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Effect of intermittent inspiratory leaks on measurement of lung clearance index using nitrogen and sulfur hexafluoride

To the Editor:

Leaks during inert gas washout are a major potential source of measurement error in multiple-breath washout (MBW) testing. Visible leaks require exclusion of the whole test repeat [1], whilst undetected leaks may lead to significant errors in estimation of washout indices such as lung clearance index (LCI) and functional residual capacity (FRC) [2]. A recent study attempted to assess the impact on FRC and LCI of leaks of varying magnitude and type using clinically generated data modified to replicate the impact of leaks [2]. This approach is limited by the source data and the assumption that all leaked gas is mixed evenly. The authors, however, showed that the impact of expiratory leaks during nitrogen (N_2) MBW was dependent on their size, duration and the point at which they occurred in washout. In contrast, inspiratory leaks invariably led to substantial increases in both FRC and LCI as a result of the introduction of fresh tracer gas into the lungs (room air, containing 80% N_2). The size of leaks being modelled, however, was substantial (10–50% of tidal volume) and at a level that it is hoped should be visible during testing. Smaller leaks may well be common but may not be visible, yet in the case of N_2 washout, may still cause significant inaccuracy in washout indices. Given the recognised differences in sulfur hexafluoride (SF_6) and N_2 washouts, we were interested to discover what level of inspiratory leak would have negligible impact on LCI_{N_2} and to compare this to LCI_{SF_6}, where small leaks of inspired air do not introduce new tracer gas into the lungs. In order to do this, we have used a recently described mathematical lung model of wash-in–washout that allows a more detailed interpretation of leak impact in situations of minimal leak.

A previously developed computer simulation of gas ventilation and transport in the airway tree was used to model MBW (model M in [3]). To simulate bronchoconstriction, we applied constrictions (80% reduction in diameter) to 0%, 10% and 20% of the small airways (those originally between 1 and 2.5 mm in diameter) in the network model. Constricted airways were selected uniformly at random once for each case (10% and 20%), and that airway tree generated was then used to simulate MBW for every combination of leak fraction and start time.

A leak was simulated by modifying the measured flow rate by a factor of (1−LeakFrac) for leak fractions up to 10%. We modelled pre-capillary leaks that lasted for three breaths only (applied to both inspiration and expiration) and these were introduced at the start of inspiration at a given point in washout in each simulation. For N_2 leaks, an inert gas concentration of LeakFrac×c_0 (where c_0 is the starting concentration, which for N_2 is equivalent to its concentration in air) was introduced for the mouth boundary condition on inspiration to account for N_2 inhaled from the room air.

LCI was calculated as the interpolated number of lung turnovers to reach an end-tidal concentration of $c_{et}=0.025c_0$. Physiological parameters of the model were FRC 3 L, tidal volume 1 L, airway dead space 0.12 L and upper-airway dead space 0.05 L.

The baseline model predictions were $LCI_{N_2}=\{5.0, 6.2, 8.2\}$ and $LCI_{SF_6}=\{5.2, 6.4, 8.4\}$ for 0%, 10% and 20% of the small airways constricted, respectively. Leaks typically altered measurements made with N_2 more

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Even small air leaks can have a significant impact on LCI measured using N_2. This is particularly the case for leaks that occur towards the end of washout. In contrast, leaks generally have a much smaller impact on LCI measured by SF_6. http://ow.ly/az7b30lG5Ku

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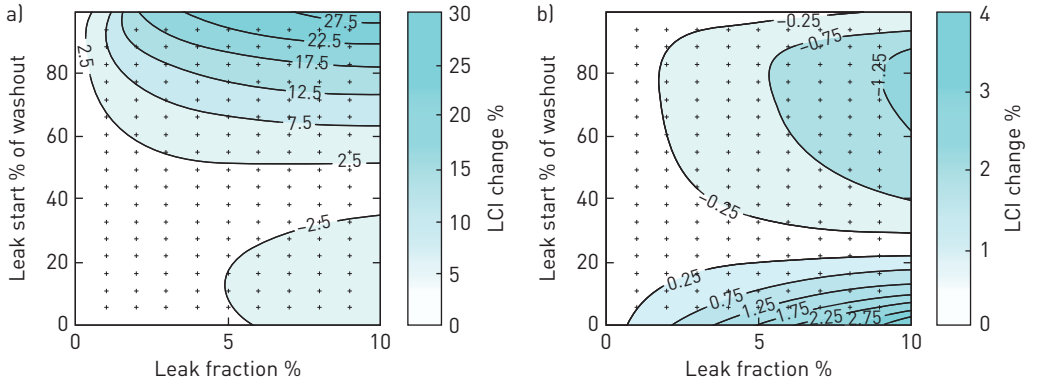

