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ORIGINAL ARTICLE: CYSTIC FIBROSIS—PEDIATRIC & ADULT

The utility of moment ratios and abbreviated endpoints of the multiple breath washout test in preschool children with cystic fibrosis

Michelle Shaw MSc[1] | Martinus C. Oppelaar BSc[1,2] | Renee Jensen RRT[1] | Sanja Stanojevic PhD[1] | Stephanie D. Davis MD[3] | George Retsch-Bogart MD[3] | Felix A. Ratjen MD[4]

[1]Translational Medicine Program, Research Institute, Hospital for Sick Children, Toronto, Ontario, Canada

[2]Department of Paediatric Pulmonology, Radboud University Medical Center, Amalia Children's Hospital, Nijmegen, The Netherlands

[3]Division of Pediatric Pulmonology, Department of Pediatrics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

[4]Division of Respiratory Medicine, Department of Pediatrics, Hospital for Sick Children, Toronto, Ontario, Canada

Correspondence
Felix A. Ratjen, Research Institute, Hospital for Sick Children; Division of Respiratory Medicine, Department of Pediatrics, Hospital for Sick Children, 555 University Avenue, Toronto, ON M5G 1X8, Canada.
Email: Felix.Ratjen@sickkids.ca

Abstract

Background: The multiple breath washout (MBW) test may be most useful in tracking disease progression over time to inform treatment decisions. In the clinical setting, alternative outcomes, which can be obtained quickly and easily, may facilitate interpretation of clinically relevant changes in lung function.

Methods: In this secondary analysis of data from 78 cystic fibrosis (CF) and 72 healthy control (HC) subjects between the ages of 2.6 and 5.9 years, MBW was performed at enrollment, 1, 3, 6, 9, and 12 months, as well as during symptomatic visits using the Exhalyzer D (EcoMedics AG, Duernten, Switzerland). The lung clearance index, $LCI_{2.5,}$ was compared to moment ratios (M_1/M_0 and M_2/M_0) at the standard cutoff (1/40th of starting tracer gas concentration) as well as LCI_5 and moment ratios at 1/20th of the starting concentration (M_1/M_0 at LCI_5, and M_2/M_0 at LCI_5).

Results: All outcomes were able to distinguish between health and disease. LCI_5 reduced testing time by 40% and increased feasibility by more than 10%. The limits of biological reproducibility in healthy children were similar between $LCI_{2.5}$ (15%), LCI_5 (12%), M_1/M_0 at $LCI_{2.5}$ (14%), and M_1/M_0 at LCI_5 (12%), but markedly larger for M_2/M_0 at $LCI_{2.5}$ (30%) and M_2/M_0 at LCI_5 (25%). Each outcome deteriorated significantly with worsening pulmonary symptoms, the magnitude of deterioration was greatest for M_2/M_0.

Conclusions: In preschool children with CF, LCI_5 was more feasible to obtain and track disease progression. The second moment ratio was most sensitive to pulmonary symptoms, but had the greatest variability both within and between subjects.

KEYWORDS
cystic fibrosis (CF), pulmonary function testing (PFT)

1 | INTRODUCTION

Measures of ventilation inhomogeneity, obtained by the multiple breath washout (MBW) test, have consistently identified lung disease early in young children with cystic fibrosis (CF),[1-3] as well as other respiratory conditions.[4] The lung clearance index (LCI) is the most commonly reported MBW outcome; the LCI represents the number of lung turnovers, expressed as functional residual

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capacity, required to reduce the concentration of an inert gas to 1/40th of its starting concentration ($LCI_{2.5}$).[5] Other MBW outcomes include moment ratios, which evaluate the shape or skewness of the entire washout curve as an alternative means of assessing ventilation inhomogeneity within the lungs.[6] Since early CF lung disease is thought to originate in the peripheral airways, moment ratios may be more sensitive in identifying subtle changes in these smaller airways as this measure places more emphasis on the end of the washout. In addition, the calculation of moment ratios is less influenced by irregular breathing pattern, which could be an advantage in unsedated young children.

