RESPIRATION AND THE AIRWAY

Measurement of functional residual capacity by modified multiple breath nitrogen washout for spontaneously breathing and mechanically ventilated patients

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Editor’s key points

The authors developed a modified multiple breath nitrogen washout method for functional residual capacity measurement that relies on end-tidal gas fractions and alveolar tidal volume measurements as inputs without requiring measurements of volume of nitrogen or oxygen.

This method was feasible and provides improved precision, equivalent accuracy, and repeatability compared with existing methods during ventilation with variable ventilation patterns in volunteers and intensive care patients.

Background. There is a need for a bedside functional residual capacity (FRC) measurement method that performs well in intensive care patients during many modes of ventilation including controlled, assisted, spontaneous, and mixed. We developed a modified multiple breath nitrogen washout method for FRC measurement that relies on end-tidal gas fractions and alveolar tidal volume measurements as inputs but does not require the traditional measurements of volume of nitrogen or oxygen. Using end-tidal measurements, not volume, reduces errors from signal synchronization. This study was designed to assess the accuracy, precision, and repeatability of the proposed FRC system in subjects with variable ventilation patterns including some spontaneous effort.

Methods. The accuracy and precision of measurements were assessed by comparing the novel N2 washout FRC values to the gold standard, body plethysmography, in 20 spontaneously breathing volunteers. Repeatability was assessed by comparing subsequent measurements in 20 intensive care patients whose lungs were under controlled and assisted mechanical ventilation.

Results. Compared with body plethysmography, the accuracy (mean bias) of the novel method was −0.004 litre and precision [1 standard deviation (SD)] was 0.209 litre [mean (SD)] [20.1 (5.9)% of body plethysmography]. The difference between repeated measurements was 0.009 (0.15) litre [mean (SD)] [0.4 (6.4)%]. The coefficient of repeatability was 0.31 litre (12.7%).

Conclusions. The modified multiple breath nitrogen washout method for FRC measurement provides improved precision and equivalent accuracy and repeatability compared with existing methods during ventilation with variable ventilation patterns. Further study of the novel N2 washout method is needed.

Keywords: lung, functional residual capacity; measurement techniques; model, mathematical; monitoring, intensive care

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Measurements of functional residual capacity (FRC) have great potential for improving care for patients undergoing mechanical ventilation, for example, by guiding ventilation management to improve gas exchange in patients with acute lung injury and acute respiratory distress syndrome.1 2 Traditional methods of FRC measurement3 –6 have been valuable for researching disease progression and monitoring ambulatory patients but are often impractical at the bedside because they are bulky, expensive, sensitive to leaks, and require uncommon tracer gases. Recent research has addressed the need for better bedside utility through volume-based methods such as nitrogen or oxygen washin/washout and multiple breath nitrogen washout.7–14 The volume-based systems depend on the accuracy of the volume measurement (flow × concentration). Although the volume-based methods have proven to be clinically acceptable [1 standard deviation (SD) of the error=8.5%] with unconscious subjects under controlled mechanical ventilation (CMV),15 their precision during the more irregular ventilatory frequency and tidal volume of spontaneous ventilation, which can lead to large errors in volume measurement, has yet to be demonstrated (1 SD of the error=13.1–15.8%).8 10 15

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Fewer than half of intensive care patients' lungs are mechanically ventilated with CMV. Thus, there is a need for a bedside FRC measurement method that is accurate, precise, and repeatable in all modes of ventilation, when controlled, assisted, spontaneous, and mixed. We have developed an FRC measurement system that is not volume-based and requires fewer than 2 min to set up. The inputs for our FRC measurement system include end-tidal gas fraction and alveolar tidal volume, but do not include traditional measurements of volume of oxygen ($V_{O_2}$) or nitrogen ($V_{N_2}$).

To assess the clinical performance of our new system, we designed a feasibility study in subjects with variable ventilation patterns including some spontaneous effort. The goals of this study were: (i) to evaluate the accuracy and precision of the modified multiple breath nitrogen washout FRC measurement system compared with body plethysmography, the clinical gold standard, in spontaneously breathing volunteers and (ii) to assess the repeatability of duplicate FRC measurements in intensive care unit (ICU) patients whose lungs were mechanically ventilated under pressure control and pressure support mechanical ventilation.

