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Eur Respir J 2015; 46: 1811–1814 | DOI: 10.1183/13993003.00377-2015 | Copyright ©ERS 2015

Multiple breath washouts in children can be shortened without compromising quality



To the Editor:

Lung clearance index (LCI) derived from multiple breath washout (MBW) is a sensitive, noninvasive measure of ventilation heterogeneity and is used for the assessment of cystic fibrosis (CF) [1], asthma [1] and primary ciliary dyskinesia (PCD) [2]. LCI is the number of lung turnovers (functional residual capacity (FRC)) required to washout an inhaled inert gas to 1/40 of its initial concentration: a historically set end-point of no physiological significance [3]. The number of lung turnovers needed to wash out the gas, and hence the LCI, increases with disease severity. It is non-effort-dependent and requires only passive cooperation. The test can be time-consuming, especially with severe airway obstruction as more time is required to wash out the tracer gas. This is a particular problem in young children, in whom a test lasting several minutes is intolerable. This could be shortened by stopping the test at a higher concentration of tracer gas. We propose that instead of 1/40 of the initial concentration being used as an end-point (“LCI standard” (LCI_{std})), the concentration could be raised to 1/30 (LCI_{0.75}), 1/20 (LCI_{0.5}) or 1/10 (LCI_{0.25}) of the starting concentration of tracer gas, or using a fixed time period of washout, for example 20 s, or a fixed number of breaths.

In 17 preschool children (median age 3.9 years), our pilot data showed that only 35% could perform LCI_{std}, but 65% completed LCI_{0.5} [4].

Two studies, demonstrated that LCI_{0.5} can be performed in school age children with CF with the same diagnostic performance as LCI_{std} [5, 6] and a recent study [7] showed LCI_{0.5} is sensitive to improvements with dornase alpha and hypertonic saline in CF. We aimed to investigate the utility of shortened washouts in school age children with asthma, PCD and CF, and to assess the sensitivity of change in LCI to two interventions (intravenous antibiotics in CF [8] and intramuscular triamcinolone injection in severe asthma [9]). We hypothesised that LCI measurements can be shortened without compromising the quality of the information obtained and are as responsive to therapeutic intervention as LCI_{std}.

We performed a retrospective analysis of previously collected data from MBW measurements at the Royal Brompton Hospital (London, UK) between January 2008 and May 2014. All research studies had been approved by the appropriate research ethics committees, and informed consent obtained. Data from 20 children with CF (median age 13.85 years, seven male), 19 with PCD (median age 13.89 years, six male), 21 with asthma (median age 13.29 years, 12 male) and 17 healthy controls (median age 9.76 years, nine male) were analysed initially, followed by data from 32 children with asthma who had MBW prior to and 1 month after an intramuscular injection of triamcinolone, and a cohort of 17 people with CF who had MBW at the beginning and end of a course of intravenous antibiotics. LCI_{std} data for the CF intervention cohort have been reported

TABLE 1 Data from the shortened multiple breath washout

LCI	ULN	Abnormal n/N			Correctly categorised %			Mean (range) time saved s			Mean time saved %			Mean intra-test CV (%)	
		Asthma	CF	PCD	Asthma	CF	PCD	Asthma	CF	PCD	Asthma	CF	PCD	LCI	FRC
LCI_{std}	7.30	5/21	15/20	17/19										4.7	5.2
LCI_{0.75}	6.18	2/21	14/20	16/19	90.5	95	100	17 [5–49]	21 [4–47]	22 [6–68]	18	17	22	5.1	5.2
LCI_{0.5}	5.60	3/21	13/20	14/19	90.5	90	94.7	26 [9–67]	26 [6–69]	36 [16–82]	26	27	28	5.4	5.4
LCI_{0.25}	5.03	3/21	12/20	11/19	90.5	85	94.7	33 [11–67]	39 [14–83]	47 [18–97]	34	36	41	5.3	5.5

School age children with asthma (n=21), cystic fibrosis (CF) (n=20) and primary ciliary dyskinesia (PCD) (n=19) completed a minimum of two SF₆ multiple breath washouts per child. Upper limit of normal (ULN) lung clearance index (LCI) (mean+sd*1.96) calculated from healthy controls. Correctly categorised data was calculated as a percentage of the correctly predicted values using the ULN. Coefficient of variance (CV) calculated from the mean of the coefficient of variance of the intra-test functional residual capacity (FRC) and LCI (sd/mean). Time saved in each of the shortened MBWs is to their respective end-points. LCI_{std} had a mean duration of 69 s in healthy controls (range 34–119), 93 s in asthma (range 50–144), 97 s in CF (range 41–150) and 114 s in PCD (range 54–203). LCI_{std}: 1/40 of the initial concentration of tracer gas; LCI_{0.75}: 1/30 of the initial concentration of tracer gas; LCI_{0.5}: 1/20 of the initial concentration of tracer gas; LCI_{0.25}: 1/10 of the initial concentration of tracer gas.

previously [8]. MBW tests were performed according to a standardised protocol [3], using a photoacoustic gas analyser (Innocor, Odense, Denmark), and 0.2% sulfur hexafluoride (SF₆) as the inert tracer gas. We measured LCI_{std} and FRC and then calculated LCI and FRC at the predetermined earlier end-points described above.

