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**Early detection of cystic fibrosis lung disease: multiple-breath washout vs. raised volume tests**


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**Keywords:** cystic fibrosis, ventilation inhomogeneity, infant, child, forced expiratory manoeuvres.
Abstract

Lung clearance index (LCI), a measure of ventilation inhomogeneity derived from the multiple-breath inert gas washout (MBW) technique has been shown to detect abnormal lung function more readily than spirometry in preschool children with Cystic Fibrosis (CF), but whether this holds true during infancy is unknown.

Objectives: We compared the extent to which parameters derived from the MBW and the raised volume (RVRTC) technique identify diminished airway function in infants with CF when compared with healthy controls.

Methods: Measurements were performed during quiet sleep with the tidal breathing MBW technique being performed prior to forced expiratory manoeuvres.

Results: Measurements were obtained in 39 infants with CF (mean [SD] age: 41.4[22.0]w) and 21 controls (37.0[15.1]w). CF subjects had significantly higher respiratory rate (38 [10] vs. 32[5] bpm) and LCI (8.4[1.5] vs. 7.2[0.3]), and significantly lower values for all forced expiratory flow-volume parameters compared with controls. Girls with CF had significantly lower FEV$_{0.5}$ and FEF$_{25-75}$ than boys (mean [95% CI girls–boys]: -1.2[-2.1, -0.3] for FEV$_{0.5}$ Z-score; FEF$_{25-75}$: -1.2[-2.2, -0.15]). When using both the MBW and RVRTC techniques, abnormalities were detected in 72% of infants with CF, with abnormalities detected in 41% on both techniques and a further 15% by each of the two tests performed.

Conclusions: These findings support the view that inflammatory and/or structural changes in the airways of children with CF start early in life, and have important implications regarding early detection and interventions. Monitoring of early lung disease and functional status in infants and young children with CF may be enhanced by using both the MBW and the RVRTC.
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Introduction

There has been increasing recent interest in assessing lung function in infants and pre-school children, in order to detect early cystic fibrosis (CF) lung disease.[1-6] Parameters derived from forced expiratory manoeuvres have traditionally been used to monitor lung function in older CF patients and forced expiratory volume in 1 second (FEV₁) is still considered to be a predictor of prognosis in subjects with moderate to severe CF lung disease.[7,8] Although infants cannot perform such manoeuvres, forced expiratory flow-volume loops can be obtained by substituting voluntary effort with application of an external pressure to the chest and abdomen to force expiration. Adaptations of these measurements have enabled ‘full’ forced expiratory manoeuvres using the raised lung volume rapid thoraco-abdominal compression (RVRTC) technique to be obtained from sleeping infants.[9] Forced flows and volumes obtained over an extended volume range (from near total lung capacity) have been shown to be more sensitive in detecting diminished airway function in infants with CF when compared to the tidal rapid thoracic compression (RTC) technique.[10-12] By contrast, several studies have shown that many younger children with CF have spirometry results that fall within the normal range,[4,13,14] and that indices of gas mixing derived from inert gas multiple-breath washout (MBW) may be more sensitive than spirometry in detecting early airway disease in both pre-school and school-age children with CF.[1,4,15]

Reduced gas mixing efficiency or ‘increased ventilation inhomogeneity’ can result from differences in specific ventilation between lung units joined at branch points in the conducting airways. It can also result from interaction between convective and diffusive mixing, due to geometrical asymmetries, including unequal narrowing of airways at branch points in the lung periphery close to the gas exchange zone.[16,17] Disease processes that affect the peripheral airways will therefore lead to increased ventilation inhomogeneity. One of the indices of ventilation inhomogeneity that can be derived from the MBW is the lung clearance index (LCI), a measure of gas mixing efficiency calculated from the relative ventilation required to clear a tracer gas from the lung.[1,4,16] We have previously shown that the LCI detects abnormal lung function more readily than spirometry in preschool[1] and school age children[4,13] with CF, but whether this is true during infancy is unknown. It is particularly important to establish which test(s) should be used in specific clinical scenarios during infancy due to the complexity of these measurements and limited period of sleep in which to complete all assessments. Our hypothesis was that in infancy, LCI would also be more sensitive than forced expiratory manoeuvres. Therefore, the aim of this study was to compare the extent to which parameters derived from the MBW and RVRTC techniques identify diminished airway function in a cohort of infants with CF when compared with healthy controls.

METHODS

A full description of study methods is provided in the online supplement.

Infants and young children, diagnosed with CF before two years of age, were recruited to this study towards the end of the first phase of the London CF Collaboration (LCFC) from five specialist CF centres in London.[6] Results from these infants have not been published previously. Healthy controls (HC) born at the Homerton University or University College Hospitals in London were recruited as part of ongoing epidemiological studies.[18,19] All subjects were tested at the infant respiratory laboratory at the Institute of Child Health, London using identical equipment and protocols. Subjects with a history of respiratory illness requiring hospitalization, congenital abnormalities, and requirement for assisted ventilation or
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gestational age < 36 weeks were ineligible. The study was approved by the North Thames Multi-Centre Research Ethics Committee and the local Research Ethics Committees of the participating hospitals, and informed written consent was obtained from all parents. For children with CF, information on genotype, date of diagnosis, mode of presentation and previous respiratory infection was obtained from the clinical centre. Attempts were made to test all subjects at least three weeks after any respiratory tract infection. Testing needed to be rescheduled on several occasions for two infants with CF who had repeated respiratory exacerbations. A decision was therefore made to perform the tests once they were clinically stable. Both these infants, had been asymptomatic for 14 days prior to testing. Body weight and crown-heel length were measured as described previously[20] and expressed as sex-specific Z-scores.[21] All subjects were studied supine, during quiet sleep following sedation with an oral or rectal dose (60-100 mg kg⁻¹) of chloral hydrate. Heart rate and oxygen saturation were monitored continuously during the tests (CO₂SMO Monitor, Novametrix Medical Systems Inc., Wallingford, CT, USA). The MBW technique was always performed prior to the raised volume technique.

