Evaluation of a CO_2 Partial Rebreathing-Based Functional Residual Capacity Measurement Method for Mechanically Ventilated Patients

Lara Brewer, M.S. and Joseph Orr, Ph.D.

Department of Bioengineering in Anesthesiology, University of Utah, Utah

Abstract: There is a need for an automated bedside functional residual capacity (FRC) measurement method that can continually monitor both the size and a change in size of a patient's lung volume during mechanical ventilation without the use of bulky equipment, expensive tracer gases or step increases in inspired oxygen fraction. We developed a CO_2 rebreathing method for FRC measurement that simply requires data from a volumetric capnometer (partial pressure of end-tidal carbon dioxide ($PetCO_2$) and volume of CO_2 eliminated (VCO_2) for the measurement. This study was designed to assess the accuracy, precision and repeatability of the proposed FRC measurement system during stable ventilation. Methods: Accuracy and precision of measurements were assessed by comparing the CO_2 rebreathing FRC values to the gold standard, body plethysmography, in nine spontaneously breathing volunteers. Repeatability was assessed by comparing subsequent measurements in nine intensive care patients whose lungs were under mechanical ventilation. The accuracy and precision of the CO_2 FRC measurement during mechanical ventilation were then compared to the reference method, modified multiple breath nitrogen washout, in the same ICU patients. Results: Compared to body plethysmography, the accuracy (mean bias) of the CO_2 method was -0.085 L and precision (1 standard deviation) was 0.033 L (-2.3 ± 9.2% of body plethysmography). The accuracy in the mechanically ventilated patients was -0.055 L and precision was 0.336 L (-2.6% ± 17.5% of nitrogen washout). The difference between repeated FRC measurements in the ICU patients was 0.020 ± 0.42 L (mean ± standard deviation) (1.1 ± 23.4 %). Conclusions: The CO_2 rebreathing method for FRC measurement provides acceptable accuracy and repeatability compared to existing methods during ventilation with mechanical ventilation. Further study of the CO_2 rebreathing method is needed.

INTRODUCTION

Monitoring functional residual capacity (FRC) is an important means of assessing the pulmonary status and the effect of ventilator setting in patients with acute respiratory failure requiring mechanical ventilation[1]. FRC has been used to size the mechanically ventilated lung in acute lung injury (ALI) since the injured lung volume is smaller than predicted for a given patient height[2]. Once the lung has been sized, the tidal volume can be scaled appropriately so as to not provoke additional volutrauma during mechanical ventilation. An automated bedside method is needed for continual monitoring of the FRC so that the mechanical ventilator can be set appropriately in response to the progression of and recovery from ALI. An automated bedside FRC monitor employed during mechanical ventilation should not be bulky, rely on expensive tracer gases or require a step increase in inspired oxygen fraction.

We have developed an automated bedside FRC measurement system that is based on the partial rebreathing signals obtained from the $NICO_2$ cardiopulmonary monitor (model 7300, Philips-Respironics, Wallingford, CT). The signal resulting from the partial rebreathing period provides the largest single-breath step change during the transition from the last breath of rebreathing to the first breath of non- rebreathing, and this single-breath transition signal can be used to measure FRC. The FRC measurement signal is comprised of the change in excreted CO_2 (VCO_2) and the change in partial pressure of end-tidal CO_2 ($PetCO_2$) during the transition. Although the signal differences obtained during the transition are somewhat small due to the limited degree of rebreathing achieved by partial rebreathing, it appears possible to measure FRC for patients whose lungs are mechanically ventilated under controlled mechanical ventilation.

The aims of this study were to 1) evaluate the accuracy and precision of the CO_2 FRC method compared with the body plethysmography method in healthy volunteers and 2) assess the accuracy, precision and repeatability from FRC measurements taken in mechanically ventilated intensive care unit (ICU) patients from both the CO_2 rebreathing signal and the nitrogen washout signal. For the mechanically ventilated ICU patients, the nitrogen washout FRC was the reference method.