Methods

Device description

Figure 1 shows the device setup. Carbon dioxide was measured using an infrared analyser 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 $O_2$ analyser (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 analysers automatically re-zeroed periodically to avoid baseline drift.

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 ($F_{ETN_2}$) was calculated as: $F_{ETN_2} = 1 - F_{ETO_2} - F_{ETCO_2}$.

FRC evaluation by modified multiple breath nitrogen washout

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. Figure 2 illustrates the resulting decrease in the logarithm of end-tidal nitrogen fraction as 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 with 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 the 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...
Where 3 was the number of modelled lung compartments, each compartment washing out at a different rate.

The lung compartments and corresponding nitrogen washout curves can be mathematically modelled 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 modelled, but it is possible to choose fewer or more than three lung compartments. If the model is tuned correctly, the combination of the modelled 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 (Fig. 3). The sum of the three modelled lung compartment volumes is equal to the FRC.

Each of the lung compartments was modelled 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 that each lung compartment would have a predictable nitrogen concentration with each breath during the washout:

$$\hat{F}_{A}N_{2(C-n)} = \hat{F}_{A}N_{2(C-n-1)} \times W$$

where $\hat{F}_{A}N_{2(C-n)}$ was the modelled alveolar $N_2$ fraction in the lung compartment for the present breath, $\hat{F}_{A}N_{2(C-n-1)}$ the modelled alveolar $N_2$ fraction in the lung compartment for the previous breath, and $W$ the alveolar dilution ratio, which was unique to each lung compartment:

$$W = \frac{V_{Comp}}{(V_{T_C} + V_{Comp})}$$

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

$$V_{T_C} = \frac{1}{3} \times (V_{T_I} - VD_{aw} - VD_{app})$$

where 3 was the number of modelled lung compartments, $V_{T_I}$ the measured inspiratory tidal volume, $VD_{aw}$ the airway dead space, and $VD_{app}$ the apparatus dead space. $VD_{aw}$ and $VD_{app}$ were measured for each breath throughout the study via volumetric capnography by the mainstream NICO2 sensor, which uses 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 $\hat{F}_{A}N_2$ of the three modelled lung compartments were averaged to produce a single, modelled end-tidal nitrogen fraction estimate for all the breaths in the washout period:

$$\frac{\hat{F}_{ET}N_{2(m)}}{\sum_{i=1}^{n} V_{Comp}} = \frac{\sum_{i=1}^{n} F_{A}N_{2(i)}(0)}{\sum_{j=1}^{n} \left( V_{Comp} + V_{Comp} \right)}$$

where $\hat{F}_{ET}N_{2(m)}$ was the modelled end-tidal nitrogen fraction for each breath of the measurement period containing $m$ breaths and 3 compartments and $F_{A}N_{2(i)}(0)$ 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 (washin).

**Determination of FRC by the multiple compartment model**

First, the $F_{ET}N_2(0)$ 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

![Fig 3](image-url)  
*Fig 3* The FRC was modelled as three lung compartments and the modelled change in the nitrogen fraction in the compartments during the washout period was compared with the washout signal measured by the sensors.
reported as the FRC volume:

\[ \text{FRC} = \sum_{j=1}^{3} V_{\text{Comp},j} \] (5)

It should be noted that this calculation ignored the storage of N\(_2\) from the tissues. The effect of N\(_2\) storage on the FRC measurement should be small (<100 ml).\(^{17}\)

**Correction for shallow breaths**

For very shallow breaths that do not clear the airway dead space, the end-tidal gas concentration is diluted by the inspired gas remaining in the airway, resulting in end-tidal gas measurements not reflective of the N\(_2\) concentration in the alveoli. To address this sampling issue, the end-tidal nitrogen fraction was only recorded for breaths larger than twice the size of the measured airway dead space. The alveolar ventilation recorded from a disregarded, small breath \([V_{T_{C0}}]\) was added to the measured ventilation of the subsequent breath \([V_{T_{C(i+1)}}]\) to maintain an accurate record of cumulative alveolar ventilation.

