Is Lung Clearance Index (LCI) Affected by the Severity of Lung Disease in CF?

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Abstract

Background: LCI has been proven an effective tool in the detection of lung disease in CF.

Objectives: a) To assess the correlation of ventilation inhomogeneity indices with structural damages of the lung, among different groups of disease severity and b) To compare the associations among MBW parameters with spirometry and CT.

Method: Forty-four children and adolescents with CF participated in the study. Spirometry and multiple breath washout tests were performed. All children had a HRCT scan. The study population was divided into two groups, according to FEV1, % predicted values: Group A: ≥ 85% predicted (normal) and Group B: 40-84% predicted (mild-moderate disease).

Results: The patients’ mean age was 12.9 (5.67; 23.25) years, mean FEV1: 91.22 ± 24.22% and mean LCI: 10.72 ± 3.51. Children of Group A had significantly lower LCI, compared to Group B (p<0.001). Among the whole study group all the ventilation inhomogeneity indices were correlated with FVC%, FEV1 % and FEF25-75% and the severity and extent of bronchiectasis, the generation of bronchial division and the presence of emphysema (p<0.05). Among patients with normal FEV1, MBW parameters showed stronger correlation with the structural changes of HRCT, while among patients with mild-moderate lung disease, they showed stronger correlation with spirometry.

Conclusion: MBW is a reliable method to assess the structural and functional lung disease in CF. However in mild disease ventilation inhomogeneity outcomes were better associated with CT changes, while in mild - moderate disease MBW outcomes were better associated with spirometry.

Keywords: Lung clearance index; Ventilation inhomogeneity; Cystic fibrosis; Bhalla score; Children; Multiple breath washout

Introduction

The persistent lung infection and inflammation, as well as the airway obstruction by viscid, dehydrated secretions lead to progressive lung disease with irreversible damages and decreased pulmonary function in patients with Cystic Fibrosis (CF) [1,2]. It is essential to have surrogate markers in order to define the disease severity status [3], to detect the lung destruction in earlier stages [4,5] or to estimate the effectiveness of a treating intervention [6-12]. An appropriate outcome measure has to meet some criteria: It must reflect the presence and severity of the disease. That means that changes in the marker should closely match changes in real outcome. It also must be readily measurable and reflect significant clinical improvement as a response to a therapeutic regime [13].

Forced Expired Volume in 1st second (FEV1) measured with spirometry, has traditionally been used as the most common lung function parameter to assess the disease's impact on pulmonary function and is still recognized as a good predictor of outcome in cases with moderate-to-severe CF lung disease [14-16]. However, spirometry is difficult to be performed by preschoolers and infants, not only because it requires special equipment [17,18], but also because FEV1 is now of less value in monitoring children with CF, due to its lack to assess early or mild CF lung disease [19-22]. Structural damages may be present in High Resolution Computed Tomography (HRCT) in one third of CF children with normal spirometry [20-25].

High Resolution Computed chest Tomography (HRCT) is considered the gold standard for detecting bronchiectasis [26]. It can identify early and advanced structural damages [5,23,27-29] that correlate with the disease severity and progression among CF patients [23,24,30]. Various methods have been used to quantify structural abnormalities [25,31]. A few clinical trials have used HRCT as an outcome measure in young CF children [1,25]. Computed Tomography is a reproducible method but it cannot be repeated for monitoring CF lung disease in short time intervals because of the high radiation exposure. Although there has been an attempt to reduce the dose of radiation used in CT scanning in the last decade, its use should be restricted [31,32]. Furthermore, young children have to undergo sedation or general anesthesia in order to obtain high quality images of HRCT [29].

Computed Tomography scores have shown a good correlation with Lung Clearance Index (LCI) [5,32-34], a marker being measured by the Multiple Breath Washout method (MBW). MBW is a non-invasive and safe test for assessing ventilation inhomogeneity. LCI is the most common index of uneven ventilation distribution and has recently been proposed as a sensitive marker for the detection of early pulmonary changes in CF [35-37] and the assessment of treatment effectiveness [6-12]. LCI seems to allow earlier detection of disease, compared to FEV1 [36,37]. A significant advantage of LCI measurements is that it can be feasible from early age to adulthood and is not affected by age, weight, height and sex, with an exception for infants [38-41].

