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Utility of lung clearance index in the evaluation of chronic respiratory diseases of childhood: a narrative review

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Utility of lung clearance index in the evaluation of chronic respiratory diseases of childhood: a narrative review

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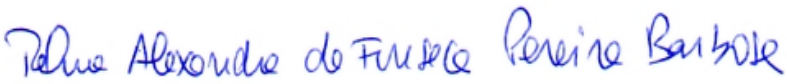

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ABSTRACT

The multiple breath wash-out (MBW) test determines how effectively gases distribute in the lungs. The Lung Clearance Index (LCI) is its major outcome, and it is a sensitive indicator of early lung function impairment and presence of peripheral airway disease. Small airway changes result in insufficient gas mixing, which is referred to as ventilation inhomogeneity (VI). The number of lung turnovers needed to clear a certain tracer gas is determined by LCI to assess VI.

Spirometry, the primary lung function test utilized in many obstructive lung diseases, focuses primarily on large airway function and is insensitive to small airway disease. As a result, one of the key advantages of LCI is that it detects early peripheral airway disease more accurately. Furthermore, because MBW is performed during tidal respiration, minimal co-operation is need and it is appropriate for younger patients who are unable to complete the vigorous manoeuvres required for spirometry.

Many obstructive respiratory conditions initiate in small airways during childhood before patients are clinically symptomatic or being recognized by lung functional tests like spirometry. Studies have shown that LCI can detect clinically significant changes and, thus, allow for early interventions. The introduction of technical norms for MBW and commercial devices has enabled MBW to be employed in clinical studies, with potential usefulness for clinical practice. This review summarizes the current evidence regarding the clinical value of LCI in children with cystic fibrosis (CF), primary ciliary dyskinesia (PCD), and asthma.

Keywords: Lung Clearance Index | Multiple Breath Washout | Respiratory Function Tests | Cystic Fibrosis | Ciliary Motility Disorders | Asthma

RESUMO

O teste de respiração múltipla (MBW) avalia a eficiência da mistura de gases nos pulmões. O seu principal resultado é o índice de clearance pulmonar (LCI), que constitui uma medida sensível da deterioração precoce da função pulmonar e da presença de atingimento das vias aéreas periféricas. Pequenas alterações das vias aéreas resultam numa mistura insuficiente de gases, o que é designado por falta de homogeneidade da ventilação (VI). O número de rotações pulmonares necessárias para eliminar um gás inerte é determinado pelo LCI para avaliar a VI.

A espirometria, o teste convencional para a avaliação da função pulmonar numa variedade de doenças pulmonares, centra-se principalmente na função das grandes vias aéreas e é insensível na deteção de anomalias nas pequenas vias aéreas. Consequentemente, uma das principais vantagens do LCI é o facto de detetar precocemente e com maior precisão o atingimento das vias aéreas periféricas. Além disso, como o MBW é efetuado durante a respiração corrente e requer uma cooperação mínima, é adequado para os doentes mais jovens que não conseguem efetuar as manobras de esforço necessárias para a espirometria.

Muitas doenças respiratórias obstrutivas crónicas começam nas vias aéreas periféricas durante a infância, antes do aparecimento de sintomas ou de serem reconhecidas através da espirometria. Estudos demonstraram que o LCI pode detetar alterações clinicamente relevantes, permitindo assim intervenções precoces. A introdução de normas técnicas para o teste de MBW e de equipamento comercial permitiu a utilização do MBW na investigação clínica, com potencial utilidade na prática clínica. Esta revisão resume as evidências atuais sobre o valor clínico do LCI em crianças com fibrose cística (FC), discinesia ciliar primária (PCD) e asma.

Palavras-chave: Índice de Clearance Pulmonar | Teste de Respiração | Testes de Função Respiratória | Fibrose Quística | Doenças de Motilidade Ciliar | Asma

ABBREVIATIONS

CEV – Cumulative Expired Volume
CF – Cystic Fibrosis
CFTR – Cystic Fibrosis Transmembrane Conductance Regulator
CT – Computed Tomography
$FEF_{25-75\%}$ – Forced mid-expiratory flow
FeNO – Fractional exhaled nitric oxide
FEV1 – Forced Expiratory Volume in one second
FRC – Functional Residual Capacity
FVC – Forced Vital Capacity
HRCT – High-Resolution Computed Tomography
ICS – Inhaled Corticosteroid
LCFC – London Cystic Fibrosis Collaboration
LCI – Lung Clearance Index
MBW – Multiple Breath Washout
MR – Moment Ratios
NPV – Negative Predictive Value
PCD – Primary ciliary dyskinesia
Pex – Pulmonary Exacerbations
PPV – Positive Predictive Value
SABA – Short-acting b2-agonists
VI – Ventilation Inhomogeneity

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INTRODUCTION

Many obstructive respiratory conditions initiate in small airways during childhood before patients are clinically symptomatic or being recognized by lung functional tests like spirometry. The primary spirometric outcomes are forced expiratory volume in one second (FEV1) and forced vital capacity (FVC), which provide information mostly on large airway structures and are, hence, insensitive to detect initial small airway disease (1). This has fueled interest in the multiple breath washout (MBW) test for assessing peripheral small airway disease through the evaluation of ventilation distribution. The Lung Clearance Index (LCI) constitutes the primary MBW outcome and it is the most precise indicator for quantifying ventilation inhomogeneity (VI) (2).

