

Measurement of Functional Residual Capacity of the Lung by Nitrogen Washout/Wash-in in Mechanically Ventilated ICU Patients

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Abstract

Background: *We evaluated the functionality, feasibility of use at the bedside and repeatability of subsequent Functional Residual Capacity (FRC) measurements in mechanically ventilated ICU patients using a new system. The newly developed system had previously been assessed for accuracy in spontaneously breathing human volunteers.*

Materials and Methods: *We measured the FRC of the lungs of 20 mechanically ventilated ICU patients using the nitrogen washout/wash-in technique. Duplicate measures in each of the patients were analyzed for repeatability.*

Results: *The squared correlation coefficient for the linear regression between repeated measurements was $r^2 = 0.92$ ($n = 39$); $y = 0.99x + 0.03$. The bias \pm Standard Deviation was -0.009 ± 0.212 L (-0.4 ± 8.9 %). The limits of agreement (mean $\pm 2 \times$ SD) were between -0.42 and 0.41 L (-17.9 to 17.1 %).*

Conclusion: *These results indicate FRC measurement is repeatable within a clinically acceptable range. This method compares favorably with other methods recently reported in the literature. This system could possibly be used in space to monitor lung volume, especially as it relates to pulmonary disease in weightlessness.*

INTRODUCTION

Functional residual capacity (FRC) measurements could provide useful information for patients undergoing mechanical ventilation. FRC may be helpful in guiding ventilation management or following disease progression in patients with acute lung injury (ALI) and its most severe

form, the acute respiratory distress syndrome (ARDS).^{1,2} Traditional methods of FRC measurement³⁻⁷ are valuable for researching disease progression and monitoring ambulatory patients. They are, however, of limited utility at the bedside due to difficulty of use, high expense, and impracticality during mechanical ventilation. FRC measurement at the bedside in mechanically ventilated patients has recently been reported by several researchers, who evaluated newly refined systems based on nitrogen or oxygen wash-in/ washout⁸⁻¹⁴ and Electrical Impedance Tomography (EIT).¹⁵⁻¹⁷ Limitations of the current wash-in/washout methods include a requirement for sophisticated algorithms to attempt to correct for sidestream sampling errors during positive pressure ventilation¹⁸ or an assumption of stable minute ventilation,^{19,20} which is uncommon in critically ill patients receiving assisted mechanical ventilation. Patient secretions can also obstruct the sidestream sampling line, leading to measurement error. A limitation of EIT use in the intensive care unit (ICU) is that FRC quantification remains difficult. Some researchers have addressed the quantification challenge by first using nitrogen wash-in/washout to provide the initial baseline FRC measurement, from

which changes in lung volume can be calibrated and calculated.²¹

We aimed to develop a FRC measurement system that is simple, accurate and reliable in the ICU environment, where highly variable tidal volume and patient secretions are commonplace. Together with sensors that are appropriate for the ICU environment, the nitrogen washout principle is well-suited for application in this environment because it can be initiated without interruption to mechanical ventilation and does not require patient cooperation or manual intervention to complete a measurement.

The nitrogen washout method evaluated here stems from work by Hashimoto et al.²² and has been validated by a bench lung model, evaluated with an animal study,²³ and assessed for accuracy in human volunteers. The principle advantage of this method is that it does not require gas exchange measurement of any specific gas flow (e.g., VO_2 or VN_2), making it robust in the presence of spontaneous or assisted ventilation. Since VO_2 and VN_2 are not required parameters, the method may be applied with any type of gas analyzer. It also opens up the design possibility of a monitor that is independent from the ventilator. Finally, this method is effective when F_{IO_2} is greater than 80%, which is not currently possible for commercially available systems reliant on VO_2 monitoring.

The specific goal of this study was to assess the functionality and feasibility of FRC measurements in mechanically ventilated ICU patients, the majority of whom demonstrated patient-triggered ventilation. No reference technique was available for the mechanically ventilated patients, so we

evaluated the repeatability of successive measurements. The spontaneous breath effort present in this group of ICU study subjects represents the source of the noisiest type of breath signal for FRC measurement. As such, this study was developed to evaluate the nitrogen washout/wash-in method under realistic clinical circumstances.

METHODS

This protocol was designed to evaluate the feasibility, functionality, and repeatability of FRC measurements at the bedside for a mechanically ventilated ICU patient.

