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Applications of lung clearance index in monitoring children with cystic fibrosis

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Abstract

A sensitive, reproducible and feasible measure of lung function for monitoring the respiratory health is a prerequisite for the optimization of management of the patients with cystic fibrosis (CF). Spirometry has been considered the method of choice, although it is applicable only in children older than 6 years of age, as good cooperation is necessary for its proper performance. However, over the last 15 years, scientific interest in gas dilution techniques and particularly in multiple breath wash out (MBW) method has been revived. The most commonly reported index of MBW is lung clearance index (LCI). The aim of this review is to present the most recent developments in the application of LCI as a monitoring index of respiratory status of CF patients. LCI is a sensitive and reproducible marker of ventilation inhomogeneity. It is more sensitive than spirometry and, unlike spirometry; it can be performed across the whole pediatric age range. Since it is dependent on body size, until at least the age of 6 years, the relative and not the absolute changes are more appropriate for providing clinically meaningful conclusion on ventilation inhomogeneity. Until now, MBW has been mainly used as a research tool. Based on the currently available data LCI cannot safely predict high-resolution computed tomography findings in children with CF, especially in infants. It can be used as an end-point measure for the assessment of beneficial effect of interventions. However, its utility as an outcome measure for the efficacy of therapeutic interventions seems to be dependent on the pathophysiologic mechanisms that underlie each intervention. It seems that more studies, especially longitudinal ones, are required in order to fully clarify the clinical usefulness of LCI, not only in the research setting, but also in every day practice

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Core tip: We herein present an overview of the applications of lung clearance index (LCI) in monitoring the respiratory health status of children with cystic fibrosis (CF). LCI is a more sensitive marker than spirometry and unlike spirometry it can be performed across the entire pediatric age range. At present, it is mostly used in research settings. However, as more data become available from longitudinal studies, it may be proved to be a very useful marker of respiratory status monitoring in children with CF, able to identify early those who are at risk for deterioration and allowing the early application of more aggressive interventions.

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INTRODUCTION

Cystic fibrosis (CF) is a chronic inherited disorder that mainly impairs the lung health and the nutritional status of the affected individuals. Advances in the early diagnosis of the disease, optimal monitoring of the lung health and timely implementation of the appropriate available therapies have improved the quality of life of CF patients as well as their longevity^[1]. The use of a sensitive, reproducible and feasible measure of lung function for monitoring the respiratory health and documenting stability or progression of the pulmonary disease is a prerequisite for the optimization of the patients' management. For decades, conventional spirometry, like in many other respiratory disorders, was the technique of choice for evaluating respiratory status in CF patients^[2,3]. However, this technique is not applicable in infants and toddlers as adequate cooperation and coordination are required for performing the test. Additionally, even in cooperative subjects of the appropriate age, peripheral extension of bronchiectasis, as it is seen on the CT scans, may deteriorate faster compared to the spirometric indices^[4,5]. This implies that spirometry is not sufficiently sensitive for evaluating lung health in CF patients. For these reasons, scientific interest in gas dilution techniques, in particular multiple breath wash out (MBW) measurements, has been revived over the last decade.

The aim of this review is to present an overview of the recent developments in the application of lung clearance index (LCI), the main MBW outcome, in monitoring the respiratory status of children with CF.

HISTORICAL-TECHNICAL BACKGROUND OF MBW

MBW test was first described by Fowler *et al*^[6], in 1952. Fowler developed a method, which could measure the extent of uneven ventilation by obtaining pulmonary nitrogen clearance curves of single breath washouts from healthy subjects and from patients with cardiorespiratory diseases^[6]. This method was laborious and initially received little attention. However, technological evolution and modifications in the nitrogen washout curves led to a replenishment of interest in the application of the method in the clinical setting^[7]. The method has been used successfully since 1985 in young children who could not cooperate to perform conventional spirometry, as only spontaneous tidal breathing is required for MBW test^[8].

