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Correlation Between Lung Clearance Index (LCI) and Forced Expiratory Volume (FEV_1) in Children with Cystic Fibrosis (CF): A Cross-Sectional Study

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Abstract

Background: The Lung Clearance Index (LCI) serves as a non-uniform ventilation index utilized for monitoring pulmonary function in patients with cystic fibrosis (CF). Lung Clearance Index exhibits higher sensitivity compared to forced expiratory volume in 1 second (FEV1) for early detection of lung disease and does not necessitate active patient cooperation, as required for FEV1 measured through spirometry. Presently, FEV1 is the standard parameter employed for monitoring lung function in CF patients.

Objectives: The objective of this study was to assess the correlation between LCI and FEV1 in patients with cystic fibrosis.

Methods: This cross-sectional study enrolled children aged 6 to 18 years with confirmed CF diagnosis, who were referred to the CF clinic at Children's Medical Center Hospital (Tehran, Iran). Participants completed consent forms and subsequently underwent pulmonary function tests. Lung Clearance Index was calculated using the exhaling-D device via the Multiple Breath Washout (MBW) method, followed by FEV1 assessment through spirometry.

Results: The study included 52 patients with an average age of 12 years, among whom 52% were males. The mean ± standard deviation of FEV1 and LCI were 80.2% ± 25.3 and 8.9 ± 2.8, respectively. A significant inverse relationship was observed between these two parameters in the study ($r = -0.49$, $P = 0.001$).

Conclusions: These findings further underscore the potential utility of LCI, which offers ease of administration and demonstrates high reliability and accuracy compared to FEV1 for monitoring pulmonary function in CF patients.

Keywords: Children, Cystic Fibrosis, Forced Expiratory Volume, Lung Clearance Index, Mulitple Breath Washout

1. Background

Cystic fibrosis (CF) is an autosomal genetic disorder caused by various types of mutations in the transmembrane conductance regulator (CFTR) gene located on chromosome 7. Three tests are used to diagnose CF: (1) The sweat test, which measures the amount of sweat chloride (with sweat chloride levels ≥ 60 mEq/L considered indicative of CF) and serves as the gold standard test; (2) a genetic test to detect the most common point mutations and deletions; and (3) nasal potential differences (NPD), which measures the voltage across nasal epithelium (1).

The most common cause of mortality and morbidity in CF patients is advanced lung disease (2). Conversely, one of the most important clinical features of children with CF is acute exacerbation caused by respiratory tract infections, further reducing lung function. Therefore, aggressive treatment of primary lung disease and its exacerbations is crucial to prevent this decline (2). Spirometry, the most common pulmonary function test, is routinely used for older children to monitor lung function. Forced expiratory volume in the first second (FEV_1), measured during spirometry, assesses respiratory function and is useful for categorizing the severity of lung diseases (3). However, FEV_1 is generally considered difficult to measure in children under 6 years of age, despite the fact that most declines in lung function occur in this age group (4).

Lung Clearance Index (LCI), derived from multiple breath washout (MBW) recordings, is a practical parameter that detects early changes in lung function in children with CF with greater sensitivity than spirometry. Multiple breath washout, which calculates LCI, has had the potential to diagnose lung diseases at an early stage since the 1940s. In recent years, the popularity of this test has increased for assessing small airway disease (2, 3). Several studies have demonstrated that LCI is highly sensitive compared to spirometry for detecting airway obstruction at the early stages of CF and is increasingly used as a clinical indicator (5, 6). Lung Clearance Index can be measured with a child's normal tidal breathing pattern at any age, including infancy, and it offers numerical advantages over FEV_1, such as being performed at all ages, being non-invasive, and not requiring the passive cooperation of the child (7).

In younger children, elevated LCI levels may indicate a higher risk of developing severe lung involvement in the future (3). In healthy individuals up to the age of 18, LCI levels are almost constant (2). However, for patients with conditions such as asthma, bronchopulmonary dysplasia, and chronic obstructive pulmonary diseases like cystic fibrosis, LCI levels can increase (3). Various LCI cutoff points have been reported in many studies, ranging from 7.8 to 8.2 (8). Lung Clearance Index values above 10 indicate significant lung disease, while values above 12 indicate severe advanced compromise (9).

Cystic fibrosis is the most common life-limiting autosomal recessive disease among white people, with respiratory problems being among the most common causes of mortality and morbidity associated with this disease. Due to the limitations of spirometry in young children, this study was designed. The aim of this study was to determine the correlation between LCI and FEV1 to assess the validity of LCI for evaluating CF lung disease.

