Agreement Between Functional Residual Capacity Estimated via Automated Gas Dilution Versus via Computed Tomography in a Pleural Effusion Model

Jeronimo Graf MD, Arnoldo Santos MD, David Dries MD, Alexander B Adams MPH RRT FAARC, and John J Marini MD

BACKGROUND: The measurement of functional residual capacity (FRC) in ventilated patients could help track the extent of acute lung disease, monitor recruitment of unstable lung units, or guide the use of PEEP. Quantitative analysis of computed tomography (CT) images of the lungs is currently the accepted standard for FRC measurement (FRC-CT), but is impractical for routine use. Gas dilution and gas tracer technologies, while attractive for research applications, require specialized equipment and skills missing from the clinical setting. We simultaneously evaluated FRC-CT and FRC determined by a ventilator-incorporated wash-in/wash-out (FRC-WI/WO) method in an animal model of unilateral pleural effusion that varied the fluid volume instilled and the applied PEEP. METHODS: A swine model ($n = 6$) of unilateral pleural effusion was created by injecting boluses of radio-opaque fluid (iopromide) (13 mL/kg and then 26 mL/kg) into the right thoracic cavity. FRC-CT and FRC-WI/WO were simultaneously obtained, at 2 PEEP levels, at baseline and at both pleural-effusion volumes. RESULTS: A correlation coefficient (r^2) of 0.89 between FRC-CT and FRC-WI/WO revealed concordance between the techniques, with directional agreement and acceptable bias and precision under all tested conditions. CONCLUSIONS: We found excellent concordance between FRC-WI/WO and FRC-CT in an animal model of unilateral pleural effusion that stressed the capability of this technology. The technical advantage of the wash-in/wash-out technique is its incorporation into ventilator operation without requiring adjustments to ventilation. *Key words: functional residual capacity; mechanical ventilation; pleural effusion; monitoring; chest mechanics.* [Respir Care 2010;55(11):1464–1468. © 2010 Daedalus Enterprises]

Introduction

Functional residual capacity (FRC) (the absolute volume from which tidal inflation begins) is routinely measured in pulmonary function laboratories to evaluate subacute and chronic lung diseases. In intensive care applications the monitoring of FRC in ventilated patients could potentially track the extent or progression of acute lung disease, monitor recruitment of unstable lung units, or guide the use of PEEP. Unfortunately, the technological quest to bring reproducible FRC measurements to the bedside has been elusive.[1]

Quantitative analysis of computed tomography (CT) images of the lungs at end-expiration is the accepted standard

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for FRC measurement (FRC-CT). While CT enables highly accurate estimation of FRC, the repeated use of FRC-CT is clearly impractical.[2] Methods that employ gas dilution and gas tracers would appear to be more feasible for monitoring applications in the critically ill. In research applications, FRC has been estimated with open-circuit and closed-circuit methods that require mass spectrophotometry[3,4] or detection of helium,[5-7] sulfur hexafluoride,[8,9] nitrogen,[10] or the respirable gases, CO_2 and O_2.[11,12] Each technique makes theory-based assumptions and each has been reported accurate in specific settings.[3-12] However, the accuracy in acute applications in which recruitment and heterogeneous mechanics complicate gas-dilution measurement has not been extensively validated. Moreover, circuit or lung leaks, gas trapping, and FRC variation due to spontaneous ventilation can cause measurement errors and inconsistencies. While acknowledging such shortcomings, the major deterrent to adoption of FRC monitoring in the intensive care unit has been the expense and inconvenience of extra equipment, not the accuracy of the measurements.

