Title: Feasibility of Lung Clearance Index (LCI) in a clinical setting in pre-school children

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Abstract

Introduction: Lung function testing in pre-school children in the clinical setting is challenging. Most cannot perform spirometry and many infant lung function tests require sedation. Lung clearance index (LCI) derived from the multiple breath washout (MBW) test has been shown to be sensitive to early disease changes but may be time consuming and so a shortened test (LCI0.5) may be more feasible in young children. We sought to establish feasibility of MBW in unsedated pre-school children in a clinic setting, and hypothesised use of LCI0.5 would increase success rates.

Methods: 116 pre-school children (28 healthy controls, 88 respiratory disease), median age 4.0 (range 2-6) years performed MBW test unsedated in a clinic setting, using sulphur hexafluoride (SF6) as a tracer gas and an adapted photoacoustic gas analyser.

Results: 81/116 (70%) completed LCI and 72% completed LCI0.5. Test success increased significantly in patients over 3 years (0% <2.5yrs, 33% 2.5-3yrs, 70%>3yrs, $p<0.0001$). LCI was elevated in those with respiratory disease compared with healthy controls.

Conclusions: MBW is feasible in a clinic setting in unsedated pre-schoolers, particularly in those over 3 years old, and LCI is raised in those with respiratory disease. Use of LCI0.5 did not increase success rate in pre-schoolers.

Keywords: Pre-school wheeze, lung function test, paediatric, airways disease

Abbreviations: LCI (Lung clearance index); MBW (multiple breath washout); CF (cystic fibrosis); PCD (primary ciliary dyskinesia); BMI (body mass index); MV wheeze (multi-trigger wheeze); EV wheeze (episodic viral wheeze).

Introduction:

Pulmonary function tests (PFTs) play an important role in the diagnosis and management of airway diseases. However, their use in pre-school children remains restricted to research and specialised centres. Spirometry is the most common test used both in research and in clinical practice to assess lung function, but it requires significant patient co-operation and co-ordination and is challenging for pre-school children, especially those under 4 years[1,2], and therefore is not routinely used clinically in this age group. The multiple-breath inert gas washout test (MBW) offers an alternative method of obtaining data on paediatric lung function, and is particularly attractive for young children because it requires minimal coordination and only passive co-operation. MBW allows calculation of Lung Clearance Index (LCI), which is defined as the number of lung turnovers required to washout an inhaled inert gas to $1/40^{th}$ of its initial concentration, which in this study we have termed LCI standard (LCI_{STD}) [3]. The set end-point relates to the sensitivity of the formerly available gas analysers rather than relating to any physiological factor[4]. The best test-end point has yet to be established, and various different ones have been suggested. In particular, $LCI_{0.5,}$ in which the end point occurs at $1/20^{th}$ of gas concentration rather than $1/40^{th}$ [3], requires a shorter test-time without loss of information when compared to LCI_{STD}.

LCI is raised in the presence of inflammation, infection, remodelling or other pathology that may lead to ventilation inhomogeneity [5-7] and has been extensively utilised within a research setting in pre-school children. In CF it has been shown to correlate with high resolution computed tomography (HRCT) scan results[8,9], more frequently abnormal than other infant lung function testing parameters[10], and predicts future deterioration in lung function [11], and it is known to be elevated in children with pre-school multi-trigger wheeze[12]. However, success rates are unknown within a clinical setting, where test duration may be a limiting factor, because of limited patient cooperation and time pressures within clinic. We hypothesised that $LCI_{0.5}$ would significantly increase test feasibility within a clinical setting, in comparison to LCI_{STD} in pre-school children (aged 2-5 years). We aimed to determine the feasibility of measuring LCI in pre-school children with a range of airway diseases in a clinic setting.

Methods

This prospective feasibility study was conducted at the Royal Brompton Hospital from January 2015 to December 2015. All parents / carers gave written, informed consent for their child to participate. Approval was obtained from NRES Committee South East Coast - Brighton & Sussex, REC number 10/H1101/69.

Subjects

Children with recurrent wheeze, CF, primary cilia dyskinesia (PCD), recurrent cough and respiratory infections were recruited from the out-patient clinic. Inclusion criteria were; age between 2-6 years with respiratory disorders diagnosed using conventional criteria[13-15]. Wheeze was doctor diagnosed (by tertiary paediatric respiratory physician) or parent reported, but confirmed using a video questionnaire {{249 Saglani,S. 2005}}. A healthy, age-matched control group was recruited from children of colleagues and siblings of patients attending the clinic. Exclusion criteria were; preterm <35 weeks gestation, or weight less than 10 kg.

