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ASTHMA (V ORTEGA, SECTION EDITOR)

Current Needs Assessment for Using Lung Clearance Index for Asthma in Clinical Practice

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Abstract

Purpose of Review Asthma pathophysiology has shown that remodeling of the bronchial airways mainly affects the small rather than large airways. The severity of asthma is conventionally measured by forced expiratory volume 1 (FEV1) but this maneuver is insensitive to changes in distal airways with smaller diameter. The aim of this review is to evaluate the current evidence supporting LCI as a clinical tool for assessing small airways disease in asthma patients, as well as whether it is useful as a treatment response parameter in severe therapy-resistant asthma (STRA) patients.

Recent Findings There is an increasing need for novel tests that can assess distal airway disease in asthma. Lung Clearance Index (LCI) may be a useful test for assessing more severe airway obstruction and the persistence of small airway disease. LCI measurement has been shown to be more sensitive than spirometry in cystic fibrosis (CF), but its clinical utility in asthma has not been thoroughly investigated. LCI abnormalities may be a sensitive marker for the persistence of small distal airway disease and may be associated with a more severe asthma endotype unresponsive to inhaled glucocorticoids.

Summary There is a need to identify other lung function tests for asthma that can identify early airway remodeling while simultaneously measuring the rate of lung function impairment. When compared to other conventional methods, multiple-breath washout (MBW) measures the lung clearance index (LCI), a more sensitive predictor of early airway disease that is feasible to perform in children. The goal of this review is to evaluate the current evidence of LCI as a clinical tool in asthma patients.

Keywords Lung Clearance Index · Multiple breath washout · Ventilation inhomogeneity · Asthma

Abbreviations

LCI	Lung Clearance Index
MBW	Multiple breath washout
FEV1	Forced expiratory volume 1
CF	Cystic fibrosis
VI	Ventilation inhomogeneity
FeNO	Fractional exhaled nitric oxide
RW	Recurrent wheezers
ACQ5	5-item Asthma Control Questionnaire
DA	Difficult asthma
PCD	Primary ciliary dyskinesia
CACh	Cold dry air challenge
HC	Healthy controls
VDP	Ventilation defect percent
N2-MBW	Multiple breath nitrogen washout
STRA	Severe therapy-resistant asthma
ICS	Inhaled corticosteroids
LABA	Long acting beta agonist
BDP/F	Beclometasone dipropionate/formoterol
pMDI	Pressurized metered dose inhaler

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Introduction

Current asthma pathophysiology evidence from biopsy samples of preschool children with wheeze suggests that remodeling of the bronchial airways is more common throughout the small conductive airways rather than the larger airways [1, 2]. Since airway remodeling begins at an early stage,

improvements in the treatment of children of preschool age may result in better preserved lung function into adulthood [2].

The severity of asthma is conventionally diagnosed by clinical history of symptoms confirmed by objective measurements using spirometry or pulmonary function testing to assess the forced expiratory volume in the 1st second of exhalation (FEV1). In clinical practice, an obstructive defect is confirmed by a variation in airflow limitation and/or rapid improvements in FEV1 after bronchodilation [3]. However, FEV1 is an insensitive marker for monitoring changes in distal airways of smaller diameter [4, 5] since most asthma children have a normal or near-normal FEV1 since lung function deterioration is slow [6].

There is a need to identify other lung function tests for asthma that can identify early airway remodeling while simultaneously measuring the rate of lung function impairment. Multiple-breath washout (MBW) measures the lung clearance index (LCI), a more sensitive predictor of early airway disease that is feasible to perform in children compared to other conventional methods [7]. Measurement of LCI has been shown to be more sensitive than spirometry in cystic fibrosis (CF); however, the clinical utility in asthma has not been adequately explored. The purpose of this review is to assess the current evidence of LCI as a clinical tool in asthma patients and whether it is useful as a treatment response parameter in severe therapy-resistant asthma (STRA) patients.