FIGURE 1 Contour plot showing % change in lung clearance index (LCI) due to leaks for the case when 10% of the small airways are constricted. The shading indicates magnitude of the change (from light to dark) and the labelled contour lines also show the direction of change (positive indicating an increase and negative a decrease). This was plotted using a range of leak fractions and start times using a) nitrogen and b) sulfur hexafluoride washout, where each dot indicates a single simulation. Note the differences in scale with a) 5% and b) 0.5% change between contour lines.

severely than those with SF_6, as the extra inspired N_2 during washout affects both FRC measurement and washout duration.

Changes in LCI of >7.5% were simulated for N_2 leaks only when introduced later in washout (figure 1a), reaching over 25% for a 10% leak fraction beginning in the final 10% of washout. Notably, even very small leaks (1–2% leak fraction) sustained for only three breaths were enough to cause clinically significant increases in LCI_{N_2} (>7.5%) if introduced late in the washout. This is caused by the extra N_2 inhaled from room air prolonging the washout by preventing the end-tidal concentration from reaching 2.5% of the initial concentration as early as it would have done otherwise.

Leaks during SF_6 washout affect LCI only *via* the measurement of FRC and behave the same as the intermittent expiratory-only leaks as characterised by Lenherr *et al.* [2], increasing LCI_{SF_6} if introduced early in the washout and decreasing LCI_{SF_6} if introduced late (figure 1b). The maximal observed change in LCI_{SF_6} was 4% (10% leak fraction at start of washout). Leaks in N_2 show the reverse effect, showing a much larger magnitude effect later in washout for all cases simulated. This effect was diminished in models with greater bronchoconstriction, as most of the extra N_2 introduced was washed in and out of better ventilated lung regions more quickly than resident N_2 was washed from the constricted regions. However, with 20% of small airways constricted, there remained increases of up to 19% in LCI_{N_2} (simulated for a 10% leak fraction starting at the final breath of washout). The relative change in LCI_{SF_6} due to leaks was not significantly changed from figure 1b in either the case of 0% or 20% of small airways constricted.

The data from this study complement those from the earlier study by Lenherr *et al.* [2], also published in *ERJ Open Research*. The main differences are that we have concentrated on the combined effect of inspiratory and expiratory leaks, and used a sophisticated computer lung model to look at the impact of minor leaks (three breaths, up to a maximum of 10% tidal volume) on washout outcomes. Using this approach, we have shown that LCI measurement is exquisitely sensitive to inspiratory air leaks during N_2 MBW, even when these may be too small to pick up from watching the MBW trace. This is particularly relevant for leaks that occur very late in washout, where a leak of just 2% of tidal volume was predicted to cause up to an 18% increase in LCI_{N_2}. We have also seen that very small leaks occurring at the start of washout may not have a detectable effect on LCI. Furthermore, the impact of leaks is diminished in those with more severe ventilation heterogeneity since the inspired (leaked) tracer gas is preferentially washed in and then out of the best ventilated lung regions. In all cases, in contrast to the situation described here for nitrogen MBW, washout of SF_6 was barely affected by small leaks, being changed by only the small volume of additional air introduced. Unrecognised leaks may contribute to the differences between clinically measured SF_6 and N_2 washout indices, which can be very substantial [4, 5]. This study emphasises the need for experienced staff to be highly vigilant when carrying out MBW testing. Since it may be impossible to always be certain that there has been no minimal leak (particularly at the level modelled here), it also illustrates an additional advantage of SF_6 as a washout gas.

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