NOVEL BEDSIDE TECHNIQUES FOR FUNCTIONAL RESIDUAL CAPACITY MEASUREMENT

by

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ABSTRACT

Functional residual capacity (FRC) is the gas volume remaining in the lung following a normal expiration. The size of the FRC may be compromised as result of many pathophysiologic factors, including anesthesia, obesity, acute lung injury, and acute respiratory distress syndrome. Without sufficient FRC volume, both blood oxygenation and carbon dioxide excretion are limited, leading to hypoxemia, carbon dioxide retention, and possible morbidity and mortality.

Clinicians have long recognized the potential for improved care from FRC measurement availability, and researchers have been looking for an effective means of bedside FRC assessment during mechanical ventilation for decades. FRC measurement is useful, for example, for guiding ventilation management to improve gas exchange for patients with reduced FRC. Traditional methods of FRC measurement have been valuable for researching disease progression and monitoring ambulatory patients, but are impractical at the bedside. Recent research has proposed better bedside utility through volume-based methods such as nitrogen or oxygen wash-in/ washout to help address the need for FRC measurement. However, the proposed volume-based methods give lower measurement precision during ventilation with spontaneous effort or high airway pressure. Furthermore, these volume-based systems cannot be used with circle breathing systems which are commonly found in the operating room. Thus, the need remains for automated, accurate bedside FRC measurement systems that can be used in the intensive

care unit and the operating room during many modes of ventilation, including controlled, assisted, spontaneous and mixed.

This dissertation describes the development, clinical feasibility testing and clinical accuracy assessment of two novel bedside models for FRC measurement that use tracer gas washin/washout. The first model, called the modified multiple breath nitrogen washout model, makes use of end-tidal gas measurements to measure FRC. Using end-tidal measurements instead of volume reduces errors from signal synchronization. The second model, which is called the partial rebreathing carbon dioxide model, allows FRC measurement during fixed inspired oxygen concentration, making FRC measurement possible in the operating room, where circle breathing systems are common. Both FRC measurement methods demonstrate good accuracy, are compatible with any ventilator brand and can easily be moved from patient to patient for bedside measurement.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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CHAPTER 1

INTRODUCTION

Functional residual capacity (FRC), the gas volume remaining in the lungs following a normal expiration, has traditionally been difficult to measure at the bedside. Maintaining enough FRC volume for sufficient gas exchange, however, is an important underlying concern of many ventilation strategies and treatments for patients under mechanical ventilation. Currently, surrogate measures such as lung compliance, arterial partial pressure of oxygen and carbon dioxide, and pulmonary dead space fraction are used to evaluate the effectiveness of treatment strategies aiming to increase the FRC and improve gas exchange. Now, new monitoring technology and modern computing capacity provide the opportunity to develop an automated bedside FRC measurement technique that can be used independently or in conjunction with surrogate measures to detect important changes in FRC, guide treatment and improve outcome. This thesis proposes novel methods that advance the state of the art for automated, bedside measurement of FRC during mechanical ventilation.

1.1 Background and Significance

The residual gas volume in the lungs following normal expiration is called functional residual capacity (FRC). The primary role of the FRC is to buffer against large intrabreath changes in the partial pressure of oxygen in the alveoli (P_AO_2), thereby

providing ample oxygen for blood oxygenation. FRC volume is not actively regulated; it is determined by the passive mechanical relationship between the chest wall and the lungs.

In both resting and exercising healthy individuals, the FRC volume is approximately 2.2 liters.[1] During anesthesia, FRC is reduced by about 20% in normal patients, and 85-90% of all adults develop collapsed lung tissue during anesthesia.[2] In morbidly obese patients or patients with chronic obstructive lung disease (COPD), FRC is reduced by as much as 50%[3] in anesthesia. A reduction in FRC leads to compression atelectasis, an increased ventilation/perfusion (V/Q) mismatch, and ultimately an increase in the alveolar-arterial oxygen gradient. Postoperatively, FRC is also reduced, and has been associated with postoperative hypoxemia, atelectasis, and pneumonia. Reduced FRC is also a contributor to postoperative morbidity and mortality.[4] With compromised FRC volume, the mean P_AO_2 is lower and the intrabreath changes in P_AO_2 are larger, resulting in reduced availability of oxygen for the pulmonary capillary blood. Furthermore, a small FRC reduces the potential for removal of carbon dioxide from the body. With a smaller FRC, the mean P_ACO_2 is higher and the intrabreath changes in P_ACO_2 are larger, resulting in reduced capacity for removal of carbon dioxide from the blood.

Collapsed alveolar lung tissue can be re-expanded in healthy lungs with a vital capacity maneuver[2] and can be re-recruited with recruitment maneuvers and increased positive end-expiratory pressure (PEEP).[4] If the FRC is increased too much, however, the lungs may become injured and the cardiac output may be reduced. Assessment and tracking of FRC is critical in patients with lung disease, such as Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS), which is often accompanied by

refractory hypoxemia, decreased lung compliance, and an acute decrease in FRC.[5] FRC has long been recognized as a key parameter for treating hypoxemic patients.[6] FRC is also useful for scaling delivered tidal volume to measured, injured lung size rather than to a predicted, larger, healthy lung size during mechanical ventilation.[7] Access to bedside FRC measurement in clinical practice, however, remains limited.

Conventional techniques for measuring FRC include washout/wash-in methods, dilution methods, and body plethysmography.[8-12] These methods have been widely used for research, but not for routine clinical practice in the intensive care unit because they are complicated, expensive, may require manual intervention and patient cooperation, and are cumbersome to use during mechanical ventilation.[13-16] For example, East[9] developed an automated sulfur hexafluoride (SF_6) method for use during mechanical ventilation. Although the method was accurate and capable of bedside measurements, a commercial product was never released because of the requirement for injection of a special tracer gas into the breathing circuit.

Body plethysmography FRC measurement, which is based on Boyle's law (that the volume of gas varies in inverse proportion to the pressure applied under constant temperature), is highly accurate, precise and repeatable.[12] Two pressure sensors (one at the box wall and one at the mouthpiece) are used in conjunction with the known box volume to measure the FRC volume of the subject as they pant gently at end-expiration (FRC) against a closed shutter. The FRC volume measured by body plethysmography includes all intrathoracic gas. While body plethysmography is the gold standard for ambulatory patients and has been used in anesthetized patients,[11,17] the requirement of

placing the subject in a rigid box makes the method too burdensome and difficult to use during mechanical ventilation.

Nitrogen washout with an open circuit method has been under investigation for FRC measurement since 1940.[8] To initiate a measurement, the inspired fraction of oxygen is changed from baseline to 1.0 to wash out all nitrogen from the lungs. The total volume of nitrogen inspired and expired with each breath and the change in end-tidal nitrogen concentration are recorded during the washout measurement. The inspired fraction of oxygen is then returned to baseline and the volume and concentration changes of nitrogen are again measured as nitrogen washes back into the lungs. Nitrogen washout measures the volume of the FRC which is in communication with ventilation, but it does not measure "trapped gas," where airway closure prohibits washout. Recent simplifications and refinements of the measurement technique have improved the utility of the nitrogen washout method for bedside monitoring during mechanical ventilation.[15,18] GE Healthcare has introduced a FRC measurement method as an optional software package (FRC INview, GE Healthcare, Madison, WI) for one of their ventilators (Engstrom Carestation, GE Healthcare, Madison, WI). While the nitrogen washout/wash-in method has been shown to be accurate during stable, controlled mechanical ventilation,[18] it has not yet been demonstrated as accurate or precise during assisted mechanical ventilation. The expensive requirement of using a specific ventilator for FRC measurement may also limit widespread clinical adoption of the method.

The difficulty of FRC measurement at the bedside has previously been a limitation to the wider use of FRC measurements, especially during the evolution and treatment of acute lung injury.[19] As some have suggested,[14] the cost and complexity of

current FRC techniques may conventionally be considered too high in view of the relative simplicity of surrogate measures such as airway compliance or blood gas measurements. Thus, there remains a need for an automated, inexpensive, bedside FRC measurement method that is accurate, precise and repeatable throughout the uneven breath patterns typically found during assisted mechanical ventilation, as well as in all modes of ventilation, including controlled, spontaneous and mixed. There is also a need for a FRC measurement system that can be used with circle breathing systems that are not capable of creating a step change in inspired oxygen fraction and for patients in whom a step change in inspired oxygen cannot be tolerated at all, such as patients requiring a high inspired oxygen fraction to maintain arterial blood oxygen saturation.

Two gases commonly found in air can be readily used as the tracer gas for an automated, stand-alone FRC measurement system: nitrogen and carbon dioxide. Nitrogen-based FRC measurement systems have been the most extensively investigated, with the earliest system being developed in 1940.[8] Nitrogen is a suitable choice as a tracer gas because of its low blood solubility. It is also relatively simple to achieve a large change in inspired nitrogen concentration for a reliable FRC measurement by increasing the fraction of inspired oxygen. The largest possible change for inspired nitrogen is a change from approximately 79% to 0% nitrogen, which can be achieved by increasing the inspired oxygen from 21% to 100%. After ventilation for several minutes with 100% inspired oxygen, for example, all nitrogen originally in the lung is washed out. Large changes in nitrogen concentration produce a large signal to noise ratio and the possibility for accurate, precise and repeatable FRC measurements, even during assisted mechanical ventilation during which breath patterns and volumes are often irregular. A nitrogen-

based FRC measurement is compatible with any ventilator that can quickly alter inspired oxygen fraction, and it does not require the addition of other gases or bulky equipment. Like all washout FRC measurements, the nitrogen-based FRC measurement accounts for the ventilated alveoli, including the portion of the alveoli that are more poorly ventilated, but not the "trapped gas." With a high signal to noise ratio and the ability to measure the ventilated, "communicating," FRC at the bedside, a nitrogen-based measurement system demonstrates the accuracy and precision necessary to support spot checking the FRC volume with one or two individual measurements. A nitrogen-based system is simple to use and can readily be automated.

Carbon dioxide has also been investigated as a tracer gas for FRC measurement even though it is highly soluble in blood and tissue.[20] If solubility is properly accounted for, carbon dioxide may have advantages over nitrogen for FRC measurement in several application areas. First, unlike nitrogen, a carbon dioxide-based FRC measurement system does not require a step change in inspired oxygen and can therefore be used for patients who cannot tolerate such a change in inspired oxygen concentration. Second, circle breathing systems commonly used in the operating room are not capable of creating the step change in inspired oxygen needed for the nitrogen FRC measurement. A carbon dioxide-based system is compatible with any type of ventilator and many inhaled anesthetics. Third, the carbon dioxide-based FRC measurement is readily automated for use during mechanical ventilation since the measurement signal can be initiated by a monitor ($NICO_2$, Philips Medical, Wallingford, CT) that makes use of a partial rebreathing system to noninvasively estimate pulmonary capillary blood flow and cardiac output. The partial rebreathing system induces a small change in the partial pressure of

end-expired CO_2 for 35 seconds once every three minutes. The maximum change observed in the CO_2 signal is approximately 4 mmHg, which is roughly a 9-12% change from baseline. It may therefore be possible to use the small, observed change in CO_2 during the washout at the end of rebreathing to estimate the FRC in addition to the cardiac output during stable, controlled mechanical ventilation.

1.2 Research Contributions

This dissertation develops and investigates the clinical feasibility, accuracy and repeatability of two novel methods (based on nitrogen and carbon dioxide) for measuring FRC at the bedside during mechanical ventilation. The novel nitrogen-based method relies on a model of the change in concentration of nitrogen within the lung rather than on a measurement of nitrogen volume expired and inspired with each breath during FRC measurement, as traditional methods do. The carbon dioxide-based washout method is extended to include a correction for carbon dioxide solubility in simultaneously measured pulmonary capillary blood flow. As stated in the previous section, there are advantages and disadvantages of each tracer gas method, so we chose to develop and clinically assess both methods in parallel during the course of this research. Each of the novel methods requires input parameters derived breath-by-breath from the flow and gas concentration signals to calculate FRC. The first step of development for both methods identified the best means of obtaining the input parameters for the FRC measurement. Of the input parameters in question, airway dead space volume is frequently estimated based on body weight, and we considered using the dead space estimate rather than the measured value obtained from each breath. We evaluated the accuracy of the estimate because it is

important for calculating the alveolar ventilation for each breath, another parameter required for FRC measurement.

To test clinical feasibility, both nitrogen- and carbon dioxide-based tracer gas methods evaluated changes in FRC subsequent to changes in mechanical ventilator settings and lung injury in an animal model. In clinical testing, accuracy and precision were first established by comparing the two systems to the gold standard body plethysmography. There is no gold standard for FRC measurement during mechanical ventilation, and therefore individual measurements from both systems were then assessed for repeatability in intensive care patients. The nitrogen system further served as a surrogate gold standard for the carbon dioxide system during mechanical ventilation. All clinical data were analyzed retrospectively during model development to ensure the systems were reliable across all types of study subjects.

Research contributions of this work include: 1) A confirmation that a body weight-based estimate of anatomic dead space is not a good substitute for volumetric capnography-derived dead space measurements used for real-time calculation of alveolar tidal volume, 2) a multiple-compartment model of the lung that describes the multiple breath nitrogen washout curves resulting from a step change in inspired oxygen and a clinical assessment of the accuracy of the resulting FRC measurements, 3) evaluation of a novel, on-airway fast oxygen sensor for a novel application of FRC measurement and 4) an extension of the method for FRC assessment using carbon dioxide as the tracer gas during mechanical ventilation and a clinical study of the accuracy of the FRC measurements. The automated bedside measurement of FRC is promising for both

methods, provided future testing shows accuracy is clinically acceptable for patients with significant lung injury.

This dissertation is organized as follows: Chapter 2 examines patient respiratory and demographics data and demonstrates that real-time measurements of anatomic dead space are required in favor of equation-based predictions for accurate alveolar ventilation measurement. Both parameters are needed in the models to calculate FRC. Chapter 3 investigates the feasibility of two tracer gas methods for FRC determination during mechanical ventilation for animals with both healthy lungs and an oleic acid model of acute lung injury. The FRC measurements of both methods track changes in positive end-expiratory pressure even during lung injury, indicating measurement is possible during mechanical ventilation. Chapter 4 investigates the accuracy, precision and repeatability of the modified multiple breath nitrogen washout FRC model in healthy, spontaneously breathing volunteers and also in intensive care patients whose lungs are mechanically ventilated. FRC measurements are accurate and repeatable, even during variable ventilation patterns, and the precision is improved compared to other published methods. Chapter 5 assesses the accuracy, precision and repeatability of the partial carbon dioxide rebreathing FRC method during steady ventilation patterns in healthy volunteers and also in intensive care patients whose lungs are mechanically ventilated. The observed accuracy indicates automated bedside measurement during controlled mechanical ventilation may be possible with the partial carbon dioxide rebreathing method; automation makes it feasible to trend FRC values for hours or days. Each of these chapters has been published, accepted for publication, or submitted for publication.

Finally, Chapter 6 summarizes conclusions from this work and suggests future work in this area of research.

1.3 References

1. Lumb AB. Nunn's Applied Respiratory Physiology, 5th ed. Woburn, MA: Butterworth Heinemann; 2000:67-68.

2. Rothen HU, Neumann P, Berglund JE, Valtysson J, Magnusson A, Hedenstierna G. Dynamics of re-expansion of atelectasis during general anaesthesia. Br J Anaesth 1999; 82(4):551-556.

3. Damia G, Mascheroni D, Croci M, Tarenzi L. Perioperative changes in functional residual capacity in morbidly obese patients. Br J Anaesth 1988;60(5):574-578.

4. Wahba RWM. Perioperative functional residual capacity. Can J Anaesth 1991;38(3): 384-400.

5. Shapiro BA: Airway pressure therapy for acute restrictive pulmonary pathology. In: Critical Care: State of the Art. Vol 2. Shoemaker WC, Thompson WL (Eds.) Fullerton, CA, Society of Critical Care Medicine, 1981, pp. II(C) 1-53.

6. Bergman NA. Distribution of inspired gas during anesthesia and artificial ventilation. J Appl Physiol 1963;18:1085-1089.

7. Mattingley JS, Holets SR, Oeckler RA, Stroetz RW, Buck CF, Hubmayr RD. Sizing the lung of mechanically ventilated patients. Crit Care 2011;15(1):R60.

8. Darling RC, Cournand A, Richards DW. Studies on the intrapulmonary mixture of gases. Iii. An open circuit method for measuring residual air. J Clin Invest 1940; 19(4):609-18.

9. East TD, Wortelboer PJM, van Ark E, Bloem FH, Peng L, Pace NL, Crapo RO, Drews D, Clemmer TP. Automated sulfur hexafluoride washout functional residual capacity measurement system for any mode of mechanical ventilation as well as spontaneous respiration. Crit Care Med 1990;18(1):84-91.

10. Di Marco F, Rota Sperti L, Milan B, Stucchi R, Centanni S, Brochard L, Fumagalli R. Measurement of functional residual capacity by helium dilution during partial support ventilation: in vitro accuracy and in vivo precision of the method. Intensive Care Med 2007;33(12):2109-15.

11. Hedenstierna G, Löfström B, Lundh R. Thoracic gas volume and chest-abdomen dimensions during anesthesia and muscle paralysis. Anesthesiology 1981;55:499-506.

12. Dubois AB, Botelho SY, Bedell GN, Marshall R, Comroe JH. A rapid plethysmographic method for measuring thoracic gas volume: a comparison with a nitrogen washout method for measuring functional residual capacity in normal subjects. J Clin Invest 1956;35(3):322-6.

13. Wauer HJ, Lorenz BA, Kox WJ. FRC-Messung bei beatmeten Intensivpatienten. Anaesthesist 1998;47:844-855.

14. Hedenstierna G. The recording of FRC Is it of importance and can it be made simple? Intensive Care Med 1993;19:365-366.

15. Fretschner R, Deusch H, Weitnauer A, Brunner JX. A simple method to estimate functional residual capacity in mechanically ventilated patients. Intens Care Med 1993;19:372-376.

16. Bellani G, Patroniti NA, Pesenti A. Measurement of functional residual capacity during mechanical ventilation. In: Yearbook of Intensive Care and Emergency Medicine. Berlin: Springer-Verlag; 2010:143-153.

17. Westbrook PR, Stubbs SE, Sessler AD, Rehder K, Hyatt RE. Effects of anesthesia and muscle paralysis on respiratory mechanics in normal man. J Appl Physiol 1973; 34:81-86.

18. Olegard C, Sondergaard S, Houltz E, Lundin S, Stenqvist O. Estimation of functional residual capacity at the bedside using standard monitoring equipment: a modified nitrogen washout/washin technique requiring a small change of the inspired oxygen fraction. Anesth Analg 2005;101(1):206-212.

19. Goodman LR, Fumagalli R, Tagliabue P, Tagliabue M, Ferrario M, Gattinoni L, Pesenti A. Adult respiratory distress syndrome due to pulmonary and extrapulmonary causes: CT, clinical, and functional correlations. Radiology 1999;213(2):545-52.

20. Gedeon A, Krill P, Osterlund B. Pulmonary blood flow (cardiac output) and the effective lung volume determined from a short breath hold using the differential Fick method. J Clin Monit Comput 2002;17(5):313-21.

CHAPTER 2

MEASUREMENT OF ANATOMIC DEAD SPACE*

2.1 Abstract

2.1.1 Background

Anatomic dead space (also called airway or tracheal dead space) is the part of the tidal volume that does not participate in gas exchange. Some contemporary ventilation protocols, such as the Acute Respiratory Distress Syndrome Network protocol, call for smaller tidal volumes than were traditionally delivered. With smaller tidal volumes, the percentage of each delivered breath that is wasted in the anatomic dead space is greater than it is with larger tidal volumes. Many respiratory and medical textbooks state that anatomic dead space can be estimated from the patient's weight by assuming there is approximately 1 mL of dead space for every pound of body weight. With a volumetric capnography monitor that measures on-airway flow and CO_2, the anatomic dead space can be automatically and directly measured with the Fowler method, in which dead space equals the exhaled volume up to the point when CO_2 rises above a threshold.

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*Accepted for publication in *Respiratory Care*, July 2008. Original article titled: "Anatomic Dead Space Cannot be Predicted by Body Weight."

2.1.2 Methods

We analyzed data from 58 patients (43 male, 15 female) to assess the accuracy of 5 anatomic dead space estimation methods. Anatomic dead space was measured during the first 10 min of monitoring and compared to the estimates.

2.1.3 Results

The coefficient of determination (r^2) between the anatomic dead space estimate based on body weight and the measured anatomic dead space was $r^2 = 0.0002$. The mean ± SD error between the body weight estimate and the measured dead space was 60 ± 54 mL.

2.1.4 Conclusions

It appears that the anatomic dead space estimate methods were sufficient when used (as originally intended) together with other assumptions to identify a starting point in a ventilation algorithm, but the poor agreement between an individual patient's measured and estimated anatomic dead space contradicts the assumption that dead space can be predicted from actual or ideal weight alone.

2.2 Introduction

The anatomic dead space (also called airway, tracheal, or series dead space) is the part of the tidal volume (V_T) that remains in the conducting passages at the end of inspiration and therefore does not participate in gas exchange. During expiration the gas from the conducting passages has the same composition as it did in inspiration; it is commonly referred to as wasted ventilation. Anatomic dead space was first measured with a fast nitrogen analyzer by Fowler[1] in 1948. In 1952 DuBois[2] described an anatomic

dead space measurement technique using a rapid CO_2 analyzer, and in 1954 Bartels et al[3] found that several indicator gases, including oxygen and carbon dioxide, all gave the same value for anatomic dead space and could therefore be used interchangeably.

Many current textbooks[4-7] suggest a simple method of estimating anatomic dead space based on the patient's body weight or predicted body weight. Specifically, they suggest that anatomic dead space is approximately 1 mL per pound of body weight. Because this dead space estimation technique has been so widely disseminated, many clinicians apply the 1 lb = 1 mL rule in clinical practice.

The observation that anatomic dead space is roughly correlated with body weight seems to have been first put forth by Radford[8] in 1955. Radford's article described ventilation standards he had developed to predict an individual's required ventilation based on their body weight and sex. As part of the development of the ventilation standard, he presented anatomic dead space data and estimated dead space values for 11 patient groups that comprised 131 subjects, ages newborn to 59.6 ± 6.3 y, mean body weight range 8-170 lb. Radford plotted the mean dead space as a function of the mean body weight for each one of the 11 groups, and observed a "remarkable, but approximate, rule that the respiratory dead space in milliliters (at body temperature and pressure saturated) equals the body weight in pounds."

Contemporary ventilation protocols such as that of the Acute Respiratory Distress Syndrome (ARDS) Network,[9] which call for smaller V_T as part of a lung-protection strategy for patients with ARDS or acute lung injury, result in a larger percentage of each breath being wasted in the anatomic dead space volume, compared to ventilation with larger V_T. When a weight-based estimate of anatomic dead space is incorrect, the

assumed alveolar minute ventilation may be much smaller or larger than the actual alveolar minute volume, which can lead to unintentional hypoventilation if the dead space estimate is too small, or an unintentionally large alveolar V_T if the dead space estimate is too large. Unintentional hypoventilation could be made worse by a breathing circuit that includes excessive apparatus dead space.[10,11]

Anatomic dead space can be calculated with the Fowler equal-area method, which is based on volumetric capnography.[1] We analyzed data collected with a respiratory profile monitor that provides volumetric CO_2 analysis, to study how well the estimated anatomic dead space predicted the measured anatomic dead space in a group of mechanically ventilated patients.