**Accuracy and precision testing**

**Protocol**

Twenty healthy volunteers consented to an IRB-approved protocol that compared the FRC measurement obtained via modified multiple breath nitrogen washout to that of the body plethysmography method. Subject inclusion started before January 2009 and therefore the study was not registered in a public trial registry. Subjects were seated upright throughout the study period. For each subject, a set of nitrogen washout and body plethysmography FRC measurements were recorded in a 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, chronic obstructive pulmonary disease (COPD), history of smoking, and existing upper respiratory tract infection.

The subjects were instructed to wear a nose clip and breathe normally through a mouthpiece connected to the device. The gas analysers were calibrated with calibration gas before the experiment. A ventilator operating in its engineering diagnostics mode (Esprit, Philips Medical, Carlsbad, CA, USA) was used as a gas blender to create the specified \(F_{I_{O_2}}\) at a flow rate of 50 litre min\(^{-1}\). One-way valves were used to prevent rebreathing. First, the \(F_{I_{O_2}}\) was set to 0.3 and a period of 20 min was allowed for stabilization. Then, the nitrogen washout FRC measurement was initiated by switching the inspired oxygen fraction to 0.5. After a period of 5 min was allowed for nitrogen washout, the inspired oxygen fraction was increased to 1.0. Again, the washout was continued for 5 min. The inspired oxygen fraction was again set to 0.3 for 20 min and the two-step increases in oxygen were each repeated once. The average FRC from the four measurements was recorded. Upon analysis of the data, washout to a stable plateau value was confirmed for all measurements as defined by the \(sd\) of \(F_{E_{T}} N_{2}\) from five successive breaths of <0.05.

**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, USA) 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 (sd) if not otherwise stated. The modified nitrogen washout FRC measurements were assessed for agreement with body plethysmography FRC by means of the 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) \(\times\) sd of the difference].

**Repeatability testing**

**Device description**

Figure 4 shows the device setup. Carbon dioxide and flow were measured in the same way as in the accuracy testing. 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). The sidestream oxygen sensor was replaced with a mainstream photoluminescence analyser (modified NICO2, Philips-Respironics). The response time \((T_{10–90})\) of the mainstream oxygen sensor to a step change of \(O_2\) concentration was 220 ms.

**Protocol**

In compliance with the IRB-approved study protocol, 20 ICU patients (12 women and 8 men) whose lungs were intubated and mechanically ventilated were enrolled in the FRC measurement study after consent was obtained. Patient
inclusion started before January 2009, and therefore, the study was not registered in a public trial registry. Inclusion criteria included heart rate between 50 and 150 beats min \(^{-1}\), \(S_\text{PO}_2 \geq 90\%\), and mean, systolic, and diastolic pressures between 65 and 150, 90 and 180, and 50 and 110 mm Hg, respectively. Exclusion criteria included severe respiratory failure, as indicated by \(pH < 7.25\); tidal volume \(< 400\) ml; ventilatory frequency \(> 35\) bpm; haemodynamic instability, defined as a mean arterial pressure of \(< 65\) mm Hg despite treatment with pressors; PEEP \(> 5\) cm H\(_2\)O; and severe COPD, defined as FEV\(_1\) \(< 50\%\) of the predicted value. Patients with potential for elevated intracranial pressure, chest tubes or recent history of haemopneumothorax, blunt chest trauma, or documented low cardiac output states were also excluded.

Five of the enrolled patients were treated with pressure control ventilation, and the other 15 were treated with pressure support ventilation. The gas analysers were calibrated with calibration gas before the experiment. A respiratory therapist temporarily disconnected the circuit to place the device between the tracheal tube and the Y-connector of the ventilator tubing. The ventilation was allowed to stabilize for 1 h after sensor placement before FRC measurements were taken.

FRC measurements were taken by increasing the \(F_{\text{O}_2}\) from the clinically determined, set baseline to 1.0 for 5 min and then returning the \(F_{\text{O}_2}\) setting to the set baseline level for 5 min. The average FRC from the two resulting nitrogen curves was taken as one measurement. First, two nitrogen washout measurements were completed. After \(\sim 30\) min, 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 the SD of \(F_{\text{ETN}_2}\) from five successive breaths of \(< 0.05\).

Raw data of flow and gas concentrations from each breath were processed digitally as described above to calculate cumulative alveolar ventilation and nitrogen concentration. Modified multiple breath nitrogen washout FRC measurement was calculated with the same multiple compartment method used for the accuracy testing.

