

Measurement of Functional Residual Capacity of the Lung by Partial CO₂ Rebreathing Method During Acute Lung Injury in Animals

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Abstract

Background: We measured Functional Residual Capacity (FRC) of the lungs with a CO₂ 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 by oleic acid. We compared the FRC from partial CO₂ rebreathing with those of a nitrogen washout reference method. **Materials and Methods:** Using an approved animal protocol, general anesthesia was induced and maintained with propofol in six swine (38.8-50.8 kg). In both the mechanical lung analog and the animals, a partial CO₂ rebreathing monitor (NICO₂, Respironics Inc., Wallingford, CT) was placed in the breathing circuit between the endotracheal tube and the Y-piece. The partial CO₂ rebreathing signal obtained from this monitor was used to calculate FRC. FRC was also measured with a nitrogen washout measurement technique. In the animals, we collected data from healthy lungs and then subsequent to a lung injury that simulated the conditions of ARDS/ALI which was created by intravenously infusing 0.09 mL/kg of oleic acid over a 15-minute period. At each stage of the experiment, the positive end-expiratory pressure (PEEP) was set to 0, 5, 10, and 15 mmHg H₂O. At each PEEP level, we compared the average of three FRC measurements from CO₂ rebreathing to the average of three nitrogen washout reference measurements. **Results:** The correlation coefficient for the linear regression between CO₂ rebreathing and nitrogen washout measurements in the animals was $r^2 = 0.89$ ($n = 50$). The average error of the CO₂ washout system was -87 mL with limits of agreement (LOA) ± 263 mL. In the mechanical lung, the average error in the FRC measured by the CO₂ wash-in system was 37 mL with LOA ± 103 mL, which was equivalent to 1.7% of the true FRC. The correlation coefficient was $r^2 = 0.96$. **Conclusion:** These results indicate FRC measurement by CO₂ rebreathing can reliably detect a decrease in FRC during lung injury and can reflect the response of the FRC to treatment with PEEP.

Introduction

Measurement of the Functional Residual Capacity (FRC) of the lung using Computed Tomography (CT) has been found to be a sensitive indicator of decreased aeration and increased consolidation during the progression of Acute Respiratory Distress Syndrome and Acute Lung Injury (ARDS/ALI), as well as the reversal of the compromised state following appropriate ventilator treatment^{1,2}. Suter² found that the highest FRC coincides with maximum oxygen transport and the highest static compliance (C_{stat}) at a specific PEEP. Hedenstierna³ concluded that measurement of FRC is critical for finding optimal settings of the ventilator.

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 upper and lower inflection points of the alveolar pressure/volume curve, to guide ventilator settings⁴. However, mechanics-based measurements have proven difficult to use for guiding ventilator settings⁵ because aeration of the injured lung is dynamic and heterogeneous⁶. Direct measurement of FRC could allow ventilation to be set by volume rather than by pressure.

Although CT has been useful for defining 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 two decades, each of which is based on either nitrogen washout or dilution of tracer gases. The techniques include closed-circuit helium dilution^{7,8}, open-circuit nitrogen washout⁹⁻¹¹, and open-circuit Sulfur Hexafluoride (SF₆) washout^{12,13}. Additionally, FRC has been estimated by electrical impedance tomography (EIT)¹⁴ and a single-breath hold Fick method¹⁵. These methods are expensive, difficult and time consuming to use at the bedside, impractical for continual use, or require an intolerably large change in the fraction of inspired oxygen (O₂) to complete the measurement.

We propose here a carbon-dioxide (CO₂) wash-in method that allows automatic and continual measurement of FRC in mechanically ventilated subjects. The new method measures FRC using the "CO₂ wash-in" signals during the onset of a partial CO₂ rebreathing maneuver that is automatically initiated every 3 minutes by a CO₂ rebreathing noninvasive cardiac output monitor (NICO₂, Respironics Inc, Wallingford CT). In an oleic acid model of ARDS/ALI in mechanically ventilated animals, we measured the FRC before, during and after lung injury with two methods: the CO₂ wash-in method and the nitrogen washout technique. The aims of the study were

to evaluate the new method in a mechanical lung model and to compare the measures of FRC by the two methods with each other in mechanically ventilated animals during induced lung injury. We demonstrate that the CO₂-based FRC measurement can be used to trend the effects of lung injury and track the response to treatment.

