Published in final edited form as:

Respir Physiol Neurobiol. 2012 September 30; 183(3): 224–233. doi:10.1016/j.resp.2012.06.031.

Relating indices of inert gas washout to localised bronchoconstriction

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Abstract

Asthma is typically characterised by increased ventilation heterogeneity. This can be directly inferred from the visualisation of ventilation defects in imaging studies, or indirectly inferred from indices derived from the multiple-breath nitrogen washout (MBNW). The basis for the understanding of the MBNW indices and their implication for changes in structure and function at the largest and smallest scales in the lung has been facilitated by mathematical models for inert gas transport. A new model is presented that couples airway resistance and regional tissue compliance, for simulation of the effect of 'patchy' bronchoconstriction - as inferred from imaging studies - on the Scond index of ventilation heterogeneity. Patches of reduced washin gas concentration can emerge by constricting only the terminal bronchioles within localised regions, however this pattern of constriction is insufficient to affect Scond; Scond from this model is only sensitive to constriction that occurs within entire contiguous regions. Furthermore the model illustrates the possibility that the MBNW may not detect gas trapped in ventilation defects..

Keywords

asthma; lung simulation; multiple breath nitrogen washout; regional ventilation imaging

1. Introduction

Regional ventilation heterogeneity is generally increased in the asthmatic lung, and can be inferred from integrated measurements of lung function such as the multiple breath nitrogen washout (MBNW), or from imaging the lung *in vivo* (De Lange et al., 2006; Petersson et al., 2007; Simon, 2005; Tajik et al., 2002; Tzeng et al., 2008). The advantage of the MBNW in comparison to imaging methods is that the test is relatively inexpensive and doesn't involve ionising radiation. An index that is considered reflective of regional ventilation heterogeneity (Scond) can be derived from the MBNW, as explained by Verbanck et al. (1998) and described in Appendix A. In the context of asthma, Scond has been shown to be sensitive to bronchoconstriction (Verbanck et al., 2001; Verbanck et al., 1998), and to be a predictor of airway hyper-responsiveness (a hallmark of asthma) independent of airway

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inflammation (Downie et al., 2007); it may therefore represent a persistent change in the conducting airways of asthmatics. Present understanding of Scond is dependent on interpretation of lung gas mixing physiology through mathematical and computational models (e.g. (Verbanck and Paiva, 1990)). While these models form the cornerstone of current understanding of the MBNW, to date they have not been extended to enable study of gas mixing in the asthmatic lung. Several other mathematical modelling studies have given new insights into the relationship between local airway constriction and integrated lung function (Tgavalekos et al., 2005; Venegas et al., 2005), however understanding of the contribution of constriction to the Scond index remains incomplete.

The reduction in airway lumen that occurs during asthmatic bronchoconstriction does not occur uniformly throughout the airway tree. That is, the reversible airway obstruction that characterises asthma leads to the development of regional ‘ventilation defects’ (Campana et al., 2009; Tzeng et al., 2008), the number and size of which appears to be correlated with asthma severity (Altes et al., 2001). A ventilation defect could – in theory - arise through constriction of a single airway leading to the defect, or through constriction of multiple smaller airways within the defect. Tgavalekos et al. (2005) have suggested that the most likely scenario is for multiple airways within a defect region to be significantly constricted, along with moderate constriction of airways outside of the defect. We speculate that in the context of the MBNW, a non-ventilated region that does not participate in the washout would not contribute to a rise in Scond. That is, it is not known whether Scond is sensitive to the ‘severity’ of the ventilation defects (whether they are partially or completely unventilated).

The central question of this study is whether experimentally-consistent trends in Scond will be predicted by a model in which bronchoconstriction occurs in spatial clusters that give rise to ‘ventilation defects’. To address this question we have developed a new mathematical model for the transport of inert washin gas in the lung. The model includes several features that are essential for this study: spatially-distributed and anatomically-based airway geometry, which introduces heterogeneity of airway resistance in an anatomically consistent manner; non-linear tissue elasticity, which interacts with airway resistance and introduces flow sequencing; and a ventilation distribution that is sensitive to both compliance.