**Statistical analysis**

Data are presented as mean values (SD) if not otherwise stated. The repeatability of the measurements was evaluated by comparing each measurement to the subsequent one taken in the same patient. The mean and SD of the differences and the coefficient of repeatability \((2 \times \text{SD of the differences})\) were calculated. Descriptive statistics were performed for repeated measures using linear regression and the Bland–Altman analyses. A probability value of \(< 0.05\) was considered as significant.

**Results**

**Accuracy and precision**

Eleven males and nine females participated in the study. The mean age of the subjects was 31 (11.5) yr. The mean height was 174 (10.6) cm. The mean weight was 71 (12.1) kg. FRC measured by body plethysmography was 3.55 (0.87) litre with range 2.3–5.6 litre.

Figure 5 shows the Bland–Altman analysis of agreement between the modified multiple breath nitrogen washout and body plethysmography FRC. The bias \((N_2-\text{body plethysmography})\) was \(-0.004\) with precision \((1 \text{ SD of the error})\) of \(0.209\) litre \(\pm 0.1\) (5.9)% of body plethysmography and 95% limits of agreement of \(-0.41\) to 0.41 litre \((\pm 11.7\% \text{ to } 11.5\% \text{ of body plethysmography})\

**Repeatability**

The mean measured nitrogen washout FRC was 2.4 (0.7) litre (range 1.18–3.63 litre). See Table 1 for patient characteristics.

![Fig 5 The Bland–Altman plot comparing agreement between the FRC evaluated by modified multiple breath nitrogen washout and body plethysmography. The red line indicates the mean bias and the green lines mark the 95% limits of agreement.](image-url)
Table 1  ICU patient characteristics. C, Caucasian; H, Hispanic; PS, pressure support; PC, pressure control; Set \( F_{O_2} \), baseline \( F_{O_2} \) level; Vent. days, number of days the patient was on the ventilator; Vent. day of study, the day of mechanical ventilation on which we monitored the patient; ALI, acute lung injury; ARDS, acute respiratory distress syndrome. *Same patient, monitored on different days as per IRB protocol

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<th>Race (C/H)</th>
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Fig 6  The Bland–Altman plot comparing differences between the repeated modified multiple breath nitrogen washout FRC measurements. The red line indicates the mean bias and the green lines mark the 95% limits of agreement.
The mean age was 57 (17). The mean weight was 87 (28) kg. The mean set baseline $F_{O2}$ was 0.41 (0.09).

Figure 6 shows that the mean difference between repeated measurements was 0.009 (0.15) litre [0.4 (6.4)]% and the 95% limits of agreement were between −0.29 and 0.31 litre (−12.1% to 12.8%). The coefficient of repeatability was 0.31 litre (12.7%). Subsequent measurements were not statistically different ($p=0.73$). Linear regression analysis between the first and second measurements yielded $R^2$ of 0.96 ($n=39$), $y=0.99x+0.01$ (Fig. 7). The mean absolute difference between duplicate measurements was 0.12 litre (5.0%).

**Discussion**

This study of a novel multiple breath nitrogen washout method for FRC measurement demonstrated accuracy of −0.004 litre (−0.1% of body plethysmography), precision of 0.209 litre (5.9%), and repeatability of 6.4%. The precision we observed was better and the accuracy and repeatability were equivalent to existing methods during ventilation with variable breath patterns including some spontaneous effort. Our method is more precise because it used $F_{ET}N_2$ rather than volume of expired nitrogen or oxygen as an input. Improved measurement precision can better inform titration of therapeutic changes to mechanical ventilator settings to restore normal FRC and increase gas exchange for patients treated with many modes of mechanical ventilation, including controlled, assisted, mixed, and spontaneous.

