Curvilinearity provides additional information to lung clearance index only in a minority of children with early cystic fibrosis lung disease

To the Editor:

Advances in technology and international consensus guidelines [1] make multiple breath washout (MBW) testing feasible in many settings, particularly in cystic fibrosis (CF) centres, and in paediatrics, as many children and young people with respiratory disease may have normal spirometry [2].

The most commonly used MBW parameter is the lung clearance index (LCI) which is feasible over a wide age range [3], sensitive to early disease [2], abnormal in a range of conditions [4–7], and (in CF) it is correlated with changes on high-resolution computed tomography scans [8, 9]. LCI is often described as a measure of small airway function, it in fact gives information about disease in the large and small airways causing ventilation inhomogeneity.

Although the changes in LCI with disease makes it a useful test, it may be possible to obtain more specific information about unequal ventilation by using the additional MBW parameters. The fall in tracer gas concentration during MBW has a characteristic decay curve shape, with an increasingly more pronounced long "tail" in more obstructed patients, representing lung units with long time constants. There have been several methodologies presented for describing this, such as moment ratios and fast–slow compartment analysis [10, 11], including a conceptually simple analysis called curvilinearity (Curv).

This phenomenon was described experimentally [12, 13], and was termed "specific ventilation inhomogeneity" (SVI). Using lung model simulation, they showed SVI resulted when a fixed portion of the lung receives a decreasing proportion of ventilation, or an increasing portion of the lung receives fixed reduced ventilation. To calculate Curv, the slope of a log plot of the first half of the washout is compared with the slope of the second half, with increasing values representing an increasingly long "tail". A Curv of zero would be a homogenous single unit, a Curv of one would contain an infinitely slow emptying unit. Inequality of ventilation, which drives increased SVI, can be caused by reversible changes within the lung such as inflammation, and so in theory may represented some of the earliest signs of CF lung disease.

Although Curv was described in 2013, it is not routinely calculated from MBW traces in available commercial protocols. Commercial software follows the MBW protocols described by many investigators [2, 14–16] where the mean of two or three natural tidal breathing MBW tests are used to calculate indices. However, VERBANCK et al. [12, 13] used a protocol wherein subjects aimed for a fixed pre-specified tidal breath volume throughout the test, and then used software to average the MBW curve across the readings from multiple trials.

We hypothesised that Curv could be calculated from the mean of normal tidal breathing MBW tests similar to the commercial protocols, with results comparable to those of Verbanck and co-authors, and would provide additional information compared with LCI alone.

The methodology of calculating Curv from an MBW curve was outlined by VERBANCK et al. [12, 13] previously and can be calculated in commercial spreadsheeting software (*e.g.* Microsoft Excel) providing a breath-by-breath data table of the washout is available. In brief, the total LCI is calculated and halved, and the washout divided into two halves at this point on a log axis. The slopes of the two halves are then divided to give a ratio.
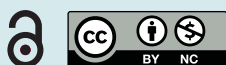
Shareable abstract (@ERSpublications)

Curvilinearity, as calculated from multiple-breath washout, is abnormal in a small number of children with cystic fibrosis when other tests are still normal https://bit.ly/3p9QAV4

We calculated Curv from MBW tests from 36 healthy controls and 78 children and young people with CF (median age 14.1 years, range 7.5–17.6 years), in whom LCI had been reported previously. We used a photoacoustic gas analyser and a sulfur hexafluoride (SF_6) washout protocol [7, 16]. We recorded forced expiratory volume in 1 s (FEV_1) z-score from routine clinic spirometry in the CF patients.

For healthy controls, the mean±SD Curv was 0.19±0.09, giving an upper limit of normal (ULN) of 0.37. Curv was significantly higher in CF (mean±SD 0.40±0.14, t-test p<0.0001), with 59 out of 78 patients (76%) having abnormal results. When the data were visually inspected, Curv and LCI were highly correlated in subjects with LCI <10. However, in patients with LCI >10 there was no correlation with Curv appearing to reach a plateau (see figure 1).

