
Abstract
We developed a modified nitrogen washin/washout technique based on standard monitors using inspiratory and end-tidal gas concentration values for functional residual capacity (FRC) measurements in patients with acute respiratory failure (ARF). For validation we used an oxygen-consuming lung model ventilated with an inspiratory oxygen fraction (FiO₂) between 0.3 and 1.0. The respiratory quotient of the lung model was varied between 0.7 and 1.0. Measurements were performed changing FiO₂ with fractions of 0.1, 0.2, and 0.3. In 28 patients with ARF, duplicate measurements were performed. In the lung model, an FiO₂ change of 0.1 resulted in a value of 103 ±5% of the reference FRC value of the lung model, and the precision was equally good up to an FiO₂ of 1.0 with a value of 103 ±7%. In the patients, duplicate measurements showed a bias of -5 ml with a 95% confidence interval [-38; 29 ml]. A comparison of a change in FiO₂ of 0.1 with 0.3 showed a bias of -9 ml and limits of agreement of [-365; 347 ml]. This study shows good precision of FRC measurements with standard monitors using a change in FiO₂ of only 0.1. Measurements can be performed with equal precision up to an FiO₂ of 1.0.

Introduction
Ventilator treatment of the patient with acute respiratory failure (ARF) is aimed at opening up the lung, keeping it open, preserving gas exchange, and avoiding baro- and volutrauma (1-3). In the absence of a clinically acceptable method for determination of the functional residual capacity (FRC), surrogate indicators, such as the static pressure/volume curve and the upper and lower inflection points or the alveolar pressure/volume curve, have been used (4-6). Suter et al. (7) identified a positive end-expiratory pressure (PEEP) where maximum oxygen (O₂) transport coincided with the highest static compliance and highest FRC. The FRC is thus a key for rational ventilator setting (8).

Measurements of FRC have hitherto mainly been obtainable in research situations either by dilution of gas with low solubility by rebreathing in a closed system, or by multiple breath washout technique. Suitable gases are sulfur hexafluoride (SF6), helium (He), O₂, and nitrogen (N₂). SF₆, otherwise well suited, is not approved for human use by regulatory authorities (9,10). Helium is mainly used in the rebreathing technique, where the slow response of the detector is not a problem (11,12). O₂ has the advantage of being easy to monitor with standard monitoring equipment, with a reasonable response time (13-15), but the O₂ consumption must be corrected for, which is difficult at high inspiratory O₂ fraction (FiO₂). N₂ can be measured with a mass spectrometer technique, but can also be calculated as the residual of O₂ and carbon dioxide (CO₂), which are the only other two components of ventilator gas (16-18). The main problem with both O₂ and N₂ as tracer gases is that changes of FiO₂ of more than 0.2 fractions are required for adequate measurements of FRC (14,16). In severely ill ARF patients this has not been acceptable. Another problem inherent in the conventional N₂ multiple breath washout (NMBW) technique using side stream gas analysis is the synchronization of gas flow and concentration measurements. This has to be performed prior to the continuous integration of flow and direct or indirect N₂ concentration from O₂ and CO₂ measurements (17).

We have developed a NMBW using standard clinical O₂ and CO₂ sensors and flow meters to minimize the step change in O₂ and washout period. The aim of this study was to validate the method for FRC measurements in an O₂-consumption/CO₂-producing lung model and to test the reproducibility in mechanically ventilated patients.
Methods

To avoid the synchronization problems we have focused on alveolar \(N_2\) exchange calculated from inspiratory and end-tidal plateau gas concentrations of \(O_2\) and \(CO_2\). A basic assumption is that inhomogeneity in alveolar gas distribution, reflected in steeply increasing or decreasing end-expiratory plateaus, is constant throughout the measurement procedure. Another assumption is that cellular metabolism and gas exchange between lung capillary blood and alveoli are stable during the washout/washin procedure.