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Little is known about associations of MBW with other lung outcome parameters in different disease stages. The aim of this study was a) to assess the correlation of partial indices of ventilation inhomogeneity with structural damages of the lung, among different groups of disease severity and b) to compare the associations among MBW parameters with spirometry and CT.

Methods

Subjects

Forty-eight CF children and adolescents that were followed up at the CF centre of Aristotle University of Thessaloniki were recruited in this prospective study from June 2012 to May 2015. Four patients were excluded because of their low lung function (FEV₁ <40% predicted) and their inability to complete the MBW test. Finally, a total of 44 eligible CF patients over the age of 5 years were recruited. This study was approved by the Ethical Committee of Aristotle University of Thessaloniki.

The study population was divided into two groups, according to FEV₁ % predicted values: a) ≥ 85% predicted (normal, Group A) and b) <85% predicted (mild or moderate disease, Group B).

Study design

All patients were admitted in our department and were evaluated with spirometry, HRCT and multiple breath washout tests as part of their annual review. Patients were stable with no history of a pulmonary exacerbation or acute respiratory tract infection over the past month. Cough swab and sputum cultures were cultured and height, weight and BMI were recorded.

HRCT scans were performed on Asteion Toshiba CT scanner. Slices measuring 1.5 mm at 10 mm intervals were obtained during suspended respiration. Additional expiratory scans were obtained in older cooperative children at 20 mm intervals. Each CT scan was scored by two experienced and blinded radiologists using the modified “Bhalla” scoring system [42]. The mean value of the scores of the two blinded radiologists was calculated in order to establish most accurate results. The following findings were evaluated: severity and extent of bronchiectasis, severity of peribronchial thickening, generation of bronchial division involved, and extent of mucus plugging, sacculation or abscess formation, bullae, emphysema, atelectasis and consolidation. The higher value of Bhalla score, the more abnormalities in the lung are present.

Spirometry was performed according to ATS/ERS standards [43] using an electronic spirometer (Vitalograph 2120, Vitalograph Ltd Ennis, Ireland). Patients performed at least three efforts [44]. FEV₁, Forced Vital Capacity (FVC) and Forced Expiratory 25-75% (FEF₂₅-₇₅) were recorded. The results were expressed as percentage predicted.

MBW measurements were performed according to ATS/ERS standards [45] using a validated ultrasonic flow measuring system for measuring flow, volume and molecular mass (EXHALYZER D, Ecomedics, Switzerland) [46]. The duration of a MBW test is on average 2-5 min per maneuver in a healthy subject, but longer in subjects with airway obstruction [47], while LCI success rate ranges between 70% to 85% in CF patients [48].

The apparatus consisted of a respiratory mass spectrometer and a flow-meter which recorded N₂ concentration and inspiratory and expiratory flows close to mouth. The dead-space of reducer and bacterial filter was 20 ml and 11 ml respectively. Calibration of the system and environment setting correction were performed daily. During the MBW tests the subject was sitting upright, wore a nose clip and was encouraged to breathe normally via a mouthpiece connected to a bacterial filter. When the patient achieved normal and steady breathing with steady tidal volumes and flows through the air supply (consisted of 78% N₂ and 21% O₂), the 100% O₂ supply was on. As a consequence, the concentration of the tracer gas (N₂) was started to reduce. The washout phase continued until the end-tidal N₂ concentration reached 1/40th of its starting concentration, corresponding to approximately 2.5% of it. LCI is defined as a number of times lung turn overs (as represented by FRC) have to turn over to the clear the lungs from nitrogen (N₂). LCI (LCI₅₃) reflects N₂ washout until 1/40th of the starting N₂ end-tidal concentration (cet), i.e., 2.5% and LCI reflects N₂ washout until 1/20th of the starting N₂ concentration (cet), i.e., 5% [49-53]. So, the sicker the child is, the more air it must breathe to clear its lungs from the tracer gas.

