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Maximal Expiratory Flow at FRC ($V'_{\max_{\text{FRC}}}$):

Methods of Selection and Differences in Reported Values

Anastassios C. Koumbourlis, MD, MPH^{1,2,*}, Xin C. Chen, MS³, J. Sunil Rao, PhD³, Mark D. Schluchter, PhD³, Kirk Easley, MS³, Andrew A. Colin, MD⁴, Peter Hiatt, MD⁵, Meyer Kattan, MD⁶, Kevin McCarthy⁷, Robert B. Mellins, MD¹, Hannah Peavy, MD⁸, Arnold C.G. Platzker, MD⁹, Suzanne Steinbach, MD¹⁰, Andrew Ting, MD⁶, Michael D. Weisner, PhD¹¹, Mary Ellen B. Wohl, MD⁴, and for the Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted Human Immunodeficiency Virus (P²C² HIV) Study Group and National Heart, Lung and Blood Institute

¹Pediatric Pulmonary Division, Columbia-Presbyterian Medical Center, New York, New York

²Critical Care Division, Columbia-Presbyterian Medical Center, New York, New York

³Departments of Biostatistics and Epidemiology, Cleveland Clinic Foundation, Cleveland, Ohio

⁴Children's Hospital/Harvard Medical School, Boston, Massachusetts

⁵Critical Care Center, Texas Children's Hospital, Houston, Texas

⁶Pediatric Pulmonary and Critical Care Division, Mount Sinai School of Medicine, New York, New York

⁷Department of Pulmonary and Critical Care Medicine, Cleveland Clinic Foundation, Cleveland, Ohio

⁸National Heart, Lung and Blood Institute, Bethesda, MD

⁹Division of Pediatric Pulmonology Children's Hospital, Los Angeles, California

¹⁰Boston University School of Medicine, Boston, Massachusetts

¹¹Equilibrated BioSystems, Inc., Smithtown, NY

Summary

We compared three methods of reporting maximal expiratory flow ($V'_{\max_{\text{FRC}}}$) measured in partial expiratory flow-volume curves (PEFVCs) at the point of functional residual capacity (FRC). PEFVCs were obtained with the rapid thoracoabdominal compression technique (RTC) on a total of 446 occasions in 281 HIV-negative, asymptomatic infants (4.8–28.1 months old). Three different expressions of $V'_{\max_{\text{FRC}}}$ were recorded: 1) the highest measured flow ($\max V'_{\text{FRC}}$), 2) the mean of the three highest flows ($\text{mean} 3V'_{\text{FRC}}$), and 3) the flow at FRC in a composite curve ($\text{comp} V'_{\text{FRC}}$) consisting of PEFVCs, obtained at different jacket pressures and superimposed at their distal limb. The numerical value of $\max V'_{\text{FRC}}$ was 7.4% ($\pm 5.6\%$) higher than the $\text{mean} 3V'$

V'_{FRC} , and 11.9% ($\pm 17.7\%$) higher than the $\text{comp}V'_{FRC}$; the $\text{mean}3V'_{FRC}$ was 5% ($\pm 18.3\%$) higher than the $\text{comp}V'_{FRC}$. Bland-Altman analysis was used to evaluate the agreement between the three indices. The mean difference and 95% limits of agreement were: $\text{max}V'_{FRC} - \text{mean}3V'_{FRC}$, 14 ± 18 ml/sec; $\text{max}V'_{FRC} - \text{comp}V'_{FRC}$, 23 ± 58 ml/sec; and $\text{mean}3V'_{FRC} - \text{comp}V'_{FRC}$, 10 ± 52 ml/sec. The differences between the slopes of the three indices (regressed against height) were statistically significant, although clinically unimportant. We conclude that despite their high correlation, the $\text{mean}3V'_{FRC}$ and $\text{max}V'_{FRC}$ should not be used interchangeably, and that the composite analysis, although useful, does not improve the reproducibility of $V'_{\text{max}FRC}$, and thus it cannot be recommended for routine use in its current form.

Keywords

rapid thoracoabdominal compression; partial expiratory flow-volume curves; maximal expiratory flow; infant pulmonary function testing

INTRODUCTION

For the past three decades, the rapid thoracoabdominal compression (RTC) technique has been the most widely used method for infant pulmonary function testing (PFT).¹⁻⁷ The technique allows the performance of partial expiratory flow-volume curves (PEFVCs), and lower airway function is assessed on the basis of the value of the maximal forced expiratory flow rate at the point of functional residual capacity (FRC) ($V'_{\text{max}FRC}$). Serial measurements under gradually increasing jacket pressures are performed until there is no further increase in the measured flow. $V'_{\text{max}FRC}$ is then reported either as the single highest recorded flow, or more often as the mean of the three highest recorded flows with or without conditions about the accepted variability between them.³⁻⁷ The magnitude and clinical importance of the difference between these two indices have not been studied systematically.

