Measurement of Functional Residual Capacity of the Lung by Nitrogen Washout, Carbon Dioxide Rebreathing and Body Plethysmography in Healthy Volunteers

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Abstract

Background: *We measured Functional Residual Capacity (FRC) of the lungs with three methods in healthy volunteers. The three techniques included a CO_2 partial rebreathing technique, nitrogen washout technique, and the reference technique for ambulatory patients, body plethysmography.*

Materials and Methods: *After granting consent to an IRB-approved protocol, each of the 20 healthy volunteers participated in FRC measurement by three methods, including body plethysmography, carbon dioxide (CO_2) rebreathing, and nitrogen washout. Gas concentration and volume data were collected from the distal side of a mouthpiece during spontaneous ventilation for the washout and rebreathing measurements. The FRC was measured twice with a nitrogen washout measurement technique and then signals from five partial CO_2 rebreathing measurement cycles were collected. Finally, the nitrogen washout FRC measurements were repeated twice. We compared the average CO_2 rebreathing FRC measurements and the average nitrogen washout FRC measurements to the body plethysmography FRC measurements for each subject through statistical methods of linear regression analysis and Bland-Altman Analysis.*

Results: *The squared correlation coefficient for the linear regression between nitrogen washout and body plethysmography measurements was $r^2 = 0.91$ (n = 35). The bias ± Standard Deviation was 0.054 ± 0.373 L.*

Conclusion: *These results indicate FRC measurement by nitrogen washout correlate well with the body plethysmography reference standard in ambulatory, spontaneously breathing subjects. This method could possibly be used in space to monitor lung function.*

Introduction

Functional Residual Capacity (FRC) measurements may be useful as a guide for ventilation management or as a way to follow disease progression for patients with acute lung injury and ARDS[1,2]. While traditional methods of FRC measurement are valuable for researching disease progression and for monitoring ambulatory patients, they have been of limited utility at the bedside due to difficulty of use, high expense, and impracticality during mechanical ventilation. FRC measurement at the bedside for mechanically and spontaneously ventilated patients has recently been reported by several researchers, who evaluated systems based on nitrogen washout[3-7] and Electrical Impedance Tomography[8,9].

The nitrogen washout and CO_2 rebreathing methods have previously been validated by our research group with the use of a bench lung model. We also previously evaluated both methods in an animal study[10]. The aim of this study was to evaluate the accuracy of the two FRC measurement systems compared to the clinical gold standard for ambulatory patients, body plethysmography, in healthy, spontaneously breathing volunteers.

Methods:

Testing protocol

Twenty healthy volunteers (9 women and 11 men) consented to an IRB-approved monitoring protocol which included measurement of FRC using each of three methods in a single data collection session. The three methods included body plethysmography (the clinical gold standard), nitrogen washout and partial CO_2 rebreathing. 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 upper respiratory tract infection.

Subjects were seated upright throughout the study period. For each washout measurement session, a series of nitrogen washout measurements was completed, followed by a series of partial rebreathing measurements and ended with a second set of nitrogen washout measurements. The nitrogen measurements were repeated in order to test whether they remained stable both subsequent to the rebreathing measurements and with time. Body plethysmography measurements were randomized to be taken before and after the washout measurement session in order to prevent bias introduced by the order of measurements.

Body Plethysmography Method

Body plethysmography FRC measurement was conducted by trained staff in the Pulmonary Department of the University of Utah Health Sciences Center according to the manufacturer's specifications for the Collins body plethysmograph (Model BP, Warren E. Collins Inc., Braintree, MA). In brief, the measurement was performed as follows: the subjects were seated upright inside the chamber with the door closed and a nose clip in place. The subjects were instructed to breathe quietly through the mouthpiece until a stable end-expiratory level was achieved (usually 3 to 10 tidal breaths). When the patient was at or near FRC, the shutter was closed at end-expiration for 2-3 seconds, and the subject was instructed to pant gently at a frequency between 0.5 and 1 Hz. Next, the shutter was opened and the subject was first requested to fully expire to yield a measure of Expiratory Reserve Volume and then to perform a slow Inspiratory Vital Capacity maneuver. A series of 3-5 technically satisfactory panting maneuvers was recorded. Three measurements of FRC within 5% were obtained, in accordance with lung volume measurement guidelines[11, 12]. The mean of the individual body plethysmography measurements was recorded as the reference FRC for each volunteer.