2. Methods

2.1 Structural and functional model

Previous modelling studies have used idealised conducting airway geometries, typically based on the symmetric model of Weibel (1963), whereas the model in this study was geometrically customised to the left lung of a single subject. The single lung model simplification assumes that the left and right lung contribute equally to the MBNW, and that neglecting one lung will not affect the interpretation of the model results. That is, the left lung was ventilated with half of the whole lung tidal volume. Our results could be affected if the geometry of the airways and lung shape in this individual were markedly different from the population, however we have confirmed that this model lung geometry has no significant differences. The single lung was used to minimise the size of the computational model while still including sufficient anatomical detail to address the questions of this study. The model comprises anatomically based geometry and functional equations to predict localised ventilation distribution and concentration of inhaled marker gas. The components of the model are: image-based conducting airway geometry and symmetric acinus geometry, a one dimensional (1D) advection-diffusion equation for inert gas transport, an equation of motion, and distributed tissue compliance. The acinus was modelled as a single path symmetric model for reasons of computational efficiency. The methods for deriving the

image-based model have previously been described in several papers (Tawhai et al., 2004; Tawhai et al., 2000) and are summarised in Appendix B.

Advective and diffusive gas transport was modelled using a 1D equation for transport in the conducting and alveolated airways:

$$A \frac{\partial c}{\partial t} + av \frac{\partial c}{\partial x} = aD \frac{\partial^2 c}{\partial x^2} \quad (1)$$

where c is concentration, t is time, D is a binary diffusion coefficient, x is distance, a is duct cross-sectional area, A is duct plus alveolar cross-sectional area, v is velocity. Note that this equation is for an inert gas that is not exchanged with the blood, and that any increase in cross-section along an airway is accounted for in the finite element (FE) formulation. The conducting airways are assumed to be rigid: all volume change occurs in the respiratory airways. The advection-diffusion equation requires specifying the velocity v within each airway; v is dependent on the distribution of ventilation, which in turn depends on the regional tissue compliance, the change in pleural pressure (P_{pl}) during breathing, the airway geometry (via resistance), and the gas properties. In previous studies of the MBNW, the distribution of ventilation was either assumed to be uniform over the lung, a linearly weighted distribution (Tawhai and Hunter, 2001) or a prescribed polynomial approximation to experimental measurements (Cruz et al., 1997). Studying structure-function relationships in the asthmatic lung necessitates a model that redistributes ventilation in response to bronchoconstriction, i.e. where v is predicted rather than prescribed. The ventilation distribution was therefore simulated by solving a flow model that is sensitive to airway structure and tissue compliance. The details of this flow model are given in Appendix C. In brief, we adapted an equation of motion for the balance of air and tissue pressures during air flow (Ben-Tal, 2006) to represent flow to multiple individual acini, with enhanced resistance due to the bifurcating airway geometry (Pedley et al., 1970), and regionally varying tissue compliance. The flow model comprises an equation for Poiseuille resistance (supplemented with additional energy dissipation using Pedley et al.'s (1970) approximation) for each airway, conservation of mass at each airway bifurcation, and an equation of motion at each terminal bronchiole/acinar 'unit'. The time-varying velocity field from the flow model was used for simulation of inert gas transport by Equation (1). Note that exchange of respiratory gases with the circulation was neglected, and exchange of inert gas was assumed negligible.