**Measurement of lung function**

The equipment and procedure for performing MBW in infants was similar to that for pre-school children which has been described in detail previously.[1,16] A facemask sealed to the infant’s face using therapeutic putty was used for both the MBW and RVRTC tests. Flow was measured with a pneumotachometer, and gas concentrations using a respiratory mass spectrometer. In brief, each test consisted of two phases. During the wash-in phase the infant inspired a dry air mixture containing 4% sulphur hexafluoride (SF₆). Wash-in was undertaken using a simple bias flow system and continued until the inspiratory and expiratory SF₆ concentrations were stable and equal to within 0.1%, for a minimum of 5 breaths. The washout phase using room air commenced when the bias flow was disconnected during expiration. This washout phase continued until the end tidal SF₆ concentration was consistently below 0.1% (i.e. < 1/40th of starting concentration). Functional residual capacity (FRC) and LCI were calculated as described previously[22,23] and in the on-line supplement. LCI is defined as the number of lung turnovers (i.e. number of FRCs) required to clear the lungs to 1/40th of the starting concentration of the tracer gas. The mean FRC and LCI from three technically acceptable washouts were calculated. Z-scores for FRC were calculated from published reference equations.[24] Since insufficient data are currently available to calculate Z-scores for LCI during infancy, values that were greater than 1.96 SD above the mean from healthy controls recruited to this study were considered to be elevated.

Measurements of airway function at raised lung volume were performed as described previously[11,25] and in accordance with recent recommendations,[9] using Jaeger Masterscreen (see on-line supplement). Three to five lung inflations to a pressure of 30 cmH₂O (2.94kPa) were administered before inflating the jacket to force expiration. This manoeuvre was repeated until at least three acceptable and reproducible FEFV curves were obtained. Parameters including forced expiratory volume in 0.5 second (FEV₀.₅), forced vital capacity (FVC), forced expiratory flow at 75% of expired forced vital capacity (FEF₇₅) and forced expiratory flow between 25-75% FVC (FEF₂₅₋₇₅) were reported from the “best” raised volume curve, defined as the technically acceptable FEFV curve with the highest sum of FVC and FEV₀.₅.[9] Z-scores for FEV₀.₅, FEF₇₅, FEF₂₅₋₇₅, and FVC were calculated from published equations.[26] A Z-score less than -1.96 (below the 2.5th centile) was defined as diminished airway function.
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DATA ANALYSIS

Comparisons of group characteristics and respiratory function between the groups were performed using t-tests, Mann-Whitney U tests, chi-square or exact tests as appropriate (StatXact v4.01). Receiver Operating Characteristic curves were used to compare the diagnostic abilities of MBW and RVRTC parameters with respect to identifying abnormal lung function. Logistic regression models were used to investigate combined effects and the independence of any associations identified.

Power of study

Previous work from this department has shown that differences in FEV\textsubscript{0.5} equating to at least 1 Z-score (i.e. 1 SD) are likely to be observed between groups of infants with and without CF.[11] A sample size of 15 children per group would be sufficient to detect a difference equivalent to 1 SD in FVC, FEV\textsubscript{0.5}, FEF\textsubscript{75} and FEF\textsubscript{25-75} between CF and control groups with 80% power at 0.05 significance level.

RESULTS

Lung function measurements were attempted in 69 (27 HC; 42 CF) subjects. Data were incomplete in 8 subjects as they woke before completing the test protocol while data from one control subject failed quality criteria for the RVRTC. Thus successful measurements from both the MBW and RVRTC techniques were available from 60 infants (39 CF). Group characteristics of these infants are summarized according to health status in Table 1. It can be seen that, at birth, there were no significant differences between the groups in any of the background characteristics.
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Table 1: Group characteristics at birth

<table>
<thead>
<tr>
<th></th>
<th>CF (n=39)</th>
<th>Control (n=21)</th>
<th>Mean (95% CI) Difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys (%)</td>
<td>12 (31%)</td>
<td>9 (43%)</td>
<td>-12% (-36%, 12%)</td>
</tr>
<tr>
<td>Gestational age (w)</td>
<td>39.0 (2.1)</td>
<td>39.7 (1.2)</td>
<td>-0.8 (-1.6, 0.1)</td>
</tr>
<tr>
<td>Birthweight (kg)</td>
<td>3.0 (0.6)</td>
<td>3.3 (0.4)</td>
<td>-0.3 (-0.6, 0.02)</td>
</tr>
<tr>
<td>Birthweight (Z-score)</td>
<td>-0.5 (1.1)</td>
<td>-0.3 (0.8)</td>
<td>-0.2 (-0.8, 0.3)</td>
</tr>
<tr>
<td>Maternal smoking during pregnancy (%)</td>
<td>12 (31%)</td>
<td>6 (29%)</td>
<td>2% (-22%, 24%)</td>
</tr>
<tr>
<td>Maternal ethnic group: % White</td>
<td>36 (92%)</td>
<td>20 (95%)</td>
<td>-3% (-16%, 16%)</td>
</tr>
<tr>
<td>Maternal history of asthma (%)</td>
<td>14 (36%)</td>
<td>5 (24%)</td>
<td>12% (-13%, 33%)</td>
</tr>
</tbody>
</table>

Results expressed as mean (SD) unless otherwise specified.
*Difference calculated as CF–control

Characteristics of infants at time of test are summarized in Table 2. Children with CF were studied at a similar mean age though over a slightly wider age range than the controls (CF: 7.6-94.1w; HC: 15.3-77.9w). Mean [range] corrected postnatal age at CF diagnosis was 10.3 [-2.6 to 64.1]w. Time interval between diagnosis and lung function testing was (mean [range]) 31.1 [4.7 to 86.3]w, this interval being similar in boys and girls.