Truncating the washout to earlier time points (eg, 1/20th of starting concentration; LCI_5) has been suggested as an alternative outcome as testing time can be reduced by up to 30% compared with $LCI_{2.5}$, while still differentiating health from disease in school-aged children with mild-to-moderate CF lung disease.[7-9] Reducing test time could not only facilitate the implementation of MBW in busy clinical settings, but also increase feasibility in young children. However, using indices measured earlier in the washout may affect sensitivity. We have previously described that the sensitivity to detect treatment effects in interventional studies is lower at cutoffs earlier than 2.5%[6] and in infant studies, cutoffs from later in the washout were identified as more sensitive in identifying early functional changes.[10] In the clinical setting, the MBW test will be useful in tracking disease progression over time as well as defining whether symptoms associated with clinical deterioration lead to worsening lung function. Currently, there is limited information about the utility of moment ratios and LCI at 1/20th, the starting concentration (LCI_5) for these clinical scenarios.

The aim of this study was to assess whether moment ratios and LCI at 1/20th of the starting concentration of the inert gas, track disease, and capture worsening of lung disease during symptomatic events. In addition, we aimed to quantify the impact of earlier MBW cutoffs on both the feasibility and the duration of testing in preschool age children.

2 | METHODS

2.1 | Study design

This is a secondary analysis of a previously published dataset that included 148 subjects (78 CF; 72 healthy controls [HC]) between the ages of 2.6 and 5.9 years.[2] Briefly, subjects were recruited from three North American CF centers in Toronto, Canada; Indianapolis, Indiana; and Chapel Hill, North Carolina. Local ethics board approval was obtained at each site (REB/IRB# 1000036303, 1401277863 and 13-1258, respectively). Patients with CF were recruited from their respective clinics, and healthy children from friends and family, and outpatient clinics. All children were free of acute respiratory infection within 4 weeks of the enrollment visit. MBW tests were performed at enrollment, 1, 3, 6, 9, and 12 months, as well as during symptomatic visits outside of the scheduled study visits. A symptomatic visit was defined as increased pulmonary symptoms and/or treatment with antibiotics.[3]

2.2 | MBW outcomes

MBW testing was performed during relaxed and stable tidal breathing using the Exhalyzer D (EcoMedics AG, Duernten, Switzerland), with special adaptions for preschool-aged children,[2] including use of a facemask with therapeutic putty, a bacterial filter with smaller dead space, and video-based distraction. All subjects performed the test to the standard endpoint of 1/40th starting concentration, and test quality was assessed up to this point.[11] Moment analysis was performed as previously described.[5,12,13] Briefly, we calculated the area under the curve of normalized end-tidal nitrogen concentration (Cnet), Cnet was multiplied by the lung turnovers (TO), and Cnet multiplied by TO^2 was plotted against TO. These calculations represented moment zero (M_0), moment one (M_1), moment two (M_2), and were expressed as moment ratio one (M_1/M_0) and moment ratio two (M_2/M_0). In both M_1/M_0 and M_2/M_0, a higher value represents a greater proportion of slow-ventilating lungs and worse ventilation inhomogeneity. M_2/M_0 gives more weight to the tail of the curve, where the most poorly ventilated lung units contribute a greater proportion of the gas concentration. $LCI_{2.5}$ was compared with moment ratios (M_1/M_0 and M_2/M_0) at the standard cutoff (1/40th of starting tracer gas concentration) as well as LCI_5 and moment ratios calculated posttest at 1/20th of starting concentration (M_1/M_0 at LCI_5 and M_2/M_0 at LCI_5).