Recent technical developments enable repeated FRC estimation in ventilated patients without the need for supplemental apparati. Noninvasive methods have been integrated into ventilators that use high-speed O_2[13-16] and O_2-CO_2[2,17-21] detectors to quantify nitrogen or oxygen flux (FRC wash-in/wash-out [FRC-WI/WO]) during step changes in F_{IO_2}. Changes in detected nitrogen concentration relate to the quantity in functional alveolar mass or FRC. FRC-WI/WO methods have been validated by FRC-CT in convenience-sampled patient-comparison studies.[3,8] Our study probed the accuracy of the FRC-WI/WO technique with a tightly controlled swine model characterized by mechanical heterogeneity and highly recruitable lung.

Methods

This study was approved by the Animal Care and Use Committee of Regions Hospital. We used 6 Yorkshire swine. Anesthesia was induced with 6.6 mg/kg tiletamine and 2 mg/kg xylazine, followed by continuous dosing of ketamine (15 mg/kg/h), xylazine (2 mg/kg/h), and acepromazine (0.15 mg/kg/h) to maintain deep, continuing anesthesia. Monitoring of electrocardiogram, bi-spectral electroencephalogram analysis, and limb reflexes assured adequate anesthesia. Femoral artery pressure and blood gases were continuously monitored via indwelling catheter (Diametrics, Roseville, Minnesota). Baseline ventilation was established and maintained with a tidal volume of 9 mL/kg, an inspiratory-expiratory ratio of 1:2, and an F_{IO_2} of 0.5. Frequency was adjusted to maintain a P_{aCO_2} of 35–45 mm Hg, with PEEP set to either 1 cm H_2O or 10 cm H_2O. A chest tube (#24 French) was positioned in the dorsal aspect of the right pleural space via a small thoracotomy. The animal was then transported to the CT suite, where FRC was determined via FRC-WI/WO (Carestation, E-COVX, General Electric, Madison, Wisconsin) at PEEP of 1 cm H_2O, followed by an end-expiratory 64-slice CT scan (LightSpeed VCT, GE Healthcare, Milwaukee, Wisconsin). The CT acquisition parameters were 120 kVp, tube current 173–575 mA, collimation of 64×0.625 mm, pitch of 1, and a gantry rotation time of 0.5 s. The images were reconstructed with "standard" kernel, with slice thickness of 2.5 mm and reconstruction field of view of 220–300 mm (pixel size 0.43–0.59 mm).

The FRC-WI/WO technique is a 3–5 min procedure that does not alter ventilation or require any additional equipment. Details of the FRC-WI/WO technique and associated calculations have been previously published.[3,18] We accepted the mean of the FRC-WI and FRC-WO values as the FRC determination. This sequence was repeated with PEEP of 10 cm H_2O, to cause an FRC increase. Moderate and large ipsilateral right pleural effusions were simulated by instilling isotonic radio-opaque contrast fluid volumes of 13 mL/kg and then 26 mL/kg into the right pleural cavity to reduce FRC (with tidal recruitment and collapse), at both PEEP levels. The isotonic radio-opaque solution was 100 mL of iopromide (Ultravist Injection, Bayer HealthCare, Germany, 300 mg iodine per mL) + 800 mL of 0.9% saline + 100 mL deionized water. End-expiratory CT images were obtained at each combination of PEEP and pleural effusion.

The CT images were traced manually, in a consistent manner that identified the circumferences of the lungs from anatomic landmarks in every slice (85–110 images per acquisition). The frequency-distribution histograms of Hounsfield units (the densities) from each slice were determined and compiled for each CT scan. The densities of the cuboids (the 3-dimensional CT region of smallest resolution) were multiplied by the cuboid dimension, and the number of respective cuboids for each density to calculate a lung volume for each scan.

Analysis

We compared the FRC-CT and FRC-WI/WO values for each effusion and PEEP condition. To assess agreement we calculated the mean of the differences (bias) and the standard deviation of the differences (precision). We constructed a Bland-Altmann plot to identify trends between the comparisons.

