Modelling responses of the inert-gas washout and MRI to bronchoconstriction

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ABSTRACT

Many lung diseases lead to an increase in ventilation heterogeneity (VH). Two clinical practices for the measurement of patient VH are in vivo imaging, and the inert gas multiple breath washout (MBW). In this study computational modelling was used to compare the responses of MBW indices LCI and $S_{\text{cond}}$ and MRI measured global and local ventilation indices, $\sigma_r$ and $\sigma_{\text{local}}$, to constriction of airways in the conducting zone of the lungs. The simulations show that $S_{\text{cond}}$, LCI and $\sigma_r$ behave similarly to each other, all being sensitive to increases in the severity of constriction, while exhibiting little sensitivity to the depth at which constriction occurs. In contrast, the local MRI index $\sigma_{\text{local}}$ shows strong sensitivity to depth of constriction, but lowered sensitivity to constriction severity. We finish with an analysis of the sensitivity of MRI indices to grid sizes, showing that results should be interpreted with reference to the image resolution. Overall we conclude that the application of both local and global VH measures may help to classify different types of bronchoconstriction.

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1. Introduction

Many diseases, such as asthma, emphysema and cystic fibrosis are characterised by ventilation heterogeneity (VH), which can be driven by constriction or closure of airways in the lungs. Therefore, accurate measurements of VH are of high utility in clinical settings. Typically these measurements are inferred through simple lung function tests such as spirometry and plethysmography, or through more complex tests such as oscilometry (Oostveen et al., 2003), inert-gas washouts (Robinson et al., 2013), or in vivo imaging (de Lange et al., 2006; Simon, 2005; Tzeng et al., 2009).

A clinical test for VH that is becoming increasingly common is the inert gas multiple breath washout (MBW) (Macleod et al., 2009; Robinson et al., 2013; Verbanck et al., 2003). In short, the MBW is performed in one of two ways: either air mixed with an inert-gas (such as SF$_6$ or $^3$He) is washed-in (breathed in until it is assumed to have equilibrated in the lungs) by the patient and then washout of the gas is performed by switching the patient back to an air mixture without the gas; or in the case of N$_2$ washouts, since N$_2$ is already present in air, no wash-in is performed, and instead a washout is performed using pure oxygen. By monitoring the exhaled gas concentrations during the washout process, a number of VH indices can be derived. These include the Lung Clearance Index (LCI), $S_{\text{cond}}$, and $s_{\text{acin}}$ (Verbanck et al., 1998) (for exact definitions of each, the reader is referred to Appendix A). The uptake of the MBW as a clinical test of VH has in large part been driven by the correlation of MBW indices with clinician classifications of many lung diseases, including cystic fibrosis (CF) (Aurora et al., 2004, 2005; Horsley et al., 2008) and asthma (Gustafsson, 2007; Verbanck et al., 1999). However, due to the complex nature of the test indices, precise understanding of how the indices respond to VH has yet to be achieved (Robinson et al., 2013).

Since its initial development, understanding of the MBW has been advanced by a combination of clinical and computational studies. Key to this was the concept of time constants (Otis et al., 1956), a measure of how effectively different pulmonary regions of the lung ventilate. Typically, computational studies of the MBW have used transport equations to simulate gas transfer throughout the breathing cycle. Early models (Cruz et al., 1997; Han et al., 2001; Verbanck and Paiva, 1990) were simulated on idealised branching geometries based on the work of Weibel (1963). Later work used image processing to construct more realistic simulation geometries from patient CT scans (Tawhai and Hunter, 2001; Mitchell et al., 2012). Results from these studies have suggested that indices from the MBW respond positively to increases in bronchoconstriction driven VH. The studies have also strengthened the understanding that regional differences in time constants can significantly alter flow behaviour. However, there is still uncertainty about exactly what drives changes in the indices.
A range of different imaging techniques have also been shown to successfully resolve ventilation distribution heterogeneity, including scintigraphy, computed tomography (CT), and positron emission tomography (Simon, 2005; Tajik et al., 2002; Tzeng et al., 2009). However, while these techniques can produce high resolution images, the use of ionising radiation limits application in many clinical settings, particularly paediatric, and longitudinal studies.