FRC was calculated from the Cumulative Volume of Expired N₂ divided by the difference between end-tidal gas concentration at the start and end of washout. The washout curve of the tracer gas during MBW represents the flow and gas concentration plotted against time. Moment Ratios (MR) are indices that have been defined to quantify the degree of ventilation inhomogeneity as can be plotted at the inert gas washout curve. The first and second moments (μ₁ and μ₂) express the degree of skewing of the washout curve and are increased when there is an increased release of inert gas (N₂) at a later stage of the washout. A plot of concentration-normalized end-tidal concentration of N₂ (Cet₅₃) versus lung volume turnover number (TO) is necessary to calculate MR. The moments 0,1 and 2 (μ₀, μ₁ and μ₂) are determined using the Kolmogorov-Smirnov test and then Pearson or Spearman correlation analysis was used to investigate correlations between MBW parameters. The Student T-test was used to compare the LCI values between different groups. A multivariate regression with stepwise method was performed including every Bhalla score parameter as a dependent variable and lung function parameters as independent variables. The level of significance was taken as p<0.05. Statistical analysis was performed using SPSS for Windows version 20.0 (SPSS IBM SPSS Statistics 20).

Results

A total of 44 CF children and adolescents (23 females and 21...
Correlations of LCI and spirometry/Bhalla score among the total study group

Correlation analysis among the total population showed significant correlation between LCI and spirometric parameters: FVC%, FEV1%, and FEF25-75% of predicted (p<0.001). Twenty patients (47.6%) with normal FEV1% had abnormal LCI. A significant correlation was found between LCI and total Bhalla score (p<0.001, r²=0.846) (Figure 2). Several significant correlations were detected between LCI and the partial Bhalla score parameters: severity of bronchiectasis, extent of bronchiectasis, generation of bronchial divisions (p<0.001), presence of emphysema (p<0.01) and mucus plugging (p<0.05). The sensitivity of the LCI to detect structural lung damage was 96.8%, the specificity was 83.3% and the positive predictive value was 93.4%.

Multivariate regression analysis using stepwise method of the total population showed that LCI was the only predictor of most of the partial parameters of Bhalla score: severity of bronchiectasis (r²=0.575, p<0.001, 95% CI:0.127; 0.220), extent of bronchiectasis (r²=0.376, p<0.001, 95% CI:0.133; 0.310), peribronchial thickening (r²=0.395, p<0.001, 95% CI:0.084; 0.190), generation of bronchial divisions (r²=0.694, p<0.001, 95% CI:0.197; 0.300), extent of mucus plugging (r²=0.343, p<0.001, 95% CI: 0.072; 0.182) and sacculation or abscess formation (r²=0.279, p<0.001, 95% CI:0.036; 0.107) (Figure 3).

Correlations of LCI and spirometry/Bhalla score in Group A and B

LCI was correlated with FEV1% predicted (r=-0.383, p=0.049).

<table>
<thead>
<tr>
<th>Population characteristics</th>
<th>Total population</th>
<th>Group A</th>
<th>Group B</th>
<th>p</th>
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<tbody>
<tr>
<td></td>
<td>Mean or N</td>
<td>Mean</td>
<td>Mean</td>
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<tr>
<td></td>
<td>SD or %</td>
<td>SD or %</td>
<td>SD or %</td>
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<tr>
<td>Number of patients, males %</td>
<td>44</td>
<td>27</td>
<td>17</td>
<td>0.056</td>
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<tr>
<td>Age (years) (mean, SD)</td>
<td>12.93</td>
<td>11.4</td>
<td>15.36</td>
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<td>Height (cm) (mean, SD)</td>
<td>144.45</td>
<td>140.67</td>
<td>150.47</td>
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<tr>
<td>z-score (mean, SD)</td>
<td>-0.41</td>
<td>-0.28</td>
<td>-0.73</td>
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<td>Weight (kg) (mean, SD)</td>
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<td>37.41</td>
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<td>z-score (mean, SD)</td>
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<td>0.77</td>
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<td>BMI (kg/m²) (mean, SD)</td>
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<td>18.26</td>
<td>18.48</td>
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<tr>
<td>z-score (mean, SD)</td>
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<td>0.30</td>
<td>-1.03</td>
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<tr>
<td>∆F508 homoyzous (N, %)</td>
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<td>8</td>
<td>7</td>
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<tr>
<td>∆F508 heterozygous (N, %)</td>
<td>18</td>
<td>11</td>
<td>7</td>
<td>0.604</td>
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<td>P. aeruginosa status: (N, %)</td>
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<td>Negative</td>
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<td>15</td>
<td>0</td>
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<tr>
<td>Intermittent</td>
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<td>0.231</td>
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<tr>
<td>Chronic</td>
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<td>4</td>
<td>13</td>
<td>0.756</td>
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<tr>
<td>Pancreatic insufficient (N, %)</td>
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<td>25</td>
<td>17</td>
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<td>Bhalla score (mean, SD)</td>
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<td>5.70</td>
<td>11.00</td>
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<td>FRC (mean, SD)</td>
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<td>2.129</td>
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<td>LCI (mean, SD)</td>
<td>10.72</td>
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<td>LCI_5 (mean, SD)</td>
<td>6.59</td>
<td>5.76</td>
<td>7.90</td>
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<td>Scond (mean, SD)</td>
<td>0.024</td>
<td>0.016</td>
<td>0.034</td>
<td>0.041</td>
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<td>Sacin (mean, SD)</td>
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<td>0.133</td>
<td>0.005</td>
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<td>M1/M0 (mean, SD)</td>
<td>2.32</td>
<td>1.98</td>
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<td>M2/M0 (mean, SD)</td>
<td>12.62</td>
<td>9.4</td>
<td>18.76</td>
<td>0.113</td>
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<tr>
<td>FVC % (mean, SD)</td>
<td>92.1</td>
<td>102.5</td>
<td>75.58</td>
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<tr>
<td>FEV1% (mean, SD)</td>
<td>91.2</td>
<td>107.19</td>
<td>65.86</td>
<td>0.000</td>
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<tr>
<td>FEF50% (mean, SD)</td>
<td>86.56</td>
<td>108.34</td>
<td>51.98</td>
<td>0.000</td>
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</table>