This narrative review will focus on the LCI parameter of the MBW test, with the goal of summarizing the technical aspects of the MBW test and reviewing the current available data on the utility of LCI for both investigation and clinical applications in three pediatric chronic respiratory diseases: cystic fibrosis (CF), and primary ciliary dyskinesia (PCD) and asthma.

METHODS

This narrative review is based on research and analysis of published scientific papers indexed in the electronic databases PubMed, ScienceDirect, and Scopus, as well as publications in the Journal of Cystic Fibrosis, World Journal of Clinical Pediatrics, BMC Pulmonary Medicine, Pneumology Journal, and The Lancet Respiratory Medicine, applying essentially the key words previously mentioned. Related articles referred to in the reference sections of some of the retrieved articles were also considered.

The study was limited to publications published between 2009 and 2022; articles not authored in English or with inaccessible full texts were excluded.

1. Multiple Breath Washout

1.1 Method and Test Procedure

MBW measures ventilation distribution by measuring the ability of the lungs to release an inert tracer gas throughout a given number of exhalations. Gas distribution is even across the lungs in healthy individuals; however, in the presence of airway obstruction, this distribution is disrupted by the diminished caliber of the peripheral airways, resulting in inefficient gas mixing. Therefore, in conditions of airway obstruction, the time required to remove the tracer gas in MBW test is longer, demonstrating the existence of insufficient gas mixing, referred as VI. The LCI is defined as a global measure of VI, equivalent to the number of lung turnovers required for clearing the lungs of an inert tracer gas. (1, 2)

MBW is divided into two distinct phases, wash-in and wash-out, and can be completed in two different methods:

- Using an extrinsic inert tracer gas, such as sulfur hexafluoride (SF_6), which requires an inhalation phase in which the gas mix is inhaled until an equilibrium is attained (wash-in) following a wash-out phase (breathing room air).
- Using an intrinsic tracer gas, such as nitrogen (N_2), no inhalation phase is necessary; only the washout phase is performed using a FiO_2 of 100%.

Regardless of whether an extrinsic or intrinsic gas is used, the test is concluded when the tracer gas concentration achieves 1/40 (2.5%) of the original concentration, defining the LCI (3). The MBW execution is illustrated in Figure 1.

The test is carried out during tidal respiration and requires little cooperation, making it appropriate for usage from infancy through adulthood. A relaxing setting and a qualified operator, in addition to a prior explanation and demonstration of the test technique, are required to ensure good test quality. The test must be performed at least two to three times to obtain valid results, with each test taking between two and ten minutes and totaling approximately thirty minutes, depending on the degree of severity of the patient's lung condition. LCI is defined as the mean of 2-3 successive washout maneuvers (2, 3).

In infants, the test is done in the decubitus position under sedation, with appropriately sized face masks. For older children and adults, the test is frequently done while seated, using a mouthpiece and nose clip. For younger children, watching a film is encouraged, while for teenagers and adults, visual feedback on the breathing pattern is recommended (2, 3).

1.2 MBW OUTCOMES AND ANALYSIS

MBW calculates three different outcomes: LCI, functional residual capacity (FRC) and moment ratios (MR). The FRC is an estimate of the amount of air present in the ventilated sections of the lung after tidal expiration. LCI and MR are VI indicators (3). However, LCI is more commonly used, as it has been shown to be more sensitive (2).

The FRC is determined by dividing the cumulative expired volume (CEV) of the tracer gas by the difference in gas concentration between the beginning and finish of the washout procedure. The CEV represents the cumulative amount of expired air during the washout period. As a result, LCI, a volume ratio, is calculated as CEV divided by FRC (LCI=CEV/FRC). In the presence of VI, more tidal breaths (higher CEV) are needed to wash-out the tracer gas from the lungs, resulting in a higher LCI value (2, 3). The total amount of lung volume turnovers necessary to clear the lungs of a tracer gas to 1/40 (2.5%) of its initial concentration is defined as the LCI. In a healthy individual, LCI levels are around 5-7 units, values above this range indicate the presence of peripheral airway disease (2, 4).

Monitoring LCI variability over time is critical for establishing a link between these changes and clinically meaningful events. Value changes can be explained by either measurement mistakes or physiological variations, which is proportional to the degree of impairment; hence, patients with greater LCI levels will also have higher variability. Because of this, using absolute changes as markers of a clinically significant event may overestimate changes in patients with higher LCI baseline values while undervaluing changes in patients with lower values. Therefore, studies support the use of relative changes over absolute ones to assess clinically significant variations (1). One research with children aged 6 to 17 years defended that a 17% relative rise in pediatric CF patients may be indicative of lung disease progression (1, 5, 6). Meanwhile, another study supported that LCI's alterations of 25% or less could be considered clinically meaningful in school-aged children and adolescents with CF (6, 7). In line with these findings, another study indicated that a relative change in LCI of 15% can be regarded significant in preschool children (6, 8).

