Tracking Lung Clearance Index and chest CT in mild cystic fibrosis lung disease over a period of three years

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KEYWORDS
Ultra-low-dose chest computed tomography; Bhalla-score; Lung Clearance Index; Multiple Breath Washout; Mild Cystic Fibrosis lung disease

Summary
Introduction: Lung disease remains the main cause of morbidity and mortality in patients with Cystic Fibrosis (CF). To detect lung disease before clinical symptoms become apparent, sensitive tools are essential. Spirometry is used for monitoring, but the FEV1 remains frequently normal throughout childhood. The Lung Clearance Index (LCI) calculated from Multiple Breath Washout (MBW) was introduced at the CF centre Innsbruck in 2007 for assessing ventilation inhomogeneity in patients with mild lung disease.

We hypothesized that LCIs in 2007 are of prognostic value for the presence or absence of structural lung changes in later years.

Methods: Between 2007 and 2010 MBW, spirometry and ultra-low-dose HR-CT were prospectively tracked in 36 patients (6–53 years) with a mean FEV1 ≥80% predicted in 2007.

Results: At study start the majority of patients had abnormal CT scores and LCI results. While CT and spirometry remained largely stable throughout the study, LCI results slightly improved but still correlated with CT scores in 2010. LCI results in 2007 correlated with CT scores in 2010 while FEV1 did not. In 86% the LCI value in 2007 was indicative for the presence or absence of structural lung changes in 2010.

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Introduction

Following considerably intensified treatment strategies over the last decades, life expectancy and quality of life have been greatly improved for patients with Cystic Fibrosis (CF). However, lung disease remains the main cause of morbidity and mortality [1,2]. Detecting early signs of CF lung disease and, where appropriate, earlier onset of treatment may further improve prognosis and outcome [3].

Thus, sensitive methods for monitoring early lung disease in CF are required for both, clinical and research purposes, e.g. the development and evaluation of new treatment strategies that are appropriate to halt progression before irreversible lung damage has occurred [4,5].

Development of bronchiectasis is the most important component of CF lung disease. Thus, computed chest tomography (CT) is the reference method for detecting early and advanced bronchiectasis [6]. CT of the lungs has received increasing attention in recent years particularly for assessing early stages of CF lung disease that are not detectable by conventional spirometry [7–9]. However, there remains concern regarding repeated radiation exposure from routine CT, particularly with respect to the increasing life expectancy of patients with CF [10,11]. Therefore in most countries repeated routine CT is not commonly performed for monitoring. While international efforts for developing a standardized low-dose protocol are still ongoing, in Innsbruck yearly CTs in patients with CF have been performed using an internal ultra-low-dose protocol and a modified Bhalla score for interpretation since 2001.

Conventional lung function tests are routinely performed at least 4 times a year from approximately age 4–5 to assess extent and progression of CF lung disease although the majority of paediatric patients present normal results with a relatively large inter- and intra-individual variability throughout childhood. Most commonly, the forced expiratory volume in one second (FEV₁) is reported for clinical and research purposes. However, there is increasing scientific evidence that FEV₁ has a low sensitivity for detecting early pulmonary disease, since studies demonstrated structural pulmonary changes in patients with normal spirometry [6,8,12]. For early intervention studies, the use of spiro-metric parameters as outcome parameters would require unrealistically large sample sizes and long study durations because of its low sensitivity and high variability.

Inert gas Multiple Breath Washout (MBW) for assessing ventilation inhomogeneity (VI) is a non-invasive and safe lung function test that has been shown to be sensitive for detecting early pulmonary changes in CF [13–16]. Several indices of ventilation inhomogeneity, such as the Lung Clearance Index (LCI) can be calculated from the washout curves documenting the presence and quantifying the extent of VI. The LCI reflects overall VI within the peripheral and communicating zones of the lungs [17]. In cross-sectional studies the majority of paediatric patients with CF had abnormal LCI results, even in the presence of a normal FEV₁ [13–15,18,19]. In three recent studies the LCI was used as outcome parameter for assessing the effect of inhaled hypertonic saline and Dornase-alpha in young patients with CF [20–22]. Furthermore, LCI had a high sensitivity to detect abnormal imaging results in cross-sectional studies. However this was more obvious in school-age children than in infants [19,23–25]. Implementing longitudinal measurements of LCI into routine lung function testing in CF centres may thus be of clinical and prognostic value and may contribute to reduce radiation exposure, particularly in young patients with CF.

