitment in patients with ARDS/ALI caused by endotracheal tube suctioning.<sup>30</sup>

It is imperative to use the minimum level of PEEP and volume therapies to recruit the lung, since barotrauma and volutrauma are risks associated with the treatments. If on-line FRC measurements were available, it would be possible to quickly confirm improvement in FRC following treatment with the most conservative approach possible. It has also been suggested that FRC could be a tool for the early detection of lung over-inflation, by studying the predictive value of the ratio between PEEP-induced increase

in FRC and PEEP-induced alveolar recruitment derived from the pressure-volume curves.<sup>4</sup> It remains to be seen whether earlier detection and treatment of ARDS/ALI will affect outcome.

An alternative to the open-lung strategy has been termed “lung rest,” which is characterized by low airway pressure to prevent recruitment/derecruitment, small  $V_T$ , and occasional sigh breaths or biologically variable ventilation.<sup>31–35</sup> Whether using the open-lung or the lung-rest strategy, the common intent is the prevention of repetitive alveolar collapse and expansion.<sup>36</sup> In either approach, continual monitoring of FRC would indicate an improvement or worsening of the FRC so that the clinician could be alerted that application of one of the strategies is required or has been successful.

The ability of the lungs to exchange gas is driven by both ventilation and perfusion. Appropriate ventilator strategies must include the consideration that PEEP may significantly affect the amount and distribution of the pulmonary perfusion, even at modest pressure levels. It would be useful to be able to use the same rebreathing signals to assess both the ventilation and the perfusion of the lung. The partial  $CO_2$  rebreathing monitor avails several other cardiopulmonary measures from the same signals needed for FRC measurement, such as compliance, pulmonary capillary blood flow, pressure-volume curves, and  $\dot{V}_{CO_2}$ , each of which is an important factor in the analysis of gas exchange efficiency. For example, pulmonary capillary blood flow measurements could indicate a decrease in perfusion if excessive PEEP were used.

The main drawback of the  $CO_2$ -based FRC measurement techniques is that  $CO_2$  is a soluble indicator gas that is carried in the blood. Changes in the alveolar concentration affect the volume of  $CO_2$  delivered to the alveoli, which makes the assumption of delivery of  $CO_2$  to the alveoli by the blood less valid with each breath as rebreathing progresses. This limitation restricts analysis to the first or last breath of rebreathing. The use of a single breath for the measurement requires analysis of small changes in the signals, which may lead to measurement errors, especially when FRC is large. Another drawback of using  $CO_2$  as the indicator gas is that it is stored in the tissues of the lung and in the blood. The volume that is directly measured includes both the effective  $CO_2$  storage volume of the lung tissue and the blood. We apply the empirically derived multiplicative factor of 0.38 to reduce the effective lung volume to the gas volume that is the FRC. This factor is similar to that of 0.45 that Gedeon et al<sup>15</sup> selected for their studies. This factor might be expected to be affected by increased tissue volumes, such as in edematous ARDS, but in this study the same factor was applied in both healthy and injured lungs, where the volume of fluid in the lung changed significantly. The application of a factor for pulmonary capillary blood flow or



correction in  $V_T$  from one breath to the next did not improve the repeatability or the comparison data in these studies, which is probably because the animals were mechanically ventilated and pulmonary capillary blood flow was not actively altered during the studies.

Based on the limitation of  $\text{CO}_2$ , it may be reasonable to use the  $\text{CO}_2$ -based FRC measurement as a trend monitor rather than as an indicator of absolute gas volume in the lung. As with all tracer gas methods, the  $\text{CO}_2$  wash-in method measures only the part of the FRC that takes part in gas exchange, or the effective FRC. Methods such as computed tomography and body plethysmography also include the part of the FRC that is not communicating. Rylander et al<sup>30</sup> noted that the tendency to underestimate the FRC with a tracer gas was aggravated in ARDS because of the uneven distribution of ventilation. He estimated that the sulfur hexafluoride FRC method measured two thirds of the true end-expiratory lung volume; this limitation applies to the  $\text{CO}_2$  wash-in technique as well.

### Conclusions

In summary, convenient FRC measurement, combined with knowledge of cardiac output and other traditional measures, could be useful for guiding and monitoring the success of a recruitment maneuver, PEEP, and posture changes in treating lung injury. Such a monitor could simplify the maintenance of recruitment and oxygenation with minimal PEEP following a recruitment maneuver. Knowledge of FRC could aid in achieving alveolar stability, thereby protecting alveoli from shear stress and overdistention. If the method for measuring FRC were simple enough to use at the bedside, it might also be possible to detect de-recruitment sooner than by waiting to observe deleterious effects on  $P_{aO_2}$ .