Due to the limitations of imaging techniques involving ionising radiation, magnetic resonance imaging (MRI) techniques have gained traction as alternative tests for VH. In particular, proton MRI (Bauman et al., 2009; Biederer et al., 2012; Så et al., 2010) and hyperpolarised gas MRI (Fain et al., 2007; Möller et al., 2002; van Beek et al., 2004) have exhibited increased uptake, and strong improvements in resolution and cost. From MRI data, measurements can be made of how well ventilated each voxel in an image is. From this, a series of different measures of VH can be derived, at either a global (Biederer et al., 2012; Horn et al., 2014) or local (Tzeng et al., 2009) scale.

MRI techniques have become more viable due to reductions in time, alongside improvements in image resolution. However, the relative cost, and lack of standardised imaging protocols have limited large scale uptake (Biederer et al., 2012). Equally, while there is a vast array of literature relating MBW indices to lung disease classification, there are fewer studies investigating the relationship of MRI outputs to disease classification. Some recent preliminary studies have investigated the relationships between MRI and MBW within the same patient groups (Capaldi et al., 2015; Horn et al., 2015; Horsley et al., 2014). However, to the best of our knowledge no full studies in the literature have analysed this relationship in significant detail, or confirmed preliminary results.

In this paper we aim to use computational investigations to better understand the relationship between MBW and MRI derived indices, and how they respond to bronchoconstriction. By simulating the MBW and ventilation on a virtual lung structure, under a variety of different bronchoconstriction scenarios, we investigate how test indices respond to constriction of airways in the conducting zone. Comparison of the MBW and MRI indices show that \( s_{\text{cond}} \), LCI and global ventilation variance primarily respond to the severity of the bronchoconstriction, while local ventilation variance primarily responds to the degree of regionalisation in the constriction. Alongside this, we give insights to the sensitivity of MRI indices to grid resolution.

2. Methods

2.1. Ventilation model

Within our study, simulations were performed on a structural representation of the lungs, created through a combination of segmentation of a subject CT scan for the central airways (to generation 6–10) and algorithmic airway generation (to an average generation 16). The structural model used in this study was taken from a set presented by Bordas et al. (2015), with segmentation and algorithmic generation based on the work of Petita et al. (2004) and Tawhai et al. (2004). The airway tree structure consisted of 78,834 branches, 39,420 of which were terminal bronchioles. Each terminal bronchiole was connected to a unique elastic acinar region, which expanded and contracted over time in accordance to pleural pressure changes.

The exponential model used in this study is a mixture of the exponential model used in this study is a mixture of the exponential model described by Horsfield et al. (1976)
\[
\log d(x) = (x - N) \log(R_0 s) + \log(d_0),
\]
where \( d \) is the airway diameter, \( x \) is the Strahler order (Strahler, 1957) of the branch, \( N \) is the maximum Strahler order of the tree,
$d_n$ is the maximum diameter, and $R_dS$ is the anti-log of the slope of the airway diameter plotted against Strahler order, taken as 1.4. For more details on the airway tree set, the reader is referred to the work of Bordas et al. (2015). Airway radii in the structure were taken as static, with all volume changes in the lungs occurring in the acinar units that subtend the terminal bronchioles.

To infer the ventilation distribution from the lung structure, we assumed a pressure driven flow profile, the details of which are presented in Appendix B. In short, the velocity ($u$) in each branch is driven by the pressure gradient over the branch, with flow being conserved at each bifurcation. The flow model incorporates Poiseuille resistance with a correction term for energy dissipation proposed by Pedley et al. (1970). The expansion and contraction of each acinar region was driven by flow in the associated terminal bronchiole, changes in pleural pressure, and the region's tissue compliance. The pleural pressure was taken as sinusoidal, with a breathing period of 4 s. The amplitude was chosen to enforce tidal breathing of 1 L per cycle, above a functional residual capacity of 2.5 L.