METHODS

Evaluation Aims:

1) Evaluate the accuracy and precision of the CO_2 FRC method compared with the body plethysmography method in healthy volunteers (stable spontaneous ventilation only) in whom Body Plethysmography FRC measurements were also taken.

2) Assess the accuracy, precision and repeatability of FRC measurements taken in ICU patients whose lungs were mechanically ventilated and nitrogen washout FRC measurements were also taken.

Aim 1: Accuracy and precision of the CO_2 FRC method compared with body plethysmography

Device Description
Figure 1 shows the device setup. Carbon dioxide was measured using an infrared analyzer and flow was measured using a differential pressure-type pneumotach, both of which are integrated in the $NICO_2$ mainstream sensor (Model 7300, Philips-Respironics, Wallingford, CT, USA). Oxygen was measured using a sidestream paramagnetic O_2 analyzer (Capnomac, Datex, Helsinki, Finland). The response times (T_{10-90}) of the carbon dioxide, flow and oxygen sensors were 60, 100 and 470 ms, respectively. Each of the analyzers automatically re-zeroed periodically to avoid baseline drift.

FRC Evaluation by the CO_2 Rebreathing Method
FRC measurements from the CO_2 washout method were made using an on-airway infrared CO_2 analyzer, while airway flow was measured using an integrated differential pressure-type pneumotach, both of which are integrated in the $NICO_2$ partial rebreathing cardiac output monitor. The monitor automatically actuates a pneumatic valve to commence partial CO_2 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 CO_2 washout method, only the first breath of the transition out of rebreathing is needed, wherein the changes in end-tidal and volumetric CO_2 are recorded. Figure 2 depicts a typical CO_2 rebreathing signal.
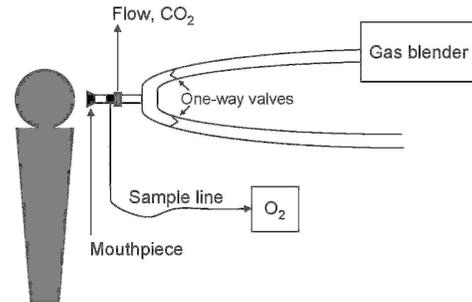

Figure 1: The device setup for the accuracy and precision study comprised a mouthpiece, sensors of flow, O_2, and CO_2, a blender to provide specific gas mixtures at 50 L min^{-1}, and one-way valves to prevent rebreathing.
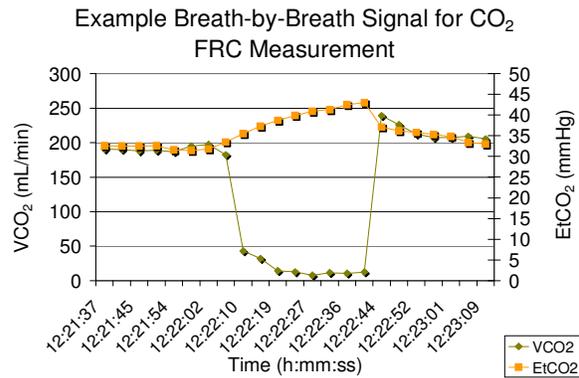

Figure 2: Changes in $PetCO_2$ and corresponding changes in VCO_2 with rebreathing during a 3-minute measurement period.

The FRC measurement calculations are derived as follows:

$$FRC \times fCO_{2(n)} + K \times Tissue \times fCO_{2(n)} + PCBF \times \Delta t \times cCO_{2(n)} =$$
$$FRC \times fCO_{2(n+1)} + K \times Tissue \times fCO_{2(n+1)} + PCBF \times \Delta t \times cCO_{2(n+1)} + \dot{V}_d CO_2 - \dot{V}_e CO_2 \quad [1]$$

where FRC is the volume of the FRC, $fCO_2(n)$ is the fraction of end-tidal CO_2 in the current breath n, $f_{CO2}(n+1)$ is the fraction of end-tidal CO_2 in the next breath n+1, K is the tissue factor of approximately 0.3, Tissue is the volume of the lung tissue in which CO_2 may be dissolved, PCBF is the pulmonary capillary blood flow measured by the $NICO_2$ rebreathing monitor, t is the time period of the breath, cCO_2 is the content of CO_2 of the PCBF, Vd_{CO2} is the rate of CO_2 being excreted from the patient measured at the mouth during rebreathing, and Ve_{CO2} is the rate of CO_2 being excreted from the patient measured at the mouth for the first breath when rebreathing is ended.