The initial impetus for the current study was to assure the comparability of data generated at multiple sites performing infant PFTs as part of a large multicenter study.⁸ The specific objective was to provide standard analytic techniques and to establish uniform criteria for the reporting of the $V'_{\text{max}FRC}$. Thus, we performed a systematic comparison of the two most commonly used expressions of $V'_{\text{max}FRC}$, i.e., the mean of the three highest recorded flows ($\text{mean}3V'_{FRC}$) and the highest recorded flow rate ($\text{max}V'_{FRC}$), in order to determine their variability and the magnitude of their difference. In addition, we evaluated a novel method of determination of $V'_{\text{max}FRC}$, based on the construction of a composite flow-volume curve, consisting of PEFVCs overlapping on their descending limb.⁹

METHODS

The data analyzed in this study were obtained from the database of a large multicenter study evaluating prospectively the pulmonary and cardiovascular complications of vertically transmitted HIV infection. The design of the study was described in detail elsewhere.¹⁰ All patients included in this analysis were HIV-negative, asymptomatic infants. The Institutional Review Board at each of the participating centers approved the study, and informed consent

was obtained from the subject's parent or guardian before enrollment. All tests were performed on the Sensormedics 2600 Infant Pulmonary Function Lab (Sensormedics Corp., Yorba Linda, CA) under sedation with oral chloralhydrate (50–100 mg/kg), according to the guidelines of the ATS/ERS Joint Committee.⁶

Detailed guidelines for the recording, reporting, and analysis of the data were agreed upon by all participating centers. The starting compression pressure (jacket pressure) was 30–40 cmH₂O, and it was increased in increments of 10 cmH₂O thereafter. At least two PEFV curves were obtained at each level of jacket pressure. The testing ended when an increase in jacket pressure level did not produce an increase in V'_{FRC} , or when the jacket pressure exceeded 80–100 cmH₂O. After the testing session ended, the highest flow rate at FRC ($\max V'_{FRC}$) and the mean of the three highest measured flows at FRC ($\text{mean}3V'_{FRC}$) were recorded for each patient. Each test was then analyzed with the use of a special software program developed specifically for the P²C² study. The program provided a graphic interface allowing multiple curves to be moved along the volume axis, so they could be superimposed on their descending limb. The initial curve was selected among those obtained with the jacket pressure before the highest (usually between 50–70 cmH₂O), because of concerns that the highest compression pressure may result in a decrease in lung volume due to atelectasis.¹¹ Various curves among those with the highest expiratory volume (V_e), the highest V'_{FRC} , or the highest peak flow were then superimposed on their descending limb, and a composite curve was automatically constructed by the software. The composite curve had to consist of at least three PEFVCs produced by at least two different jacket pressures. If their overlapping segment was over a volume equivalent to at least 20% of the exhaled tidal volume (calculated automatically by the software program), it was considered as evidence of flow limitation. The flow at the point of FRC of the composite flow-volume curve ($\text{comp}V'_{FRC}$) was then recorded (Fig. 1).

The agreement between the three indices was explored by Bland-Altman analysis, which plots the difference or the percent difference between two measurements against their combined mean.¹² The regression-based 95% limits of agreement for $V'_{\max FRC}$ were also calculated as described by Bland and Altman,¹² using the earliest PFT study per child ($n = 281$). Regressions of the three indices vs. height from 281 children, and 446 studies, were compared in a single longitudinal regression model that accounted for correlations among the three indices at the same visit and across visits (SAS Proc Mixed).¹³ All statistical tests were two-tailed, and $P = 0.05$ was considered statistically significant.

RESULTS

Data from 446 studies performed on 281 patients were included in the analysis. Of 281 patients, 145 (52%) were male. The group contained 148 (53%) black non-Hispanic infants, 84 (30%) Hispanic infants, 37 (13%) white non-Hispanic infants, and 12 (4%) from other racial groups. The median age was 12 months (range, 5–28 months), and the median height was 73 cm (range, 54–92 cm). The PEFVCs used in this analysis were obtained with a mean ($\pm$ SD) jacket pressure of 72 ± 19 cmH₂O. The mean ($\pm$ SD) difference between the lowest and highest of the three values that were used to compute the $\text{mean}3V'_{FRC}$ (expressed as percentage of the largest) was $15\% \pm 10\%$ (median, 12.5; interquartile range, 7.1–20.2).