For total lung compliance, a standard value of 0.2 L cm H2O−1 (Galetke et al., 2007; Mittman et al., 1965) was chosen. This value was distributed unevenly across the lungs, to account for gravitational effects seen in previous clinical studies (Hopkins et al., 2007; Kaneko et al., 1966; Musch et al., 2002). For both the MBW and MRI the gravitational compliance gradient was applied in the dorso-ventral axis, pertaining to the tests being performed in the supine position. Due to computational constraints, a linear distribution of compliance was chosen over more complex models in the literature, such as in Swan et al. (2012). Consistent with studies in the literature (Kaneko et al., 1966; Musch et al., 2002) a gradient strength of 1.5% cm−1 was applied.

2.2. Model of the MBW

The MBW was simulated using a convection transport equation:

$$\frac{\partial AC}{\partial t} = -u \frac{\partial AC}{\partial x},$$

where $x$ is the axial direction of the flow, $t$ is time, $C(x, t)$ is the concentration of the gas within air, $A$ is the cross-sectional area of the airway, and $u$ is the air velocity. The branch area $A$ is taken as constant within each branch, with differences between connected branches accounted for in the finite volume formulation of the model.

Mass transfer between acinar regions and the conducting zone was driven by flow rates from the terminal bronchioles. Within each acinar region, gas mixing was assumed instantaneous, with each region being characterised by a single gas concentration. For more details on the model, and the numerical scheme, the reader is directed to the supplemental materials.

Simulations were started from the washout phase, with a uniformly distributed initial gas concentration of 4%. Initially the wash-in phase was also simulated, however, even under high VH scenarios, no significant difference in test indices was seen. During washout an inspiratory tracheal boundary concentration of 0% was applied. During expiration, gas was removed at the trachea proportional to the flow rate in the branch.

2.3. Calculation of MRI indices

There are many competing standards for MRI indices within the literature. For simplicity, we chose two different indices; a global ventilation measure, and a local ventilation measure. We first define the ventilation ratio (Horn et al., 2014) of a region as

$$r = \frac{V_f}{V_f + V_r},$$

where $V_f$ is the fresh gas entering a region over an inhalation, and $V_r$ is the residual gas at the end of exhalation. Within our model, we can directly calculate an $r$ value for each acinar region, based on volume changes over the breathing cycle.

To approximate an MR image, we overlay a 3D grid to the lung structure, and take the mean $r$ value of all acinar regions within each voxel (grid rectangular prism). From the set of voxel $r$ values, the global ventilation variance ($\sigma^2$) was defined as the variance of the total set. The local variance ($\sigma^2_{\text{local}}$) was defined as the variance relative to a local mean, such that

$$\sigma^2_{\text{local}} = \frac{1}{N} \sum_{i=1}^{N} (r_i - r_{\text{local}})^2,$$

where $r_{\text{local}}$ is the mean $r$ value of all voxels sharing an edge with voxel $i$, and $N$ is the total number of voxels.

For results within this study, we have applied a grid mesh consisting of 80 × 80 × 80 rectangular prisms giving a voxel resolution of 4 mm × 2.6 mm × 3.5 mm, consistent with clinical MRI studies in

![Fig. 2. Relationship between $s_{\text{local}}$ (left) and LCI (right) and $\sigma_r$. Data has been split into three groups based on constriction severity: less than 80% (blue), 80–90% (red) and greater than 90% (yellow). A positive relationship can be seen until constriction levels pass 80%.](attachment:image.png)
Fig. 3. Variation of $s_{\text{med}}$, LCI, $\sigma$, and $\sigma_{\text{local}}$ against constriction depth (Strahler order). Results have been separated into six different constriction severity bands. For each band, the median output (line) is presented alongside an inner band representing the interquartile range (dark blue), and an outer band to the minimum and maximum values (light blue). The MBW indices show no consistent correlation with depth, but the MR indices respond more clearly, with $\sigma_{\text{local}}$ having the strongest and most consistent response.
2.4. Protocol for selecting bronchoconstriction scenarios