After adjusting for age and sex, children with CF were significantly shorter and lighter. Among children with CF, modes of presentation, prior hospital admission before lung function testing, presence of *Pseudomonas aeruginosa* infection on routine cough swabs and weight and length Z-scores at time of test did not vary between the sexes (see on-line supplement).
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Table 2: Group characteristics at test

<table>
<thead>
<tr>
<th></th>
<th>CF (n=39)</th>
<th>Control (n=21)</th>
<th>Mean (95% CI) difference*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrected PNA†</td>
<td>41.4 (22.0)</td>
<td>37.0 (15.1)</td>
<td>4.5 (-5.2, 14.1)</td>
<td>0.359</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>8.1 (1.8)</td>
<td>8.5 (1.2)</td>
<td>-0.5 (-1.4, 0.4)</td>
<td>0.286</td>
</tr>
<tr>
<td>Weight (Z-score)</td>
<td>-0.7 (1.1)</td>
<td>0.0 (0.7)</td>
<td>-0.7 (-1.1, -0.2) ‡</td>
<td>0.005</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>70.6 (7.2)</td>
<td>72.2 (4.9)</td>
<td>-1.6 (-4.8, 1.5)</td>
<td>0.312</td>
</tr>
<tr>
<td>Length (Z-score)</td>
<td>0.08 (1)</td>
<td>1.1 (0.8)</td>
<td>-1.0 (-1.5, -0.5) §</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current maternal smoking: (%)</td>
<td>11 (28%)</td>
<td>5 (24%)</td>
<td>4% (-20%, 25%)</td>
<td>0.709</td>
</tr>
<tr>
<td>Current parental smoking (%)</td>
<td>19 (49%)</td>
<td>8 (38%)</td>
<td>11% (-15%, 34%)</td>
<td>0.424</td>
</tr>
</tbody>
</table>

Results are presented as mean (SD) unless specified.
* Difference calculated as CF – control;
† Postnatal age (PNA) corrected for gestational age (GA), i.e. actual PNA – (40 – GA) weeks
‡ p < 0.05; § p < 0.001
## Association between LCI and parameters derived from RVRTC.

Lung function results are summarised in Table 3.

<table>
<thead>
<tr>
<th></th>
<th>Cystic Fibrosis</th>
<th>Healthy Controls</th>
<th>Mean (95% CI) difference*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate (min⁻¹)</td>
<td>38.2 (9.7)</td>
<td>32.0 (5.2)</td>
<td>6.2 (2.3, 10.0)</td>
<td>0.009</td>
</tr>
<tr>
<td>Respiratory rate (Z score)†</td>
<td>0.8 (1.4)</td>
<td>-0.3 (0.9)</td>
<td>1.1 (0.4, 1.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Tidal volume (mL)</td>
<td>70.3 (24.2)</td>
<td>71.3 (14.3)</td>
<td>-1.0 (-12.5, 10.6)</td>
<td>0.865</td>
</tr>
<tr>
<td>Minute ventilation (mL.min⁻¹)</td>
<td>2524 (543)</td>
<td>2235 (374)</td>
<td>287 (22, 554)</td>
<td>0.035</td>
</tr>
<tr>
<td>FRC&lt;sub&gt;MBW&lt;/sub&gt; (mL)</td>
<td>170 (54)</td>
<td>156 (38)</td>
<td>14 (-13, 41)</td>
<td>0.295</td>
</tr>
<tr>
<td>FRC&lt;sub&gt;MBW&lt;/sub&gt; (Z-score)‡</td>
<td>-0.27 (1.0)</td>
<td>-1.0 (0.9)</td>
<td>0.7 (0.3, 1.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>LCI</td>
<td>8.4 (1.5)</td>
<td>7.2 (0.3)</td>
<td>1.2 (0.7, 1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;0.5&lt;/sub&gt; (Z-score)</td>
<td>-1.6 (1.4)</td>
<td>0.1 (0.9)</td>
<td>-1.7 (-2.3, -1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FVC (Z-score)</td>
<td>-1.2 (1.0)</td>
<td>-0.1 (0.8)</td>
<td>-1.1 (-1.6, -0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEF&lt;sub&gt;75&lt;/sub&gt; (Z-score)</td>
<td>-1.8 (1.5)</td>
<td>-0.3 (0.9)</td>
<td>-1.4 (-2.1, -0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEF&lt;sub&gt;25-75&lt;/sub&gt; (Z-score)</td>
<td>-1.9 (1.5)</td>
<td>-0.4 (1)</td>
<td>-1.5 (-2.2, -0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;0.5&lt;/sub&gt;/FVC (Z-score)</td>
<td>-0.43 (1.26)</td>
<td>0.27 (0.81)</td>
<td>-0.70 (-1.23, -1.16)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Results expressed as mean (SD) unless specified otherwise
Abbreviation: CI = Confidence Interval; †Difference calculated as CF – control;
† according to prediction equation by Ranganathan et al[27];
FRC<sub>MBW</sub>: corrected for equipment and mask deadspace
‡ according to prediction equations for He dilution by Stocks and Quanjer[24]
For absolute values of RVRTC results, please see Table E2, on-line supplement.

The mean (SD) LCI for the healthy controls was 7.2 (0.3). Thus LCI values >7.8 (mean +2 SD) were considered to be elevated. Infants and young children with CF had significantly higher respiratory rate (RR), minute ventilation, FRC Z-score and LCI (Fig 1), and
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significantly lower values for all FEFV parameters when compared with healthy controls (Figures 2a - c). Although mean RR was significantly higher in young children with CF, when this was expressed as a Z-score\[27\], only 5/39 (13\%) had a RR above the normal range (> 1.96 SD). Furthermore, there was no correlation between RR and either LCI or FEV\(_0.5\). FRC\(_{MBW}\) in infants and young children with CF was significantly higher (mean [95\% CI]: 0.73 [0.25, 1.22] Z-score) compared to controls (Table 3).

Twenty two (56.4\%) infants and young children with CF had an abnormally high LCI (Figure 1 and 2), all but 9 of whom also had abnormally low forced flows and/or volumes (Figures 2a-c). Six (15\%) of CF subjects had abnormal RVRTC values in the presence of a normal LCI (Figures 2a-c). Thus while both techniques detected abnormalities in a similar proportion of infants with CF, these groups did not represent exactly the same infants. This is further illustrated in Figure 3 showing the area under the Receiver-Operator Characteristic curve (AUC\(_{ROC}\)) for LCI and FEV\(_{0.5}\) Z-score. Both parameters had similar power to discriminate between lung function in young children with and without cystic fibrosis (AUC\(_{ROC}\) (SE) for LCI and FEV\(_{0.5}\) Z-score were 0.834 (0.05) and 0.836 (0.05) respectively). Similar patterns were observed between LCI and FEF\(_{5-75}\) parameters.