A simpler FRC measurement method that would be more widely used in clinical medicine could help bring about broader clinical answers to questions such as the relationship between FRC and disease progression (eg, edema and fibrosis), the rate of recruitment after application of PEEP, the effect of fluid balance, and the relationship between gas exchange and FRC. We have shown that reproducible FRC measurements can be made with  $\text{CO}_2$ . This method requires no interruption or changes to mechanical ventilation and could be used continually to monitor FRC in ARDS/ALI patients.

### REFERENCES

- Rylander C, Hogman M, Perchiazzi G, Magnusson A, Hedenstierna G. Functional residual capacity and respiratory mechanics as indicators of aeration and collapse in experimental lung injury. *Anesth Analg* 2004;98(3):782–789.
- Suter PM, Fairley HB, Schlobohm RM. Shunt, lung volume and perfusion during short periods of ventilation with oxygen. *Anesthesiology* 1975;43(6):617–627.
- Hedenstierna G. The recording of FRC—is it of importance and can it be made simple? *Intensive Care Med* 1993;19(7):365–366.
- Rouby JJ, Lu Q, Goldstein I. Selecting the right level of positive end-expiratory pressure in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2002;165(8):1182–1186.
- de Chazal I, Hubmayr RD. Novel aspects of pulmonary mechanics in intensive care. *Br J Anaesth* 2003;91(1):81–91.
- Markstaller K, Eberle B, Kauczor HU, Scholz A, Bink A, Thelen M, et al. Temporal dynamics of lung aeration determined by dynamic CT in a porcine model of ARDS. *Br J Anaesth* 2001;87(3):459–468.
- Pelosi P, Cereda M, Foti G, Giacomini M, Pesenti A. Alterations of lung and chest wall mechanics in patients with acute lung injury: effects of positive end-expiratory pressure. *Am J Respir Crit Care Med* 1995;152(2):531–537.
- Patroniti N, Bellani G, Manfio A, Maggioni E, Giuffrida A, Foti G, Pesenti A. Lung volume in mechanically ventilated patients: measurement by simplified helium dilution compared to quantitative CT scan. *Intensive Care Med* 2004;30(2):282–289.
- Fretschner R, Deusch H, Weitnauer A, Brunner JX. A simple method to estimate functional residual capacity in mechanically ventilated patients. *Intensive Care Med* 1993;19(7):372–376.
- Wrigge H, Sydow M, Zinserling J, Neumann P, Hinz J, Burchardi H. Determination of functional residual capacity (FRC) by multibreath nitrogen washout in a lung model and in mechanically ventilated patients: accuracy depends on continuous dynamic compensation for changes of gas sampling delay time. *Intensive Care Med* 1998;24(5):487–493.
- Zinserling J, Wrigge H, Varelmann D, Hering R, Putensen C. Measurement of functional residual capacity by nitrogen washout during partial ventilatory support. *Intensive Care Med* 2003;29(5):720–726.
- Jonmarker C, Jansson L, Jonson B, Larsson A, Werner O. Measurement of functional residual capacity by sulfur hexafluoride washout. *Anesthesiology* 1985;63(1):89–95.
- Larsson A, Linnarsson D, Jonmarker C, Jonson B, Larsson H, Werner O. Measurement of lung volume by sulfur hexafluoride washout during spontaneous and controlled ventilation: further development of a method. *Anesthesiology* 1987;67(4):543–550.
- Hinz J, Hahn G, Neumann P, Sydow M, Mohrenweiser P, Hellige G, Burchardi H. End-expiratory lung impedance change enables bedside monitoring of end-expiratory lung volume change. *Intensive Care Med* 2003;29(1):37–43.
- Gedeon A, Krill P, Osterlund B. Pulmonary blood flow (cardiac output) and the effective lung volume determined from a short breath hold using the differential Fick method. *J Clin Monit Comput* 2002;17(5):313–321.
- Olegard C, Sondergaard S, Houtz E, Lundin S, Stenqvist O. Estimation of functional residual capacity at the bedside using standard monitoring equipment: a modified nitrogen washout/washin technique requiring a small change of the inspired oxygen fraction. *Anesth Analg* 2005;101(1):206–212.
- Magnusson L, and Spahn D. New concepts of atelectasis during general anesthesia. *Br J Anaesth* 2003;91(1):61–72.
- Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes; *Eur Respir J* 2005;26(3):511–522.
- Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998;338(6):347–354.
- Brunet F, Jeanbourquin D, Monchi M, Mira JP, Fierobe L, Armanigandis A, et al. Should mechanical ventilation be optimized to blood

