Hyperinflation is Associated with Increased Respiratory Rate and is a More Sensitive Measure of Cystic Fibrosis Lung Disease During Infancy Compared to Forced Expiratory Measures

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Keywords: Pulmonary function testing, pulmonary physiology, cystic fibrosis, infant pulmonary function

Dear Pediatric Pulmonology Editors,

On behalf of all co-authors, we affirm that the manuscript entitled “Hyperinflation is Associated with Increased Respiratory Rate and is a More Sensitive Measure of Cystic Fibrosis Lung Disease During Infancy Compared to Forced Expiratory Measures” is being submitted only to Pediatric Pulmonology and will not be submitted elsewhere while under consideration. All co-authors have reviewed and approved the manuscript. Please address correspondence to:

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ABSTRACT

Background: The goal of this study was to identify clinical features associated with abnormal infant pulmonary function tests (iPFTs), specifically functional residual capacity (FRC), in infants with cystic fibrosis (CF) diagnosed via newborn screen (NBS).

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We hypothesized that poor nutritional status in the first 6-12 months would be associated with increased FRC at 12-24 months. **Methods:** This study utilized a combination of retrospectively and prospectively collected data from ongoing research studies and iPFTs performed for clinical indications. Demographic and clinical features were obtained from the electronic medical record. Forced expiratory flows and volumes were obtained using the raised volume rapid thoracoabdominal technique (RVRTC) and FRC was measured via plethysmography. **Results:** A total of 45 CF NBS infants had iPFTs performed between 12-24 months. Mean forced vital capacity, forced expiratory volume in 0.5 second, and forced expiratory flows were all within normal limits. In contrast, the mean FRC z-score was 2.18 (95%CI=1.48, 2.88) and the mean respiratory rate (RR) z-score was 1.42 (95%CI=0.95, 1.89). There was no significant association between poor nutritional status and abnormal lung function. However, there was a significant association between higher RR and increased FRC, and a RR cutoff of 36 breaths/min resulted in 92% sensitivity to detect hyperinflation with 32% specificity. **Conclusions:** These results suggest that FRC is a more sensitive measure of early CF lung disease than RVRTC measurements and that RR may be a simple, non-invasive clinical marker to identify CF NBS infants with hyperinflation.

**INTRODUCTION**

Cystic fibrosis (CF) is the most common life-limiting genetic disease in Caucasians and pulmonary disease remains the primary etiology of morbidity and mortality in CF. Lung disease in CF is present during infancy and events early in life play a critical role in long-term outcomes. Early *Pseudomonas aeruginosa* (Pa) infection, elevated free neutrophil elastase in bronchoalveolar lavage fluid, history of wheeze and history of hospitalizations
are some risk factors in infancy and early childhood associated with lower lung function and/or bronchiectasis in later childhood\textsuperscript{1-4}. Nutritional status within the first years of life predicts lung function in later childhood\textsuperscript{4-6}. Despite the advent of newborn screening (NBS), CF lung disease continues to occur in the youngest population; however, it is often present without symptoms\textsuperscript{7-11}. Given that lung function in infancy tracks into preschool years\textsuperscript{12-14}, identifying sensitive clinical markers of early disease is imperative. Early identification will lead to treatment and intervention, ultimately preventing or mitigating CF lung disease.

The ability to assess lung disease during infancy remains challenging\textsuperscript{15-17}. Chest computed tomography is a sensitive measure of early CF lung disease, but requires sedation and exposure to radiation\textsuperscript{1,18}. Infant pulmonary function tests (iPFTs) detect early lung disease but require sedation and a high level of technical skill\textsuperscript{16,19}. The success rate of obtaining forced expiratory flows (FEF) via the raised volume rapid thoracoabdominal technique (RVRTC) in multicenter clinical trials is not as high as obtaining functional residual capacity via plethysmography (FRC\textsubscript{pleth})\textsuperscript{16,17,19}. Although FRC\textsubscript{pleth} has been measured in studies of infants with CF, data from infants diagnosed via NBS are more limited, with only one other cohort previously described\textsuperscript{7,9,16,20,21}. Given that early CF lung disease begins in the small peripheral airways, FRC may be a more sensitive measure of early CF lung disease when compared to forced expiratory flows. In CF NBS infants, there is limited information correlating FRC with clinically useful indicators of early lung disease.

