

RESEARCH LETTER

### Multiple-breath washout measurements can be significantly shortened in children

Multiple-breath washout (MBW)-derived lung clearance index (LCI) is a sensitive measure of ventilation inhomogeneity in patients with cystic fibrosis (CF), but LCI measurement is time consuming. We systematically assessed ways to shorten LCI measurements.

In 68 school-aged children (44 with mild CF lung disease) three standard nitrogen (N<sub>2</sub>) MBWs were applied. We assessed repeatability and diagnostic performance of (1) LCI measured earlier from three MBW runs and (2) LCI measured at complete MBW (1/40th of starting N<sub>2</sub> concentration) from two runs only.

Compared with the standard LCI from three complete MBW runs, the new LCI based on three N<sub>2</sub>MBW runs until 1/20th, or two complete runs until 1/40th, provided similar or better repeatability as well as sensitivity and specificity for CF lung disease. Alternative ways to measure LCI reduced test duration in children with CF by 30% and 41%, respectively.

LCI measurements can be reliably shortened in children. These new MBW protocols may advance the transition of LCI from research into clinical settings.

Multiple-breath washout (MBW)-derived lung clearance index (LCI) is a sensitive measure of increased ventilation inhomogeneity in cystic fibrosis (CF) lung disease.<sup>1 2</sup> However LCI is rarely

measured routinely due to time-consuming protocols, that is, at least three MBW runs with tracer gas washout until 1/40th of its starting concentration.<sup>3</sup> In this prospective study, we systematically assessed ways to shorten LCI measurements in school-aged children with CF, and in healthy controls.

We used a previously described nitrogen (N<sub>2</sub>) MBW equipment (Exhalyzer D, Eco Medics AG, Switzerland)<sup>4</sup> and measured standard LCI (LCI<sub>std</sub>) in 80 children (50 with CF) aged 5.7–16.9 years. Alternative MBW outcomes were (1) mean LCI derived from empirically chosen earlier time points based on three MBW runs and (2) mean LCI from two complete runs. Quality criteria for alternative LCI were defined as (1) predictive value (R<sup>2</sup>) for LCI<sub>std</sub>>90%, (2) coefficient of variation (CV) ≤7% and (3) sensitivity and specificity for CF lung disease within ±3% of LCI<sub>std</sub> (detailed in the online supplementary (OLS)).

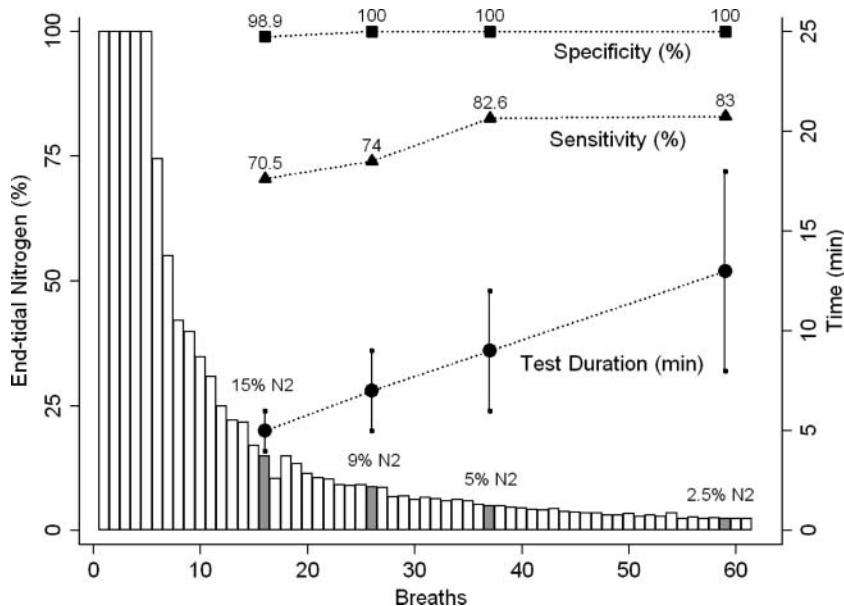
Technically acceptable triplicate N<sub>2</sub>MBW (n=204) were obtained in 68 (31 boys) children (44 with CF). N<sub>2</sub>MBW until 5% N<sub>2</sub> (LCI<sub>5</sub>), that is, 1/20th of N<sub>2</sub> starting concentration, was the earliest time point to meet all quality criteria (figure 1). LCI<sub>5</sub> predicted 93% of LCI<sub>std</sub> (table 1 and figure 1 OLS). CV of LCI<sub>5</sub> was 5.1%, and 5.4% for LCI<sub>std</sub> (table 2 OLS). LCI<sub>5</sub> and LCI<sub>std</sub> were both highly specific (100%), and provided a sensitivity of 82.6% and 83.0%, respectively, for CF lung disease (figure 1). Time savings were on average (95% CI) 3.7 (3.1–4.4) min. (30%) in CF. LCI from two complete runs also met the quality criteria and provided

significant time savings (table 3 and figure 2 OLS). Detailed results and figures are given in the OLS.

By convention, at least three MBW runs until 1/40th were recommended to measure LCI due to N<sub>2</sub> sensor characteristics, estimated N<sub>2</sub> blood gas exchange, and possibly due to lack of online quality control. We show that LCI measurements can be reliably shortened. Both new LCI measures may enhance feasibility and acceptance in younger children and in patients with more advanced lung disease. In children with predominantly mild CF lung disease, LCI based on two MBW runs seems attractive, as complete washout is usually achieved fast. This was confirmed in a retrospective study by Robinson *et al*<sup>5</sup> where LCI of two complete runs adequately identified increased ventilation inhomogeneity in CF. LCI<sub>5</sub> may be more applicable in advanced lung disease where complete N<sub>2</sub>MBW is time consuming. Further studies are needed to establish the applicability of shortened MBW for different populations and settings. Long-term repeatability and response to intervention need to be compared between shortened MBW protocols. Detailed discussion on methodological and physiological aspects are provided in the OLS.

Both new LCI measures based on three N<sub>2</sub>MBW runs until 1/20th, or two runs until 1/40th, significantly shorten MBW in children without compromising diagnostic performance for increased ventilation inhomogeneity in mild CF lung disease. These data support the transition of LCI measurement from research into clinical routine.

**Figure 1** Diagnostic performance and duration of nitrogen multiple-breath washout. A typical example of a nitrogen multiple-breath washout (N<sub>2</sub>MBW) curve in a boy with cystic fibrosis schematically illustrates the course of diagnostic accuracy and test duration for the lung clearance index (LCI) measured at various time points (grey bars). End-tidal N<sub>2</sub> concentration normalised to 100% (left y-axis) is plotted (white bars) against washout breaths (x-axis). By convention, N<sub>2</sub>MBW is performed until 1/40th (2.5% N<sub>2</sub>) of the N<sub>2</sub> starting concentration to measure LCI. We calculated LCI at arbitrary earlier time points: 15%, 9% and 5% N<sub>2</sub> (grey bars). Specificity (rectangles) and sensitivity (triangles) for CF lung disease increase over the washout. Mean±SD of test duration (right y-axis) are displayed as circles.



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