Satisfaction with Lung Clearance Index Testing as Compared to Spirometry Performed Before and After Hospitalization for Cystic Fibrosis Pulmonary Exacerbation

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Abstract

Introduction: Patients with Cystic Fibrosis (CF) have intermittent Pulmonary Exacerbations (PEx) with increased cough and decreased pulmonary function. Lung Clearance Index (LCI) measures ventilation inhomogeneity using inert gas or nitrogen washout. LCI is increased in CF compared to healthy subjects. LCI decreases after treatment for CF PEx; whereas, forced expiratory volume in 1 second predicted ($FEV_{1\%}$) increases. Relationships between objective measures ($FEV_{1\%}$, LCI by nitrogen washout) and qualitative measures (Patient Satisfaction) surrounding treatment for PEx have not been reported.

Materials and Methods: Subjects > age 7 years, admitted for treatment of PEx, were recruited. After informed consent/assent, spirometry and LCI (Nitrogen Washout) were performed at the beginning and end of treatment for PEx. A short questionnaire evaluated patient satisfaction with LCI and spirometry at both time points.

Results: Twenty-five patients with CF (9-25 years), performed spirometry and LCI before and after hospitalization for CF PEx. There was better satisfaction with LCI compared to PFT, (mean score 1.7 versus 2.8; LCI easier to perform) (p < 0.01). There was an average decline in LCI of 1.5 units (±1.16, p <0.01); $FEV_{1\%}$ increased by 10.1% (± 9.6, p< 0.01). There was a moderate inverse relationship between mean change in LCI and mean change in $FEV_{1\%}$ predicted (r= - 0.43, p<0.01).

Conclusion: LCI was well tolerated by people with CF and was perceived to cause less cough and trouble breathing than spirometry. There was a moderate inverse correlation between LCI and $FEV_{1\%}$; both tests detect improvement in airways obstruction following treatment for CF.

Keywords: Cystic Fibrosis; Lung Clearance Index (LCI); Multiple Breath Washout (MBW); Patient Experience; Patient Satisfaction; Pulmonary Exacerbation

Abbreviations:

CF	:	Cystic Fibrosis
PEX	:	Pulmonary Exacerbations
LCI	:	Lung Clearance Index
$FEV_{1\%}$	:	Forced Expiratory Volume in 1 Second, Percent Predicted
PFT	:	Pulmonary Function Test
$FEF_{25-75\%}$	:	Forced Expiratory Flow Between 25 And 75% Volume, Percent Predicted

Introduction

Cystic Fibrosis (CF) is an inherited disease resulting in progressive lung damage, including chronic inflammation, endobronchial infection, and bronchiectasis. Pulmonary function tests in people with CF demonstrate airways obstruction, which over time leads to respiratory failure [1]. Patients with CF have pulmonary

exacerbations (PEx), characterized by periods of increased cough and sputum production, increased fatigue, malaise and/or weight loss, combined with decreased pulmonary function [2]. PEx are associated with increased morbidity and mortality and are generally treated with admission to the hospital for intravenous antibiotics and increased airway clearance therapies [1,3]. Symptoms usually improve in 1 to 2 weeks, unless lung disease is severe, and then may take longer. To assess for objective improvement, patients have lung function tests including spirometry (measuring forced expiratory flows such as $FEV_{1\%}$ and $FEF_{25-75\%}$) before and toward the end of hospitalization. Spirometry is widely available but requires reliable and repeated maximal forced expiratory efforts that can lead to coughing and fatigue. It is rarely used in children under age 6 years because cooperation is needed to perform the required maneuvers. Since spirometry values are dependent on height, percent predicted values must be used in growing children.

Lung Clearance Index (LCI) is a lung function test that can measure ventilation inhomogeneity in the lungs by using the Multiple Breath Washout (MBW) technique using either nitrogen or another inert gas such as SF_6 MBW measures the number of lung turnovers required to washout an inert gas such as nitrogen to 1/40th of the starting concentration. A high value indicates abnormal ventilation distribution. The technique is reproducible and does not require forced expiratory efforts, thus it can be performed even in young children [4]. LCI measurements are not dependent on age, height or gender [5]. They may indicate obstruction even when standard forced maneuvers are in the normal range [6]. However, in patients with severe obstruction, the time to clear the inert gas may be prolonged [7].

LCI is increased in people with CF compared to healthy subjects [8,9] and has been shown to improve (Decrease) after treatment for CF PEx [10]. $FEV_{1\%}$ predicted usually improves (Increases) during the same treatment period [11]. Change in $FEV_{1\%}$ is the standard measure of adequate treatment for PEx but the forced maneuver may cause cough; change in LCI is not the standard measure of adequate treatment of PEx but may (or may not) be easier to perform. Patient satisfaction with LCI has been briefly examined with a two-item questionnaire using the Innocor^{TM} SF_6 washout device during a stable visit, but has not been reported using a nitrogen washout device or during a period of exacerbation compared to spirometry [9]. We aimed to compare patient and parent satisfaction with LCI using a nitrogen washout device compared to standard Pulmonary Function Testing (PFT) and to compare the change in LCI to the change in $FEV_{1\%}$ predicted before and after treatment for CF PEx.