It is assumed that the CO_2 excretion rate during the baseline period during 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. The equation is simply a 1-breath wash-out method using a soluble gas. Only the first breath is used because the 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. It is assumed 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.

The CO_2 rebreathing-based FRC equation can be simplified to:

$$FRC = \frac{\Delta VCO2}{\Delta fCO2} - \frac{PCBF \times \Delta t \times \Delta cCO2}{\Delta fCO2} - TissueFactor \ [2]$$

$$\text{where } TissueFactor = K \times \frac{\Delta VCO2}{\Delta fCO2} \text{ and}$$

$$\Delta cCO2 = \Delta fCO2 \times BaroP \times DissociationCurve.$$

Testing Protocol

Nine healthy volunteers consented to an IRB-approved protocol that compared the FRC measurement obtained via CO_2 rebreathing to that of the body plethysmography method. Subjects were seated upright throughout the study period. For each subject, a set of CO_2 rebreathing and body plethysmography FRC measurements were recorded in randomized order. The ambulatory volunteers qualified for study inclusion if they were between the ages of 18 and 65. Exclusion criteria included known cardiac or pulmonary disease, including but not limited to asthma, COPD, history

of smoking, and existing upper respiratory tract infection.

CO_2 Rebreathing Method

The subjects were instructed to wear a nose clip and breathe normally through a mouthpiece connected to the device. The gas analyzers were calibrated with calibration gas prior to the experiment. A ventilator operating in its engineering diagnostics mode (Esprit, Philips Medical, Carlsbad, CA) was used as a gas blender to create the specified F_IO_2 at a flow rate of 50 L min^{-1} and F_IO_2 set to 0.3. One-way valves were used to prevent rebreathing. A series of four rebreathing measurements was initiated by the $NICO_2$ monitor, which included 35 seconds of partial rebreathing every 3 minutes. Upon analysis of the data, stability of the ventilation volume was confirmed for all accepted measurements as defined by coefficient of variation of tidal volume from five successive breaths of less than 0.08 L. The average FRC from the accepted measurements was recorded.

FRC Evaluation by Body Plethysmography Method

Body plethysmography FRC measurement was conducted by trained staff in the Pulmonary Laboratory at the University of Utah Health Sciences Center in accordance with the manufacturer's specifications using the Collins body plethysmograph (Model BP, Warren E. Collins Inc., Braintree, MA) and standard plethysmography equations[18]. Three measurements of FRC within 5% of each other were obtained[19-20]. The mean of the individual measurements was recorded as the reference FRC for each volunteer.

Statistical Analysis

Data are presented as mean values ± standard deviation (SD) if not otherwise stated. The CO_2 rebreathing FRC measurements were assessed for agreement with body plethysmography FRC by means of Bland-Altman statistics, which yielded the mean difference (bias) and precision (1 SD of the difference) in addition to the upper and lower 95% limits of agreement (bias ± 1.96*SD of the difference).

Aim 2: Assess the accuracy, precision and repeatability from FRC measurements taken in ICU patients whose lungs were mechanically ventilated

Device Description

Carbon dioxide and flow were measured in the same way as in the volunteer accuracy testing of Aim 1. The one-way tubing and gas blender of the accuracy testing setup were replaced by the patient's breathing circuit and ventilator (Puritan Bennett 840, Covidien-Nellcor and Puritan-Bennett, Carlsbad, CA, USA). A mainstream photoluminescence analyzer (modified $NICO_2$, Philips-Respironics, Wallingford, CT, USA) was used to monitor end-tidal oxygen partial pressure. The response time (T_{10-90}) of the mainstream oxygen sensor to a step change of O_2 concentration was 220 ms.