1.3 TRACER GAS FOR MBW

The selection of tracer gas for MBW might be challenging because it can have an influence on the outcomes (3). The main question stands on whether to use nitrogen (N_2-MBW) or sulfur hexafluoride (SF_6-MBW).

Using an intrinsic tracer gas, such as nitrogen (N_2), has the benefit that the needed oxygen is widely accessible and cost-effective for medicinal purposes. Nitrogen is present as a resident gas in all parts of the lung, ensuring high sensitivity in the detection of abnormalities, allowing MBW to be performed without a wash-in phase, which shortens the test duration and thus contributes to greater patient adherence (2, 3). The primary downside is that breathing under a FiO_2 of 100% throughout the procedure was demonstrated to alter breathing cycles in infants (9). However, no influence on the breathing pattern has been recorded in school-aged children (10).

When sulfur hexafluoride (SF_6) is utilized, a tracer gas combination is provided during the wash-in phase and there is no need to increase the FiO_2 (2). Its use, however, has been linked to transitory hypopnea in preterm and healthy infants (11, 12). At the concentration employed for MBW, sulfur hexafluoride has a limited solubility in water and body tissues and is not harmful. The primary issues with this tracer gas are its high cost and restricted availability, as it is classified as a greenhouse gas, it cannot be used for medical usage in some countries (2, 3).

In 2016, a new MBW methodology was published that allowed the use of SF_6-MBW in the same device previously used for N_2-MBW (EXHALYZER D, Eco Medics AG) (13). A higher value of FRC and LCI was found with N_2 compared with SF_6 in healthy infants, which was interpreted as a result of exposure to a FiO_2 of 100% with N_2-MBW. Therefore, recommendations have since been made for the use of SF_6-MBW in infants (14, 15).

In May 2021, an improved software (SPIROWAVE version 3.2.1) was developed to provide an improved N_2 signal in EXHALYZER D. Using this improved software, a strong agreement between the two tests was found. These findings imply that the improved N_2-MBW could be employed in infants in the future, allowing for the use of the same tracer gas in all pediatric age ranges and allowing longitudinal research on ventilatory distribution development using a single MBW method. The effects of N_2 tissue excretion and hypoventilation, previously described as an adverse effect of high O_2 exposure, are probably much smaller than previously thought. LCI values reported with the improved N_2-MBW were found to be more accurate and physiologically appropriate (13).

2. MBW and Spirometry: Vantages and Advantages

The main lung function test used in many obstructive lung diseases is spirometry; Spirometry is now recognized as being insufficiently sensitive to detect small airway disease since this test predominantly examines large airway function. The main concern is therefore that, in patients with normal spirometric results, significant abnormalities in small airways may still exist (1, 16).

LCI, as assessed by MBW, outperforms spirometry as a sensitive indicator for detecting small airway disease. One of the key advantages of this parameter is that early detection and care of the disease before permanent airway damage is established can significantly impact the course of lung disease (2, 16).

While the MBW test can be performed on tidal breathing, which is suitable for the whole pediatric age range, spirometry is only appropriate in children older than 6 years old due to the need for adequate patient cooperation (6, 16).

The test time, on the other hand, is one of the greatest barriers to the adoption of LCI in clinical practice; the entire test duration might be up to 30 minutes. The tracer gas used also has an impact on the time required; using SF_6-MBW (wash-in and wash-out) takes twice as long as using N_2-MBW (wash-out phase only) (1, 2).

Another downside of LCI is that it becomes less helpful in individuals with significant airway obstruction as the disease progresses. As a result, in more severe conditions, it may not be as useful as spirometry (1).

3. Application of LCI in children with Cystic Fibrosis

3.1 LCI correlation with lung imaging methods

In CF, structural lung abnormalities develop at a young age; the main anatomical alterations are bronchiectasis and small airway disease. Currently, the gold standard tool for diagnosing these structural anomalies is a chest computed tomography (CT) scan (6, 17). However, radiation concerns limit the regularity with which CT scans can be conducted and its use as a routine exam (18). Therefore, there is a growing interest in developing a noninvasive and sensitive marker that

could potentially be used routinely in clinical practice to track structural lung disease progression (17).

