



Lung Clearance Index and High-Resolution Computed Tomography Scores in Primary Ciliary Dyskinesia

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Rationale: Lung clearance index (LCI) is a more sensitive measure of lung function than spirometry in cystic fibrosis (CF) and correlates well with abnormalities in high-resolution computed tomography (HRCT) scanning. We hypothesized LCI would be equally sensitive to lung disease in primary ciliary dyskinesia (PCD).

Objectives: To test the relationships between LCI, spirometry, and HRCT in PCD and to compare them to the established relationships in CF.

Methods: Cross-sectional study of 127 patients with CF and 33 patients with PCD, all of whom had spirometry and LCI, of which a subset of 21 of each had HRCT performed. HRCT was scored for individual features and these features compared with physiological parameters.

Measurements and Main Results: Unlike in CF, and contrary to our hypothesis, there was no correlation between spirometry and LCI in PCD and no correlation between HRCT features and LCI or spirometry in PCD.

Conclusions: We show for the first time that HRCT, spirometry, and LCI have different relationships in different airway diseases and that LCI does not appear to be a sensitive test of airway disease in advanced PCD. We hypothesize that this results from dissimilarities between the components of large and small airway disease in CF and PCD. These differences may in part lead to the different prognosis in these two neutrophilic airway diseases.

Keywords: spirometry; high-resolution computed tomography; lung clearance index

Primary ciliary dyskinesia (PCD) and cystic fibrosis (CF) are both autosomal recessive disorders, with clinical phenotypes dominated by respiratory disease. Both disorders are characterized by, albeit different, defects of mucociliary clearance, chronic bacterial infection, neutrophilic inflammation (1–5), and progressive worsening of obstructive lung disease. In PCD, mucociliary

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Lung clearance index (LCI) is a more sensitive measure of lung function than spirometry in cystic fibrosis (CF) and correlates well with abnormalities in high-resolution computed tomography scanning. This relationship in primary ciliary dyskinesia (PCD), another neutrophilic airways disease with a milder prognosis than CF, is currently unknown.

What This Study Adds to the Field

We show for the first time that HRCT, spirometry, and LCI have different relationships in different airway diseases, and that LCI does not appear to be a sensitive test of airway disease in advanced PCD.

clearance is impaired because respiratory cilia are dyskinetic and nonmotile, with relatively normal respiratory secretions, whereas in CF, the primary defect is of increased mucus viscosity and loss of airway surface liquid, leading to secondary ciliary dysfunction. However, for reasons that remain incompletely understood, the phenotype of PCD is much milder than that seen in CF, with less morbidity from lung disease and longer life expectancy (6).

Patients with both diseases are monitored routinely in the clinic with spirometry, most commonly FEV₁ and FVC. However, there is increasing recognition that spirometry may be insensitive to early pulmonary disease in CF (7, 8). There may be structural damage on high-resolution computed tomography (HRCT) in children with normal spirometry (9); this may also be the case in PCD (10).

As part of the search for more sensitive measures of early lung disease, there has been increasing focus on the lung clearance index (LCI) derived from multibreath washout tests (MBW). The MBW is an established, noninvasive technique to measure gas mixing efficiency in the lung (11). The LCI is defined as the number of volume turnovers of the lungs required to reduce an inert gas to 1/40th of its starting concentration and has been shown to be elevated in many conditions, such as CF and asthma (12, 13).

In CF, LCI becomes abnormal earlier than spirometry, and in later-stage disease it correlates well with FEV₁ (7, 12). It is more sensitive than spirometry at detecting structural abnormalities on HRCT scans (8, 14, 15) and has been used as a sensitive outcome measure in interventional trials (16, 17). LCI also has other advantages in being non-effort dependent and applicable to younger age groups. The role of LCI in PCD has been much less studied. One cross-sectional study (18) showed that gas-mixing

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indices were abnormal in most patients with PCD, including those with a normal FEV₁, but lung structure was not assessed, and there was no CF comparator group.

We hypothesized that LCI would be a more sensitive marker of lung disease in PCD than conventional spirometry and that there would be similar relationships between spirometry, LCI, and HRCT to those observed in CF. We aimed to assess the relationships between LCI and conventional physiological and radiological measures of lung disease in PCD.

Some of the results of these studies have been previously reported in the form of an abstract (19).