A subgroup of patients, based on availability, were asked to return for a follow-up visit to assess if success or failure was consistent on a second occasion.

Multiple breath washout technique

The primary objective was to achieve three MBW measures as previously described [16,17] using a modified photoacoustic gas analyser[18] (Innocor^{TM}) during a routine outpatient visit. All measurements were undertaken by one member of staff. Full details are included in the online supplement (OLS). Children sat upright in a chair (those unwilling to sit alone sat held upright on parents' lap), with nose clips attached and breathed through a mouthpiece (Medisize, Hillegom, Netherlands). They were encouraged to breathe gently through the mouthpiece whilst watching a DVD playing.

0.2% SF_6 was used as a tracer gas for the wash-in/out phases. LCI was calculated by dividing the cumulative expired volume by the functional residual capacity. Any result that had an FRC value more than 10% different from the other two measures was discarded. End-point was LCI_{STD}, at which the tracer gas reached 1/40th of its original concentration. However if a

child was unable to reach that point, $LCI_{0.5}$ was used, in which the gas reached $1/20^{th}$ of its starting value. Any measurement that did not reach $LCI_{0.5}$ was regarded as a fail. Reasons for failure were noted. A test was judged successful if at least 2 repeatable traces were obtained.

Statistical Analysis

Sample size was opportunistic. Demographic data such as height, weight and age were reported as median and range. Group differences in continuous data were analysed using the Mann-Whitney U test, or Kruskal–Wallis one-way analysis of variance followed by a Bonferroni correction for more than 2 groups. $p<0.05$ was accepted as statistically significant. Chi squared was used to compare success rates between groups. Wilcoxon signed rank test was used to assess stability between visits. 95% confidence limits of the mean differences were used to assess stability of longitudinal data. Data analyses were performed using Graphpad Prism version 6 (Graphpad Software, Inc., San Diego, CA, USA).

Results:

Feasibility of LCI in preschool children

116 children (median age 4.1 [range 2.1-5.9] years) were included (see Table 1 for demographics). Thirty nine had recurrent wheeze (median age 3.9; range 2.1-5.9), 7 had PCD (median age 5.5; ranged 3.7-5.8), 16 had CF (median age 4.9; range 2.1-5.9), 26 other respiratory conditions (see OLS for details of diagnoses), (median age 3.8; range 2.2-5.6) and 28 healthy controls (median age 4.1; range 3.2-5.8). 83/116 (73%) successfully completed LCI_{STD}. LCI success rates at different ages are shown in Figure 1. Those under 3 had a success rate of 14%, and those over 3 a success rate of 80% ($p\leq0.0001$).

On further analysis, no child under 2.5 years of age completed the test. Between 30-40% of those aged between 2.5 and 3.5 completed the test. 85% of those over 3.5 completed the test. 3 additional children completed $LCI_{0.5}$ having been unable to complete a LCI_{STD}. Two of these children were under 3.5 years old.

Success rate was 70% for boys and 68% for girls. 28/39 (71%) wheezers, 12/16 (75%) CF, 6/7 (85%) PCD, 15/26 (57%) with other respiratory conditions and 20/28 (71%) healthy controls completed LCI_{STD} (Table 2).

Among all children that completed both LCI_{std} and $LCI_{0.5}$, mean time to complete a single washout (to calculate LCI_{STD}) was 67 seconds, and time to complete a single washout $1/20^{th}$ starting concentration (to calculate $LCI_{0.5}$) was 50 seconds, a reduction in test time of 17 seconds (25% of test duration), as washin remains the same in both LCI_{std} and $LCI_{0.5}$ tests.

Reasons for failed tests

The reasons for failure to complete LCI are summarised in Figure 2. The most common was non-cooperation/refusal to perform the test (29%), followed by inability to tolerate the nose clips (19%), lack of understanding (25%), inability to maintain a proper seal around the mouth piece (15%) and being afraid to attempt to the test (12%).

LCI results in children with respiratory conditions and healthy controls

Results of LCI_{STD} and $LCI_{0.5}$ are shown in Table 2. Upper limit of normal (ULN) calculated from these healthy controls was 7.7; there were abnormal results in all disease groups. Healthy controls had a significantly lower LCI compared to children with respiratory diseases other than recurrent wheeze (Figure 3A). There was no difference in LCI between controls and all wheezers. However, when children with wheeze were divided into those with episodic viral wheeze and those with multiple-trigger wheeze [19], the multiple-trigger wheezers had a significantly higher LCI than the episodic viral wheezers (Figure 3B) and healthy controls.