Currently, little is known about the longitudinal course of the LCI and its prognostic value for patients with CF. There is one retrospective [26] and one prospective [3] longitudinal study, tracking spirometry and MBW in paediatric patients beyond infancy. From the prospective data the authors concluded that an abnormal LCI in preschool age predicts any lung function abnormalities in early school age and that a normal LCI in preschool age usually remains normal until school age. To date there are no studies which prospectively track MBW in comparison to CT. At the CF centre in Innsbruck, ultra-low-dose chest CT is performed on a yearly basis in all patients since 2001 and yearly measurement of the LCI was introduced in 2007.

We hypothesized that the LCI would be as sensitive as chest CT in detecting pulmonary changes. In the present study, we prospectively evaluated MBW, spirometry and chest CT over a period of three years in a relatively healthy group of patients with CF who had a normal FEV₁ at study start.

The aim was 1) to investigate the longitudinal course of the LCI in comparison to spirometry and CT and 2) to examine whether LCI results sampled in 2007 are of prognostic value for structural lung abnormalities diagnosed from CT in 2010.

Methods

Study design

This is a prospective, longitudinal observational study in a group of school children, adolescents and few adults with mild CF lung disease. During the study period of three years four test occasions at intervals of approximately one year were aimed pro participant.
Setting

Measurements were carried out between 2007 and 2010 at the CF centre of the Medical University Innsbruck located at the Department of Paediatrics. Outpatients in a stable clinical state were studied during one of their quarterly routine visits to the CF centre. Test occasions were postponed in patients with acute exacerbations. The routine diagnostic workup for CF patients was performed as usual. A reduced clinical status, detection of pathogens in routine throat swaps or observation of a deteriorated lung function was followed by intensified therapy..

A quality management system for diagnostic and therapeutic policies is in place at the CF centre that had been certified according to DIN EN ISO 9001:2008. Treatment procedures are in accordance with the standards of care reported by the European Cystic Fibrosis Society. Prophylactic antibiotics are not used routinely. A protocol of early eradication of Pseudomonas aeruginosa infection has been installed. Patients are on standard mucociliary clearance therapy. Starting in 2007, the majority of patients inhaled hypertonic saline for preventive purposes.

Newborn screening (NBS) was implemented in Tyrol in 1992.

Participants

The CF patient database at the Medical University Innsbruck which contains information on 160 patients was screened to identify patients who had an annual average FEV1 > 80% of the predicted normal value (at a minimum of 4 measurements) during the preceding year and a stable clinical status. The study cohort was selected from all patients who were scheduled for a routine visit between May and August 2007.

The study was approved by the local ethics committee. Parental informed written consent and patient assent was obtained prior to the measurements.

Protocol

At any test occasion lung function testing was performed after a session of standard physiotherapy. Demographic and clinical data were documented subsequently.

Each subject started assessment of lung function with 2–3 technically acceptable MBW measurements. For MBW patients were in a sitting position wearing a nose clip, breathing through a mouthpiece while watching a video. Spirometry was then performed according to ATS/ERS recommendations [27, 28].

Longitudinal assessment of lung function was performed at intervals of one year during the patients’ routine visits in the CF centre.

Yearly CT scans were timed as close as possible to the test occasions for assessment of lung function but for ethical reasons also in accordance to the patient’s individual protocol.

Measurements

Spirometry

Spirometry was performed according to ATS/ERS standards [27, 28] using a Master Screen Bodyplethysmograph (Erich Jaeger, Germany).

Primary outcome of spirometry was the forced expiratory volume in one second (FEV1). Forced expiratory flow at 75% expired volume (FEF75%) was calculated as secondary outcome and further parameters such as forced vital capacity (FVC) were calculated for quality control purposes only.

Results were expressed as Z-scores (SD) according to the reference equations by Quanjer et al. with a lower limit of normal defined as –1.96 z-scores [29].