Table 1: Population characteristics.
Correlations of the rest of MBW parameters and spirometry/Bhalla score correlation analysis among the total population showed significant correlation between LCI, μ₁/μ₀ and μ₂/μ₀, and spirometric parameters: FVC%, FEV₁% and FEF₅₀% of predicted (p<0.001). Several significant correlations were detected between LCI, μ₁/μ₀ and μ₂/μ₀ and the partial Bhalla score parameters: severity of bronchiectasis, extent of bronchiectasis, generation of bronchial divisions (p<0.001), presence of emphysema (p<0.01) and mucus plugging (p<0.05).

In Group A (patients with normal spirometry) all the indices of MBW showed a good correlation with the severity and extent of bronchiectasis and generation of bronchial divisions (LCI, (p<0.05), μ₁/μ₀ (p<0.001) and μ₂/μ₀ (p<0.001)). Among patients with mild to moderate disease (Group B) LCI correlated with FVC% (r:-0.533, p=0.028), FEV₁% (r:-0.804, p<0.001), FEF₅₀% (r:-0.512, p=0.036) and the severity of bronchiectasis (r:0.501, p=0.041), μ₁/μ₀ correlated with FEV₁% (r:-0.648, p=0.005) and FEF₅₀% (r:-0.754, p<0.001), the extent of bronchiectasis and the generation of bronchial divisions (p:0.519, r:0.033), μ₁/μ₀ with FEV₁% (r:-0.703, p=0.002), FEF₅₀% (r:-0.726, p=0.001), the extent of bronchiectasis and the generation of bronchial divisions (r:0.519, p=0.033) and Sacin with FEV₁% (r:-0.659, p=0.004), FEF₅₀% (r:-0.511, p=0.036).

Discussion
This study assessed the correlation of MBW parameters with conventional lung function parameters measured with spirometry and structural damages that were assessed by HRCT. It was demonstrated that classic ventilation inhomogeneity indices i.e., LCI, μ₁/μ₀, μ₂/μ₀, Scin and Sacin, as well as the recently used LCI, were well correlated with FVC%, FEV₁% and FEF₅₀% and the severity and extent of bronchiectasis, the generation of bronchial division and the presence of emphysema. To our knowledge, this is the first study that: a) investigates the correlation between MBW parameters and CT parameters, among different groups of lung disease severity and b) explores the relationship of LCI, with spirometric and CT parameters. It was shown that MBW parameters had stronger correlation with structural changes on HRCT among patients with normal FEV₁%, while MBW parameters had stronger correlation with spirometry among patients with mild or moderate lung disease. Therefore, LCI was a good predictor of structural damages with high sensitivity and showed a positive predictive value in both groups.