Throughout the measurement period, raw data of flow and gas concentrations were sampled with a frequency of 100 Hz and processed digitally using custom-written, validated software to provide inspired and end-tidal O_2 and CO_2 measurements and tidal volumes. End-tidal nitrogen fraction ($F_{ET}N_2$) was calculated as: $F_{ET}N_2 = 1 - F_{ET}O_2 - F_{ET}CO_2$.

FRC Evaluation by Modified Multiple Breath Nitrogen Washout (reference method)

During multiple breath nitrogen washout measurement, resident nitrogen in the lung is washed out subsequent to a step increase in F_IO_2. With each additional breath of alveolar ventilation at the increased level of F_IO_2 (and corresponding reduced F_IN_2), the nitrogen concentration in the lung is diluted. End-tidal nitrogen fraction is a measurement of nitrogen remaining in the lung (alveoli) for each breath throughout the washout. The resulting decrease in the logarithm of end-tidal nitrogen fraction is a function of the increase in cumulative alveolar tidal volume. The slope of the line is related to the size of the FRC; a small FRC will result in a steeper slope compared to a large FRC. Note that data from both large and small breaths appear on the same line that relates gas concentration and cumulative alveolar ventilation. Rather than measurement of the volume of a gas that leaves the lungs, the technique relies on estimation of alveolar nitrogen concentration during washout and alveolar tidal ventilation of variable size.

A healthy lung with normal and uniform distribution of ventilation behaves as one compartment and the resulting nitrogen washout curve is a single exponential. In a diseased or injured lung with non-uniform ventilation distribution, the resulting washout curve is slower and appears to contain more than one compartment, with each compartment washing out at a different rate.

The lung compartments and corresponding nitrogen washout curves can be mathematically modeled with a multiple compartment system that describes the volume-to-ventilation ratio of the lung compartments. For the work presented here, three lung compartments were modeled. If the model is tuned correctly, the combination of the modeled lung compartment nitrogen washout curves will match the single nitrogen washout curve observed at the mouth (breath-by-breath $F_{ET}N_2$) during the measurement. The sum of the three modeled lung compartment volumes is equal to the FRC.

Each of the lung compartments was modeled separately as a first order difference equation based on mass conservation of nitrogen subsequent to a step change in inspired nitrogen and given ventilation. As such, it was assumed each lung compartment would have a predictable nitrogen concentration with each breath during the washout:

$$\hat{F}_A N_{2C[n]} = \hat{F}_A N_{2C[n-1]} \times W, \qquad [3]$$

where $\hat{F}_A N_{2C[n]}$ was the modeled alveolar N_2 fraction in the lung compartment for the present breath, $\hat{F}_A N_{2C[n-1]}$ was the modeled alveolar N_2 fraction in the lung compartment for the previous breath, and W was the alveolar dilution ratio, which was unique to each lung compartment:

$$W = \frac{V_{Comp}}{\left(VT_C + V_{Comp}\right)}, \qquad [4]$$

where V_{Comp} was the modeled lung compartment volume and VT_C was the tidal ventilation of each modeled lung compartment, which was calculated as:

$$VT_C = \frac{1}{3} \times \left(VT_I - VD_{aw} - VD_{app}\right). \qquad [5]$$

3 was the number of modeled lung compartments, VT_I was measured inspiratory tidal volume, VD_{aw}

was the airway deadspace and VD_{app} was the apparatus deadspace. VD_{aw} and VD_{app} were measured for each breath throughout the study via volumetric capnography by the mainstream $NICO_2$ sensor, which employs Fowler's method of VD_{aw} measurement. The mainstream volumetric capnometer enabled breath-by-breath measurement of effective alveolar ventilation, which was critical information for this method since it measured re-inspired VD_{aw} and VD_{app} in addition to tidal volume. Neither of the dead space volumes contributes to effective alveolar ventilation, and therefore they do not contribute to the change in alveolar nitrogen concentration during the washout period.