2. Objectives

This study aimed to provide further evidence supporting the use of LCI as an alternative parameter to FEV_1 in children under the age of 6 to assess pulmonary function in CF patients.

3. Methods

3.1. Study Design

This study was cross-sectional Children with CF aged 6 - 18 years were referred to the CF clinic at Children's Medical Center Hospital (Tehran, Iran) and were selected for 1 year (2018 - 2019).

3.2. Inclusion Criteria

The children included in this study were over 6 years old and under 19 years old. The definitive diagnostic criteria for cystic fibrosis included two positive sweat tests (sweat chloride ≥ 60 mEq/L) and the presence of common mutations in the CFTR gene. The NPD test was not performed in our center.

3.3. Exclusion Criteria

Patients who were unable to undergo spirometry or MBW testing were excluded from the study. Additionally, patients who did not experience exacerbations in the last month and those whose parents did not provide consent to participate in the study were also excluded.

3.4. Sample Size

This study aimed to determine the correlation between two quantitative (numerical) variables: (1) LCI, (2) FEV1.

According to the statistical reference (10) and the following formula, the sample size was calculated to be a minimum of 29 samples required.

$$N = \left[\frac{Z_a + Z_b}{c}\right]\left[\frac{Z_a + Z_b}{c}\right] + 3$$

Where the alpha error is 0.05, Z_a is equal to 1.96, and where the beta error is 0.2, Z_b will be 0.84. The goal was to determine the high correlation at r = 0.5. All demographic information, disease data, and results of the tests were recorded in the relevant questionnaires.

3.5. Intervention

All eligible children referred to the CF clinic of Children's Medical Center Hospital underwent MBW firstly to measure LCI and then spirometry to obtain FEV_1. The LCI was measured by the multiple breath nitrogen washouts method through the Exhalizer-D Eco med device. The child breathes normally (tidal) and exhales through a mouthpiece or mask; thus, the exhaled gases are analyzed. Lung Clearance Index can be calculated as the total exhaled volume (from the beginning to the end of the test) divided by the child's functional residual capacity (FRC) (as a number without a unit). The MBW test was repeated twice for each patient. Generally, different techniques, tracer gases, and tools are employed to derive the LCI. In our study, Sulfur Hexafluoride 4% (SF6 4%) was used to measure LCI according to the ATS (American Thoracic Society) standard. As mentioned above, the cut-off points of LCI have been reported for 7.8 - 8.2 in some investigations. We determined the value of 7.8 for the LCI cut-off point based on the available reference, Lum et al. (8).

Forced expiratory volume was measured through a spirometer (Medisoft® Micro 6000). Spirometry was performed while patients sat upright, and nasal clips were placed on the nose to keep the nostrils closed. Patients took a deep inspiration and exhaled as quickly and forcefully as they could into the tube. The volume of exhalation (presented as a percentage) was measured in the first second and varied according to the child's height and weight. Spirometry was repeated for each patient three times to ensure the results were relatively consistent. The highest value among the three tests was used as the result. Bronchodilators were not administered. This test and its accuracy were assessed based on ATS standards and criteria.

3.6. Ethical Considerations

Confidentiality and personal information of patients were maintained and accessible only to the researchers in this field. This study also included parental consents. Spirometry and MBW have been considered as routine parts of the follow-up program for CF patients, and no additional costs were imposed. This study was approved by the ethics committee of Tehran University of Medical Sciences (Ethical code: IR.TUMS.CHMC.REC.1397.4908).

3.7. Statistical Analysis

Data were displayed as mean ± standard deviation and statistically analyzed by SPSS software (version 22). A *t*-test was used to calculate the correlation coefficient between 2 variables (FEV_1 and LCI). Chi-square statistic was used to show whether the relationship between patients' cooperation in spirometry and LCI measurements exists. In order to compare LCI level changes in bronchiectasis patients, ANOVA test was employed.

4. Results

A total of 52 patients were included with a median age of 12 ± 2.74 years (ranging from 6 to 18 years), and 52% were males. The mean age of initial symptom onset was 4 months for both genders. The mean age at diagnosis was 4 months after symptom onset. The distribution of the percentage of predicted FEV_1 values is shown in Table 1. The resulting values are used to grade the severity of the patient's disease. Fifty percent of patients had an FEV_1 greater than 80% of the predicted value and were considered normal. Twenty-three percent of patients had an FEV_1 with more than 60% and less than 80% of predicted values and were considered moderate. Twenty-seven percent of patients showed severe grade as their obtained FEV_1 was less than 60%. There was no significant difference between the 2 genders in terms of the distribution of FEV_1 (P = 0.58, t-test). The lowest FEV_1 was obtained for 33% and the highest FEV_1 was reported as 129%. The distribution of LCI values has also been reported in Table 1.