Among the healthy controls, there was no difference in any of the lung function parameters according to sex. By contrast, while FVC and LCI were similar, FEV\(_{0.5}\) and FEF\(_{25-75}\) were significantly lower in girls with CF, (mean [95\% CI girls - boys]: -1.2 [-2.1, -0.3]; p = 0.014 for FEV\(_{0.5}\) Z-score; -1.2 [-2.2, -0.15]; p = 0.026 for FEF\(_{25-75}\) Z-score).

The children with CF had increased LCI values and diminished FEV\(_{0.5}\) Z-scores. These variables were independently and significantly associated with CF within a logistic model (adjusted OR for an increase of 1 unit in LCI = 6.4(1.4, 29.8), p = 0.017; adjusted OR for an increase in 1 FEV\(_{0.5}\) Z-score was 0.36 (0.17, 0.77), p = 0.009). This pattern of independence is illustrated in figure 2a. After accounting for differences in FEV\(_{0.5}\) Z-score and LCI, the other parameters (FVC and FEF\(_{25-75}\)) were not additionally predictive. When using both the MBW and RVRTC techniques, abnormalities were detected in 72\% of infants with CF, 41\% on both techniques and a further 15\% by each of the two tests performed.

No clear pattern was observed between results from either the MBW or the RVRTC techniques with respect to mode of presentation, history of respiratory illness, or symptoms at test (see Figures E1-3, on-line supplement). Diminished forced flows and volumes in the presence of a normal LCI were however only found in those with recent cough (Figures E3 a-c, on-line supplement).
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DISCUSSION

This is the first study to compare the use of MBW and RVRTC in infants. Amongst this cohort, abnormalities were detected in 72% of infants with CF, 41% had abnormal results in both techniques and a further 15% by each of the two separate tests. This suggests that in contrast to studies in older children in whom spirometry has been shown to be a relatively insensitive means of detecting early changes in airway function,[1,4,15] the RVRTC detected airway abnormalities in a similar proportion (albeit different individuals) as the MBW, with FV0.5 and FEF25-75 being the most sensitive forced expiratory parameters. Thus, complementary information may be obtained by undertaking both tests. Girls with CF had significantly lower Z-scores for FV0.5 and FEF25-compared to boys with CF, but the number of boys studied was small (n=12).

When expressed as Z scores, FRC was lower than predicted (mean [SD] -1[0.9]) in healthy subjects. This probably reflects differences in technique (SF6 instead of He), equipment (lower deadspace) and changes in protocol for data acquisition and analysis [19] in the current study when compared to studies from which prediction equations were derived.[24] The significantly higher FRC in subjects with CF compared with controls, suggests the presence of hyperinflation in the former.

Strengths and limitations

A potential limitation of this study is that infants were not tested immediately after diagnosis or neonatal screening, this cross-sectional study of children < 2 years of age being undertaken as soon as our technology for the MBW technique had been adapted for infants. However, in a previous cohort of CF infants, we found FV0.5 was significantly reduced shortly after diagnosis and did not appear to catch up during infancy and early childhood despite treatment.[6] We had no ‘gold standard’ of either inflammation or airway structural changes with which to relate our results. Significant relationships between an elevated neutrophil count from bronchoalveolar lavage and lung function have been demonstrated during the first few years of life in children with CF,[2,28] although parameters derived from BAL are rarely predictive within individuals due to marked inter-subject variability. At the time of this study, bronchoalveolar lavage was rarely undertaken in asymptomatic infants with CF at the London centres. Similarly, although it has been suggested that in children with CF, modern imaging techniques, such as high resolution computed tomography (HRCT) can identify structural changes long before spirometric changes are observed,[29-31] routine use of HRCT in infants and young children with CF remains controversial,[32] especially before ionising radiation had been reduced to current lower levels.

In addition to adapting the MBW for measurements in infants and young children, one of the greatest strengths of this study was the availability of prospectively recruited healthy control subjects which enabled direct comparison of results using identical techniques and measurement conditions as well as with published reference data, derived from subjects of similar age.[25,26] All RVRTC measurements and analyses were undertaken according to current guidelines and recommendations.[9] Despite using slightly different equipment and software to that reported previously, the healthy infants had RVRTC results similar to that predicted[26] and to those we have reported previously.[11]
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There are currently insufficient data to calculate accurate prediction equations or Z-scores for LCI during infancy. Although it has been suggested that there may be a slight negative age dependency of LCI in healthy infants during the first months of life,[33,34] most of the infants in this study were over six months of age when these effects are less marked, and all but one of the healthy controls had results that fell within the normal range established for preschool children i.e. < 7.8.[1] While it can be argued that a higher upper limit for LCI of 8.0[35] should be applied to infants under six months of age, only one infant with CF would have been re-classified as having an LCI within the normal range, had we used this approach.

Relationship with previous studies of lung function in infants and young children with CF

Despite the popularity of the tidal RTC technique,[36-38] recent studies have suggested that the raised volume technique is a more sensitive means of identifying diminished airway function in infants with CF.[11,12] There is now clear evidence that the MBW technique detects abnormal lung function more readily in both preschool and school age children with CF than spirometry[1,13,15] but this does not appear to be the case during infancy.

To our knowledge, only three published studies have used MBW to assess lung function in infants with CF,[39-41] none of which assessed the relative sensitivity of the MBW compared with other techniques. Our study is the first to compare FEFV indices derived from the RVRTC technique with LCI in infants and young children with CF and emphasizes the importance of reporting both flow and volume parameters from the RVRTC.[25,42] As previously reported,[27] we found that respiratory rate was significantly elevated in infants and young children with CF, although there was no correlation between respiratory rate and LCI, FEF_{25-75} or FEV_{0.5}. This suggests that these parameters may reflect different aspects of the early pathology of CF and that respiratory rate is influenced by factors other than airway obstruction or by airway properties that remain undetected by either of the techniques used.