A Monte Carlo random sampling approach was used to select bronchoconstriction scenarios. Each scenario was characterised by a constriction severity, and a constriction depth. Constriction severity was the percentage that a chosen branch was constricted (had its radius reduced) by, Strahler order, the minimum number of branches between a branch and the nearest terminal bronchiole, was used as the marker of depth, with Strahler order 1 corresponding to terminal bronchioles, and 10 corresponding to lobar bronchi. Strahler order was used instead of branch generation, as the mechanics of the model are more strongly driven by behaviour at the terminal bronchioles (and in the respiratory zone) than at the trachea. An investigation using branch generation as the depth marker is presented in supplemental material.

For each simulation, a constriction severity (0–99%) and constriction depth (Strahler order, 1–10) were uniformly randomly chosen, and 20% of branches at that depth were constricted to the chosen severity. Airway constriction was applied in a spatially coherent manner through adaptation of work by Leary et al. (2012), meaning constricted branches passed on some of their constriction to the next generation. The diameter of a branch j with a parent branch i that has undergone constriction, inherited part of this constriction, such that

\[ d_j = \phi d_i \left( \frac{d_{\text{base},i}}{d_{\text{base},i}} \right) + (1 - \phi)d_{\text{base},j}, \]

where \( d_{\text{base}} \) denotes the diameter of the airway before constriction, and \( \phi \) is known as the coherence parameter.

Simulations in this study were applied using coherence of 60%, meaning each child branch inherited 60% of the parent’s constriction, each grandchild inherited 36% and so on. The value \( \phi = 0.6 \) was chosen as it provided significant spatial coherence and smoothness, but has been shown to not significantly affect the variance of airway resistances (Leary et al., 2012).

Each simulation was performed until the mean exhaled gas concentration fell below 1/40th of the mean exhaled concentration of the first breath for three consecutive exhalations, and at least six turnovers had occurred (for definition of a turnover, see Appendix A). Following this, the LCI, \( S_{\text{cond}} \), \( \sigma_r \) and \( \sigma_{\text{local}} \) were calculated and a voxel map was generated.

3. Results

As a reference, we give the baseline values for LCI, \( S_{\text{cond}} \), \( \sigma_r \) and \( \sigma_{\text{local}} \) produced with the model as 4.948 turnovers, 0.0012 L⁻¹, 0.00016, and 2.19 × 10⁻⁵ respectively.

We note that within all simulations mass conservation was achieved to within 0.01% of original mass. Convergence of the numerical scheme in space and time was also checked (with details given in the supplemental material).

3.1. Response of MBW and MRI indices to constriction severity

Within Fig. 1 we see the response of the MBW and MRI indices to increasing constriction severity. Initially we see all four indices exhibit a positive response, however, as severity approaches 100% the MBW indices monotonically decrease back towards baseline. This is representative of the inability of the MBW to detect airway closure, as seen previously in the literature (Mitchell et al., 2012). Considering the response of \( \sigma_{\text{local}} \), we also see an increase as constriction severity increases. However, the strength of this response is weaker and more noisy than that of the other indices.

In Fig. 2 we show the correlation between \( \sigma_r \) and the MBW indices, with results separated into three severity bands: <80%, 80–90%, and >90%. We see that initially the indices correlate strongly, but that this correlation breaks down as airway closure is approached.

3.2. Response of MBW and MRI indices to constriction depth

Fig. 3 shows the change in the four indices as constriction depth becomes more proximal (Strahler order increases). To separate out the response from constriction severity, results have been grouped into six different severity bands: <50%, 50–75%, 75–85%, 85–90%, 90–95%, 95–100%. Considering the MBW indices, only a weak dependence on constriction depth is noted, with the nature of the dependence changing across each severity band. As depth becomes more proximal, a small rise in variance of both indices was seen, however, there is no clear trend in mean values.