The MBW procedure consists of two phases, a wash in and a wash out phase^[9]. During the wash in phase the subject breaths an inert exogenous gas of known concentration, more commonly sulfur hexafluoride, until the concentration of the expired gas reaches the concentration of the delivered gas. At this point the wash out phase of the procedure starts. When nitrogen, which is an inert intrinsic gas, is used

there is no wash in period. During the wash out phase, the subject inhales room air (if an exogenous gas was used in the wash in phase), or 100% oxygen (if the gas used in the wash in phase was nitrogen). The wash out period is considered to be complete when the inert gas concentration reaches the 1/40th of the initial level^[10].

A number of parameters have been suggested for the description of the wash out curve (flow and gas concentration plotted against time). The most commonly used is LCI, whereas mixing ratio and moment ratio are less often reported^[11].

LCI is defined as the number of lung turnovers that are required to reduce the inert gas concentration to the 1/40th of the initial concentration. It is calculated by dividing cumulative expired volume/functional residual capacity. LCI is, therefore, an easy to compute and simple to understand index and it is considered the preferred outcome parameter of ventilation inhomogeneity in CF studies^[12].

CHARACTERISTICS OF MBW TECHNIQUE AND LCI MEASUREMENT

Feasibility

As only relaxed tidal breathing is required for MBW test and the derived LCI index^[10], the test is expected to be feasible even in preschoolers. Quiet breathing is performed through a facemask or a mouthpiece according to the age of the child. The success rate of the test in the clinical setting, in unsedated preschoolers older than 3.5 years of age, ranged from 75%-100%^[13]. Longitudinal monitoring seems to be possible in this age group as preschoolers who completed the first test were also able to complete the test at the follow up visit^[13]. Similar success rate (78%-87%) was observed in the research setting^[14]. However, the test is feasible only under sedation in infants and preschoolers younger than 3.5 years of age. In this age group the success rate ranged from 78.9%-100% in sedated subjects, who were either healthy or suffered from CF and other lung diseases^[15].

Short and long term repeatability of LCI

The mean coefficient of variation of LCI measurements in subjects with CF, within one test occasion, was between 4 to 8% in most studies^[16], with wide, however, range, when reported. These values indicate that LCI is a rather reproducible test.

The knowledge of LCI fluctuation over time is essential for understanding when differences in sequential measurements represent clinically meaningful changes of ventilation inhomogeneity, and not simply measurements variability. The short and long term variability of LCI measurements was acceptable in healthy children and adolescents, ranging from 4.2%-5.1% for one and six months intervals respectively^[17]. These observations indicate that the absolute change of LCI > 1 unit represents a clinical relevant change^[17]. Likewise, Singer *et al*^[18] found that the coefficient of repeatability between tests occasions performed 24 h apart, was 0.96 in children with CF compared to 0.62 in controls. Their results also indicate that a change of LCI of at least 1 unit is clinically meaningful in children with CF. However, later it was shown by Svedberg *et al*^[19] that higher LCI values were associated with higher variability for both intra and inter test measurements. Therefore expressing in absolute numbers the clinical relevant change of LCI may lead to over-representation of clinical meaningful change. According to Svedberg *et al*^[19]'s data a relative increase of > 17% (compared to a previous measurement in a clinically stable CF patient) may be an indicator of lung disease deterioration. Green *et al*^[20] suggested that a change of LCI > 25%, between sessions, indicate a clinically relevant change. As the upper limit of normal Svedberg *et al*^[19] used 1.64 SD whereas Green *et al*^[20] 1.96 SD. In agreement with these findings, Oude Engeberink *et al*^[21] corroborated that in preschool children a relative change of LCI > ± 15% is considered clinically relevant and confirmed the observation that LCI variability was proportional to its mean. Therefore, they also supported the view that the expression of LCI change in absolute numbers is biased.

Reference values

Although it was initially considered that LCI was an age independent index in healthy subjects, Lum *et al*^[22] showed that LCI was dependent on body size. Absolute reduction of LCI, which was large enough to be considered of clinical significance, was observed till 6 years of age, whereas thereafter LCI was almost stabilized till early adulthood. Therefore, appropriate reference equations are needed throughout childhood in order to reliably interpret the LCI results. However, it should be noted, that reference data should not be generalized to all different MBW systems or inert gases^[23].