METHODS

Recruitment

Thirty-three subjects with PCD and 127 subjects with CF diagnosed on standard criteria (20–22) were recruited for spirometry and LCI. All were clinically stable at the time of testing, with FEV₁ of greater than 40% predicted. A subgroup of 21 patients with PCD entered a more detailed study, which also included an HRCT scan. These subjects were matched as closely as possible for age, sex, and chronic infection with *Pseudomonas aeruginosa* with subjects with CF participating in an observational study of biomarkers in preparation for the UK CF Gene Therapy Consortium gene therapy study (the Run-In Study [23]). All measurements in each subject were performed on the same day, with spirometry performed first, and at least 30 minutes before LCI. Demographics are shown in Table 1.

Spirometry

Spirometry (EasyOne; ndd Medical Technologies, Andover, MA) was performed according to American Thoracic Society/European Respiratory Society recommendations (24). Subjects completed a minimum of three forced expiratory maneuvers, and FEV₁ (L) and FVC (L) were expressed as z scores (25, 26).

MBW

MBW was performed using a photoacoustic gas analyzer (Innocor, Odense, Denmark), modified to include a separate Pneumotach (Hans Rudolph, Shawnee, KS), using 0.2% sulfur hexafluoride (SF₆) tracer gas (BOC, Guildford, UK) in a bias-flow system as reported by other authors previously (11, 13). Tests were analyzed using the Washout software (with thanks to Per Gustaffson, Department of Pediatrics, Central Hospital, Skövde, Sweden) and included in this dataset if a minimum of two of the three tests met acceptability criteria. The primary outcome measure was LCI, and functional residual capacity from MBW (FRC_{MBW}) was also calculated.

TABLE 1. DEMOGRAPHICS

	n	Mean Age (yr)	Sex (m)	FEV ₁ z Score*	Infection with <i>Pseudomonas aeruginosa</i> †
All patients					
PCD	33	24.66	12	-2.99 (-0.1 to 6.08)	11 (33.4)
CF	127	16.26	54	-1.88 (2.3 to 5.48)	83 (65.4)
HRCT cohort					
PCD	21	31.2	11	-2.93 (-0.1 to -6.08)	10 (47.6)
CF	21	29.8	11	-3.05 (-0.82 to -5.48)	13 (61.9)

Definition of abbreviations: CF = cystic fibrosis; HRCT = high-resolution computed tomography; PCD = primary ciliary dyskinesia.

All patients studied and those undergoing matching and CT scanning (HRCT cohort). In the HRCT cohort, patients with CF and PCD were matched for age, sex, and infection with *Pseudomonas aeruginosa*.

*Data are presented as median (range).

†Data are presented as No. (% of total).

HRCT

HRCT scans were on a 64-channel multidetector scanner (Siemens Somatom Zoom; Siemens Medical Solutions, Erlangen, Germany). Each CT scan comprised contiguous thin sections (1.25 mm) through the entire volume of the lungs obtained during inspiration and also interspaced (1-mm sections at 10-mm increments) at end-expiration. A high-spatial-resolution algorithm was used for image reconstruction.

The CTs were scored independently by two radiologists who specialize in thoracic imaging. All the scoring was performed directly from workstations with access to image manipulation including window settings (default: width 1,500 Hounsfield units, center -500 Hounsfield units).

The presence and severity of specific CT features was recorded for each lobe (individual scoring system). The features studied were extent of bronchiectasis, severity of bronchiectasis, bronchial wall thickness, small and large mucus plugs, and air trapping (27). A comparison of this score with the more commonly used Brody score (28) is in the online supplement.

Statistical Analysis

There are no data in the literature to inform a power calculation, and so sample size was opportunistic. Data were analyzed using SPSS (version 17.00; IBM, Armonk, NY) and Graphpad (version 5.0; Graphpad Software, La Jolla, CA). Data are nonparametric unless otherwise stated. Mann-Whitney test was used for comparison of groups and Student *t* test for parametric data. Correlations between measures were assessed with Spearman *r* unless otherwise stated. *P* values of less than 0.05 were considered significant.

RESULTS

Physiological Comparisons

In the PCD group as a whole (*n* = 33), there was no relationship seen between LCI and FEV₁ (Figure 1a); in contrast, there was