Ultra-low-dose chest computed tomography

The monitoring programme at the CF centre in Innsbruck includes yearly ultra-low-dose volumetric thin-section multi-detector computer tomography scanning (MDCT) in all CF patients. Axial images were obtained in a supine position during a single deep inspiration hold and covered the entire lung parenchyma from the base to the apex of the lung using a 16- or 64-slice CT scanner (GE Lightspeed 16 or Lightspeed Volume CT, Milwaukee, USA) with the following settings: 120 keV, 10 mA, rotation time 0.8 s, 1.25 mm sections, 1.25 mm interval. The displayed dose length product (DLP) ranged from 8.50 to 22.52 mGy·cm, and the calculated estimation of mean effective dose generated by this protocol yielded 0.15 mSv (range: 0.12–0.33 mSv) [30]. Scans were scored by two independent experienced radiologists of the Department of Radiology who were blinded to the patients’ identity, to their clinical status and to the results of lung function tests.

A modified Bhalla score is commonly used for clinical interpretation of results at the CF Centre Innsbruck. The modified Bhalla score covers nine items that can be weighted with 0–3 or 0–2 points respectively: 1) severity (0–3 points), 2) expansion (0–3 points) and 3) peripheral expansion (0–3 points) of bronchiectasis, 4) airway wall thickening (0–3 points), 5) mucus plugging (0–3 points), 6) presence of bullae (0–3 points), 7) presence of emphysema (0–2 points), 8) presence of abscesses (0–3 points) and 9) presence of consolidations (0–2 points) [31, 32].

A score of 25 points corresponds to a normal lung. The lower limit of normal was defined as ≥24/25 points [19].

MBW

The ultrasonic technology and the side stream ultrasonic flow sensor (USFS) prototype system (EasyOne Pro, MBW Module, ndd Medizintechnik AG, Zurich, Switzerland) was described previously [33]. Briefly, the system consists of a mainstream ultrasonic transducer for flow sampling, a side stream ultrasonic transducer for temperature independent sampling of the molar mass (MMss) and a side stream infrared CO2 analyzer (DUE/ETCO2 Module, Welch Allyn OEM Technologies, Beaverton). The gas bias flow system that provides valve-controlled tracer gas delivery containing 4% sulfurhexafluoride (SF6), 21% oxygen and balanced nitrogen (Linde AG, Germany) is automatically removed during the washout phase, thus reducing the apparatus dead space to a minimum. Calibration of the system and
time delay correction of the side stream signals were performed as described previously [34,35].

To start a measurement, subjects breathed quietly through the mouthpiece. The bias flow is automatically switched to the tracer gas at end expiration. Equilibrium is defined as a visually stable plateau of the MMVs signal. The bias flow is then switched back into room air for washout, which is finished when the SF₆ concentration falls below 2.5% (1/40) of the starting level.

FRC was calculated from the cumulative volume (CEV) of expired SF₆ divided by the difference between end-tidal gas concentration at the start and end of the washout. LCI was calculated as the CEV divided by the FRC. Analysis has been described in detail previously and was performed according to recommendations published recently [17]. The upper limit of normal (group mean + 2SD) for the LCI (<7) was derived from a healthy population that was investigated with the same method, test procedure, equipment and by the same observers [34]. LCI results >8 and ≤9 were defined as moderately and >9 and as markedly increased.

In patients with CF, where manifestation of lung disease is likely to be present, a time frame of 30–40 min is required for a complete MBW test including 2–3 single washouts.

WBreath® software (version 3.371.0) was used for data acquisition, storage and analysis.

Other tests
Additional information on CF patients concerning genotype, microbiology, pancreas function and type of CF manifestation was obtained from in and outpatient records and from the CF patient database.

Statistics
Group data for age, weight, height, BMI, FEV₁-z, FEV₇₅-z and CT are reported as mean and standard deviation (SD).

Individual data for the LCI are reported as the mean (standard deviation, SD) of 2–3 technically acceptable measurements within one test occasion for each subject. Group data are then expressed as mean (SD). The intra coefficient of variation (CV[%] = (SD/mean) ×100) was calculated to assess the within-test repeatability of the LCI at any test occasion for quality control purposes.