Lung Clearance Index: Background

The MBW test assesses the efficiency of gas distribution and mixing within the lungs. MBW provides a measure of lung volume (functional residual capacity) and ventilation inhomogeneity (VI) due to the heterogeneous distribution of pulmonary disease [8, 9]. To perform the MBW technique, the patient tidally breathes an inert gas (tracer gas) through a modified face mask or mouthpiece. This gas (helium, nitrogen, or sulfur hexafluoride) is first "washed in," then "washed out" wearing a nose-clip during the washout cycle [10].

A built-in animation is used to assist the patient achieve a steady breathing pattern. Alternatively, 100% oxygen can be inhaled to wash out the residual gas from the lungs. A range of VI parameters can be calculated, including measurement of the overall VI, the LCI, and the indices Scond, which represents the VI on conductive airways, and Sacin, which represents the VI on acinar airways [9, 11].

In 1952, Becklake described for the first time measurement of LCI in patients with emphysema by estimating the liters of ventilation necessary to eliminate nitrogen from the airways while the subject inspires 100% oxygen [8]. Higher LCI values reflect a greater VI which correlates with worsening lung disease. LCI has been proven to be useful as a predictor of early airway disease in CF [9]; however, in asthma, there is still discordance regarding its clinical utility [12]. Studies suggest that LCI is elevated in school-age children and adults with asthma even when spirometry is in the normal range [13].

The Current Evidence Supporting LCI in Asthma

There are several factors that can affect LCI including age (a preschool asthma group had a significantly higher LCI z-score than a school-age group) [13], body size (LCI decreased in a nonlinear pattern as height increases) [14], and exercise-induced bronchoconstriction [12]. Otherwise, clinical factors, past hospitalizations, use of oral glucocorticoids or emergency visits, type of controller therapy, treatment dosage, or spirometric parameters were not significantly associated with an elevated LCI [13].

There is no consensus for establishing the ideal LCI cut-off point in healthy subjects, CF patients, or children with asthma. However, some studies have determined LCI means±SD or median range values (Table 1). In the clinical setting, different factors should be considered in order to discriminate between healthy vs asthmatic patients including the closed circuit wash-in method, the different gas tracers used as sulfur hexafluoride (SF_6) or nitrogen (N_2) [15], and the type of flow sensor [16].

LCI showed advantages over spirometry as a way to monitor "silent" airway remodeling whereas MBW may be a useful tool to track the progression of early airway structural disease that is not currently detected by spirometry [2, 11]. Macleod et al. [11] reported that post-bronchodilator LCI was increased in presumably well-controlled asthma children with normal FEV1, indicating residual disease and abnormal gas mixing.

Bronchoconstriction in asthma results in patchy ventilation defects causing obstructive symptoms and impaired gas exchange and distribution of inhaled medications [17]. Svenningsen et al. [18] demonstrated that magnetic resonance imaging ventilation defect percent (VDP) and LCI were strongly correlated, although only VDP was an excellent predictor of asthma control. Farrow et al. [19] described that changes in lowest ventilation regions were predicted by LCI before and after a methacholine provocation test using single photon emission computed tomography.

Inflammation is linked to asthma severity and control, FeNO, or sputum eosinophil count are used to titrate inhaled glucocorticoid doses in adults with asthma [20]. LCI detects residual airways disease independently of inflammation, as a normal FeNO does not correlate with a higher LCI [11]. In contrast, Kouký et al. [21]

Table 1 Previous LCI variability studies in different subset of patients with asthma