2.2 Simulating clustered bronchoconstriction

Tgavalakos et al. (2005) have previously demonstrated that development of a ventilation defect requires a high degree of constriction in multiple airways leading to the defect, although there is no definitive conclusion as to how and to what extent the constrictions occur: constriction of airways that lead to a defect could be isolated to the terminal airways, they could be sited in single large airways, or in multiple intermediate airways. It is also not clear whether these airways are completely or partially closed. Because of this uncertainty we considered three cases: (1) constricting a random 10 % of the airways in a specified generation, (2) constricting the terminal bronchioles that lie distal to the selected airways in case 1, and (3) constricting the airways from case 1 and all of the airways distal to them. In each of the three cases the remainder of the lung remained unchanged. Five levels of constriction (diameter reduction) are presented: 20, 40, 60, 80 and 90 % from initial diameter (i.e. to 80, 60, 40, 20, and 10 % of baseline). These constriction patterns give rise to a maximal defect volume (120 – 140 mL) as a percentage of lung volume of approximately 10 – 12 %. This is modest in comparison to estimates from SPECT scanning following Technegas inhalation (31 ± 6 %) (King et al., 1998) and PET following washout of ^{13}N (41 ± 21 % in supine and 25 ± 14 % in prone) (Harris et al., 2009), but consistent with the wider range of volumes estimated from inert gas dilution (25 to 273 mL) (King et

al., 2005). Tzeng et al. (2008) found that the percent defect volume was smallest in the less severe asthmatics (as low as $5.4 \pm 4.5\%$) so the model may be most consistent with mild bronchoconstriction.

2.2 Boundary conditions and data analysis

Washin was simulated for oxygen/nitrogen (O_2/N_2), with $D = 22.5 \text{ mm}^2 \cdot \text{s}^{-1}$. The model was initialised to a fractional concentration (of O_2) of zero. During inspiration the fractional concentration at the tracheal entrance was fixed at value 1; during expiration the concentration at this location was free to change (zero diffusive flux boundary condition).

S_n and S_{cond} were calculated for all simulation studies. Plots of S_n against TO or breath number are presented as supplementary material. To present results from bronchoconstriction simulations, the concentrations were normalised by the baseline distribution of washin gas. The expected (idealised) concentration (C_E) in the terminal airways after the first breath is $C_E = (V_T - V_D)/(V_T + V_A)$, where C is concentration, V_T is tidal volume, V_D is dead space volume, and V_A is alveolar volume. The normalised concentration (C_N) was calculated as $C_N = C_{S-c} \cdot C_{E-b} / C_{S-b} \cdot C_{E-c}$ where the subscript 'S' refers to the simulation result from the model, and subscripts b and c indicate baseline and constricted, respectively. C_N is a correction factor that accounts for any differences in $V_A/V_T/V_D$ between the simulations.

The lung clearance index (LCI) was calculated as the number of lung turnovers required to reach a mean expired N_2 concentration that was 2.5% of the initial (alveolar) N_2 concentration. LCI was calculated for baseline and for each simulation condition.

3. Results

3.1 Ventilation and gas distributions for zero and baseline resistance

Ventilation distribution in a model with zero resistance was compared with ventilation distribution in the baseline model, to quantify the influence of baseline airway resistance. That is, ventilation distribution was determined completely by the tissue compliance in the zero resistance model. The airway resistance at baseline was $4.95 \times 10^5 \text{ Pa} \cdot \text{mm}^{-3} \cdot \text{s}^{-1}$ ($5.05 \text{ cmH}_2\text{O} \cdot \text{L}^{-1} \cdot \text{s}^{-1}$), corresponding to an anatomic dead space of 38.6 mL (note that this excludes the upper airway, trachea, and right lung). Figure 1(a) shows the spatial distribution of acinar ventilation as gravitational (cranio-caudal) lung height against ventilation to acini grouped within 12 mm 'slices' of the model. Error bars indicate $\pm$ one SD of the mean in the respective slice. Figure 1(b) shows mean acinar specific ventilation in the same slices (calculated as the volume change of an acinus divided by its initial volume) $\pm$ one SD, against lung height. Figure 1(c) and Figure 2 provide two illustrations of the washin gas concentration. Figure 1(c) shows mean washin gas concentration per slice against lung height. Figure 2 illustrates the gas concentration within the left lung model geometry.

The baseline airway tree resistance had minimal effect on the regional distribution of ventilation (Figure 1(a)) or specific ventilation (Figure 1(b)). Similarly, the effect on the regional distribution of O_2 during inhalation was small (Figure 1(c)). This shows that the gas diffusivity contributed to a small degree of heterogeneity in concentration within a gravitational slice. However, despite the minimal change in the overall distribution of inhaled gas, S_{cond} was almost doubled between the zero resistance and baseline simulations, from 0.0161 L^{-1} to 0.0278 L^{-1} . This is indicative of an increase in flow sequencing, i.e. a contribution of the airway resistance to variability in the time constants of different tissue units.