Several studies have been conducted to evaluate if LCI is as informative as CT scans in the detection of structural lung disease in children with CF (17, 19). LCI has demonstrated to have higher sensitivity than other lung function tests (spirometry and plethysmography) in detecting lung structural disease. LCI and high-resolution CT (HRCT) appear to have comparable sensitivity in diagnosing CF structural lung abnormalities, with a total CT score agreement of 81% (19). However, in two studies, one with patients aged 6 to 10 years (19) and the other with patients aged 0 to 16 years (17), LCI demonstrated to have a high positive predictive value (PPV) yet a significantly reduced negative predictive value (NPV) for detecting lung structural abnormalities in preschoolers and school-aged children. According to these findings, a normal LCI score does not rule out the existence of HRCT abnormalities. Children with advanced lung disease had a higher likelihood of having both LCI and HRCT abnormalities, whereas children with mild lung disease showed less agreement between the two parameters. Thus, it was suggested that in a clinical setting, LCI could not be used as a substitute of CT scans to detect structural abnormalities; however, in school-aged children, LCI might be used as the initial test to investigate the existence of structural lung damage, and HRCT could be conducted in cases where it is normal (17, 19). If this criterion had been used in the first mentioned trial, 83% of HRCTs would have been avoided in this study. Implementing this strategy into clinical practice has several advantages, including more frequent monitoring of lung disease in CF patients, lower radiation exposure, and significant cost savings (19). It is important to highlight that the two statistical measurements used in the previous studies, the PPV and NPV, are dependent on the prevalence of structural lung disease in the respective population studied and should not be generalized to a population with a different prevalence (17).

On the contrary, LCI appears to be insensitive to detect early structural abnormalities in infants with CF (17). Studies have shown that LCI does not predict the presence of structural abnormalities in this age. Infants with abnormal LCI have greater air-trapping expansion, but there is no association with bronchiectasis. It should be noted that infants with CF have less advanced structural lung damage than older children and findings from older children should not be generalized to infants and younger ones (20).

A two-year longitudinal investigation in structural lung disease progression and its correlation with spirometry and MBW was conducted with patients with CF aged 6 to 18 years. The extent of structural disease was evaluated using PRAGMA-CF (Perth-Rotterdam Annotated Grid Morphometric Analysis for CF, a rating system for mild structural lung disease). No significant progression was observed, however the baseline LCI was strongly linked to follow-up PRAGMA-CF outcomes, showing that having a stable baseline LCI was a good predictor of stability in structural

lung disease over these two years. Maintaining a stable LCI throughout time was associated with a risk of approximately 15% of structural disease progression; thus, having a stable LCI did not completely rule out the disease progression. However, significant increases in LCI over time (> 25% change) raised the likelihood of structural lung disease progression by more than 50%. Therefore, authors suggested that MBW outcomes could be used as a reference for posterior CT scan performance in children with CF, as the probability of progression seems to be low when MBW outcomes are stabilized.

In contrast to previous studies, LCI revealed a low PPV for detecting structural abnormalities in this study. The authors attributed this finding to the small size of the sample and the possibility that LCI may identify progressive lung disease earlier than structural changes are captured by CT scans. Half of the individuals had mismatch between their LCI and CT results, and some children had a growing LCI with no progression of structural lung disease. As a result, although stable LCI values were related with minimal structural lung disease progressions, this disparity underlines the fact that these two approaches evaluate distinct components of CF lung disease (21).

3.2 Utility of LCI in Pulmonary Exacerbations

Acute respiratory episodes, such as pulmonary exacerbations (Pex), have a significant impact on the course of lung disease in CF patients, and are considered a risk factor for future lung transplantation and greater mortality (22, 23). Only bronchoalveolar lavage and chest CT scans have been demonstrated to detect airway inflammation and predict Pex requiring hospitalization during the asymptomatic periods. Unfortunately, neither of these tests is suitable for clinical routine pediatric monitoring (22, 24).

Respiratory events in children might have varied clinical presentations, making it difficult to differentiate between self-limited viral infections and more serious events (23). Spirometry is the only lung functional parameter currently used to guide treatment decisions; however, most mild respiratory episodes do not result in significant changes in spirometry (23, 25). Because of its great sensitivity in detecting early lung illness, the LCI appears to be a potential parameter for this goal, and its use has been increasing in both stable and Pex settings (26).

Evidence reports that LCI has a higher sensitivity than FEV1 in the detection of functional impairment in Pex on children with CF. LCI could be a significant tool in the diagnosis and monitoring therapy response in children with acute respiratory events. The MBW test is projected to become a useful test in clinical practice since LCI can provide additional information about lung function,

particularly in younger children who cannot perform spirometry. In older children, LCI may be effective as a supplement to spirometry, as each parameter evaluates a different aspect of the airways, combining both outcome measures is preferable to using a single one (23, 26, 27).

LCI reactivity to acute respiratory events was verified overall; however, what constitutes a clinically relevant change in LCI is still uncertain (23). Previous research has found that the LCI's intrinsic variability is around 15% (8). However, while investigating the LCI correlation with Pex, researchers called this threshold into question. According to Walicka-Serzysko et al., an increase of 10% or more is a stronger signal for detecting acute respiratory episodes in clinical practice and may indicate the need for medical monitoring and further study (26). In concordance, Perrem et al. results were interpreted using a 10% threshold to reflect clinical practice and a 15% threshold as a sensitivity analysis and results of both domains led to similar interpretations (23). However, it must considered that the study in which the clinically significant change was reported as a difference of more than 15% was conducted only with preschool children (aged 2.6 to 6 years)(8), whereas the two aforementioned articles were conducted with school-aged children (23, 26).