Nitrogen Washout Method

Oxygen was analyzed using a side stream paramagnetic O_2 analyzer (Deltatrac, Datex, Helsinki, Finland). 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 Medical, Wallingford, CT). Each of the analyzers automatically re-zeroes periodically to avoid baseline drift. The gas analyzers were calibrated with calibration gas prior to the experiment. Gas for the side stream analyzer was sampled at both inspiratory and expiratory locations, while the mainstream sensor was placed between the side stream gas sampling adaptor and the mouthpiece.

Raw data of flow and gas concentrations were sampled with a frequency of 100 Hz and processed digitally using custom-written software to generate end-tidal and volumetric O_2 and CO_2 measurements and tidal volumes as described previously[3,10,13]. Throughout the measurement period, inspired and expired volumes and concentrations of oxygen and carbon dioxide were recorded to a notebook computer. Nitrogen was calculated as the balance of oxygen and carbon dioxide.

The subjects were instructed to wear a nose clip and breathe normally through a mouthpiece. One-way valves and a blender were used to prevent rebreathing and achieve the step-increase in oxygen. First, the inspired oxygen fraction (F_{IO2}) was set to 0.3 and a period of 20 minutes 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 up to five minutes was allowed for the washout to continue to completion, the inspired oxygen fraction was increased to 1.0. Again, the washout was continued to completion for a period of up to five minutes. The inspired oxygen fraction was again set to 0.3 and the two step increases in oxygen were repeated.

The volume of alveolar ventilation and the change in nitrogen concentration following each change in F_{IO2} were used to calculate FRC in a variation of the multiple compartment model proposed by Hashimoto[14]:

Compartment Ventilation = (1 / Number of compartments)* (iTV - VDaw - Apparatus DS), [1]

where Number of compartments is assumed to be 3, iTV is inspiratory tidal volume, VDaw is the measured airway deadspace, and Apparatus DS is the measured apparatus deadspace.

CompartmentN2(n) = CompartmentN2(n-1) * Compartment Volume / (Compartment Ventilation + Compartment Volume), [2]

where Compartment Volume is initially estimated as 1000 mL.

Average Compartment N2 = CompartmentN2(n) * 1/Number of compartments. [3]

The Compartment Volume was adjusted until the Average Compartment N_2 matched the measured $FetN_2$. The compartment volumes were summed to calculate the FRC. It should be noted that this calculation ignores the excretion of N_2 from the tissues. The effect of N_2 excretion on the FRC measurement should be small (less than 100 ml)[11]. Both average and individual nitrogen washout measurements were compared to the body plethysmography reference value.

CO_2 Rebreathing Method

The subjects were instructed to wear a nose clip and breathe normally through a mouthpiece. One-way valves and a blender were used to prevent rebreathing and maintain an inspired oxygen fraction of 0.3. CO_2 was analyzed via an infrared CO_2 analyzer, while airway flow was measured using a differential pressure-type pneumotach, both of which are integrated in the on-airway sensor of the $NICO_2$ monitor (Philips Medical, Wallingford, CT). A partial rebreathing measurement was automatically activated once every three minutes by the $NICO_2$ monitor. The FRC measurement was based on a portion of the signal generated from the partial rebreathing sequence which is normally utilized for noninvasive pulmonary capillary blood flow (PCBF) measurement. The partial rebreathing period lasted 35 seconds once every three minutes, and the parameters analyzed for the FRC measurement were obtained from the last breath of rebreathing and the first breath subsequent to the end of the rebreathing phase. Thus, the FRC measurement was based on the carbon dioxide washout of one breath. All data related to the flow and concentrations of the breaths were automatically recorded to a computer for subsequent analysis.

