VENTILATION HETEROGENEITY IN THE ACINAR AND CONDUCTIVE ZONES OF THE NORMAL AGEING LUNG

Online Supplement

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1. Principle and computation of Sacin and Scond from phaseIII slope analysis :

The MBW normalized slope analysis technique identifies the various mechanisms of ventilation heterogeneity generating a phaseIII slope, attributing these to either the conductive airways (where convection predominates) or the acinar air spaces (where diffusion and convection interact). In the conductive lung zone, a non zero phaseIII slope is due to flow asynchrony between lung units with a different specific ventilation (by differential convection into each unit). Around the entrance of the acinus, a structural asymmetry in terms of heterogeneity in the cross section of any two daughter branches, or in the volume of the two subtended units, results in a non zero phaseIII slope, by the interplay of convection and diffusion. The solid lines in the right panel of Figure OS1 illustrate that the former mechanism generates a steady increase in Sn, while the latter quickly obtains a horizontal Sn asymptote. Considering these two Sn constituents for each breath to be approximately additive, it is possible to define two characteristic indices Sacin and Scond representing ventilation heterogeneity generated at branch points in the acinar and conductive lung zones, respectively (left panel of Figure OS1). Scond can then defined as the slope of the regression line of Sn versus lung turnover (TO) between 1.5 and 6 lung turnovers. Sacin is the Sn value of the first breath minus the contribution from Scond to the first breath (Scond multiplied by TO of the first breath).

2. Impact of instrumental dead space on LCI, Sacin, Scond

While core and supplemental datasets showed a very similar age dependency, there was an offset between absolute LCI values gathered from the two participating laboratories, while this was not the case for Sacin and Scond (Fig1-3). The only difference between both setups was the re-inspired dead space and its effect can be predicted as follows. For LCI, it is possible to roughly predict the magnitude of change that can be expected with a change of instrumental dead space from 15ml to 50ml. For that purpose, we can consider a lung of volume VL, as a sum of anatomical dead space (VD_{anat}) and alveolated space volume (V_{alv}), tidal volume VT, and instrumental dead space, i.e., instrumental dead space being re-inspired (VD_{instr}). By simple mass balance in a model where dead space is a non-expanding transit space, the alveolar concentration in subsequent washout breaths (breath number, n) is then given by :

$$CN_2^{alv}(n) = CN_2^{alv}(n-1) . (VD_{instr}+VD_{anat}+V_{alv})/(VD_{instr}+VD_{anat}) \qquad (1)$$

As an example, this was done here for

$VL=3000ml$; $V_{alv}=2750ml$ and $VD_{anat}=250ml$;

$VT=1000ml$; $VD_{instr}=15$ ml or 50ml

and the resulting LCI for 15 and 50ml instrumental dead space is respectively, 5.20 and 5.49, i.e., a LCI difference of 0.3. While more elaborated computations could be done, with compartmental models,[27] incorporating the influence of ventilation heterogeneity, the above simple calculation shows that the degree of LCI change predicted by a 35ml increase in VDinstr is of the same order as the differences in LCI between the core and supplemental data sets, observed in Fig3B (the LCI difference averaged 0.5).

In contrast to the effect of re-inspired dead space on LCI, its effect on Sacin and Scond is almost impossible to simply predict or simulate. From MBW experiments in 4 excised mongrel dogs lobes,[30] the influence of re-inspired instrumental dead space on MBW indices very similar to Sacin and Scond, has been tested experimentally for a wide range of VD_{instr}/VT (0.2-0.8). Given that both acinar and conductive ventilation heterogeneity may behave very differently in humans versus mongrel dogs, an extrapolation of the proposed correction formula's (that are empirical and may be valid only under the experimental conditions used in,[30]) can only be speculative. However, when applying these to our situation where VD_{instr}/VT varies from 0.015 to 0.05 (i.e. much less than the 0.2 lower limit considered in,[30]), the predicted impact on Sacin and Scond would be respectively -6% and -11%.

As a test case, we actually assessed the impact of increasing dead space from 15 to 50ml, on two subjects (males, 35 and 53 years) : Sacin changed by 0.001 and 0.013 L^{-1}, i.e., an average 0.007 L^{-1} Sacin increase (or +8%); Scond changed by -0.002 and -0.006 L^{-1}, i.e., an average -0.004 L^{-1} Scond decrease (or -15%); LCI changed by 0.40 and 0.55, i.e., an average 0.48 LCI increase (or +8%). These changes need to be considered with respect to the age dependencies obtained for Sacin, Scond and LCI across panels B of Figures 1-3, and even if LCI was particularly sensitive to re-inspired dead space volume, age dependency of LCI remained similar between both laboratories.

3. Automated phase III slope analysis

Central to the automated analysis is the algorithm used to determine the volume at where phaseIII is assumed to start, and this is done by first determining a break point between phaseII and phaseIII by segmented linear regression. The lower limit for phaseIII slope computation is then set at this break point volume plus 50% of the phaseII volume. The upper limit for phaseIII slope computation is the last data point of each expiration. The phaseIII slope is then divided by the mean expired concentration; when expired volume exceeded 1L, mean expired concentration was considered only up to 1L. Before submitting all normalized phaseIII slopes (from all 3 MBW tests) for Scond and Sacin computation (as illustrated in Figure OS1), data post-processing features were implemented in order to first discard phaseIII slopes outliers. These include :

3.1. Criteria for excluding individual breaths from a given MBW test :
- Exhaled volume >1.4L
- Exhaled volume < 0.950L

3.2. Criteria for excluding a MBW test :
- FRC differs by more than 25% of the median FRC.
- Any of the volume-based breath exclusion criteria is met for more than 1/3 of the expirations of a given test

3.3. Procedure for excluding outliers in Sn vs TO plot (of all 3 MBW tests combined) in 3 steps:
1. Linear regression of Sn points in the interval TO=1.5 - 6
2. If one or several individual Sn value fall outside the 95% confidence interval, exclude these.
3. Repeat linear regression of Sn points in the interval TO=1.5 – 6 to obtain Scond.

FIGURE LEGENDS

Figure OS1 : Scatterplots of normalized phaseIII slopes (Sn) from 3 MBW tests obtained in one subject, and the corresponding Sacin and Scond indices computed for that subject; only those Sn values for breaths meeting the criteria listed under 3.1 are represented.

Panel A: Closed symbols are the Sn values actually used for Scond and Sacin computation. Also shown is the regression line, the slope of which corresponds to Scond; in this example, the average value for Sn of the first breath is 0.095 L^{-1} from which part of Scond is subtracted to obtain Sacin=0.077 L^{-1}. Crosses correspond to Sn values that would get removed as outliers during the automatic procedure (see 3.3.).

Panel B: Simulated Sn underlying Sacin and Scond computation, decomposing over all Sn into a convection-dependent Sn (with a steady increase as a function of turnover throughout the MBW) and a diffusion-convection dependent Sn (producing a horizontal asymptote early on in the MBW).