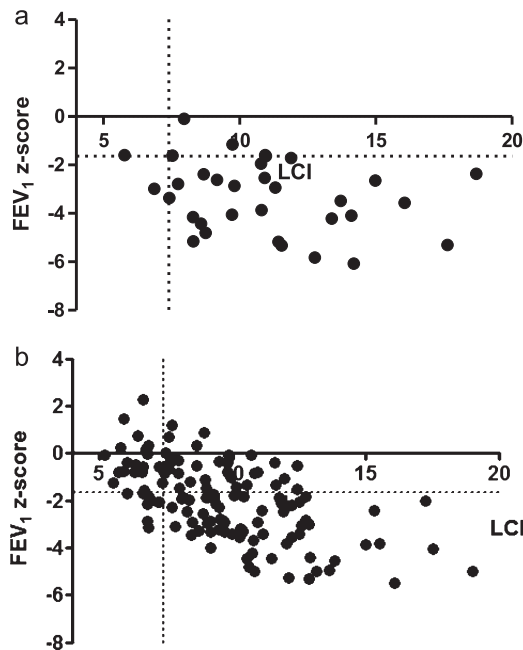


Figure 1. (a) FEV₁ versus lung clearance index (LCI) in the full primary ciliary dyskinesia cohort. There is no significant relationship seen (*P* = 0.081, *r* = -0.31, *n* = 33). Dotted lines represent the upper (LCI) and lower (FEV₁) limits of normal for both measures. (b) FEV₁ versus LCI in the full cystic fibrosis (CF) cohort. The two are strongly correlated (*P* < 0.0001, *r* = -0.60, *n* = 127). LCI shows a superior sensitivity in patients with CF compared with FEV₁. Thirty-five patients have an abnormal LCI while still having normal spirometry, compared with the seven having an abnormal FEV₁ and normal LCI.

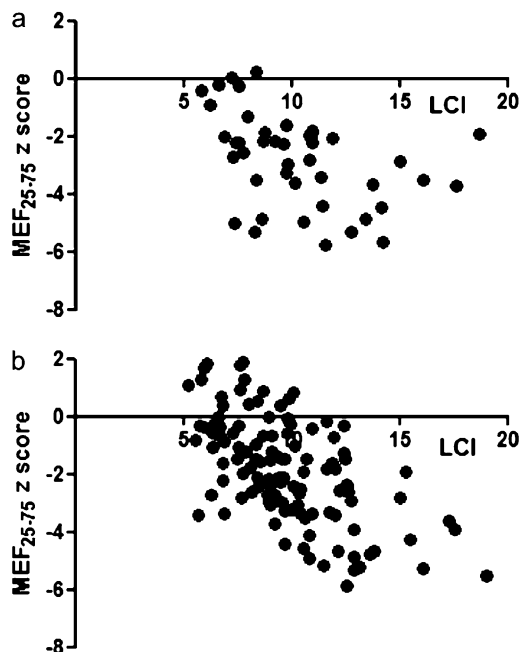


Figure 2. (a) Midexpiratory flow between 25 and 75% of vital capacity ($MEF_{25-75\%}$) is correlated with lung clearance index (LCI) in primary ciliary dyskinesia ($P = 0.001$, $r = -0.5$). (b) $MEF_{25-75\%}$ is correlated with LCI in cystic fibrosis ($P < 0.0001$, $r = -0.6$).

a significant correlation in the CF group ($n = 127$), with a higher (worse) LCI correlating with a lower FEV_1 (Figure 1b).

Where only one of the tests was abnormal, this was more likely to be LCI in both disease groups: 2 patients with PCD had a normal LCI but abnormal FEV_1 , whereas 5 patients had normal FEV_1 but abnormal LCI; 7 patients with CF had a normal LCI but an abnormal FEV_1 , whereas 35 patients with CF had normal FEV_1 but abnormal LCI.

Midexpiratory flow between 25 and 75% of vital capacity ($MEF_{25-75\%}$) and LCI correlated similarly in both disease groups ($P = 0.001$, $r = -0.5$ for PCD; $P < 0.0001$, $r = -0.6$ for CF).

There was no difference between FEV_1 , $MEF_{25-75\%}$, or LCI between the two disease groups in the subgroups undergoing HRCT. Despite the smaller numbers, the correlation between FEV_1 and LCI was the same as for the overall groups (Table 2).

We compared the patients who were and were not included in the scanning study. The patients included in the HRCT scanning group were older and had worse lung function compared with those who were not selected (see Figure E6 in the online supplement).

Structural Disease on HRCT

Multiple HRCT features were significantly worse in the CF group compared with the PCD group (Table 3), including extent and severity of bronchiectasis, wall thickness, and large plugs. There was no significant difference between the groups in small plugs and air trapping. Consolidation and ground-glass opacification scores were very low (only one patient scored above 0) and were not further analyzed.