Methods:

Nitrogen Washout Method

A variation of the FRC measurement using nitrogen washout method published by Olegard et al.⁴⁰ was used as the reference measurement. This method has been described in the literature but is not commercially available. In the our implementation, the nitrogen washout method required a brief (less than five minute) step-increase in the inspired oxygen fraction of 0.2 (e.g. from 0.4 to 0.6 F_{IO2}). The volume of released nitrogen and the change in nitrogen concentration following the change in F_{IO2} were used to calculate FRC.

Oxygen was analyzed using a side stream paramagnetic O₂ analyzer (Datex, Helsinki, Finland). CO₂ was measured using an infrared analyzer and flow was measured using a differential pressure-type pneumotach, both of which are integrated in the NICO₂ mainstream sensor (Model 7300, Respironics-Novametrix, Wallingford, CT). The gas analyzers were calibrated with calibration gas prior to the experiment. Each of the analyzers automatically re-zeroes repeatedly to avoid baseline drift. Gas for the side stream analyzer was sampled at the ventilator circuit wye piece, while the mainstream sensor was placed between the gas sampling adaptor and the endotracheal tube. Both inspired and expired gases were measured continuously.

Raw data of flow and gas concentrations were sampled with a frequency of 100 Hz and processed digitally using custom-written software to generate end-tidal and volumetric O₂ and CO₂ measurements and tidal volumes. We calculated VO₂ from the directly measured VCO₂ and the min/max difference in the O₂ signal. We assume that since the waveform of the fast oxygen signal is an inverted, scaled version of the capnogram, VO₂ can be calculated as VCO₂ multiplied by the min/max difference in the O₂ divided by the min/max difference in CO₂ [9,40]. We calculated end-tidal and mixed F_{N2} as the balance gas (F_{N2} = 1 - F_{O2} - F_{CO2}). Nitrogen excretion was calculated as the difference between expired volume multiplied by mixed expired N₂ fraction and inspired volume multiplied by inspired N₂ fraction. After at least 2 minutes of baseline data had been collected, the nitrogen washout FRC measurement was initiated by increasing the F_{IO2} by 0.2 for each measurement within the range of 0.3 to 1.0. Typically, the successive step changes in F_{IO2} for three measurements were 0.4 to 0.6, 0.6 to 0.8, and 0.8 to 1.0. The volume of excreted N₂ (VN₂) was recorded during washout. The washout at each step

change of F_{IO2} was allowed to continue to completion before the next measurement was begun.

The series of measurements was completed within about 10 minutes with the hope that absorption atelectasis caused by the higher FiO₂ would be minimized. Typical time to atelectasis for FiO₂ of 0.4 is 120 minutes, for FiO₂ of 0.8 is 60 minutes, and for FiO₂ of 1.0 is 50 minutes⁴¹.

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:

$$VN_2 / (F_{etN_{2ini}} - F_{etN_{2end}}), \quad [1]$$

where VN₂ is the volume of nitrogen leaving the lungs during the test, F_{etN_{2ini}} is the initial fraction of end-tidal nitrogen prior to the increase in F_{IO2}, and F_{etN_{2end}} is the fraction of end-tidal nitrogen at the end of the test. It should be noted that this calculation ignores the excretion of N₂ from the tissues. The effect of N₂ excretion on the FRC measurement should be small (less than 100 ml) and consistent across the animals used in our study⁴². As the published studies describing methods of estimating the volume of N₂ excretion in response to increased FiO₂ assume human rather than porcine subjects, we elected to ignore the effect of N₂ excretion in our calculations⁴².

Repeatability of the FRC measurements made using the successive increases in F_{IO2} was observed by recording and comparing individual measurements. The average measured FRC with the nitrogen washout method was used as the reference value for comparison with the CO₂-based measurements.