The carbon dioxide washout FRC measurement method was based on the system as previously reported[10]. The final calculation is:

$$FRC = 0.40 * (VCO2steady - VeCO2(n))/(FCO2(n-1)-FCO2(n)), \qquad [4]$$

where $VCO2_{steady}$ is the volume of CO_2 excreted in the last breath of rebreathing, $VeCO2_{(n)}$ is the CO_2 excreted in the first breath following rebreathing, $FCO2_{(n-1)}$ is the fraction of end-tidal CO_2 in the first breath following rebreathing, and $FCO2_{(n)}$ is the fraction of end-tidal CO_2 in the last breath of rebreathing. This equation assumes that a steady state condition was achieved for the CO_2 excretion rate during the rebreathing phase such that the CO_2 excretion rate was equal to the rate of CO_2 elimination from the blood to the FRC.

The partial rebreathing CO_2 washout FRC measurement was completed and recorded five times, the minimum and maximum values were removed from each session, and the average values of the remaining points were compared to the reference method of FRC measurement.

Statistical Analysis

The mean FRC measurements recorded from each the carbon dioxide washout method and the nitrogen washout method were compared to those of the body plethysmography method by means of regression analysis and Bland-Altman statistics. The individual nitrogen washout measurements were also statistically compared to the reference value.

Results

11 males and 9 females participated in the study. Average age of the subjects was 31.3 years (range of 18 to 62). Average height was 68.5 inches (range of 59.5 to 76). Average weight was 156 pounds (range of 111 to 209 pounds). Average measured Body Plethysmography FRC ± SD was 3.55 ± 0.87 L with a minimum of 2.3 L and a maximum of 5.6 L.

Comparison of Nitrogen Washout and CO_2 Rebreathing to Body Plethysmography

Linear regression analysis between the average nitrogen washout FRC measurements and the body plethysmography reference FRC for each set of measurements yielded a squared correlation coefficient of $r^2 = 0.91$ (n = 35). The bias ± SD was -0.054 L ± 0.373 L.

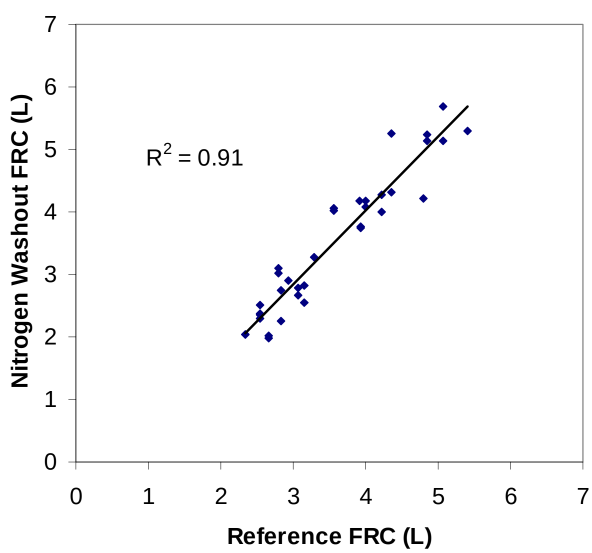

Figure 1: Linear regression analysis of average nitrogen washout FRC and body plethysmography FRC measurements.