\(O_2\) was analyzed using a side stream paramagnetic \(O_2\) analyzer with a response time of \(< 480\) ms (95% of full gain, manufacturer’s specification). \(CO_2\) was analyzed using a side stream infrared analyzer with a response time of \(< 360\) ms (95% of full gain, manufacturer’s specification). The gas analyzers were calibrated with a calibration gas with concentrations relevant to the measurements to be performed. After calibration the analyzers are automatically zeroed repeatedly to avoid baseline drift. Gas for breath-by-breath analysis of inspiratory and end-tidal concentrations was sampled at the y piece, and gas for analysis of mixed expired concentrations was sampled from a mixing box, 5 L volume, with a fan, connected to the expiratory outlet of the ventilator. Sampled gas was returned to the expiratory limb of the breathing system. Ventilation volumes were analyzed with a side stream spirometer based on an augmented Pitot methodology (19). The spirometer is zeroed automatically every second second. These analyzers were all part of an AS/3 modular monitoring system (Datex-Ohmeda, Helsinki, Finland).

Raw data of flow and gas concentrations were sampled with a frequency of 25 Hz and processed by the monitor software, which provides inspiratory and end-tidal gas concentrations, as well as tidal volume values, which then were collected by Collect S/S, ver. 4.0 software (Datex-Ohmeda) with a sampling frequency of 1 Hz. These data were exported to customized software, Testpoint (Capital Equipment Corp., Bedford, NH) for analysis and calculation of FRC.

Baseline \(O_2\) consumption (\(VO_2\)) and \(CO_2\) production (\(VCO_2\)) were determined with indirect calorimetry measurements using the gas analyzer of the monitor in the mixing box for a period of 30 s in order to calculate the alveolar ventilation. The inspiratory minute ventilation (\(V_I\)) was calculated by Haldane transformation from the measured expiratory minute ventilation (\(V_E\)) with the assumption that there was no net exchange of \(N_2\). Expiratory alveolar minute ventilation, \(V_{AE}\) was calculated according to Bohr’s formula:

\[
V_{AE} = \frac{VCO_2}{FETCO_2}
\]

(1) \(\text{IFETCO}_2 \text{=} \text{end-tidal carbon dioxide fraction}\)

The inspiratory alveolar minute ventilation (\(V_{AI}\)) was calculated as the difference between \(V_I\) and \(V_E\) plus the expiratory alveolar minute ventilation:

\[
V_{AI} = (V_I - V_E) + VAE
\]

The inspiratory and expiratory alveolar tidal volumes (\(V_{TAI}\) and \(V_{TAE}\)) were calculated from the alveolar minute ventilation and the breathing frequency. Breath-by-breath \(N_2\) exchange (\(V_{TN2}\)) was calculated as the difference between inspired and expired \(N_2\) volume:

\[
V_{TN2} = (FiN2 x V_{TAI}) - (FetN2 x V_{TAE})
\]

(3)

where \(FiN2\) is the inspiratory \(N_2\) fraction, \(FetN2\) is the end-tidal \(N_2\) fraction, \(FiO2\) is the end-tidal \(O_2\) fraction, \(FiN2 = 1 - FiO2\), and \(FetN2 = 1 - FetO2 - FetCO2\).

The inspiratory and end-tidal \(O_2\) and \(CO_2\) concentrations were acquired breath-by-breath from the monitor output.

\[
\sum V_{TN2} / (FiN2_{in} - FiN2_{end})
\]

(4)

where \(FiN2_{in} - FiN2_{end}\) is the difference in inspiratory \(N_2\) concentration between start and end of washout. Calculations were based on a period of 3 time constants, when 95% of washin/washout was completed.

Lung Model

\(CO_2\) output was achieved by delivery of \(CO_2\) into the single alveolus of the model via a precision electronic flow controller. \(O_2\) consumption was achieved by combustion of hydrogen in a mini-Bunsen burner where \(2H_2 + O_2 = 2H_2O\), i.e., the \(O_2\) consumption equals half of the delivered volume of hydrogen. An electronic flow regulator also controlled the hydrogen flow. Combustion took place in the single alveolus of the lung model (20,21). The respiratory quotient (\(RQ\)), which is the ratio \(VCO_2/VO_2\), could be varied freely by adjusting the settings of \(VCO_2\) and \(VO_2\) of the lung model. The basal FRC of the lung model was 1.8 L and was increased stepwise to 2.8 and 3.8 L by addition of volume to the single alveolus.