CO₂ Wash-in Method

FRC measurements with the CO₂ wash-in method were made using an on-airway infrared CO₂ analyzer, while airway flow was measured using an integrated differential pressure-type pneumotach, both of which are integrated in the NICO₂ partial rebreathing cardiac output monitor. The monitor automatically actuates a pneumatic valve to commence partial CO₂ rebreathing once every three minutes. The rebreathing period lasts 35 seconds and is used to measure pulmonary capillary blood flow (PCBF). To calculate the FRC using the CO₂ wash-in method, only the first breath of the rebreathing period is needed, wherein the changes in end-tidal and volumetric CO₂ are recorded. Figure 1 depicts a typical CO₂ rebreathing signal. The calculations are as follows:

$$V_{FRC} * f_{CO2(n)} = V_{FRC} * f_{CO2(n-1)} + V_{bCO2} - V_{eCO2} \quad [2]$$

$$V_{FRC} [f_{CO2(n)} - f_{CO2(n-1)}] = V_{bCO2} - V_{eCO2}, \quad [3]$$

where V_{FRC} is the volume of the FRC, f_{CO2(n)} is the fraction of end-tidal CO₂ in the current breath n, f_{CO2(n-1)} is the fraction of end-tidal CO₂ in the previous breath n-1, V_{bCO2} is the rate of CO₂ passing from the blood into the

FRC, and V_{eCO_2} is the rate of CO_2 being excreted from the patient measured at the mouth.

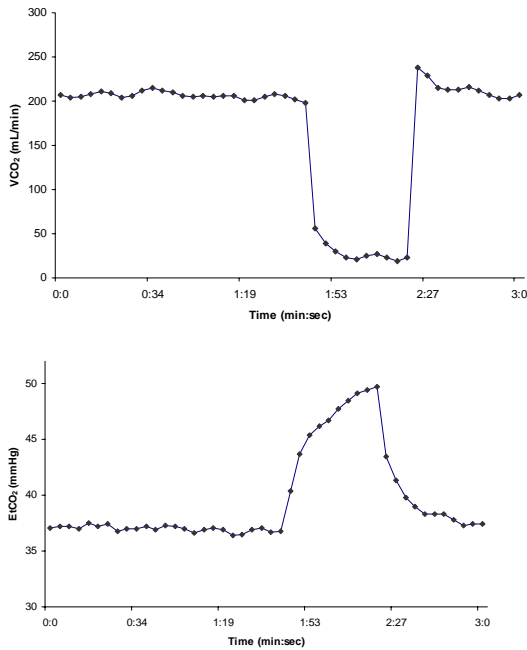


Figure 1: Changes in $etCO_2$ and corresponding changes in V_{CO_2} with rebreathing during a 3-minute period.

It is assumed that the CO_2 excretion rate during the baseline period before rebreathing 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.

$$V_{FRC} = \frac{V_{CO_2 \text{ baseline}} - V_{CO_2(n)}}{[f_{CO_2(n)} - f_{CO_2(n-1)}]} \quad [4]$$

The numerator of this equation 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_2 delivery to the alveoli. Evaluating only a single breath minimizes this error.

The actual volume measured by this method includes not only the FRC but also the effective volume of the other stores of CO_2 in the lung, including the lung tissue and the blood. To compensate for these extra CO_2 storing sites, the FRC is calculated as:

$$FRC = 0.45 * (V_{CO_2 \text{ baseline}} - V_{CO_2(n)}) / (f_{etCO_2_1} - f_{etCO_2_2}) \quad [5]$$

The factor of 0.45 has been described by Gedeon¹⁵ to account for the use of CO_2 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 tidal volume, but for the purposes of this study, these assumptions provide reasonable estimates for 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_2 excretion rate had reached a steady state during rebreathing such that the CO_2 excretion rate was equal to the rate of CO_2 elimination from the blood to the FRC. This would be called the CO_2 washout FRC, and is calculated as:

$$FRC = 0.45 * (V_{CO_2 \text{ steady}} - V_{CO_2(n)}) / (f_{etCO_2_2} - f_{etCO_2_1}), \quad [6]$$

where $V_{CO_2 \text{ steady}}$ is the CO_2 excreted in the last breath of rebreathing in the steady state, $V_{CO_2(n)}$ is the CO_2 excreted in the first breath following rebreathing, $f_{etCO_2_2}$ is the fraction of end-tidal CO_2 in the first breath following rebreathing, and $f_{etCO_2_1}$ is the fraction of end-tidal CO_2 in the last breath of rebreathing. This method assumes that a steady state condition was achieved during rebreathing.