Results

The swine had a mean ± SD weight of 30.4 ± 3.7 kg. FRC values were simultaneously obtained via FRC-WI/WO (average of the FRC-WI/WO values) and FRC-CT, under

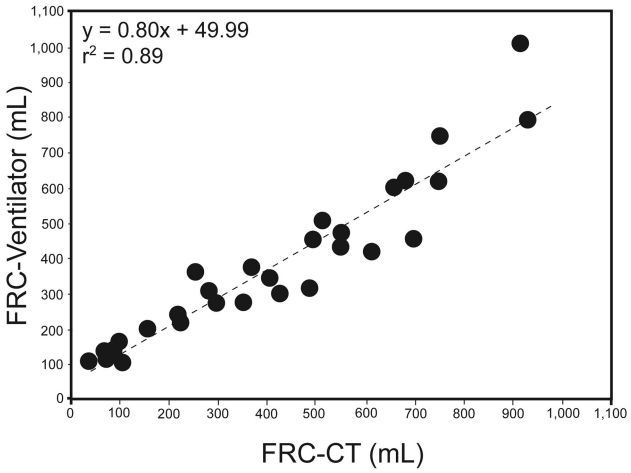

Fig. 1. Functional residual capacity measured via computed tomography (FRC-CT) versus via a wash-in/wash-out method (FRC-WI/WO).

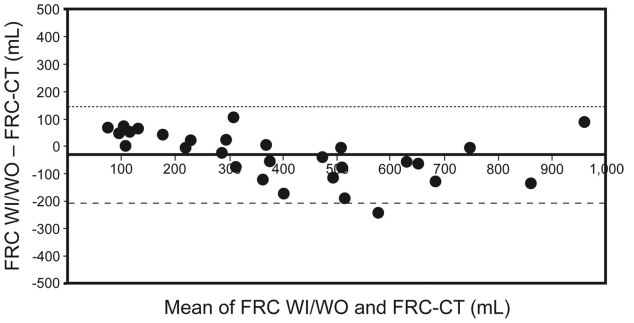

Fig. 2. Bland-Altman plot of the differences between functional residual capacity measured via computed tomography (FRC-CT) versus via a wash-in/wash-out method (FRC-WI/WO). The bias (mean difference) was −32 mL, and the precision (standard deviation of the differences) was ± 88 mL. The range of differences was 106 mL to −244 mL.

6 conditions: PEEP of 1 cm H_2O or 10 cm H_2O, and 3 levels of simulated effusion: 0, 13, and 26 mL/kg, The 2 FRC measurement techniques agreed closely ($r = 0.94$, $r^2 = 0.89$ (Fig. 1). Concordance between the techniques is displayed in a standard Bland-Altman plot (Fig. 2). The differences between the methods had a bias (mean difference) of −32 mL and a precision (standard deviation of the differences) of 88 mL. Figure 3 shows representative CT images of each condition. The addition of 26 mL/kg of fluid to the right hemithorax (simulated effusion) markedly reduced the aerated lung, to near-complete right-lung collapse, accompanied by severe bilateral lung compression that coincided with mean FRC-CT and CT-WI/WO values of only 86 mL and 142 mL, respectively. Figure 3 also displays the effect of restoring lung volume via application of PEEP. Both FRC methods measured similar mean increases in FRC to 474 mL (FRC-CT) and 387 mL (FRC-WI/WO) with the PEEP increased to 10 cm H_2O.

Discussion

This study demonstrates the accuracy of noninvasively measuring FRC via an integrated ventilator wash-in/wash-out system. Changes in FRC imposed by manipulations of pleural fluid volume and/or PEEP agreed closely with those measured by computed tomography. CT imaging demonstrated that PEEP induced dramatic lung recruitment in this model. Because instilling liquid into the right pleural space caused major FRC reductions and reversible atelectasis, the wash-in/wash-out method we tested appears to closely track changing mechanical characteristics in response to lung compression and PEEP.