The $\hat{F}_AN_2$ of the three modeled lung compartments were averaged to produce a single, modeled end-tidal nitrogen fraction estimate for all the breaths in the washout period:

$$\hat{F}_{ET}N_{2\mu[n]} = \frac{1}{3}\sum_{j=1}^{3} F_AN_2(0)\prod_{i=1}^{n}\left(\frac{V_{Comp_j}}{V_{C[i]} + V_{Comp_j}}\right), n = 1,2,...m,$$
[6]

where $\hat{F}_{ET}N_{2\mu[n]}$ was the modeled end-tidal nitrogen fraction for each breath of the measurement period containing m breaths and 3 compartments and $F_AN_2(0)$ was the initial nitrogen fraction in the lung, measured as baseline end-tidal nitrogen fraction before the washout period. The result of equation 4 corresponded to the breath-by-breath end-tidal nitrogen fraction signal recorded from the sensors during the FRC measurement. The same model applies during an increase in nitrogen concentration (wash-in).

First, the $F_AN_2(0)$ for each of the model compartments was set to the observed baseline $F_{ET}N_2$ value. In an iterative process, the computer algorithm then tested all possible combinations in 5 mL multiples over a wide range of physiologically possible lung compartment volumes (25-5000 mL) to identify the combination of lung compartment volumes required to minimize the squared difference between the simulated nitrogen curve of equation #4 and the $F_{ET}N_2$ curve measured by the sensors. Once the compartment volumes had been identified, they were summed and reported as the FRC volume:

$$FRC = \sum_{j=1}^{3} V_{Comp_j}$$
[7]

Testing Protocol

In compliance with the IRB-approved study protocol, 9 ICU patients (6 women and 3 men) whose lungs were intubated and mechanically ventilated were enrolled in the FRC measurement study after consent was obtained. Inclusion criteria included heart rate between 50 and 150 bpm, SpO_2 greater than or equal to 90% and mean, systolic, and diastolic pressures between 65 and 150 mmHg, 90 and 180 mmHg, and 50 and 110 mmHg, respectively. Exclusion criteria included severe respiratory failure, as indicated by pH less than 7.25; tidal volume less than 400 mL; respiratory rate greater than 35; hemodynamic instability, defined as a mean arterial pressure of less than 65 mmHg despite treatment with pressors; positive end-expiratory pressure (PEEP) greater than 5 cm H_2O; and severe COPD, defined as FEV1 less than 50% of the predicted value. Patients with potential for elevated ICP, chest tubes or recent history of hemopneumothorax, blunt chest trauma, or documented low cardiac output states were also excluded.

All enrolled patients were treated with mechanical ventilation. The gas analyzers were calibrated with calibration gas prior to the experiment. A respiratory therapist temporarily disconnected the circuit to place the device between the endotracheal tube and the Y-connector of the ventilator tubing. The ventilation was allowed to stabilize for one hour after sensor placement before FRC measurements were taken.

FRC Measurements

A series of FRC measurements was taken from each the CO_2 rebreathing method and the reference method in randomized order. For the CO_2 rebreathing method series of measurements, the $NICO_2$ monitor was activated to complete automated measurements. Partial rebreathing data (end-tidal CO_2 and CO_2 excretion in response to partial rebreathing) were collected for 12 minutes (4 rebreathing cycles, 3 minutes each) with the automated $NICO_2$ monitor. Reference FRC measurements were taken by increasing the F_IO_2 from the clinically determined, set baseline to 1.0 for 5 minutes and then returning the F_IO_2 setting to the set baseline level for 5 minutes. The average FRC from the two resulting nitrogen curves was taken as one measurement. First, two nitrogen washout measurements were completed. After approximately thirty minutes, two more nitrogen washout measurements were completed. Upon analysis of the data, washout to a stable

plateau value was confirmed for all measurements as defined by standard deviation of $F_{ET}N_2$ from five successive breaths of less than 0.05. Raw data of flow and gas concentrations from each breath were processed digitally as described above to calculate cumulative alveolar ventilation and nitrogen concentration in preparation as inputs for the nitrogen washout FRC measurement.

