Editorial Comment

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Validation of Multiple-Breath Washout Equipment: From Bench to Clinic and Possible Pitfalls

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In recent years, there has been a renaissance of studies using multiple-breath washout (MBW) tests in different populations with varying lung diseases. To date, measures obtained from the MBW have followed two parallel paths. First, the lung clearance index (LCI) has been shown to be a sensitive marker of cystic fibrosis and applicable in routine clinical practice or as study outcome in a predominantly paediatric population [1–6]. Other outcomes, such as the slope of phase III parameters (S_{acin} and S_{cond}), have been found to predict disease course in asthmatic patients [7–10] and other respiratory conditions, but predominantly in adult populations [11–13].

An important outcome of this renaissance is the recently published ERS/ATS consensus statement on inert gas washout tests [14]. This document gives an overview on existing techniques, practical suggestions with regard to the measurement itself and clear advice for validating new equipment. Importantly, it highlights the need for further characterization and validation work with regard to the test procedure, equipment and analysis methods. This cannot be emphasized enough, as comparable validation studies were never done for basic tests that are much more widely used, such as spirometry, body plethysmography or $T_{L}CO$. Before results of MBW can be compared between centres or even multi-centre trials can be performed, these kinds of validation studies are extremely important to guarantee comparability and identify sources of errors.

In this regard, Gonem et al. [15] are to be congratulated for the thorough validation study of the Innocor system published in this issue of *Respiration*. The authors do not hesitate to report openly the current drawbacks of the equipment and nicely show that functional residual capacity (FRC) underestimation at low lung volumes will result in a very relevant overestimation of LCI at those low lung volumes [15]. These results are surprising as they oppose the previous assumption that LCI might be more robust to measurement errors compared to FRC, as LCI is a ratio of lung volumes and possible measurement errors might cancel out. This is not the case, and the measured overestimation in LCI is clinically important. Moreover, this type of error may be problematic when using the same equipment in patients with a wide age range, leading to incorrect physiological conclusions based on possible technical issues [16, 17].

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Despite some speculation in the discussion section, it remains unclear whether the error in FRC measurement is due to hardware settings or software algorithms. Besides the points mentioned by the authors, such as nonlinearity of flow/volume measurements, other possible sources of error are (i) the exact method of measurement and subtraction of re-inspired sulphur hexafluoride; (ii) the flow gas delay (delay between the point where the volume and the gas concentration is measured), and (iii) the way of handling different rise times of analysers. It is interesting to note that a similar but less pronounced FRC measurement bias was observed in a preliminary study based on mass-spectrometric technology (AMIS 2000, Innovision) [18]. In the latter study, the same lung model, a flow metre, tracer gas (sulphur hexafluoride) and software package were used. In contrast, other MBW devices were less prone to FRC bias using the same lung models but different hardware set-ups and software packages [19, 20].

The influence of these sources of error on the final results is of course specific to each set-up. It will also differ for the different gases used, e.g. gas viscosity will influence flow gas delay [21]. From the results of the paper, it is also clear that the younger the patient (and the lower tidal volumes and residual volumes), the larger the influence of the above-mentioned points on the final results. Importantly, the relative effect of each source of error will be different depending on the MBW outcome. If for example slope analysis (S_{cond} and S_{acin}) is performed (during expiration), flow gas delay should be ideally determined during expiration. If, however, LCI is calculated, flow gas delay during inspiration seems more important (to correctly measure re-inspired gas). Furthermore, response time of the analysers is critically important for S_{acin} and S_{cond}, however, less of a problem for LCI.

Other areas of the MBW, such as the breathing manoeuvre itself, require further work. Most validation studies have used constant tidal volumes. While this seems valid for adult patients, children breathe not only at lower tidal volumes but also with more variability than adults, with clear implications on MBW outcomes [22]. Whether this variable breathing needs to be implemented in future validation studies currently remains unclear. A lung simulator with built-in ventilation heterogeneity that can produce an alveolar plateau and a decay curve leading to a constant LCI and S_{cond} has not been created to date. Whether it is possible to create such a device is unclear; however, it would be incredibly useful in the validation of MBW tests.

Taken together, the increasing number of validation studies of different MBW devices and for different age and disease groups [19, 20, 23] clearly shows that we are moving in the right direction. The current study of Gonem et al. [15] is in this regard a very nice piece of work as the authors openly report limitations of the device and estimate their implications on outcome measures.

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