Testing protocol

In compliance with the IRB-approved study protocol, 20 mechanically ventilated, intubated ICU patients (12 women and 8 men) were enrolled in the FRC measurement study. Patients were mechanically ventilated with a Puritan Bennett 840 (Puritan-Bennett, Covidien, Boulder, CO, USA). Five patients were treated with pressure control ventilation, and the other 15 patients were treated with pressure support ventilation. A modified, combined, on-airway oxygen, carbon dioxide and flow sensor of the NICO₂ monitor (Philips Respironics, Wallingford, CT) was used to collect and record data from each breath to a computer (Figure 1). The response time (T10-90) of the oxygen sensor to a step change of O₂ concentration is approximately 220 ms. The analyzer automatically re-zeroes periodically to avoid baseline drift. A respiratory therapist temporarily disconnected the circuit to place the sensor between the wye piece and the endotracheal tube. The ventilation was allowed to stabilize for one hour subsequent

to sensor placement before FRC measurements were taken.

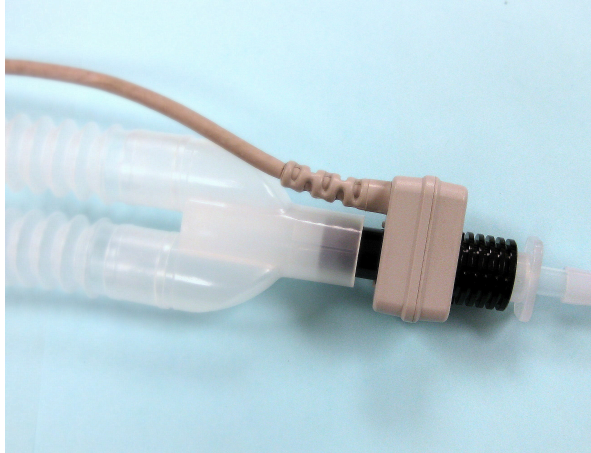


Figure 1. The combination flow, O₂, and CO₂ sensor used in the mechanically ventilated ICU patients.

Nitrogen washout measurements were taken by increasing the F_{IO₂} from the clinically determined baseline to 1.0 for a period of 5 minutes and then returning the F_{IO₂} setting to the 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 one hour, 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_{EN₂} 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 nitrogen volumes and concentrations. Nitrogen washout FRC measurement was calculated with the same multiple compartment method

used to process the volunteer data in previous studies.

Statistical Analysis

Data are presented as mean values \pm SD if not otherwise stated. The repeatability of the measurements was evaluated by comparing each measurement to the subsequent measurement taken in the same patient. Descriptive statistics were performed using regression analysis and Bland-Altman statistics for repeated measures.

Nitrogen-Based FRC Measurement

The volume of alveolar ventilation and the change in nitrogen concentration following each change in F_{IO₂} were used to calculate FRC in a variation of the multiple compartment model proposed by Hashimoto²², which describes the volume-to-ventilation ratio of several compartments of the lung. Each of the compartments is modeled separately as a first order difference equation based on mass conservation of nitrogen following a step change in inspired nitrogen and given ventilation. As such, it is assumed each compartment will have a predictable nitrogen concentration following a breath:

$$N_{2C[n]} = N_{2C[n-1]} \times W, \quad [1]$$

where N_{2C[n]} is the modeled N₂ fraction of the present breath in the compartment, N_{2C[n-1]} is the modeled N₂ fraction from the previous breath of the compartment, and W is the alveolar dilution ratio, which is unique to each compartment:

$$W = \frac{V_{Comp}}{(V_c + V_{Comp})}, \quad [2]$$

where V_{Comp} is the Initial Compartment Volume and V_c is the ventilation to each compartment, which is calculated as:

$$V_c = \frac{1}{K} \times (TV_I - VD_{aw} - VD_{app}). \quad [3]$$

K is the number of modeled compartments, TV_I is average inspiratory tidal volume, VD_{aw} is the average measured airway deadspace and VD_{app} is the apparatus deadspace. VD_{aw} and VD_{app} were measured throughout the study via volumetric capnography. For this study, individual measurements from each breath were used in equation 3 to calculate compartment ventilation rather than using average values.