In comparison to FEV1, LCI detected a decline in lung function in school-age children with acute respiratory episodes who were assessed to have a less severe clinical state and hence did not receive antibiotic treatment. At the follow-up, nearly a quarter of these children had not returned to baseline LCI levels. These findings suggest that mild symptomatic occurrences, which are sometimes clinically underestimated, may have a higher influence on patients' lung disease progression than predicted, and that LCI is capable of capturing those instances (23). In concordance, a study conducted with preschoolers, worsening of LCI was also seen in symptomatic patients in whom the clinical decision was made not to treat. This demonstrates LCI's potential utility in clinical practice in guiding physicians with treatment decisions (27).

In another study, a proportion of patients' LCI improved between the stable state and the onset of Pex; a few factors can explain the difference in LCI results. The presence of respiratory deformities due to fibrosis and inflammatory processes (more pronounced at Pex) contributes to mucus retention, resulting in complete obstruction of airways that were partially ventilated prior to the Pex and, paradoxically, a reduction in VI, and, consequently, on LCI values is observed (26). This reflects the higher variability of LCI in situations of severe lung impairment (1).

As for measurement of lung function after treatment, overall LCI values tended to improve (23, 26, 27), although lung function did not always entirely recover to baseline. These findings are consistent with the idea that acute respiratory episodes contribute to the progression of lung disease among patients with CF (23).

Another study attempted to investigate whether spirometry and MBW data could aid in estimating time away from hospitalization in children and adolescents with CF. There was a five-

month difference in total free time without hospitalization between patients with abnormal FEV1 and LCI (4 months without hospitalization) and patients with normal FEV1 and abnormal LCI (9 months without hospitalization). Patients with normal FEV1 and LCI values, on the other hand, had an interval of 11 months. This finding supports the utility of MBW as a viable technique for monitoring lung disease progression in children with CF, as well as the hypothesis that spirometry alone may no longer be sensitive enough for detecting or monitoring lung disease progression (22).

3.3 LCI RESPONSE TO CFTR MODULATORS THERAPY

The advancement of multidisciplinary care, in conjunction with the development of conventional treatments such as CFTR modulators, have had an important positive impact on the natural history of CF (18). Treatments may be useful if initiated prior to the onset of significant lung disease (28). Ivacaftor therapy resulted in substantial increases in lung function as measured by FEV1 with spirometry (29, 30). Ivacaftor has been authorized for children from 6 months old, and it delays of lung disease progression and maintains optimal spirometric lung function levels from infancy through the beginning of adulthood (26, 31). LCI has demonstrated to have superior sensitivity in diagnosing airway disease in its early stages in children with CF when compared to spirometry, and it can also be utilized in preschool children, thus it could be a useful parameter to assess treatment efficacy (32).

Several research studies have been performed to study the influence of CFTR modulator therapy on LCI in CF pediatric patients. One multicenter observational study, GOAL (observational study in CF patients with the G551D mutation), analyzed changes in LCI levels in children aged 3 to 5 years old from baseline to one month and six months after starting ivacaftor therapy. A decrease in relative change from baseline of 23.6% at 1 month and 24.6% at 6 months was reported (32), representing a clinically significant change in preschool children (described as a change greater than 15% (8). Thus, these results demonstrate a quick and persistent improvement in LCI with ivacaftor and support the hypothesis that LCI is a suitable parameter for monitoring treatment efficacy to CFTR modulators in preschoolers (32).

Another investigation studied the effects of lumacaftor/ivacaftor in children with CF aged 6 to 11 years old who had the F508del CFTR mutation. All individuals had normal percent predicted FEV1 (baseline mean of 91.4%) but abnormal LCI values, indicating the existence of small airway disease. LCI values improved significantly throughout 24 weeks of CTFR modulator medication, with significant improvements at each medical visit compared to baseline. The discovery of this

advantage in LCI versus no significant rise in percent predicted FEV1 in this sample supports the idea that LCI may be a more sensitive measure than spirometry in assessing the therapeutic impact in individuals of this age (33).

Comparable research was carried out in patients of the same age range to assess the efficacy and safety of the combination of tezacaftor/ivacaftor. At baseline it was detected the presence of small airway disease (with a mean LCI of 9.56) and relatively preserved lung function in spirometry. After only two weeks of treatment, the results showed a large and rapid improvement in LCI, which persisted in all participants throughout the remainder of the study. Although the observed absolute change was small (-0.51), the authors suggested that these results may be clinically significant in association with other studies (34).

The primary concern identified by the investigators is that a minimal clinically significant decrease in LCI is not yet definitely established (33, 35). However, these findings support the potential utility of LCI over spirometry in this area due to its high sensitivity in detecting response to treatment in the small airways in preschool children who are unable to undergo spirometry and in school-aged children with well-preserved lung function on spirometry.