Study	Age group (years)	Study subjects	LCI value as mean±SD or median (range)	Comments
Gustafsson [9]	Mean age 15 years	18 HC 11 CF 15 moderate asthma	6.5 11.5±3.3* 8.7±1.3*	N2-MBW LCI was markedly greater in the CF group than in asthma After bronchodilator therapy, LCI showed significant reduction in the asthma group ($p < 0.01$)
Macleod et al. [11]	5–16	29 HC 31 children with asthma	6.24±0.47* 6.69±0.91* 6.82 pre- vs. 6.64±0.69* post-bronchodilation	SF6 LCI remained significantly higher even though use of bronchodilator in children with asthma
Sonappa et al. [41]	4–6	72 HC 28 episodic wheeze 34 multiple-trigger wheezer	6.6 (6.5–6.7)* 6.7 (6.5–6.9)* 7.4 (7.1–7.8)*	SF6 After bronchodilation, multiple-trigger wheezers were associated with increase of 11% ($p <.001$) in LCI compared with episodic (viral) wheezers
Sonappa et al. [42]	4–6	72 HC 28 severe wheezers	6.6 (6.2–6.9)* 6.8 (6.6–7.5)*	LCI did not correlate with past RBM thickness
Verbanck et al. [43]	27±8 HC 43±5 stable asthma	60 HC 50 stable asthma	6.02±0.31 6.55±0.61	N2-MBW
Keen et al. [44]	6–18	74 HC 47 asthma	6.07±0.35* 6.44±0.63*	SF6 + 4% helium + 21% oxygen + balance nitrogen LCI demonstrated a clinically significant dysfunction of the small conducting airways in pediatric asthma FeNO and MBW in combination may be useful tools when evaluating the utility of new therapies for asthma in children
Zwitserloot et al. [45]	HC: −12.1 (5.3–20.8) Asthma: 11.3 (4.7–17.4)	42 HC 32 asthma	6.21±0.38 6.48±0.48*	SF6 Use of salbutamol had no significant effect on LCI for the group
Kjellberg et al. [46]	44 (18–61)	Physician-diagnosed asthma: 109 females 87 males 60 ever smokers (54 ex-smokers; 6 current smokers) 136 never smokers	7.72 (6.36; 17.67) 7.85 (6.60; 20.65)* 8.34 (6.38; 20.65)* 7.69 (6.36; 17.67)	N2-MBW LCI is higher in smokers and in adult men Reduced FEV1, a positive smoking history, and/or blood eosinophilia identified “a small airway asthma subtype” Targeting peripheral airways could lead to improvements on asthma outcomes and reduce the degree of distal airways dysfunction

Table 1 (continued)

Study	Age group (years)	Study subjects	LCI value as mean±SD or median (range)	Comments
Svenningsen et al. [18]	46±12	18 severe poorly controlled asthma	10.5±3.0	N2-MBW Ventilation defect percent VDP and LCI were strongly correlated Asthma MRI ventilation, but not LCI was significantly worse in those with worse ACQ and AQLQ
Farrow et al. [19]	40.9±18.8	14 asthma	Baseline (turnovers) 10.3±2.25 13.8±3.23* post-methacholine	N2-MBW Lung regions with the lowest ventilation (Ventlow) change were predicted by baseline Sacin and by LCI
Steinbacher et al. [47]	6.5–18.6	43 patients clinical asthma remission: 33 normoresponsive 10 airway hyperresponsiveness (AHR)	LCI2.5: 6.77±0.41 LCI2.5: 6.83±0.54* -LCI2.5 post-CACh: 8.32±1.64* -LCI2.5 post-bronchodilation: 6.64±0.46*	N2-MBW AHR group showed significant increases in LCI after CACh and significant decreases in LCI after salbutamol
Arianto et al. [23]	0–6	403 HC 144 asthma/persistent wheeze	6.96±1.14 6.95±0.93	N2-MBW LCI did not differ significantly between children with vs. without asthma/persistent wheeze
Knihtila et al. [12]	5–10	19 HC 42RW 16 persistent troublesome cough 20 patients: EIB (exercise-induced bronchoconstriction)	6.81 (6.41–7.33) 6.87 (6.52–7.47) 6.43 (6.08–6.55)	N2-MBW MBNW indices showed no difference between the groups LCI was associated with EIB (p=0.044)
Lu et al. [22]	0.96 (0.23–1.95) 1.60 (0.62–2.93)	113 HC 37 RW	6.74±0.49 7.15±0.93	SF6/helium Elevated FeNO was associated with abnormal LCI values in infants with recurrent wheeze suggesting a more severe endotype of RW
Smith et al. [28]	10.7 (8.3–13.5)	10 controlled asthma 44 poorly controlled asthma	LCI2.5: 7.1 (6.6–9.3) LCI2.5: 7.9 (7.2–9.5)	LCI and Sacin were not different according to control status, and Scond and Scond % were significantly higher in children with poorly controlled versus controlled asthma
de Gouveia Belinelo et al. [24]	9.8±0.37 10.1±0.3 11.4±2.7	13 HC 7 asthma 23 severe asthma	7.3±1.0* 7.6±1.2* 10.5±2.3*	N2-MBW LCI remained abnormal in the majority of children despite significant improvements in other clinical and lung function outcomes
Trinkmann et al. [26]	HC: 47±19 Asthma: 55±18	47 HC 91 patients with bronchial asthma	LCI2.5: 7±0.9* LCI5: 5.6±0.6* LCI2.5: 8.6 ±1.8* LCI5: 6.6 ±1.3*	SF6 VI is increased as compared to non-asthmatic controls persisting in asthmatic patients with normal spirometry

