CHEST

Lung Clearance Index in Adults and Children With Cystic Fibrosis

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BACKGROUND: Lung clearance index (LCI) has good clinimetric properties and an acceptable feasibility profile as a surrogate end point in cystic fibrosis (CF). Although most studies to date have been in children, increasing numbers of adults with CF also have normal spirometric findings. Further study of LCI as an end point in adults with CF is required. Therefore, the purpose of this study was to determine the clinimetric properties of LCI across the age range of people with CF.

METHODS: Clinically stable adults and children with CF and age-matched healthy control subjects were recruited.

RESULTS: LCI and spirometry data for 110 subjects with CF and 61 control subjects were collected at a stable visit. The CF Questionnaire-Revised (CFQ-R) was completed by 80 of 110 subjects with CF. Fifty-six subjects with CF completed a second stable visit. The LCI coefficient of variation percent was 4.1% in adults and 6.3% in children with CF. The coefficient of repeatability of LCI was 1.2 in adults and 1.3 in children. In both adults and children, LCI (area under the receiving operator characteristic curve [AUC^{ROC}] = 0.93 and 0.84, respectively) had greater combined sensitivity and specificity to discriminate between people with CF and control subjects when compared with FEV_1 (AUC^{ROC} = 0.88 and 0.60, respectively) and forced expiratory flow at 25% to 75% of the curve (AUC^{ROC} = 0.87 and 0.68, respectively). LCI correlated significantly with the CFQ-R treatment burden in adults ($r = -0.37$; $P < .01$) and children ($r = -0.50$; $P < .01$). Washout tests were successful in 90% of subjects with CF and were perceived as comfortable and easy to perform in both adults and children.

CONCLUSIONS: These data support the use of LCI as a surrogate outcome measure in CF clinical trials in adults as well as in children. CHEST 2016; 150(6):1323-1332

KEY WORDS: cystic fibrosis; lung clearance index; outcome measure

ABBREVIATIONS: AUC^{ROC} = area under the receiving operator characteristic curve; CF = cystic fibrosis; CFQ-R = Cystic Fibrosis Questionnaire-Revised; CoR = coefficient of repeatability; CV = coefficient of variation; $FEF_{25\%-75\%}$ = forced expiratory flow at 25% to 75% of the curve; HC = healthy control; ICC = interclass correlation coefficient; LCI = lung clearance index; MBW = multiple breath washout; ROC = receiving operator characteristic curve; ULN = upper limit of normal

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Lung clearance index (LCI), a measure of ventilation inhomogeneity derived from multiple breath washout (MBW) tests, has good clinimetric properties and an acceptable feasibility profile as a surrogate end point in cystic fibrosis (CF).[1,2] The majority of studies have been in children,[2] in whom it has the most potential as a useful marker to detect early changes in lung disease. These studies have shown good short- and medium-term repeatability of LCI readings in health and disease[3-6] and correlation with parameters of chest CT,[7-9] body plethysmography,[10] spirometry (FEV_1, forced expiratory flow at 25% to 75% of the curve [$FEF_{25\%-75\%}$]),[11,12] and markers of pulmonary inflammation and infection.[3] LCI has also been shown to be more sensitive than FEV_1 in predicting[11] and detecting[4,13,14] early lung disease. In addition, LCI predicts pulmonary exacerbations and correlates with respiratory symptoms as measured by the CF Questionnaire-Revised (CFQ-R).[15] The responsiveness of LCI in children with CF has also been demonstrated after intervention with hypertonic saline[6,16] and deoxyribonuclease,[17] and in children and adults receiving ivacaftor.[18] Furthermore, MBW testing is considered feasible in an outpatient setting.[5]

Studies of LCI involving adults with CF have also demonstrated encouraging results but are fewer in number.[8,19-22] As increasing numbers of adult patients with CF also have normal FEV_1, more sensitive end points are required to assess new therapies in this age group.[23] Improved survival means that adults are beginning to outnumber children in most developed countries,[24] and a large proportion of clinical trials are aimed at adults in whom efficacy must be demonstrated prior to testing treatments in younger patients. A recent workshop report has highlighted the potential use for LCI in older subjects with normal FEV_1;[25] however, gaps in the current evidence remain concerning intervisit reliability, correlation with patient-reported outcomes and patient acceptability. Furthermore, only one study has directly compared adults and children with CF.[26] Further research is required to validate LCI as an outcome measure across the age range in CF.

In this study, we determined the intravisit repeatability, sensitivity, and specificity and the intervisit repeatability of LCI compared with FEV_1 and $FEF_{25\%-75\%}$. We also assessed the correlations between LCI, FEV_1, $FEF_{25\%-75\%}$, and CFQ-R domain scores and determined the feasibility and acceptability of LCI. Results were reported separately for adults and children with CF. Some results of this work have been presented in abstract format.[27-29]

Methods

Adults and children with CF were recruited as part of a larger study investigating the prevalence and potential pathogenicity of anaerobic bacteria in subjects with CF lung disease. Subjects with CF were recruited during routine outpatient appointments at the adult and pediatric CF Centres of the Belfast Health and Social Care Trust (Belfast City Hospital and Royal Belfast Hospital for Sick Children). All subjects were enrolled for the first study visit when clinically stable (cross-sectional arm). Subjects were aged ≥ 6 years, had a confirmed diagnosis of CF[30] and were clinically stable (with no pulmonary exacerbation requiring IV antibiotics in the previous 4 weeks). A subgroup of subjects (≥ 12 years) were recruited to a longitudinal arm in which repeated stable visits were performed at 3-month intervals. Because of the difficulties of collecting sputum samples from subjects < 12 years old, these subjects participated in the cross-sectional study only. The current study reports on MBW, spirometric and questionnaire data only.

An exclusion criterion for MBW testing specifically was infection with *Burkholderia cepacia* complex (due to equipment infection control issues). On obtaining written informed consent, subjects were enrolled for a study visit and completed a CFQ-R, a MBW test and two visual analogue scales (VAS) for evaluating the ease and comfort of MBW testing and spirometry. For the second stable visit, procedures were completed in the same order.

Adult and child healthy control (HC) subjects were invited to attend a single study visit by means of e-mail circulation among work colleagues at Queen's University Belfast and Belfast Health and Social Care Trust. Subjects were aged ≥ 6 years and had no history of a respiratory condition or use of antibiotics in the previous 4 weeks. On obtaining written informed consent, subjects completed spirometry and a MBW test.

All subjects were recruited during a 32-month period (October 2010 to June 2013). This study was approved by the Office for Research Ethics Committees Northern Ireland (reference number: 10/NIR01/41).

Participants individually completed an age-appropriate version of the CFQ-R before any other procedure. Children aged 6 to 11 years completed the questionnaire with the assistance of the researcher or a parent if necessary. Adolescent and adult data for subjects aged ≥ 14

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