The MRI indices appear to respond to changes in depth in more consistent ways. The global index shows a consistent increase as depth becomes more proximal. The response is much weaker than the index’s response to constriction severity, but is clearly present. As severity increases though, the response appears to become weaker, disappearing as closure is approached.

The local MRI index \( \sigma_{\text{local}} \) appears to show the most consistent dependence on constriction depth. For each severity band, \( \sigma_{\text{local}} \) peaks at Strahler order 2, then monotonically decreases as depth becomes proximal. The variance of this response decreases significantly as severity increases, forming very tight bands as airway closure is approached. This, alongside the results in Fig. 1 suggests that local VH indices such as \( \sigma_{\text{local}} \) may more easily detect constriction depth than global indices. This is further illustrated in Fig. 4 which gives a series of ventilation maps corresponding to high constriction severity at varying depths, with each producing similar \( \sigma_r \) values, but strongly different \( \sigma_{\text{local}} \) values.

3.3. Sensitivity of \( \sigma_{\text{local}} \) to changes in voxel size

The calculation of \( \sigma_{\text{local}} \) is performed in reference to a local neighbourhood. Thus, the index is clearly dependent on the
Fig. 5. Variation of $\sigma_{\text{local}}$ against constriction depth under various grid resolutions. Three different grid resolutions have been used: very coarse (top), coarse (middle), medium (bottom). For each grid resolution, results have been separated into six constriction severity bands. For each severity band the median output (line) is presented alongside an inner band to the interquartile range (dark blue), and an outer band to the minimum and maximum values (light blue). Changes in grid resolution strongly affect $\sigma_{\text{local}}$ changing the depth at which the index maximises.

size of the neighbourhood. To address this we analyse the response of $\sigma_{\text{local}}$ to changes in constriction depth, under different grid resolutions. For comparison to the grid resolution used in this study (80 × 80 × 80), three different resolutions were used: medium (40 × 40 × 40); coarse (20 × 20 × 20); and very coarse (10 × 10 × 10). Note that we present no results for finer resolutions than 80 × 80 × 80, due to the number of acinar regions present in the model, meaning higher resolutions resulted in too many empty voxels to give accurate representations of ventilation.

In Fig. 5 we give the results of this analysis. As the figure shows, $\sigma_{\text{local}}$ is strongly affected by image resolution. As resolution decreases, the depth at which $\sigma_{\text{local}}$ maximises becomes more
proximal, peaking at Strahler orders 3, 5 and 7 for the medium, coarse and very coarse resolutions respectively. This suggests that while a local VH parameter can help identify constriction depth, interpretation must be made with careful reference to the imaging resolution.

4. Discussion

In this study, a mathematical model for gas transport within the lungs was applied to the comparative analysis of how MBW and MRI indices respond to bronchoconstriction in the conducting zone. The model was simulated on a structural representation of the conducting airways, constructed through image processing of a subject CT scan, with airway diameters being replaced by an idealised healthy model, given in the work of Horsfield et al. (1976). By simulating and calculating MBW and imaging indices over a large range of constriction severities and depths, analysis could be made about the sensitivity of these indices as detectors of bronchoconstriction.

4.1. Comparison of MBW and MRI indices

Comparative analysis of MBW and MRI indices produced interesting insights. As seen in Fig. 1, LCI, \( s_{\text{cond}} \) and \( \sigma_r \) all responded positively to increases in constriction severity. Unlike the MBW indices though, \( \sigma_r \) remained unaffected by the development of airway closure. This is logical, considering closed airways do not participate in the distribution of ventilation at the mouth, but will still be resolved as unventilated by an MRI. The ability of MRI indices to detect airway closure may offer explanation to outliers in correlations of the two measures, as seen in recent preliminary clinical studies (Capaldi et al., 2015; Horn et al., 2015; Horsley et al., 2014).

As noted in Fig. 3, despite strong dependence on constriction severity, the three indices showed only weak relationships with constriction depth. While previous studies in the literature (Robinson et al., 2010; Verbanck et al., 1998, 2003) have shown sensitivity of the MBW to constriction in the small airways, the results in this study suggest that the more dominant response may be severity of airway constriction.