Statistical Analysis
Data are presented as mean values ± SD if not otherwise stated. The CO_2 rebreathing FRC measurements were assessed for agreement with modified nitrogen washout FRC by means of Bland-Altman statistics, which yielded the mean difference (bias) and precision (1 SD of the difference) in addition to the upper and lower 95% limits of agreement (bias ± 1.96*SD of the difference). The repeatability of the measurements was evaluated by comparing each measurement to the subsequent one taken in the same patient. The mean and standard deviation of the differences were calculated. Descriptive statistics were performed for repeated measures using linear regression and Bland-Altman analyses.

RESULTS

Aim 1: Accuracy and precision of the CO_2 FRC method compared with body plethysmography
Figure 3 compares the CO_2 rebreathing FRC with the Body Plethysmography FRC in spontaneously breathing subjects:
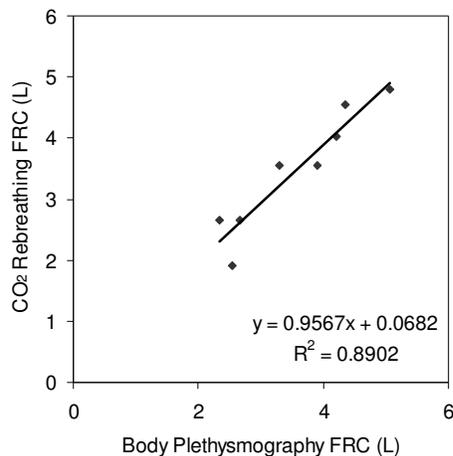

$$y = 0.9567x + 0.0682$$
$$R^2 = 0.8902$$

Figure 3: linear regression analysis of CO_2 rebreathing and Body Plethysmography FRC.

Figure 4 illustrates a Bland-Altman analysis of the CO_2 rebreathing FRC method and body plethysmography. Bland-Altman statistics (CO_2-reference) for the volunteer data are as follows:

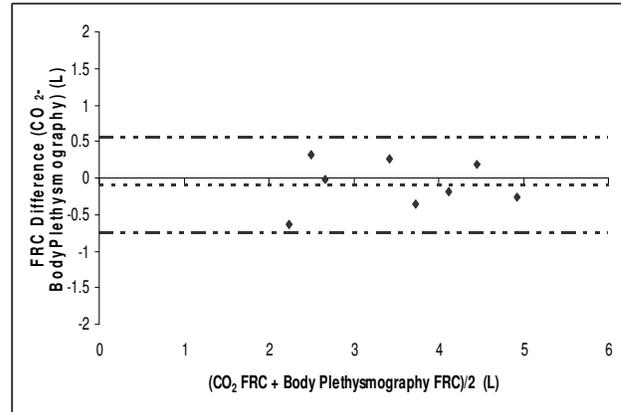|		
Accuracy	-0.085 L	-2.3%
Precision	0.033 L	9.2%

Figure 4: Bland-Altman plot comparing agreement between the functional residual capacity evaluated by CO_2 rebreathing and body plethysmography. The black dotted line indicates mean bias, and the dashed lines mark the 95% limits of agreement.

