Commentaries on Viewpoint: Using the same cut-off for sulfur hexafluoride and nitrogen multiple-breath washout may not be appropriate

A COMPARISON BETWEEN NITROGEN AND SULFUR HEXAFLUORIDE DURING MULTIPLE-BREATH WASHOUT

TO THE EDITOR: Multiple-breath washout (MBW) is commonly used in the diagnosis and monitoring of cystic fibrosis (CF) lung disease and other lung diseases (4, 5). Nitrogen (N2) and sulfur hexafluoride (SF6) are tracer gases frequently utilized in MBW and the same 2.5% cut-off concentration point is used for both gases (5). Yammine et al. (5) provide interesting evidence showing that MBW measurements using the same cut-off point for N2 and SF6 are not comparable to one another.

Lung clearance index (LCI) and functional residual capacity (FRC), indicators of lung function, have been often assessed via SF6-MBW (5). However, N2-MBW presents an alternative that is interchangeable. For example, small amounts of endogenous N2 are released from surrounding tissues markedly affecting LCI measurements (1). N2 also has a smaller molar mass than SF6 providing N2 a higher diffusion rate (1). A study by Jensen et al. (2), which also compared SF6- and N2-MBW, revealed that N2-MBW may more accurately reflect the degree of damage in peripheral airways due to SF6 not entering into poorly ventilated lung units.

In our view, evidence has shown MBW to effectively assess CF. Because MBW requires minimal patient effort (3), it is applicable in all age groups. Nevertheless, further studies are needed to evaluate the sensitivity, feasibility, and comparability of MBW using each tracer gas, as well as consistent guidelines for test analysis and instrument specifications (5).

REFERENCES


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COMMENTARY ON VIEWPOINT: USING THE SAME CUT-OFF FOR SULFUR HEXAFLUORIDE AND NITROGEN MULTIPLE-BREATH WASHOUT MAY NOT BE APPROPRIATE

TO THE EDITOR: Yammine et al. (4) show that tissue nitrogen excretion affects the breath number to achieve the 2.5% cut-off during nitrogen-based multiple breath washout (N2-MBW) and thus the calculation of the lung clearance index (LCI). However, the mathematical model used to account for the contribution of effects of excreted nitrogen on progression of a multiple breath nitrogen washout. Although this adjustment achieves the authors’ goals of harmonizing their results with those from other methodologies, because they recognize this is probably an over-simplification. Relative contribution of excreted nitrogen is far greater at the end of washout, where it may contribute 20% of the measure N2 signal (2). This correction of the washout signal is primarily mathematical rather than physiological and would rightly be heavily criticized were it applied in reverse to an alternative inert gas during washout.

More importantly, the issues identified may be due less to the use of nitrogen as a tracer gas and more to do with the specific apparatus used, which is highly sensitive to inaccuracies in alignment of the three separate signals (4). In patients, this has already been shown to produce much higher FRC and LCI than SF6 washout using a mass spectrometer (1) or an Innocor analyzer, and in our own practice produces prolonged washouts with much higher FRC even than plethysmography. A recent report comparing it to an alternative nitrogen washout system showed very poor agreement in LCI and FRC (3). Because it appears to be the outlier in all these systems, the error may lie internally and may have much less to do with excreted nitrogen or the effects of 100% O2 on lung physiology.

REFERENCES

Letters to the Editor

1514

The tissue nitrogen does not provide an accurate estimate of the effect size. The tissue nitrogen component also impacts the calculation of FRC, which increases as the washout proceeds and more tissue nitrogen contributes to the measurement. What remains to be addressed is whether this tissue nitrogen contribution can be adequately quantified and corrected for, which is challenging considering its distribution likely changes over the course of the washout as well as with disease state (2, 3).

In addition, agreement between systems using distinct tracer gases is affected by the different algorithms used to calculate gas concentrations (which in the case of nitrogen are not measured directly) and differences in gas properties affecting diffusibility into poorly ventilated areas. Nonresident tracer gases such as sulfur hexafluoride (SF6) require a wash-in phase; therefore an incomplete wash-in will result in a smaller calculated FRC as observed in our previous studies comparing SF6 and N2 FRC to that measured by body plethysmography (1). On the positive side, it has been shown that both N2 and SF6-based MBW measurements can differentiate health and disease and detect treatment effects; thus the ultimate question is whether any correction for tissue nitrogen will improve the precision of N2-MBW outcomes and their clinical research utility.

REFERENCES


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COMMENTARY ON VIEWPOINT: USING THE SAME CUT-OFF FOR SULFUR HEXAFLUORIDE AND NITROGEN MULTIPLE-BREATH WASHOUT MAY NOT BE APPROPRIATE

TO THE EDITOR: Measures of ventilation heterogeneity using multiple breath washout has arrived at the doorstep of clinical respiratory medicine. We now have standards documents (2), prediction equations (4), and numerous papers (3) describing the clinical utility of the test for it to now go “live.” Despite our enthusiasm for the test, there are still theoretical and methodological sticking points that need to be clarified. Yammine et al. (5) recently published one such point—the choice of inert gas. The literature has been careless on this point, where, in some cases the choice of gas has not been fully acknowledged and reasoned. The choice of gas has a significant impact on the various measures of ventilation heterogeneity and the standards document goes to some length in addressing the issue. Yammine et al. suggest tackling the issue by providing a mathematical correction based on theoretical modelling to generate cut-offs for each gas. However, such a process will only be as good as the accuracy of the physiological assumptions applied to the model. For the mathematical model to be tested, specific reference equations and relevant clinical studies in a range of clinical conditions would need to be done using both tracer gases. As mentioned in a recent editorial in another journal (1), we can never lose sight that the physiological outcome that we are trying to measure is ventilation heterogeneity. The indices and methodology that measure ventilation heterogeneity with the greatest accuracy, precision, and ease of use will be the one adopted in the clinic.

REFERENCES


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