With the lung model \(VCO_2/VO_2\) set at 200/200 and 200/240 ml/min, precision of FRC measurements was tested using step changes of \(FiO2\) with 0.1, 0.2 or 0.3.

With FRC set at 1.8, 2.8 or 3.8 L the lung model was ventilated with an \(FiO2\) of 0.4, 0.7, and 1.0. During measurements with lung model FRC set at 1.8 L, \(VCO_2/VO_2\) was set at 140/200, 170/200 and 140/140 ml/min, resulting in a \(RQ\) of 0.7, 0.85 and 1.0, respectively. During measurements with lung model FRC set at 2.8 L, \(VCO_2/VO_2\) was set at 200/280, 140/165 and 170/170 ml/min, resulting in a \(RQ\) of 0.7, 0.85 and 1.0, respectively. During measurements with lung model FRC set at 3.8 L, \(VCO_2/VO_2\) was set at 170/240, 200/235 and 200/200 ml/min, resulting in a \(RQ\) of 0.7, 0.85 and 1.0, respectively.
For FRC measurements, N₂ washin was achieved by reducing FiO₂ by 0.1 and N₂ washout was achieved by changing FiO₂ back to the original setting. Thus, each measurement was the average of a washin-washout procedure changing FiO₂ sequentially from 0.4 to 0.3 to 0.4, from 0.7 to 0.6 to 0.7 or from 1.0 to 0.9 to 1.0.

The lung model was ventilated with a Siemens Servo 900C ventilator (Siemens-Elema, Solna, Sweden) at a respiratory rate of 12, 15 or 19/min and a minute ventilation set at 8, 10 or 12 L/min. During the evaluation of different step changes of FiO₂, an FiO₂ between 0.3 and 0.6 was used. In the evaluation of the effect of high FiO₂ on FRC measurements, inspiratory O₂ concentration was set at 0.4, 0.7, and 1.0.

### Patients

The Ethical Committee of the Medical Faculty at Göteborg University approved the study and informed consent was obtained from the patients or next of kin. Measurements were performed in 28 patients whose demographics are presented in Table 1. All patients were ventilated with a Servo 900C or 300 ventilator in volume control mode, with FiO₂ 0.3-0.6, inspiration 25%, end-inspiratory pause 10% and a respiratory frequency of 12-20/min.

In 18 patients FRC was measured during a stable PEEP level already set for clinical reasons by changing FiO₂ stepwise up and then back down by 0.1, 0.2 or 0.3 to achieve N₂ washout/washin measurements. After a stabilization period the measurement was started, with a step increase in FiO₂ of 0.3 to induce a washout of N₂. After a new steady-state was reached, as indicated by the concentration difference between inspiratory and end-tidal O₂.

### Table 1

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>P/F (mmHg)</th>
<th>LIS</th>
<th>FRC mean (ml)</th>
<th>Coefficient of variation (%)</th>
<th>Number of measurements</th>
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<td>26</td>
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<td>56</td>
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<tr>
<td>6</td>
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<td>73</td>
<td>AAA repair</td>
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<td>2885</td>
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<td>1985</td>
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<tr>
<td>18</td>
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<tr>
<td>21</td>
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<td>73</td>
<td>AAA repair</td>
<td>315</td>
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<td>2645</td>
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<tr>
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<td>F</td>
<td>69</td>
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<td>2621</td>
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<tr>
<td>25</td>
<td>M</td>
<td>25</td>
<td>Orthopic liver transplantation</td>
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<td>225</td>
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<td>F</td>
<td>70</td>
<td>Liver tumor resection</td>
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<td>1</td>
<td>1890</td>
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<td>27</td>
<td>M</td>
<td>57</td>
<td>Orthopic liver transplantation</td>
<td>205</td>
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<td>1827</td>
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<td>12</td>
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<td>28</td>
<td>M</td>
<td>49</td>
<td>Hepatic failure</td>
<td>214</td>
<td>2.5</td>
<td>1827</td>
<td>12.0</td>
<td>12</td>
</tr>
</tbody>
</table>

ALL = acute lymphatic leukemia; AAA = abdominal aortic aneurysm; COPD = chronic obstructive pulmonary disease; CHF = chronic heart failure; SDH = subdural hematoma.