Feasibility of outcomes at earlier cutoffs was determined in a subset of 40 CF subjects at a screening visit and at one randomly selected follow-up visit. Some trials may not meet test quality criteria at the standard endpoint (1/40th starting concentration), but could meet these criteria at the earlier cutoff (1/20th starting concentration). Given this, the 80 test occasions were re-evaluated for quality at 1/20th the starting concentration. Feasibility was compared between the proportion of test occasions with at least two good quality trials at the standard and earlier cutoff. Testing time was calculated using the total number of breaths (prephase and washout) to each endpoint multiplied by the respiratory rate for each trial. The time between trials was assumed to be 1.5 times the previous trial. The total testing time for each endpoint was determined as the time required to obtain at least two acceptable trials.

3 | STATISTICAL METHODS

Receiver operator characteristic curves were used to compare the sensitivity and specificity of each outcome to differentiate between health and disease. Mixed-effect linear regression models, with age as the time variable, were used to determine the longitudinal progression of each outcome. The limits of biological reproducibility were estimated using pooled pairwise changes between all-time points using a mixed-effect model.

Changes of each outcome within-subjects at the onset of pulmonary symptoms were assessed as a percent change from baseline. Baseline visits were defined as the first preceding asymptomatic visit. All statistical analyses were performed with Stata 15.1 (StataCorp, College Station, TX).

4 | RESULTS

In total, 70 HC and 78 CF subjects had acceptable MBW data to contribute to the analysis. Progression of lung disease was calculated from 324 repeated measurements in HC and 368 measurements in CF. Each participant with CF contributed an average of 5 measurements (range 1-9). In the CF subgroup, 104 visits were classified as symptomatic.

All outcomes were able to distinguish between health and disease at the first study visit (Figure 1). The area under the curve (AUC) for the $LCI_{2.5}$ (0.864) was comparable and not statistically different from the other outcomes (AUC range 0.807-0.843). Each of the outcomes demonstrated worsening of ventilation inhomogeneity with age in the CF group relative to the healthy subjects (Figure 2). The limits of biological reproducibility in healthy children were similar between $LCI_{2.5}$ (15%), LCI_5 (12%), M_1/M_0 (14%) at $LCI_{2.5}$, and M_1/M_0 at LCI_5 (12%), but markedly larger for M_2/M_0 at $LCI_{2.5}$ (30%) and M_2/M_0 at LCI_5 (25%). Each of the outcomes deteriorated significantly with worsening pulmonary symptoms (Figure 3), the magnitude of deterioration was greatest for M_2/M_0, but was similar for the other outcomes.

In 80 randomly selected test occasions, 62 (78%) were acceptable for $LCI_{2.5}$ and 73 (92%) were acceptable for LCI_5. In all but one test occasion, feasibility was higher for LCI_5. The median time estimated to obtain two good quality trials at LCI_5 was 6.7 minutes (IQR 5.0-10.7 minutes), which represents approximately 6.3 minutes (43%) time saving compared with $LCI_{2.5}$.

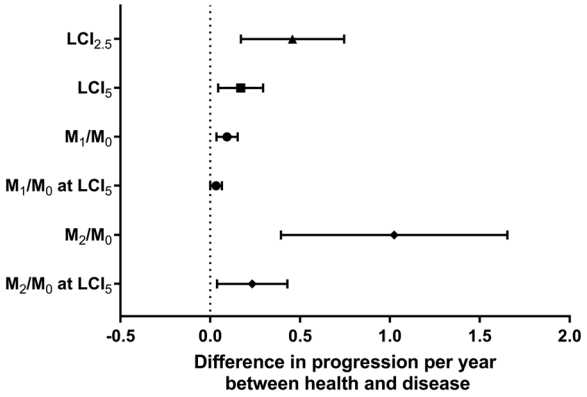

FIGURE 2 Forest plots summarizing the rate of change with age in CF relative to healthy children over the study period for each of the outcomes. Estimates represent the interaction coefficients from mixed models representing the additional deterioration in each outcome per year between health and disease. CF, cystic fibrosis; LCI, lung clearance index