While Tepper and colleagues[41] reported that CF infants presenting with a combination of failure to thrive and pulmonary symptoms had significantly lower pulmonary function compared to other modes of presentation, we did not observe this distinction between groups (see Fig E1, on-line supplement).

Clinical significance of results

In contrast to findings in preschool and school age children, in whom the LCI was found to be far more discriminative in identifying abnormal airway function than any spirometric parameter,[1,13] our results suggest that, among infants, the two techniques have similar discriminative ability (Fig 3). Given that tests were performed earlier in the course of the disease, we anticipated a lower incidence of airway abnormalities overall, and this was indeed the case with respect to the LCI, where only 56% of subjects had abnormally high values during infancy as opposed to 73% when tested during the preschool years[1] and virtually all children at school age.[13,15] By contrast, the proportion of children with CF with abnormal FEFV parameters during the first two years of life was much higher in both this and previous studies[6,11,43] than observed in such subjects during the preschool years.[1] This increased sensitivity of the RVRTC during early life could reflect differences in technique, associated for example with the application of highly standardised lung inflations and external thoraco-abdominal compressions to force expiration, but probably also reflects developmental differences, including the high compliance of the chest wall and airways, reduced airway
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calibre and increased tendency to airway closure. Such differences make infants more prone
to reduced airway function and respiratory problems even in the presence of relatively mild
infection or inflammation,[44] and could increase the sensitivity of FEFV manoeuvres to
detect early lung disease. Differences in posture further complicate comparison of results
between infants and older subjects. With young subjects being tested supine, the increased
tendency to airway closure would be more exaggerated in the presence of lung pathology and
may result in gas trapping in some children. With increasing airway closure in infants with
CF lung disease, regions which are poorly ventilated and which would be reflected by a high
LCI in older subjects, may present an LCI within the normal range, despite reductions in
FEFV parameters.

The highest values of LCI (>13.0) were observed in two CF infants with previous hospital
admissions for bronchiolitis, both of whom also had abnormal FEFV parameters (Figure 2).
Despite recovering from their initial illness, both these infants were still on inhaled
bronchodilator therapy at time of testing. One of these infants had evidence of cough and
wheeze at time of test while the other was asymptomatic (on-line supplement Fig E3). Exclusion
of these infants from the analysis did not change the level of significant difference
in lung function parameters between those with CF and controls. Similarly, sex differences
remained more marked in girls compared to boys with CF.

Although healthy female infants have consistently been shown to have better airway function
than their male counterparts,[25,44] this was not apparent for the children with CF in this
study, in whom diminished airway function was more marked amongst the girls (Figure 2).
While this finding will need to be verified in a larger cohort to ensure that it is not simply due
to a type I error, this is the first study where airway function have been observed to be poorer
in girls with CF during the first two years of life. A recent single centre study found no
significant sex differences in either FEV₁ or growth centiles in school age children with
CF,[45], but there have been many previous reports suggesting that affected males survive
longer than females and that school age girls with CF exhibit significantly poorer lung
function[15] and higher respiratory morbidity and mortality,[46] resulting in a four year
difference in median survival[47] than their male counterparts.

The clinical significance of abnormal LCI or diminished forced expiratory parameters in
infants with CF has yet to be determined. In lung disease, such as CF, asymmetric narrowing
of the airway lumen is expected to occur at branch points throughout the airway tree, and may
be caused by inflammation, scarring or obstruction by mucus, or be secondary to changes in
airway tone. Histopathology studies have shown that CF lung disease frequently affects the
peripheral airways.[48] However, the most important consideration is whether impaired gas
mixing represents early changes of CF lung disease, which will subsequently progress, or is
an epiphenomenon, present in most children with CF. Results from this study have shown that
abnormalities of both ventilation inhomogeneity and forced expiratory parameters can be
detected in a large proportion of infants with CF during the first two years of life but, due to
the timing of the tests and the fact that they were applied to a population that was not
diagnosed by neonatal screening, they cannot yet tell us whether either of these techniques
have the ability to detect the onset of abnormal airway function, whether they are suitable as
outcome variables for new treatments aimed specifically at preventing lung damage, and
whether they will be useful for predicting the long term outcome; questions that can only be
answered by carefully designed longitudinal studies from birth to school age.
LCI in infants with CF

CONCLUSIONS

This study demonstrates that a large proportion of infants with CF has abnormal lung function assessed either by MBW or the raised volume technique, and that the two techniques provide complementary information during the early course of CF lung disease. These findings support the view that inflammatory and/or structural changes in the airways of children with CF start early in life, and have important implications regarding early detection and intervention if lung health is to be optimized in these subjects. The discrepancy between ventilation distribution and FEFV parameters in some children suggests that they reflect different structural or functional abnormalities of the airways and the lung parenchyma. In order to identify CF lung disease as early as possible, we suggest that both the RVRTC and MBW techniques should be used, ideally commencing shortly after birth in a population diagnosed by neonatal screening.
ACKNOWLEDGEMENTS

The authors thank the families who participated in this study, Dr Padmaja Subbarao for her help in data collection, and Professor Kate Costeloe and Dr Jane Hawdon for their support and permission to recruit infants from Homerton University Hospital NHS Trust and University College London Hospital respectively. Rosemary Castle sadly passed away before this manuscript was written.

COMPETING INTERESTS

SL: None declared; PG: None declared; HL: None declared; GH: None declared; AB: None declared; SC: None declared; AFH: None declared; JP: None declared; SR: None declared; JStr: None declared; AW: None declared; CW: None declared; HW: None declared and JS: None declared.

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Portex Ltd (SL and JS); European Respiratory Society long-term research fellowship (HL); Innovative Medizinische Forschung, University of Münster and the Gesellschaft für Pädiatrische Pneumologie, Germany (GH) and Cystic Fibrosis Trust (SR). Research at the Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust benefits from R&D funding received from the NHS Executive.

JS was responsible for the study design; SR set up the recruitment/referral process; HL, GH, SL and AFH recruited and measured infants and together with JS and PG, calculated and interpreted lung function parameters; RC was responsible for the database; SL and AW were responsible for statistical analysis; SL, JS and PG drafted the manuscript. AB, SBC, CD, JP, SR, JStr, CW and HW were LCFC collaborators and recruited infants with CF to the study. All authors contributed to interpretation and commented on the manuscript.