2.3 Methods

The study was performed at the University of Utah Health Sciences Center. The study was approved by our investigational review board, and informed consent was not required. We analyzed data from 58 patients (43 male, 15 female) who were tracheally intubated, mechanically ventilated and sedated, in either the operating room (42 patients) or the intensive care unit. (16 patients), who had been admitted for coronary artery bypass graft or valve repair surgeries. The data set had been previously collected to measure end-tidal CO_2, carbon dioxide production, and Fick cardiac output. Mean ± standard deviation patient characteristics included: age 63.2 ± 13.8 y (range 14-81 y), body weight 188 ± 42 lb (range 110 – 301 lb), height 172.9 ± 9.8 cm (range 149-198 cm), predicted ideal body weight 149 lb, and body surface area 2.01 ± 0.26 m^2. Ventilation settings were left to the clinician's discretion.

The patients were monitored with a volumetric CO_2 monitor that has a combination CO_2 and flow sensor ($NICO_2$, Respironics, Wallingford CT). This monitor calculates anatomic dead space on a breath-to-breath basis, by analyzing the expiratory volume at which the CO_2 signal transitions from anatomic to alveolar CO_2, using the Fowler method[1] (Figure 2.1). For each patient the mean anatomic dead space was measured with data collected during the first 10 min of monitoring and compared to the values predicted by five published prediction methods,[8,12-16] which are based on actual body weight or ideal body weight and an allowance for the presence of an endotracheal tube (ETT).

In 21 patients there was an elbow placed in the breathing circuit between the ETT and the volumetric capnometry sensor. With those patients we subtracted a volume of 6 mL from the measured anatomic dead space, to compensate for the dead space added by the elbow. For all other patients the ETT was connected directly to the volumetric capnometry sensor, so no compensation was required.

The most frequently published anatomic dead space prediction equation is cited in many general and respiratory physiology texts.[4-7] This method was published by Radford[8] and simply states that 1 lb of actual body weight corresponds to 1 mL of anatomic dead space. A second, commonly used method, published by Nielsen,[12] uses the ideal body weight, based on the patient's height:

1 mL of dead space = 1 lb of ideal body weight. [2.1]

Ideal body weight is calculated as:

45.5 + (0.91 x (height in cm - 152.4)) x 2.2046 [2.2]

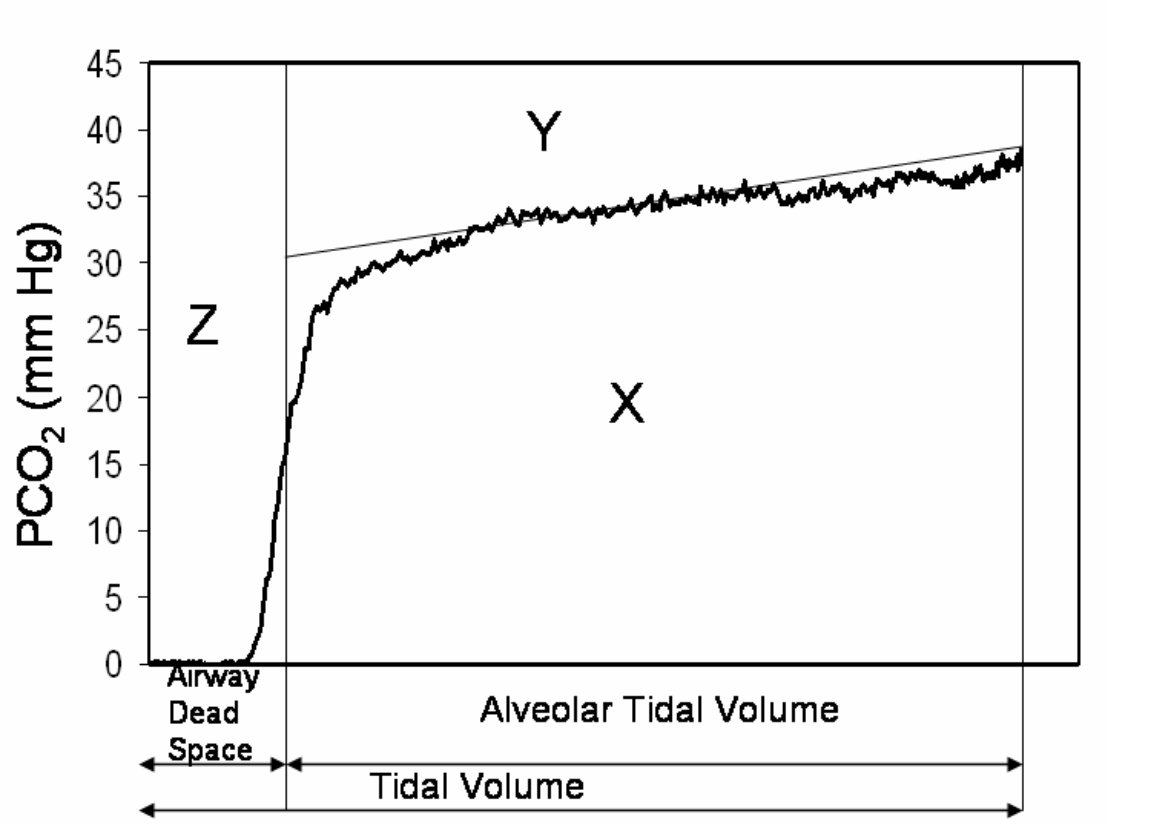

Figure 2.1: Volumetric capnogram depicting the derivation of anatomic and alveolar dead space. Anatomic, or airway, dead space is identified as the vertical line that bisects the rise on the capnogram during exhalation. Alveolar dead space is identified by the letter Y.

for females, and

$$50 + (0.91 \times (\text{height in cm} - 152.4)) \times 2.2046 \quad [2.3]$$

for males.[9,13]

A refinement by Nunn and Hill[14] of the 1 mL = 1 lb method states that estimated anatomic dead space should be decreased by 72 mL if the patient is intubated, to account for the extrathoracic volume bypassed by the ETT:

$$1 \text{ mL} = 1 \text{ lb actual body weight} - 72 \text{ mL}. \quad [2.4]$$

Casati et al[15] proposed reducing the estimate of 1 lb = 1 mL by 50% to account for the volume bypassed by the airway-maintenance devices:

$$1 \text{ mL} = 0.5 \times 1 \text{ lb of actual body weight}. \quad [2.5]$$

The Suwa and Bendixen method[16] uses a similar, related approach that estimates dead space as two thirds of the patient's weight:

$$1 \text{ mL} = 0.66 \times 1 \text{ lb of actual body weight}. \quad [2.6]$$

We used spreadsheet software (Excel, Microsoft, Redmond, Washington) to conduct the linear regression analysis and to calculate all statistics. The mean and standard deviation were calculated for respiratory rate, number of dead space measurements, V_T (mL, mL/kg ideal body weight, and mL/kg measured body weight), positive end-expiratory pressure (PEEP), inspiratory time, measured anatomic dead space, and predicted dead space. With each of the published prediction methods, we

calculated the coefficient of determination (r^2), mean bias ± 95% confidence interval (CI), standard deviation of the bias, and limits of agreement (mean bias ± 2 standard deviation) ± CI between the measured and estimated values.[17] For 2 methods to be used interchangeably, we defined clinically acceptable mean bias and limits of agreement to be small enough that the estimation allowed the patient to be ventilated within 10% of the intended delivered ventilation. For each method we also calculated the ratio of the mean measured anatomic dead space to predicted anatomic dead space.

2.4 Results

Figure 2.2 illustrates the regression analysis for measured anatomic dead space versus ideal body weight. The r^2 for the regression of the measured and predicted anatomic dead space was 0.0002 for each prediction method except the Nielsen method, which had r^2 of 0.058.

Figure 2.3 illustrates the Bland-Altman analysis for the Suwa method, which was the method with the lowest bias.

Table 2.1 reports the r^2 values, mean bias, standard deviation of the bias and limits of agreement for the five methods. When we used the ideal body weight instead of actual body weight in the Nunn, Casati, and Suwa methods, the r^2 was 0.058 (Table 2.2).

The mean and standard deviation of the measured anatomic dead space were calculated for each patient. The mean measured anatomic dead space was 128 mL, and the mean intrapatient standard deviation of the measurements was 4.3 mL (range 1.2– 8.7 mL). Table 2.3 shows the measured and calculated respiratory variables.

The ratio of mean measured anatomic dead space to mean predicted anatomic dead space was 1:1.10 with Nunn's classic method (actual weight - 72 mL), and 1:1.7 for

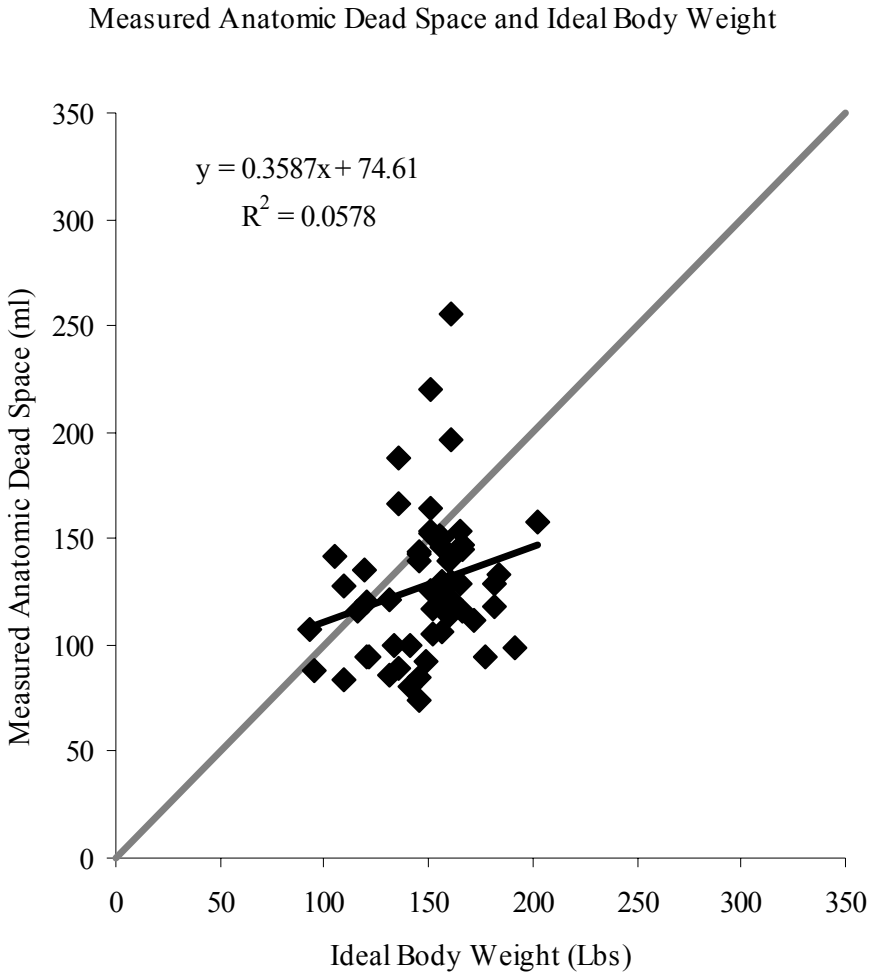

Figure 2.2. Regression analysis of measured anatomic dead space versus ideal body weight.

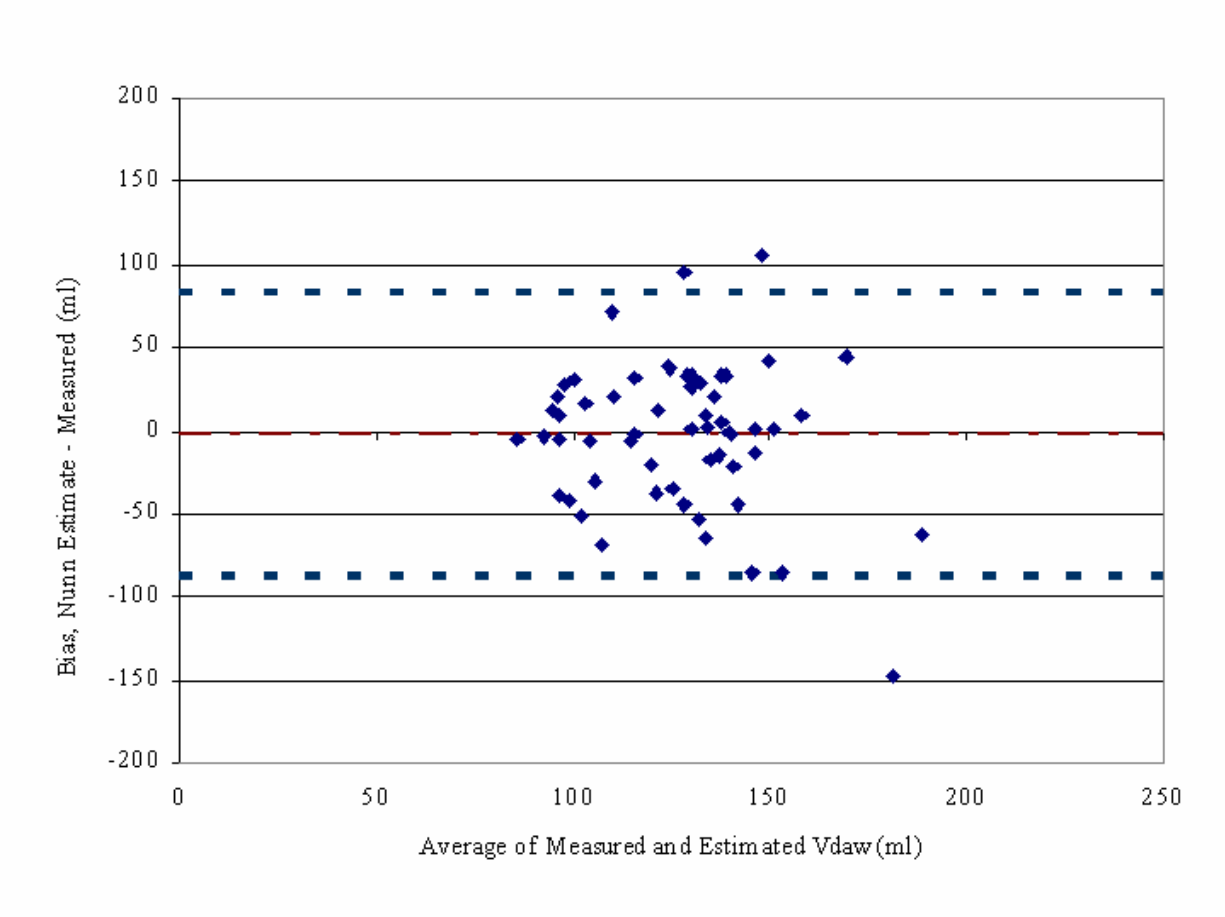

Figure 2.3. Bland-Altman analysis of Suwa's estimate and measured anatomic dead space.

Table 2.1. Results From 5 Methods of Estimating Anatomic Dead Space

Method*	r^2	Mean Bias (mL)	95% CI of Bias (mL)	SD Bias (mL)	Limits of Agreement
Radford[8]	0.0002	59.9	45.7 to 74.1	53.9	–45.7 to 165.5
Nielsen[12]	0.058	20.9	11.5 to 30.3	35.9	–49.5 to 91.3
Nunn[13]	0.0002	–12.1	–26,3 to 2.1	53.9	–117.7 to 93.5
Casati[14]	0.0002	–34.1	–44.5 to –23.7	39.7	–111.9 to 43.7
Suwa[15]	0.0002	–2.7	–14.2 to 8.8	43.8	–88.6 to 83.1

* Methods:
Radford: anatomic dead space in mL = weight in pounds
Nielsen: anatomic dead space in mL = ideal weight in pounds
Nunn: anatomic dead space in mL = weight in pounds – 72 mL
Casati: anatomic dead space in mL = 0.5 × weight in pounds
Suwa: anatomic dead space in mL = 0.66 × weight in pounds
CI = confidence interval

Table 2.2. Results From 3 Methods of Estimating Anatomic Dead Space Using Ideal Body Weight Rather Than Actual Weight

Method*	r^2	Mean Bias (mL)	95% CI of Bias (mL)	SD Bias (mL)	Limits of Agreement
Nunn	0.058	–51.1	–60.5 to –41.7	35.9	–121.5 to 19.3
Casati	0.058	–53.6	–62.3 to –44.9	33.0	–118.3 to 11.1
Suwa	0.058	–28.7	–37.5 to –19.9	33.6	–94.6 to 37.1

* Methods:
Nunn: anatomic dead space in mL = ideal weight in pounds – 72 mL
Casati: anatomic dead space in mL = 0.5 × ideal weight in pounds
Suwa: anatomic dead space in mL = 0.66 × ideal weight in pounds
CI = confidence interval
IBW = ideal body weight

Table 2.3. Respiratory Variables

Variable	Mean ± SD
Respiratory rate (breaths/min)	10.3 ± 2.3
Measurements per subject	103.5 ± 23.0
V_T (mL)	770.8 ± 193.7
V_T (mL/Kg ideal weight)	11.5 ± 2.6
V_T (mL/Kg actual weight)	9.3 ± 2.5
PEEP (cmH_2O)	2.3 ± 2.0
Inspiratory time (s)	1.9 ± 0.5
Dead Space (mL)	
Measured	128.0 ± 33.8
Radford method	187.9 ± 42.3
Nielsen method	148.9 ± 22.7
Nunn method	115.9 ± 42.3
Casati method	94.0 ± 21.2
Suwa method	125.3 ± 28.2

PEEP = positive end-expiratory pressure.

the method ideal body weight - 72 mL. The ratios that were the closest to 1:1 were the Suwa method (1:1.02, with actual weight) and the Nielsen method (1:1.29).

2.5 Discussion

The poor correlation in the present data set between patient weight and measured anatomic dead space appears to conflict with the common practice of estimating anatomic dead space from body weight. Generally, it appears that the mean anatomic dead space in milliliters corresponds to the mean body weight in pounds for the overall population, since the line of identity passes through the data cluster. However, based on the variability of the measured values in our data for a given weight or ideal weight, there is no basis for estimating an individual patient's anatomic dead space volume from the body weight or ideal body weight. The Bland-Altman analysis, with both mean bias and limits of agreement, confirms that estimation and measurement are not interchangeable methods. Even if we had defined clinically acceptable mean bias and limits of agreement to be within 25% of the intended minute ventilation, for a V_T of 330 mL (121 lb person ventilated with 6 mL/kg), none of the estimates of anatomic dead space could have been used interchangeably with the measurement.

We also repeated the Bland-Altman analyses on log-transformed data to give the methods the best possible chance to agree. The repeated analysis did not change our conclusion that the methods are not interchangeable. Bear in mind that the standard deviation values in Table 2.3 for each of the dead space estimation methods are representative of the range of heights and weights observed in this data set. A limitation of our study is that we obtained measurements from a relatively small number of patients. The r^2, bias, and standard deviation may be different with a larger sample size.

In Radford's original paper,[8] which proposed the 1 lb = 1 mL rule, the anatomic dead space was plotted as a function of body weight. On his plot the error bars indicate that the standard deviation of the anatomic dead space measurements was approximately 40 mL, which is similar to what we observed with the Radford method. Radford emphasized that the rule of 1 mL dead space per pound of body weight gives only a rough approximation of anatomic dead space, as evidenced by the large standard deviations of the data he presented. He warned that it is probably not justifiable to extend the dead-space-to-bodyweight relationship to patients who weigh more than 200 lb. Radford also elected to ignore the evidence that anatomic dead space increased with age, for the purpose of his ventilation guidelines, because it was a small effect and was offset by the decreased carbon dioxide production with age. In fact, Radford did not advocate the use of a dead space estimate for anything but a way to simplify the ventilation guidelines he was proposing. It appears that the practice of estimating dead space from body weight has become a matter of convenience, but it was not Radford's intended message. His proposed ventilation guidelines, on the other hand, have stood the test of time and are still in wide use today as a starting point for setting automatic support ventilation and weaning protocols.[18,19]

Radford's ventilation nomogram, which was based on body weight, sex, and breathing frequency, required adjustment for the change in anatomic dead space associated with endotracheal intubation. For intubated patients he recommended a rough correction of subtracting from the total V_T a volume corresponding to half the body weight. This was based on the observation that the volume of the oronasal dead space and upper part of the trachea are approximately 50% of the total anatomic dead space.[20]

Clearly, Radford did not intend the approximate 1:1 correlation between weight and anatomic dead space in the overall population to be used as an independent estimate of an intubated patient's anatomic dead space.

Anatomic dead space is not a fixed value for each individual; it is influenced by several factors, most importantly, position of the neck and jaw, anesthesia, drugs that act on the bronchiolar musculature, and ventilator settings.[4] These factors are likely to change during a ventilated patient's hospital stay, which supports repeated measurement rather than a one-time estimation of the anatomic dead space.

Precise knowledge of the anatomic dead space is more important with a smaller V_T, as in the ARDS Network ventilation recommendations.[9] The percentage of each breath lost to anatomic dead space ventilation increases as the V_T decreases. As an example, consider the average patient in our data set, who weighed the predicted 149 lb. With the ARDS Network protocol of 6 mL/kg ideal body weight, the V_T would be set to 406 mL. Our mean measured anatomic dead space was 128 mL, so 32% of every breath would be lost to dead-space ventilation. If V_T were set at 12 mL/kg, only 16% of each breath would be lost to dead space.

The Nunn method (ideal body weight) had a mean bias of -51.1 mL, compared to the measured value. If the average subject in our data set had been ventilated at 6 mL/kg ideal body weight, the measured alveolar V_T would have been 15% smaller than the estimate. If a clinician were to use the estimated rather than the measured dead space value, a respiratory rate of 20 breaths/min (minute ventilation of 8 L/min) could unintentionally lead to hypoventilation, because the alveolar minute ventilation would be 1 L/min less than assumed.

The mean bias results from each of the estimation methods reveal that the effective alveolar ventilation can be greater or less than expected if the patient-to-patient variation in anatomic dead space is not considered. In other words, if two patients with the same height, weight, and metabolic rate had different anatomic dead space volumes, the same ventilation protocol could yield different $PaCO_2$ values simply because their effective alveolar ventilations were different.

In the present study the mean clinician-selected V_T was 11.5 ± 2.6 mL/kg of ideal body weight (see Table 2.3). We performed a linear regression analysis of the differences between the estimate methods and the measured dead space versus V_T in mL/kg ideal body weight. The r^2 range was 0.017 - 0.16, which correspond to p values (for r) of 0.33 and 0.002, respectively. For actual V_T the r^2 range was 0.0016 - 0.077, which correspond to p values (for r) of 0.77 and 0.035, respectively. Therefore, in the present data set, we observed a range of very small r^2 values, with a range of no association to weak statistical association for the relationship between the V_T size and the measurement error of the estimates.