5 | DISCUSSION

In preschool children with CF, MBW outcomes calculated earlier in the washout (eg, 1/20th the starting concentration) tracked disease progression were sensitive to lung function changes associated with increased pulmonary symptoms, reduced testing time by 40%, and increased feasibility by more than 10%. LCI_5 may thus represent a

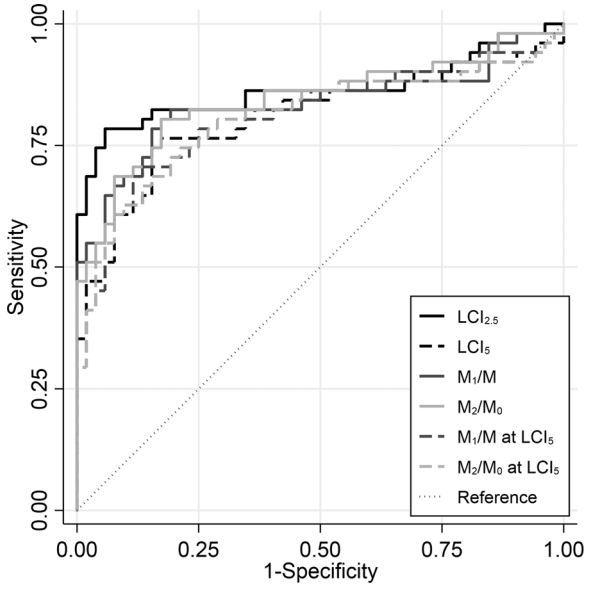

FIGURE 1 ROC analysis demonstrated that all measures of MBW are similarly able to distinguish between health and disease. LCI, lung clearance index; MBW, multiple breath washout; ROC, receiver operator characteristic

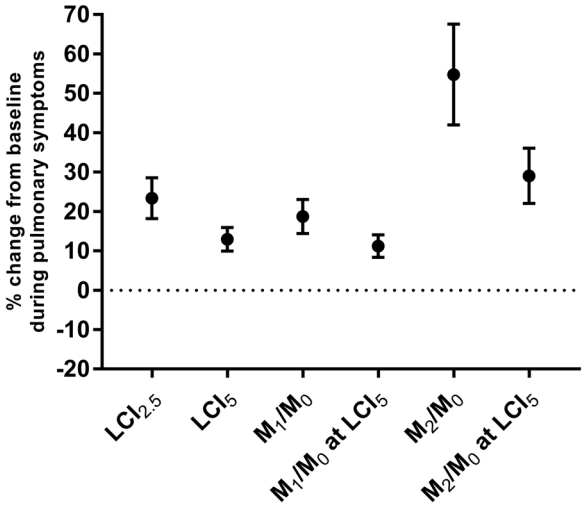

FIGURE 3 Percent changes in each MBW outcome with pulmonary symptoms. The magnitude of worsening was similar between the outcomes, except M_2/M_0 at $LCI_{2.5}$. Estimates are based on a mixed effects regression model with the bars representing the 95% CI around the coefficient. CI, confidence interval; LCI, lung clearance index; MBW, multiple breath washout

feasible outcome for use in clinical monitoring of ventilation inhomogeneity. The second moment ratio had the strongest signal to detect changes with pulmonary symptoms; however, M_2/M_0 was more variable both within and between subjects than the other outcomes, and while this outcome is more sensitive at the group level, its high variability may limit its utility to monitor visit-to-visit change at the individual level.