The difference between regional ventilation normalised by mean acinar volume (Figure 1(b)) and the regional tracer gas concentration (Figure 1(c)) illustrates that the diffusive transport of gas is by itself capable of inducing some variability in the tracer gas distribution.

3.2 Basic baseline function

LCI for the baseline model was 4.94 TO, which is lower than physical measurements in healthy adults (6.7 ± 0.4 TO, Horsley et al. (2008)) but consistent with two-unit mathematical models that include heterogeneous specific ventilation (Verbanck et al. 2012). Figure 3 illustrates flow asynchrony from this model, calculated for acini in bands along the gravitational axis. At this scale it is apparent that there is a very modest – but distinct – amount of asynchrony. Less than 0.05% of the acini displayed convective pendelluft (one acinus emptying while another filled) at the time when inspiration changed to expiration.

3.3 The effect of clustered bronchoconstriction

The effect on regional gas distribution and S_{cond} are shown for simulation of MBNW at baseline and for each of the constriction conditions (the three cases of clustered bronchoconstriction, and the five constriction levels).

3.3.1 Case 1: constricting 10 % of 12th generation airways—The first case considered constriction of randomly selected generation 12 airways. Note that these airways were distributed over several Horsfield orders, so the volume of tissue that they subtended was not equal for each airway (120 – 140 mL, representing 10 – 12 % of the lung volume). Results for constriction of 10 % of the 12th generation airways are listed in Table 1. The decreases in dead space (max –2.1%) and increases in airway resistance (max 2.63 %) were small. There was a small decrease in S_{cond} for all levels of constriction, with the greatest effect when the airways were constricted by 60 % (to 40 % of baseline diameter). Ventilation defects did not develop for this constriction pattern. That is, constriction of individual airways in a single generation - even by 90 % of baseline – was insufficient to significantly reduce ventilation to the distal tissue in the model. The LCI remained unchanged from baseline for all levels of constriction.

3.3.2 Case 2: constricting terminal bronchioles distal to 10% of 12th generation airways—The second case considered constriction of spatially clustered terminal bronchioles distal to the 12th generation airways from case 1. When only the terminal airways were constricted, the gas redistributed only at very high levels of bronchoconstriction as illustrated in Figure 4. Note however that the only level of constriction that showed an increase in S_{cond} was the 80 % constricted state (Table 2); the increase in S_{cond} for this constriction was considerable, and resulted in a negative S_{acin} .

3.3.3 Case 3: constricting all airways distal to 10 % of the airways in a specified generation—The third case considered constriction of spatially clustered and contiguous subsets of the airway tree, clustered distal to airways selected from generations 10, 12, and 14. Results for constriction of 10 % of the 10th, 12th, and 14th generation airways and all airways distal to them are summarised in Table 3. The ventilation distribution was traced visually in the model by examining the regional concentration of O₂ washed into the model at the end of the first breath normalised by the regional distribution of concentration at the end of the first breath in the baseline model (Figure 4). There was a strong increase in S_{cond} at 60 – 80 % constriction, dependent on the generation of constriction. This coincided with the onset of regional redistribution of ventilation that is apparent in Figure 4. S_{cond} then declined at very high levels of constriction. In Figures 4 and 5 the ventilation distribution is normalised against the ventilation at baseline. The concentration of washin

gas in the constricted regions at 20 and 40% constriction was higher than in the remainder of the lung, whereas for larger constriction the concentration of washin gas within the defect regions decreased. Imposing a small amount of constriction increased the time constant to the defect units. As a result they received less of the deadspace gas, but as their time constants were not critically reduced they still received most or all of the ventilation that they would have at baseline. At 60 – 80% constriction the time constants were critically reduced and the concentration of washin gas in the subtended units was decreased.