4.2. Local MRI indices

The local imaging index \( \sigma_{\text{local}} \) exhibits a reversal of this behaviour. As shown in Figs. 1, 3 and 4 the index shows strong correlations to constriction depth, despite only weak correlations to severity. However, the results in 5 suggest a high sensitivity to voxel size, meaning interpretation must be made with reference to the imaging resolution. As noted in Section 2.3 there are many competing standards for MRI indices within the literature. Other choices in the literature have attempted to normalise the effect of neighbourhood size that \( \sigma_{\text{local}} \) exhibited, through scaling, and the use of covariance (Tseng et al., 2009). Within this work we have demonstrated the importance and utility of local MRI indices, however, the comparative evaluation of local MRI indices is a clear area for future research.

The results presented in this study show clear relationships and distinctions between how MBW and imaging indices respond to bronchoconstriction. Some of the trends, such as the failure of the MBW under airway closure have been exhibited in previous studies (Mitchell et al., 2012). However, to our knowledge, this is the first study that has investigated the relationship between MBW and MRI derived indices in such detail.

4.3. Limitations of the study and future work

In considering the limitations of the study, it should be noted that the baseline values of \( s_{\text{cond}} \) and LCI produced by the model before constriction were lower than standard healthy values reported in the literature (Verbanck et al., 1997). This can be partially explained as resulting from the simplifying assumptions made in the model, which led to an underestimation of heterogeneity. The development of more complex models, which incorporate airway elasticity, dynamic compliance, and more detailed acinar region structures, will be undertaken in future work.

The exhibited maximum values of \( s_{\text{cond}} \) were also higher than values seen in the literature for patients exhibiting bronchoconstriction (Verbanck et al., 1997). The constriction of a small number of airways at a specific depth, by identical amounts will naturally lead to sharp distinctions between the time constants of healthy and unhealthy regions. These distinctions would be sharper than what would be seen clinically, where the transition between healthy and unhealthy regions occurs as a spectrum. This difference explains the higher index values exhibited in severe VM regimes, as well as the observation that most significant index changes occurred once constriction severity exceeded 50%. This aligns with the aim of our study, which was to investigate how test indices respond to structural changes in the lung, and not to specifically recreate patient scenarios.

Finally, this study investigated bronchoconstriction within the conducting zone of the lungs. This is most typical of lung diseases such as asthma. However, other common lung diseases such as emphysema and chronic obstructive pulmonary disease (COPD) are more strongly characterised by regional compliance heterogeneity. While other studies have incorporated disease-driven heterogeneity in respiratory zone compliance (Henry et al., 2012; Milic-Emili et al., 2007; Tawhai and Hunter, 2001), there are still large questions surrounding the use of the MBW in detection of this type of respiratory zone heterogeneity. The development of detailed models of the acinar regions of the lungs, and the application of these models to the investigation of disease-driven regional compliance heterogeneity, is a future area for research.

5. Summary

The simulations performed in this study suggest that LCI, \( s_{\text{cond}} \), and \( \sigma_r \) are all quite sensitive to increases in constriction severity. Under severe constriction, \( \sigma_r \) appears to remain a strong predictor, while the MBW indices decrease back towards baseline, as expected. This leads to a strong correlation between the MBW indices and \( \sigma_r \) except under airway closure. Despite strong dependence on constriction severity, all three indices exhibit only weak dependence on constriction depth. Local VM imaging indices such as \( \sigma_{\text{local}} \) appear to relate more strongly to constriction depth. However, the nature of the relationship is dependent on image resolution, meaning care must be taken in interpretation.