The objective of our study was to identify clinical features associated with abnormal lung function, specifically FRC, in CF NBS infants. We hypothesized that poor
nutritional status in the first 6-12 months of life is associated with more hyperinflation at 12-24 months of age.

METHODS

Study Design

This study utilized a combination of retrospectively and prospectively collected data. The retrospective data were acquired from 23 infants who had iPFTs performed at Riley Hospital for Children from 2012-2018 as part of clinical care and 12 infants who underwent iPFTs as part of other research studies (ClinicalTrials.gov NCT01973192 and NCT04026360). We prospectively recruited an additional 10 infants followed at the CF Center at Riley Hospital for lung function testing, bringing the total sample size to 45 infants.

The inclusion criteria were (1) an age at time of iPFTs of 12-24 months of age and (2) a diagnosis of CF through NBS. Exclusion criteria included gestational age less than 36 weeks. The study was approved by the Indiana University Institutional Review Board and informed written consent was obtained from the parents of prospectively recruited infants.

Clinical data, including mutation analysis, ethnicity, respiratory cultures, antibiotic and systemic steroid courses, smoke exposure, history of wheezing and nutritional indices, were obtained from the electronic medical record. Nutritional status indices obtained for this study were weight-for-age (WFA) and weight-for-length (WFL) z-scores based on the Centers for Disease Control growth charts during the first 24 months of life. Weight and crown-heel lengths were obtained during CF clinic visits and during iPFT testing.

Measurement of Lung Function

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All iPFTs were performed using the Jaeger BabyBody device (CareFusion, San Diego, California) equipment. Infants were clinically stable at time of testing without illnesses in the preceding 2 weeks. Two patients within the retrospective cohort were hospitalized within 28 days of iPFT testing. Infants were sedated with 50-100 mg/kg oral chloral hydrate and cardiopulmonary monitoring was performed throughout testing. FRC was measured using plethysmography. Forced expiratory flows were obtained using the RVRTC technique. All lung function parameters were obtained according to published guidelines. Infant PFT values were converted to z-scores based on previously published reference equations. Respiratory rate data were obtained from tidal breathing analysis in 37 infants during iPFT testing for a minimum period of 20-30 breaths and from the vital signs flowchart in 8 infants while a facemask was in place after sedation was administered. Only iPFT data that met published quality control criteria were used for analysis.

**Statistics**

Data were examined for calculation and distribution for statistical analysis using SAS v9.4 (SAS institute, Cary, NC). A power analysis performed prior to the study showed that with a sample size of 44, an alpha level of 0.05 and power ≥ 0.80, we could detect a significant association between the clinical variables with iPFT z-scores when the correlation was as low as 0.41. Statistical significance was defined as p ≤ 0.05. For categorical variables, frequency and percentage analysis were performed. For continuous iPFT variables, mean and 95% confidence intervals were calculated. Chi-square analysis was used to evaluate the proportion of infants in each group with abnormal FRC vs. forced expiratory volume in 0.5 seconds (FEV<sub>0.5</sub>) parameters. To determine the
association between WFA/WFL z-score and lung function, Pearson correlation coefficients were calculated. Associations between lung function and categorical clinical risk factors were calculated using Student’s t-test or Mann-Whitney U test as appropriate. Correlation between FRC and respiratory rate (RR) was determined using Spearman rank-sum and Pearson correlation coefficients. Since our data were not normally distributed, we reported the result from Spearman, a non-parametric test that is less influenced by the effect of outliers. Because our final sample size was relatively small, we chose to include all of the data from all the infants in the study after confirming that they had no change in clinical status prior to performing iPFTs. We compared FRC z-score to both absolute RR and RR z-score. Since the results were similar, we have chosen to report the absolute RR results, since this is more clinically applicable. We performed additional analyses to assess the independent contribution of sex, race, and weight at testing in our model. We conducted analyses stratifying infants into normal versus obstruction or hyperinflation. For these analyses, we defined obstruction as an FEV_{0.5} z-score < -2 and hyperinflation as FRC z-score > 2. To identify the respiratory rate cutoff that yielded the best combination of sensitivity and specificity in predicting hyperinflation, we used logistic regression with Youden’s Index.