The mean ($\pm$ SD) values of the three indices (in ml/sec) were: $\max V'_{\text{FRC}}$, 215.4 ± 122.3 ; $\text{mean} 3V'_{\text{FRC}}$, 200.9 ± 116.9 ; and $\text{comp} V'_{\text{FRC}}$, 191.0 ± 113.9 . The correlation coefficients between indices ranged from 0.96–0.99. The slopes for the three flow indices vs. height were significantly different from zero. The differences between slopes were small in magnitude.

The mean numerical difference between each pair of indices, as well as the percent difference between them, is presented in Table 1. Equations describing the relationships between the three indices were also explored by fitting a regression through the origin of each pair of indices (Table 1).

The mean ($\pm$ SD) differences (ml/sec) calculated with Bland-Altman analysis were: $\max V'_{\text{FRC}} - \text{mean} 3V'_{\text{FRC}}$, 14 ± 12 ml/sec; $\max V'_{\text{FRC}} - \text{comp} V'_{\text{FRC}}$, 23 ± 35 ml/sec; and $\text{mean} 3V'_{\text{FRC}} - \text{comp} V'_{\text{FRC}}$, 10 ± 32 ml/sec. Although the lowest difference was found between $\text{mean} 3V'_{\text{FRC}}$ and $\text{comp} V'_{\text{FRC}}$, the best overall agreement was between $\max V'_{\text{FRC}}$ and $\text{mean} 3V'_{\text{FRC}}$ because they had the lowest standard deviation. Since proportional differences were seen when comparing $\text{mean} 3V'_{\text{FRC}}$ and $\max V'_{\text{FRC}}$, a regression approach for nonuniform differences was also used to assess agreement (Fig. 2). The regression-based 95% limits of agreement were as follows: $\max V'_{\text{FRC}} - \text{mean} V'_{\text{FRC}}$, ± 18 ml/sec; $\max V'_{\text{FRC}} - \text{comp} V'_{\text{FRC}}$, ± 58 ml/sec; and $\text{mean} V'_{\text{FRC}} - \text{comp} V'_{\text{FRC}}$, 52 ml/sec.

DISCUSSION

Our study presents a comprehensive comparison of three different expressions of maximal flow at the point of FRC, measured in PEFV curves produced with the RTC technique. Our database (the largest derived from a single study) consisted of data collected prospectively in laboratories utilizing exactly the same equipment and following uniform protocols for the performance, recording, analysis, and quality control of the tests. We found that the difference between the numerical values of the three expressions of $V'_{\max \text{FRC}}$ is actually small and probably clinically unimportant. Moreover, we found that the accuracy of the measurement did not actually increase with the use of more sophisticated methods of analysis such as the composite curve.

Our analysis focused on the technical aspects of the PEFV curves, and not on the effects of any particular disease process on lung function. Thus, although our data were derived from a rather unique population (HIV-negative infants born to HIV-positive mothers), our findings are applicable to any infant undergoing testing with the RTC technique. The general applicability of our study is strongly supported by the findings of the recently published multicenter study on normative values of $V'_{\max \text{FRC}}$ in healthy infants by Hoo et al.¹⁴ Using a similar analysis to ours, these investigators reported that the “best” (i.e., highest) recorded flows were related to the “mean of the three highest” by the equation: “best $V'_{\max \text{FRC}}$ ” = $1.07 \times \text{mean } V'_{\max \text{FRC}}$, which is virtually identical to the equations derived from our patient population (Table 1).

Flow limitation in healthy individuals was demonstrated to occur with pleural pressures of 10 cmH₂O.^{15–17} Therefore, the range of jacket pressures used in our and other clinical

studies (40–100 cmH₂O) should be sufficient to produce flow limitation (assuming that at least 20% of this pressure is being actually transmitted to the lungs).^{18,19} However, because the transmission rate is quite variable,^{18–20} flow limitation may not be achieved even when high jacket pressures are used. This may explain, at least in part, the failure to produce flow limitation reported by some investigators.