Groups were compared using the non-parametric Kruskal–Wallis test and the Mann–Whitney U-test. Pre- and post-intervention values were compared using the non-parametric Wilcoxon matched pairs test. All p-values <0.05 were considered as statistically significant.

Upper limits of normality from the 17 healthy controls, the number of results correctly characterised as abnormal or normal, and the time saved both as an absolute value and the percentage of the total washout for each shortened washout is shown in table 1.

MBW from 29 asthmatic school-children (8–16 years) were analysed before and 1 month after an intramuscular injection of triamcinolone, given as a trial of steroid responsiveness [10]. There was a significant improvement in LCI_{std} (p=0.001) and in all the shortened LCI measurements after triamcinolone (p=0.02). 17 CF patients (age 12–45 years) were studied before and 2 weeks after intravenous antibiotics. LCI_{std} and LCI_{0.5} showed a significant improvement after intravenous antibiotics (p=0.03 and p=0.04, respectively); however, this change was not seen for LCI_{0.25} and LCI_{0.75}.

There was no increase in variability seen in LCI_{0.25}, LCI_{0.5} or LCI_{0.75} when compared with LCI_{std}, (coefficient of variation for both LCI and FRC was 5% for both LCI_{std} and shortened measures) and so using these shortened washout indices as an endpoint should not affect the power calculations of any future prospective study.

There was no significant difference between the FRC calculated at 1/40 of tracer gas concentration and that calculated at any of the alternative end-points for normal or any patient groups (data not shown).

We also calculated LCI after fixed time points (30 s and 45 s) and fixed number of breaths (10 and 15) but the results were much less sensitive to disease state and intervention (data not shown) so we have not pursued this approach further.

To our knowledge, this is the first study to demonstrate the shortened LCI_{0.5} maintains diagnostic performance in PCD and asthma, and also shows a significant change following therapeutic interventions in most patients with CF and asthma. A weakness was that the study was performed in school age children and adults who were able to complete a full MBW, whereas it is likely that shortened washouts will be most useful in younger pre-school children who are not able to do this. However, it was necessary to initially assess the shortened washouts in children who had comparable data from the full washout. This would have been impractical in pre-schoolers as so many are unable to complete the test. Although upper limits of normal have been calculated, the healthy control group was small and more subjects are required to give robust values.

The shortened MBWs in the asthma group had the lowest percentage correctly identified as abnormal or normal. However, only five out of 21 children with asthma had an abnormal LCI_{std} and, in this small group, a very small number of incorrectly characterised results [2] disproportionately skewed the data. However, it cannot be said from these data that a normal LCI_{0.5} excludes an abnormal LCI_{std}. We showed that shortened washouts were sensitive to change following an intervention, however, LCI_{std} showed a significantly greater change than the shortened LCI measurements, likely due to loss of information from a shortened washout,

leading to decreased sensitivity. If shortened washouts are used, the possibility of false negative but not false positive results needs to be considered. We have shown in a cross-sectional study that LCI measurements can be shortened and, although there is some loss of information, meaningful results can still be obtained. Furthermore, the two longitudinal intervention studies have shown that shortening the time of the measurements to 1/20 (LCI_{0.5}) allows demonstration of a response to an intervention in most cases.

LCI_{0.5} was the best-performing surrogate measure for LCI_{std} when proportion of time saved and correlation with LCI_{std} were assessed. Further work confirming the utility of shortened LCI in response to an intervention is needed including prospective confirmation in pre-school children.



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Shortened LCI is quicker to perform with no loss of measurement quality and could be used in young children <http://ow.ly/SyC5a>

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Received: March 26 2015 | Accepted after revision: July 27 2015 | First published online: Oct 09 2015

Conflict of interest: Disclosures can be found alongside the online version of this article at erj.ersjournals.com

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Eur Respir J 2015; 46: 1814–1816 | DOI: 10.1183/13993003.00791-2015 | Copyright ©ERS 2015

Use of chest radiography in the 22 highest tuberculosis burden countries



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To the Editor:

An estimated 9 million new tuberculosis (TB) cases and 1.5 million deaths were caused by *Mycobacterium tuberculosis* in 2013 [1], more than 80% of which occurred in the 22 highest TB burden countries (HBCs). Among the confirmed incident cases, 4.9 million were pulmonary TB (PTB), of which 58% were bacteriologically confirmed. For many of these cases, chest radiography (CXR) was used as an important tool for triaging, particularly in smear-negative patients, to select patients for further microbiological workup with culture