3.4 LCI AS A PREDICTOR OF LUNG DISEASE PROGRESSION

Physicians have questioned if LCI levels in infancy or early childhood may provide information regarding a patient's prognosis and disease progression (6). The main goal of diagnosing early lung disease in children with CF is to be able to start pharmacological treatment before irreversible lung damage takes place (36). LCI has been reported to get worse over time and during Pex in preschoolers with CF, implying that it might constitute a valuable indicator for tracking progression of the disease (37).

The London Cystic Fibrosis Collaboration (LCFC) evaluated lung function progression in CF during the first two years of life. Lung function changes were minor and temporary during this period, and no marked correlation was seen between the LCI z-score at two years of age and that at three months or one year. As a result, it was determined that in the first two years of life LCI scores do not predict disease progression (6, 38).

LCFC also did a prospective controlled study to see if an abnormal LCI in preschoolers (3-5 years) predicted an abnormal LCI in school age (6-10 years). A positive correlation was reported, indicating that an abnormal LCI in younger ages predicted later impairment of lung function in CF children. Preschool LCI values were found to have a PPV of 94% for prediction of abnormal

spirometry and LCI outcomes, but an NPV of 62%. Preschool FEV1 readings, on the other hand, had a PPV of 100% but an NPV of only 25%. The higher NPV of the LCI is crucial since physicians and investigators in this field face the greatest difficulties in distinguishing children with early moderate lung disease and children without lung disease. These data support the importance of LCI as a measure of early lung disease, as well as its possible application as a medical and scientific outcome in children with CF (36).

A more recent study, also undertaken by the LCFC, evaluated LCI changes in children to determine if preschool LCI levels could be used to predict lung disease severity in adolescence. Since 1999, infants with CF have been followed prospectively, and MBW measures and HRCT scans have been conducted. MBW was performed using SF_6 as a tracer gas, the equipment and methodology remained consistent across time, and the BRODY-II CF-CT score (a score system that evaluates the lobar location, level of severity, as well as the extent of a wide variety of CF lung disease CT scans features, notably in children) was used to evaluate CT scans. LCI increased by 0.18 units each year as they grew older. The findings of this study demonstrate that preschool LCI levels in children with CF correspond with teenage LCI levels. Elevated LCI levels in preschool-aged children were linked to higher LCI levels and structural lung abnormalities in adolescence, showing that LCI had predictive value in the progression of lung disease evolution. These findings, along with the knowledge that preschool LCI levels have higher sensitivity than spirometry, show that LCI levels are a helpful measure for identifying children who would benefit from early focused therapeutic intervention aimed at modifying lung disease progression (39).

3.5 Feasibility of LCI

A prospective multicenter study was undertaken by the Translational Lung Research Center of Heidelberg and implemented across three centers of the German Center for Lung Research with the goal of establishing and verifying a standardized SF_6-MBW in infants and preschoolers to evaluate LCI feasibility in the detection of early lung disease in CF. The participants were 73 infants and preschoolers (aged 0 to 5.1 years), 49 of whom had cystic fibrosis (CF), 14 had other respiratory illnesses (one of which had PCD), and 10 were healthy controls. SF_6-MBW was established as an accurate test with excellent rate of success in infants under sedation and preschoolers with CF along with other lung disorders. According to reports, even in centers without previous experience in performing the MBW test, multicenter LCI can be effectively implemented in a clinical trial network. The evidence shows that LCI is sensitive enough to detect lung function impairment in a multicenter context with proper initial instruction and surveillance by a specialized pediatric lung

function laboratory. As a result, these data suggest the use of LCI as a non-invasive tool not only for detecting and monitoring early lung disease, but also as a possible outcome in early intervention clinical studies (40). Later, the same center did another study with awake preschool children using the N_2-MBW test, and the results confirmed MBW feasibility and sufficient success rates (41).

In November 2017, the CF Centre Copenhagen began performing 3-monthly longitudinal MBW testing on infants. Once they reached the age of three months, the participants were allowed to join the program. The test was performed while the participant was sedated after receiving intranasal dexmedetomidine. The LCI was established using the SF_6-MBW test, which was carried out by professional operators. The researchers reported an 88% success rate, suggesting that longitudinal quarterly assessment of LCI in a clinical context is feasible and that intranasal dexmedetomidine is an appropriate sedative choice for infants. Despite the fact that various difficulties were raised, such as the time required for the exam (median of 125 minutes) for both staff and family in this study, parental adherence was high. However, the authors emphasize the importance of both technical instructions and verified reference material for MBW application in order to achieve the best MBW execution for research and therapeutic uses (42).

4. Application of LCI in children with Primary Ciliary Dyskinesia

PCD is an autosomal recessive genetic condition that causes ciliary dysfunction caused by ciliary protein structure and/or function abnormalities. PCD and CF are both multisystemic diseases defined by poor mucociliary clearance, which induces the formation of mucus in the small airways at an early stage, eventually leading to progressive obstructive lung disease with persistent endobronchial inflammation and infection (43). Airway involvement manifests itself early in life, with more than 80% of PCD newborns experiencing respiratory distress within 24 hours after birth. However, there is limited data on the initial course of pulmonary disease during childhood (43, 44). As PCD and CF lung disease share various traits, LCI may be an effective measure for assessing early airway disease in PCD (43).