Flow limitation is assumed to occur after more than 50–70% of vital capacity has been exhaled. This is a volume range that is likely to include the point of FRC.^{16,17} However, in spontaneously breathing infants, FRC is known to be quite variable, affected by factors such as changes in end-expiratory level, respiratory rate, and sleep state. Therefore, the lack of change in V'_{FRC} with increases in jacket pressure may be due to true flow limitation, but it may also be the result of changes in the transmission of jacket pressure and/or of changes in FRC. As an alternative to these uncertainties, our group evaluated the composite technique. The technique is based on the assumption that similar to maximal expiratory flow-volume (MEFV) curves, the overlapping segment of PEFVCs, superimposed in their distal end, is flow-limited as it is in overlapping MEFV curves. The rationale of the composite is supported by the findings of Henschen and Stocks, who showed that even PEFVCs with considerably different V'_{maxFRC} may share an overlapping segment that can be superimposed on the distal (flow-limited) end of the MEFV curve.²¹ The flow at FRC in the composite curve ($compV'_{FRC}$) was calculated automatically by the software, and it was assumed to be flow-limited if it were within the overlapping segment. The fact that the value of $compV'_{FRC}$ was highly correlated to the other two indices suggests that they all represent points located very close to each other on the flow-limited segment. Unfortunately, although the composite provided a reliable qualitative assessment of flow limitation, it did not decrease the variability seen in the other indices, and therefore it cannot be recommended for routine use in its current form.

It is obvious that the RTC technique in its current form has considerable limitations affecting its accuracy and reliability. Ideally, infant PFTs should be performed with methods that allow the inflation of the lungs to total lung capacity and their full emptying to residual volume. The deflation flow-volume curve technique generally satisfies these conditions by allowing total control of the patient's respiration and consistent transmission of preset inflating and deflating pressures.²² However, it requires endotracheal intubation, sedation, and (if possible) muscle relaxation of the patient, and therefore it cannot be used in the general population. The raised volume technique, a modification of RTC that has become available during recent years (after the testing of infants in the P²C² study had been concluded), has shown promise in closing this gap.^{23,24} The technique allows the performance of near-maximal flow-volume curves that can provide reliable measurements of forced expiratory flows measured at different points of forced vital capacity, thus obviating exclusive reliance on V'_{maxFRC} .

In conclusion, our analysis suggests that the difference between the highest flow at FRC and the mean of the three highest flows at FRC is very small and probably without any real physiologic or clinical importance. However, even small numerical differences may lead to erroneous comparisons if they are used interchangeably. The considerably more complex analysis of PEFV curves with the composite curve, although qualitatively reliable, did not

increase the objectivity of the measurement, and therefore it is not recommended for routine use in its current form. However, it could become a useful adjunct for the detection of flow limitation when it cannot be ascertained by $V'_{\max_{\text{FRC}}}$ alone.

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Fig. 1. Representative schematic diagram of a composite curve (thick line) consisting of multiple PEFVC (thin lines) obtained with different jacket pressures. Dashed vertical lines are cursors, placed at either end of flow-limited segment and used to determine slope and extrapolated RV (RVextr).

Fig. 2. Regression-based 95% limits of agreement for $V'_{\max FRC}$. Top: $mean3V'_{FRC}$ and $compV'_{FRC}$. Middle: $maxV'_{FRC}$ and $compV'_{FRC}$. Bottom: $maxV'_{FRC}$ and $mean3V'_{FRC}$. For each pair of indices, solid line is fitted regression, and two dashed lines represent 95% limits of agreement.

TABLE 1Differences and Regression Equations for $\max V'_{\text{FRC}}$, $\text{mean}3V'_{\text{FRC}}$, and $\text{comp}V'_{\text{FRC}}$ ¹

Index (n = 446)	Difference (ml/sec)	% difference	Equation
$\max V'_{\text{FRC}} - \text{comp}V'_{\text{FRC}}$			$\max V'_{\text{FRC}} = 1.109 \times \text{comp}V'_{\text{FRC}}$
Mean $\pm$ SD	24.4 $\pm$ 36.3	12.2 $\pm$ 17.7	R = 0.974
Median (IQR)	16.0 (4.0–38.0)	8.8 (1.8–20.0)	
$\max V'_{\text{FRC}} - \text{mean}3V'_{\text{FRC}}$			$\max V'_{\text{FRC}} = 1.071 - \text{mean}3V'_{\text{FRC}}$
Mean $\pm$ SD	14.5 $\pm$ 13.2	7.4 $\pm$ 5.6	R ² = 0.998
Median (IQR)	10.7 (6.0–18.7)	6.1 (3.4–10.2)	
$\text{mean}3V'_{\text{FRC}} - \text{comp}V'_{\text{FRC}}$			$\text{mean}3V'_{\text{FRC}} = 1.035 - \text{comp}V'_{\text{FRC}}$
Mean $\pm$ SD	9.9 $\pm$ 32.0	5.6 $\pm$ 17.1	R ² = 0.976
Median (IQR)	4.8 (–6.7–21.7)	3.0 (–4.2–11.9)	

¹ % difference is numerical difference as a percentage of highest value. IQR, interquartile range. Equations were based on earliest PFT study per child (n = 281), and they were calculated by a regression through origin of each pair of indices.