The accuracy and precision [−0.1 (5.9)%] [mean (SD)] of the error] of our $F_{ET}N_2$-based washout system compared favourably with an expired $O_2$ volume-based ($V_{O2}$) washout system evaluated in two studies [2.6 (13.1)%] and [−11.7 (15.8)]% in spontaneously breathing patients. GE Healthcare currently offers the only commercially available system for $O_2$ volume-based FRC measurement in patients with mechanically ventilated lungs, but it has not been evaluated in spontaneously breathing patients. Published accuracy data for the GE system only provide results for an evaluation using a passive lung model with CMV; accuracy was between 1% and 3% and precision was between 4% and 6% of the reference volume, depending on the $F_{IO2}$ step change used.7

The repeatability of our system (SD of the error=6.4%) for ICU patients treated with partial ventilatory support was better than GE Healthcare’s manufacturer declaration of within 10% and was comparable with results (SD of the error=6.5%) obtained using a mass spectrometer and a system evaluation with 250 measurements in 36 patients (SD of the error=6.5%). 10 Olegard and colleagues1 reported 1 SD of the error of 0.178 litre during CMV, which is slightly higher than the 0.15 litre (6.4%) SD of the error we observed with our system. The data analysed in our study included patient-triggered ventilation via a pressure support mode, which typically results in highly variable tidal volumes and breath rates that increase the error in integration of flow and concentration waveforms for volume-based methods. For our group of 20 patients, the average tidal volume was 491 (88) ml [5.6 (1) ml kg$^{-1}$] and the average ventilatory frequency was 26 (7.0) bpm; the coefficient of variation in tidal volume was 0.21 (0.07) and in ventilatory frequency was 0.16 (0.08). The good repeatability we observed even during highly variable ventilation patterns indicates that it should be possible to quickly detect changes in and adjust FRC during patient-triggered, assisted mechanical ventilation.

The modified multiple breath nitrogen washout method described here is analogous to the work published by Hashimoto and colleagues, who used an electrical analogue model of the lung to describe gas distribution in six compartments. By manually altering potentiometers, he adjusted the modelled $F_{ET}N_2$ until it matched the recorded $F_{ET}N_2$ signal and then found FRC from the experimentally determined parameters. The process was limited to offline analysis of 6–18 breaths of uniform volume and an assumed airway dead space volume. In contrast, the method tested here accounted for the tidal volume, apparatus dead space, and airway dead space measured for each breath. The method searched out the optimal lung compartment volumes needed to estimate the observed $F_{ET}N_2$ signal for each series of measurements. Both our model and Hashimoto’s centre on the change in nitrogen concentration within the lung (alveoli) in response to a step change in inspired oxygen rather than on the precise volume of nitrogen or oxygen leaving or entering the lungs.

The novel FRC measurement is based on end-tidal gas measurements and therefore does not rely on calculating a change in $V_N$ or $V_O$, as other methods do, for example, by estimation of $V_O$ from measured $V_{CO2}$ and an assumed respiratory quotient (RQ). The change in gas viscosity during the washout manoeuvre is not an applicable issue since measurements of $V_O$ are not required. In contrast to volume-based methods, it is possible to use end-tidal measurements that are not perfectly synchronous, which leads to higher precision and repeatability of FRC.
measurements during variable ventilation patterns. The use of end-tidal gas measurements and a mainstream gas analysis eliminated the need for corrections required by other systems due to sampling delay, response, or synchronization errors. Further noise reduction was achieved by eliminating the end-tidal gas measurements of the very shallow breaths. It may also be true that FRC itself is somewhat variable during spontaneous and assisted ventilation, which is an unavoidable error for any system.

Like Olegard’s system, this method assumes: (i) cellular metabolism and gas exchange between lung capillary blood and alveoli are stable and (ii) the non-homogeneity in alveolar gas distribution is constant throughout the measurement period. Both assumptions are necessary for end-tidal gas measurement use. Unlike the Olegard system, an assumed RQ is not required by our method to allow FIO2 to increase up to 1.0. Assumptions made by other systems related to fixed RQ, ventilation volumes, and ventilatory frequencies may be valid for some patients during CMV, but they will likely not hold true for a required 5–10 min measurement period during spontaneously triggered, assisted ventilation and the associated variable breath patterns.

One advantage of the method evaluated here is that VTalv did not need to be estimated from average values of VCO2, which varies with tidal volume size and contributes to error. Instead, VTalv was directly measured by the mainstream, integrated CO2 and flow sensor of the NICO2 monitor and was calculated breath-by-breath by subtracting the Fowler’s airway dead space and apparatus dead space from the directly measured tidal volume. The main drawback of using mainstream volumetric capnography is the possibility for patient secretions to accumulate on the sensor window or within the differential pressure tubing. To ameliorate these issues, the sensor is heated to maintain a dry sensor window, and the differential pressure tubing is periodically purged with a volume of air to clear any secretions. We did not observe any problems with the mainstream sensor during data collection.

