# Wavering in the breeze: is multiple breath washout useful in primary ciliary dyskinesia?

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It has long been known that first second forced expired volume ($FEV_1$) is insensitive both to distal airway disease and also structural lung disease as measured by high-resolution CT (HRCT).[1] Furthermore, monitoring airway diseases has become harder as successful therapies have limited the rate of deterioration, making change in $FEV_1$ less and less useful in clinical practice and as an endpoint in randomised controlled trials. Accordingly, we have had to deploy novel measures (or in the case of multiple breath washout (MBW), rediscovered old techniques). The use of MBW to calculate lung clearance index (LCI) and calculate other, more sophisticated phase 111 analyses has taken off in the last decade or so. The most salient data have come from cystic fibrosis (CF). LCI has been shown in cross-sectional studies to be abnormal more often than spirometry or plethysmography;[2 3] in longitudinal studies, LCI becomes abnormal before these other measures;[4] it predicts future lung function[5] and CF lung attacks;[6] it is sensitive to interventions such as treatment of a CF lung attack with intravenous antibiotics;[7] and has been used as an endpoint in randomised controlled trials,[8–10] particularly in children in whom spirometry is normal or nearly normal.[11] Cross-sectional comparisons with HRCT have shown that LCI is very sensitive to structural airway wall disease[12 13] and can reduce the number of HRCT scans in the CF clinic. Furthermore, the normal values of LCI flat line throughout life, other than slight rises in the very young[14] and the elderly.[15] LCI clearly has limitations—there is no signal from areas of the lung that are unventilated or ventilated with a very long time constant; so tying off the left main bronchus will halve functional residual capacity, but LCI will remain normal. Notwithstanding this, LCI is clearly and rightly here to stay, but new developments need us to pause for thought.

The first is the inevitable changes in methods. The early studies were done using wash in of an inert gas, usually sulfur hexafluoride ($SF_6$), with the gas analyser being a mass spectrometer. However, the use of $SF_6$ is increasingly problematic; it is a green house gas, and use is increasingly being restricted, so newer devices use old-fashioned nitrogen ($N_2$) washout. The two cannot be considered equivalent; first, $N_2$ is resident in the alveolar space and does not have to be washed in, unlike $SF_6$. This may mean that $N_2$ and $SF_6$ LCI signals come from differing areas of the lung. The diffusivities are different, and there is some tissue $N_2$ production. Finally, inhaling 100% oxygen has at least the potential to alter baseline physiology. The next issue is equipment; a new generation of analysers have become available, and it is by no means clear that they are adequate for the job, particularly in small children, whose low tidal volumes and rapid respiratory rates mandate the use of analysers with a fast response time. Unfortunately, it has never been easier to buy a piece of kit off the shelf or at a conference and use it to generate numbers that may be devoid of meaning. The disciplines of conventional physiological measurements must be respected, but often are not.

The next development has been the application of MBW to other airway diseases. Two manuscripts served as a rude awakening. Green *et al*[16] reported on 27 children and adolescents with primary ciliary dyskinesia (PCD) and showed that LCI measured using $SF_6$ and an AMIS 2000 mass spectrometer (Innovision, Odense, Denmark) was frequently abnormal when $FEV_1$ was normal, but inspection of their raw data revealed patients with PCD with normal or near-normal LCI and very abnormal $FEV_1$, rather different from CF. The authors relied on Swedish normal data for MBW, an acknowledged weakness of the manuscript. Irving *et al*,[17] using $SF_6$ and a photoacoustic analyser (Innocor, Odense, Denmark), compared the relationships between MBW, spirometry and HRCT in PCD (n=33) and CF (n=127). The expected relationships were seen in CF, a useful positive control, but by contrast, in PCD, LCI did not correlate with either spirometry or HRCT, and appeared not to be a particularly sensitive marker of airway disease. However, in adult non-CF, non-PCD bronchiectasis, LCI did appear to be sensitive,[18 19] as in CF; and the speculation was that there was something different about primary ciliary dysfunction as against diseases like CF and idiopathic bronchiectasis that are characterised by secondary disease. All nice and tidy, story done and dusted, right?

In this issue of *Thorax*, a third PCD manuscript appears,[20] which draws very different conclusions! Boon *et al* studied 38 children and young adults with PCD, as well as 70 age-matched healthy controls, performing MBW using $N_2$ washout and an Exhalyzer D (Ecomedics, Duernten, Switzerland). They found no patients with a normal LCI and abnormal $FEV_1$, and also showed correlations between HRCT scores and LCI. They carefully rehearse possible reasons for the discrepant results, including measurement differences, different HRCT scoring systems and patient severity; they certainly have a more mildly affected group than reported in the other papers. The purist might object to the describing of p=0.083 as 'marginally non-significant'—is my girlfriend marginally pregnant? Power could certainly be an issue, but all three studies were of similar size, and in particular since both this study and Irving *et al* showed consistent although opposite relationships between MBW and spirometry, as well as HRCT, it seems likely that both findings are accurate; indeed, investigator incompetence seems a highly unlikely cause of these discrepant results. Nonetheless, the fact that the carefully done manuscript by Boon *et al* finds a tight relationship between $FEV_1$ and LCI in PCD, whereas two others, equally careful, do not warrants careful thought.

This being the case, what does it mean for LCI and PCD, and indeed MBW in general? What is the way forward, given there is a big need for randomised controlled trials of treatment in PCD, and $FEV_1$ is unlikely to be a suitable outcome, whereas the simplicity of MBW is very attractive. The one thing we do *not* need is a combination of these studies in a meta-analysis; this is not so much combining apples and pears as apples and soda water. The dilemma could be resolved by performing LCI using both $N_2$ washout and $SF_6$ in the same patients with CF and PCD, encompassing a range of severities, and relating the results to spirometry and HRCT. In the meantime, lessons should be learned from these discrepant results before MBW is uncritically applied to all airway diseases of all severities.

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The first general fundamental physiological point applying to all studies is to be sure that your equipment is fit for purpose from first-hand knowledge, not relying on the manufacturers. Careful and regular calibration is mandatory, as is the ability to produce high-quality traces and values in normals consistent with the work of others. Equipment that is perfectly adequate for a teenager may fall woefully short in a 2 year old. What these three studies have highlighted is that results with one MBW technique in a group of patients of particular severity cannot uncritically be translated into another setting with different equipment and a different patient group, even with the same specific disease. Further physiological work is needed to sort out the reasons for the current confusing discrepancies; but until that is done, those who are designing PCD studies would do well to pilot MBW with their proposed equipment in patients with comparable disease severity as those going into the planned trial. One way of doing this would be to look at sensitivity to detect improvement in response to intravenous antibiotics for a PCD lung attack.[7] Whatever the explanation for the discrepant findings discussed here, Boon *et al* have done us a great service in their carefully performed and scholarly study by highlighting the extreme potential dangers of uncritical minds using sophisticated, but deceptively easy to use, physiological tools.

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