

Multiple-breath inert gas washout test and early cystic fibrosis lung disease

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An ideal lung function test should be easy to obtain, and involve no risk to the subject. In order to be of value, it should be able to help diagnosis, assist prognosis, monitor disease progress or measure the effect of therapeutic interventions.¹

Regular spirometry measurement is an accepted component of clinical monitoring of adults and school-age children with cystic fibrosis (CF). Specifically, the forced expired volume in 1 s (FEV₁), or its rate of decline, is commonly used to monitor disease progression in individuals, and as an outcome measure in clinical trials. However, as the survival of subjects with CF improves,² there has been a shift towards closer monitoring and more aggressive treatment of early CF lung disease.³ As a consequence, two major disadvantages to the use of FEV₁ in early CF lung disease have become apparent. Many school-age children with CF now have FEV₁ within the normal range, even though they probably have lung disease.³ Also, reliable forced expiratory manoeuvres are difficult to obtain in children under the age of 5 years, with testing in infants being largely confined to specialist laboratories,⁴ and testing in preschool children relatively novel.⁵

There are good theoretical reasons why spirometry may be insensitive to early CF lung disease. First, airway disease in CF is known to be non-uniformly distributed. As flow measured during forced expiration is the integrated output of all airways,⁶ then it is possible that minor alterations of airway calibre in some lung regions may be masked by normal function in other regions. Secondly, airway obstruction in CF is partly due to intraluminal mucus, and this may be dislodged by a forced expiratory manoeuvre. Thirdly, spirometry is insensitive to changes in the peripheral airways, as the large total cross-sectional area in the lung periphery prevents flow limitation in this region,⁷ even in the presence of disease.

For the researcher, the relative insensitivity of FEV₁ in mild disease mandates ever larger sample sizes to demonstrate significant benefit in intervention studies. This is particularly challenging for interventions aimed at subjects with very early or mild disease, where baseline FEV₁ will be within the normal range (ie, within two standard deviations of the mean of the non-CF population). For the clinician, the decision to increase or reduce treatment in subjects with mild disease may need to rely on symptoms and microbiology, as spirometry results may remain normal.

The two most commonly cited alternative measures are high resolution CT (HRCT) scans and measures of ventilation distribution from multiple-breath inert gas washout (MBW) tests. The potential utility of HRCT as an outcome measure has been discussed extensively,⁸ and there has been important progress in standardising data acquisition and scoring systems for interpretation of these studies.⁹ However, the main limitation of HRCT as an outcome measure is the risk of radiation exposure, which limits the number of scans that can be performed each year.¹⁰

MBW describes the analysis of changes in exhaled tracer gas concentration over a series of tidal expirations. This can be performed using resident N₂ as the marker gas, or alternatively an inhaled marker gas can be employed. In the former case, washout is performed with 100% oxygen, which can be provided via a bias flow or demand valve. In the latter case it is first necessary to 'wash-in' a tracer gas.⁵ Washout can then be performed with air. The most straightforward method for analysing an MBW is to study the progression of the end-tidal marker gas concentration, plotted against either time, breath number or an index of cumulative expired volume. From the last of these plots, it is possible to calculate the lung clearance index (LCI)⁵ which is the cumulative expired volume required to clear this inert gas from the lungs to 1/40th of the starting concentration, divided by the functional residual capacity (FRC).

An increase in LCI indicates inhomogeneity of ventilation distribution, or inefficient gas mixing, and this index is therefore predicted to rise in the presence of mild CF lung disease.