Table 1. Distribution of Forced Expiratory Volume (FEV1) and Lung Clearance Index (LCI) Values

Tests	Values	No. (%)
FEV1	Normal % ≥ 80	26 (50)
	80% > FEV1 > 60%	12 (23)
	Severe ≤ 60%	14 (27)
LCI	> 7.8	23 (43.1)
	7.8 - 12	28 (54.9)
	˃ 12	1 (2(

Abbreviations: FEV1, forced expiratory volume; LCI, Lung Clearance Index.

The lowest and highest LCI measurements were 3.8 and 16, respectively. There was no significant difference between the 2 sexes in terms of LCI distribution (P = 0.62, *t*-test). For spirometry, 88% of patients had reliable cooperation, and 12% had relative cooperation. However, for LCI measurements, patients exhibited absolute cooperation. Our results have indicated that the cooperation of patients was significantly different in LCI and FEV_1 measurements (P = 0.03, chi-square test). Two variables, LCI and FEV_1, were significantly inversely related (r = -0.49, P = 0.001, Pearson correlation coefficient test). This relationship has been illustrated in the regression plots in Figure 1.

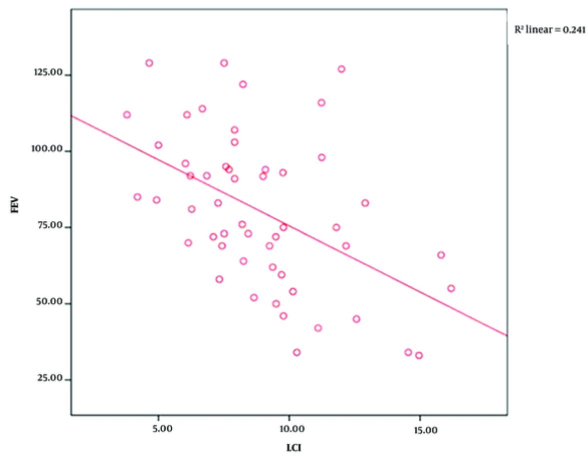

Figure 1. Correlation between forced expiratory volume (FEV1) and lung clearance (LCI) values for CF patients.

Essentially, to assess lung involvement, chest CT scans were performed for the patients. CT scan results have shown that 47.83% of patients had lung involvement with bronchiectasis changes (first group). 23.91% showed lung involvement without bronchiectasis changes (second group), and 28.26% showed no involvement with a normal CT scan (third group). Table 2 has compared the FEV_1 and LCI with the lung involvement depicted in the CT scan. The LCI value was significantly elevated in the bronchiectasis group compared to the other groups (P = 0.02, ANOVA).

Table 2. Comparison of Forced Expiratory Volume (FEV_1) and Lung Clearance Index (LCI) Indices with Lung Involvement Shown in CT Scan

Tests	First Group (with Bronchiectasis)	Second Group (Without Bronchiectasis)	Third Group (Normal)	P-Value
FEV1	71 ± 24	74 ± 16	97 ± 19	0.006
LCI	10.1 ± 2.8	7.9 ± 1.9	7.8 ± 3.2	0.02

Abbreviations: FEV1, forced expiratory volume; LCI, Lung Clearance Index.

In addition, compared to the other groups, the bronchiectasis group showed lower FEV_1 (P = 0.006, ANOVA). Patients were assessed for Body Mass Index (BMI) and height. Fifty-one percent showed a BMI below 5%. In the group with a normal BMI, FEV_1 was significantly higher; however, the LCI did not show any significant difference between the 2 groups. Normal stature is defined as height above 5% for age and sex, and short stature is defined as height below 5%. Twenty-two percent of patients had short stature. In children with normal and short stature, the mean FEV_1 was 87% and 59%, respectively, which also showed significant differences for these two groups (P = 0.001, *t*-test). The mean LCI in the short stature group was reported as 9.5, which was significantly higher than the value in the normal height group (8.7) (P = 0.05, *t*-test). Throat culture results were available for 45 patients. Thirty-five percent of children had a current Pseudomonas infection; 16.5% had a past history of Pseudomonas infection, and 47.4% had no history of this infection. In these three groups, the risk of bronchiectasis was evaluated. Patients with a positive throat culture for Pseudomonas infection (those with current and past infection) showed bronchiectasis (56%), compared to the non-Pseudomonas group (36%). This difference was statistically significant (P = 0.02, chi-square). *Pseudomonas aeruginosa* infection, with an odds ratio of 2.275, increases the chance of bronchiectasis. According to Table 3, FEV_1 was considered the gold standard for CF follow-up in this study; therefore, the sensitivity and specificity of the LCI were calculated as 70% and 80%, respectively. In agreement with the ROC curve, the cut-off point of LCI was computed as 8. In this study, eight patients had normal FEV_1 while their LCI was abnormal (Table 3).