We also analyzed the influence of outliers on ventilation settings. The r^2 for measured dead space and VT (mL/kg ideal weight) was originally 0.06, and it was 0.005 after outliers were removed. Similarly, when outliers of inspiratory time were removed, r^2 decreased from 0.19 to 0.12. We had previously tested the effect of PEEP on anatomic dead space and found a strong correlation between increased PEEP (from 0 cm H_2O to 20 cm H_2O) and increased measured anatomic dead space, but in the present data set, which has a small range of PEEP, removing the outliers changed r^2 from only 0.05 to 0.07.

Quantification of physiologic dead space is clinically important. Nuckton et al observed that an increased dead space fraction (V_D/V_T) is independently associated with mortality in patients with ARDS.[21] Unfortunately, that study reported only the total pulmonary dead space, so it is not possible to reanalyze their results to separate anatomic dead space and alveolar dead space. In a subsequent paper, Kallet et al[22] found that patients with ARDS who had lower V_D/V_T had a better survival rate: the difference in V_D/V_T between survivors and nonsurvivors was about 0.1. A large proportion of the total dead space is anatomic dead space. Our data show that when the contribution of the variability in the anatomic dead space is considered, the V_D/V_T can change by ± 0.13 solely because of patient-to-patient differences in anatomic dead space. This means that the variability in anatomic dead space contributes to V_D/V_T measurements by a similar magnitude as the difference observed between survivors and nonsurvivors. It is likely that the prognostic value of V_D/V_T measurements is related to ventilation-perfusion mismatch and not to the percent of each breath lost in anatomic dead space. However, if anatomic dead space variability is not considered, then the relationship between V_D/V_T and ventilation-perfusion mismatch is weakened.

Consider a patient with a low V_D/V_T and an abnormally small anatomic dead space. Based on the V_D/V_T this patient might be considered to have a favorable prognosis, when in fact serious ventilation-perfusion mismatch problems are masked by the small anatomic dead space. The solution proposed by Moppett et al[23] is to calculate the ratio of alveolar dead space to alveolar V_T, rather than the total V_D/V_T. That is, measure the anatomic dead space, then subtract the anatomic dead space from both the total dead space and the V_T before calculating the ratio. The resulting V_D/V_T would be a

ratio of alveolar dead space to alveolar V_T. Moppett et al speculated that the association Nuckton[21] and Kallet[22] observed between dead space ratio and mortality was probably due to disturbed ventilation-perfusion matching, and that the alveolar dead space ratio would be even more strongly associated with mortality. Drummond and Fletcher[24] pointed out that right-to-left shunting (intrapulmonary or intracardiac) affects the total dead space measurement, but not the anatomic dead space measurement. The idea of measuring anatomic dead space to estimate the uniformity of alveolar ventilation goes back to 1944.[25-28] We suggest the use of direct anatomic dead space measurement in future studies, to develop better descriptions of the changes that occur in the alveolar dead space with lung injury.

It is important to ensure that the patient receives adequate V_T by minimizing unnecessary apparatus dead space.[10,11] Apparatus dead space affects both alveolar V_T and V_D/V_T, and Nuckton[21] and Kallet[22] ensured their V_D/V_T analyses were carried out with minimal apparatus dead space. Correct assessment of the effect of all series dead space (anatomic and apparatus) requires calculating the apparatus dead space and adding that volume to the estimated anatomic dead space. Direct measurement with volumetric capnography should combine both anatomic and apparatus dead volume into a single volume.

2.6 Conclusions

All these issues point to the need to use direct measurements of anatomic dead space, rather than estimation. The errors associated with estimations are less important with a larger V_T, but with a smaller V_T the percentage of each breath lost to anatomic dead space ventilation is greater. With volumetric capnography it is simple to directly

measure anatomic dead space under every condition and use that measurement to inform treatment.

2.7 References

1. Fowler WS. Lung function studies II: the respiratory dead space. Am J Physiol 1948;154(3):405-416.

2. DuBois AB, Fowler RC, Soffer A, Fenn WO. Alveolar CO2 measured by expiration into the rapid infrared gas analyzer. J Appl Physiol 1952;4(7):526-534.

3. Bartels J, Severinghaus W, Forster RE, Briscoe WA, Bates DV. The respiratory dead space measured by single breath analysis of oxygen, carbon dioxide, nitrogen or helium. J Clin Invest 1954;33(1):41-48.

4. Nunn's applied respiratory physiology, 6th edition. Philadelphia: Elsevier; 2005:118-120.

5. Respiratory physiology: the essentials, 2nd edition. Baltimore: Lippincott Williams & Wilkins; 1979:19.

6. Hlastala MP, Berger AJ. Physiology of respiration. Oxford University Press; 1996:73-74.

7. Ganong WF. Review of medical physiology, 19th edition. Stamford, Connecticut: Appleton & Lange; 1999.

8. Radford EP Jr. Ventilation standards for use in artificial respiration. J Appl Physiol 1955;7(4):451-460.

9. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342(18):1301-1308.

10. Hinkson C, Benson M, Stephens L, Deem S. The effects of mechanical dead space on PaCO2 in patients receiving lung-protective ventilation (abstract). Respir Care 2006;51(11):1140.

11. LeBourdelle`s G, Mier L, Fiquet B. Comparison of the effects of head and moisture exchangers and heated humidifiers on ventilation and gas exchange during weaning trials from mechanical ventilation. Chest 1996;110(5):1294-1298.

12. Nielsen L. Assessing patients' respiratory problems. Am J Nurs 1980; 80(12):2192-2196.

13. Devine BJ. Gentamicin therapy. Drug Intell Clin Pharm 1974;8:650- 655.

14. Nunn JF, Hill DW. Respiratory dead space and arterial to end-tidal carbon dioxide tension difference in anesthetized man. J Appl Physiol 1960;15:383-389.

15. Casati A, Fanelli G, Torri G. Physiological dead space/tidal volume ratio during face mask, laryngeal mask and cuffed oropharyngeal airway spontaneous ventilation. J Clin Anesth 1998;10(8):652-655.

16. Suwa K, Bendixen HH. Change in PaCO2 with mechanical dead space during artificial ventilation. J Appl Physiol 1968;24(4):556-562.

17. Mantha S, Roizen MF, Fleisher LA, Thisted R, Foss J. Comparing methods of clinical measurement: reporting standards for Bland and Altman analysis. Anesth Analg 2000;90(3):593-602.

18. Petter AH, Chiole´ro RL Cassina T, Chassot P, Mu¨ller XM, Revelly JP. Automatic "respirator/weaning" with adaptive support ventilation: The effect on duration of endotracheal intubation and patient management. Anesth Analg 2003;97(6):1743-1750.

19. Sulzer CF, Chiole´ro R, Chassot P, Mueller X, Revelly J. Adaptive support ventilation for fast tracheal extubation after cardiac surgery: a randomized controlled study. Anesthesiology 2001;95(6):1339-1345.

20. Rohrer F. [Der Stro¨mungswiderstand in den menschlichen Atemwegen und der Einfluss der unregelma¨ssigen Verzweigung des Bronchialsystems auf den Atmungsverlauf in verschiedenen Lungenbezirken]. Pflu¨gers Archiv Euro J Physiol 1915;162(5-6):225-299. *Article in German*.

21. Nuckton TJ, Alonso JA, Kallet RH, Daniel BM, Pittet JF, Eisner MD, Matthay MA. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. N Engl J Med 2002;347(17):850-852.

22. Kallet RH, Alonso JA, Pittet JF, Matthay MA. Prognostic value of the pulmonary dead-space fraction during the first 6 days of acute respiratory distress syndrome. Respir Care 2004;49(9):1008-1014.

23. Moppett IK, Gornall CB, Hardman JG. The dependence of measured alveolar deadspace on anatomical deadspace volume. Brit J Anaesth 2005;95(3):400-405.

24. Drummond GB, Fletcher R. Editorial II: Dead space: invasive or not? (editorial) Brit J Anaesth 2006;96(1):4-7.

25. Bateman JB. The measurement of intrapulmonary mixing and pulmonary midcapacity ("functional residual air"). Proc Staff Meet Mayo Clin 1946;21:112.

26. Birath G. Lung volume and ventilation efficiency; changes in collapse-treated and non-collapse-treated pulmonary tuberculosis and in pulmonectomy and lobectomy. Acta Med Scand 1944; (Suppl):154S.

27. Darling RC, Cournand A, Richards DW Jr. Studies on intrapulmonary mixture of gases: forms of inadequate ventilation in normal and emphysematous lungs, analyzed by means of breathing pure oxygen. J Clin Invest 1944;23(1):55-67.

28. Riley RL, Cournand A. Ideal alveolar air and the analysis of ventilation- perfusion relationships in the lungs. J Appl Physiol 1949; 1(12):825-847.

CHAPTER 3

FEASIBILITY STUDY*

3.1 Abstract

3.1.1 Background

Several techniques for measuring the functional residual capacity (FRC) of the lungs in mechanically ventilated patients have been proposed, each of which is based on either nitrogen wash-out or dilution of tracer gases. These methods are expensive, difficult, time-consuming, impractical, or require an intolerably large change in the fraction of inspired oxygen. We propose a CO_2 wash-in method that allows automatic and continual FRC measurement in mechanically ventilated patients.

3.1.2 Methods

We measured FRC with a CO_2 partial rebreathing technique, first in a mechanical lung analog, and then in mechanically ventilated animals, before, during, and subsequent to an acute lung injury induced with oleic acid. We compared FRC measurements from partial CO_2 rebreathing to measurements from a nitrogen wash-out reference method. Using an approved animal protocol, general anesthesia was induced and maintained with propofol in 6 swine (38.8 –50.8 kg). A partial CO_2 rebreathing monitor was placed in the

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breathing circuit between the endotracheal tube and the Y-piece. The partial CO_2 rebreathing signal obtained from the monitor was used to calculate FRC. FRC was also measured with a nitrogen wash-out measurement technique. In the animal studies we collected data from healthy lungs, and then subsequent to a lung injury that simulated the conditions of acute lung injury/acute respiratory distress syndrome. The injury was created by intravenously infusing 0.09 mL/kg of oleic acid over a 15-min period. At each stage of the experiment, the positive end-expiratory pressure (PEEP) was set to 0, 5, 10, or 15 cm H_2O. At each PEEP level we compared the average of 3 CO_2 rebreathing FRC measurements to the average of three nitrogen wash-out reference measurements. We also tested the FRC measurement system with a mechanical test lung in which the true FRC could be directly measured.

3.1.3 Results

The squared correlation for the linear regression between CO_2 rebreathing and nitrogen wash-out measurements in the animals was $r^2 = 0.89$ ($n = 50$). The average error of the CO_2 wash-out system was -87 mL and the limits of agreement were ± 263 mL. In the mechanical test lung, the average error of the FRC measured via the CO_2 wash-in system was 37 mL, and the limits of agreement were ± 103 mL, which was equivalent to 1.7% of the true FRC. The squared correlation was $r^2 = 0.96$.

3.1.4 Conclusion

These results indicate that FRC measurement via CO_2 rebreathing can reliably detect an FRC decrease during lung injury and can reflect the response of the FRC to treatment with PEEP.

3.2 Introduction

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

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

Although computed tomography has been useful for determining the pathophysiology and progression of ARDS/ ALI and for demonstrating the usefulness of the FRC measurement to actively control lung volume during mechanical ventilation, the method is regarded as risky and cumbersome to use regularly at the bedside for monitoring the evolution of lung injury and the effects of the ventilatory strategy. Several other techniques for FRC measurement in mechanically ventilated patients have been proposed during the past 2 decades, each of which is based on either nitrogen wash-out or

dilution of tracer gases. The techniques include closed-circuit helium dilution,[7,8] open-circuit nitrogen wash-out,[9–11] and open-circuit sulfur hexafluoride wash-out.[12,13] Additionally, FRC has been estimated via electrical impedance tomography[14] and a single-breath-hold Fick method.[15] These methods are expensive, difficult and time consuming at the bedside, impractical for continual use, or require an intolerably large change in the fraction of inspired oxygen (F_{IO2}) to complete the measurement.

We propose here a CO_2 wash-in method that allows automatic and continual measurement of FRC in mechanically ventilated subjects. The new method measures FRC using the "CO_2 wash-in" signals during the onset of a partial CO_2 rebreathing maneuver that is automatically initiated every three min by a CO_2 rebreathing noninvasive cardiac output monitor ($NICO_2$, Respironics, Wallingford, Connecticut). In an oleic acid model of ARDS/ ALI in mechanically ventilated animals, we measured the FRC before, during, and after lung injury, with two methods: CO_2 wash-in and nitrogen wash-out. The aims of the study were to evaluate the new method in a mechanical lung model and to compare FRC measurements with the two methods in mechanically ventilated animals during induced lung injury. We demonstrate that the CO_2-based FRC measurement can be used to trend the effects of lung injury and track the response to treatment.

3.3 Methods

3.3.1 Nitrogen Wash-Out Method

We used a variation of the nitrogen wash-out FRCmeasurement method published by Olegard et al[16] as the reference measurement. This method has been described in the literature but is not commercially available. In our implementation, the nitrogen wash-out

method required a brief (< 5 min) 0_2 step increase in F_{IO_2} (eg, from 0.4 to 0.6). The volume of released nitrogen and the change in nitrogen concentration following the change in F_{IO_2} were used to calculate FRC.

Oxygen was analyzed with a sidestream paramagnetic O_2 analyzer (Datex, Helsinki, Finland). CO_2 was measured with an infrared analyzer, and flow was measured with a differential pressure-type pneumotachometer, both of which are integrated in the $NICO_2$ mainstream sensor (model 7300, Respironics-Novametrix, Wallingford, Connecticut). The gas analyzers were calibrated with calibration gas prior to the experiment. Each of the analyzers automatically re-zeros periodically to avoid baseline drift. Gas for the sidestream analyzer was sampled at the ventilator circuit Y-piece, and the mainstream sensor was placed between the gas sampling adaptor and the endotracheal tube. Both inspired and expired gases were measured continuously.

The raw data of flow and gas concentration measurements were sampled at 100 Hz and processed digitally using custom-written software to generate end-tidal and volumetric O_2 and CO_2 measurements and tidal volume (V_T). We calculated oxygen consumption from the directly measured CO_2 consumption (V_{CO_2}) and the minimum/ maximum difference in the O_2 signal. We assumed that since the waveform of the fast oxygen signal is an inverted, scaled version of the capnogram, oxygen consumption can be calculated asV_{CO_2} multiplied by the minimum/ maximum difference in the O_2 divided by the minimum/ maximum difference in CO_2.[9,16] We calculated end-tidal and mixed nitrogen fraction (F_{N_2}) as the balance gas (F_{N_2} - 1 - F_{O_2} - F_{CO_2}). Nitrogen excretion was calculated as the difference between expired volume multiplied by mixed expired N_2 fraction and inspired volume multiplied by inspired N_2 fraction. After at least 2 min of

baseline data had been collected, the nitrogen wash-out FRC measurement was initiated by increasing the F_{IO_2} by 0.2 for each measurement, within the range of 0.3 to 1.0. Typically, the successive step changes in F_{IO_2} for three measurements were 0.4 to 0.6, 0.6 to 0.8, and 0.8 to 1.0. The volume of excreted N_2 (V_{N_2}) was recorded during wash-out. The wash-out at each step change of F_{IO_2} was allowed to continue to completion before the next measurement was begun.

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

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:

$$V_{N_2}/(F_{etN_2end} - F_{etN_2ini}) \qquad [3.1]$$

where V_{N_2} 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_{IO_2}, 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 N_2 from the tissues. The effect of N_2 excretion from the tissues on the FRC measurement should be small (< 100 mL) and consistent across the animals used in our study.[18] Because the published studies that describe the methods for estimating the volume of N_2 excretion in response to increased F_{IO_2} assume human rather than porcine subjects, we elected to ignore the effect of N_2 excretion in our calculations. [18]

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

3.3.2 CO_2 Wash-In Method

FRC measurements with the CO_2 wash-in method were made with an on-airway infrared CO_2 analyzer, while airway flow was measured with an integrated differential pressure-type pneumotachometer, both of which are integrated in the $NICO_2$ partial rebreathing cardiac output monitor. The monitor automatically actuates a pneumatic valve to commence partial CO_2 rebreathing once every 3 min. The rebreathing period lasts 35 seconds and is used to measure pulmonary capillary blood flow. To calculate the FRC with the CO_2 wash-in method, only the first breath of the rebreathing period is needed, wherein the changes in end-tidal and volumetric CO_2 are recorded. Figure 3.1 depicts the typical CO_2 rebreathing signals.

The calculations are as follows:

$$FRC \times FCO2(n) = FRC \times FCO2(n-1) + VbCO2 - VeCO2 \quad [3.2]$$

$$FRC \times [FCO2(n) - FCO2(n-1)] = VbCO2 - VeCO2 \quad [3.3]$$

where $F_{CO_{2(n)}}$ is the fraction of end-tidal CO_2 in the current breath (n), $F_{CO_{2(n-1)}}$ is the fraction of end-tidal CO_2 in the previous breath (n-1), V_{bCO_2} is the volume per breath of CO_2 passing from the blood into the FRC, and V_{eCO_2} is the volume per breath of CO_2 being excreted from the patient, measured at the mouth.

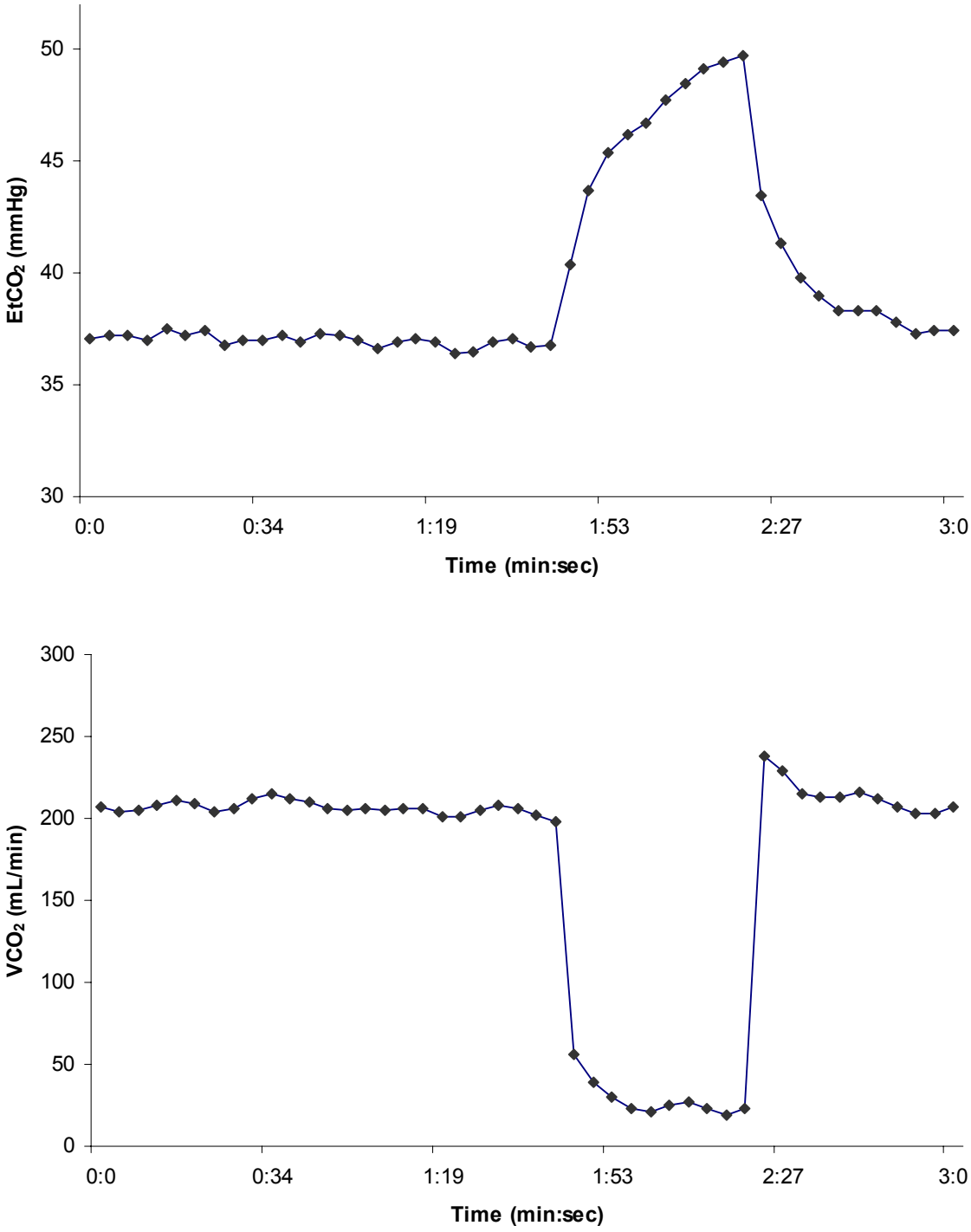

Figure 3.1. Example rebreathing signals. Changes in end-tidal CO_2 ($P_{et}CO_2$) (above) and corresponding changes in CO_2 elimination (VCO_2) with rebreathing during a 3-min period (below).

It is assumed that the CO_2 excretion rate during the baseline period before rebreathing $V_{CO2baseline}$ is at a steady state and that the amount of CO_2 eliminated per breath at the mouth is equal to the volume eliminated from the blood in the alveoli.

$$FRC = (VCO2baseline - VeCO2(n))/(FCO2(n) - FCO2(n–1)) \quad [3.4]$$

The numerator of equation 4 reflects the amount of CO_2 in excess of the amount delivered by the blood and retained in the FRC due to rebreathing. This equation is simply a one-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 that error.

The actual volume measured by this method includes not only the FRC but also the effective volume of the other stores of CO_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:

$$FRC = 0.45 \times (VCO2baseline - VeCO2(n))/(FCO2(n) - FCO2(n-1)) \quad [3.5]$$

The factor of 0.45 was described by Gedeon et al[15] 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 V_T, but for the purposes of this study these assumptions provide reasonable estimates of FRC.

It should also be noted that the last breath of rebreathing could also be used instead of the first breath, provided that the CO_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 wash-out FRC, calculated as:

$$FRC = 0.45 \times (VCO2steady - VCO2(n))/ (FCO2(n-1) - (FCO2(n)) \quad [3.6]$$

where $V_{CO2steady}$ is the volume of CO_2 excreted in the last breath of rebreathing in the steady state, $V_{CO2(n)}$ is the CO_2 excreted in the first breath following rebreathing, $F_{etCO2(n-1)}$ is the fraction of end-tidal CO_2 in the first breath following rebreathing, and $F_{etCO2(n)}$ 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.