The corresponding author, Sooky Lum, confirms that this manuscript has been prepared in accordance with (the) Thorax guidelines for authors, and that the manuscript meets the requirements as outlined in the checklist above.

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FIGURE LEGENDS

Figure 1: LCI, plotted against postnatal age. Open circles represent healthy controls and symbols represent infants and young children with CF.

Figures 2: Relationship between LCI and a) FEV\textsubscript{0.5} Z-score, b) FVC Z-score and c) FEF\textsubscript{25-75} Z-score according to disease status and sex. The dashed horizontal line represents the upper range of normality for LCI in healthy infants. The dashed vertical line represents the lower 95\% limit of normality (i.e. only 2.5\% of healthy controls have Z-scores below this level) for FEV\textsubscript{0.5}, FVC and FEF\textsubscript{25-75}. Any results to the left of this line are unusually low. FEFV Z-scores were calculated from published reference equations. Infants in the Right lower quadrant had normal results from both tests. This included all but one of the healthy controls who had an unusually low FEF\textsubscript{25-75}. Those in the Left upper quadrant had abnormal results from both tests. Those in the Right upper quadrant had abnormally high LCI but normal forced expiratory parameters while those in the lower Left quadrant had LCI within normal limits but diminished FEV or FEF parameters. Diminished flows in the presence of a normal LCI were predominantly observed among girls, and those with recent cough. See also Fig E3, on-line supplement.

Figure 3: Receiver operator curves for lung clearance index and forced expired volume in 0.5s Z-score. The outcome variable is the detection of CF lung disease. Both parameters had similar power to discriminate between lung function in young children with and without cystic fibrosis.
LCI in infants with CF

Reference List


LCI in infants with CF


LCI in infants with CF


30 de Jong PA, Muller NL, Pare PD, Coxson HO. Computed tomographic imaging of the airways: relationship to structure and function. Eur Respir J 2005;26:140-152.


LCI in infants with CF


LCI in infants with CF


Lung Clearance Index vs. Forced expiratory volume 0.5s (Z-score) for HC girls, HC boys, CF girls, and CF boys.
LCI in infants with CF_OLS

**Early detection of cystic fibrosis lung disease: multiple breath washout vs. raised volume tests**

**On-line supplement**

**MATERIALS AND METHODS**

Infants and young children diagnosed with CF by a positive sweat test and/or positive genotype for CF mutations[1] under the age of two years were recruited to the London CF Collaboration from five specialist CF centers in London (Royal Brompton Hospital, Great Ormond Street Hospital, King’s College Hospital, Royal London Hospital and University Hospital Lewisham) between September 2001 and December 2002.

**MEASUREMENT OF LUNG FUNCTION**

There are currently no international standards for using the MBW in infants but the equipment and procedure for performing MBW in pre-school children in our laboratory has been described in detail previously.[2] While the procedure for performing MBW in infants was identical to that used in pre-school children, the equipment used differed in terms of smaller pneumotachometer and connectors. Residual deadspace of the mask (by water displacement) was estimated to be 50% of measured volume, i.e. 7.5 or 10 mL for Rendell-Baker mask size 1 or 2, respectively.[3]. Dead-space of the other components was also measured by water displacement and the system dead-space was separated into two components:

- The pre-capillary dead-space was defined as the dead-space between the infant’s lips and the capillary inlet (i.e. dead-space of the mask).
- The post-capillary dead-space was defined as the dead-space between the capillary inlet and the end of the expiratory port of the pneumotachometer, and was measured as 5 mL.

In the current study, a Rendell-Baker Soucek facemask was applied to the infant’s face using therapeutic putty to form an airtight seal. The same facemask was used for both MBW and RVRTC tests. Flow was measured by a Fleisch No. 0 pneumotachometer, and gas concentrations were measured by a respiratory mass spectrometer (AMIS 2000; Innovision...
LCI in infants with CF_OLS

A/S, Odense, Denmark). In brief, each test consisted of two phases. During the wash-in phase the infant inspired a dry air mixture containing 4% sulphur hexafluoride (SF₆), 4% helium, 21% oxygen, and balance nitrogen. Helium was included to allow further analyses of ventilation distribution, results of which are not presented here. The SF₆ was the marker gas used for calculating functional residual capacity (FRC) and the lung clearance index (LCI) reported in this study. Wash-in was undertaken using a simple bias flow system and continued until the inspiratory and expiratory SF₆ concentrations were stable and equal to within 0.1%, for a minimum of 5 breaths. The washout phase using room air commenced when the bias flow was disconnected during expiration. This washout phase continued until the end tidal SF₆ concentration was consistently below 0.1% (i.e. 1/40th of starting concentration).

FRC was determined from the cumulative volume of exhaled marker gas (SF₆) divided by the difference in end-tidal SF₆ concentration at the start of the washout and end-tidal SF₆ concentration at completion of the washout. LCI is defined as the number of lung turnovers (i.e. number of FRCs) required to clear the lungs to 1/40th of the starting concentration of the tracer gas. The lung clearance index (LCI) was calculated by dividing the cumulative expired volume by the FRC, as described previously.[4,5] For this calculation, both the FRC and cumulative expired gas volume were corrected for post-capillary dead-space, but not for pre-capillary dead-space, as the latter correction would have involved assumptions about gas mixing within the facemask apparatus. The mean LCI from three (minimum two) technically acceptable washouts was calculated, and is presented here. Mean FRC was reported from the same washouts after further correction for pre-capillary dead-space.
LCI in infants with CF