Materials and Methods

For this exploratory study, we enrolled a convenience sample of subjects > age 7 years, consecutively admitted to Women and Children's Hospital of Buffalo for treatment of PEx. After informed consent was obtained (including assent, as indicated) spirometry and LCI (in that order) were performed by the subjects at the beginning and end of treatment for PEx. Lung function tests were performed at least in duplicate. If hypertonic saline was part of the treatment regimen, it was withheld before study pulmonary function tests because it can exacerbate cough. Nose clips were applied and spirometry was performed according to American Thoracic Society (ATS) criteria [12]. Satisfaction with testing was assessed with a four-item questionnaire with a Likert scale for each test (1= greatest satisfaction, 5= least satisfaction) at the beginning and end of hospitalization and a mean score was generated (Table 1).

Question 1: This test was hard to do
Question 2: This test made me cough.
Question 3: I had trouble breathing during this test.
Question 4: I would have trouble doing this test again.

Table 1: Four-Item Questionnaire for Assessment of Patient Satisfaction with Regular Pulmonary Function Test (PFT) and for LCI. Each question was answered on a Likert scale: (1=Strongly Disagree, 2= Disagree, 3= Neutral, 4= Agree, 5= Strongly agree). A mean score was generated for PFT and for LCI before and after hospitalization.

Multiple breath nitrogen washout was performed according to CF Foundation Therapeutics Development Network standards using N_2 MBW with an open circuit, bias flow system (Exhalyzer D®, EcoMedics A G ®, and D u e r n t e n , Switzerland) and associated software (Spiroware 3.1 EcoMedics AG) [8]. Basic demographic information was collected. Height, weight and oxygen saturation were measured and recorded.

Statistical Analysis

Continuous variables were summarized using the following descriptive summary statistics: the number of subjects (n), mean, SD, median, range; while categorical variables were summarized using counts and percentages. The change in airways obstruction as measured by calculations of lung clearance index measured at the start and end of hospitalization with intravenous antibiotic treatment for pulmonary exacerbation of CF was tested by paired t-test.
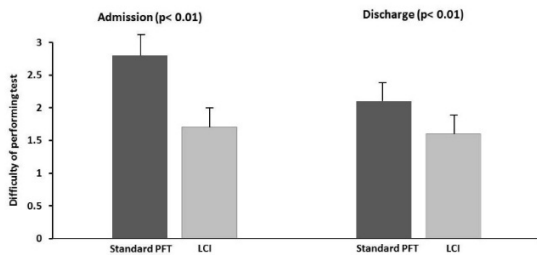
Pearson's correlation was used to compare the change in LCI versus the change in $FEV_{1\%}$, $FEF_{25-75\%}$ predicted and specific conductance, respectively, before and after hospitalization for treatment of CF PEx. Patient satisfaction with use of spirometry and multiple breath washout for measurement of lung clearance index was summarized by counts and percentages. All analysis was carried out by SAS 9.3 (Cary, NC).

1.   Results

Between August 2014 and October 2015, 25 patients with CF (9-25 years) were enrolled (64% female). Thirty-nine percent were F508del homozygotes and 48% were F508del heterozygotes; 57% grew Pseudomonas and 39% grew MRSA in sputum cultures. There were 23 unique subjects in the study (2 consented during 2 different hospitalizations), and 21 complete data sets. One subject withdrew consent before testing, one withdrew due to sinus pain after one LCI maneuver. Two subjects performed LCI at the beginning but not at end of hospitalization; their satisfaction data was still counted (one had vomiting before discharge test maneuvers and one did not want to participate in the discharge test because she was anxious to be discharged). The mean time between tests was 8.7 days (range 5-15 days).
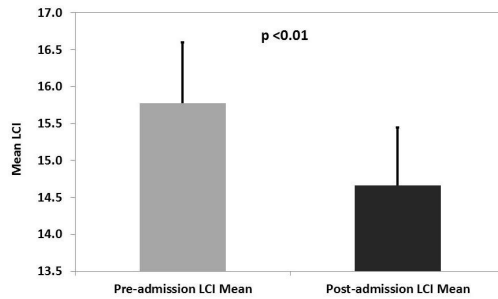
There was better satisfaction with LCI as compared to PFT, (average mean score 1.7 compared to 2.8 before hospitalization, and 1.6 compared to 2.1 after hospitalization (Figure 1), respectively, indicating greater ease of performing test (p < 0.01). Patients reported less cough and trouble breathing with performing LCI as compared to PFT (questions # 2 and 3, respectively).