The end-tidal fraction of nitrogen from the compartments is summed to produce a single, modeled signal which corresponds to the breath-by-breath signal observed at the mouth:

$$N_{2\mu[n]} = \frac{1}{K} \sum_{j=1}^K N_0 \prod_{i=1}^n \left(\frac{V_{Comp_j}}{(V_{C[i]} + V_{comp_j})} \right), n = 1, 2, \dots, m, \quad [4]$$

where $N_{2\mu[n]}$ is the end-tidal fraction of nitrogen modeled for each breath for the measurement period containing m breaths and K compartments and N_0 is the initial nitrogen fraction. The same model applies during nitrogen wash-in.

The reliance on end-tidal gas concentration measurements is a potential limitation of this method in the presence of occasional small breaths such as those possibly present in spontaneously breathing

patients receiving mechanical ventilation in the pressure support mode. For very small breaths that do not clear the airway deadspace, the end-tidal gas concentrations are diluted by the inspired gas remaining in the airway, resulting in end-tidal gas measurements that do not reflect the concentration in the alveoli. To address this limitation, the end-tidal nitrogen was only recorded for breaths larger than twice the size of the measured airway deadspace. The alveolar ventilation recorded from the disregarded, small breath was added to the ventilation of the subsequent breath to maintain an accurate record of cumulative alveolar ventilation.

Compartment volumes were selected using a global search algorithm that selects the combination of compartment volumes that yields the best fit to the observed N_2 washout curve. In this algorithm, the starting N_2 value is loaded into the modeled compartments and the washout curve is generated as the average of the N_2 concentration in the separate compartments. This process is repeated using a wide range of simulated compartment volumes. The combination of volumes that minimizes the squared difference between the simulated and observed N_2 washout curve is selected. The sum of these volumes is reported as the FRC. It should be noted that this calculation ignores the storage of N_2 from the tissues. The effect of N_2 storage on the FRC measurement in should be small (less than 100 ml)²⁷. The first FRC measurement was compared to the second measurement for all repeated measures in each mechanically ventilated patient.

RESULTS

Mean measured nitrogen washout FRC was 2.38 ± 0.78 L with a minimum of 0.98 L and a maximum of 4.23 L. Mean age was 57.3 ± 17.2 . Mean weight was 87.2 ± 28.9 kg. Mean set F_{IO_2} was 0.41 ± 0.09 .

Linear regression analysis between the first and second measurements yielded an r^2 of 0.92 ($n= 39$), $y = 0.99x + 0.03$ (Figure 1).

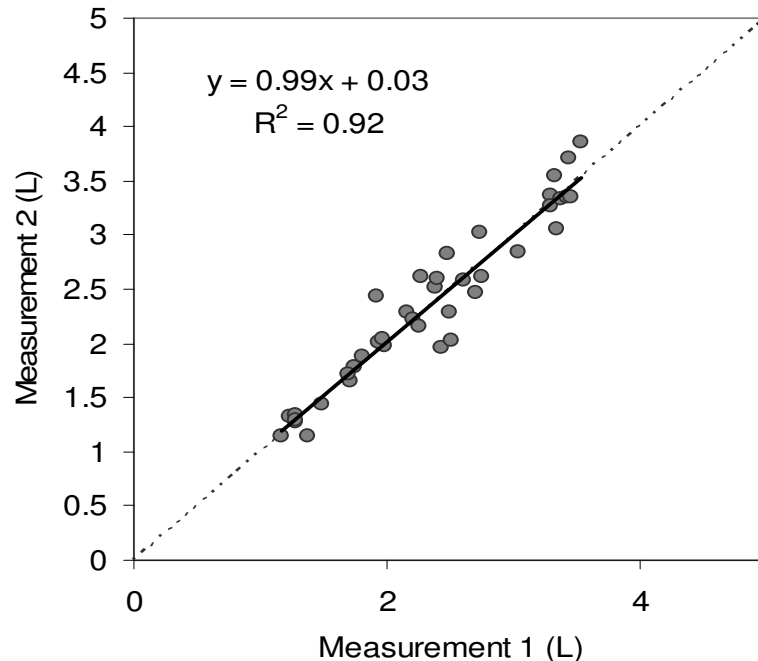


Figure 1: Linear regression analysis of the first and second FRC measurements.