The FETN2-based system presented here does not require specific mechanical ventilator settings, a particular ventilator brand, patient cooperation, or manual intervention to measure FRC. An FETN2-based washout monitor could be both independent from and compatible with any ventilator that can make step changes in FIO2 since the only parameters required for the FRC measurement are end-tidal oxygen and carbon dioxide fractions and alveolar tidal volume. A limitation of our implementation, however, is that the change in FIO2 was adjusted manually. The system is currently designed to recognize a manual step change in FIO2 and automatically start the FRC analysis. For continual FRC monitoring, the method could instead be integrated with a ventilator and automated.

One concern related to ventilation with high FIO2 is the possibility of absorption atelectasis. In the repeatability testing protocol, the FIO2 was always turned from baseline up to 1.0, regardless of the starting point for FIO2, in order to simplify protocol execution. We assumed that 5 min was not enough time for atelectasis to form, as absorption atelectasis has been shown to develop after ~45 min at FIO2 of 1.0. However, with an automated system, it could be possible to standardize a smaller step size and limit exposure to extremely high FIO2.

It would be valuable in future testing to analyse the accuracy with smaller step changes in FIO2, especially for patients who require high baseline FIO2 for arterial oxygenation. The accuracy and precision study was performed with FIO2 step sizes of 0.2 and 0.5, and both step sizes provided accurate FRC measurements. It is likely that the mean step size of 0.6 we used in the repeatability testing is larger than necessary for reliable measurement. Based on analysis by other groups, we expect that a smaller FIO2 step change could be used without significant loss in accuracy.

Limitations of this study include the limited degree of lung disease in the patient set and lack of a gold standard for FRC measurement in patients with mechanically ventilated lungs. Owing to IRB restrictions, the ICU patients we studied were generally the healthiest among the patients in the ICU, and several of those tested were within 2 days of extubation. It would be interesting in future studies to monitor ICU patients throughout the evolution of disease and subsequent treatment.

An important subject for future research is to analyse the accuracy compared with a reference technique such as computed tomography in intensive care patients with significant lung disease. The ICU accuracy analysis would be valuable for evaluating how increased alveolar dead space and disturbed ventilation–perfusion configuration affect the measurement. The FETN2-based method applies the same assumption of constant non-homogeneity in alveolar gas distribution throughout the measurement period that other volume-based nitrogen washout methods do. Theoretically, this method will be prone to less error due to the use of end-tidal measurements in place of volume to estimate the change in nitrogen within the lungs if the assumption does not hold, but it would require a higher fidelity simulation or additional clinical research to investigate whether this is true.

There remain few published studies of the utility of FRC measurement in critically ill patients, but recently there has been renewed interest in and reports of FRC measurement in clinical situations such as after suctioning, during weaning, and with application of PEEP. There is currently one commercially available system (FRC INviewTM, Engstrom Carestation, GE Healthcare, Chalfont St Giles, UK). As clinicians gain experience with reliable and precise FRC measurement during patient treatment, the role of FRC measurement will be more clearly defined. Further clinical studies should also evaluate the value of volume-to-ventilation distribution measurements made possible by a multiple compartment model such as the one presented here.

In conclusion, we have shown that FRC assessment with the FETN2-based nitrogen washout technique provides improved precision and good accuracy in an evaluation.
with body plethysmography in spontaneously breathing volunteers. We have also demonstrated clinically acceptable repeatability in the ICU during controlled and assisted mechanical ventilation. The system can be used in the ICU environment, where highly variable ventilation patterns resulting from various degrees of spontaneous effort are commonplace. The measurement technique, which does not require measurement of volume of expired nitrogen or oxygen, demonstrated improved precision compared with volume-based systems recently evaluated in similar settings. The robust performance of the novel technique during ventilation with changing breath patterns suggests that further study of the $\text{Fe}_2\text{N}_2$-based nitrogen washout FRC measurement technique is needed.

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Conflict of interest

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