CORRELATION OF LCI WITH FINDINGS FROM LUNG IMAGING

The main structural abnormalities that characterize the CF lung disease are bronchiectasis and small airways disease^[24]. These structural components are clearly depicted by high-resolution computed tomography (HRCT), an accurate modality at delineating not only the extent and severity of advanced lung disease but also early lung disease^[25]. However, its routine use for monitoring CF lung disease has been questioned because of the risk posed by the radiation exposure^[26]. Nevertheless, spirometric indices cannot predict the HRCT findings as structural abnormalities were not uncommon in children with CF and normal spirometric parameters^[4]. By contrast, LCI is a more sensitive indicator than spirometric indices for predicting HRCT abnormalities in CF lung disease^[27]. In a retrospective study of school age children and adolescents with CF^[27] the sensitivity of LCI for detecting HRCT defined abnormalities ranged from 85% to 94% depending on the type of lung damage (bronchiectasis, air trapping, or HRCT score). Therefore, LCI values within the normal range almost precluded the possibility of CF lung disease detectable by HRCT scan. These findings were corroborated by another prospective cross-sectional study in young patients with CF (aged 6-26 years) who had normal FEV1 (> 80% predicted)^[28]. It should be noted that due to technical reasons, in this sample population there was an interval up to 243 d between CT performance and LCI measurement. In this population LCI had a sensitivity of 88% to detect structural lung abnormalities of HRCT, a positive predictive value of 88% but a negative predictive value as low as 63%. Therefore, these findings also supported the notion that an abnormal chest CT is unlikely, but not impossible, in the presence of a normal LCI. Later, another study^[29] was conducted in a population of children with CF, aged 6-10 years, who underwent lung function tests, including LCI measurement, and volumetric HRCT on the same day. This study showed that LCI and HRCT scans have similar sensitivity to detect CF lung diseases with an overall concordance of 81% for total CT score. However, they found a positive predictive value of 88% and a low negative predictive value of 44% for LCI in relation to the detection of HRCT structural abnormalities indicating that a normal LCI did not preclude abnormal HRCT findings. The results of this study are not comparable to the respective results of the two preceding ones as there were methodological differences that are beyond the scope of this review to be presented in detail.

It seems that the age of patients is an important factor for the relation of LCI values with structural lung damage detected by HRCT. In a study (AREST CF program)^[30] that assessed infants with CF diagnosed with newborn screening, it was shown - after controlling for age and infection status - that LCI values were not correlated with the presence of bronchiectasis but only with air trapping.

In accordance to the AREST study^[30], a more recent study^[31] that included pediatric patients with CF across the entire pediatric age spectrum (0-16 years) showed that LCI was not sensitive for the detection of structural abnormalities in infancy. By contrast, in preschool and school age children an elevated LCI had an 85% positive predictive value for the detection of bronchiectasis, but a low negative predictive value of 55% indicating that a normal LCI could not rule out bronchiectasis in almost half of the cases.

Furthermore, a longitudinal three year study^[32], which consisted of patients 6-53 years old, showed that 86% of LCI values in the first year of the study were indicative of the presence or absence of structural lung changes depicted by HRCT scan three years later.

Magnetic resonance imaging has also been used, in research setting, for the detection of early lung disease in children across the entire age range^[33]. It was shown that there was a strong age independent correlation of LCI with airway thickening/bronchiectasis detected by MRI. A moderate correlation with mucus plugging/perfusion abnormalities was also observed. The majority of false negative LCI results were detected in the younger children of the study.

Therefore, at present, LCI could not replace HRCT scans in CF children, particularly the younger ones. More longitudinal studies are needed to explore whether LCI could be used as a potential predictor of the presence and the extent of structural lung damage detected by HRCT, in older children and adolescents.

LCI AS A MEASURE OF EFFICACY OF THERAPEUTIC INTERVENTIONS

As LCI is a sensitive marker of ventilation inhomogeneity and it is easily performed

even in infants, clinical trials were performed to evaluate whether LCI is a reliable outcome measure for the detection of treatment effects of variable interventions.