P/F ratio (PaO₂/FiO₂) and Lung Injury Score (LIS) according to Murray et al. (25). The functional residual capacity (FRC) column shows the mean of 8-12 FRC measurements at baseline positive end-expiratory pressure (PEEP).
concentrations reaching the same level as before the start of the washout procedure, a step decrease of FiO₂ of 0.3 to induce a washin of N₂ was performed. This sequence was then repeated after steady-state was reached again, using a step change in FiO₂ of 0.2, and then finally followed by a sequence using a step change in FiO₂ of 0.1. The measurement sequence, using step changes of 0.3, 0.2, and 0.1, was then repeated. Each washout or washin procedure was analyzed during 3 time constants equivalent to 95% of a complete washin or washout procedure.

In 17 patients (7 of whom were among the 18 patients in whom different step changes of FiO₂ were evaluated) the FRC was measured at 2 different PEEP levels, 5-8 cm H₂O apart, by increasing and decreasing FiO₂ by 0.1.

Results are presented as mean ± SD. Comparisons between patient measurements with different step changes of FiO₂ as well as duplicate measurements were performed using Bland and Altman analysis (22).

Results

Lung Model

The different FRCs of the lung model were measured with good precision using the modified NMBW method, irrespective of the level of FiO₂ or ∆FiO₂ used (Figs. 1 and 2). When step changes of FiO₂ of 0.1, 0.2 or 0.3 were used, minimal differences in precision were observed: 103 ±5%, 101 ±6% and 102 ±4%, respectively, of the reference volume of the lung model. When ventilating the lung model with increasing FiO₂ levels from 0.3, including levels of 0.7 and 1.0, where the O₂ consumption was calculated from the CO₂ production with a default RQ of 0.85, a very high precision of measurements was seen irrespective of the FiO₂ used (Fig. 2). At FiO₂ of 0.3-0.4, 0.7, and 1.0, the measured values were 100 ±6%, 103 ±8%, and 103 ±7% of the reference FRC of the lung model. When the RQ of the lung model was varied between 0.7 and 1.0 using the default RQ value (0.85) for the NMBW algorithm, there was a small overestimation of FRC (116 ±187 ml) at a true RQ of 0.7. At a true RQ of 0.85 the overestimation was only 36 ±192 ml. In comparison, a true RQ of 1.0 resulted in a minimal underestimation of FRC (-19 ±197 ml). These corresponded to 4%, 1.3% and -0.7% of the true FRC volume, respectively. The difference between washout and washin measurements in the lung model using a step change in FiO₂ of 0.1 was 14 ±187 ml, corresponding to 0.5% of the true FRC volume.

Patients

Analysis of each washin or washout procedure was performed during 3 time constants, which corresponded to a duration of about 80-120 s. In 2 patients with a very large FRC of more than 4 L the duration was >150 s. Comparisons in 28 patients of duplicate measurements of FRC (mean of a washin and washout procedure) at FiO₂ steps of 0.1, 0.2, 0.25, and 0.3 showed a bias of -5 ml with a 95% confidence interval [CI] [-38, 29 ml] (Fig. 3). In 17 patients, measurements of FRC were performed as duplicate washin/washout procedures at 2 PEEP levels (~7 cm H₂O difference) using stepwise changes of FiO₂ varying from 0.1 to 0.25. The bias of repeated measurements was -22 ml with a CI [-60, 16 ml] (Fig. 4).
When comparing FRC measured using an FiO2 step change of 0.1 or 0.3 (mean of washin and washout), a bias of -9 ml with limits of agreement ±356 ml was found (Fig. 5). Comparing the washin with the washout procedures using a step FiO2 of 0.1 resulted in a bias of 149 ml with limits of agreement of 484 ml.