Bench Validation of the CO_2 Wash-In Method Using a Lung Model:

A training/test lung (Michigan Inst.; Grand Rapids; MI) was driven by a Siemens 900c ventilator (Siemens-Elma, Sweden) and infused with 250 mL/min CO_2 . A fan inside the lung completely mixed the gases. V_{CO_2} and $etCO_2$ measurements were obtained from the NICO₂ monitor. Partial rebreathing was automatically begun by the monitor once every 3 minutes. PEEP was changed from 0 (FRC = 1.47 L) to 20 cm H_2O in steps of 5 cm H_2O to increase the FRC to a maximum of 2.75 L. At each PEEP level, two CO_2 wash-in based FRC measurements were recorded and the known volume of the mechanical lung was recorded. At the end of the experiment, the PEEP was reduced back to zero, and the measurements were again recorded. The average CO_2 wash-in measurements at each PEEP step were compared with linear regression and Bland-Altman statistics to the known volumes.

Bench Validation of the Nitrogen Washout Method Using a Lung Model:

The training/test lung was set up as described for the CO_2 validation. O_2 was measured using a paramagnetic fast oxygen sensor (Capnomac, Datex, Helsinki, Finland) (Figure 2). Step changes in N_2 were imposed in the simulator by increasing F_{IO_2} from 0.7 to 0.9. PEEP was applied at 4 different levels, from 0 to 20 cm H_2O . The PEEP was returned back to zero for the final measurement set. At each PEEP step, the known value of FRC was recorded and two nitrogen washout 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.

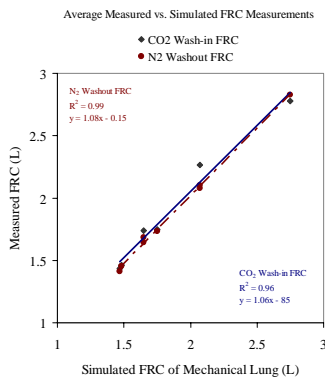


Figure 2: Regression analyses of CO₂ Wash-in FRC, Nitrogen Washout FRC and the simulated FRC of the mechanical lung.

Animal Testing Protocol

Using an approved animal research protocol, six healthy pigs of mixed gender (38.8-50.8 kg) were fasted with free access to water overnight before they were given an intra-muscular bolus of Telazol (4 mg/kg). Following tracheal intubation, the animals were ventilated with a mechanical ventilator (Esprit, Respiration, Carlsbad, CA) with a tidal volume of 10 mL/kg, FiO₂ of 0.4, and an inspiratory to expiratory time ratio of 1:2. The respiratory rate was adjusted to maintain the non-rebreathing end-tidal pCO₂ near 35 mmHg. 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 by a continuous infusion of propofol (100-300 ug/kg/min), with a target mean blood pressure of 100 mmHg. The animals were paralyzed with a continuous infusion of pancuronium (1 mg/kg/hr). 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 using the measured arterial and venous blood gas data. Lactated ringers solution was given intravenously at a rate of six mL/kg/hr throughout the experiment. The NICO₂ monitor was placed in the breathing circuit between the endo-tracheal tube and the wye-piece. The partial CO₂ rebreathing signals obtained from this monitor were used to calculate FRC.