Our severity-staged heterogeneous model presented a trial for this FRC-WI/WO method. At the higher liquid volume, ipsilateral lung was compressed to a nearly gasless state, while the ventilatory burden was carried by the "baby lung" created by the effusion. Extensive tidal recruitment occurred in both the "wet" and "dry" pleural compartments. FRC estimates were performed repeatedly under several amounts of compressive fluid. The 2 measuring techniques continued to agree closely at all volumes of pleural liquid, even when FRC-CT decreased to as low as 48 mL of aerated volume. Furthermore, the method retained accuracy when tidal recruitment was prevalent, as well as during higher PEEP conditions, when tidal recruitment was minimal. We can only speculate about the minor overestimates by FRC-WI/WO at low volumes and underestimates at moderate volumes. The FRC-WI/WO measure is based on several assumptions that may be slightly violated at low volumes[3,19] and sequestered lung units will be detected by FRC-CT only at moderate volumes.

Although increasing and maintaining recruitment is a primary goal of monitoring lung mechanics, traditional measurements of tidal compliance are often misleading as a guide to setting PEEP when chest-wall mechanics are unaccounted for and FRC remains unknown. Measuring esophageal pressure enables estimation of transpulmonary pressure, but does not account for lung heterogeneity. In calculations of tidal compliance, transpulmonary pressure is best referenced to absolute lung volume, enabled by FRC determinations; tracking FRC changes after PEEP adjustments is an attractive complement to routine tidal compliance calculations. As a measure of volume within open lung units, FRC indirectly reflects the prevalence of lung units that remain closed due to effusion, pneumonia, atelectasis, lung flooding, or inflammatory edema

Clinical Estimation of FRC

Aerated FRC has long been advocated as an important metric,[2] as it reflects the combined influences of lung com-

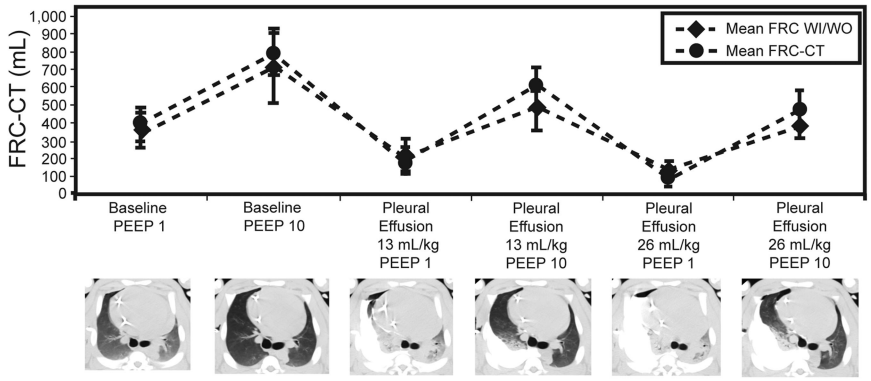

Fig. 3. Mean functional residual capacity measured via computed tomography (FRC-CT) versus via a wash-in/wash-out method (FRC-WI/WO) in the 6 experimental conditions, with a corresponding representative CT image below each condition. Note the considerable lung expansion when PEEP was 10 cm H_2O, and the bilateral lung collapse caused by each pleural-effusion volume when PEEP was 1 cm H_2O.

pliance, chest-wall compliance, pleural-space-occupying fluids, and airway distending pressure (ie, PEEP). Although a variety of gas-dilution and tracer[8,9] methods have been developed for noninvasive estimation, the challenge of conveniently, repeatedly, and reliably assessing FRC has prevented its use as a practical tool for clinical purposes. In 2004, Rylander et al determined gas exchange, lung mechanics, and FRC via FRC-CT with concurrent CT imaging in an oleic-acid-injury model.[22] Compared to tidal compliance, they concluded that FRC was a more sensitive indicator of changes in lung-tissue aeration and recruitment. Cross-sectional validation studies of FRC measured via gas dilution have uniformly reported that raising PEEP, as anticipated, increases FRC in animal models, in ventilated patients with normal lungs, and in those with primary or secondary pulmonary disorders.[19,20] Published investigations have also shown that FRC may help characterize the extent of lung pathology in patients with COPD and acute lung injury/acute respiratory distress syndrome.[4,10,17,18,20]