3.3.3 Bench Validation of the CO_2 Wash-In Method With a Lung Model

A training/test lung (Michigan Instruments, Grand Rapids, Michigan) was driven by a ventilator (900c, Siemens-Elema, Solna, Sweden) and infused with 250 mL/min CO_2. A fan inside the lung completely mixed the gases. V_{CO2} and end-tidalCO_2 measurements were obtained from the $NICO_2$ monitor. Partial rebreathing was automatically induced by the monitor for 35 seconds every 3 min. PEEP was changed from 0 cmH_2O (FRC = 1.47 L) to 20 cmH_2O in steps of 5 cmH_2O, to increase the FRC to a maximum of 2.75 L. At each PEEP level, 2 CO_2-wash-in-based FRC measurements were recorded, and the known volume of the mechanical lung was also recorded. At the end of the experiment, the PEEP was reduced back to zero, and the measurements were again recorded. The averageCO_2 wash-in measurements at each PEEP step were compared via linear regression and Bland-Altman statistics to the known volumes.

3.3.4 Bench Validation of the Nitrogen Wash-Out Method with 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). 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 four different levels, from 0 cm H_2O 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 wash-out-based FRC measurements were recorded. The average measurements at each PEEP step were compared with linear regression and Bland-Altman statistics to the known volumes.

3.3.5 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 intramuscular bolus of Telazol (4 mg/kg). Following tracheal intubation, the animals were ventilated with a mechanical ventilator (Esprit, Respironics, Carlsbad, California) with a V_T of 10 mL/kg, F_{IO_2} of 0.4, and an inspiratory-expiratory time ratio of 1:2. The respiratory rate was adjusted to maintain the nonrebreathing end-tidal P_{CO_2} near 35 mm Hg. An 18-gauge arterial cannula was inserted into the femoral artery to continuously measure blood pressure and to facilitate arterial blood gas samples. General anesthesia was maintained via continuous infusion of propofol (100 -300 ug/kg/min), with a target mean blood pressure of 100 mm Hg. The animals were paralyzed with a continuous infusion of pancuronium (1 mg/kg/h). A flow-directed pulmonary artery catheter was inserted into the jugular vein and advanced until the tip rested in the pulmonary artery, as

assessed by hemodynamic waveforms. Mixed venous blood gas samples were drawn from the catheter tip. Venous admixture (shunt fraction) was calculated with the measured arterial and venous blood gas data. Lactated ringers solution was given intravenously at 6 mL/ kg/h throughout the experiment. The $NICO_2$ monitor was placed in the breathing circuit between the endotracheal tube and the Y-piece. The partial CO_2 rebreathing signals obtained from that 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 the PEEP was set to 0, 5, 10, and 15 cm H_2O. At each PEEP level we compared the average of 3 FRC measurements from CO_2 wash-in to the average of three nitrogen wash-out measurements. To ensure that the effects of each PEEP adjustment had stabilized, no FRC measurements were made in the first 20 min after each PEEP change. Then, partial rebreathing data (end-tidal CO_2 and CO_2 excretion in response to partial rebreathing) were collected for 12 min (four rebreathing cycles, 3 min each) with the $NICO_2$ monitor. Next, three reference nitrogen wash-out measurements were recorded. After collecting the nitrogen wash-out data, the PEEP was increased to the next level and the next measurement sequence was repeated. Arterial blood gas measurements were collected between the CO_2 wash-in and nitrogen wash-out measurements at each PEEP level. Average cardiac output (measured via bolus thermodilution), heart rate, arterial blood pressure, pulmonary artery blood pressure, and oxygen saturation, were also noted at each PEEP level.

Following FRC measurement at each of the 4 PEEP levels in healthy lungs, lung injury was created to simulate ARDS/ALI by infusing 0.09 mL/kg of oleic acid though

the proximal port of the pulmonary artery catheter. A syringe pump was used to deliver the acid continuously over a 15-min period. We allowed 1 hour for the injury to develop before resuming comparison FRC data collection. Injury was confirmed by decreased static lung compliance and lung auscultation. After the lung injury had been created, we repeated the data collection procedure at each PEEP level: 0, 5, 10, and 15 cm H_2O. The average FRC measurements made with each of the methods at each PEEP level were compared via regression analysis and Bland-Altman statistics.

3.4 Results

3.4.1 Bench Validation Results: Comparison with the Known Lung Volume

In the bench validation, the average error in the FRC measured by the CO_2 wash-in system was 37 mL with limits of agreement (LOA) ± 201 mL, which was equivalent to 1.7% of the true FRC. The squared correlation was r^2= 0.96 (Figure 3.2).

The average error in the FRC measured by the CO_2 washout system was 508 mL with limits of agreement (LOA) ± 370 mL, which was equivalent to 27% of the true FRC. The correlation coefficient was r^2= 0.95. We observed that, because of the limitations of the physical lung model, the requirement of the CO_2 wash-out method that steady state end-tidal CO_2 be attained during rebreathing was not met.

The average error with N_2 wash-out was 6 mL with LOA ± 83 mL, which was -0.02% of the true FRC. The squared correlation was r^2 = 0.99 (see Figure 3.2).

3.4.2 Bench Validation CO_2 Measurement Repeatability

The average error in the FRC measured by the CO_2 wash-in system with duplicate measurements was 61 mL with LOA ± 103 mL. The squared correlation for duplicate

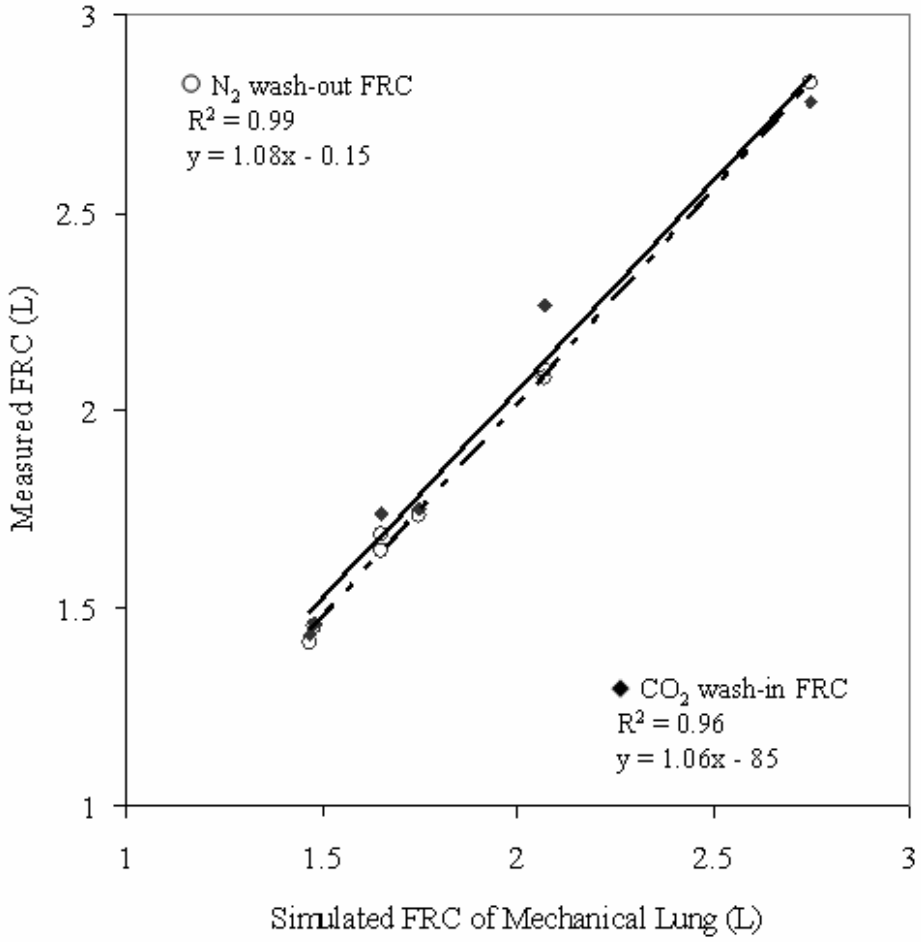

Figure 3.2. Regression analyses with the simulated functional residual capacity (FRC) of the mechanical lung. FRC measurements from the CO_2 wash-in method and the nitrogen wash-out method versus the simulated reference value.

measurements was r^2= 0.97. The average error in the FRC measured with the CO_2 wash-out system with duplicate measurements was -10 mL, with LOA of ± 109 mL. The squared correlation for duplicate CO_2 wash-out measurements was r^2= 0.99.

3.4.3 Animal Testing Results

In the healthy phase of the experiment, the median PaO_2/FiO_2 ratio was 443 (range: 307-570) with an FiO_2 of 0.3. Subsequent to the oleic acid injury, the median PaO_2/FiO_2 was 153 (range: 120-172). During the injury phase, the FiO_2 was 0.4 in all animals except one, which had a PaO_2/FiO_2 of 169 with an FiO_2 of 0.7.

Figure 3.3 shows the individual CO_2 wash-out FRC measurements from animal 3 and depicts the change in FRC during evolution of the oleic acid induced ALI, as well as recovery of FRC volume following PEEP therapy.

3.4.4 Comparison of CO_2 Methods with Nitrogen

Wash-out FRC Measurements

When compared with nitrogen washout, the average error in the FRC measured by the CO_2 wash-out system was -87 mL, with LOA of ± 263 mL (Figure 3.4). The correlation coefficient was r^2= 0.89 (n = 50) and the slope was 1.018. For the ALI phase alone, r^2 was 0.75, the slope was 1.13 and the bias was -77 mL, with LOA of ± 276 mL (n = 26).

When CO_2 wash-in data were compared with nitrogen wash-out, the average error was -3 mL, with LOA of ± 346 mL. The squared correlation was r^2= 0.75 (n = 43).

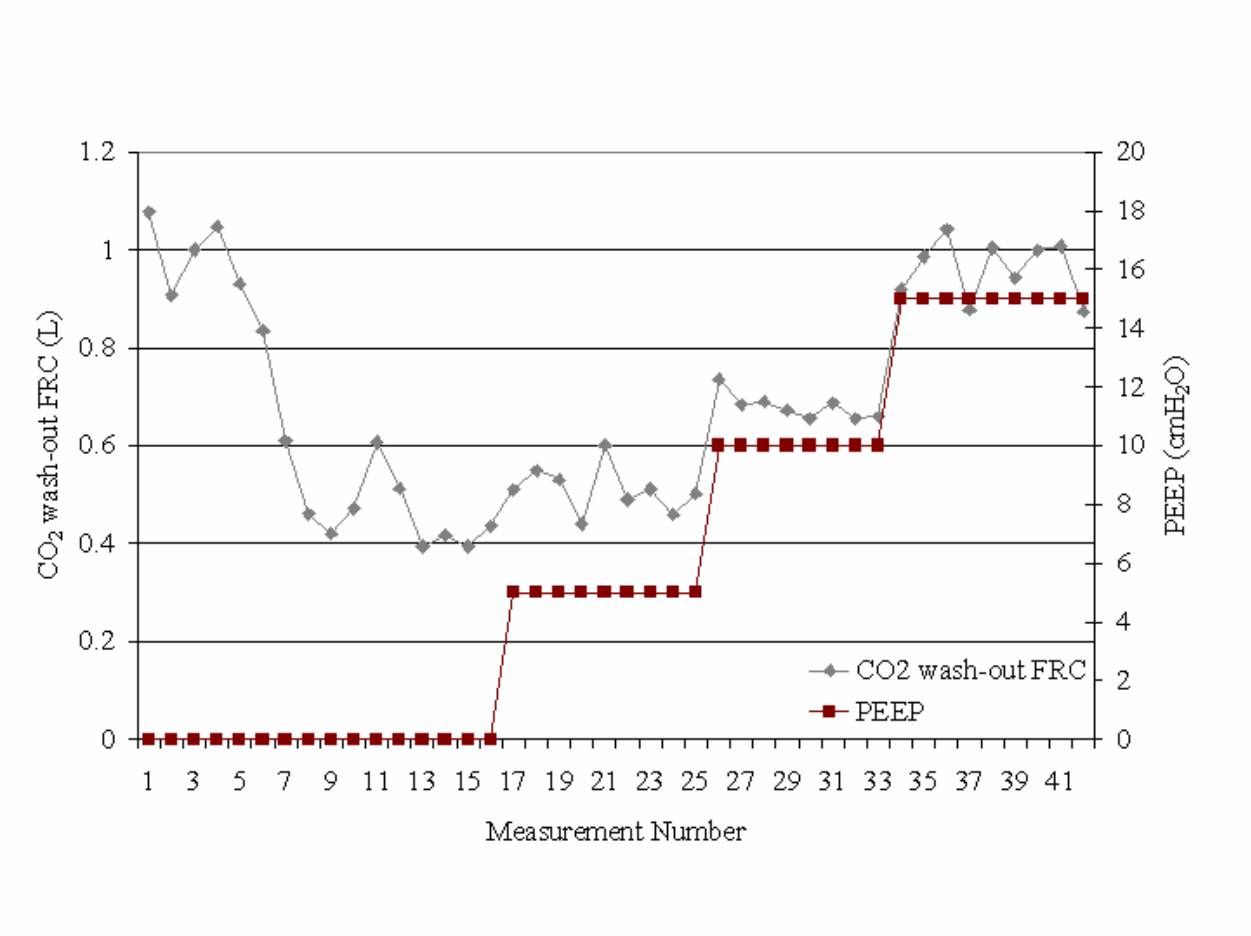

Figure 3.3. Trend of CO_2 wash-out functional residual capacity. Values were measured during evolution of and ventilator treatment for acute lung injury. PEEP = positive end-expiratory pressure.

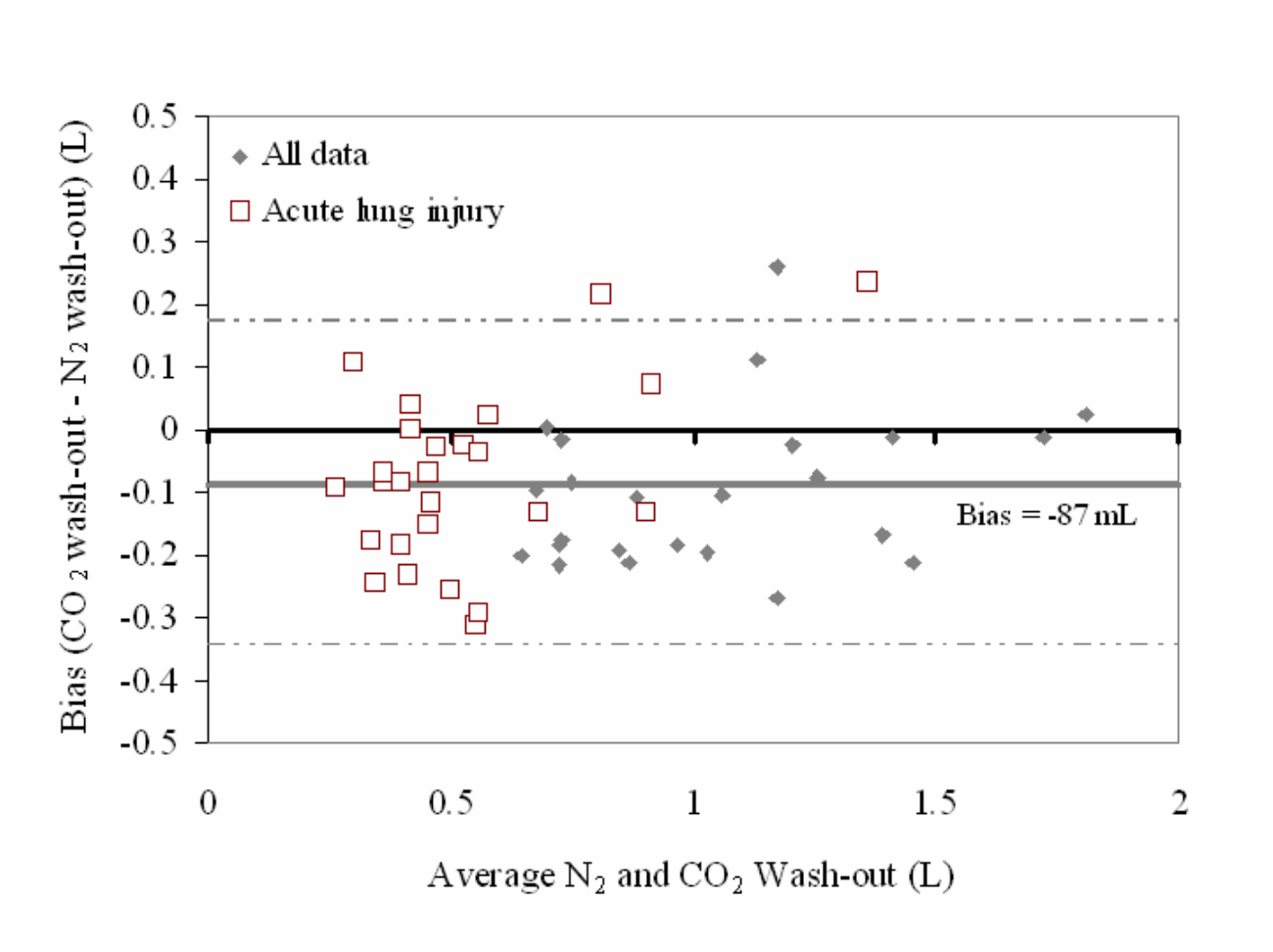

Figure 3.4. Bland-Altman comparison of CO_2 wash-out and nitrogen-wash-out functional residual capacity (FRC) measurement techniques.

3.4.5 CO_2 Wash-out and Wash-In FRC Measurement

Technique Repeatability

Regression of duplicate CO_2 washout measurements at each PEEP resulted in an r^2= 0.98 for all data combined and r^2= 0.96 for just the ALI phase. The average error at each PEEP in the FRC for duplicate CO_2 washout measurements was 2.9 mL with LOA of ± 124 mL for all data (n = 357) (Figure 3.5) and 3.8 mL ,with LOA of ± 95 mL for the ALI phase (n = 140).

Regression of duplicate CO_2 wash-in FRC measurements resulted in an r^2= 0.93 for all data combined and r^2= 0.87 for just the ALI phase. The CO_2 wash-in repeatability bias for all data together was 1 mL with LOA of ± 183 mL (n = 360). For the ALI phase only, the wash-in repeatability bias was 7 mL, with LOA of ± 161 mL (n = 147).

3.4.6 Nitrogen Wash-Out Repeatability

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

3.5 Discussion

We found good repeatability and clinically acceptable limits of agreement and bias between the proposed CO_2 technique and the nitrogen wash-out method for FRC measurement. The CO_2 technique allows automated, continual measurements of lung volume in mechanically ventilated subjects with ALI. An update in the measurement can occur in less than 3 min, which is rapid enough to be of clinical use. The method does not

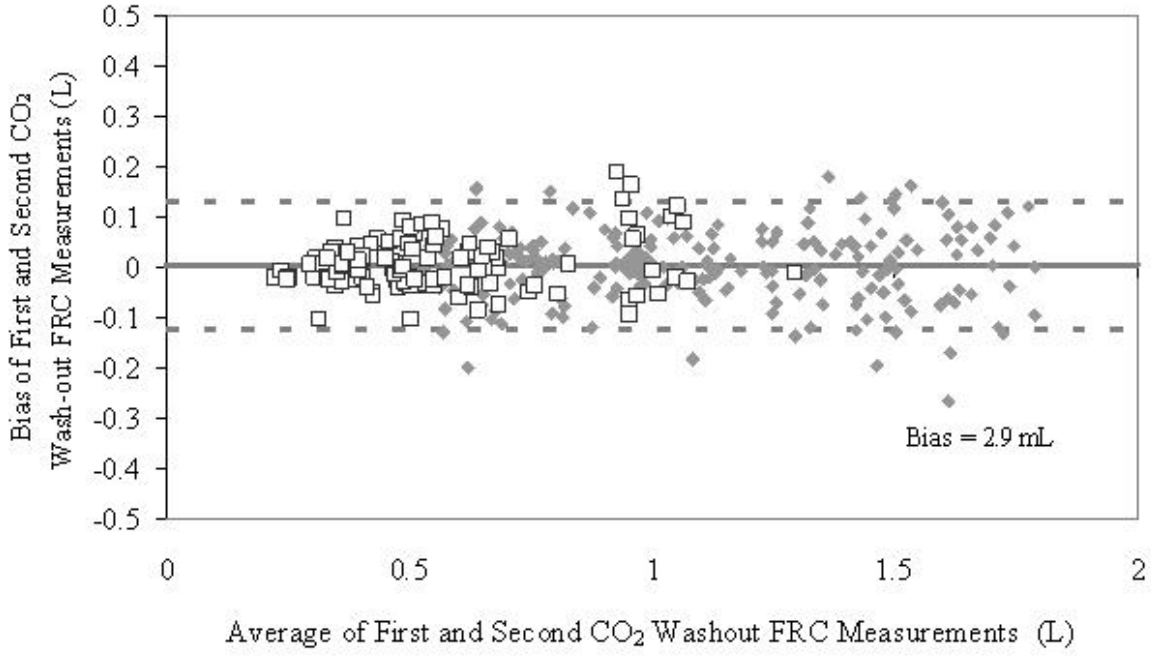

Figure 3.5. Bland-Altman comparison of the first and second CO_2 wash-out functional residual capacity (FRC) measurements. Measurements were taken during healthy lung and injured lung phases.

require a change in the ventilator settings and therefore could run independently and provide a trend of FRC measurements without clinician intervention. Since the method is repeatable, the clinician could also obtain early feedback from individual measurements regarding the physiologic response to changes made in PEEP and other ventilator settings.

CO_2 wash-out showed better LOA for both the comparison of accuracy and the comparison of repeatability than CO_2 wash-in did in these subjects. This is probably because the signal-to-noise ratio of the first wash-out breath is slightly better, as long as steady state has been reached during the partial rebreathing period before the step change to nonrebreathing is actuated. Further testing is needed to determine whether CO_2 wash-in or wash-out (or a combination of the two) is the best approach. The CO_2 wash-in measurement makes use of the first breath of rebreathing, whereas the wash-out measurement is based on the last breath of rebreathing. The wash-out measurement requires the assumption that steady state has been reached during the rebreathing period.

We observed no systematic difference between the CO_2 wash-out and the nitrogen wash-out techniques. Each method responded similarly to the loss of aeration during the evolution of lung injury and to an increase in PEEP. This was expected, since both methods measure the communicating gas (i.e., the gas that flows into and out of the lung during tidal ventilation) rather than the whole enclosed gas volume. The nitrogen wash-out method had a better signal-to-noise ratio than either CO_2 method at larger FRCs. The repeatability of our implementation of the nitrogen wash-out was similar to what Olegard et al.[16] reported. They found a bias of -5 mL, with limits of agreement of approximately -380 mL to 375 mL.

Subsequent FRC measurements taken according to our protocol of successive, stepwise increases in F_{IO_2} for a period of about 10 min did not show a decrease in FRC with each increase in F_{IO_2}. If we had observed a decrease with each subsequent measurement, we might have assumed that increasing the F_{IO_2} had lead to absorption atelectasis. We observed no systematic difference between the first FRC measurement, which was taken at a lower F_{IO_2}, and the subsequent measurement, which was taken at a higher F_{IO_2} . The average squared correlation between subsequent measurement pairs was $r_2 = 0.97$, with an average difference of 12 mL. This implies that the method is insensitive to differences in F_{IO_2} and that increases in F_{IO_2} did not create a change in FRC due to absorption atelectasis or a similar effect.