RESULTS

Study Population

Figure 1 shows the derivation of the study cohort. A total of 45 infants were included in this study. Of the 57 patients with previous iPFTs, 35 met our inclusion and exclusion criteria. Fourteen infants followed at the CF Center at Riley were eligible for iPFTs for the prospective cohort during the study period and the parents of 12 infants (87%) agreed
to testing. Eleven infants ultimately underwent iPFT, of which 10 (91%) yielded research-quality data. Clinical characteristics of the cohort are described in Table 1. The majority of infants were Caucasian (95.6%) and had homozygous Class I, II or III mutations (93.1%). The most common respiratory infection detected was methicillin-sensitive *Staphylococcus aureus* (66.7%) and 35.6% of the cohort had a history of at least one positive Pa respiratory culture. Oral antibiotic use in the first year was high, with 91.1% of infants receiving at least one course and a median of 2 courses of antibiotics.

**Lung Function Data**

Research-quality FRC and FEV$_{0.5}$ data were obtained in 96% and 100% of infants, respectively. As demonstrated in Table 2, the forced vital capacity (FVC) z-score was decreased, but all other RVRTC data were within normal limits. In contrast to the RVRTC data, the mean FRC z-score was significantly elevated at 2.18. No significant difference in tidal volume was found in infants with or without hyperinflation. Figure 2 demonstrates that the proportion of patients with hyperinflation (44%) was significantly higher than infants with diminished FEV$_{0.5}$ (7%) (p<0.001). Mean RR was also significantly elevated, and correlated with FRC (Figure 3) with a Spearmen correlation coefficient of 0.377 (p=0.01). This correlation remained significant when excluding the 2 infants with recent hospitalization, adjusting for age, sex and weight. Using logistic regression to calculate Youden’s index, we found that a RR cutoff of 36 breaths/min resulted in 92% sensitivity to detect hyperinflation with 32% specificity.

**Risk Factors for Abnormal Lung Function**

We next examined the association between clinical risk factors and abnormal lung function (Table 3). No significant association was seen between WFA or WFL z-scores at
3 months of age, 6 months of age or 6 months prior to iPFT and lung function z-scores. No significant association was seen between WFA or WFL z-score at 6 months of age and raw lung function values (data not shown). We did not observe any significant association between clinical risk factors and hyperinflation. Consistent with previously reported literature \(^3,28\), a history of wheezing (p=0.02) and smoke exposure (p=0.05) were associated with diminished FEV\(_{0.5}\).

**DISCUSSION**

In this mixed cohort of retrospectively and prospectively collected iPFT data from CF NBS infants, we found that hyperinflation was more common than diminished FEV\(_{0.5}\) and FEF. Furthermore, RR was elevated and correlated with increased FRC. These results suggest that FRC is a more sensitive measure of early CF lung disease and that measurement of RR may be a simple, non-invasive clinical marker to identify CF NBS infants with hyperinflation.