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Appendix A. Multiple breath washout indices

To calculate the major MBW indices, the expired volume, and expired gas concentration must be measured for the duration of the washout phase. The expired gas concentration is typically plotted against time, and referred to as the washout curve. An example washout curve for \(^3\)He is given in Fig. 6.
Fig. 6. Multiple breath washout indices. A simulated $^3$He multiple breath washout curve (top left). The profile for the 1st breath (right, black line) is given, with the $s_B$ slope before normalisation overlaid (red dashed line). Inhaled volume (i.e. volume above FRC) for the test is also given (bottom right). The total set of $s$-values is given (bottom left), with the slope $s_{cond}$ overlaid (black dashed line), and the index $s_{acin}$ plotted (grey triangle). These figures were generated from simulation of the baseline (no constriction) scenario of this study.

Three major indices are commonly taken from an MBW test: the Lung Clearance Index, $s_{cond}$ and $s_{acin}$. The Lung Clearance Index (LCI) is the amount of time taken from the start of the washout phase until mean exhaled concentration over an exhalation drops below 1/40th of the initial exhaled concentration. To normalise between patients, this time is expressed as the number of lung turnovers performed, turnovers being the cumulative expired volume divided by the individual’s functional residual capacity (FRC).

The other two measures derived from the MBW are more complex in definition. For each exhalation, a plot of exhaled gas concentration over cumulative expired volume is generated, as seen in Fig. 6. Typically this plot undergoes four distinct phases, an initial plateau, a steep rise, a second plateau, and a final rise. An $s_{Ubf}$ value is defined as the slope of the third phase of each curve, divided by the mean exhaled concentration over the third phase.

The statistic $s_{cond}$ is defined as the mean gradient of the $s_{Ubf}$ values between turnovers 1.5–6, and $s_{acin}$ as the $s_{Ubf}$ value from the first exhalation, minus the contribution from the $s_{cond}$ slope. An example of this is given in Fig. 6. We note that typically in the literature, models of the MBW without diffusion produce $s_{Ubf}$ curves that extrapolate to zero at turnover 0 (Hamid et al., 2005). As seen in Fig. 6, the $s_{Ubf}$ curve from the baseline scenario of this model extrapolates to a small, but non-zero amount. We believe that this is due to the nature of the ventilation model, allowing for variation in ventilation of different acinar regions, even in the baseline scenario.

**Appendix B. Ventilation model**

The velocity ($u$) in each branch in the lungs was assumed to be proportional to the pressure difference across the branch ($\Delta P$), such that

$$\Delta P = R(Q) Q,$$

where $Q=Au$ is the flow rate, and $A$ is the branch cross-sectional area. The resistance function $R(Q)$ is taken as a Poiseuille resistance, with a correction term for energy dissipation proposed by Pedley et al. (1970). At each branch bifurcation, flow is conserved, meaning

$$Q_{upper} = \sum Q_{lower},$$

where subscripts upper and lower denote the proximal and distal branches in the bifurcation.

Each terminal branch $i$, is connected to an acinar region with volume $V_{acin,i}$, whose expansion is driven by the flow rate in the terminal branch

$$\frac{d}{dt} V_{acin,i} = Q_i.$$
Finally, each $V_{\text{acini}}^{i}$ remains proportional to the difference between pleural pressure ($P_{\text{pl}}$) and pressure at the distal end of each terminal branch ($P_{R(i)}$), meaning

$$P_{R(i)} - P_{\text{pl}} = \frac{1}{C_{i}} V_{\text{acini},i},$$

where $C_{i}$ is the compliance of acinar region $i$. The pleural pressure was specific as sinosoidal with period 4s, and amplitude chosen to enforce tidal breathing of 1L per breath cycle, above a function residual capacity of 2.5L. To close the system an atmospheric pressure boundary condition $(P = 0)$ was applied at the trachea.

### Appendix C. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [http://dx.doi.org/10.1016/j.resp.2016.09.009](http://dx.doi.org/10.1016/j.resp.2016.09.009).

### References


### Discussion

Finally, the discussion section should elaborate on the significance of the findings and the implications for future research. It should address any limitations of the study and suggest potential areas for future investigation. The conclusions should be clear and concise, summarizing the key findings and their implications.

### Conclusion

In conclusion, the study demonstrated that... The findings have important implications for... Future research could explore... Overall, the study provides...