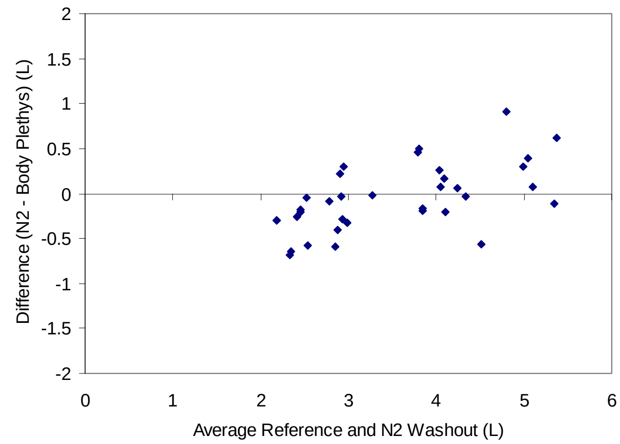

Figure 2: Bland-Altman plot comparing the average FRC from the nitrogen washout method and that from body plethysmography.

Linear regression analysis between the individual nitrogen washout FRC measurements and the body plethysmography reference FRC yielded a squared correlation coefficient of $r^2 = 0.86$ (n = 73). The bias ± SD was -0.065 L ± 0.458 L.

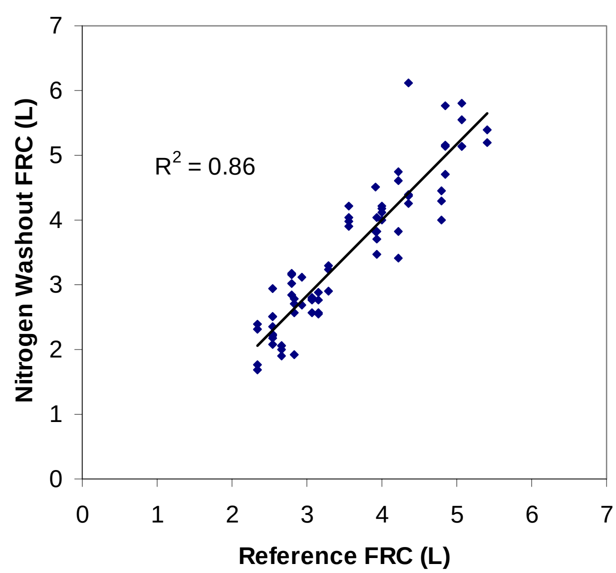

Figure 3: Linear regression analysis of individual nitrogen washout FRC and body plethysmography FRC measurements.

Linear regression analysis between the average CO_2 rebreathing FRC and the body plethysmography FRC yielded a squared correlation coefficient of $r^2 = 0.48$ and a slope of 1.0 (n = 19). The bias ± SD was -0.43 L ± 0.91 L.

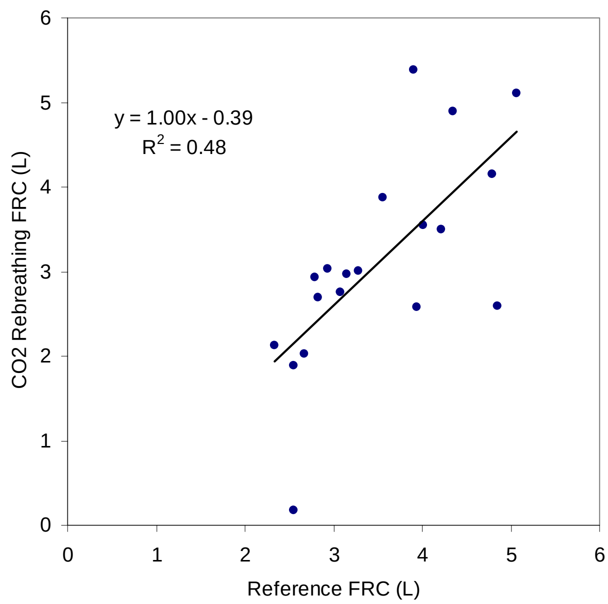

Figure 4: Linear regression analysis of the CO_2 rebreathing FRC and the body plethysmography FRC measurements.