Chronic lung disease remains the most common cause of morbidity and mortality among CF patients [55]. Measurement of lung function is significant to assess the severity and determine the progression of CF lung disease [3]. Spirometry is the most commonly used method for clinical monitoring of CF lung function and the equipment is available in most respiratory centers. FEV₁ has proved to be a good predictor in clinical monitoring of CF lung disease and mortality among CF patients [55]. Measurement of lung function is significant to assess the severity and determine the progression of CF lung disease [3]. Spirometry is the most widely used method for clinical monitoring of CF lung disease and the equipment is available in most respiratory centers. FEV₁ has proved to be a good predictor in clinical monitoring of CF lung disease and mortality among CF patients [55]. Measurement of lung function is significant to assess the severity and determine the progression of CF lung disease [3]. Spirometry is the most commonly used method for clinical monitoring of CF lung function and the equipment is available in most respiratory centers. FEV₁ has proved to be a good predictor in clinical monitoring of CF lung disease and mortality among CF patients [55]. Measurement of lung function is significant to assess the severity and determine the progression of CF lung disease [3]. Spirometry is the most commonly used method for clinical monitoring of CF lung function and the equipment is available in most respiratory centers. FEV₁ has proved to be a good predictor in clinical monitoring of CF lung disease and mortality among CF patients [55]. Measurement of lung function is significant to assess the severity and determine the progression of CF lung disease [3]. Spirometry is the most commonly used method for clinical monitoring of CF lung function and the equipment is available in most respiratory centers. FEV₁ has proved to be a good predictor in clinical monitoring of CF lung disease and mortality Among patients with mild to moderate disease (Group B), LCI was correlated with FEV₁% (r:-0.734, p=0.001), FEF₅₀% (r:-0.569, p=0.017), the severity (r: 0.565, p=0.018) and extent of bronchiectasis (r: 0.570, p=0.017) and the generation of bronchial divisions (r=0.570, p=0.017). The sensitivity of the LCI to detect structural lung damage in Group B was 100% and the positive predictive value was 100%.

the severity and extent of bronchiectasis (p<0.001) and generation of bronchial divisions (p<0.001) among patients with normal spirometry (Group A). In group A, the sensitivity of the LCI to detect structural lung damage was 93.3%, the specificity was 83.3% and the positive predictive value was 87.5%. Among patients with mild to moderate disease (Group B), LCI was correlated with FEV₁% (r:-0.734, p=0.001), FEF₅₀% (r:-0.569, p=0.017), the severity (r: 0.565, p=0.018) and extent of bronchiectasis (r: 0.570, p=0.017) and the generation of bronchial divisions (r=0.570, p=0.017). The sensitivity of the LCI to detect structural lung damage in Group B was 100% and the positive predictive value was 100%.
patients suffering from CF has been noted [3,4,33-34,58-63] MBW is a non-invasive method, feasible to be performed and without the risk of radiation exposure [64]. A lot of studies have suggested that LCI has the advantage over FEV1 to detect CF lung disease in earlier stages [21,36,38,64-68]. A more sophisticated analysis of the SnIII has revealed the Scond and Sacin, as indices to detect the mechanisms of ventilation inhomogeneity and the location of the different ventilated lung units. So, the Scond estimates the Convection-dependent Inhomogeneity (CDI) through the conducting airways and the Sacin estimates the Diffusion Convection Interaction Dependent Inhomogeneity (DCDI) at the mouth of the acini [38,40,47]. LCI is easily applicable in infants and preschoolers because passive cooperation is only required during measurement. Moment Ratios (MR) calculated with this method, has been also used as indices of uneven ventilation distribution in later stages of the gas washout [4] and is suitable to differentiate health from disease [69]. In the present study a strong correlation was shown between ventilation inhomogeneity indices LCI, LCI, μ/μ, and μ/μ and spirometric parameters FVC%, FEV1% and FEF25% in the total population.

As far as the correlation with CT is concerned, LCI, LCI, μ/μ, and μ/μ were found to have a close relationship with the severity and extent of bronchiectasis, the generation of bronchial division, the presence of mucus plugging and both LCI and Moments Ratio (MR) with emphysema. LCI also showed high sensitivity (92.3%) and positive predictive value (97.3%) to detect structural damages on HRCT. Consequently, LCI can be used as a reliable index for monitoring lung structure.