The protocol was divided into two phases: a healthy lung phase and an oleic acid lung injury phase that simulated ARDS/ALI. In the healthy lung phase of the experiment, the positive end-expiratory pressure (PEEP) was set to 0, 5, 10, and 15 cm H₂O. At each PEEP level, we compared the average of three FRC measurements from CO₂ wash-in to the average of three nitrogen washout measurements. To ensure the effects of each PEEP adjustment had stabilized, no FRC measurements were made in the first 20 minutes after each PEEP change. Then, partial rebreathing data (end-tidal CO₂ and

CO₂ excretion in response to partial rebreathing) were collected for 12 minutes (4 rebreathing cycles, 3 minutes each) with the NICO₂ monitor. Next, three reference nitrogen washout measurements were recorded. After collecting the nitrogen washout data, the PEEP was increased to the next level and the next measurement sequence was repeated. Arterial blood gas measurements were collected between the CO₂ wash-in and nitrogen washout measurements at each PEEP level. Average cardiac output (measured by bolus thermodilution), heart rate, arterial blood pressure, pulmonary artery blood pressure and oxygen saturation were also noted at each PEEP level.

Following measurement of FRC at each of the four PEEP levels in healthy lungs, the lung injury was created to simulate adult respiratory distress syndrome (ARDS) 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-minute period. We allowed one hour for the injury to develop before resuming comparison FRC data collection. Injury was confirmed by decreased static lung compliance and auscultation of the lung. After the lung injury had been created, we repeated the data collection procedure at each PEEP level: 0, 5, 10, and 15 mmHg H₂O.

The average FRC measurements made with each of the methods at each PEEP level were compared using 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 CO₂ wash-in system was 37 mL with limits of agreement (LOA) \pm 201 mL, which was equivalent to 1.7% of the true FRC. The correlation coefficient was $r^2 = 0.96$ (Figure 3). The average error in the FRC measured by the CO₂ washout system was 508 mL with limits of agreement (LOA) \pm 370 mL, which was equivalent to 27% of the true FRC. The correlation coefficient was $r^2 = 0.95$.

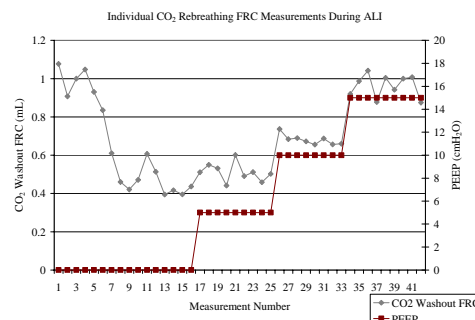


Figure 3: Trend of CO₂ washout FRC measured during evolution of and ventilator treatment for Acute Lung Injury.

The average error using N₂ washout was 6 mL with LOA \pm 83 mL, which was -0.02% of the true FRC. The correlation coefficient was $r^2 = 0.99$ (Figure 4).

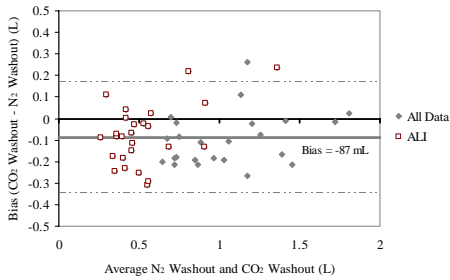


Figure 4: Bland-Altman comparison between CO₂ Washout and Nitrogen Washout FRC measurement techniques.

Bench Validation CO₂ Measurement Repeatability

The average error in the FRC measured by the CO₂ wash-in system with duplicate measurements was 61 mL with LOA \pm 103 mL. The correlation coefficient for duplicate measurements was $r^2 = 0.97$. The average error in the FRC measured by the CO₂ washout system with duplicate measurements was -10 mL with LOA \pm 109 mL. The correlation coefficient for duplicate CO₂ washout measurements was $r^2 = 0.99$.

Animal Testing Results

In the healthy phase of the experiment, the median PaO₂/FiO₂ ratio was 443 (range: 307-570) with FiO₂ of 0.3. Subsequent to the oleic acid injury, the median PaO₂/FiO₂ ratio was 153 (range: 120-172). During the injury phase, the FiO₂ was 0.4 in all animals except one, which had a PaO₂/FiO₂ ratio of 169 with FiO₂ of 0.7.

Figure 5 shows the measured FRC in animal #3 depicting a typical evolution oleic acid-induced acute lung injury and improvement following PEEP therapy.