Table 1 (continued)

Study	Age group (years)	Study subjects	LCI value as mean±SD or median (range)	Comments
Irving et al. [25•]	6–18 years	64 children with asthma prescribed high-dose asthma therapy: 43 STRA 21 DA 21 HC 39 STRA received intervention with intramuscular triamcinolone	7.40 (5.58–12.34) 6.55 (5.77–7.75)* 6.53 (5.57–7.35)* Baseline 7.46 (6.10–12.38) After 4 weeks: 6.94 (5.70–12.50)*	SF6 There is a subgroup of children with STRA with abnormal LCI who improve following parenteral steroids suggesting these children may have distal airway eosinophilic inflammation which is not responsive to ICS
Anagnostopoulou et al. [48•]	6–18	180 healthy Caucasian children	LCI2.5: 7.04±0.45 (6.16–7.91) LCI5: 5.10±0.32 (4.47–5.73)	N2-MBW LCI increased with age, this increase was negligible (0.04 units·year^{-1} for LCI2.5%)
Tang et al. [27•]	29.9±13.6	19 uncontrolled asthma	LCI (turnovers) before vs. after ICS/LABA Pre: 8.21±1.82 Post: 7.62±1.3* LCI (*z*-score) Pre: 4.47±2.59 Post: 3.50±2.22*	N2-MBW Greater improvement in ACQ5 after ICS/LABA treatment was predicted by a more abnormal baseline LCI (*z*-score) ROC analysis showed good discriminative performance of baseline Scond (*z*-score) and LCI (*z*-score) for a clinically significant improvement in ACQ5 score
Koucký et al. [21]	HC 8.3 (0.48–18.1) CF 8.4 (0.6–17.2) PCD 8.1 (0.6–15.8) Asthma 9.5 (0.5–16.6)	19 HC 24 CF 11 with PCD 15 with asthma	Mean (95% confidence interval) 7.9 (7.3–8.4)* 12.5 (11.2–13.8)* 11.8 (9.2–14.3)* 9.3 (8.2–10.3)*	N2-MBW No relationship between RBM thickness and VI was found in asthma. This suggests different structure-function relationships in these diseases
Vilmann et al. [7]	Preschool children	30 HC 35 physician-diagnosed asthma	LCI2.5: 7.15 (6.03–9.47) LCI5: 5.04 (4.28–5.90) LCI2.5: 7.39 (6.42–11.97) LCI5: 4.98 (4.42–6.47)	N2-MBW was feasible in the majority of preschool children but there were not significant differences in LCI between asthma and HC

SD standard deviation, *ACQ5* 5-item Asthma Control Questionnaire, *DA* difficult asthma, *PCD* primary ciliary dyskinesia, *CF* cystic fibrosis, *CACh* cold dry air challenge, *HC* healthy control

*p=0.005 (significance of the difference between groups)

demonstrated a high LCI in patients with eosinophilic chronic airway inflammation (allergic bronchial asthma). Lu et al. [22] reported that FeNO was significantly higher in recurrent wheezer (RW) infants with abnormal LCI, suggesting a more severe endotype of RW.

Further evidence suggests that LCI may be able to assess more severe airway obstruction and persistence of small airway disease [23, 24]. LCI is elevated in children with recurrent asthma exacerbations requiring treatment with oral glucocorticoids, in recurrent wheezers, in severe therapy-resistant asthma (STRA), and in patients refractory to inhalant therapies [13, 22, 24, 25•, 26, 27•]. It is well known that clinical and lung function outcomes improve after a multidisciplinary intervention in children with severe asthma; however, LCI remained abnormal [24]. In contrast, some studies did not find LCI to be a reliable predictor of asthma control [7, 12, 28, 29].