Repeat LCI measurements in pre-school children in a clinic setting

19 children underwent MBW on a second visit. The median duration between the first and second visit was 84 (range 24-210) days. 4/19 (21%) patients did not complete $LCI_{0.5}$ or

LCI_{STD} on either visit. 13/19 (68%) patients successfully completed LCI_{STD} on both visits (Figure 4). 9 patients were clinically stable with no changes to management between visits, while 4 had changes made to treatment during this period (Figure 4). Overall there was no significant change in LCI between the first and second visit for the whole group (Wilcoxon signed rank test, p=0.83), and the 95% confidence limits of differences between measurements in the 9 stable patients were 0.25+/-0.32 of an LCI unit.

Discussion:

We have shown that LCI is feasible in a clinic setting in pre-school children aged between 3.5-6 years (75-100% success). However, success rate in those between 3-3.5 years was considerably less (44%), falling to 30% for children aged 2.5-3 years and zero in those under 2.5 years old. Interestingly, and contrary to our hypothesis, $LCI_{0.5}$ as a test end-point offered no significant increase in success rate compared to LCI_{STD}, but $LCI_{0.5}$ may increase feasibility rates in children less than 3 years old. There was an overall reduction in washout test time of 17 seconds when using the $LCI_{0.5}$ as the end-point. To our knowledge, this is the first study to investigate feasibility of MBW in pre-school children in less than 30 minutes and with one member of staff present, simulating a situation that may be viable in a busy outpatient clinic. Success rates overall for those older than 3 years were good, and these can be used to inform estimated sample sizes in future studies.

The main limitation of the study was the MBW methodology. The tracer gas used was SF_6 which is a greenhouse gas, and future use may be limited by environmental requirements. As a result, nitrogen analysers are increasingly being used. Furthermore, results obtained from nitrogen washout cannot be directly applied to those obtained by SF_6 [5]. However, at the time of starting this study there was no widely accepted pre-school protocol for a nitrogen washout on the commercially available equipment. Also, although the photoacoustic gas analyser (Innocor) used met the ATS/ERS recommendations for children above 10 kg in weight, this methodology is a custom made configuration. However, the photoacoustic system is available to measure LCI using a closed circuit method, which does not have

limitations on gas availability, and is currently undergoing validation in pre-schoolers (ERJ Open Res 2016; 2: 00042-2015). Overall, it is likely that, since it was child factors which limited success rates, these will be equally applicable to other equipment.

In agreement with published data, we found LCI was raised in children with CF, PCD, and multiple trigger wheeze, compared to healthy controls, and LCI in multiple trigger wheezers was higher than in episodic viral wheeze [6,17]. This is important as it shows LCI a clinical setting provided reliable data that reflects previous findings from studies in which the test had been undertaken in a research setting. Moreover, the data suggest LCI may be a sensitive monitoring tool for the management of pre-school wheeze. It has been shown previously that LCI is increased in younger children compared to those aged 6 and over [20], as a result, reference equations for calculating z-scored LCI were generated. However, the reference equations were based on mass spectrometry data using a dual gas washout, and using sedation in the youngest subjects. This was felt to be significantly different from our methodology, so we could not assume these equations could be applied. We therefore included contemporaneous healthy controls to make comparisons with our disease patients.

Overall, the success rates in children younger than 3 were poor, even $LCI_{0.5}$ was not feasible in this age group, suggesting that unsedated MBW in these patients may not be achievable in the clinical setting. However, after age 3 years, results improved and most children completed a technically acceptable MBW which, coupled with the increased LCI seen in some conditions, suggests LCI may be a feasible monitoring tool. Using $LCI_{0.5}$ did not increase the feasibility compared to LCI_{STD}. Only three of the 86 children who performed the test for long enough to reach the $1/20^{th}$ tracer gas concentration cut-off would not continue to the $1/40^{th}$ standard cut-off. This is an unexpected finding in this group as it was assumed that tolerance of the test would be relatively brief and any time saved would improve success rates. Previous work assessing the usefulness of $LCI_{0.5}$ was undertaken in school aged children [1,3], however pre-school children have a shorter washout period, because of a raised respiratory rate and more efficient lung emptying, so the benefit of $LCI_{0.5}$ may only be relevant in older children and adults.

Previous data on success of LCI in pre-school children in the research setting have shown {{40 Aurora,P. 2005}}an overall success rate of 79%, compared to 73% in our clinical setting. Success rates in all children over 3.5 years were also extremely good in the research setting (78-87%) compared to ours in the clinical setting (75-100%). Even in a research setting success of LCI measurement in children under 3 years was only 40%. In a clinical setting this reduced to 30% in 2.5-3 year olds and 0 in those under 2.5 years.