The mean difference between repeated measurements was -0.009 L (-0.4%) ± 0.212 L (8.9%). The limits of agreement (mean $\pm 2 \times$ SD) were between -0.42 and 0.41 L (-17.9 to 17.1%) (Figure 2). Mean absolute difference between duplicate measurements was 0.16 L (6.6%).

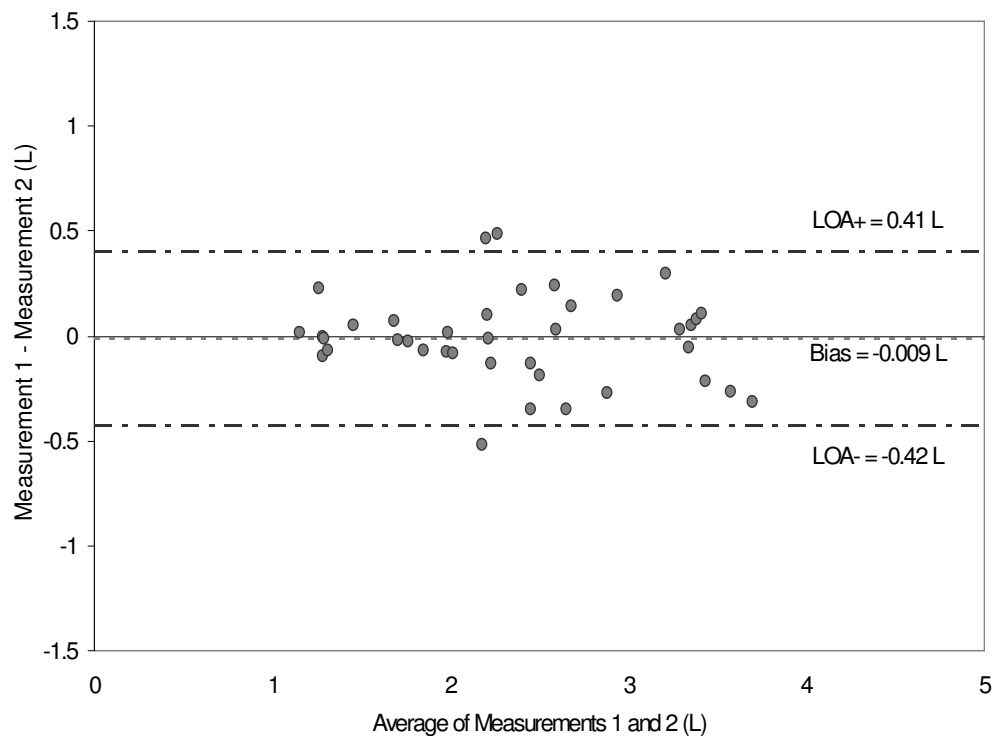


Figure 2: Bland-Altman analysis of the first and second FRC measurements.

DISCUSSION

We designed a stand-alone functional residual capacity measurement system based on nitrogen washout/wash-in that can be used for ICU patients during assisted or controlled mechanical ventilation. In a previous study, we first conducted a volunteer study comparing our system and algorithm with a commercial body plethysmography system since we did not have a direct comparison system that could be used in the ICU. We observed clinically acceptable accuracy compared to body plethysmography during spontaneous ventilation.

The ATS standard for lung volume measurements²⁵ states that repeated nitrogen washout measurements for spontaneously breathing patients should agree within 10%. The satisfactory repeatability demonstrated in these ICU data for patients receiving primarily assisted ventilation confirms that FRC measurement is possible at the bedside for patients receiving partial ventilatory support. In their testing with repeated measures of FRC at the bedside with a similar system, Olegard et al.⁸ reported a standard deviation of 0.178 L, which is comparable to the 0.212 L (8.9%) standard deviation we observed in these ICU patients. The data Olegard et al. analyzed were from patients under controlled mechanical ventilation, while the data we analyzed in this study included patient-triggered ventilation via pressure support mode. For this group of 20 patients, the average tidal volume was 490.6 ± 87.8 mL and the average respiratory rate was 25.7 ± 7.0 mL; the coefficient of variation in tidal volume was 0.205 ± 0.07 and in respiratory rate was 0.161 ± 0.08 . Together, the

accuracy and repeatability results indicate it should be possible to detect and evaluate changes in FRC during evolution of lung injury or subsequent to alterations in therapy such as recruitment maneuvers and PEEP changes, even during patient-triggered, assisted ventilation.