Measurements of airway function at raised lung volume were performed as described previously.[6] Measurements were performed in accordance with recent recommendations,[7] using a prototype version of Jaeger software developed for Jaeger Masterscreen (version 4.54), and used in conjunction with manual inflation using Neopuff Infant Resuscitaire (Fisher & Paykel Healthcare, Auckland, New Zealand) as previously described.[8,9] Briefly, the respiratory muscles were relaxed by administering three to five lung inflations to a pressure of 30 cm H₂O before inflating the jacket to force expiration from raised lung volume. This maneuver was repeated until a minimum of three acceptable and reproducible flow-volume (F-V) curves was obtained. Parameters calculated from the raised volume technique, including forced expiratory volume in 0.5 seconds (FEV₀.₅), forced vital capacity (FVC), forced expiratory flow at 75% of expired forced vital capacity (FEF₇₅) and forced expiratory flow between 25-75% FVC (FEF₂₅-₇₅) were reported from the “best” raised volume curve. The latter was defined as the technically acceptable forced expiratory F-V curve with the highest sum of FVC and FEV₀.₅.[7]

DATA ANALYSIS

Within-test repeatability for all parameters was expressed as the coefficient of variation (CV%) i.e. 100 * [SD / mean]. CV₁LCI was 4.4% (2.8%) in children with CF, and 3.8% (1.8%) in healthy controls (mean [95% CI] difference: 0.9%, [-0.8, 1.9]). Within-subject variability for parameters derived from the RVRTC technique was similar in both groups and to that reported previously.[10] Results for LCI, FEV₀.₅, FEF₇₅, FEF₂₅-₇₅ and FVC and their associated CVs were compared for the CF and control groups.
L CI in infants with CF_OLS

RESULTS

Details of CF subjects according to specific genotype are summarized in Table E1.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔF508 / ΔF508</td>
<td>24 (62%)</td>
</tr>
<tr>
<td>ΔF508 / other*</td>
<td>12 (31%)</td>
</tr>
<tr>
<td>1161delC / 1161delC</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Other / unknown second mutation</td>
<td>2 (5%)</td>
</tr>
</tbody>
</table>

* Of these 12 children, five had unknown second mutations, four had G542X mutation and the remaining one each had 1898+1G-A, 1717-1G-A and R560T mutations.

Fifteen (38%) of the CF cohort presented with meconium ileus, 5 (13%) with antenatal bowel pathology (two of whom also had meconium ileus), 17 (44%) presented with failure to thrive or malabsorption syndromes, nine (23%) were diagnosed after recurrent chest infections (seven of whom also had malabsorption syndrome) and five (13%), with a family history of CF. Fourteen infants required hospital admission for intravenous antibiotic therapy between diagnosis and lung function testing for respiratory exacerbations: six on two occasions, one on four occasions, the rest only once. Thirteen (33%) had had Pseudomonas aeruginosa isolated from routine clinical cough swabs on at least one occasion. Eleven (28%) had had no clinical evidence of respiratory disease as ascertained by clinical history prior to testing.

Full details of lung function results are summarized in Table E2.
## LCI in infants with CF_OLS

### Table E2: Lung function results compared by diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Cystic Fibrosis (n = 39)</th>
<th>Healthy Controls (n = 21)</th>
<th>Mean (95% CI) difference*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate (min⁻¹)</td>
<td>38.2 (9.7)</td>
<td>32.0 (5.2)</td>
<td>6.2 (2.3, 10.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Respiratory rate (Z score)†</td>
<td>0.8 (1.4)</td>
<td>-0.3 (0.9)</td>
<td>1.1 (0.4, 1.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Tidal volume (mL)</td>
<td>70.3 (24.2)</td>
<td>71.3 (14.3)</td>
<td>-1.0 (-12.5, 10.6)</td>
<td>0.865</td>
</tr>
<tr>
<td>Minute ventilation (mL.min⁻¹)</td>
<td>2524 (543)</td>
<td>2235 (374)</td>
<td>287 (22, 554)</td>
<td>0.035</td>
</tr>
<tr>
<td>FRC&lt;sub&gt;MBW&lt;/sub&gt; (mL)</td>
<td>170 (54)</td>
<td>156 (38)</td>
<td>14 (-13, 41)</td>
<td>0.295</td>
</tr>
<tr>
<td>FRC&lt;sub&gt;MBW&lt;/sub&gt; (Z-score)‡</td>
<td>-0.27 (1.0)</td>
<td>-1.0 (0.9)</td>
<td>0.7 (0.3, 1.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>LCI</td>
<td>8.4 (1.5)</td>
<td>7.2 (0.3)</td>
<td>1.2 (0.7, 1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;0.5&lt;/sub&gt; (mL)</td>
<td>226 (76)</td>
<td>293 (59)</td>
<td>-67 (-105, -28)</td>
<td>0.001</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;0.5&lt;/sub&gt; (Z-score)</td>
<td>-1.6 (1.4)</td>
<td>0.1 (0.9)</td>
<td>-1.7 (-2.3, -1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; (mL) †</td>
<td>291 (103)</td>
<td>354 (68)</td>
<td>-62 (-115, -9)</td>
<td>0.022</td>
</tr>
<tr>
<td>FVC (mL)</td>
<td>299 (111)</td>
<td>362 (75)</td>
<td>-62 (-117, -8)</td>
<td>0.025</td>
</tr>
<tr>
<td>FVC (Z-score)</td>
<td>-1.2 (1.0)</td>
<td>-0.1 (0.8)</td>
<td>-1.1 (-1.6, -0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEF&lt;sub&gt;75&lt;/sub&gt; (mL.s⁻¹)</td>
<td>208 (94)</td>
<td>306 (78)</td>
<td>-99 (-147, -51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEF&lt;sub&gt;75&lt;/sub&gt; (Z-score)</td>
<td>-1.8 (1.5)</td>
<td>-0.3 (0.9)</td>
<td>-1.4 (-2.1, -0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEF&lt;sub&gt;25-75&lt;/sub&gt; (mL.s⁻¹)</td>
<td>399 (146)</td>
<td>554 (114)</td>
<td>-155 (-228, -82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEF&lt;sub&gt;25-75&lt;/sub&gt; (Z-score)</td>
<td>-1.9 (1.5)</td>
<td>-0.4 (1)</td>
<td>-1.5 (-2.2, -0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;0.5&lt;/sub&gt;/FVC</td>
<td>0.77 (0.1)</td>
<td>0.81 (0.06)</td>
<td>-0.04 (-0.08, 0.0)</td>
<td>0.061</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;0.5&lt;/sub&gt;/FVC (Z-score)</td>
<td>-0.43 (1.26)</td>
<td>0.27 (0.81)</td>
<td>-0.70 (-1.23, -1.16)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Results expressed as mean (SD) unless otherwise specified.