Surprisingly, intolerance of the nose clip seemed to be a major hurdle in achieving a successful measurement, although this has also been recently reported as a significant source of discomfort in adults (ERJ Open Research reference). Use of facemasks could reduce this problem and these have been used in other studies, albeit with sedation for the youngest subjects [7,20,21]. However masks also introduce additional dead space, which further reduces the pool of equipment that is suitable for pre-school use and may lead to poor measurements. In addition, use of a face-mask often requires two operators (as the mask must be held in place tightly throughout to prevent any leaks) which reduces its application in a busy outpatient clinic. On the basis of the current data, an LCI_{STD} rather than $LCI_{0.5}$ should always be attempted in pre-school children. There are several strategies that could be applied to try further to increase the success rate. The first would be to address the issue of nose-clips, which proved a common reason for failure. We used standard lung function testing clips manufactured for older children and adults, it may be that a specialist design or possibly commercially available clips designed for comfort when swimming may be more appropriate for preschool children. Although there are drawbacks to using facemasks, it may be that a full feasibility assessment in a clinical situation would be beneficial.

All children who completed the first visit LCI were able to complete the second visit LCI. This is encouraging as it suggests that long term monitoring or multi-visit trials will be possible in this age-group. Although this group was small, LCI was stable in those with stable disease.

In conclusion, LCI is feasible in an outpatient setting for pre-schoolers aged 3 years and over, although rarely successful in children younger than this. Encouragingly, the results are comparable to those obtained in a research setting.

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	Healthy Control	Wheeze	CF	PCD	Other
Number (n)	28	39	16	7	26
Age in decimal years (median; range)	4.1 (2.11- 5.77)	3.9 (2.07- 5.89)	4.9 (2.11- 5.95)	5.5 (3.66- 5.83)	3.8 (2.17- 5.63)
Gender M/F	12/11	24/15	10/6	3/4	15/12
Height in centimetres (mean; range)	102.1 87- 115	103.3; 83-121	104.1; 86.7- 118.5	107.7; 97.5- 113.0	101.5; 88.0- 116.5
Height (centiles, median;range)	50^{th} (25^{th} – 98^{th})	50^{th} (2^{nd}- 98^{th})	50^{th} (9^{th} -98^{th})	50^{th} (25^{th}-75^{th})	25^{th} (2^{nd}-99.6^{th})
Weight in kilograms (mean; range)	21.34; 11.40- 23.90	17.40; 10.10- 23.10	17.86; 13.10- 28.00	17.02; 14.80- 19.10	16.10; 12.20- 22.30
Weight (centiles)	62.5^{th} (9^{th} – 99.6^{th})	75^{th} (0.4^{th} -99.6^{th})	62.5^{th} (9^{th} – 99.6^{th})	50^{th} (9^{th}- 91^{st})	50^{th} (9^{th} – 99.6^{th})
Body Mass Index (BMI) (mean)	20.5	16.3	16.5	14.7	15.6
BMI (centiles)	50^{th} (9^{th} – 99.6^{th})	75^{th} (0.4^{th} – 99.6^{th})	75^{th} (9^{th} – 99.6^{th})	62.5^{th} (25^{th} -98^{th})	62.5^{th} (25^{th} – 91^{st})

Table 1 - Demographics. (PCD= primary ciliary dyskinesia, CF=cystic fibrosis) Healthy control children had a higher BMI than those with respiratory disease. More wheezers were male than female.

	Episodic Wheeze	MT Wheeze	PCD	CF	Other	Healthy	Total
LCI (median; range)	6.05; 5.62-8.81	6.70; 6.06-10.84	7.39; 6.39-8.67	7.09; 6.25-13.90	6.34; 5.99-12.00	6.32; 5.39-7.64	6.43; 5.39-13.90
$LCI_{0.5}$ (median; range)	4.51; 4.19-5.63	4.64; 4.15- 6.68	5.33; 4.34-6.02	5.05; 3.22-7.87	4.73; 4.18-7.54	4.61; 3.86-5.71	4.72; 3.22-7.87
Success rates (success/total; %)	17/21; 81%	11/18; 61%	6/7; 85%	12/16; 75%	15/26; 57%	20/28; 71%	81/116; 70%

Table 2 – LCI results and success rates. (PCD= primary ciliary dyskinesia, CF=cystic fibrosis, MT wheeze = multi-trigger wheeze) There were abnormal results in all disease groups. The highest success rates were in PCD patients, and the lowest in those with other respiratory conditions (not wheeze, CF or PCD).