LCI, FEV₁-z, FEV₇₅-z and CT were tracked between 2007 and 2010 using paired t-tests for calculation of mean differences between the test occasions, 95%confidence intervals and p-values. Pearson correlations were used to compare the CT with LCI and FEV₁ results.

Furthermore the individual LCI change between 2007 and 2010 was compared to the 95% confidence interval (2.5th to 97.5th centiles) [3] derived from our previous studies on assessment of the within subject variability of the LCI in healthy controls [34]. For this study same method, test procedure and equipment were used.

Based on these limits, LCI results in 2010 were classified as improved, unchanged and deteriorated.

The statistical package used was SPSS version 20.0 for Windows.

Results
N = 36 patients with a FEV₁-z > -2 at the first test occasion in 2007 and at least two further documented test occasions including assessment of lung function and CT were included into final analysis. All participants were in a stable clinical status during the test occasions.

Patient flow and availability of data is presented in Table 1. The median interval (range) between performance of lung function and CT was 33.5 (243 to –173) days in 2007 and 0.0 (–27 to 202) days in 2010. In 2010 the majority of patients performed lung function and CT on the same day and 26/35 (72%) completed data collection within ±3 days.

Patient characteristics at study start are listed in Table 2. The course of demographic data between 2007 and 2010 is summarised in Table 3.

Outcome data
Repeated MBW measurements were successfully implemented into routine quarterly visits at the CF centre Innsbruck. Separate test occasions at intervals of approximately one year were feasible and well tolerated.

Spirometry
Group means of spirometry for all test occasions are summarised in Table 4. In accordance with the inclusion criteria, all patients had a normal FEV₁-z in 2007 that remained normal in 2010 apart from 3 individuals (8.6%) whose FEV₁-z was –2.16, –2.2 and –2.7 in 2010. Mean difference of FEV₁-z between 2007 and 2010 was 0.286 (p = 0.069, 95% CI 0.023; 0.60).

34 patients (94.4%) started with a normal FEV₇₅-z in 2007 that remained normal in 32 (91.4%) in 2010. Abnormal results of FEV₇₅-z in 2007 and 2010 ranged between –2.1 and –2.9. The mean difference of FEV₇₅-z between 2007 and 2010 was –0.053 (p = 0.752, 95% CI –0.391; 0.285).

Ultra-low-dose chest computed tomography
Group means of modified Bhalla scores for each test occasion are summarised in Table 4. Mean difference of the
modified Bhalla score between 2007 and 2010 was −0.09 points (p = 0.692, 95% CI −0.522; −0.350).

In both years, 2007 and 2010, 29 out of 36 patients (81%) had a score below the lower limit of normal (<24 Points). Between 2007 and 2010 no one switched from an abnormal score to a normal score or vice versa: Scores in 20 patients (55.5%) remained stable, deteriorated in 5 patients (14.0%) and improved in 11 patients (30.5%). The extent of individual changes was distributed as follows: 2 patients with −1 point deterioration, 2 patients with −2 points deterioration, 1 patient with −5 points deterioration, 8 patients with +1 point improvement and 3 patients with +2 points improvement.

### MBW

Group means of MBW for all test occasions are summarised in **Table 4**. The intra individual within test repeatability (CV %) at each test occasion was 7.0, 5.9, 5.0 and 6.0 for the FRC, and 7.0, 6.5, 6.1 and 5.4 for the LCI.

From 2007 to 2010, mean LCI improved (i.e. decreased) by −0.726 (p = 0.001, 95% CI 0.318; 1.135).

83% (30 out of 36) of the patients had abnormal LCI results in 2007 while 53% (17 out of 32) presented abnormal LCI results in 2010.

32 paired LCI values measured in 2007 and 2010 were available for comparing individual changes in LCI with the 2.5th to 97.5th centiles derived from healthy controls (−0.017−0.348) [34]. Compared to these limits, in 22 patients (69%) LCI significantly improved after three years, 6 (19%) showed a deterioration and 4 (12%) had stable LCI results.