Discussion:

We observed acceptable accuracy for the nitrogen washout FRC measurement method for this group of healthy, spontaneously breathing volunteers, both when average measurements were analyzed and when individual values were considered. The ATS standard for lung volume measurements states[11] that repeated nitrogen washout measurements should be within 10% of each other. This nitrogen washout system was within 1.5% of the mean gold standard reference value, with a standard deviation of 10%. The individual measurements compared quite similarly to the average measurements with respect to r^2, bias and standard deviation. Thus, the individual measurements may likely be accurate enough to be of use clinically and in place of the measurement sets. The individual measurement requires approximately 6 minutes to complete, while a set of measurements would take 11-21 minutes. Therefore, it may be advantageous to employ a single FRC measurement at the bedside rather than a set of measurements in order to save time while not losing significant accuracy.

The bias of the CO_2 rebreathing method was 12% of the average gold standard value, which was a factor of 10 larger than the bias for the nitrogen washout method. The signal generated for the nitrogen washout method was significantly bigger than that for the carbon dioxide method, and consequently the accuracy of the nitrogen method was better in this group of spontaneously breathing subjects. Given the underlying assumptions of the CO_2 method and the restriction of analyzing only one breath, the CO_2 method will likely be of limited use in spontaneously breathing patients. The carbon dioxide rebreathing system is especially susceptible to noise caused by variations in breath size, so spontaneously breathing subjects are not the best population for this method. Mechanically ventilated patients, in contrast, would be better subjects for this method. The main advantage of the CO_2 rebreathing method is that it is fully automated and can be used for several hours at a time. With automated measurement, it may be possible to track the size of the FRC with time in mechanically ventilated patients.

Future studies will examine whether the more stable signal from mechanically ventilated patients provides better input data for measurement stability of the carbon dioxide rebreathing method. Other planned analysis includes comparison of CO_2 rebreathing and nitrogen washout values with each other for these spontaneously breathing subjects as well as measurement repeatability for each method.

This study demonstrated that nitrogen washout FRC measurements can be made accurately for spontaneously breathing subjects. Therefore, the method could likely be applied to monitor an ambulatory astronaut's lung volume. Future studies will examine whether repeatable nitrogen washout FRC measurements can reliably be made in mechanically ventilated patients.

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

3. 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.

4. 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 Mar;104(3):598-604.

5. Wolfgang Eichler, Jan Schumacher, Angela Roth-Isigkeit, Jörg Braun, Hermann Kuppe and Karl-Friedrich Klotz. Automated Evaluation of Functional Residual Capacity by Oxygen Washout. J Clin Monit Comput. 2002 Apr-May;17(3-4):195-201.

6. H. Heinze, B. Sedemund-Adib, M. Heringlake, U. W. Gosch, H. Gehring, and W. Eichler. 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., May 1, 2008; 106(5): 1491 - 1494.

7. Maisch S, Boehm SH, 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 May;33(5):912-6.

8. HOdenstedt, S Lindgren, C Olegård, K Erlandsson, S Lethvall, A Åneman, O Stenqvist and S Lundin. Slow moderate pressure recruitment maneuver minimizes negative circulatory and lung mechanic side effects: evaluation of recruitment maneuvers using electric impedance tomography, Intensive Care Med. 2005 Dec;31(12):1706-14.

9. Meier T, Luepschen H, Karsten J, Leibecke T, Grossherr M, Gehring H, Leonhardt S. Assessment of regional lung recruitment and derecruitment during a PEEP trial based on electrical impedance tomography. Intensive Care Med. 2008 Mar;34(3):543-50.

10. 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.

11. Wanger J et al., "Standardisation of the measurement of lung volumes," Eur Respir J 26, no. 3 (2005): 511-522.

12. 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.

13. 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.

14. T. Hashimoto, A. C. Young, and C. J. Martin. Compartmental analysis of the distribution of gas in the lungs. J Appl Physiol 23: 203-209, 1967.