Although there have been several iPFT studies in CF NBS infants, few have reported FRC data \(^7,8,29,30\). Some of the FRC measurements in previous studies were performed using multiple breath washout (MBW), which has been shown to underestimate hyperinflation when compared to plethysmography in infants \(^31\). In a multicenter iPFT study of CF infants primarily diagnosed clinically, hyperinflation was more common than diminished FEV\(_{0.5}\) \(^16\). Our results are similar, suggesting that early diagnosis of CF through NBS does not prevent hyperinflation. The only other study to report FRC\(_{\text{pleth}}\) in CF NBS infants has been from the London Cystic Fibrosis Collaboration \(^7,9,11\). FRC was elevated in this Collaborative, but hyperinflation was less common and obstruction, as measured by FEV\(_{0.5}\), was more common in this group when compared to our cohort. Our
finding that hyperinflation was much more common than decreased FEV\(_{0.5}\) in CF NBS infants highlights that small airway obstruction is present in early life. It is also consistent with chest computed tomography findings that demonstrate that air trapping is the earliest and most prevalent sign of lung disease in CF NBS infants\(^2\).

Elevated RR in children and infants with CF has been described previously\(^{32-34}\). These studies have not shown an association between RR and FEF or tidal breathing indices, although one study cohort did report an association between elevated RR and increased lung clearance index (LCI) in infants with CF\(^{34,35}\). However, this study did not report an association between RR and FRC obtained via MBW, which may underestimate FRC\(_{\text{pleth}}\). They also did not define RR thresholds associated with abnormal LCI. With a cutoff RR of 36, we demonstrated a high sensitivity for identifying infants with hyperinflation as measured through FRC\(_{\text{pleth}}\), a sign of early lung disease. In contrast to measurement of FRC\(_{\text{pleth}}\) in infants, which requires a high degree of technical skill and expensive equipment, measurement of RR during quiet sleep is much simpler, non-invasive and does not require sedation, suggesting it may be a clinically useful marker of infants at an increased risk of more severe early lung disease.

Similar to previous studies, we found that wheezing and second-hand smoke exposure were associated with worse lung function\(^3,28\). A history of Pa infection was also associated with lower lung function, but this was not statistically significant in our cohort. Several studies have shown a relationship between early nutritional status and lung function at 6-12 years\(^5,6,36\), and similar to other iPFT studies we observed lower WFA z-scores in our cohort\(^7,8\). However, we were unable to demonstrate that lower nutritional indices in early infancy were associated with lower lung function later in
infancy. Potential reasons for this include the possibility that FEF and FRC_{pleth} are not sensitive enough to detect a significant association or that 6 months was an insufficient time between lung function and the measured outcomes to detect a significant association.

Our results have potential implications for clinical care and research. Hyperinflation was significantly more common than decreased FEF and FEV_{0.5}, suggesting that it may be a more sensitive measure of early lung disease and could serve as an additional sensitive measure for research studies evaluating early infant CF lung disease. Measurement of FRC_{pleth} requires less technical skill compared to FEF, but the equipment is still expensive and not widely available. RR correlated significantly with hyperinflation. Since RR can easily be obtained during quiet sleep without the need for specialized equipment, our results suggest that RR could serve as a clinical marker for early CF lung disease. However, the role of RR monitoring during quiet sleep in CF infants needs further study before it can be used in routine clinical practice \cite{37}.

There are several limitations to our study. This is a single-center study, which could limit generalizability. However, our cohort had similar clinical characteristics compared to other CF NBS studies. Our sample size was also relatively small, although it was comparable to other iPFT studies in CF infants \cite{7-9,38}. A larger study cohort would also have reduced the apparent presence of outliers, as well as the effect of any remaining outliers. Our retrospectively obtained iPFT data came from clinically indicated tests, which may have biased our study cohort towards greater disease severity. To help reduce selection bias, we recruited a cohort of clinically mild infants and asymptomatic infants who had iPFTs as part of other research studies. Although the cohort may still have been
biased towards more severe disease, this would not have affected the association between RR and FRC. RR was measured during sedation with chloral hydrate and while a facemask was in place. While these variables may have altered the actual respiratory rate numbers, it should not have affected the correlation we demonstrated. As with all iPFT studies, there is a paucity of normal reference data and we relied on the same data utilized by other studies. Although our reference values for FRC were obtained from a different study from which we obtained our FVC, FEV_{0.5}, FEF_{25-75}, and FEF_{75} reference values, they were all performed on the same equipment using the same methods and sedation protocol.