**Discussion**

We have modified and simplified a conventional NMBW method for measurement of functional residual capacity in ventilator-treated patients. The problems with continuous synchronization and integration of flow and gas concentration measurements have been circumvented by using the end-tidal and inspiratory O2 and CO2 concentration output signals from a standard side stream gas monitor and flow measurements from the ventilator. The method can be used with a step change of only 10% in inspiratory O2 concentration. In patients without chronic obstructive pulmonary disease (COPD), a washin or washout procedure takes less than 4 minutes to complete, resulting in a short and small change of alveolar O2 concentration. The method demonstrated high precision during lung model evaluation, and good reproducibility in patients; it is thus possible to use in patients with high inspiratory O2 concentrations as well.

The main problem concerning NMBW for routine clinical use is that N2 requires either a mass spectrometer or a Raman scattering technique for direct analysis. In patients in whom no gases other than O2, CO2, and N2 are present, N2 can be calculated as the residual by measurement of O2 and CO2. Fretschner et al. (16) presented a technique using a main-stream CO2 analyzer and a side-stream O2 analyzer. As the two wave forms are inversely congruent, they could be synchronized with a pneumotachograph measurement of gas flow for integration of flow and N2 concentrations. The synchronization procedure is very sensitive, however, especially when a substantial shift of inspiratory O2 concentration is made (30% in [16]). In this case, a small error in the synchronization may lead to gross miscalculations of N2 volume.

We used side-stream O2 and CO2 analyzers with marginally different response and delay times. By using only the plateau values of end-tidal and inspiratory gas concentrations, differences in delay and response times become unimportant, and there is no need for continuous synchronization. The correct calculation only requires that tidal flow/volume and inspiratory and end-tidal gas concentrations be tied to each other for each breath for correct calculations.
Eichler et al. [15] used a similar approach in a study of O\textsubscript{2} washin/washout measurements of FRC. Their O\textsubscript{2} sensor had a response time of 1.5 seconds, however, which is a limitation, as respiratory rate must be kept below 20/min for acceptable detection of end-tidal plateau values. Also, the slow response time of their O\textsubscript{2} sensor affected the measurement of the first end-tidal values after changing O\textsubscript{2} concentration, resulting in an overestimation of FRC of 400-500 ml.

The response time of < 500 milliseconds of the O\textsubscript{2} sensor in this study is fast enough to detect even the very first end-tidal plateau value correctly after making a step change in FiO\textsubscript{2} and permits higher respiratory rates. The only necessary assumption is that the dead space for O\textsubscript{2} and CO\textsubscript{2} is equal (23). One could object that the difference in response time would result in the inspiratory and end-tidal O\textsubscript{2} concentration being a little too small and large, respectively, and not comparable to the corresponding CO\textsubscript{2} values. If a stepwise change in FiO\textsubscript{2} causes a change in time constants of different parts of the lung, there could be an effect on the calculations of FRC. However, we saw no signs in the curve forms indicating such a time-constant change, and a reasonable assumption is that the lung compartment characteristics are identical before and after the washin or washout measurement procedure. Also, it must be noted that errors caused by differences in response time during a washin procedure will be counterbalanced by the same errors during the following washout procedure. The precision of our measurements is well within the limits proposed by Hedenstierna [8] specifically addressing FRC measurements [16].