In only one case (60 % constriction of 10 % of airways at generation 10 and below) was there any visual change in the apical to basal heterogeneity of the model. In this case the apical to basal heterogeneity increased, which was consistent with the large increase in Scond in this case.

The results in Figures 4 and 5 and Tables 2 and 3 illustrate that only in the case where a large number of conducting airways were constricted was there a significant effect on Scond. It is possible to generate a ventilation defect by only constricting the terminal airways, however as Scond is expected to increase in asthmatics the model results are most consistent with the postulate that ventilation defects arise from constriction in many small airways in the defect region (Tgavalekos et al., 2005).

Figure 6 presents defect volume determined by thresholding O₂ concentrations in the parent airways and the terminal airways. This estimated defect volume is expected to be smaller than the known maximal model defect volume (the volume below and including the constricted parent branch), but more similar to imaging studies where defect volume is estimated from thresholding image intensity. Figure 6 illustrates that the concentration of tracer gas at the distal end of the parent branch differed from that in the subtended terminal bronchioles. This implies that at high levels of constriction, back-diffusion to the parent branch influenced the washin gas concentration due to the low flow of gas through the parent branch. In this case the gas in the ventilation defects was clearly not communicated to the mouth.

Baseline FRC estimated from mass balance of the gas washout (Wrigge et al. 1998) was 1.18 L, in comparison to the initialised model FRC of 1.22 L. The baseline difference of ~40 mL can be partly explained by the residual gas concentrations at the point at which the mouth concentration reached 1.5% of the initial N₂ concentration. The remaining 1.8% difference is attributed to non-uniformity of residual gas, and cumulative error in the model over the duration of the washouts. Table 3 lists further FRC volumes estimated from N₂ washout during model constriction. The estimated FRC correlates only weakly with Scond (R = 0.30) when data is pooled from all of the case 3 studies, but more strongly with LCI (R = 0.63).

The branchpoints were checked for the presence of better ventilated units not emptying preferentially at the beginning of expiration, at baseline and during bronchoconstriction. For each branchpoint in the model, if a subtended unit had a specific ventilation that was 1% lower than the other subtended unit then it was deemed to be emptying preferentially last, despite being better ventilated during inspiration. At baseline only 0.05% of the branchpoints showed evidence of this. For each constriction simulation the proportion of branchpoints with the best ventilated subtended unit not emptying preferentially first was < 1%, except for the 80% constriction cases in which the proportion was ~3%. Convective pendelluft is present in only a subset of these branchpoints (i.e. <0.05% at baseline).

4. Discussion

This study has presented a new mathematical model for studying the simultaneous contributions of ventilation defects, airway branching asymmetry, and distributed tissue compliance to the evolution of the Scond index that is derived from the MBNW test. The model predicts Scond at baseline that is comparable to previous experimental results (Verbanck et al., 2004; Verbanck et al., 1997). The results of visual development of ventilation defects (Figures 4 and 5) in concert with tabulated changes in Scond (Tables 1–3) support previous model findings (Tgavalekos et al., 2005), that constriction of multiple airways within a ‘defect region’ is most consistent with the functional and imaged changes that are observed in asthma. Further, the model demonstrates that elevation in Scond could be attributable to the severity of constriction within the defect regions, and that near closure of the defect results in non-communication of the gas with the exhalate, hence reducing Scond.

Previous mathematical modelling (Verbanck and Paiva, 1990) has shown the importance of flow sequencing and differences in the regional turn over of lung units in developing a positive Scond. Where the new model differs from previous models is that it couples heterogeneous pathway resistances to a gravitational distribution of tissue compliances via an equation of motion. This allows flow sequencing to emerge as a consequence of variability in the time constants of the model, rather than through its prescription. This is therefore the first study to examine the effect of airway resistance on Scond using a ventilation distribution model that is sensitive to changes in airway structure (specifically via increased resistance) and tissue compliance distribution.