The potential value of LCI as an outcome measure is supported by a series of cross-sectional studies, which have demonstrated that children and adults with CF have an abnormal LCI even in the presence of a normal FEV₁.^{11–13} There is moderate to strong correlation between LCI and the modified Brody score obtained from HRCT, with two studies suggesting that these two measures detect abnormalities in adults and children with similar frequency.^{14 15}

In order to determine whether LCI can genuinely function as a marker for early disease, it is also necessary to demonstrate that the outcome improves in response to recognised treatments, and that it corresponds to more established markers on long-term follow-up. The one longitudinal study reported to date was based on clinically collected data, and suggested that LCI becomes abnormal earlier than FEV₁.¹⁶ Two studies have demonstrated that LCI in subjects with established disease responds variably to a course of intravenous antibiotics.^{17 18} The flaw of both of these studies is that the subjects had established lung disease, and it is possible that ventilation inhomogeneity may increase rather than decrease following treatment in subjects with established bronchiectasis, if airways that were previously completely obstructed are partly opened by treatment. This may explain why most subjects in these studies showed some improvement in LCI following treatment, but a minority showed deterioration.

In this issue of *Thorax* (see page 379) Amin and colleagues report a study in which 20 children with CF who had FEV₁ ≥ 80% predicted were given hypertonic or isotonic saline in a 4 week crossover trial, separated by a 4 week washout.¹⁹ In addition to LCI, the investigators recorded FEV₁ and the CF Questionnaire-Revised (CFQ-R) as primary outcomes. Baseline characteristics including the LCI were not significantly different between study periods. Four weeks of twice-daily inhalation of hypertonic saline resulted in a significant decrease (improvement) in LCI versus isotonic saline, whilst there was no significant change in FEV₁ or CFQ-R. The authors point out that the absolute increase in FEV₁ recorded following 4 weeks of hypertonic saline was 62 ml, which is similar to that reported from the positive trial of Elkins *et al*, but that in this case a relatively small sample size produced a *p* value > 0.05.

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This will be recognised as a landmark study, as it is the first to demonstrate a clear improvement in LCI in response to a recognised CF treatment in a population with normal spirometry results. The study is well designed and, in addition, the mass spectrometer-based sulfur hexafluoride (SF₆) MBW hardware and software is identical to that employed in numerous previous studies, and consistent with recent taskforce recommendations for this technique.⁵ The researchers could be criticised for not employing a control group, and also for not paying sufficient attention to the baseline variability of their outcome measures when interpreting the effect of their intervention; however, both are minor criticisms.

There are still challenges ahead for researchers intending to utilise LCI as an outcome measure in early CF. Long-term prospective longitudinal studies tracking LCI from infancy into adulthood are required, but data collection for such studies is inevitably lengthy and complex. Ultimately it will be necessary to demonstrate that children with CF managed with regular LCI monitoring have better outcomes than peers monitored by more conventional methods. In parallel, clinicians will expect that manufacturers develop MBW systems that are cheaper and more robust than the current home-built systems, and validated to the same standards. This author is not aware of any commercially available system that currently meets these standards, but it is possible to report two developments. One is a system built around a modified photo-acoustic gas analyser and employed by the UK gene therapy consortium.¹³ The second is a modified ultrasonic flowmeter

system developed by a German group, and currently employed in a German multicentre trial.^{20, 21} Both have been validated against the mass spectrometer system developed by Gustafsson *et al*,¹² and show great promise, at least for LCI measurement in preschool children and above. At present the researchers' modifications have not been commercialised by the manufacturers, but there is potential for the future.

Competing interests None.

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Effects of steroid therapy on inflammatory cell subtypes in asthma

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Asthma is a chronic condition that usually develops after environmental exposures in

genetically predisposed individuals.¹ It is considered an inflammatory disease leading to airway structural changes (remodelling), both of these processes being involved in the development of airway hyper-responsiveness (AHR) and variable airway obstruction.² When inflammation and

remodelling increase to a sufficient degree, symptomatic asthma occurs.³

Although asthma has been recognised for a very long time as a heterogeneous condition, recent efforts have been devoted to better characterising its various phenotypes.⁴ The term 'phenotype' refers to 'a set of observable characteristics of an individual or group resulting from the interaction of its genotype with its environment'. Although these phenotypes may overlap or possibly vary over time, their characterisation may help to identify the predominant mechanisms involved and specific patterns of clinical presentation, predict clinical outcomes and may guide treatment. There is still, however, a lack of data in this field.

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