The CF cohort had a mean±SD FEV_1 z-score of −1.99±1.4 and a mean±SD LCI of 9.63±2.3. Nine patients had normal LCI, Curv and FEV_1 z-score. All remaining patients had at least one abnormal result (LCI abnormal in 57 out of 78 patients, Curv in 62 out of 78, and FEV_1 in 50 out of 78), and 41 patients had abnormal results for all three tests. Of the 62 patients with abnormal Curv, six had normal LCI and FEV_1, so Curv was able to pick up an additional 10% of patients with abnormal SVI, but normal LCI.

We concluded that Curv was feasible in tidal volume protocols giving similar mean values and ULN to that obtained previously [12, 13]. However, it only provided a small amount of additional clinical information in most patients with CF. It also plateaus at LCI values above 10, implying any utility for this measure is in milder disease. The mean Curv in our group of patients was lower than that in adults [10, 11], but it is not possible to say from this cross-sectional cohort whether this results from age differences or more extensive lung disease.

There are limitations to our study. In this historical cohort, spirometry results in the CF patients were relatively poor, and the relationships with MBW may be different in fitter patients, for example those now taking modulator therapies. Also, our conclusions are based on cross-sectional analysis rather than longitudinal data, and so we cannot rule out that there may be additional functionality to Curv as a long-term monitoring tool.

The data presented here are SF_6 washouts, whereas current commercial protocols favour nitrogen washout. Although this may limit the transferability of these findings, they will not be affected by the recent changes made to the protocol of the Exhalyzer D instrument [17], which would have affected measurements of both LCI and Curv on that system.

These tests were collected and originally analysed according to a standard operating protocol based on LCI calculation used by us and other authors previously [7, 16] and there is no previous literature as to acceptable variability in Curv. For this study we took a pragmatic approach of accepting tests that met the LCI acceptability criteria, and in which Curv did not vary by more than 20%. We acknowledge that this is a compromise, but it seems likely that LCI validity will remain the primary quality control measure for MBW and so we would support this 20% variability as a pragmatic starting point for further work on this measure.

Overall, Curv has limited additional clinical utility, but is abnormal in a small group of patients where LCI is still normal. It may be that Curv is more sensitive to extremely early airways disease, or that a particular pathology is associated with discrepant LCI and Curv results, but this needs prospective testing.
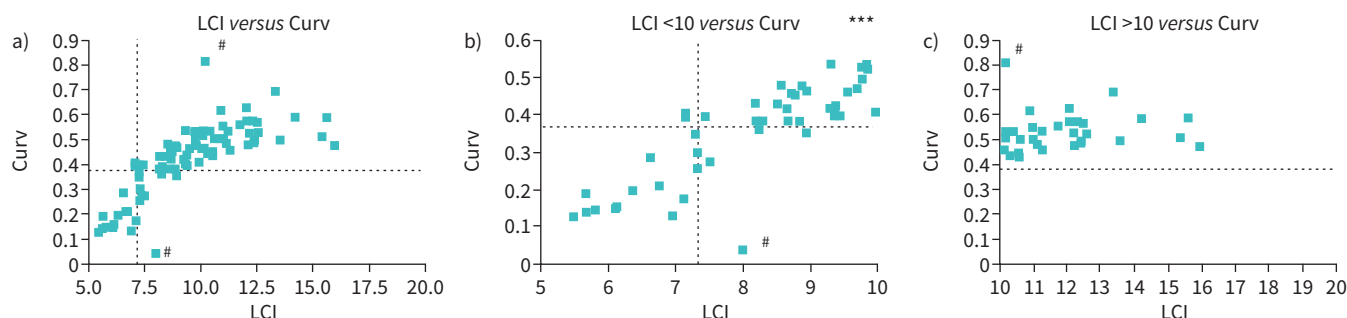

FIGURE 1 Curvilinearity (Curv) versus lung clearance index (LCI) in patients with cystic fibrosis. a) The overall result is not linear. b) The correlation between LCI and Curv in patients with mild changes (LCI<10 Pearson's r of 0.8, p<0.001). c) There is no correlation between LCI and Curv at higher LCI values. #: outliers, shown in both relevant panels. ***: p<0.001.