Lambermont et al recently confirmed a direct relationship between FRC and airway pressure as PEEP was decremented from 20 to 0 cm H_2O in oleic-acid-injured swine.[19] Joint FRC and tidal compliance measurements during PEEP titration appeared useful in seeking to maximally recruit unstable lung units while avoiding over-distention.[19] Bikker et al examined the relationship between oxygen exchange and FRC in ventilated patients.[20] The relatively poor correlation between them can be explained by aerated lung units that are under-perfused or over-distended, by hypoxic vasoconstriction, or by unaccounted-for changes of F_{IO_2} induced by the measuring technique. As such investigations suggest, gas-dilution measurements of FRC hold considerable promise, but their clinical deployment has been constrained by our inability to conveniently perform them.

A nitrogen wash-out technique that uses fast-response O_2 sensors for assessing FRC in ventilated patients was described in 1982.[12] In 1993, Fretschner et al introduced an integrated nitrogen wash-in/wash-out technique that measured FRC via a rapid CO_2 sensor during step changes in F_{IO_2}.[13] Limitations to expanded use of this method included the need for a 0.3 step change in F_{IO_2} and the need to synchronize signals from the flow and gas sensors. Although not CT-verified, that method appeared to present the prospect of tracking directional changes in lung volume in response to therapeutic interventions. Ventilatory pattern could remain unaltered during the measurement, and extensive equipment modifications were not required. In 28 patients with acute respiratory failure, Olegard et al used a refinement of the FRC-WI/WO technique with only 0.1 steps of F_{IO_2},[18] and lung-model testing to verify the fidelity of the technique. Calculations were performed by detection of end-inspiratory/end-expiratory gas fractions and the technique did not require synchronization of flow and gas sensor signals.

Previous verification studies evaluated respirable gas measurements of FRC with CT imaging or inert tracer-gas standards.[3,8,14,15,17] In 2004, Pesenti et al compared FRC-CT to FRC determined via helium dilution in 21 patients with acute respiratory distress syndrome, and found an r^2 of 0.88 between the techniques.[8] Subsequent FRC studies in healthy volunteers and ventilated patients helped validate this tracer-gas method.[14] In 2008, Patroniti et al found comparable results in ventilated patients with an oxygen FRC-WI/WO method and the previously CT-confirmed helium-dilution method.[17] A comparison of the FRC-WI/WO method employed in our study was also tested in a 30-patient report by Chiumello and colleagues, in 2008.[3] The FRC-CT, FRC via helium dilution, and FRC-WI/WO methods were comparable.[3]

Uncontrolled, cross-sectional validation studies in patients have demonstrated associations among disease condition, PEEP settings, and FRC. Gas-dilution FRC methods appear to be measuring an important lung characteristic that supplements traditional measurements of tidal compliance.[22] Unfortunately, no published study has tracked

the progression or regression of disease over time with serial measurements of FRC. Our model simulated such a sequence of observations by instilling large volumes of pleural liquid.

Limitations

We studied only one tidal volume, and ventilated normal lungs at moderate F_{IO_2} under passive conditions. One or more of these characteristics usually do not apply in the clinical setting. FRC cannot reliably be determined by this method at very high F_{IO_2}. Circuit leaks or variable ventilatory patterns will cause measurement errors that can invalidate results, so deep sedation may be necessary for consistency during FRC-WI/WO measurements.

Conclusions

We found concordance between FRC measured via an oxygen-based FRC-WI/WO method and quantitative FRC-CT in a challenging experimental model of unilateral pleural effusion of varying severity. The main practical advantage of the wash-in/wash-out technique is its incorporation into ventilator operation without requiring adjustments to ventilation.

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