Abbreviation: CI = Confidence Interval;  *Difference calculated as CF – control;
† n: CF = 31; HC = 20

FRC<sub>MBW</sub>: corrected for equipment and mask deadspace.
LCI in infants with CF

For interest, lung function results from subjects with CF have been plotted according to mode of presentation, history of respiratory illness, respiratory symptoms at test and sex (Figures E1-3). While no clear pattern was observed with respect to mode of presentation, abnormal lung function results using both MBW and the RVRTC techniques were observed even when subjects had no history of respiratory illness or symptoms at test, whereas, with the exception of a slight elevation of LCI in one child, the three infants diagnosed following a positive family history of CF but with no other modes of presentation had lung function within the normal range (Figure E1). Diminished forced flows and volumes in the presence of a normal LCI were only found in those with recent cough. Due to the small size of these subgroups, results presented here should be interpreted with caution, but could be of potential interest for future hypothesis generation and further investigation.
LCI in infants with CF_OLS

Figure Legends

Figure E1: Relationship between LCI and a) FEV_{0.5} Z-score, b) FVC Z-score and c) FEF_{25-75} Z-score according to mode of presentation for Cystic Fibrosis.

Legend: The dashed horizontal line represents the upper range of normality for LCI in healthy infants.[2] The dashed vertical line represents the lower 95% limit of normality (i.e. only 2.5% of healthy controls have values below this level) for FEV_{0.5} Z-score, FVC Z-score and FEF_{25-75} Z-score. Any results to the left of this line are unusually low. Z-scores are calculated from published reference equations [11]. Infants in the Right lower quadrant had normal results from both tests. This included all but one of the healthy controls who had an unusually low FEF_{25-75}. Those in the Left upper quadrant had abnormal results from both tests. Those in the Right upper quadrant had abnormally high LCI but normal forced expiratory parameters while those in the lower Left quadrant had LCI within normal limits but diminished FEV or FEF parameters.

Abbreviations: MI= Meconium Ileus; AN bowel = Antenatal bowel pathology; FTT = Failure to Thrive or mal-absorption syndrome; RI = Recurrent respiratory Illness; FH = Family history.

Figure E2: Relationship between LCI and a) FEV_{0.5} Z-score, b) FVC Z-score and c) FEF_{25-75} Z-score according to presence or absence of history of respiratory illness and/or presence of *Pseudomonas aeruginosa* infection on cough swab on at least one occasion. Legend:

Explanations for reference lines as for Figure E1.

Abbreviations: CF = Cystic Fibrosis; RI = Respiratory Illness; PA = *Pseudomonas aeruginosa*
LCI in infants with CF

Figure E3: Relationship between LCI and a) FEV$_{0.5}$ Z-score, b) FVC Z-score and c) b FEV$_{25-75}$ Z-score according to current symptoms.

Legend: Explanations for reference lines as for Figure E1.

Of the 15 (38%) infants with CF had no current symptoms at time of test, 7 had LCI above the upper limit of normality, 2 had reduced FVC and FEV$_{75}$ (not shown), 3 had diminished FEV$_{0.5}$ while 4 had diminished FEV$_{25-75}$. While many infants with cough had abnormalities of both LCI and FEFV parameters, the combination of a normal LCI but abnormal FEV$_{25-75}$ was only observed in those with current cough.
**Table E3: Group characteristics of CF cohorts**

<table>
<thead>
<tr>
<th></th>
<th>Current cohort: Lum et al</th>
<th>Ranganathan et al†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cystic Fibrosis</td>
<td>Healthy Controls</td>
</tr>
<tr>
<td>N (% boys)</td>
<td>39 (31%)</td>
<td>21 (43%)</td>
</tr>
<tr>
<td>N (% white)</td>
<td>36 (92%)</td>
<td>20 (95%)</td>
</tr>
<tr>
<td>N (%) maternal smoking</td>
<td>12 (31%)</td>
<td>6 (29%)</td>
</tr>
<tr>
<td>Gestational age (w)</td>
<td>39.0 (2.1)</td>
<td>39.7 (1.2)</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.0 (0.6)</td>
<td>3.3 (0.4)</td>
</tr>
<tr>
<td>Birthweight Z-score</td>
<td>-0.5 (1.1)</td>
<td>-0.3 (0.8)</td>
</tr>
<tr>
<td>Test age (w)</td>
<td>41.4 (22.0)</td>
<td>37.0 (15.1)</td>
</tr>
<tr>
<td>Test weight (kg)</td>
<td>8.1 (1.8)</td>
<td>8.5 (1.2)</td>
</tr>
<tr>
<td>Test weight Z-score</td>
<td>-0.7 (1.1)</td>
<td>0.0 (0.7)</td>
</tr>
<tr>
<td>Test length (cm)</td>
<td>70.6 (7.2)</td>
<td>72.2 (4.9)</td>
</tr>
<tr>
<td>Test length Z-score</td>
<td>0.08 (1)</td>
<td>1.1 (0.8)</td>
</tr>
</tbody>
</table>

*Data presented as means (SD) unless otherwise stated.
† Ranganathan et al [12]
LCI in infants with CF

Figure E1

a

b

c

LCI in infants with CF OLS

Figure E2

a

b

c

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LCI in infants with CF

Figure E3

(a) Forced expired volume in 0.5s (Z score)

(b) Forced vital capacity (Z score)

(c) Forced expiratory flow between 25-75% FVC (Z score)
LCI in infants with CF

Reference List


LCI in infants with CF


Early detection of cystic fibrosis lung disease: multiple-breath washout vs. raised volume tests

Sooky Lum, Per Gustafsson, Henrik Ljungberg, Georg Hulskamp, Andrew Bush, Siobhan B Carr, Rosemary Castle, Ah-Fong Hoo, John F Price, Sarath Ranganathan, John Stroobant, Angie Wade, Colin Wallis, Hilary Wyatt and Janet Stocks

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