Aim 2: Assess the accuracy, precision and repeatability from FRC measurements taken in ICU patients whose lungs were mechanically ventilated
The Bland-Altman graph in Figure 5 compares the CO_2 FRC measurements with the reference method, nitrogen washout FRC, in nine mechanically ventilated ICU patients.
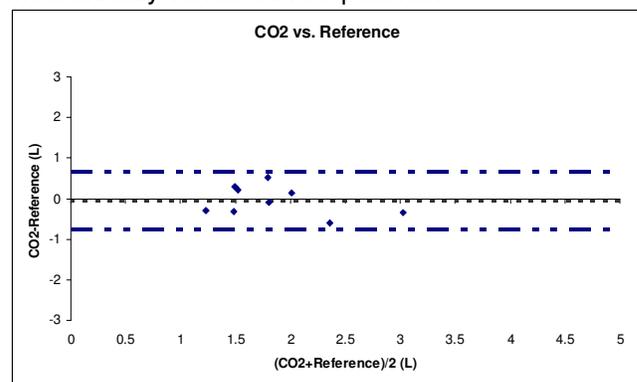

Figure 5: Bland-Altman plot comparing agreement between the functional residual capacity evaluated by CO_2 rebreathing and modified nitrogen washout. The black dotted line indicates mean bias, and the dashed lines mark the 95% limits of agreement.

Bland-Altman statistics (CO_2-reference) are as follows:

Accuracy	-0.055 L	-2.6%
Precision	0.366 L	17.5%

Figure 6 illustrates the repeatability of the individual CO_2 measurements in mechanically ventilated ICU patients (n=58). Bland-Altman statistics (measurement 1-measurement 2) are as follows:

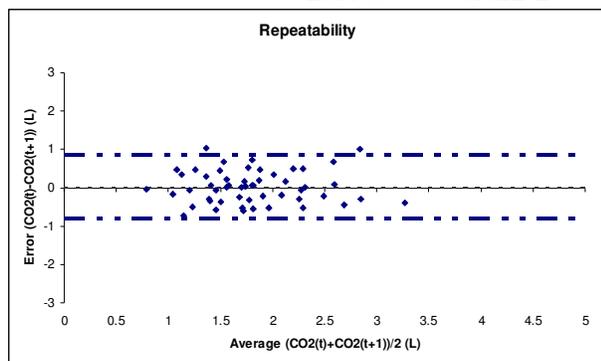|		
Average Error	1.1%	0.020 L
St.Dev. Error	23.4%	0.422 L

Figure 6: Bland-Altman plot comparing agreement between repeated measurements evaluated by CO_2 rebreathing. The black dotted line indicates mean bias, and the dashed lines mark the 95% limits of agreement.

DISCUSSION

The CO_2 rebreathing FRC measurement system showed clinically acceptable accuracy and precision of (2.3 ± 9.2%) compared to body plethysmography and (2.6 ± 17.5%) compared to modified nitrogen washout. Repeatability was also acceptable during mechanical ventilation, with subsequent measurements differing by an average of 1.1%.

In comparison, the GE nitrogen washout FRC method, which is marketed as an add-on for the GE ventilators, has been reported to have accuracy (mean bias) of 15% and one standard deviation of 18% compared to CT in mechanically ventilated patients under Controlled Mechanical Ventilation[3]. The LUFU system developed by Draeger Medical has been evaluated quite extensively in patients and volunteers. For mechanically ventilated patients under Controlled Mechanical Ventilation, the mean bias was -1.3% and one standard deviation was 8.5% compared to Helium dilution[4]. Compared to body plethysmography, the LUFU system showed a bias of 2.6% and one standard deviation of 13.1%[5]. Repeatability for the LUFU system was shown to have a bias of 1.1% and one standard deviation of 10.8% in volunteers[6].

Our results were obtained from a small data set. Further study is necessary to understand how accurate, precise, and repeatable the method is during stable mechanical ventilation.

CONCLUSION

There is some evidence that CO_2 FRC can be measured during stable ventilation, such as during mechanical ventilation. The accuracy and repeatability of average measurements are quite acceptable, but the precision is somewhat low for individual measurements. If the technique were automated in mechanically ventilated patients, several individual measurements could be averaged to improve precision. The measurement shows promise of being a good trend indicator, especially if it could be automated.

ACKNOWLEDGMENTS

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