Most commercial software already calculates and plots the log concentration of tracer gas throughout the test, and Curv would be a relatively simple addition to these protocols. For this reason, even though this may only be of benefit to a small number of patients, we would urge manufacturers to consider this addition to the software, due to the increasing use of MBW in clinical testing.

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References

1 Robinson PD, Latzin P, Verbanck S, *et al.* Consensus statement for inert gas washout measurement using multiple- and single-breath tests. *Eur RespirJ* 2013; 41: 507–522.

2 Gustafsson PM, Aurora P, Lindblad A. Evaluation of ventilation maldistribution as an early indicator of lung disease in children with cystic fibrosis. *Eur Respir J* 2003; 22: 972–979

3 Lum S, Stocks J, Stanojevic S, *et al.* Age and height dependence of lung clearance index and functional residual capacity. *Eur RespirJ* 2013; 41: 1371–1377.

4 Driskel M, Horsley A, Fretwell L, *et al.* Lung clearance index in detection of post-transplant bronchiolitis obliterans syndrome. *ERJ Open Res* 2019; 5: 00164-2019.

5 Rowan SA, Bradley JM, Bradbury I, *et al.* Lung clearance index is a repeatable and sensitive indicator of radiological changes in bronchiectasis. *Am J Respir Crit Care Med* 2014; 189: 586–592.

6 Irving S, Fleming L, Ahmad F, *et al.* Lung clearance index and steroid response in pediatric severe asthma. *Pediatr Pulmonol* 2020; 55: 890–898.

7 Irving SJ, Ives A, Davies G, *et al.* Lung clearance index and high-resolution computed tomography scores in primary ciliary dyskinesia. *Am J Respir Crit Care Med* 2013; 188: 545–549.

8 Gustafsson PM, de Jong PA, Tiddens HA, *et al.* Multiple-breath inert gas washout and spirometry *versus* structural lung disease in cystic fibrosis. *Thorax* 2008; 63: 129–134.

9 Owens CM, Aurora P, Stanojevic S, *et al.* Lung clearance index and HRCT are complementary markers of lung abnormalities in young children with CF. *Thorax* 2011; 66: 481–488.

10 Gustafsson PM, Robinson PD, Gilljam M, *et al.* Slow and fast lung compartments in cystic fibrosis measured by nitrogen multiple-breath washout. *J Appl Physiol (1985)* 2014; 117: 720–729.

11 Robinson PD, Goldman MD, Gustafsson PM. Inert gas washout: theoretical background and clinical utility in respiratory disease. *Respiration* 2009; 78: 339–355.

12 Verbanck S, Paiva M, Paeps E, *et al.* Lung clearance index in adult cystic fibrosis patients: the role of convection-dependent lung units. *Eur Respir J* 2013; 42: 380–388.

13 Verbanck S, Paiva M, Schuermans D, *et al.* Acinar and conductive ventilation heterogeneity in severe CF lung disease: back to the model. *Respir Physiol Neurobiol* 2013; 188: 124–132.

14 Robinson PD, Stocks J, Aurora P, *et al.* Abbreviated multi-breath washout for calculation of lung clearance index. *Pediatr Pulmonol* 2013; 48: 336–343.

15 Aurora P, Kozlowska W, Stocks J. Gas mixing efficiency from birth to adulthood measured by multiple-breath washout. *Respir Physiol Neurobiol* 2005; 148: 125–139.

16 Horsley AR, Gustafsson PM, Macleod KA, *et al.* Lung clearance index is a sensitive, repeatable and practical measure of airways disease in adults with cystic fibrosis. *Thorax* 2008; 63: 135–140.

17 Wyler F, Oestreich MA, Frauchiger BS, *et al.* Correction of sensor crosstalk error in Exhalyzer D multiple-breath washout device significantly impacts outcomes in children with cystic fibrosis. *J Appl Physiol (1985)* 2021; 131: 1148–1156.