Previous studies have demonstrated the ability of earlier cutoffs of MBW to differentiate health and disease.[6-8] Our findings are consistent with this earlier work, but also show that LCI_5 is able to capture disease progression and worsening of lung function with increased respiratory symptoms; two important aspects of monitoring patients' health in the clinical setting. Moreover, the within-subject between-visit variability of LCI_5 was similar to that reported for $LCI_{2.5}$,[1] suggesting that a 15% change in these outcomes can be used as an indicator of significant improvement or worsening. LCI_5 was more feasible to obtain and the shorter washout time reduced overall testing time. The time savings in our random sample of preschool children was also greater than that previously reported in older children.[8,9] Although these results are not generalizable to all ages and disease groups, MBW is most likely to be used to monitor lung function changes and guide treatment decisions in preschool children, and LCI_5 appears to be an appropriate and feasible alternative.

While potentially sufficient for the clinical setting in preschool children, monitoring early changes in infants or comparison of treatment efficacy may require longer washouts and more sensitive endpoints. Egger et al[10] found that the diagnostic performance of MBW outcomes depends on the analysis cutoff point. In infants with mild lung disease, a longer washout is necessary to discriminate between health and disease,[10] especially since newborn screened infants with CF have minimal ventilation inhomogeneity that is only slightly elevated compared with HC.[14] Although LCI_5 has advantages to $LCI_{2.5}$ in young children, and provides a suitable alternative for monitoring lung function in clinical practice, these data support $LCI_{2.5}$ as a quantitatively superior outcome in preschool children and may be the preferred outcome for interventional studies for which sensitivity and precision outweigh time savings and feasibility.

Most previous studies suggest that moment ratios provide similar information to $LCI_{2.5}$ and may not confer additional information not captured by this commonly used outcome of MBW. Moment ratios distinguished treatment effects of hypertonic saline and dornase alfa,[6] and were associated with better pulmonary function, inflammation, and lower respiratory tract infections.[15-17] However, one study from the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF) cohort suggests that air trapping is more closely related to M_2/M_0 compared with other MBW outcomes.[18] This may reflect the higher sensitivity of M_2/M_0 to capture peripheral airway involvement. In the present study, we found M_2/M_0 to increase more than any other MBW outcome during pulmonary symptoms suggesting that M_2/M_0 may provide a more sensitive outcome in this clinical setting compared with other MBW outcomes. The greater variability observed for M_2/M_0 may be due to the differences in where M_2/M_0 is calculated for each subject (ie, M_2/M_0 was calculated at the same concentration endpoint that equates to a different turn over for each subject). While this approach makes direct comparisons between subjects difficult, it may amplify the signal at the end of the washout and therefore provide a more sensitive endpoint. Translation of these findings to individual patients is however challenging since M_2/M_0 is also more variable both within-subjects and between-subjects. Synonymous to the midexpiratory flow rates at low lung volumes (eg, forced expiratory flow at 25–75% [$FEF_{25\%-75\%}$]), it is not clear whether moment ratios are a suitable test to track disease at the individual level. There are also no existing guidelines as to how moment ratios should be calculated (eg, 1.40th starting concentration, six turnovers), which limits the direct comparison of results between studies. Until further evidence is available, caution is warranted to interpret results in light of the high variability of the measure.

There are several limitations to this study that need to be acknowledged. Our findings may not be generalizable to other age groups or disease states. Importantly, the tradeoff between feasibility and discriminatory power may also differ between tracer gases; therefore, these findings are not transferrable to other tracer gases. The outcomes considered here are not an exhaustive list of all possible MBW measurements, but ones thought to be relevant and feasible for preschool children.

6 | CONCLUSION

For preschool children, LCI_5 may provide clinically relevant information. MBW outcomes obtained earlier in the washout for this age group are more feasible both in terms of testing success, as well as time saved, and provide similar information to established outcomes.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ORCID

Michelle Shaw http://orcid.org/0000-0002-0966-6779
Renee Jensen http://orcid.org/0000-0002-0877-9579
Sanja Stanojevic http://orcid.org/0000-0001-7931-8051
Stephanie D. Davis http://orcid.org/0000-0002-9390-0651
George Retsch-Bogart http://orcid.org/0000-0001-9461-1758
Felix A. Ratjen http://orcid.org/0000-0003-4057-6592