LCI was improved after the administration of dornase alpha for 28 d, in children with CF, older than 6 years of age, who had mild lung disease (FEV1 > 80%)^[34]. However, the results of this study should not be generalized in younger children as well as in children with more severe lung disease. Similar findings were observed after the administration of hypertonic saline in pediatric CF patients, aged older than 6 years, with a baseline FEV1 > 70%^[35,36]. However, these results were found only in studies with a duration of at least four weeks^[35], and children with mild lung disease^[36], whereas they were not corroborated in a trial^[37] that assessed the short term LCI change 24 h after hypertonic saline inhalation in children with a baseline FEV1 > 40%. This discordance may simply indicate that there is an additive effect of multiple doses of hypertonic saline inhalation and/or a different response in treatment in pediatric CF patients' severe lung disease. It also seems that with the use of LCI z-score (z-LCI) change as an outcome measure, a significant treatment effect was observed in infants and preschool children after the twice-daily administration of hypertonic saline for 48 wk^[38]. It needs to be emphasized here that, especially for infancy and early childhood, z-LCI changes should be evaluated in order to adjust for the body size dependence of LCI^[22].

Most recently in a randomized controlled trial^[39] which evaluated the clinical response to ivacaftor in CF children older than 6 years, with mild lung disease (FEV1 > 90%) and at least one G551D-CFTR allele, it was shown that LCI was more sensitive than spirometry in detecting response in this therapeutic intervention.

In contrast to the above-mentioned findings, the LCI response to antibiotic administration for pulmonary exacerbation was variable. In a recent systematic review^[40], it was shown that a significant but not necessarily clinically relevant treatment effect was observed in patients who received antibiotics for pulmonary exacerbations. Although there was a weak correlation with FEV1 changes, discordant results between LCI and FEV1 changes were rather common. There are several hypotheses that could explain the overall small LCI change, the considerable heterogeneity of the observed results, and the discordance with FEV1 changes which, however, are beyond the scope of this review.

It should be noted, however, that even paradoxical increase of LCI was observed after antibiotic administration for pulmonary exacerbation^[41]. It is speculated that there are non-ventilating lung units during exacerbation that do not contribute to the LCI values. Following antibiotic treatment, and due to the removal of mucus plugging, these areas become ventilated - though not fully but only partially; their partial aeration increases the LCI index^[42].

Overall, it should be recognized that the various therapeutic interventions induce LCI changes to the time interval between the intervention and the assessment of LCI; the severity of the lung disease as it is reflected by baseline spirometric indices; the different mechanisms that underlie the treatment effect of each intervention.

LCI AS A PREDICTOR FOR THE EVOLUTION OF LUNG DISEASE

A question that was raised in the literature was whether LCI values in infancy or early childhood could predict subsequent lung disease status. The London Cystic Fibrosis collaboration (LCFC) followed up a newborn-screened CF cohort up to 2 years of age^[43]. They found that z-LCI at 2 years of age were not associated with the respective results at 3 and 12 mo of age. Therefore, it was recognized in this study that up to 2 years of age LCI could not predict the evolution of the disease. It was, however, also acknowledged that a long-term follow up in preschool and school years is essential for determining whether early measured LCI could be served as a predictor of the lung disease status in childhood.

LCFC also measured LCI and spirometric indices in preschool children (3-5 years) with CF and in healthy controls^[44] and repeated the measurement during early school age (6-10 years). It was found that LCI at preschool age had a positive predictive value of 94% for predicting spirometry or LCI abnormal results, whereas the negative predictive value was as low as 62%. The future repeat of LCI and spirometry in this cohort during late childhood and adolescence will reveal whether preschool age LCI values are predictors for late childhood and adolescence lung health status in CF subjects.

There is also limited data^[45], in children aged 6-19 years, that LCI was a predictor of the occurrence of pulmonary exacerbation during the subsequent 12 mo following the measurement, even in the subgroup of patients with a normal FEV1.

It seems therefore that tracking longitudinal changes of LCI may confer to the prediction of lung health status in patients with CF. However the existing data are rather limited and more longitudinal studies are needed for the clarification of this issue.

CONCLUSION

LCI is a sensitive marker for the assessment of respiratory status of children with CF. However, more data from longitudinal studies is needed, in order to clarify which relative change is of clinical importance for identifying the patients who are at risk for respiratory deterioration. Should this information be available, the LCI would be a potential useful marker for monitoring pediatric patients with CF, in every day clinical practice. Until then several obstacles should also be overcome, taking into consideration that the results from different equipment and different inert gasses are not comparable.

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