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

Current practice involves monitoring of improvements in O_2 saturation or dynamic compliance as a measure of a successful recruitment maneuver.[19–26] However, the improvement in O_2 saturation following a recruitment maneuver is transient,[27] whereas the measurement of FRC remains a sensitive indicator of the aeration of the lung. Compliance change in early ALI/ARDS is a measure of aerated tissue, which leads to baby lung, rather than a stiff lung as previously thought.[28]

Rylander et al[1] found that FRC was a more sensitive indicator of decreased aeration and increased consolidation than is lung compliance, and he concluded that FRC might be a useful adjunct to P_{aO_2} monitoring at the bedside.

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

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 online FRC measurements were available, it would be possible to quickly confirm improvement in FRC following treatment with the most conservative approach possible. It has also been suggested that FRC could be a tool for the early detection of lung over-inflation, by studying the predictive value of the ratio between PEEP-induced increase in FRC and PEEP-induced alveolar recruitment derived from the pressure-volume curves.[4] It remains to be seen whether earlier detection and treatment of ARDS/ALI will affect outcome.

An alternative to the open-lung strategy has been termed “lung rest,” which is characterized by low airway pressure to prevent recruitment/derecruitment, small V_T, and occasional sigh breaths or biologically variable ventilation.[31–35] Whether using the

open-lung or the lung-rest strategy, the common intent is the prevention of repetitive alveolar collapse and expansion.[36] In either approach, continual monitoring of FRC would indicate an improvement or worsening of the FRC so that the clinician could be alerted that application of one of the strategies is required or has been successful.

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

The main drawback of the CO_2-based FRC measurement techniques is that CO_2 is a soluble indicator gas that is carried in the blood. Changes in the alveolar concentration affect the volume of CO_2 delivered to the alveoli, which makes the assumption of delivery of CO_2 to the alveoli by the blood less valid with each breath as rebreathing progresses. This limitation restricts analysis to the first or last breath of rebreathing. The use of a single breath for the measurement requires analysis of small changes in the signals, which may lead to measurement errors, especially when FRC is large. Another drawback of using CO_2 as the indicator gas is that it is stored in the tissues of the lung and in the blood. The volume that is directly measured includes both the effective CO_2 storage

volume of the lung tissue and the blood. We apply the empirically derived multiplicative factor of 0.38 to reduce the effective lung volume to the gas volume that is the FRC. This factor is similar to that of 0.45 that Gedeon et al. [15] selected for their studies. This factor might be expected to be affected by increased tissue volumes, such as in edematous ARDS, but in this study the same factor was applied in both healthy and injured lungs, where the volume of fluid in the lung changed significantly. The application of a factor for pulmonary capillary blood flow or correction in V_T from one breath to the next did not improve the repeatability or the comparison data in these studies, which is probably because the animals were mechanically ventilated and pulmonary capillary blood flow was not actively altered during the studies.

Based of the limitation of CO_2, it may be reasonable to use the CO_2-based FRC measurement as a trend monitor rather than as an indicator of absolute gas volume in the lung. As with all tracer gas methods, the CO_2 wash-in method measures only the part of the FRC that takes part in gas exchange, or the effective FRC. Methods such as computed tomography and body plethysmography also include the part of the FRC that is not communicating. Rylander et al [30] noted that the tendency to underestimate the FRC with a tracer gas was aggravated in ARDS because of the uneven distribution of ventilation. He estimated that the sulfur hexafluoride FRC method measured two thirds of the true end-expiratory lung volume; this limitation applies to the CO_2 wash-in technique as well.

3.6 Conclusions

In summary, convenient FRC measurement, combined with knowledge of cardiac output and other traditional measures, could be useful for guiding and monitoring the success of a recruitment maneuver, PEEP, and posture changes in treating lung injury. Such a monitor could simplify the maintenance of recruitment and oxygenation with minimal PEEP following a recruitment maneuver. Knowledge of FRC could aid in achieving alveolar stability, thereby protecting alveoli from shear stress and overdistention. If the method for measuring FRC were simple enough to use at the bedside, it might also be possible to detect de-recruitment sooner than by waiting to observe deleterious effects on P_aO_2.

A simpler FRC measurement method that would be more widely used in clinical medicine could help bring about broader clinical answers to questions such as the relationship between FRC and disease progression (eg, edema and fibrosis), the rate of recruitment after application of PEEP, the effect of fluid balance, and the relationship between gas exchange and FRC. We have shown that reproducible FRC measurements can be made with CO_2. This method requires no interruption or changes to mechanical ventilation and could be used continually to monitor FRC in ARDS/ALI patients.

3.7 References

1. Rylander C, Hogman M, Perchiazzi G, Magnusson A, Hedenstierna G. Functional residual capacity and respiratory mechanics as indicators of aeration and collapse in experimental lung injury. Anesth Analg 2004;98(3):782–789.

2. Suter PM, Fairley HB, Schlobohm RM. Shunt, lung volume and perfusion during short periods of ventilation with oxygen. Anesthesiology 1975;43(6):617–627.

3. Hedenstierna G. The recording of FRC–is it of importance and can it be made simple? Intensive Care Med 1993;19(7):365–366.

4. Rouby JJ, Lu Q, Goldstein I. Selecting the right level of positive end-expiratory pressure in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2002;165(8):1182–1186.

5. de Chazal I, Hubmayr RD. Novel aspects of pulmonary mechanics in intensive care. Br J Anaesth 2003;91(1):81–91.

6. Markstaller K, Eberle B, Kauczor HU, Scholz A, Bink A, Thelen M, et al. Temporal dynamics of lung aeration determined by dynamic CT in a porcine model of ARDS. Br J Anaesth 2001;87(3):459–468.

7. Pelosi P, Cereda M, Foti G, Giacomini M, Pesenti A. Alterations of lung and chest wall mechanics in patients with acute lung injury: effects of positive end-expiratory pressure. Am J Respir Crit Care Med 1995;152(2):531–537.

8. Patroniti N, Bellani G, Manfio A, Maggioni E, Giuffrida A, Foti G, Pesenti A. Lung volume in mechanically ventilated patients: measurement by simplified helium dilution compared to quantitative CT scan. Intensive Care Med 2004;30(2):282–289.

9. Fretschner R, Deusch H, Weitnauer A, Brunner JX. A simple method to estimate functional residual capacity in mechanically ventilated patients. Intensive Care Med 1993;19(7):372–376.

10. Wrigge H, Sydow M, Zinserling J, Neumann P, Hinz J, Burchardi H. Determination of functional residual capacity (FRC) by multibreath nitrogen washout in a lung model and in mechanically ventilated patients: accuracy depends on continuous dynamic compensation for changes of gas sampling delay time. Intensive Care Med 1998;24(5): 487–493.

11. Zinserling J, Wrigge H, Varelmann D, Hering R, Putensen C. Measurement of functional residual capacity by nitrogen washout during partial ventilatory support. Intensive Care Med 2003;29(5):720–726.

12. Jonmarker C, Jansson L, Jonson B, Larsson A, Werner O. Measurement of functional residual capacity by sulfur hexafluoride washout. Anesthesiology 1985;63(1):89–95.

13. Larsson A, Linnarsson D, Jonmarker C, Jonson B, Larsson H, Werner O. Measurement of lung volume by sulfur hexafluoride washout during spontaneous and controlled ventilation: further development of a method. Anesthesiology 1987;67(4):543–550.

14. Hinz J, Hahn G, Neumann P, Sydow M, Mohrenweiser P, Hellige G, Burchardi H. End-expiratory lung impedance change enables bedside monitoring of end-expiratory lung volume change. Intensive Care Med 2003;29(1):37–43.

15. Gedeon A, Krill P, Osterlund B. Pulmonary blood flow (cardiac output) and the effective lung volume determined from a short breath hold using the differential Fick method. J Clin Monit Comput 2002; 17(5):313–321.

16. Olegard C, Sondergaard S, Houltz E, Lundin S, Stenqvist O. Estimation of functional residual capacity at the bedside using standard monitoring equipment: a modified nitrogen washout/washin technique requiring a small change of the inspired oxygen fraction. Anesth Analg 2005;101(1):206–212.

17. Magnusson L, and Spahn D. New concepts of atelectasis during general anesthesia. Br J Anaesth 2003;91(1):61–72. 18. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes; Eur Respir J 2005;26(3):511–522.

19. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998;338(6):347–354.

20. Brunet F, Jeanbourquin D, Monchi M, Mira JP, Fierobe L, Armaganidis A, et al. Should mechanical ventilation be optimized to blood gases, lung mechanics, or thoracic CT scan? Am J Respir Crit Care Med 1995;152(2):524–530.

21. Foti G, Cereda M, Sparacino ME, De Marchi L, Villa F, Pesenti A. Effects of periodic lung recruitment maneuvers on gas exchange and respiratory mechanics in mechanically ventilated acute respiratory distress syndrome (ARDS) patients. Intensive Care Med 2000;26(5): 501–507.

22. Cakar N, der Kloot TV, Youngblood M, Adams A, Nahum A. Oxygenation response to a recruitment maneuver during supine and prone positions in an oleic acid-induced lung injury model. Am J Respir Crit Care Med 2000;161(6):1949–1956.

23. Lapinsky SE, Aubin M, Mehta S, Boiteau P, Slutsky AS. Safety and efficacy of a sustained inflation for alveolar recruitment in adults with respiratory failure. Intensive Care Med 1999;25(11):1297–1301.

24. Pelosi P, Cadringher P, Bottino N, Panigada M, Carrieri F, Riva E, et al. Sigh in acute respiratory distress syndrome. Am J Respir Crit Care Med 1999;159(3):872–880.

25. Pelosi P, Bottino N, Chiumello D, Caironi P, Panigada M, Gamberoni C, et al. Sigh in supine and prone position during acute respiratory distress syndrome. Am J Respir Crit Care Med 2003; 167(4):521–527.

26. Baba R, Paramesh K, Zwaal JW. Protective ventilation of patients with acute respiratory distress syndrome. Br J Anaesth 2004;93(1):153.

27. Fujino Y, Goddon S, Dolhnikoff M, Hess D, Amato MB, Kacmarek RM.Repetitive high-pressure recruitment maneuvers required to maximally recruit lung in a sheep model of acute respiratory distress syndrome. Crit Care Med 2001;29(8):1579–1586.

28. Gattinoni L, Caironi P, Pelosi P, Goodman LR. What has computed tomography taught us about the acute respiratory distress syndrome? Am J Respir Crit Care Med 2001;164(9):1701–1711.

29. McCann UG 2nd, Schiller HJ, Carney DE, Gatto LA, Steinberg JM, Nieman GF. Visual validation of the mechanical stabilizing effects of positive end-expiratory pressure at the alveolar level. J Surg Res 2001;99(2):335–342.

30. Rylander C, Tyle´n U, Rossi-Norrlund R, Herrmann P, Quintel M, Bake B. Uneven distribution of ventilation in acute respiratory distress syndrome. Crit Care 2005;9(2):R165–R171.

31. Martynowicz MA, Walters BJ, Hubmayr RD. Mechanisms of recruitment in oleic acid-injured lungs. J Appl Physiol 2001;90(5): 1744–1753.

32. Arold SP, Mora R, Lutchen KR, Ingenito EP, Suki B. Variable tidal volume ventilation improves lung mechanics and gas exchange in a rodent model of acute lung injury. Am J Respir Crit Care Med 2002;165(3):366–371.

33. Lefevre GR, Kowalski SE, Girling LG, Thiessen DB, Mutch WA. Improved arterial oxygenation after oleic acid lung injury in the pig using a computer-controlled mechanical ventilator. Am J Respir Crit Care Med 1996;154(5):1567–1572.

34. Suki B, Barabasi AL, Hantos Z, Petak F, Stanley HE. Avalanches and power-law behaviour in lung inflation. Nature 1994;368(6472): 615–618.

35. Boker A, Graham MR, Walley KR, McManus BM, Girling LG, Walker E, et al. Improved arterial oxygenation with biologically variable or fractal ventilation using low tidal volumes in a porcine model of acute respiratory distress syndrome. Am J Respir Crit Care Med 2002;165(4):456–462.

36. Schiller HJ, McCann UG 2nd, Carney DE, Gatto LA, Steinberg JM, Nieman GF. Altered alveolar mechanics in the acutely injured lung. Crit Care Med 2001;29(5):1049–1055.

CHAPTER 4

CLINICAL TESTING OF NITROGEN SYSTEM*

4.1 Abstract

4.1.1 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.

4.1.2 Methods

The accuracy and precision of measurements were assessed by comparing the novel N_2 washout FRC values to the gold standard, body plethysmography, in twenty spontaneously breathing volunteers. Repeatability was assessed by comparing subsequent

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measurements in twenty intensive care patients whose lungs were under controlled and assisted mechanical ventilation.

4.1.3 Results

Compared to body plethysmography, the accuracy (mean bias) of the novel method was -0.004 L and precision (1 standard deviation) was 0.209 L (-0.1 ± 5.9% of body plethysmography). The difference between repeated measurements was 0.009 ± 0.15 L (mean ± standard deviation) (0.4 ± 6.4 %). The coefficient of repeatability was 0.31 L (12.7%).

4.1.4 Conclusions

The modified multiple breath nitrogen washout method for FRC measurement provides improved precision and equivalent accuracy and repeatability compared to existing methods during ventilation with variable ventilation patterns. Further study of the novel N_2 washout method is needed.

4.2 Introduction

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 measurement[3-6] 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

wash-in/ washout and multiple breath nitrogen washout[7-14]. The volume-based systems depend on accuracy of the volume measurement (flow x concentration). While the volume-based methods have proven to be clinically acceptable (1 SD of the error = 8.5%) with unconscious subjects under controlled mechanical ventilation (CMV) [13], their precision during the more irregular respiratory rate 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].

Fewer than half of intensive care patients' lungs are mechanically ventilated with CMV[16]. 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 a 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_{O2}) or nitrogen (V_{N2}).

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: 1) to evaluate the accuracy and precision of the modified multiple breath nitrogen washout FRC measurement system compared to body plethysmography, the clinical gold standard, in spontaneously breathing volunteers and 2) to assess the repeatability of duplicate FRC measurements in ICU patients whose lungs were mechanically ventilated under pressure control and pressure support mechanical ventilation.

4.3 Methods

4.3.1 Device Description

Figure 4.1 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 ($T_{10\text{-}90}$) 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.

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: $F_{ET}N_2 = 1 - F_{ET}O_2 - F_{ET}CO_2$.

4.3.1.1 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 4.2 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

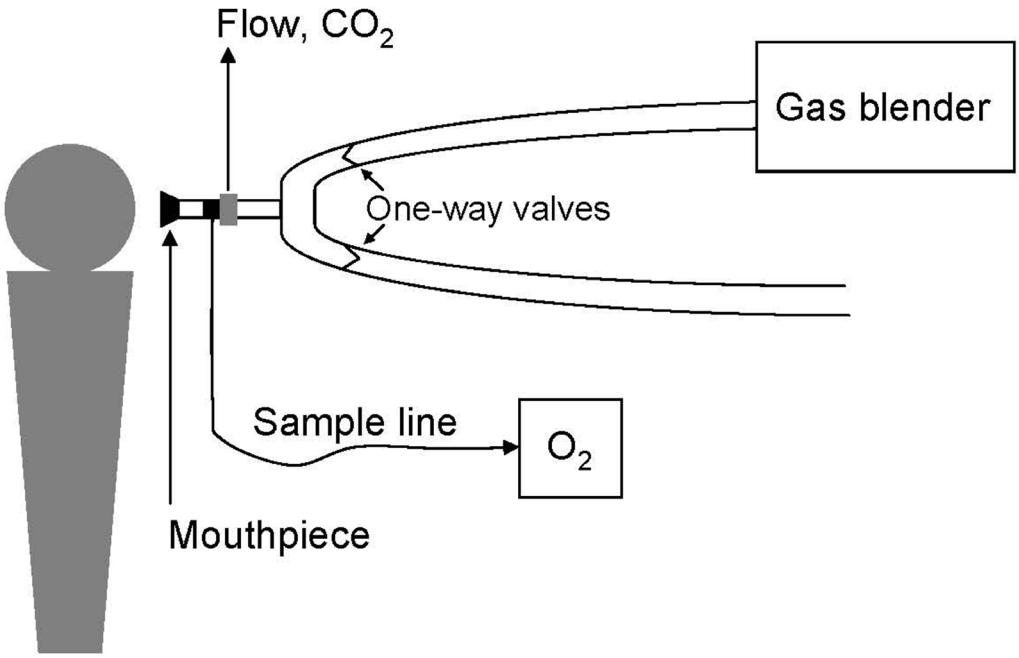

Figure 4.1: The device setup for the accuracy and precision study. The setup comprised a mouthpiece, sensors of flow, O_2, and CO_2, a blender to provide specific gas mixtures at 50 L min^{-1}, and one-way valves to prevent rebreathing.

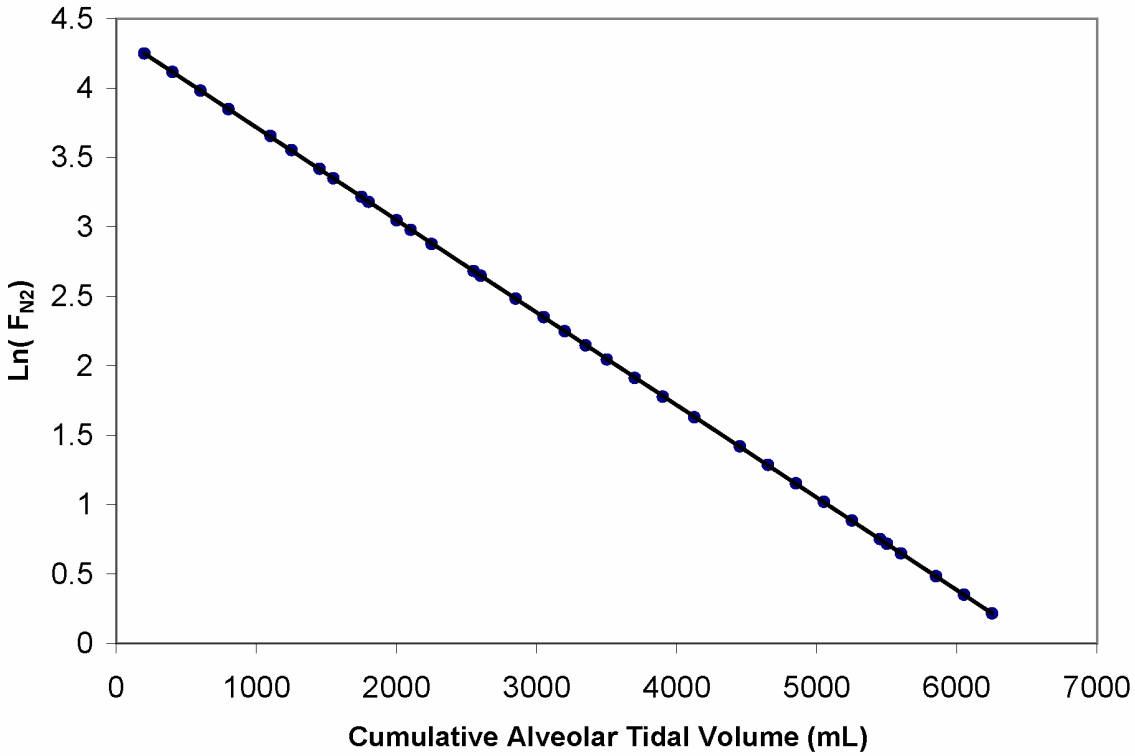

Figure 4.2: An example of the change in nitrogen modeled for one compartment during ventilation with varying tidal volumes. Expired nitrogen concentration is plotted on a logarithmic scale against cumulative alveolar tidal volume following a step increase in F_IO_2. Although the breaths are not all the same size, they fall on the same line following a change in F_IO_2 since the actual effective alveolar ventilation is measured on a breath-by-breath basis. Note that the slope of the line is related to functional residual capacity volume, with steeper slopes indicating smaller volumes.

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 nonuniform 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, but it is possible to choose fewer or more than three lung compartments. 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 (Figure 4.3). 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:

$$\hat{F}_A N_{2C[n]} = \hat{F}_A N_{2C[n-1]} \times W, \qquad [4.1]$$

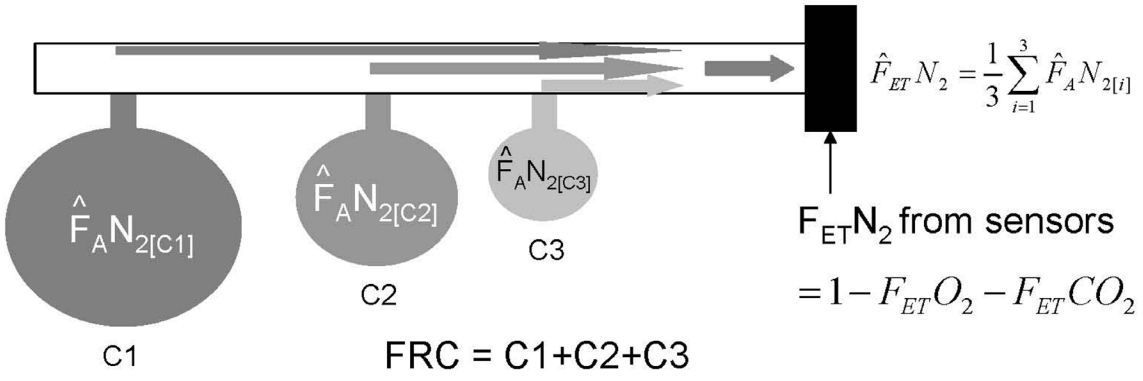

Figure 4.3: The functional residual capacity was modeled as three lung compartments. The modeled change in the nitrogen fraction in the compartments during the washout period was compared to the washout signal measured by the sensors.

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:

$$W = \frac{V_{Comp}}{\left(VT_C + V_{Comp}\right)}, \qquad [4.2]$$

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:

$$VT_C = \frac{1}{3} \times \left(VT_I - VD_{aw} - VD_{app}\right). \qquad [4.3]$$

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 deadspace 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 modeled lung compartments were averaged to produce a single, modeled end-tidal nitrogen fraction estimate for all the breaths in the washout period:

$$\hat{F}_{ET}N_{2\mu[n]} = \frac{1}{3}\sum_{j=1}^{3} F_A N_2(0) \prod_{i=1}^{n} \left(\frac{V_{Comp_j}}{V_{C[i]} + V_{Comp_j}} \right), n = 1,2,...m, \quad [4.4]$$

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 three 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).

4.3.1.2 Determination of FRC by the multiple compartment model. 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:

$$FRC = \sum_{j=1}^{3} V_{Comp_j} \quad [4.5]$$

It should be noted this calculation ignored the storage of N_2 from the tissues. The effect of N_2 storage on the FRC measurement should be small (less than 100 ml)[17].