6 out of 36 patients (17%) started with a normal LCI <7 in 2007. All of these remained normal during the study. Mean intra individual change (SD) between 2007 and 2010 was only 0.01 (0.65) (Fig. 1a).

22 out of 36 patients (61%) started with a moderately increased LCI between >7 and <9. The LCI improved in 77% (n = 17) while deterioration was observed in 23% (n = 5) until 2010. The mean intra individual change (SD) between 2007 and 2010 was 0.55 (1.13) and was thus larger than in patients with a normal LCI at study start. Nearly 50% of this subgroup switched from abnormal to normal LCI results until the end of the study (Fig. 1b).

8 out of 36 patients (22%) started with markedly increased LCI >9. All of these improved stepwise during the study. The mean intra individual change (SD) between 2007 and 2010 was 2.00 (0.54) and was thus considerably larger than in patients with a normal or moderately increased LCI at study start. 5/8 patients in this subgroup ended up with only slightly increased LCI <8 (Fig. 1c).

### Prognostic value of lung function and CT

The LCI and Bhalla score correlated in 2007 (r < 0.001, r = −0.565) and in 2010 (r = 0.001, r = 0.547), while Bhalla score and FEV1-z did not (r = 0.240, r = 0.201 and p = 0.498, r = 0.118 respectively).

Furthermore LCI in 2007 correlated with CT-scores in 2010 (r < 0.001, r = −0.554) (Fig. 2a), while FEV1-z did not (r = 0.207, r = 0.215) (Fig. 2b). Correlation of changes between 2007 and 2010 in CT scores and in LCI results failed significance (p < 0.069, r = −0.331). However, closest correlation was observed when comparing CT-scores 2007 and 2010 (p < 0.001, r = −0.933) (Fig. 2c).

4 out of 6 patients with a normal LCI in 2007 had a normal CT score in 2010 and 27 out of 30 patients with an abnormal LCI in 2007 had an abnormal CT score in 2010. Therefore in 86% the LCI in 2007 was indicative for the presence or absence of structural changes seen on CT in 2010.

However, 2 out of 6 patients with a normal LCI in 2007 had an abnormal CT score (both 22 points) in 2010. Furthermore 3 out of 30 patients with an abnormal LCI in 2007 had a normal CT score in 2010 indicating presence of VI that was not detectable by the CT score. In contrast 29 out of 36 patients with a normal FEV1-z in 2007 (81%) had abnormal CT scores in 2010 that ranged between 23 and 13 points.

### Discussion

This is the first reported study tracking MBW, spirometry and chest CT over a period of 3 years in a relatively healthy CF population including mainly school children and adolescents, but also few adults.

Yearly MBW measurements were successfully implemented into routine visits at the CF Centre Innsbruck, were feasible and well tolerated.

Our study confirms that the LCI is more sensitive than FEV1 for detecting and tracking early pulmonary changes in
CF. Longitudinal application of MBW demonstrates that the LCI is of prognostic value for the presence or absence of structural lung changes observed in CT scans in later years.

At study start the majority of patients presented abnormal CT scores and LCI results in the presence of a normal FEV1. Surprisingly, while CT and spirometry remained largely stable during the entire study period, LCI results slightly improved over the study period but still correlated with CT scores until 2010. LCI results in 2007 correlated with CT scores in 2010 (Table 4).

In 2010 an abnormal FEV1 was observed in only three patients who started with a normal FEV1, normal FEF75, decreased CT scores between 16 and 22 points and moderately increased LCIs up to 9 in 2007. FEF75, often considered as a parameter to assess peripheral airway function, was not any better with only 3 patients having abnormal values.

These few cases again support previous observations that spirometry is not sensitive for detecting early CF related VI, delays diagnosis when used without other diagnostic tools such as CT or MBW and is thus not helpful for detecting and monitoring manifestation of CF lung disease [6,8,12].

Ultra-low-dose chest computed tomography

The majority of this clinically stable study population started with abnormal Bhalla scores in 2007 and revealed no statistical change until 2010 (Fig. 2c, Table 4). In contrast, Loeve et al. [36] reported a slight but significant deterioration of CT scores in children with mild CF lung disease at intervals of two years.