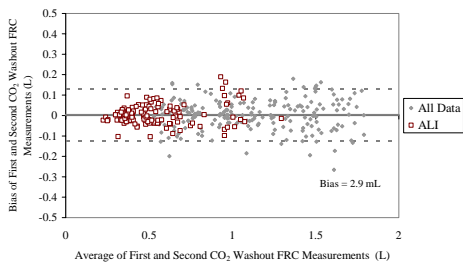


Figure 5: Bland-Altman comparison between first and second CO₂ Washout FRC measurements during healthy lung and injured lung phases.

Comparison of CO₂ Methods with Nitrogen Washout FRC Measurements

When compared with nitrogen washout, the average error in the FRC measured by the CO₂ washout system was -87 mL with LOA \pm 258 mL (Figure 6). 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 \pm 276 mL ($n = 26$).

When CO₂ wash-in data were compared with nitrogen washout, the average error was -3 mL with LOA of \pm 346 mL. The correlation coefficient was $r^2 = 0.75$ ($n = 43$).

CO₂ Washout and Wash-in FRC Measurement Technique Repeatability

Regression of duplicate CO₂ washout measurements at each PEEP resulted in $r^2 = 0.98$ 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 CO₂ washout measurements was 2.9 mL with LOA of \pm 124 mL for all data ($n = 357$), and 3.8 with LOA of \pm 95 mL for the ALI phase ($n = 140$) (Figure 7).

Regression of duplicate CO₂ wash-in FRC measurements resulted in $r^2 = 0.93$ for all data combined and $r^2 = 0.87$ for just the ALI phase. The CO₂ wash-in repeatability bias for all data together was 1 mL with 95% confidence interval of \pm 183 mL ($n = 360$). For the ALI phase only, the wash-in repeatability bias was 7 mL with 95% confidence interval of \pm 161 mL ($n = 147$).

Nitrogen Washout Repeatability

Regression of duplicate Nitrogen washout measurements resulted in $r^2 = 0.98$ 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 washout to the next was 13 mL with LOA of \pm 119 mL for all data together and 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 CO₂ technique and the nitrogen washout methods for FRC measurement. The CO₂ technique allows automated, continual measurements of lung volume in mechanically ventilated ALI subjects. An update in the measurement can occur in less than three 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, providing a trend of FRC measurements without necessitating 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.

CO₂ washout showed better LOA for both the comparison of accuracy and the comparison of repeatability than CO₂ wash-in did in these subjects. This is probably because the signal-to-noise ratio of the first washout breath is slightly better as long as steady state has been reached during the partial rebreathing period before the step change to non-rebreathing is actuated. Further testing is needed to determine whether CO₂ wash-in or washout (or a combination of the two) is the best approach. The CO₂ wash-in measurement makes use of the first breath of rebreathing, while the washout measurement is made using the last breath of rebreathing.

The washout measurement requires the assumption that steady state has been reached during the rebreathing period.

We observed no systematic difference between the CO₂ washout and the nitrogen washout 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 (i.e., the gas which flows into and out of the lung during tidal ventilation) rather than the whole enclosed gas volume. The nitrogen washout method had a better signal-to-noise ratio than either CO₂ method at larger FRCs. The repeatability of our implementation of the nitrogen washout was similar to what Olegard et al.⁴⁰ reported. They found a bias of -5 mL with 95% confidence interval of -380 and 290 mL.

Subsequent FRC measurements taken according to our protocol of successive, stepwise increases in FiO₂ for a period of about 10 minutes did not show a decrease in FRC with each increase in FiO₂. If we had observed a decrease with each subsequent measurement, we might have assumed the increasing FiO₂ had led to absorption atelectasis. We observed no systematic difference between the first FRC measurement, which was taken at a lower FiO₂, and the subsequent measurement, which was taken at a higher FiO₂. The average correlation between subsequent measurement pairs was $r^2 = 0.97$ with an average difference of only 12 mL. This implies that there was the method is insensitive to differences in FiO₂ and that increases in FiO₂ did not create a change in FRC due to absorption atelectasis or similar effect.