4.3.1.3 Correction for shallow breaths. For very shallow breaths that do not clear the airway deadspace, 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 deadspace. The alveolar ventilation recorded from a disregarded, small breath ($VT_{C[i]}$) was added to the measured ventilation of the subsequent breath ($VT_{C[i+1]}$) to maintain an accurate record of cumulative alveolar ventilation.

4.3.2 Accuracy and Precision Testing

4.3.2.1 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. Subjects were seated upright throughout the study period. For each subject, a set of nitrogen washout 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.

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}. One-way valves were used to prevent rebreathing. First,

the F_IO_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 five min was allowed for nitrogen washout, the inspired oxygen fraction was increased to 1.0. Again, the washout was continued for five 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 standard deviation of $F_{ET}N_2$ from five successive breaths of less than 0.05.

4.3.2.2 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.

4.3.2.3 Statistical analysis. Data are presented as mean values ± standard deviation (SD) if not otherwise stated. The modified nitrogen washout 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).

4.3.3 Repeatability Testing

4.3.3.1 Device description. Figure 4.4 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 analyzer (modified $NICO_2$, Philips-Respironics, Wallingford, CT, USA). The response time ($T_{10\text{-}90}$) of the mainstream oxygen sensor to a step change of O_2 concentration was 220 ms.

4.3.3.2 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. 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.

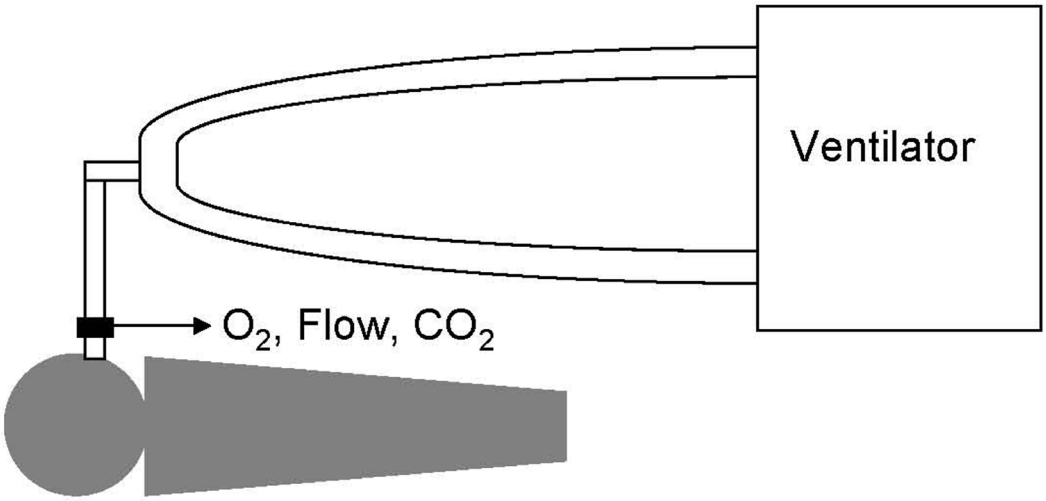

Figure 4.4: The device setup for the repeatability study. The setup comprised sensors of flow, O_2, and CO_2 and a mechanical ventilator.

Five of the enrolled patients were treated with pressure control ventilation, and the other 15 were treated with pressure support 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 were taken by increasing the F_IO_2 from the clinically determined, set baseline to 1.0 for 5 min and then returning the F_IO_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 approximately 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 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. Modified multiple breath nitrogen washout FRC measurement was calculated with the same multiple compartment method used for the accuracy testing.

4.3.3.3 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 standard deviation of the differences and the coefficient of repeatability (2 x SD of the differences) were calculated. Descriptive statistics were performed for repeated measures

using linear regression and Bland-Altman analyses. A probability value of <0.05 was considered as significant.

4.4 Results

4.4.1 Accuracy and Precision

Eleven males and nine females participated in the study. Mean age of the subjects was 31 ± 11.5 years. Mean height was 174 ± 10.6 cm. Mean weight was 71 ± 12.1 kg. FRC measured by body plethysmography was 3.55 ± 0.87 L with range 2.3 L to 5.6 L.

Figure 4.5 shows the Bland-Altman analysis of agreement between the modified multiple breath nitrogen washout and body plethysmography FRC. The bias (N_2-body plethysmography) was -0.004 with precision (1 SD of the error) of 0.209 L (-0.1 ± 5.9% of body plethysmography) and 95% limits of agreement of -0.41 to 0.41 L (-11.7 to 11.5 % of body plethysmography).

4.4.2 Repeatability

Mean measured nitrogen washout FRC was 2.4 ± 0.7 L (range 1.18 to 3.63 L). Mean age was 57 ± 17. Mean weight was 87 ± 28 kg. Mean set baseline F_IO_2 was 0.41 ± 0.09.

Figure 4.6 shows the mean difference between repeated measurements was 0.009 ± 0.15 L (0.4 ± 6.4 %) and the 95% limits of agreement were between -0.29 and 0.31 L (-12.1 to 12.8%). The coefficient of repeatability was 0.31 L (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), $y = 0.99x + 0.01$ (Figure 4.7). Mean absolute difference between duplicate measurements was 0.12 L (5.0%).

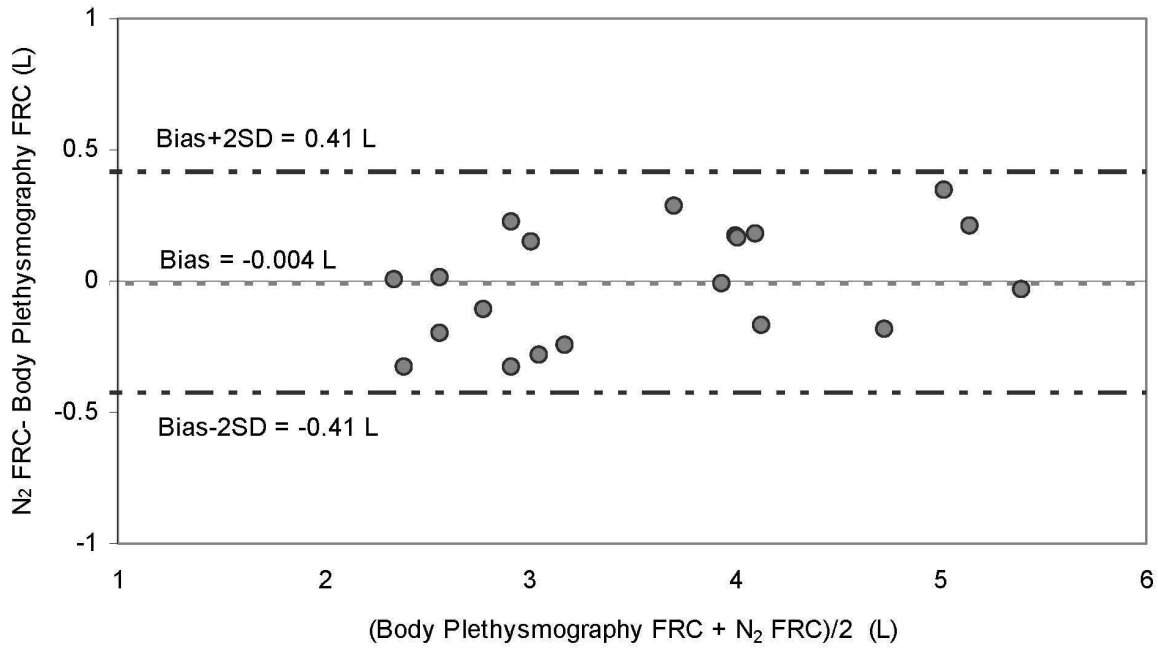

Figure 4.5: Bland-Altman plot comparing agreement between functional residual capacity by modified multiple breath nitrogen washout and body plethysmography. The black line indicates mean bias, and the dashed lines mark the 95% limits of agreement.

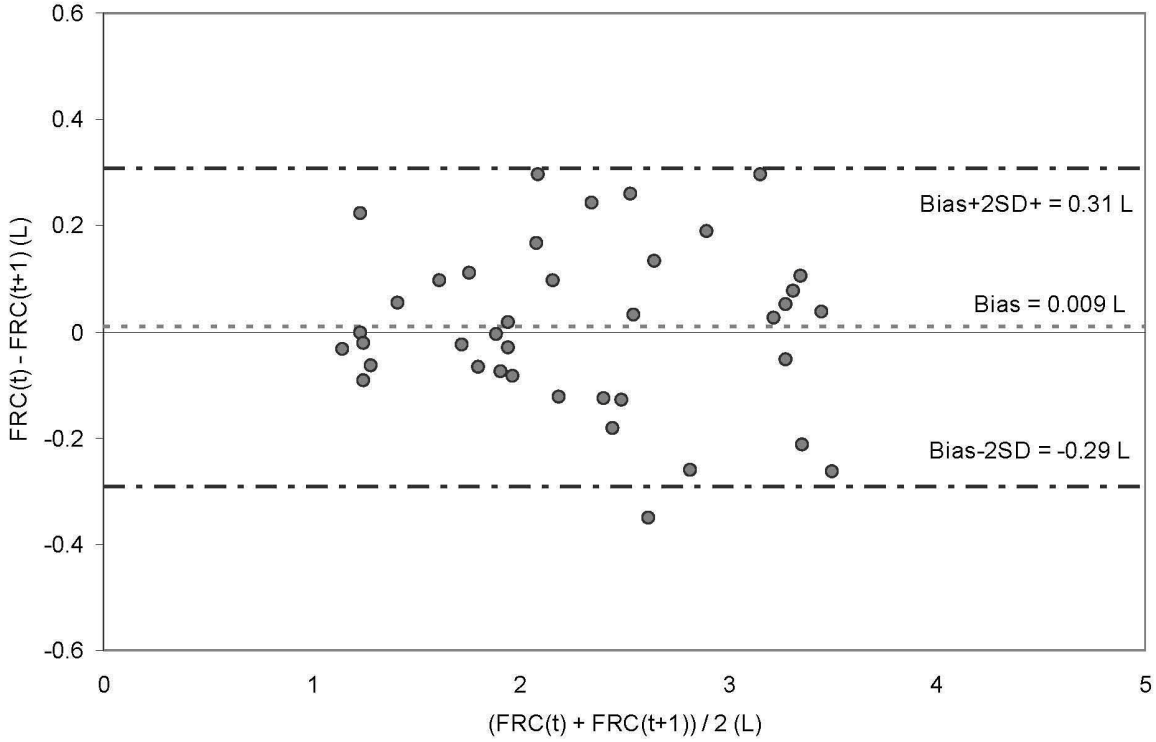

Figure 4.6: Bland-Altman plot comparing differences between the repeated modified multiple breath nitrogen washout functional residual capacity measurements. The black line indicates mean bias, and the dashed lines mark the 95% limits of agreement.

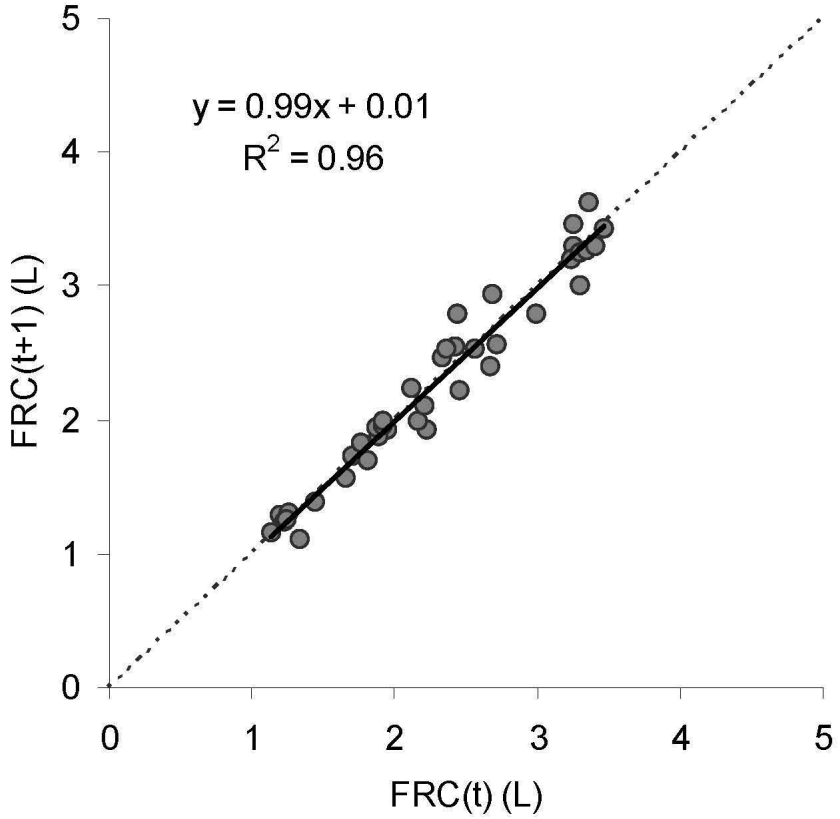

Figure 4.7: Linear regression analysis of the first and second modified multiple breath nitrogen washout functional residual capacity measurements.

4.5 Discussion

This study of a novel multiple breath nitrogen washout method for functional residual capacity measurement demonstrated accuracy of -0.004 L (-0.1% of body plethysmography), precision of 0.209 L (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 favorably 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[8 10]. 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 controlled mechanical ventilation; accuracy was between 1-3% and precision was between 4-6% of the reference volume, depending on the F_IO_2 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 to results (SD of the error = 6.5%) obtained using a mass spectrometer[14] and a system evaluation with 250 measurements in 36 patients (SD of the error = 6.5%)[13]. Olegard and coworkers[7] reported 1 SD of the error of 0.178 L during CMV, which is slightly higher than the 0.15 L (6.4%) SD of the error we observed with our system. The data analyzed in our study included patient-triggered ventilation via 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 respiratory rate was 26 ± 7.0 br min^{-1}; the coefficient of variation in tidal volume was 0.21 ± 0.07 and in respiratory rate was 0.16 ± 0.08. The good repeatability we observed even during highly variable ventilation patterns indicates 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 work published by Hashimoto and colleagues, who used an electrical analog model of the lung to describe gas distribution in six compartments[21]. By manually altering potentiometers, he adjusted the modeled $F_{ET}N_2$ 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

center 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 VN_2 or VO_2 as other methods do, for example by estimation of VO_2 from measured VCO_2 and an assumed respiratory quotient (RQ). The change in gas viscosity during the washout maneuver is not an applicable issue since measurements of VO_2 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 analyzer eliminated the need for corrections required by other systems due to sampling delay, response, or synchronization errors[22]. 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[14], which is an unavoidable error for any system.

Like Olegard's system[7], 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 assumptions are necessary for end-tidal gas measurement use. Unlike the Olegard system, an assumed RQ is not required by our method to allow F_IO_2 to increase up to 1.0. Assumptions made by other systems related to fixed RQ, ventilation volumes, and respiratory rates 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[7 13 23-25].

One advantage of the method evaluated here is that VT_{alv} did not need to be estimated from average values of VCO_2, which varies with tidal volume size and contributes to error. Instead, VT_{alv} was directly measured by the mainstream, integrated CO_2 and flow sensor of the $NICO_2$ 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 $F_{ET}N_2$-based system presented here does not require specific mechanical ventilator settings, a particular ventilator brand, patient cooperation or manual intervention to measure FRC. A $F_{ET}N_2$-based washout monitor could be both independent from and compatible with any ventilator that can make step changes in F_IO_2 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 F_IO_2 was adjusted manually. The system is currently designed to recognize a manual step change in F_IO_2 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 F_IO_2 is the possibility of absorption atelectasis. In the repeatability testing protocol, the F_IO_2 was always turned from baseline up to 1.0, regardless of the starting point for F_IO_2, in order to simplify protocol execution. We assumed 5 min was not enough time for atelectasis to form, as absorption atelectasis has been shown to develop after approximately 45 min at F_IO_2 of 1.0[26]. However, with an automated system, it could be possible to standardize a smaller step size and limit exposure to extremely high F_IO_2.

It would be valuable in future testing to analyze the accuracy with smaller step changes in F_IO_2, especially for patients who require high baseline F_IO_2 for arterial oxygenation. The accuracy and precision study was performed with F_IO_2 steps sizes of 0.2 and 0.5, and both step sizes provided accurate FRC measurements. It is likely 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[7 13], we expect a smaller F_IO_2 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. 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.

An important subject for future research is to analyze the accuracy compared to 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 (VQ) configuration affect the measurement. The $F_{ET}N_2$-based method applies the same assumption of constant nonhomogeneity 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 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 [27-28], during weaning [23] and with application of positive end-expiratory pressure[29]. 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 $F_{ET}N_2$-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 to volume-based systems recently evaluated in similar settings. The robust performance of the novel technique during ventilation with changing breath patterns suggests further study of the $F_{ET}N_2$-based nitrogen washout FRC measurement technique is needed.

4.6 References

1. Rylander C, Hogman M, Perchiazzi G, Magnusson A, Hedenstierna G. Functional residual capacity and respiratory mechanics as indicators of aeration and collapse in experimental lung injury. *Anesth Analg* 2004; 98: 782-9

2. Hedenstierna G: The recording of FRC--is it of importance and can it be made simple? *Intensive Care Med* 1993; 19: 365-6

3. Dubois AB, Botelho SY, Bedell GN, Marshall R, Comroe JH Jr. A rapid plethysmographic method for measuring thoracic gas volume: a comparison with a nitrogen washout method for measuring functional residual capacity in normal subjects. *J Clin Invest* 1956; 35: 322-6

4. East TD, Wortelboer PJ, van Ark E, Bloem FH, Peng L, Pace NL, et al. Automated sulfur hexafluoride washout functional residual capacity measurement system for any mode of mechanical ventilation as well as spontaneous respiration. *Crit Care Med* 199; 18: 84-91

5. Patroniti N, Bellani G, Manfio A, Maggioni E, Giuffrida A, Foti G, et al. Lung volume in mechanically ventilated patients: measurement by simplified helium dilution compared to quantitative CT scan. *Intensive Care Med* 2004; 30: 282-9

6. Di Marco F, Rota Sperti L, Milan B, Stucchi R, Centanni S, Brochard L, et al. Measurement of functional residual capacity by helium dilution during partial support ventilation: in vitro accuracy and in vivo precision of the method. *Intensive Care Med* 2007; 33: 2109-15

7. Olegard C, Sondergaard S, Houltz E, Lundin S, Stenqvist O. Estimation of functional residual capacity at the bedside using standard monitoring equipment: a modified nitrogen washout/washin technique requiring a small change of the inspired oxygen fraction. *Anesth Analg* 2005; 101: 206-12

8. Heinze H, Schaaf B, Grefer J, Klotz K, Eichler W. The accuracy of the oxygen washout technique for functional residual capacity assessment during spontaneous breathing. *Anesth Analg* 2007; 104: 598-604

9. Heinze H, Sedemund-Adib B, Heringlake M, Gosch UW, Gehring H, Eichler W. The Impact of Different Step Changes of Inspiratory Fraction of Oxygen on Functional Residual Capacity Measurements Using the Oxygen Washout Technique in Ventilated Patients. *Anesth Analg* 2008; 106: 1491-4

10. Maisch S, Boehm SH, Weismann D, Reissmann H, Beckmann M, Fuellekrug B, et al. Determination of functional residual capacity by oxygen washin-washout: a validation study. *Intensive Care Med* 2007; 33: 912-6

11. Chiumello D, Cressoni M, Chierichetti M, Tallarini F, Botticelli M, Berto V, et al. Nitrogen washout/washin, helium dilution and computed tomography in the assessment of end expiratory lung volume. *Critical Care* 2008; 12: R150

12. Weismann D, Reissmann H, Maisch S, Füllekrug B, Schulte J. Monitoring of functional residual capacity by an oxygen washin/washout; technical description and evaluation. *J Clin Monit Comput* 2006; 20: 251-60

13. Patroniti N, Saini M, Zanella A, Weismann D, Isgrò S, Bellani G, et al. Measurement of end-expiratory lung volume by oxygen washin-washout in controlled and assisted mechanically ventilated patients. *Intensive Care Med* 2008; 34: 2235-40

14. Zinserling J, Wrigge H, Varelmann D, Hering R, Putensen C. Measurement of functional residual capacity by nitrogen washout during partial ventilatory support. *Intensive Care Med* 2003; 29: 720-6

15. Heinze H, Eichler W. Measurements of functional residual capacity during intensive care treatment: the technical aspects and its possible clinical applications. *Acta Anaesthesiol Scand* 2009; 53: 1121-30

16. Esteban A., Anzueto A., Alía I, Gordo F., Apezteguía C., Pálizas F, et al. How is Mechanical Ventilation Employed in the Intensive Care Unit? *Am. J. Respir. Crit. Care Med* 2000; 161: 1450-8

17. Cournand A, Yarmouth I, Riley R. Influence of body size on gaseous nitrogen elimination during high oxygen breathing. *Proc Soc Exp Biol* 1941; 48: 280-4

18. Mead, J. Volume displacement body plethysmograph for respiratory measurements in human subjects. *J Appl Physiol* 1960; 15: 736-40

19. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardization of the measurement of lung volumes. *Eur Respir J* 2005; 26: 511-22

20. Blonshine S, Foss C, Mottram C, Ruppel G, Wanger J. AARC clinical practice guideline: Body plethysmography: 2001 revision and update. *Respir Care* 2001; 46: 506-13

21. Hashimoto T, Young AC, Martin CJ. Compartmental analysis of the distribution of gas in the lungs. *J Appl Physiol* 1967; 23: 203-9

22. Wrigge H, Sydow M, Zinserling J, Neumann P, Hinz J, Burchardi H, et al. Determination of functional residual capacity (FRC) by multibreath nitrogen washout in a lung model and in mechanically ventilated patients. Accuracy depends on continuous dynamic compensation for changes of gas sampling delay time. *Intensive Care Med* 1998; 24: 487-93

23. Heinze H, Sedemund-Adib B, Heringlake M, Meier T, Eichler W. Changes in functional residual capacity during weaning from mechanical ventilation: a pilot study. *Anesth Analg* 2009; 108: 911-5

24. Branson RD, Johannigman JA. Innovations in mechanical ventilation. *Respir Care* 2009; 54: 933-47

25. Choncholas G, Sondergaard S, Heinonen E. Validation and clinical application of a first order step response equation for nitrogen clearance during FRC measurement. *J Clin Monit Comput* 2008; 22: 1-9

26. Joyce CJ, Williams AB: Kinetics of absorption atelectasis during anesthesia: a mathematical model. *J Appl Physiol* 1999; 86: 1116-25

27. Lindgren S, Odenstedt H, Olegård C, Söndergaard S, Lundin S, Stenqvist O. Regional lung derecruitment after endotracheal suction during volume- or pressure-controlled ventilation: a study using electric impedance tomography. *Intensive Care Med* 2007; 33: 172-80

28. Heinze H, Sedemund-Adib B, Heringlake M, Gosch UW, Eichler W. Functional residual capacity changes after different endotracheal suctioning methods. *Anesth Analg* 2008; 107: 941-4

29. Bikker IG, van Bommel J, Reis Miranda D, Bakker J, Gommers D. End-expiratory lung volume during mechanical ventilation: a comparison with reference values and the effect of positive end-expiratory pressure in intensive care unit patients with different lung conditions. *Crit Care* 2008; 12: R145

CHAPTER 5

CLINICAL TESTING OF CARBON DIOXIDE SYSTEM

5.1 Abstract

5.1.1 Objective

There is a need for an automated bedside functional residual capacity (FRC) measurement method that does not require a step change in inspired oxygen fraction. Such a method can be used for patients who require a high inspired oxygen fraction to maintain arterial oxygenation and for patients ventilated using a circle breathing system commonly found in operating rooms, which is not capable of step changes in oxygen. We developed a CO_2 rebreathing method for FRC measurement that is based on the change in partial pressure of end-tidal carbon dioxide ($PetCO_2$) and volume of CO_2 eliminated (VCO_2) at the end of a partial rebreathing period. This study was designed to assess the accuracy and precision of the proposed FRC measurement system compared to body plethysmography and nitrogen washout FRC.