REFERENCES

1. Oude Engberink E, Ratjen F, Davis SD, Retsch-Bogart G, Amin R, Stanojevic S. Inter-test reproducibility of the lung clearance index measured by multiple breath washout. *Eur Respir J*. 2017;50: 1700433.
2. Stanojevic S, Davis SD, Retsch-Bogart G, et al. Progression of lung disease in preschool patients with cystic fibrosis. *Am J Respir Crit Care Med*. 2017;195:1216-1225.
3. Rayment JH, Stanojevic S, Davis SD, Retsch-Bogart G, Ratjen F. Lung clearance index to monitor treatment response in pulmonary exacerbations in preschool children with cystic fibrosis. *Thorax*. 2018;73:451-458.
4. Kobbernagel HE, Green K, Ring AM, et al. One-year evolution and variability in multiple-breath washout indices in children and young adults with primary ciliary dyskinesia. *Eur Clin Respir J*. 2019;6:1591841.
5. Robinson PD, Latzin P, Verbanck S, et al. Consensus statement for inert gas washout measurement using multiple- and single-breath tests. *Eur Respir J*. 2013;41:507-522.
6. Stanojevic S, Jensen R, Sundaralingam D, et al. Alternative outcomes for the multiple breath washout in children with CF. *J Cyst Fibros*. 2015;14:490-496.
7. Yammine S, Singer F, Abbas C, Roos M, Latzin P. Multiple-breath washout measurements can be significantly shortened in children. *Thorax*. 2013;68:586-587.
8. Green K, Ejlertsen JS, Madsen A, et al. Abbreviation modalities of nitrogen multiple-breath washout tests in school children with obstructed lung disease. *Pediatr Pulmonol*. 2016;51:624-632.
9. Hannon D, Bradley JM, Bradbury I, Bell N, Elborn JS, O'Neil K. Shortened Lung Clearance Index is a repeatable and sensitive test in children and adults with cystic fibrosis. *BMJ Open Respir Res*. 2014;1: e000031.
10. Egger B, Jost K, Anagnostopoulou P, et al. Lung clearance index and moment ratios at different cut-off values in infant multiple-breath washout measurements. *Pediatr Pulmonol*. 2016;51:1373-1381.
11. Jensen R, Stanojevic S, Klingel M, et al. A systematic approach to multiple breath nitrogen washout test quality. *PLoS One*. 2016;11: e0157523.
12. Saidel GM, Salmon RB, Chester EH. Moment analysis of multibreath lung washout. *J Appl Physiol*. 1975;38:328-334.
13. Schibler A, Schneider M, Frey U, Kraemer R. Moment ratio analysis of multiple breath nitrogen washout in infants with lung disease. *Eur Respir J*. 2000;15:1094-1101.
14. Nguyen TT, Thia LP, Hoo AF, et al. London Cystic Fibrosis Collaboration (LCFC). Evolution of lung function during the first year of life in newborn screened cystic fibrosis infants. *Thorax*. 2014;69: 910-917.
15. Ramsey KA, Foong RE, Grdosic J, et al. Multiple-breath washout outcomes are sensitive to inflammation and infection in children with cystic fibrosis. *Ann Am Thorac Soc*. 2017;14:1436-1442.
16. Simpson SJ, Ranganathan S, Park J, et al. Progressive ventilation inhomogeneity in infants with cystic fibrosis after pulmonary infection. *Eur Respir J*. 2015;46:1680-1690.
17. Hall GL, Logie KM, Parsons F, et al. Air trapping on chest CT is associated with worse ventilation distribution in infants with cystic fibrosis diagnosed following newborn screening. *PLoS One*. 2011;6:e23932.
18. Ramsey KA, Rosenow T, Turkovic L, et al. Lung clearance index and structural lung disease on computed tomography in early cystic fibrosis. *Am J Respir Crit Care Med*. 2016;193:60-67.

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