## MEASUREMENT OF FRC DURING ACUTE LUNG INJURY IN ANIMALS

- gases, lung mechanics, or thoracic CT scan? *Am J Respir Crit Care Med* 1995;152(2):524–530.
21. Foti G, Cereda M, Sparacino ME, De Marchi L, Villa F, Pesenti A. Effects of periodic lung recruitment maneuvers on gas exchange and respiratory mechanics in mechanically ventilated acute respiratory distress syndrome (ARDS) patients. *Intensive Care Med* 2000;26(5):501–507.
  22. Cakar N, der Kloot TV, Youngblood M, Adams A, Nahum A. Oxygenation response to a recruitment maneuver during supine and prone positions in an oleic acid-induced lung injury model. *Am J Respir Crit Care Med* 2000;161(6):1949–1956.
  23. Lapinsky SE, Aubin M, Mehta S, Boiteau P, Slutsky AS. Safety and efficacy of a sustained inflation for alveolar recruitment in adults with respiratory failure. *Intensive Care Med* 1999;25(11):1297–1301.
  24. Pelosi P, Cadringer P, Bottino N, Panigada M, Carrieri F, Riva E, et al. Sigh in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999;159(3):872–880.
  25. Pelosi P, Bottino N, Chiumello D, Caironi P, Panigada M, Gamberoni C, et al. Sigh in supine and prone position during acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2003;167(4):521–527.
  26. Baba R, Paramesh K, Zwaal JW. Protective ventilation of patients with acute respiratory distress syndrome. *Br J Anaesth* 2004;93(1):153.
  27. Fujino Y, Goddon S, Dolhnikoff M, Hess D, Amato MB, Kacmarek RM. Repetitive high-pressure recruitment maneuvers required to maximally recruit lung in a sheep model of acute respiratory distress syndrome. *Crit Care Med* 2001;29(8):1579–1586.
  28. Gattinoni L, Caironi P, Pelosi P, Goodman LR. What has computed tomography taught us about the acute respiratory distress syndrome? *Am J Respir Crit Care Med* 2001;164(9):1701–1711.
  29. McCann UG 2nd, Schiller HJ, Carney DE, Gatto LA, Steinberg JM, Nieman GF. Visual validation of the mechanical stabilizing effects of positive end-expiratory pressure at the alveolar level. *J Surg Res* 2001;99(2):335–342.
  30. Rylander C, Tylén U, Rossi-Norrlund R, Herrmann P, Quintel M, Bake B. Uneven distribution of ventilation in acute respiratory distress syndrome. *Crit Care* 2005;9(2):R165–R171.
  31. Martynowicz MA, Walters BJ, Hubmayr RD. Mechanisms of recruitment in oleic acid-injured lungs. *J Appl Physiol* 2001;90(5):1744–1753.
  32. Arold SP, Mora R, Lutchen KR, Ingenito EP, Suki B. Variable tidal volume ventilation improves lung mechanics and gas exchange in a rodent model of acute lung injury. *Am J Respir Crit Care Med* 2002;165(3):366–371.
  33. Lefevre GR, Kowalski SE, Girling LG, Thiessen DB, Mutch WA. Improved arterial oxygenation after oleic acid lung injury in the pig using a computer-controlled mechanical ventilator. *Am J Respir Crit Care Med* 1996;154(5):1567–1572.
  34. Suki B, Barabasi AL, Hantos Z, Petak F, Stanley HE. Avalanches and power-law behaviour in lung inflation. *Nature* 1994;368(6472):615–618.
  35. Boker A, Graham MR, Walley KR, McManus BM, Girling LG, Walker E, et al. Improved arterial oxygenation with biologically variable or fractal ventilation using low tidal volumes in a porcine model of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2002;165(4):456–462.
  36. Schiller HJ, McCann UG 2nd, Carney DE, Gatto LA, Steinberg JM, Nieman GF. Altered alveolar mechanics in the acutely injured lung. *Crit Care Med* 2001;29(5):1049–1055.