Half of the patients of Group A with normal spirometry were found to have an abnormal LCI. This finding confirms the greater sensitivity of LCI to detect changes in the airways, compared to spirometry. Changes in small airway dimensions, due to pathological situations, affect the distribution of ventilation among different parallel pathways and have an impact on LCI. However these small changes can contribute to the overall resistance and volumes of respiratory tract and cannot be detected by FEV1, [40].

Among patients of Group A with normal FEV1, a better correlation was found between MBW and CT parameters than FEV1 and CT parameters. This illustrates that an abnormal LCI in CF patients with normal FEV1, predicts with high sensitivity the structural damages of the lung. These findings are in accordance to the findings of Ellemunter et al. [22] who showed that 80% of patients with normal FEV1 had an abnormal LCI and pathological changes on HRCT. Gustafsson et al. [20] also showed that LCI had a greater sensitivity (85-94%) to detect bronchiectasis and other structural damages vs. FEV1 (85-94%).

On the contrary, not only LCI, but also LCI, μ/μ, μ/μ, and Sacin were significantly correlated with FEV1% and FEF25% (p<0.05) among patients of Group B with mild to moderate lung disease. Especially, LCI and LCI, were strongly correlated with FEV1% (p ≤ 0.001). Low spirometry reflects impaired lung function that is usually combined with severe ventilation heterogeneity. Significant correlation were found between LCI, LCI, and μ/μ with bronchiectasis and generation of bronchial division (p<0.05).

It is very important to detect lung abnormalities in early stages of lung disease before irreversible structural damages become present, in order to the prognosis of CF patients. LCI has been used as a feasible tool that can assess early lung disease. Gustafsson et al. [20] retrospectively analyzed data of 44 CF patients aged 5-19 year old with a wide range of lung function (FEV1=44-127%) and concluded that a normal LCI almost excludes HRCT abnormalities [20]. Although they assessed CT scans with Brody score the data of our study agree with them as LCI was proved to be the only predictor of structural changes on HRCT in both the total population and sub-groups. The results of Group A were in accordance to Ellemunter et al. [22] study that evaluated prospectively 34 patients (6-26 years) with normal spirometry. They supported that structural damages are unlikely if a normal LCI is measured. In agreement with their study, we showed a significant relationship between ventilation inhomogeneity indices and presence of bronchiectasis. Consequently, MBW measurement may be used as an appropriate method for monitoring the progression of CF lung disease mainly in preschoolers and school age children [5], while a normal LCI may prevent the radiation exposure from HRCT. In the present study, both LCI, that assesses ventilation inhomogeneity in an earlier time of the gas washout, and MR that represent the later phase of washout, seem to have a good relationship with lung structure and function, like LCI. However, they have not been proved significant predictors of lung damage.

However, there were limitations to this study. 1) When dividing patients into two groups the sample size of Group B with mild to moderately impaired spirometry, was limited and there was a wide range of FEV1%. 2) The phase III slope requires fixed tidal volumes during single breaths; that is usually not practicable for young children. So, Scond and Sacin values may be unreliable. 3) Completing MBW test is difficult and not well tolerated for patients with severe lung disease. Our study confirmed the LCI reliability to assess CF respiratory tract, as Yammine et al. [53] has recommended. Longitudinal data with a larger sample size is required to confirm the value of LCI among CF patients with abnormal spirometry and to investigate the value of LCI in advanced lung disease where MBW is time consuming.

Conclusion

In conclusion, MBW parameters (LCI LCI, μ/μ, μ/μ, Scond and Sacin) were significantly correlated with spirometric and partial parameters of Bhalla score on HRCT. So, MBW is a reliable method of assessment the structural and functional changes of respiratory tract. However, in mild disease ventilation inhomogeneity indices were better associated with CT changes, while in mild - moderate disease MBW indices were better associated with spirometry. The LCI was showed to predict CF structural lung damage among CF patients with normal and mild – moderate disease.

Contributor’s List

EH, VA and JT had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. EH, VA, AK and JT contributed substantially to the study design, data analysis and interpretation. VA performed the MBW measurements, while AK performed the CFET measurements. VG performed Bhalla scoring of the HRCT scans. All the authors contributed to the writing of the manuscript. EH and JT reviewed and edited the manuscript. EH and JT are guarantors.

Conflicts of Interest

All authors would like to confirm that there is nothing to declare.

Ethics Approval

Aristotle University of Thessaloniki Medical School Ethics Committee (IRB file No. 1/8-11-2012).
References