The Bhalla score [31] used in the present study is based on a 0–3 point system for each quality of lung impairment that allows only rough assignment to different stages of lung disease and may thus not be the optimal scoring system for tracking mild lung disease over this relatively short study duration of three years. In contrast, the Brody score is a continuous variable on a scale of 0–100 [37]. But although the Brody score is often used for investigating early CF lung disease in younger patients [36,38], reference data regarding upper limits of normal and intra- and interindividual variability are not available. As an official recommendation regarding a standard CT score for assessing structural lung changes in young patients with CF is still lacking, numerous CT scores and modifications of scores are currently in use. The radiologists at the CF centre Innsbruck have extensive clinical experiences with using the modified Bhalla score in children and adults with CF for more than 10 years. Therefore the authors decided not to change this practice for the purpose of the study.

However 30% (n = 11) of the CT scores gained 1–2 points in 2010 predominantly due to the reduction of mucus plugging. This supports the view that abnormalities seen on CT scans are potentially reversible to some extent. Furthermore all patients with an improved CT score had an improved LCI too.

3 out of 5 patients in whom the CT score worsened during the study period, lost ≥2 points. An abnormal CT in these patients was reflected by an abnormal LCI; while FEV1 and FEF75 were normal in 2007 and remained normal in two of them until 2010. It is important to note that the clinical course in these patients is characterised by lacking adherence to therapy and several clinical complications such as repeated and/or prolonged exacerbations.

MBW

Within-test repeatability of subsequent MBW tests for calculating the LCI was good and comparable to published data [18,34] using identical equipment.

In accordance with previous cross-sectional studies, the LCI correlated significantly with the CT score [23,24] in both 2007 and 2010.

None of the patients with a normal LCI in 2007 developed VI during the study period (Fig. 1a) and a normal LCI was associated with no or minor changes (22 out of 25 points) on CT.

In accordance with other paediatric CF populations [13,14,18] only a small proportion (n = 6) had a normal LCI (and CT) in 2007. Therefore, calculation of positive and negative predictive values in order to assess the predictive value of the LCI for structural changes in later years as well as direct comparison with the only prospective longitudinal study evaluating the predictive value of the LCI [3] was not appropriate. However, in 86% of the patients the LCI in 2007 was indicative for the presence or absence of structural changes seen on CT in 2010 (Fig. 2a). This illustrates a prognostic value of the LCI that was not seen for FEV1.

However, 3 out of 30 patients with an abnormal LCI in 2007 had a normal CT score in 2010 and 2 out of 6 patients with a normal LCI in 2007 had an abnormal CT in 2010 (Fig. 2a). A similar distribution of results was observed.

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<th>Table 4</th>
<th>Group means of lung function and CT between 2007 and 2010.</th>
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<tr>
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<td>2007</td>
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<td>FRC (sd) [L]</td>
<td>1.82 (0.87)</td>
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<tr>
<td>LCI (sd)</td>
<td>8.0 (1.35)</td>
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<tr>
<td>FEV1-z (sd)</td>
<td>-0.26 (0.97)</td>
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<td>FEF75-z (sd)</td>
<td>0.38 (1.09)</td>
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<td>Bhalla score (sd)</td>
<td>20.1 (3.46)</td>
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when comparing LCI and CT within one year. This illustrates, that MBW and chest CT are assessing different aspects of CF lung disease and should not replace each other. While the latter detects structural lung changes (e.g. consolidations) that have not necessarily impact on lung function (e.g. ventilation homogeneity), MBW detects potentially reversible functional impairment (e.g. mucus plugging) that is not necessarily related to structural damage observed with CT scans. Therefore correlation between LCI and CT score is expected to be less strong than correlation within one of the methods [25]. To further increase our understanding of early CF lung disease in relation to available diagnostic tools and to further prove the predictive value of parameters used for monitoring, multicentre and longitudinal studies including larger numbers of patients with normal LCI and CT will be necessary.

Over three years, LCI continuously improved in the majority of patients and the proportion of patients with an abnormal LCI decreased markedly between 2007 and 2010 (Fig. 1a–c). Mean LCI in 2010 for the group was significantly lower than in 2007 and only slightly above the upper limit of normal. However, more than 50% of the study population still had an abnormal LCI at the end of the observation period.