5.1.2 Methods

Accuracy and precision of measurements were assessed by comparing the CO_2 rebreathing FRC values to the gold standard, body plethysmography FRC, in 20 spontaneously breathing volunteers. The CO_2 rebreathing FRC measurements were then compared to nitrogen washout FRC in 20 intensive care patients whose lungs were

mechanically ventilated. For each subject, an average value of CO_2 rebreathing FRC was compared to the average gold standard method. Measurements were accepted for statistical analysis if they had been recorded from periods of stable tidal ventilation, defined as a coefficient of variation of tidal volume of less than 0.13.

5.1.3 Results

Compared to body plethysmography, the accuracy (average error) for the CO_2 rebreathing method during stable ventilation (n=8) was 0.03 L and precision (1 standard deviation of the error) was 0.29 L (0.8 ± 7.6% of body plethysmography). During stable mechanical ventilation (n=9), the accuracy was -0.02 L and precision was 0.26 L (-1.1% ± 12.6% of nitrogen washout).

5.1.4 Conclusions

The CO_2 rebreathing method for FRC measurement provides acceptable accuracy and precision during stable ventilation compared to the gold standards of body plethysmography and nitrogen washout. The results based on periods of stable ventilation best approximate the performance of the system in the likely areas of application during controlled mechanical ventilation. Further study of the CO_2 rebreathing method is needed to evaluate accuracy in a larger group of controlled mechanical ventilation patients, including patients with respiratory insufficiency and significant lung injury.

5.2 Introduction

Measurement of functional residual capacity (FRC) in intubated and mechanically ventilated patients has been proposed to optimize positive end-expiratory pressure (PEEP), assess efficacy of recruitment maneuvers and prone positioning on lung

volumes, evaluate if endotracheal suctioning has adverse consequences, and identify alveolar derecruitment without changes in mechanical ventilator settings 1-5]. FRC measurements can provide information on the amount of recruited alveolar lung tissue involved in gas exchange and the level of stress and strain the lungs are subjected to[6-9].

Several reliable methods have been developed for FRC measurement. Body Plethysmography is a gold standard for ambulatory patients, but is not suitable for use during mechanical ventilation [10]. Sulfur hexafluoride (SF_6) washout, while highly accurate, has been primarily limited to research settings since it is not approved for clinical use [11]. Nitrogen (N_2) washout is accurate and can be used at the bedside during mechanical ventilation [12]. However, the N_2 washout method requires a minimum 10% change in inspired oxygen within one breath, which is not possible with the widely used circle breathing systems during anesthesia. For intensive care patients receiving a high level of inspired oxygen fraction, it may be unacceptable to initiate a step change in inspired oxygen fraction for a FRC measurement.

We describe here a method of FRC measurement for use in intensive care and operating room patients at any level of inspired oxygen fraction using a 35-second period of partial CO_2 rebreathing. The single-breath transition from the steady state CO_2 rebreathing phase to the first breath of non-rebreathing is used to determine the FRC, which is calculated as the ratio of the change in excreted CO_2 to the change in the end-tidal CO_2 over the single breath transition.

Our goal is to test the accuracy of CO_2 rebreathing FRC measurements compared to body plethysmography and N_2 washout FRC in healthy volunteers and mechanically ventilated intensive care patients during periods of stable ventilation.

5.3 Methods

5.3.1 Device Description

Figure 5.1 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). The integrated $NICO_2$ sensor recorded parameters including end-tidal carbon dioxide ($P_{et}CO_2$), tidal volume (V_T), excreted carbon dioxide (VCO_2) and airway dead space (VD_{aw}) for each breath. Oxygen was measured using a sidestream paramagnetic O_2 analyzer (Capnomac, Datex, Helsinki, Finland). The response times (T10-90) 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.

5.3.1.1 FRC evaluation by the CO_2 rebreathing method. FRC measurements from the CO_2 washout method were made using the $NICO_2$ partial rebreathing cardiac output monitor. The monitor automatically actuates a pneumatic valve that is synched with the breaths to commence partial CO_2 rebreathing (typically 40-60%) once every 3 min. The rebreathing period lasts 35 seconds and is used to measure pulmonary capillary blood flow (PCBF) and cardiac output [13,14]. 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 excreted CO_2 are recorded. Figure 5.2 illustrates a typical CO_2 partial rebreathing measurement signal.

The change in CO_2 concentration within the FRC during the transition from one breath to the next can be written as:

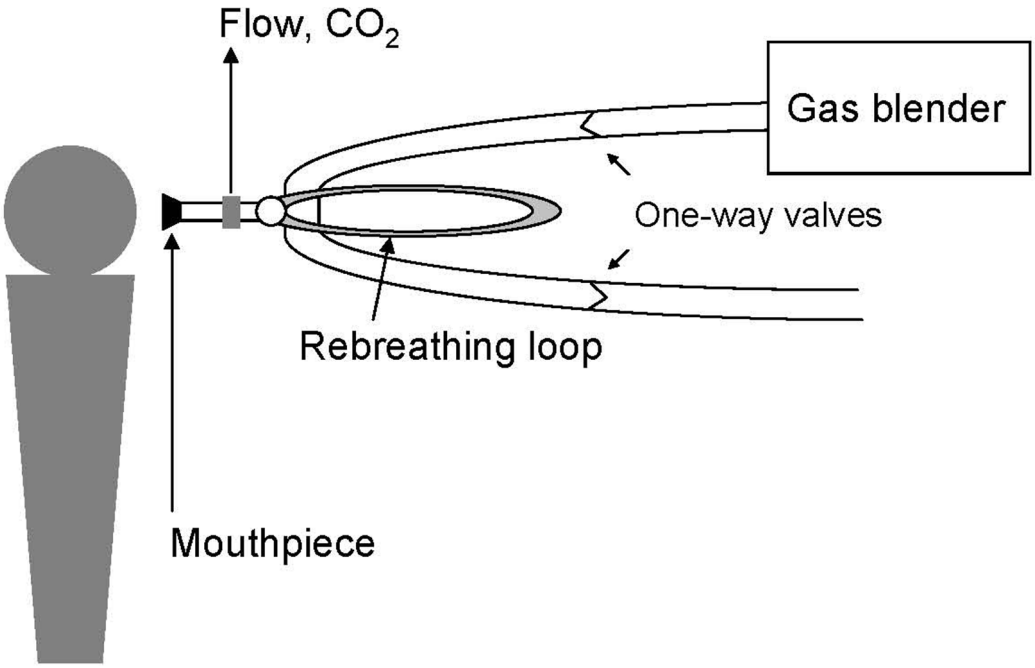

Figure 5.1: The device setup for the accuracy and precision study. The setup comprised a mouthpiece, sensors of flow and CO_2, a rebreathing loop, a blender to provide specific gas mixtures at 50 L min-1, and one-way valves to prevent rebreathing.

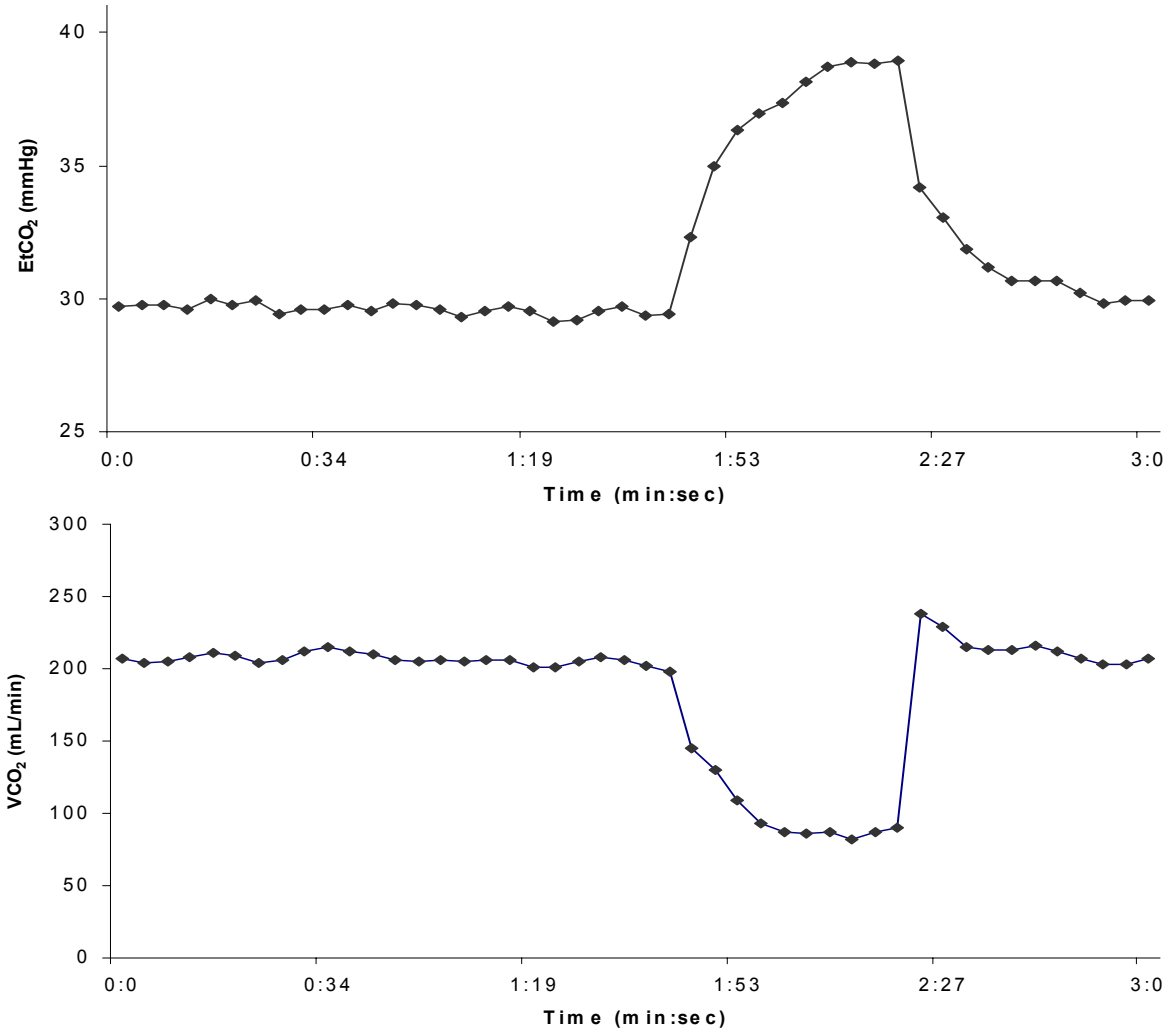

Figure 5.2: Example rebreathing signals. Changes in $PetCO_2$ (above) and corresponding changes in VCO_2 (below) with rebreathing during a 3-minute measurement period.

$$V_{FRC*} \times F_{ET}CO_{2(i)} + \dot{V}_{PCBF} \times t \times cCO_{2(i)} =$$
$$V_{FRC*} \times F_{ET}CO_{2(i+1)} + \dot{V}_{PCBF} \times t \times cCO_{2(i+1)} + V_D CO_2 - V_E CO_2,$$

where V_{FRC*} represents the functional residual capacity, $F_{ET}CO_{2(i)}$ is the fraction of end-tidal CO_2 in the current breath "i", $F_{ET}CO_{2(i+1)}$ is the fraction of end-tidal CO_2 in the next breath "i+1", V_{PCBF} is the pulmonary capillary blood flow measured by the $NICO_2$ rebreathing monitor, t is the time period of the analyzed breath, cCO_2 is the content of CO_2 of the pulmonary capillary blood flow, and V_DCO_2 and V_ECO_2 are the rate of CO_2 excreted from the patient measured by the integrated $NICO_2$ sensor during rebreathing and for the first breath after rebreathing has ended, respectively.

As it is also assumed for the cardiac out and pulmonary capillary blood flow measurements of $NICO_2$ cardiac output monitor, it is assumed that the CO_2 excretion rate has reached a steady state during rebreathing such that the CO_2 excretion rate is equal to the rate of CO_2 elimination from the blood to the FRC. The equation describes 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.

The CO_2 rebreathing FRC equation can be simplified to:

$$V_{FRC*} = \frac{\Delta VCO_2}{\Delta F_{ET}CO_2} - \frac{\dot{V}_{PCBF} \times t \times \Delta cCO_2}{\Delta F_{ET}CO_2},$$

where

$$\Delta cCO_2 = \Delta P_{ET}CO_2 \times S\,.$$

The change in cCO_2 can be approximated as a change in the partial pressure of end-tidal CO_2 ($P_{ET}CO_2$) multiplied by the slope (S) of the CO_2 dissociation curve (CO_2 volume versus partial pressure curve)[15].

Although the equation above accounts for the CO_2 stores in blood, the calculation for FRC overestimates the volume of FRC due to the effect of the CO_2 stores in lung tissue. A factor of 0.55 can be applied to adjust for both the blood and lung tissue stores of CO_2[16]. Since blood stores have already been accounted for, the factor (0.28) required to correct for the tissue stores alone is smaller:

$$V_{FRC} = (1 - 0.28) \times V_{FRC^*}.$$

5.3.2 Accuracy and Precision Compared to Body Plethysmography

5.3.2.1 Protocol. Twenty 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.

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, Respironics, 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 six rebreathing measurements was initiated by the $NICO_2$ monitor, which included 35 seconds of partial rebreathing every 3 min. Breath-by-breath measurements from the oxygen, carbon dioxide and flow sensors were recorded to a laptop computer.

Since the FRC measurement is based on a transition recorded during a single breath and because FRC itself can be variable during ventilation with highly variable tidal volume, a requirement for accurate FRC analysis by this method is stable ventilation volume. A measurement recorded during stable ventilation was defined as one with a coefficient of variation of tidal volume from five successive breaths of less than 0.13. Upon analysis of the recorded data, individual measurements were categorized as containing either stable or unstable ventilation volume. Individual measurements containing unstable ventilation volume were eliminated from further analysis. The FRC for each subject was calculated as the average of the first four individual measurements containing stable ventilation volume. Subjects for whom four stable individual measurements were not obtained were not included in the statistical analysis.

5.3.2.2 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 [17]. Three measurements of FRC within 5% of each other were obtained [18, 19]. The mean of the individual measurements was recorded as the reference FRC for each volunteer.

5.3.2.3 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). The Bland-Altman statistics were calculated using a mean of four individual CO_2 rebreathing FRC measurements for each subject. The within subject standard deviation of each measurement was verified to be constant and unrelated to the magnitude. Linear regression analysis was also performed.

5.3.3 Accuracy during Mechanical Ventilation Compared to N_2 Washout

5.3.3.1 Device description. Carbon dioxide and flow were measured in the same way as in the body plethysmography 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). A mainstream photoluminescence analyzer (modified $NICO_2$, Philips-Respironics, Wallingford, CT, USA) was used to monitor end-tidal oxygen partial pressure. The response time (T10-90) 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: $F_{ET}N_2 = 1 - F_{ET}O_2 - F_{ET}CO_2$.

5.3.3.2 Protocol. In compliance with the IRB-approved study protocol, 20 ICU patients (12 women, 8 men) whose lungs were intubated and mechanically ventilated were enrolled in the FRC measurement study after consent was obtained from their authorized representative. 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 vasoactive medications; 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 (15 with pressure support mode and 5 with pressure control mode) according to the recommendations of the clinical team and the ventilator settings were not altered for the study. The subjects' level of sedation was not altered in any way for the study, nor was neuromuscular blockade administered for ventilatory pattern management. 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. 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 activated $NICO_2$ monitor initiated six automated measurements, which included 35 seconds of partial rebreathing every 3 min. Breath-by-breath measurements from the oxygen, carbon dioxide and flow sensors were recorded to a laptop computer.

A measurement recorded during stable ventilation was defined as one with a coefficient of variation of tidal volume from five successive breaths of less than 0.10. Upon analysis of the recorded data, individual measurements were categorized as containing either stable or unstable ventilation volume. Individual measurements containing unstable ventilation volume were eliminated from further analysis. The FRC for each subject was calculated as the average of the first four individual measurements containing stable ventilation volume. Subjects for whom four stable individual measurements were not obtained were not included in the statistical analysis.

5.3.3.3 FRC evaluation by nitrogen washout. Reference FRC measurements were initiated by increasing the F_IO_2 from the clinically determined, set baseline to 1.0 for 5 min and then returning the F_IO_2 setting to the set baseline level for 5 min. The average FRC from the two resulting nitrogen curves (1 wash-in and 1 washout) was taken as one measurement. Reference nitrogen washout FRC measurements were calculated according to the equations detailed elsewhere [20].

First, two nitrogen washout measurements (2 X 1 wash-in and 1 washout) were completed. After approximately 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 standard deviation of $F_{ET}N_2$ from five successive breaths of less than 0.05.

5.3.3.4 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 Bland-Altman statistics were calculated using a mean of four individual CO_2 rebreathing FRC measurements for each patient. The within subject standard deviation of each measurement was verified to be constant and unrelated to the magnitude. Linear regression analysis was also performed.

5.4 Results

5.4.1 Accuracy and Precision Compared with Body Plethysmography

Twenty subjects were enrolled in the study. Technical difficulties in data collection resulted in two subjects not completing at least four CO_2 rebreathing FRC measurements. Of the remaining 18 subjects who completed at least four measurements, eight subjects demonstrated ventilation with stable volume (four males and four females). Mean age of the eight subjects was 30.5 ± 11.3 years. Mean height was 175 ± 13 cm. Mean weight was 68.4 ± 14.5 kg. FRC measured by body plethysmography was 3.9 ± 1.1 L with range 2.3 L to 5.4 L.

Figure 5.3 shows the Bland-Altman analysis of agreement between CO_2 rebreathing and body plethysmography FRC for the eight subjects. The bias (CO_2 - body plethysmography) was 0.03 L with precision (1 SD of the error) of 0.29 L (0.8 ± 7.6 % of body plethysmography) and 95% limits of agreement of -0.55 to 0.61 L (-14.0 to 15.7 %

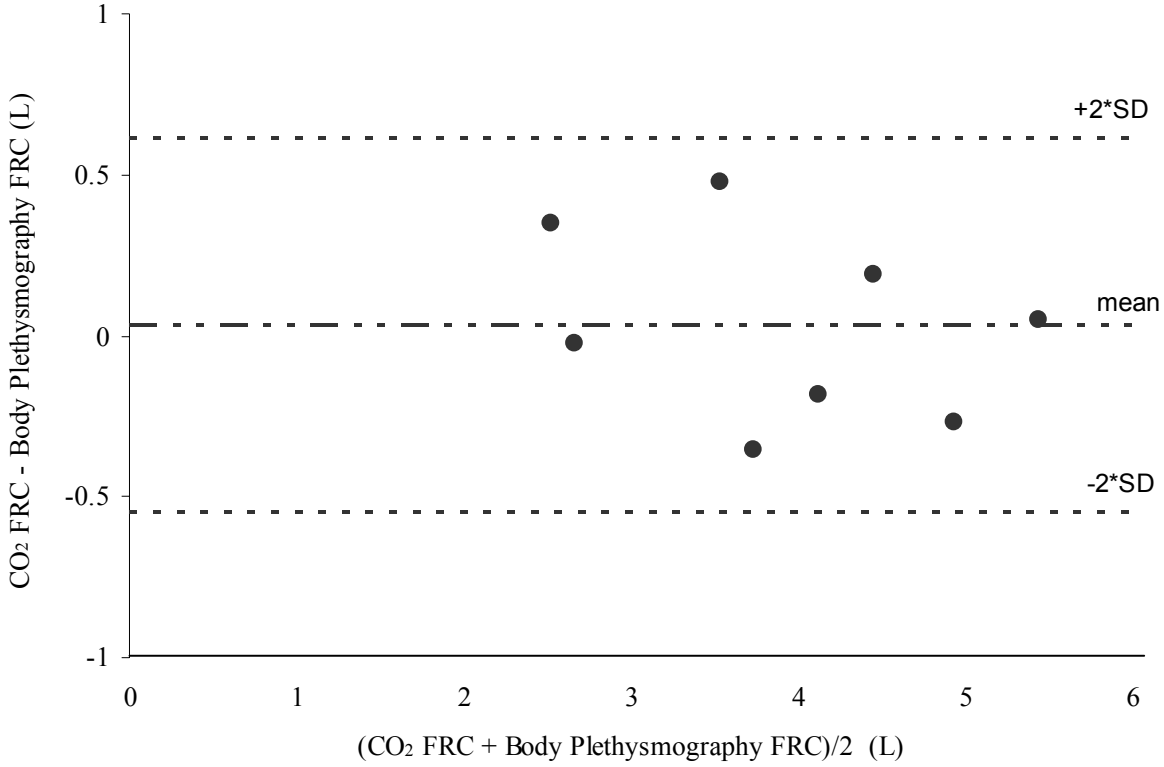

Figure 5.3: Bland-Altman plot comparing agreement between the functional residual capacity evaluated by CO_2 rebreathing and body plethysmography. The dashed line indicates mean bias, and the dotted lines mark the 95% limits of agreement.

of body plethysmography). Linear regression analysis of CO_2 and body plethysmography FRC revealed R^2 of 0.93 and slope of 0.88.

5.4.2 Accuracy during Mechanical Ventilation

Twenty subjects were enrolled in the study. Technical difficulties in data collection resulted in one subject not completing any CO_2 rebreathing FRC measurements. Five patients did not complete at least four CO_2 rebreathing FRC measurements due to interruptions caused by clinical events such as suctioning, physical therapy, bathing and treatment with nebulized medication. Of the remaining 14 subjects who completed at least four measurements, nine subjects demonstrated ventilation with stable volume (four males and five females). Mean measured nitrogen washout FRC for the nine subjects was 2.1 ± 0.66 L (range 1.4 to 3.2 L). Mean age was 56 ± 15. Mean weight was 87.6 ± 25.2 kg. Mean set baseline F_IO_2 was 0.42 ± 0.05.

The Bland-Altman plot in Figure 5.4 shows the analysis of agreement between the CO_2 FRC measurements and the reference method, nitrogen washout FRC, in nine mechanically ventilated ICU patients. The bias (CO_2 - N_2 washout) was -0.02 L with precision (1 SD of the error) of 0.26 L (-1.1 ± 12.6 % of N_2 washout) and 95% limits of agreement of -0.54 to 0.49 L (-27.7 to 23.6 % of N_2 washout). Linear regression analysis of CO_2 and N_2 washout FRC revealed R^2 of 0.86 and slope of 0.74.