In summary, this study of lung function in CF NBS infants found that hyperinflation is more common than decreased FEF, and that RR correlated with FRC. These results have potential implications for the care and study of early CF lung disease in infants. Further research is needed to evaluate the role of RR measurement as a non-invasive, simple and clinically useful marker of early CF lung disease.

ACKNOWLEDGEMENTS

The authors thank Drs DB Sanders and M Bozic for their advice and guidance during the study. Research funded through a CF Foundation Clinical Fellowship grant (MUSTON18A0-D3-SL), Indiana University CTSI grant (UL1TR001108), CF Foundation grant DAVIS08Y2 and NIH grant 5R01HL116211-03 to S Davis, T Ferkol and S Ranganathan.

References


37. Prechtl HFR. The behavioural states of the newborn infant (a review). Brain Res 1974;76:185-212.


Table 1: Characteristics of the Cohort.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation homozygous class I or II (N)</td>
<td>41  (93.1)</td>
</tr>
<tr>
<td>Pancreatic insufficient (N)</td>
<td>43  (95.6)</td>
</tr>
<tr>
<td>Male (N)</td>
<td>20  (44.4)</td>
</tr>
<tr>
<td>Caucasian (N)</td>
<td>43  (95.6)</td>
</tr>
<tr>
<td>Hospital Admission prior to iPFT (N)</td>
<td>20  (44.4)</td>
</tr>
<tr>
<td>Age at iPFT testing in months (Mean, SD)</td>
<td>15.8 (3.16)</td>
</tr>
<tr>
<td>WFA z-score at time of iPFT (Mean, SD)</td>
<td>-0.67 (0.93)</td>
</tr>
<tr>
<td>Height z-score at time of iPFT (Mean, SD)</td>
<td>-0.4 (0.98)</td>
</tr>
<tr>
<td>WFL z-score at time of iPFT (Mean, SD)</td>
<td>-0.01 (0.83)</td>
</tr>
<tr>
<td>Second hand smoke exposure (N)</td>
<td>15  (33.3)</td>
</tr>
<tr>
<td>Oral corticosteroid treatment in first year of life (N)</td>
<td>11  (24.4)</td>
</tr>
<tr>
<td>Oral antibiotics in first year of life (N)</td>
<td>41  (91.1)</td>
</tr>
<tr>
<td>Number oral antibiotics before iPFT (Median, range)</td>
<td>2  (0-10)</td>
</tr>
<tr>
<td>MSSA positive culture* (N)</td>
<td>30 (66.7)</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>MRSA positive culture* (N)</td>
<td>6 (13.3)</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em> positive culture* (N)</td>
<td>16 (35.6)</td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em> positive culture* (N)</td>
<td>8 (17.8)</td>
</tr>
<tr>
<td>WFA z-score at 6 months of age (Mean, SD)</td>
<td>-0.72 (1.1)</td>
</tr>
<tr>
<td>WFL z-score at 6 months of age (Mean, SD)</td>
<td>-0.51 (1.03)</td>
</tr>
</tbody>
</table>

Data reported as Number (Percentages) unless otherwise noted.
* Reported as ever/never positive before iPFT

**Table 2: Lung Function Data**

<table>
<thead>
<tr>
<th>iPFT Parameter</th>
<th>z-score Mean (95% CI)</th>
<th>z-score Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>-0.39 (-0.68 to -0.1)</td>
<td>-4.89 to 1.86</td>
</tr>
<tr>
<td>FEV_{0.5}</td>
<td>-0.05 (-0.46 to 0.35)</td>
<td>-5.49 to 1.82</td>
</tr>
<tr>
<td>FEF_{25/75}</td>
<td>0.37 (-0.05 to 0.8)</td>
<td>-3.25 to 3.25</td>
</tr>
<tr>
<td>FEF_{75}</td>
<td>0.09 (-0.3 to 0.49)</td>
<td>-3.12 to 2.68</td>
</tr>
<tr>
<td>Respiratory Rate</td>
<td><strong>1.42 (0.95 to 1.89)</strong></td>
<td>-0.6 to 5.33</td>
</tr>
<tr>
<td>TV</td>
<td>-0.2 (-0.54 to 0.14)</td>
<td>-1.99 to 2.4</td>
</tr>
<tr>
<td>FRC</td>
<td><strong>2.18 (1.48 to 2.88)</strong></td>
<td>-1.21 to 9.4</td>
</tr>
</tbody>
</table>