It may be argued that the yearly drop in LCI is explained by changes in methodology during the study duration. It is therefore important to note that all MBW tests were performed with the same equipment, identical protocol, software for data sampling and analysis and by the same two investigators (SF and JE).

However the majority of patients (75%) started treatment with hypertonic saline for preventive purposes between the first and the second test occasion. Even if the present study design is not appropriate to investigate the treatment effect of hypertonic saline on LCI, it seems likely that the enhancement of the mucociliary clearance contributed to the observed drop in LCI for the group that was most obvious in those individuals presenting the highest LCI-results at study start (Fig. 1c).

The post-hoc analysis in patients with and patients without treatment with hypertonic saline supports this interpretation: LCI results were similar for the two groups in 2007 (8.0 versus 8.1) and slightly different in 2008 (7.6 versus 8.2), 2009 (7.3 versus 8.2) and 2010 (7.0 versus 7.8) but these differences were not significant. Improvement of VI due to inhalation therapy with hypertonic saline has previously been observed in two controlled intervention studies in paediatric patients with CF and mild lung disease (FEV1 > 80% predicted at study start) where the authors report a significant drop in mean LCI that was similar to the present study population [20,22].

Another explanation for the observed improvement of VI may be that any worsening in CT, lung function and/or clinical status during the study period led to intensified clinical management including medical treatments, physiotherapy and additional consultations at the CF centre. The clinicians at the CF centre in Innsbruck were not blinded to the study results. Aiming to achieve optimal motivation and adherence to the multidimensional treatment regimen, CT and lung function were routinely discussed with the patients and their families after each test occasion.

Figure 1  a: Course of LCI between 2007 and 2010 in n = 6 patients with normal LCI in 2007. b: Course of LCI between 2007 and 2010 in n = 22 patients with moderately increased LCI in 2007. c: Course of LCI between 2007 and 2010 in n = 8 patients with markedly increased LCI in 2007.
In 2011 Aurora et al. reported tracking of the LCI between preschool and early school age in CF [3]. In this study, approximately one third had a significant deterioration of LCI and approximately 16% a significant improvement, while all but two LCI results remained abnormal. Compared to the present study population, the London patients had more severe lung disease despite their younger age at study start (mean LCI >9 and inclusion of patients with a reduced FEV1). However a recent study tracking LCI and forced expired volume in 0.5 s (FEV0.5) during infancy reported stable but compared to controls higher LCI results throughout the first year of life [39].

Commonly, pulmonary changes in CF identified by CT are thought to be mostly irreversible. We conclude from our data, that partial reversibility of VI may be achieved in patients with mild CF lung disease. It is likely, that intensified clinical management and particularly improvement of the mucociliary clearance, reduces mucus plugging and air way wall thickening, resulting in more homogenous ventilation. It is conceivable that ongoing optimised mucociliary clearance leads to subsequent but in comparison to LCI possibly delayed improvement of CT scores.

Another aspect with regard to the role of MBW in assessing progression of lung disease apparent from our study is that the observed lung changes are small even over the relatively long study period of three years. Longer longitudinal studies are necessary to fully understand how the LCI and other parameters of VI change over time, what a significant change is and how this parameter may help to predict prognosis.

In summary, this study indicates again that LCI derived from MBW is sensitive for detecting and tracking pulmonary changes in CF, particularly in young patients with mild lung disease. Extended structural changes are unlikely if a normal LCI is measured.

Therefore application of a chest CT may not be necessary in the presence of a normal LCI. Measuring the LCI longitudinally and prior to CT may help to reduce the individual cumulative radiation burden within the CF population. However, in a small proportion of patients, changes observed with CT are not reflected by a change in LCI, indicating that the two measures cannot be used interchangeably.

We speculate, that routine measurements of the LCI may lead to earlier intensified treatment and thus, slowing of pulmonary changes.

Finally, we conclude that the LCI has the potential to be used as surrogate marker for monitoring progression of CF lung disease and assessing the individual effect of treatment in both, clinical care and research settings.

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Conflict of interest

The authors declare that they don’t have a real or perceived conflict of interest.

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