Table 3. Determination of Sensitivity and Specificity of Lung Clearance Index (LCI) According to Forced Expiratory Volume (FEV_1)

Variables	FEV1	
	Normal	Abnormal
Normal LCI	22	1
Abnormal LCI	8	21

Abbreviations: FEV1, forced expiratory volume; LCI, Lung Clearance Index.

5. Discussion

Our findings have shown that LCI can be considered a suitable indicator for monitoring and managing CF patients and is an alternative indicator to FEV1. We found a significant inverse correlation between FEV1 and LCI (r = -0.49, P = 0.001).

The outcomes of six large studies reviewed by Sonneveld et al. previously have demonstrated a correlation between FEV1 and LCI (11). O'Neill et al. also found a significant inverse correlation between LCI and FEV1 (r = -0.62, P = 0.003) (12).

We also found eight patients with abnormal LCI, while their FEV1 was normal (reported in Table 3), which agrees with published data. As discussed earlier, LCI offers the potential to be a more useful measure for early detection of lung diseases than spirometry (13, 14). Therefore, presumably, LCI is more reliable than FEV1 in assessing pulmonary function in the early stages of pulmonary involvement in CF patients. Both LCI and FEV1 were suitable indicators to determine disease severity (15-17). In this study, these 2 parameters were also employed to grade the severity of lung diseases in the patients. A large number of patients in the bronchiectasis group had abnormal levels of LCI and FEV1 compared to non-bronchiectasis patients.

A number of pieces of evidence have demonstrated that LCI is also useful for diagnosing pulmonary exacerbation and monitoring treatment response in children with CF (13, 18), although this current study has not investigated this statement.

Pulmonary involvements are the main causes of mortality and morbidity in CF patients. Approximately, 66.8% of mortality and morbidity in CF disease is associated with respiratory involvement (19). Although FEV1 is currently used as a routine indicator to follow up and manage pulmonary involvement in CF patients and for other associated lung involvements, several studies have suggested that FEV1 can be replaced by LCI. The potential role of LCI in the diagnosis of late pulmonary complications in children suffering from cancer has been demonstrated (20). Another research has studied the importance of LCI in predicting the development of nocturnal hypoxia in children with CF (21).

In agreement with the results from the present study as well as available literature, LCI is preferable to FEV1 for several reasons. Lung Clearance Index performance is more convenient for most children, while in spirometry only 80% of patients showed reliable cooperation to measure FEV1. O'Neil et al. have reported 90% and 42% children's cooperation for LCI and spirometry performance respectively (22). Spirometry requires the active participation of patients. Spirometry performance is difficult for children under 6 years of age. However, LCI can be performed even in 3-month-old infants as it does not require the active cooperation of patients (7). Stahl have reported that LCI is feasible with a high success rate for 91.8% of infants and preschool children with CF and other lung diseases (23).

The LCI is almost constant in healthy individuals, as Fuchs et al. have found that healthy individuals might show slight changes in LCI level (24). Marcus Svedberg also has shown that children with CF who have a stable clinical condition had little changes in their LCI level (25). The LCI cutoff point does not change dramatically from infancy to adulthood, although the FEV1 index decreases with increasing age (25).

In this study, we have some limitations such as patient selection and their cooperation to monitor CF disease. Most patients above 6 years of age have significant pulmonary involvement and tend to be less cooperative to obtain spirometry results. Lack of general accessibility to Exhalizer-D is another issue. The standardization of Exhalizer has not been completed yet. Not enough experienced staff to fabricate the Exhalizer can be mentioned as another limitation. In addition, LCI does cost more compared to spirometry.

5.1. Conclusions

In our study, the results showing the relationship between FEV1 and BMI or height were consistent with previous study results. However, the relationship between LCI and BMI or height has not been well investigated.

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Footnotes

Authors' Contribution: MrM: conceptualization, design, data collection, analysis, writing, and review. BR: conceptualization, analysis, writing, and review. KE: conceptualization, study design, writing, and review. RSh: conceptualization, design, writing, and Review. FT: designs, data analysis, and reviewing. S-HM: conceptualization, design, data collection, analysis, writing, and review.

Clinical Trial Registration Code: None

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Data Availability: The data used to support the findings of this study are available from the corresponding author upon request.

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Informed Consent: Informed consent was obtained from the children or their parents to participate in this study.

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