One limitation of FRC measurement using CO₂ method is the requirement that breath-to-breath tidal volumes be fairly consistent. Since changes in tidal volume create variation in end-tidal CO₂ and the CO₂ method uses changes in end-tidal CO₂ for the calculation, any respiratory pattern in which breath-to-breath volumes are inconsistent may be unsuitable for CO₂ FRC measurements. Also, since the CO₂ methods use a single breath for the calculation, lung volumes that are not well ventilated may not be represented in the measurement.

Current practice utilizes monitoring improvements in O₂ saturation or dynamic compliance as a measure of a successful recruitment maneuver (RM)¹⁶⁻²³. However, the improvement in O₂ following a recruitment maneuver is transient²⁴, 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, leading to baby lung, rather than a stiff lung as previously thought²⁵. Rylander¹ found that FRC was a more sensitive indicator of decreased aeration and increased consolidation than lung compliance and he concluded that FRC may be a useful adjunct to PaO₂ monitoring at the bedside.

It has been shown²⁶ that when PEEP was added to lungs that exhibit repetitive alveolar collapse and expansion (RACE), the alveoli were stabilized and protected from ventilator induced lung injury (VILI). 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 fibrosis¹, 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 suctioning³⁸.

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 over-inflation of the lung by studying the predictive value of the ratio between PEEP-induced increase in FRC and PEEP-induced alveolar recruitment derived from the P-V curves²⁷. 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" and is characterized by low airway pressures to prevent recruitment/derecruitment, small tidal volumes and occasional sigh breaths or biologically variable ventilation²⁸⁻³². Whether using the open lung or the lung rest strategy, the common intention is the prevention of RACE³³. 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 respiration and perfusion. Appropriate ventilator strategies must include the consideration that PEEP may have a significant effect on 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 CO₂ rebreathing monitor avails several other cardiopulmonary measures from the same signals needed for FRC measurement, such as compliance, pulmonary capillary blood flow (PCBF), Pressure-Volume curves, and VCO₂, each of which is an important factor in the analysis of gas exchange efficiency. For example, PCBF measurements could indicate a decrease in perfusion if excessive PEEP were used.

Baumgardner et al.³⁴ found that RR affects PaO₂ oscillations almost as much as PEEP does, and they theorized that a high RR may prevent alveolar collapse in

ARDS by increasing intrinsic PEEP. They measured PaO₂ oscillations of up to 439 mmHg with a saline lavage model of ARDS, which provided evidence for variations in shunt fraction throughout the respiratory cycle (in other words, cyclic recruitment of atelectic regions). Evidence for cyclic recruitment has also been reported with CT^{35,36} and vital microscopy³⁷. Continual monitoring of FRC would allow one to detect whether increased RR could improve and maintain FRC volumes.

The main drawback of the CO₂-based FRC measurement techniques is that CO₂ is a soluble indicator gas which is carried in the blood. Changes in the alveolar concentration affect the volume of CO₂ delivered to the alveoli, making the assumption of delivery of CO₂ 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 CO₂ 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 CO₂ 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 which Gedeon et al¹⁵ selected for their studies. This factor might be expected to be affected by increased tissue volumes, such as in oedematous 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 PCBF or correction in tidal volume 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 PCBF was not actively altered during the studies.

Based on the limitation of CO₂, it may be reasonable to use the CO₂-based FRC measurement as a trend monitor rather than an indicator of absolute gas volume in the lung. As with all tracer gas methods, the CO₂ wash-in method only measures the part of the FRC that takes part in gas exchange, or the effective FRC. Methods such as CT and body plethysmography also include the part of the FRC that is not communicating. Rylander³⁹ 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 SF₆ FRC method measured 2/3 of the true end-expiratory lung volume; this limitation applies to the CO₂ wash-in technique as well.

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 RM, PEEP, and posture changes in treating

lung injury. Such a monitor could simplify the maintenance of recruitment and oxygenation with minimal PEEP following RM. Knowledge of FRC could aid in achieving alveolar stability, thereby protecting alveoli from shear stress and overdistension. If the method for measuring FRC were simple enough to use at the bedside, it may also be possible to detect de-recruitment sooner than by waiting to observe deleterious effects on PaO₂.

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 (e.g., 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 CO₂. This method requires no interruption or changes to mechanical ventilation and could be used continually to monitor FRC in ARDS/ALI patients.

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