Figure 1: Patient Satisfaction with Spirometry (Standard PFT) Versus Lung Clearance Index (LCI). Spirometry was more difficult to perform both at admission and at discharge.
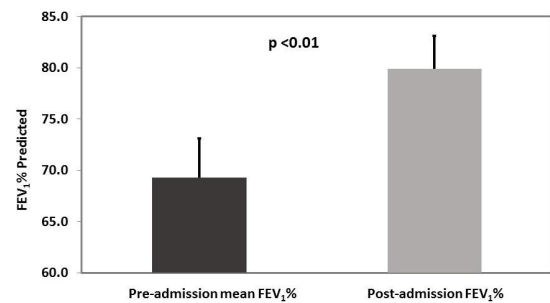
Compared to values obtained at the start of treatment for a PEx, there was an average decline in LCI of 1.5 units ($\pm$ 1.16, p <0.01) (see Figure 2a) and an increase in $FEV_{1\%}$ predicted of 10.1% ($\pm$ 9.6, p< 0.01) (Figure 2b). In 17 of the 21 complete data sets, there was a decrease in LCI and an increase in $FEV_{1\%}$ predicted. In two cases, both LCI and $FEV_{1\%}$ predicted increased slightly. In the other two cases, LCI decreased significantly (-1.19 and -2.23) but the $FEV_{1\%}$ predicted decreased by an insignificant amount (3%).

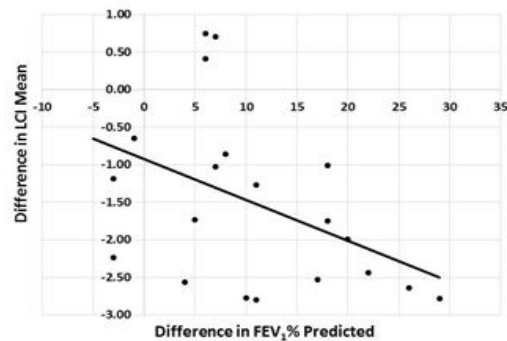Figure 2a: Mean Lung Clearance Index (LCI) Decreased During Hospitalization for PEx

Figure 2b: Mean FEV_1 % Predicted Increased During Hospitalization for PEx

There was a moderate inverse relationship between mean change in LCI and mean change in $FEV_{1\%}$ predicted (r= - 0.43, p<0.01) (Figure 3). The change in $FEF_{25-75\%}$ was not significant and there was no significant relationship between change in LCI and change in $FEF_{25-75\%}$.

Figure 3: There was a Moderate Inverse Correlation Between Decrease in Mean LCI and Increase in FEV_1% Predicted (R= - 0.431)

Discussion

In 2001 the Institute of Medicine published "Crossing the Quality Chasm", setting principles for improved care delivery. One key principle emphasized that services delivered should be patient- centered [13]. Although the patient perception of the quality of inpatient and outpatient care frequently is measured with satisfaction surveys, there are very few studies assessing patient preference with performance of diagnostic testing. In one example, if diagnostic tests are equivalent, patients prefer collection of saliva or urine over blood [14]. Lung function testing can cause coughing and dyspnea, especially at the onset of a pulmonary exacerbation of CF. LCI was well tolerated in the study and was more acceptable for ease of performance in CF patients who were admitted for PEx. Of note, this was true at the end of treatment as well as at the beginning of treatment for PEx even though spirometry is less likely to cause distress once the obstruction, infection and inflammation of PEx has been treated.

LCI values above 6.5 to 7 indicate abnormal ventilation distribution. Recently, LCI has been used to measure small airways dysfunction in children with Cystic Fibrosis (CF) who may have normal values or minimal abnormalities using standard spirometry [15]. LCI has been used to identify PEx in children [16]. We report a moderate inverse relationship between spirometry and LCI; LCI decreased while FEV1% predicted increased during hospitalization for CF PEx, as would be expected if LCI is a sensitive measure of obstruction. Of note, this inverse correlation in $FEV_{1\%}$ predicted and LCI is not always seen [17]. Similarly, we saw a discordance in $FEV_{1\%}$ and LCI in 4 out of 21 data sets.

Equipment now available for LCI research has overcome prior constraints of size, cost and lack of commercial availability. In research subjects who are younger or who have normal $FEV_{1\%}$, this test is especially helpful as an efficacy endpoint [18,19]. Another research team has shown that shorter washout periods with this system may be sufficient in children [20]. Limitations of this study include that in all cases, spirometry was performed before LCI with a short 5-10-minute break in between. This was done because priority was given to the clinical test in case the patient was too tired or unable to complete the entire testing episode. It is thought that the spirometry did not significantly impact the results of the LCI. Other studies have demonstrated there is not a significant impact of forced expiratory maneuvers on LCI results [9]. However, it is possible that the forced maneuvers led to cough clearance that made LCI less likely to cause cough. The satisfaction score we used was not validated, but it was easy to complete and directly applicable to the questions we hoped to explore. The sample size was relatively small and was from one institution, but still contributes to the experience needed with LCI for use in research studies across the country that was mentioned in a Cystic Fibrosis Foundation Workshop report [8].

Conclusions

Our data indicate that LCI testing was well tolerated by children and young adults with CF and was perceived to cause less cough and trouble breathing than standard PFT. We found a moderate inverse correlation between LCI and $FEV_{1\%}$ suggesting that both tests detect improvement in airways obstruction following treatment for pulmonary exacerbation of CF. Patient preference and acceptance should be part of the assessment of any new diagnostic test.

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