Correlations between Physiological and Structural Abnormalities

FEV_1 and HRCT features. In the CF group, FEV_1 z score correlated significantly with bronchiectasis (extent and severity) and large mucus plugs, although not with small mucus plugs, wall thickness, or air trapping. In contrast, no relationship was seen between FEV_1 and any of the CT elements in the PCD cohort. Correlations were seen between FEV_1 and global Brody score in both disease groups (CF, $r = -0.58$, $P = 0.0056$; PCD, $r = -0.52$, $P = 0.016$). All patients had abnormal HRCT; however, three patients with PCD and three patients with CF had normal spirometry. Full correlations are shown in Table 4.

LCI and CT abnormalities. In the CF group, LCI correlated with bronchiectasis (extent and severity) and air trapping (although not large or small mucus plugs or wall thickness). Once again, there were no significant correlations in the PCD group. In the CF group, the global Brody score correlated significantly with LCI ($r = 0.62$, $P = 0.0025$); this was absent in the PCD group (Figure E3). All patients had some abnormality on HRCT, and all had an abnormal LCI. Full correlations are shown in Table 4.

DISCUSSION

This study demonstrates for the first time that in PCD the relationships between LCI, FEV_1 , and HRCT are very different from those observed in CF. In CF, LCI and FEV_1 both worsen with increasing disease; in PCD the two are not correlated. LCI and $MEF_{25-75\%}$ correlate in both disease groups, supporting the concept that changes in LCI reflect distal airway changes. Because LCI is predominantly a measure of distal airway function, and FEV_1 of proximal, these results suggest a disconnect between large and small airway disease in PCD that is not seen in CF. In groups of patients with CF and PCD with similar LCI and FEV_1 , HRCT parameters (particularly bronchiectasis) are significantly worse in patients with CF compared with PCD. LCI and FEV_1 both correlate with HRCT abnormalities in CF, and LCI does so more strongly than FEV_1 , particularly with bronchiectasis scores. In PCD, LCI did not correlate with any HRCT parameters, and FEV_1 only weakly correlated with a global HRCT score. This is an unexpected finding and runs counter to our original hypothesis.

TABLE 2. THE HIGH-RESOLUTION COMPUTED TOMOGRAPHY COHORT

	n	FEV_1 z Score*	LCI*	P Value of Correlation	r Value of Correlation
PCD	21	-2.93 (-0.1 to -6.08)	10.96 (7.74 to 18.69)	0.36	-0.21
CF	21	-3.05 (-0.82 to -5.48)	12.51 (9.38 to 16.06)	0.0061	-0.56
P value†	NS	NS	NS		

Definition of abbreviations: CF = cystic fibrosis; LCI = lung clearance index; NS = not significant; PCD = primary ciliary dyskinesia.

Patients were matched for age and sex, and there was no significant difference in FEV_1 and LCI between the two groups. The relationships between the two were similar as for the full cohort, with no significant correlation in PCD but a significant relationship in CF.

* Data are presented as median (range).

† Comparison of disease groups.

TABLE 3. ELEMENTAL HIGH-RESOLUTION COMPUTED TOMOGRAPHY SCORES FOR PATIENTS WITH CYSTIC FIBROSIS AND PRIMARY CILIARY DYSKINESIA

	Extent of Bronchiectasis	Severity of Bronchiectasis	Wall Thickness	Large Mucus Plugs	Small Mucus Plugs	Air Trapping
PCD	1.83 (0–3.33)	1.33 (0–2.83)	1.5 (1–2.25)	0.5 (0–0.83)	0.67 (0–1.67)	63.34 (44.5–88.33)
CF	3.25 (0–3.92)	2.08 (0.5–2.83)	2 (1–3.08)	0.8 (0–1.33)	0.83 (0–1.33)	60 (32.5–78.33)
<i>P</i> value	0.0012	0.0179	0.0013	0.0328	NS	NS

Definition of abbreviations: CF = cystic fibrosis; NS = not significant; PCD = primary ciliary dyskinesia.

Data are presented as median (range). Extent and severity of bronchiectasis, airway wall thickness, and large mucus plugs are all significantly worse in CF than PCD. The maximum possible score is 4, except airway plugging, which is 0 to 2.

The strengths of the study include the comparison FEV₁ and LCI in a large cohort of patients. We were also able to match patients for age and sex in the HRCT substudy. Furthermore, by scoring the HRCT scans on the individual feature scoring system, rather than using a global score, we were able to explore in more detail how HRCT abnormalities differed between CF and PCD and also the individual relationships to the physiological parameters.