LCI can predict a positive response to up-titration to a high-dose combination inhaled glucocorticoid (ICS)/long acting beta agonist (LABA) treatment in uncontrolled asthma patients [27•], leading to the hypothesis that the existence of a more refractory to inhalant therapy endotype is associated with the severity of lung ventilation inhomogeneities measured by LCI.

Subsegmental narrowing of small distal airways and poorly controlled inflammation diminishes penetration of inhalant anti-inflammatory and bronchodilator medications and accelerates the deterioration in lung function [24, 30]. Inhaled drug-based therapy for asthma is largely based on particle sizes between 3 and 5 μm and their deposition occurs three to four times higher in central lung tissue than peripheral tissue [31]. This explains why many inhalers are inefficient in minimizing airway inflammation in severe asthmatics [30]. Two ways in which to target distal airways are to use inhaled medications such as ICS alone or in combination with long-acting β-agonists extra-fine particles (smaller than 2 μm) versus systemic therapy [32].

Even though larger particles may be more efficacious and achieve greater bronchodilation, smaller aerosol particles less than 1.5 μm achieve greater total deposition and farther distal airways penetration [33]. Extra-fine particles improve long-term asthma control, quality of life in real-life studies, treatment stability, and the reduction in the daily ICS dose [32, 34–36].

However, studies have found no change in spirometry, indicating that these values may not reflect the effects of small-particle aerosols on peripheral airways [34]. Beclometasone dipropionate/formoterol (BDP/F) pressurized metered dose inhaler (pMDI) which delivers 1.4–1.5-μm particle sizes showed improvement in Sacin indicating that inflammation was suppressed in peripheral airways [37], especially in patients with abnormal baseline Sacin [38].

Systemic therapy is the other way to target distal airway disease. Intramuscular triamcinolone was used in STRA patients. LCI, FEV1, Sacin, and FeNO were evaluated but only LCI and FeNO significantly improved [25, 39]. LCI showed the most potential utility of the MBW indices [40]. Irving et al. [25] proposed that LCI normalization is due to a reduction in glucocorticoid-refractory distal airway inflammation by high-dose intramuscular glucocorticoids, leading to improvement in distal gas mixing.

Concluding Remarks

These findings suggest that spirometry is not sufficient to follow the progression of severe asthma suggesting a growing need for implementing new tests as a multidomain assessment that includes evaluation of distal airways disease. LCI may be the tool that addresses physiological changes in lung function that warrant other treatment approaches.

Current evidence suggests that LCI abnormalities may be a sensitive marker for the persistence of small distal airway disease and could relate to a more severe asthma endotype unresponsive to inhaled glucocorticoids although it is possible alternative anti-inflammatory therapies have yet to be identified. This review provides evidence about appropriate use of LCI for assessment of asthma which has previously been validated as a useful test for CF.

There remain many gaps in knowledge regarding LCI to establish its clinical utility which include no standardized cut-off point for LCI in asthma patients, the lack of real-life clinical interventions evaluating the effect of extra fine particle aerosols on LCI, and the paucity of follow-up studies that determine whether early abnormalities in LCI persist and predict a diagnosis of chronic asthma and/or a more severe form of infant asthma.

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Compliance with Ethical Standards

Conflict of Interest Ivan Cherrez-Ojeda, K Robles-Velasco, María F. Osorio, JC Calderon, and Jonathan A Bernstein declare there is no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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48.• Anagnostopoulou P, Latzin P, Jensen R, Stahl M, Harper A, Yammine S, et al. Normative data for multiple breath washout outcomes in school-aged Caucasian children. Eur Respir J [Internet]. 2019 Jan 1 [cited 2021 Jan 15]; Available from: https://erj.ersjournals.com/content/early/2019/12/12/13993003.01302-2019. **This article aims to generate reference values for N2MBW outcomes in a cohort of healthy Caucasian school-aged children.**