A study involving children and adolescents with PCD compared MBW and spirometry assessment to lung function. Spirometry readings were all within or near normal ranges on average, and FEV1 values were within normal ranges in half of the patients; nevertheless, in a significant number of patients, including those with FEV1 within the normal range, the LCI was abnormal. The existence of early-onset peripheral airway disease in PCD children and LCI's higher sensitivity for its detection compared to FEV1 were confirmed. The authors concluded that MBW could be useful in

diagnosing early-stage lung disease and evaluating therapy effects in children with PCD, with the goal of slowing irreversible lung disease development and improving disease prognosis (45).

Another trial was undertaken in children aged 3 to 12 years with CF and PCD to evaluate the sensitivity of MBW and spirometry in detecting mild lung disease. The results were also consistent with the LCI's higher sensitivity compared to FEV1 in detecting early small airway disease in both conditions. It was reported that 42% of patients with PCD with normal FEV1 had abnormal LCI. It was also noted that children with CF and PCD had comparable LCI and FEV1 values, but as compared to aged-matched CF patients, PCD patients exhibited worse predicted $FEF_{25-75\%}$ (forced mid-expiratory flow) and FEV1/FVC z-scores. This shows that children with PCD may have more severe obstructive airway disease than children with CF, with lung function declining sooner in life. The fact that LCI earlier were similar in both groups and those spirometry parameters were not, highlights the fact that these two parameters assess different elements of these two respiratory disorders (46).

MBW has shown to have good feasibility and sensitivity for identifying VI in preschoolers with PCD, supporting LCI as a viable noninvasive outcome measure to diagnose and monitor early lung disease (43).

Another study found that LCI correlates with the existence of structural abnormalities in chest CT scans better than FEV1, especially in early lung disease. Although some children were included in this study, it was not limited to pediatric patients (participants ranged in age from 5 to 25 years old) (47).

5. Application of LCI in children with Asthma

Asthma is the most prevalent chronic respiratory disease of the childhood, characterized by airway inflammation and bronchial hyperresponsiveness, resulting in airflow obstruction. Diagnosis is difficult, especially in newborns and preschoolers, since traditional lung functional tests are difficult to perform in younger ages (48, 49). Although the majority of the structural modifications in asthma have been observed in the larger airways, histopathological studies have demonstrated involvement in the small airways as well (50, 51). Identifying peripheral airway disease may be important for asthma management as existing inhaled medications frequently do not reach the more distal airways, resulting in a subset of severely asthmatic children who do not respond to high-dose inhaled corticosteroids (ICS) treatment and may benefit from an alternative treatment method, such as extra-fine ICS or systemic steroid therapy (50). Considering LCI has a

higher sensitivity to detect early peripheral airway disease, it could be a useful clinical tool in monitoring childhood asthma (51).

Some studies in children and adolescents with well-controlled asthma have shown that LCI is greater when compared to healthy controls, however, it tends to stay within the normal range (52-54).

A study conducted with preschool children found that LCI did not distinguish between patients with well-controlled asthma/persistent wheeze (i.e., without history of PEx) and healthy children, implying that LCI could not play a significant role in the diagnosis of asthma. However, LCI was considerably higher in asthmatic children who had suffered PEx (requiring systemic ICS or hospital admissions) (LCI=7.36) compared to healthy children (LCI=6.95), suggesting that LCI changes are more significant in children with more severe airway obstruction (55).

Changes in LCI in response to bronchodilators such as short-acting b2-agonists (SABA) have also been studied, with mixed findings. In two studies performed with children and adolescents, LCI remained high after bronchodilator treatment (with salbutamol) while FEV1 improved slightly, showing the existence of persistent small airway disease that FEV1 could not detect. This emphasizes the fact that SABA's action is mostly observed in central airways rather than peripheral ones (53, 54). Macleod et al. noted that after bronchodilatation, fractional exhaled nitric oxide (FeNO) was normal; therefore, the present airway disease did not seem to be due to inflammation or bronchospasm, suggesting that it could be due to structural airway abnormalities, which is consistent with previous research from biopsies in children with asthma. Nonetheless, this data is limited since there was no direct correlation between VI and evidence of structural airway alterations (54). Gustafsson et al., on the other hand, reported a decrease in LCI after SABA in asthmatic patients, implying that bronchodilation alone might correct VI (56). One possible explanation for these disparities is the use of different tracer gases; the two former studies utilized SF_6, while the latter used N_2 (50).