One weakness of our study was that all patients in both HRCT groups had abnormal LCIs and HRCT scans, and our findings may not be applicable to younger patients with mild disease. We did not have ethical approval to perform HRCT on such patients, an acknowledged weakness of the study. By recruiting some patients with normal spirometry, we had hoped to look for correlations in those without established lung disease and thereby gain some insight into the sensitivity and specificity of LCI and FEV₁ in detecting HRCT abnormality in PCD. This was not possible in the current study. Despite this, LCI clearly demonstrates a greater sensitivity in detecting structural disease than FEV₁, as some patients in both disease groups had normal FEV₁ despite abnormal HRCT and LCI findings. All patients undergoing HRCT were adults and children older than 12 years, so this study provides no information about these parameters in younger children with less advanced disease.

We have confirmed the relationships in CF between LCI and FEV₁ (12, 29) and between airway physiology and HRCT (8, 14, 15). A recent paper also described a lack of relationship between LCI and FEV₁ in PCD, and our findings support this (18). Our study also shows no relationship between these physiological markers and changes in HRCT in PCD, which has not been described previously. There have been no other studies on LCI, FEV₁, and HRCT in PCD, but two previous studies also showed a weak but significant relationship between FEV₁ and global scores of HRCT scans in PCD (10, 30). There was also a weak correlation between Brody score and FEV₁ but not LCI in PCD.

PCD has a better prognosis than CF. However, when matched with patients with CF of similar demographics, including infection with *P. aeruginosa*, FEV₁ and LCI were the same in both PCD and CF. LCI is more sensitive to pathology than FEV₁ in CF, so for LCI also to show no real difference between the two disease groups was surprising. Despite these similarities, HRCT measures of both the Brody score and most of the individual feature scoring were significantly worse in CF, with bronchiectasis in particular being much more pronounced in patients with CF.

FEV₁ is known to be more sensitive to proximal rather than distal airway changes and LCI to more distal disease (12, 29, 31). Our data suggest that in CF, large and small airway disease progresses in parallel, with LCI showing abnormalities earlier than FEV₁ due to its greater sensitivity to milder, more distal disease. Both measures deteriorate as CF lung disease progresses and bronchiectasis becomes more pronounced. In contrast, in PCD, there appears to be a much greater separation between proximal and distal disease, with the severity of the two not correlated. We hypothesize that improved cough efficiency because of more normal mucus rheology in PCD compared with CF (although neither is normal [32, 33]) maintains the patency of the proximal airways: changes in FEV₁ are therefore not closely correlated with LCI or HRCT findings in PCD. It is noteworthy that FEV₁ did not discriminate the different severity of HRCT proximal airway changes in CF and PCD, again underscoring the lack of sensitivity of this measurement.

Which (if any) of LCI, FEV₁, and HRCT provides the best predictor of outcomes for patients with PCD in the medium to long term requires further exploration.

In summary, this study shows for the first time that the relationship between spirometry, LCI, and HRCT is different in PCD than in CF. Although in CF, both FEV₁ and LCI worsen with increasing lung disease as shown on HRCT, in PCD there appears to be a disconnect between large and small airway disease. We hypothesize that this may be due to improved cough clearance in PCD.

TABLE 4. CORRELATIONS BETWEEN HIGH-RESOLUTION COMPUTED TOMOGRAPHY ELEMENTS AND FEV₁ AND LUNG CLEARANCE INDEX FOR CYSTIC FIBROSIS AND PRIMARY CILIARY DYSKINESIA

	Extent of Bronchiectasis (Median)	Severity of Bronchiectasis (Median)	Wall Thickness (Median)	Small Mucus Plugs (Median)	Large Mucus Plugs (Median)	Air Trapping (Median)
PCD						
FEV ₁	NS	NS	NS	NS	NS	NS
LCI	NS	NS	NS	NS	NS	NS
CF						
FEV ₁	<i>P</i> = 0.005, <i>r</i> = -0.6	<i>P</i> = 0.01, <i>r</i> = -0.5	NS	NS	<i>P</i> = 0.04, <i>r</i> = -0.5	<i>P</i> = 0.0002, <i>r</i> = -0.7
LCI	<i>P</i> = 0.0002, <i>r</i> = 0.7	<i>P</i> = 0.008, <i>r</i> = 0.6	NS	NS	NS	<i>P</i> = 0.0004, <i>r</i> = 0.7

Definition of abbreviations: CF = cystic fibrosis; LCI = lung clearance index; NS = not significant; PCD = primary ciliary dyskinesia.

PCD shows no correlations, in contrast to the relationships seen in CF.

Author disclosures are available with the text of this article at www.atsjournals.org.

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