One advantage of the method proposed here is that alveolar tidal volume (VT_{alv}) did not need to be estimated from VCO_2 and $etCO_2$ but rather, was directly measured by the mainstream, integrated CO_2 , O_2 and flow sensor of the NICO₂ monitor. The VT_{alv} was calculated on a breath-by-breath basis by subtracting the Fowler's dead space and apparatus dead space values from the directly measured tidal volume. Additionally, this method did not rely on estimating the change in VN_2 , first by estimation of VO_2 from measured VCO_2 and an assumed RQ, since it was based on end-tidal gas measurements. Mainstream gas monitoring also eliminated the need for any measurement corrections required for sidestream analyzers due to delay, response, or synchronization errors. Assumptions^{8,18-20} related to fixed RQ, ventilation volumes, and respiratory rates may be valid during controlled mechanical ventilation, but they will likely not hold true for the required 5-10 minutes of spontaneously triggered pressure support ventilation. Additionally, unlike the Olegard method, an assumed RQ is not required by this method in order to allow FIO_2 to increase up to 1.0. For the method tested here, it is possible to use end-tidal CO_2 , end-tidal O_2 and alveolar ventilation measurements which are not perfectly synchronous, which leads to higher accuracy and repeatability during spontaneous ventilation effort. Further noise reduction was achieved by eliminating the

end-tidal gas measurements of the very shallow breaths. It may also be true that FRC is slightly variable during spontaneous and assisted ventilation;²⁸ this would be an unavoidable error for any system.

A stand-alone FRC monitor based on this method could be compatible with any ventilator for FRC measurement. However, a limitation of the implementation tested here is that the change in FIO_2 was not automatically initiated, but was adjusted manually. The system is currently designed to recognize a manual step change in FIO_2 and automatically start the FRC measurement. Alternatively, if continual monitoring were desired, the method could be integrated with a ventilator and automated changes in FIO_2 could be performed with regular intervals.

Like Olegard's system, this method assumes: 1) cellular metabolism and gas exchange between lung capillary blood and alveoli are stable and 2) the non-homogeneity in alveolar gas distribution is constant throughout the measurement period. Both of these assumptions are necessary in order to make use of the end-tidal gas concentration measurements. If these assumptions were not the case due, for example, to a change in hemodynamic stability, mainstream measurement of VO_2 and VCO_2 could theoretically allow for correction of FRC measurements for associated changes in VO_2 and VCO_2 . Likewise, FRC measurement could potentially be corrected for changes in VO_2 and VCO_2 following a recruitment maneuver if those parameters were known. These types of improvements should be addressed in future studies.

Systems based on wash-in/washout do not readily measure the volume of the lung which is poorly ventilated and therefore slow to change in gas concentration. For this reason, we anticipated this method would slightly under-estimate the measurements from body plethysmography even in healthy subjects. It may be that the expected small over-estimation error from disregarding the nitrogen storage effect was similar in magnitude, resulting in a bias near zero. Further testing in patients with poorly ventilated lung regions may be needed to determine whether the bias remains small in that case.

A limitation of this study is the limited degree of lung disease in the patient set and lack of a gold standard for FRC measurement in mechanically ventilated patients. Due 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 two days of extubation. It would be interesting in future studies to monitor ICU patients throughout the evolution of disease and subsequent to treatment. It would also be valuable in future testing to analyze this method's accuracy when smaller step changes in FIO_2 are used, as would be required for patients who require high baseline FIO_2 to maintain adequate arterial oxygenation. Based on testing carried out by other groups on similar systems,^{3,6} we expect a smaller FIO_2 step change could be used without significant loss in performance.

Utility of the FRC measurement in critically ill patients has been studied little to date, but recently there has been renewed interest in and reports of FRC measurement in clinical situations such as after suctioning,^{21,29} during

weaning¹⁸ and with application of positive end-expiratory pressure.³⁰ There is currently one commercially available system (FRC INview™, Engstrom Carestation, GE Healthcare, Chalfont St Giles, UK). As clinicians gain experience with reliable 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 satisfactory repeatability of the FRC measurement in the ICU during controlled and assisted mechanical ventilation. This measurement model compares favorably with other systems recently evaluated in similar settings. Together, these results and the accuracy results of previous studies indicate the method is reliable for monitoring FRC in ICU patients receiving mechanical ventilation.

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