To be able to measure FRC in critically ill patients with very high FiO\textsubscript{2}, the necessary step change in inspired O\textsubscript{2} must be minimized. A 0.3 step change or more has been used in a number of studies [16-18]. In the Eichler et al. [15] study of O\textsubscript{2} washin/washout measurements of FRC, the method most similar to ours, a step change of 0.7 was used in mechanically ventilated patients. A change of such a magnitude in patients with 80-100% inspiratory O\textsubscript{2} could severely affect O\textsubscript{2} delivery and saturation and makes the method less suitable for use in the intensive care unit. We evaluated step changes in FiO\textsubscript{2} of 0.1, 0.2, and 0.3 and found comparable results irrespective of size of change in FiO\textsubscript{2} (Fig. 1). Even in the presence of severe ventilation/perfusion mismatch, the effect on arterial O\textsubscript{2} content of a step change of FiO\textsubscript{2} from 1.0 to 0.9 is likely tolerated in most cases. The measurement procedure, especially in acute respiratory distress syndrome (ARDS) patients with small FRC, is very short (< 4 min). This is acceptable even in a critically ill patient. In the lung model, which is a single compartment model with good gas mixing, we chose to make the measurement over a three time constants period to cover 95% of the total washin/out. In ARDS patients with decreased FRC, this will be a fairly short period, but should be long enough to detect inhomogeneous lung pathology as well. The performance of the method in severely inhomogeneous lungs, i.e., COPD patients, was not evaluated in this study.

Our method is based on determination of baseline O\textsubscript{2} consumption and CO\textsubscript{2} production by indirect calorimetry, which is imprecise at FiO\textsubscript{2} > 0.7 and impossible at an FiO\textsubscript{2} of 1.0. Therefore we chose to calculate VCO\textsubscript{2} from mixed expiratory CO\textsubscript{2} concentration and expiratory volume and to calculate VO\textsubscript{2} from this VCO\textsubscript{2} with a default value of RQ of 0.85 when FiO\textsubscript{2} was more than 0.7. For in vitro testing, our method and a similar method [18] require a lung model with O\textsubscript{2} consumption and CO\textsubscript{2} production. In the lung model evaluation we used VO\textsubscript{2} and VCO\textsubscript{2} settings resulting in RQ of 0.7, 0.85 and 1.0. Measuring FRC with the default RQ of 0.85 as a base for calculations, when the model was ventilated with inspiratory O\textsubscript{2} concentrations up to 100%, did not affect measurement precision, which indicates that RQ has a negligible effect on precision of FRC measurements. The metabolically active lung model used in our study [20,21] has the advantage of gases having the same humidity and temperature as airway gases of patients. The impact of humidity is not tested in more conventional lung model evaluations of FRC measurements [9,10,16-18]. In this study we measured the baseline metabolic gas exchange in a mixing box on the expiratory outlet of the ventilator to make it possible for us to select different default values of RQ during the lung model study. However, in clinical practice, the capacity of the spirometry and gas module (MCOVX module, AS/3 and S/5, Datex-Ohmeda) to perform breath-by-breath indirect calorimetric gas exchange measurements can be used.

In spite of N\textsubscript{2} having a very low solubility in blood and tissue, a certain amount of N\textsubscript{2} diffuses from blood to the alveoli during a washout procedure and vice versa during a washin procedure, resulting in a slight overestimation of FRC measured by a single washout procedure and a slight underestimation of FRC measured by a single washin procedure. There is no consensus regarding the amount of tissue N\textsubscript{2} diffusing in or out of the alveoli, but 40 ml/min has been proposed when changing the FiO\textsubscript{2} by 0.8 [24]. Our method only uses an FiO\textsubscript{2} step change of 0.1, and the flux of tissue N\textsubscript{2} will be low. We propose that a normal FRC measurement is found in a combined washin/washout procedure where the tissue N\textsubscript{2} factor is eliminated, which is clearly demonstrated in the repeatability test with a very small bias when using a combined washin/washout procedure (Fig. 3). In a case where a single N\textsubscript{2} washout measurement is performed, FRC will be overestimated with around 5%, and a single washin measurement will result in an underestimation of similar magnitude.

In conclusion, we have shown that FRC measurements with high precision can be obtained using a NMBW technique based on standard gas monitoring equipment and an FiO\textsubscript{2} step change of as little as 0.1. The measurement technique has the potential of providing information on the lung volume status of severely ill ARDS patients ventilated with up to 100% O\textsubscript{2} in a clinical setting as well.

The data collection program (Collect S/5) used in this study is commercially available, but the analysis software was specially customized for the study. At present, the analysis software needed to make automatic FRC measurements possible is under development (i.e., when FiO\textsubscript{2} is increased or decreased stepwise, a measurement is automatically started), which will facilitate the clinical use.