Another study conducted with asthmatic school-age children and adolescents divided the study population into two subgroups: patients with difficult asthma when modifiable variables can be rectified, and patients with severe therapy-resistant asthma when the disease remains uncontrolled despite high dose medication and modifiable factors being addressed. Although LCI was greater in the severe therapy-resistant asthma group, many patients in the two subgroups had normal values, implying that a low LCI may not be effective in totally ruling out this subgroup, but an elevated LCI may be an indication of this phenotype. In addition, an improvement in LCI following parenteral steroids (triamcinolone) was also seen in the severe therapy-resistant asthma subgroup with a preexisting abnormal LCI. The improvement was accompanied by a decrease in FeNO, which indicates the presence of distal airway disease that is not responsive to ICS. These findings could be

due to a decrease in distal inflammation, which leads to improved gas distribution; the fact that ICS may reach only central airways due to airflow restriction; or inadequate technique execution. Nonetheless, this study shows that children with severe therapy-resistant asthma might profit from a follow-up with both spirometry and MBW, as LCI has been found to provide critical information on airway disease that spirometry alone would overlook (57).

CONCLUSION

When assessing lung function in children with CF, LCI has proven to be a sensitive test. Evidence suggests that it may become an important tool for monitoring the severity and progression of airway disease in both medical research and clinical practice (2, 6). A summary of the endpoints discussed in this review is listed below.

- With the exception of infants, LCI has a similar sensitivity to imaging methods such as CT scans in the detection of structural lung disease in pediatric age groups, and maintaining a stable LCI value was correlated with a low probability of structural lung disease progression; thus, LCI could become a potential tool for monitoring the presence of structural lung disease alongside CT scans (17, 19, 21).
- LCI was found to have a higher sensitivity than FEV1 in detecting functional impairment, and its potential clinical utility could assist physicians in identifying children who require more intensive treatment (23, 26, 27).
- CFTR modulator therapy showed an overall improvement on LCI values over time and LCI showed to be more sensitive than spirometry in assessing treatment effects, highlighting its utility as a suitable parameter for monitoring treatment response in CF children (32-34).
- A positive correlation was found between abnormal LCI levels in younger children and subsequent lung function impairment and the presence of structural abnormalities later in life, enhancing LCI's importance as a predictor of lung disease progression (36, 39).
- Recent studies indicates that SF_6-MBW and N_2-MBW are feasible tests for infants and preschoolers with CF and other lung diseases in the context of a multicenter setting, and that LCI can be implemented as a non-invasive quantitative measure for early lung disease detection and monitoring, as well as a possible outcome in studies of early intervention (40, 41).

Studies on the clinical utility of LCI in children with PCD and asthma are limited. In PCD, LCI has been shown to have higher sensitivity than spirometry in diagnosing early peripheral airway

disease in pediatric patients, suggesting it could be a valuable tool in management (43, 45, 46). In asthma, LCI is greater than healthy controls, but it tends to stay within the normal range and abnormal LCI levels have been linked to a more severe disease pattern (52-55). Further study is needed in both of these disorders to define longitudinal changes in LCI, its association with imaging modalities, and its therapeutic relevance (43, 46, 50, 51).

The main concern reported in the research was the lack of a well-defined minimal clinically significant change. Further longitudinal studies are needed to establish which relative change is clinically significant for diagnosing patients with impaired lung function who would benefit from a different treatment approach. Once this information is available, LCI could be employed for monitoring pediatric patients with CF in routine clinical practice (6).

FIGURES

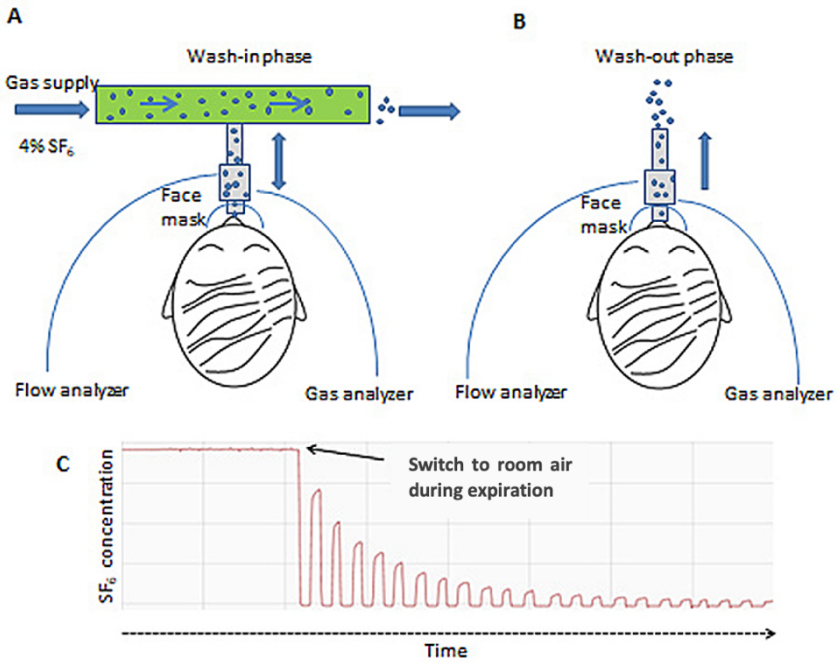

Figure 1: Schematic representation of a SF_6-MBW. A) The wash-in phase of 4% SF_6; B) The washout phase; C) The red tracing shows the variation in the SF_6 concentration during the washout-phase (3).

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