Double tracer gas single-breath washout: promising for clinics or just a toy for research?

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Double tracer gas single-breath washout is a promising test to assess ventilation inhomogeneity in the lung periphery http://ow.ly/zW41z

Ventilation inhomogeneity reflects the efficiency of gas transport in both central, convection-dependent and peripheral, diffusion-dependent airways. In recent years, there has been a renaissance of studies using inert-gas washout to assess ventilation inhomogeneity. This trend is due to promising results of multiple-breath washout (MBW) tests in different populations with various lung diseases, such as cystic fibrosis [1] and asthma [2]. Even though the MBW is becoming more widely used and better standardised, the long duration of the test is a potential impediment in daily clinical practice and in patients with severe lung disease. One alternative is to study the ventilation distribution based on one single breath, by performing the so-called single-breath washout (SBW). The SBW test is not new, having been done for the first time more than 60 years ago, by using 100% oxygen to study the washout of the resident nitrogen (N_2) [3], or by using a double tracer gas (DTG) mixture, such as helium (He) and sulfur hexafluoride (SF_6) [4]. Usually the SBW test is done during a vital capacity manoeuvre (VC-SBW) and there is a recent European Respiratory Society/American Thoracic Society consensus statement on how to perform the VC-SBW test [5]. A clear disadvantage of the VC-SBW test is the dependence on the vital capacity manoeuvre. This is particularly a problem in children younger than 12 years and, in general, results might be influenced by restricted ability of patients performing the manoeuvre [5]. Furthermore, it has been shown that deep inspiration influences expiratory slopes [6, 7]. In addition, analysis of SF_6 and He needs a mass spectrometer, which is not practical for clinical use.

These drawbacks are overcome by a recently developed SBW test that is performed during tidal breathing and uses a DTG mixture of He and SF_6 to assess ventilation inhomogeneity without the need for a mass spectrometer. The test was validated using a commercially available piece of equipment [8], and promising results with regards to differences between children with cystic fibrosis and mild asthma and healthy controls have been found [9, 10]. The test is based on unequal distribution of the two tracer gases due to their different diffusion properties. The main outcome, phase III slope (SIII), is based on the molar mass of both gases and is thought to reflect more peripheral ventilation inhomogeneity, as the DTG mixture presumably does not separate during bulk flow in convective large airways but separates into He and SF_6 in diffusion-dependent peripheral airways [11].

In this issue of the *European Respiratory Journal*, Husemann *et al.* [12] report on the variability and reproducibility of this DTG-SBW technology in healthy adult subjects and patients with chronic obstructive pulmonary disease (COPD). Not only is this the first study applying this new tidal test in adult patients, it is

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also the first to show differences in test outcomes between COPD and controls. In addition to studying DTG-SBW, the authors assessed the repeatability of different MBW outcomes, such as lung clearance index (LCI), *S*cond and *S*acin [12]. *S*cond and *S*acin are derived from the SIII from MBW, and have been found to distinguish between conductive (*S*cond) and acinar (*S*acin) ventilation inhomogeneity. In accordance with the pathophysiological background, the authors report an association of *S*acin with DTG-SBW outcomes, both of which are thought to reflect more peripheral ventilation inhomogeneity.

The study has been performed thoroughly and the authors present all results, associations of outcome parameters with breathing pattern, and possible drawbacks of the current setup, in a detailed way. Interestingly, they find an association between results of SIII from the DTG-SBW and transfer factor of the lung for carbon monoxide. This indicates the new DTG-SBW test might be useful to also assess emphysematous lung regions, as it has been shown before for the VC-SBW [3]. This adds to the existing evidence suggesting that both SBW of different gases and *S*acin from MBW have the ability to discriminate emphysema from normal subjects, and bronchiolitis obliterans syndrome in lung transplant recipients [4, 13–15]. These patient groups further demonstrate the usefulness of the inert gas washout test beyond cystic fibrosis and asthma [16–18]. Despite those promising results, it is unclear how the new test fits in exactly with current measurements of ventilatory heterogeneity. Furthermore, it is still unclear exactly what type of ventilatory heterogeneity (convection-dependent inhomogeneity or diffusion–convection-dependent heterogeneity) the test is measuring. One clear advantage of the test is the better repeatability compared with those specific markers (*S*cond and *S*acin) from MBW as shown by HUSEMANN *et al.* [12], which is a bit surprising given the amount of breaths used to calculate *S*cond. Another advantage over MBW is the short duration. Despite approaches to shorten MBW tests [19], a test of a single breath will always be shorter than a test involving multiple breaths. Most impressive, however, is how well the results resemble data from VC-SBW using mass spectrometry [20], although in the current study, an aggregated molar mass signal was measured and the test was performed during free tidal breathing.

There are some theoretical and methodological issues of this new DTG-SBW test that currently preclude it being used for clinical decision making. These include 1) the exact dependence on the underlying breathing pattern. The authors suggest that factors other than breathing pattern influence results; however, this has been studied cross-sectionally only and never been assessed systematically for this test. Studies using VC-SBW indicate that this might even be different for children and adults [21]. 2) The exact underlying anatomical changes remain unclear. Despite preliminary results using VC-SBW showing associations [22], more studies examining the association with measures of lung structure or imaging are needed. 3) Some technical issues need to be resolved, as pointed out by the authors with regards to, for example, spikes at beginning of inspiration of the test gas. This also includes the availability of commercial software for analysis. 4) The exact contribution of N_2 to the overall signal is not understood. Strictly speaking, the DTG-SBW procedure contains a partial washout of lung inherent nitrogen while the dual-tracer gas mixture is in- and exhaled. As molar mass measures only the sum of all gases, theoretically, the N_2 fraction may also influence results.

Overall, the article by HUSEMANN *et al.* [12] underlines that the DTG-SBW is a promising new test to assess ventilation inhomogeneity in the lung periphery. Whether it will find its way into clinics or is just another tool for researchers is unknown. In any case, its easy and fast application, and widespread availability, make it attractive and will help to gather more data quickly in order to answer this in the future. There are now more than 10 measures of ventilation heterogeneity derived by either SBW or MBW tests. LCI, *S*cond and *S*acin have, at this stage, led the race as validated and clinically useful tests; however, new measures, such as DTG-SBW and others, have yet to find their place in the clinic. These measures may indeed be demonstrated to be more reliable, practical measures of ventilation heterogeneity. However, we cannot lose sight of the fact that the physiological outcome that we are trying to measure is ventilation heterogeneity. Ventilation heterogeneity can mean many things depending on the test that we use (*e.g.* nuclear medicine scans) [23]. Measures of specific ventilation, convection-dependent and diffusion–convection-dependent heterogeneity have shown to be highly clinically relevant. The test that measures these physiological abnormalities with the greatest accuracy, precision and ease for the patient will be the one quite rightly adopted in the clinic.

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