**Table 3: Association between Clinical Risk Factors and Lung Function**

<table>
<thead>
<tr>
<th></th>
<th>FEV_{0.5} (z-score)</th>
<th>FRC (z-score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WFA z-score at 6 months</td>
<td>0.241; p=0.12</td>
<td>-0.012; p=0.94</td>
</tr>
<tr>
<td>WFA z-score 6 months prior iPFT</td>
<td>0.081; p=0.61</td>
<td>0.106; p=0.51</td>
</tr>
<tr>
<td>WFL z-score at 6 months of age</td>
<td>-0.080; p=0.60</td>
<td>-0.006; p=0.97</td>
</tr>
<tr>
<td>WFL z-score 6 months prior iPFT</td>
<td>-0.215; p=0.16</td>
<td>0.025; p=0.87</td>
</tr>
</tbody>
</table>

*Pseudomonas aeruginosa*

<table>
<thead>
<tr>
<th></th>
<th>FEV_{0.5} (z-score)</th>
<th>FRC (z-score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (n=29)</td>
<td>0.28 (1.06); p=0.06</td>
<td>1.82 (1.59); p=0.26</td>
</tr>
<tr>
<td>Yes (n=16)</td>
<td>-0.66 (1.70)</td>
<td>2.86 (3.28)</td>
</tr>
</tbody>
</table>

**Wheezeing**

<table>
<thead>
<tr>
<th></th>
<th>FEV_{0.5} (z-score)</th>
<th>FRC (z-score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (n=23)</td>
<td>0.41 (0.94); p=0.02</td>
<td>2.05 (2.40); p=0.74</td>
</tr>
<tr>
<td>Yes (n=21)</td>
<td>-0.60 (1.62)</td>
<td>2.30 (2.37)</td>
</tr>
</tbody>
</table>

**Smoke Exposure**

<table>
<thead>
<tr>
<th></th>
<th>FEV_{0.5} (z-score)</th>
<th>FRC (z-score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (n=26)</td>
<td>0.21 (1.05); p=0.05</td>
<td>2.39 (2.44); p=0.67</td>
</tr>
<tr>
<td>Yes (n=15)</td>
<td>-0.78 (1.68)</td>
<td>2.05 (2.42)</td>
</tr>
</tbody>
</table>

*Pearson Correlation coefficients for continuous variables. For categorical variables, values are means (standard deviations) with p-values from Student’s t-tests.
#All categorical variables are ever/never prior to iPFT
Figure 1 Derivation of the study cohort

Prospective Cohort
- 15 Eligible Subjects
  - 14 Subjects with Gestational Age > 36 weeks
    - 12 Subjects Agreed to Testing
      - 10 Subjects with Research-Quality Data
        - 45 Subjects

Retrospective Cohort
- 57 Subjects with Previous iPFTs
  - 44 Subjects Met Age Criteria
    - 43 Subjects Diagnosed via NBS
      - 41 Subjects with Gestational Age > 36 weeks
        - 23 Subjects with Clinically-obtained iPFTs
        - 12 Research Study Participants
        - 35 Subjects with Sufficient Records

Figure 2: FEVₐ₀.₅ z-score versus FRC z-score

Figure 2 *Circled area indicates those infants with hyperinflation but no significant obstruction

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Figure 3: 

*Circled area indicates those infants with hyperinflation but no significant obstruction*