5.5 Discussion

The CO_2 rebreathing FRC measurement system showed clinically acceptable accuracy (mean error) and precision (1 SD of the error) compared to both body plethysmography FRC in healthy volunteers (accuracy 0.03 L, precision 0.29 L (0.8 ± 7.6

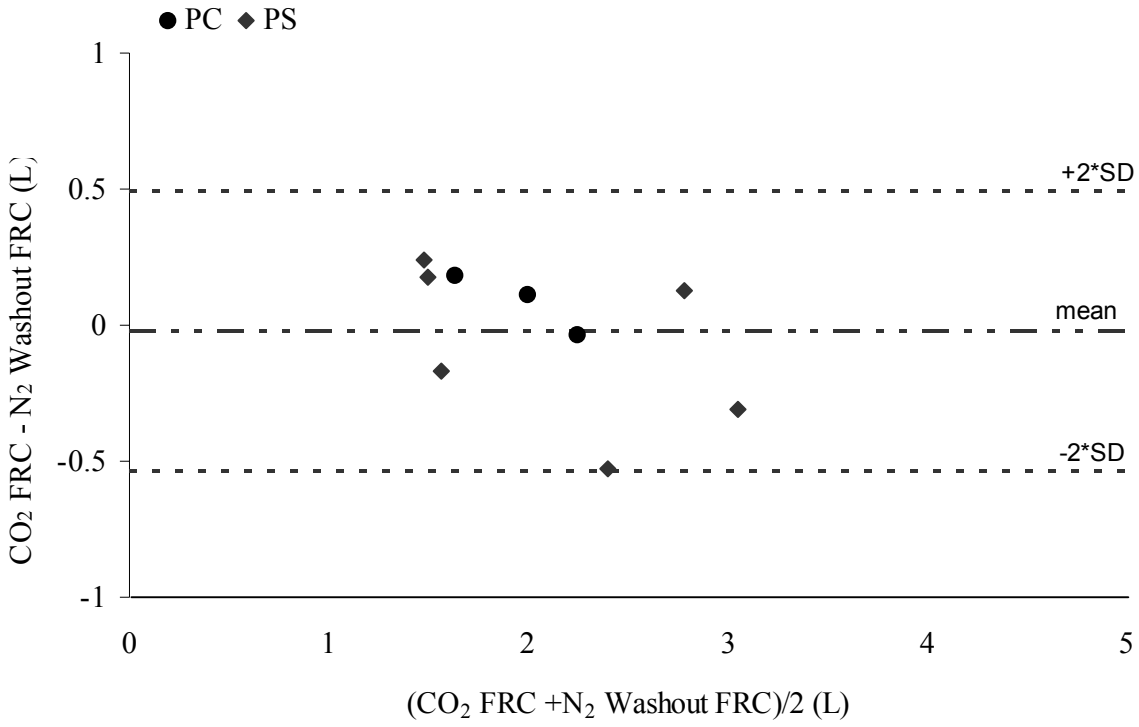

Figure 5.4: Bland-Altman plot comparing agreement between the functional residual capacity evaluated by CO_2 rebreathing and nitrogen washout. The dashed line indicates mean bias, and the dotted lines mark the 95% limits of agreement. PC was pressure control mechanical ventilation; PS was pressure support mechanical ventilation.

%)) and nitrogen washout FRC in intensive care patients (accuracy -0.02 L, precision 0.26 L (-1.1 ± 12.6 %)) with stable ventilation.

In comparison, the GE nitrogen washout FRC method, which is currently marketed as an add-on for the GE CareStation ventilators, has been reported to have accuracy (mean bias) of 15% and one standard deviation of the error of 18% compared to CT in mechanically ventilated patients under controlled mechanical ventilation [21]. Compared to body plethysmography, the LUFU system described by Heinze and colleagues showed a bias of 2.6% and one standard deviation of the error of 13.1% [22]. For mechanically ventilated patients under controlled mechanical ventilation, the mean bias was -1.3% and one standard deviation of the error was 8.5% compared to Helium dilution [23]. Repeatability for the LUFU system showed a bias of 1.1% and one standard deviation of 10.8% in volunteers [24].

The automated bedside FRC measurement system is based on the CO_2 washout signals obtained at the end of a partial CO_2 rebreathing period. Gedeon and colleagues first proposed a CO_2-based method for measuring FRC and cardiac output, implemented by using a short breath hold to perturb the gas exchange conditions in the lung [25]. The $NICO_2$ cardiopulmonary monitor (Philips-Respironics, Wallingford, CT) was developed to apply the same (Fick) principle for cardiac output measurement during mechanical ventilation. In contrast to the breath hold proposed by Gedeon, however, the $NICO_2$ automated cardiac output measurement employs a 35-second partial CO_2 rebreathing period to perturb the gas exchange conditions. The $NICO_2$ monitor does not currently perform FRC measurement. Our data support Gedeon's suggestion that it is possible to also measure FRC by exploiting a perturbation in gas exchange, which in this case is the

end of the partial rebreathing period. It may be possible for a single, non-invasive rebreathing method to automatically and continually quantify both cardiac output and FRC at the bedside during mechanical ventilation. Furthermore, the simultaneous cardiac output assessment can be used in the equations to improve accuracy in calculating FRC, as they were in this study.

The CO_2 rebreathing FRC measurement can be readily performed at any level of inspired fraction of oxygen (F_IO_2), and since it does not require a step change in F_IO_2 for measurement completion, it can be used for patients with high baseline F_IO_2 and for patients ventilated using a circle system where a step change in F_IO_2 is impossible. There may also be clinical value in knowledge of how the FRC has changed over a long period of time, such as hours or days; an automated monitor could provide averaged trending information. Of course, further studies are needed to establish the clinical utility of FRC measurement trends.

The CO_2 rebreathing method is sensitive to noise caused by instability in respiratory rate and tidal volume. A high coefficient of variation in tidal volume (i.e. greater than 15%) results in less accurate FRC measurements. CO_2 is highly soluble in lung and blood tissue, and a greater than 15% change in tidal volume from one breath to the next changes the assumption of stable CO_2 tissue solubility during the measurement period. Likewise, if the cardiac output increases or decreases more than 50% without being accounted for, the FRC will be overestimated/underestimated due to the high solubility of CO_2 in blood. Therefore, the CO_2 rebreathing method is most reliable when cardiac output and ventilation are stable, such as during controlled mechanical ventilation while hemodynamics are stable.

If the technique were automated, individual measurements could be completed until four FRC determinations with low coefficient of variation of tidal volume (< 10%) were available for inclusion in the average value. The requirement of stable tidal ventilation arises from the determination of FRC being based on a single breath of CO_2 washout. Repeating the FRC measurement until measured values are within a small range of variation is not without precedence since the AARC clinical practice guideline recommends taking multiple N_2 FRC determinations, with at least 2 trials agreeing within 10% of the mean[19]. The COV measurement threshold is a convenient method for an automated system to accomplish a similar goal.

The CO_2 rebreathing FRC method is likely best suited for patients under controlled mechanical ventilation, such as general anesthesia patients ventilated with circle breathing system or intensive care patients under controlled mechanical ventilation, both of which would likely display stable ventilation volume of < 10% COV. For this study, it was not possible to use nitrogen washout FRC as a reference with the circle breathing system (step change in oxygen is not possible), so we turned to volunteers and ICU patients for data collection. We choose to use body plethysmography and N_2 washout FRC methods as the gold standard methods for ambulatory subjects and intubated subjects, respectively. The drawback of studying patients with spontaneous or pressure controlled mechanical ventilation in place of controlled mechanical ventilation is that the tidal volume can be highly variable (typically 25-50% in this study), which increases the signal-to-noise ratio of the CO_2 FRC measurement. We aimed to analyze only the FRC measurements collected during periods of stable tidal ventilation (COV < 10%) since that would be the most similar ventilation to the areas of application of

controlled mechanical ventilation. However, analysis of the volunteer data with this threshold yielded too few points for analysis. Therefore, we were forced to increase the COV threshold for the volunteer data to COV < 13%, which yielded eight subjects for statistical analysis.

Our results were obtained from a small data set. If FRC results are analyzed from all subjects, the limits of agreement are higher, as expected due to the higher signal-to-noise ratio resulting from variable tidal volume with spontaneous ventilation. Analysis of the results for all eighteen volunteer subjects for whom four individual measurements were available, including the subjects with coefficient of variation of tidal volume of up to 0.6, resulted in accuracy (mean bias) of -0.14 L with precision (1 SD of the error) of 0.72 L (-3.9 ± 19.9 % of body plethysmography) and 95% limits of agreement of -1.55 to 1.27 L (-43.0 to 35.1 %). Analysis of the results for all 14 ICU patients for whom four individual measurements were available, including the patients with coefficient of variation of tidal volume of up to 0.4, resulted in accuracy of -0.18 L with precision of 0.69 L (-7.9 ± 29.8 % of N_2 washout) and 95% limits of agreement of -1.15 to 1.17 L (-66.3 to 50.5 %).

Further research is necessary to understand how accurate, precise, and repeatable the method is for a larger group of patients including those with lung injury and V/Q mismatch. The FRC measured by the CO_2 rebreathing method is reflective of the most accessible compartment of the ventilated lung, and as such, does not measure poorly ventilated areas where gas does not mix with each breath. Therefore, some underestimation in FRC will be due to not accounting for the poorly ventilated lung tissue, which is the area contributing the least to gas exchange. If one is interested in

measuring the poorly ventilated portion of the FRC, a 5-min nitrogen washout method may be a better choice.

In conclusion, we have shown that CO_2 rebreathing FRC can be accurately measured during stable ventilation, as assessed by comparison with body plethysmography and nitrogen washout FRC. The CO_2 rebreathing method is a good candidate for automated, long-term monitoring of trends in FRC during mechanical ventilation, even when a circle breathing system or high inspired oxygen fraction are used. Further research is needed to evaluate the accuracy compared to reference methods in a larger group of patients and during mechanical ventilation for patients with respiratory insufficiency and acute lung injury.

5.6 References

1. Bikker I, Bommel J, Reis Miranda D, Bakker J, Gommers D. End-expiratory lung volume during mechanical ventilation: a comparison with reference values and the effect of positive end-expiratory pressure in intensive care unit patients with different lung conditions. Crit Care 2008; 12:R145.

2. Dyhr T, Laursen, Larsson. Effects of lung recruitment maneuver and positive end-expiratory pressure on lung volume, respiratory mechanics and alveolar gas mixing in patients ventilated after cardiac surgery. Acta Anaesthesiol Scand 2002; 46:717-725.

3. Reutershan J, Schmitt A, Dietz K, Unertl K, Fretschner R. Alveolar recruitment during prone position: time matters. Clin Sci (Lond) 2006; 110:655-663.

4. Heinze H, Sedemund-Adib B, Gosch UW, Eichler W. Monitoring alveolar derecruitment at bedside using functional residual capacity measurements in cardiac surgery patients. Applied Cardiopulmonary Pathophysiology 2008; 12:27-32.

5. Hedenstierna G. The recording of FRC--is it of importance and can it be made simple? Intensive Care Med 1993; 19:365-366.

6. Heinze H, Eichler W. Measurements of functional residual capacity during intensive care treatment: the technical aspects and its possible clinical applications. Acta Anaesthesiol Scand 2009; 53:1121-1130.

7. Mols G, Priebe H, Guttmann J. Alveolar recruitment in acute lung injury. Br J Anaesth 2006; 96:156-166.

8. Gattinoni L, Pesenti A. The concept of "baby lung". Intensive Care Med 2005; 31:776-784.

9. Mattingley J, Holets S, Oeckler R, Stroetz R, Buck C, Hubmayr R. Sizing the lung of mechanically ventilated patients. Crit Care 2011; 15:R60.

10. DuBois AB, Botelho SY, Bedell GN, Marshall R, Julius H. Comroe J. A rapid plethysmographic method for measuring thoracic gas volume: a comparison with a nitrogen washout method for measuring functional residual capacity in normal subjects. J Clin Invest 1956; 35:322-326.

11. Jonmarker C, Jansson L, Jonson B, Larsson A, Werner O. Measurement of functional residual capacity by sulfur hexafluoride washout. Anesthesiology 1985; 63:89-95.

12. Olegard C, Sondergaard S, Houltz E, Lundin S, Stenqvist O. Estimation of functional residual capacity at the bedside using standard monitoring equipment: a modified nitrogen washout/washin technique requiring a small change of the inspired oxygen fraction. Anesth Analg 2005; 101:206-212.

13. Jaffe MB. Partial CO2 rebreathing cardiac output--operating principles of the NICO system. J Clin Monit Comput. 1999 Aug;15(6):387-401.

14. Botero M, Kirby D, Lobato EB, Staples ED, Gravenstein N. Measurement of cardiac output before and after cardiopulmonary bypass: Comparison among aortic transit-time ultrasound, thermodilution, and noninvasive partial CO2 rebreathing. J Cardiothorac Vasc Anesth. 2004 Oct;18(5):563-72.

15. Capek JM, Roy RJ. Noninvasive measurement of cardiac output using partial CO2 rebreathing.

16. Brewer LM, Haryadi DG, Orr JA. Measurement of functional residual capacity of the lung by partial CO2 rebreathing method during acute lung injury in animals. Respir Care. 2007 Nov;52(11):1480-9.

17. Mead J. Volume displacement body plethysmograph for respiratory measurements in human subjects. Journal of Applied Physiology 1960; 15:736-740.

18. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, Casaburi R, Crapo R, Enright P, van der Grinten CP et al. Standardisation of the measurement of lung volumes. Eur Respir J 2005; 26:511-522.

19. Blonshine S, Foss C, Mottram C, Ruppel G, Wanger J. AARC clinical practice guideline: body plethysmography: 2001 revision and update. Respir Care 2001; 46:506-513.

20. Brewer L, Orr, J, Sherman, M, Fulcher, E, Markewitz, B. Measurement of functional residual capacity by modified multiple breath nitrogen washout for spontaneously breathing and mechanically ventilated patients. Br J Anaesth 2011; doi: 10.1093/bja/aer220.

21. Chiumello D, Cressoni M, Chierichetti M, Tallarini F, Botticelli M, Berto V, Mietto C, Gattinoni L. Nitrogen washout/washin, helium dilution and computed tomography in the assessment of end expiratory lung volume. Crit Care 2008; 12:R150.

22. Heinze H, Schaaf B, Grefer J, Klotz K, Eichler W. The accuracy of the oxygen washout technique for functional residual capacity assessment during spontaneous breathing. Anesth Analg 2007; 104:598-604.

23. Patroniti N, Saini M, Zanella A, Weismann D, Isgrò S, Bellani G, Foti G, Pesenti A. Measurement of end-expiratory lung volume by oxygen washin-washout in controlled and assisted mechanically ventilated patients. Intensive Care Med 2008; 34:2235-2240.

24. Maisch S, Boehm S, Weismann D, Reissmann H, Beckmann M, Fuellekrug B, Meyer A, Schulte Am Esch J. Determination of functional residual capacity by oxygen washin-washout: a validation study. Intensive Care Med 2007; 33:912-916.

25. Gedeon A, Krill P, Osterlund B. Pulmonary blood flow (cardiac output) and the effective lung volume determined from a short breath hold using the differential Fick method. J Clin Monit Comput 2002; 17:313-321.

CHAPTER 6

CONCLUSIONS

6.1 Summary

This dissertation develops and tests two novel methods for automated bedside functional residual capacity (FRC) measurement. The methods were developed in parallel, with each one based on a different tracer gas: nitrogen and carbon dioxide. Feasibility testing was performed with mechanically ventilated animals. Clinical evaluation was conducted with both healthy volunteers and intensive care patients treated with mechanical ventilation.

The first method, modified multiple breath nitrogen washout, is based on a model of the lung that describes the volume-to-ventilation distribution of several compartments within the lung. The inputs for the model are the initial alveolar nitrogen concentration and breath-by-breath measurements of alveolar tidal volume. In contrast with the previously described volume-based nitrogen washout methods, this method relies on end-tidal nitrogen concentration to measure FRC. The end-tidal nitrogen concentration measurements are used to estimate alveolar nitrogen concentration. When the model parameters are tuned correctly, the modeled breath-by-breath estimates of the alveolar nitrogen concentration are a good estimate of the measured values of alveolar nitrogen concentration observed throughout a washout period. The use of end-tidal concentration measurements rather than nitrogen volume measurements makes the method reliable even

during spontaneous and assisted mechanical ventilation, during which the ventilation pattern, tidal volume, and airway pressure are often highly irregular. Using end-tidal measurements, not volume, reduces errors from signal synchronization. In contrast, volume-based FRC measurement methods are typically less precise during irregular ventilation, and have been shown to have more than twice the standard deviation of the error of the end-tidal system compared to body plethysmography. Unlike the volume-based methods, the end-tidal method can be accurately used at high inspired oxygen fraction (greater than 0.65) because it is not subject to errors introduced by Haldane transformation or assumed respiratory quotient of 0.85. Our novel, automatable, bedside method is compatible with any mechanical ventilator capable of quickly altering the inspired oxygen fraction.

In volunteer testing, we compared the modified multiple breath nitrogen washout FRC model to the gold standard body plethysmography FRC measurement system and found a mean difference of -0.1%, standard deviation of the differences of 5.9%, and 95% limits of agreement of -11.7 to 11.5% of body plethysmography. The 95% limits of agreement were improved compared to other methods tested under similar circumstances. A gold standard method was not available for accuracy testing during mechanical ventilation, so we chose to do repeatability testing in intensive care patients. The mean difference between repeated measurements was 0.4 ± 6.4% (mean ± standard deviation).

The second method proposed in this dissertation for FRC measurement makes use of carbon dioxide as the tracer gas. The carbon dioxide-based FRC measurement analyzes the single-breath transition from steady state partial rebreathing to non-rebreathing, making provisions for the high solubility of the gas in the body and the

variability in CO_2 uptake due to changes in cardiac output. The signals required for the carbon dioxide rebreathing FRC measurement can be recorded using an on-airway volumetric capnometer. In this research work, we made use of the $NICO_2$ non-invasive cardiac output monitor (Philips Medical, Wallingford, CT), which provided the breath-by-breath signals necessary for the FRC measurement and automatically initiated a 35-second partial CO_2 rebreathing period once every 3 min. The automated, portable and simple nature of the monitor provides a convenient bedside system that can take continual FRC measurements during mechanical ventilation over hours or days. Furthermore, the CO_2-based method is compatible with circle breathing systems, many anesthetic vapors, and patients ventilated with a high fraction of inspired oxygen who cannot tolerate change in inspired oxygen. Cardiac output, SpO_2, airway resistance, lung compliance, and pressure-volume loops are additional parameters simultaneously provided by the non-invasive $NICO_2$ monitor, which are useful together during titration of positive end-expiratory pressure and other mechanical ventilator settings.

In volunteer testing, we compared the CO_2 partial rebreathing FRC measurement to the gold standard body plethysmography and found a mean difference of 0.4%, standard deviation of the differences of 7.0%, and 95% limits of agreement of -13.4 to 14.2% of body plethysmography,. During mechanical ventilation for intensive care patients, the mean difference between the CO_2-based FRC and the nitrogen washout FRC was -2.6 ± 17.5% (mean ± standard deviation). The small signal-to-noise ratio of the CO_2 method restricts measurements to patients who are treated with stable mechanical ventilation.

6.2 Discussion

This work advances two methods for accurate, automated bedside FRC measurement during mechanical ventilation, with each method demonstrating advantages in different settings. The novel multiple breath nitrogen washout FRC measurement model demonstrates particularly good measurement precision, even during variable ventilation patterns. The CO_2 partial rebreathing FRC measurement model is a good candidate for trending measurements in the operating room or intensive care unit without requiring a change in inspired oxygen for a measurement. Both FRC measurement methods are compatible with any ventilator brand and can easily be moved from patient to patient as desired for bedside measurement.

With these simple-to-use FRC measurement methods, clinicians can take more frequent bedside FRC measurements, establish reference and normal FRC values for different patients and diagnoses, develop clinical guidelines for individualized treatment, monitor changes in a patient's FRC with evolution of or recovery from disease, rule out reduced FRC as a cause of hypoxemia and recommend informed mechanical ventilator setting changes. Bedside FRC measurements are therefore a critical parameter that may be used in conjunction with other parameters such as lung compliance and P_aO_2. future studies using these nitrogen- and carbon dioxide-based FRC measurement methods with improved measurement availability and accuracy may show a clinical benefit of more closely monitoring FRC. More widespread use of automated bedside FRC measurement may support investigation of broader clinical answers to questions such as the relationship between FRC and disease progression, the rate and extent of alveolar

recruitment after applying PEEP, the effect of fluid balance, and the relationship between gas exchange and FRC.

6.3 Limitations

While the clinical studies demonstrated acceptably good accuracy, precision and repeatability for both tracer gas models for FRC measurement, they were limited by several factors. First, the data collected for this work is from a relatively small number of subjects. More data should to be collected to examine the accuracy in a wider range of subjects. Second, there is no clinical gold standard for FRC measurement during mechanical ventilation. Therefore, we chose to assess accuracy compared to body plethysmography in ambulatory volunteers and repeatability of measurement during mechanical ventilation. Third, the local institutional review board did not permit FRC measurement for intensive care patients who required more than 5 cm H_2O of positive end-expiratory pressure (PEEP) during baseline mechanical ventilation. This limitation in the patient pool led to testing of the healthiest among the patients in the intensive care unit. Therefore, accuracy during significant lung injury remains a question for future research.

6.4 Future Work

These first clinical studies of the modified multiple breath nitrogen washout FRC model indicate the model has great potential for reliable for bedside use. Of course, the model should be evaluated in a larger number of patients to confirm the results before the FRC measurement can be routinely applied at the bedside to guide treatment. It would be valuable as a next step to conduct an additional clinical evaluation for the modified

multiple breath nitrogen washout FRC model with respect to accuracy for intensive care patients with significant lung injury and subsequent to changes in positive end-expiratory pressure. Possible reference methods for clinical evaluation during mechanical ventilation include helium dilution or computed tomography.

The modified multiple breath nitrogen washout method may potentially be further simplified to exclusively analyze the oxygen signal since carbon dioxide excretion is typically stable during the washout period and therefore does not contribute significantly to the FRC measurement accuracy. In essence, a simplified model would predict the multiple breath oxygen wash-in or washout signal compared to the alveolar concentration observed as end-tidal oxygen fraction. Such an analysis could be carried out, at least preliminarily, using the data already collected for this dissertation. It may also be of interest to assess the accuracy of FRC measurements using a smaller step change in inspired oxygen to initiate the washout.

The CO_2 partial rebreathing FRC measurement requires additional clinical assessment with a larger number of patients before it can be applied at the bedside to guide treatment. Of particular interest for future work is the accuracy of the method during controlled mechanical ventilation for patients with lung injury. Future testing is also warranted to determine the number of measurements required for the average FRC value when the ventilation pattern is variable.