Flow sequencing in this model is introduced by two mechanisms. First, a non-linear model of tissue compliance is used for the intact lung (Venegas et al., 1998). From our results with zero airway resistance it is clear that a heterogeneous distribution of tissue compliance (here only in the gravitational direction) is sufficient to generate flow sequencing and hence Scond. The Venegas et al. (1998) equation was used because it is a convenient representation of the nonlinear (sigmoidal) pressure-volume behaviour of the intact lung in a form where the equation parameters each have a physical meaning. Other relationships could have been used which could alter the quantitative predictions of the model. However the qualitative behaviour would be unlikely to differ unless the pressure-volume relationship was markedly different from Venegas et al. (1998), in which case it would be markedly different from the nonlinear behaviour of the intact lung. If we consider other simple mathematical descriptions that could be used for the pressure-volume relationship (linear, exponential) only the sigmoidal relationship is capable of producing flow sequencing. To explain this, consider the derivative of the equations: constant for linear, exponential for exponential. i.e. in the linear case all units have the same change of volume for a given change in pressure. In the exponential case for a lung with a dependent-to-non-dependent gradient of initial acinar volumes, the non-dependent acini receive less of the tidal volume than the dependent acini, but at no point would they contribute relatively more to expiration.

The second mechanism contributing to flow sequencing is the interaction of airway resistance with tissue compliance in the dynamic flow model (Otis et al., 1956). Time constant differences are expected to be small in a healthy lung, because the normal breathing frequency is such that large tidal differences between lung units do not arise, and consequently the gross regional distribution of ventilation is similar to that in the zero resistance case. However, the MBNW is a dynamic through-expiration test that is critically dependent on flow sequencing (Verbanck and Paiva, 1990), and it is possible for the indices that it produces to be significantly affected in the presence of increased flow sequencing without gross changes in the regional distribution of gas. This is evident in Figure 1, which

shows that the addition of heterogeneous (baseline) airway resistance to the model did not grossly alter the regional distribution of tracer gas concentration, however S_{cond} was increased.

The mechanism for generating flow sequencing shifted from being predominately compliance based in the normal lung to resistance based in the constricted lung. Prior observation of persistent ventilation heterogeneity in zero gravity (Prisk et al., 1995) could be explained by variation in regional tissue compliance that is not associated with gravity, or airway resistance of sufficient magnitude to introduce flow asynchrony. In Figure 2 we showed that while the distributed (gravity-dependent) compliance in the model is the dominant mechanism for flow asynchrony at baseline, the airway resistance also makes a marked contribution, increasing S_{cond} from 0.016 L^{-1} to 0.028 L^{-1} .

Because we are interested in understanding how increased localised resistance affects S_{cond} , we maintained a physiologically reasonable baseline resistance (for the portion of lung that the model represents) and parameterisation of the pressure-volume relationship that is appropriate for an otherwise healthy lung (one criteria being the prediction of a typical S_{cond}). Introducing constriction of a random 10 % of the 12th generation airways while all other airways remained unchanged increased the total resistance by a maximum of only ~3 %. The change in S_{cond} (Table 1) was also minimal, and did not correlate with increasing airway resistance. In fact, S_{cond} decreased slightly for this case, which is counter to the experimental observation of an increasing S_{cond} in bronchoconstriction. Similarly, for the case in which only the terminal airways were constricted, change in S_{cond} (Table 2) was not correlated with increasing resistance. In this case (illustrated in Figure 2) regions of low concentration developed without a commensurate increase in S_{cond} , consistent with the notion that a combination of concentration differences and flow sequencing differences contribute to S_{cond} . The appearance of ‘patchy’ regions of low gas concentration is typical of Hyp-He³ MRI in asthmatics. It is not clear whether these regions of low He concentration correspond to very poorly ventilated or completely non-ventilated regions, nor whether their presence is sufficient to be detected on MBNW. Our model results suggest that some defects could theoretically be visualised without any measured increase in S_{cond} , however whether this can arise physiologically is unclear.

Because of the integrated structure of the model, when constriction is present in one region the tracer gas distribution increases to the non-constricted regions (conservation of the tidal volume). The interaction between the constricted and non-constricted regions is complex: the model shows that at end expiration, the concentration of gas in the largest airway that leads to a defect can be different from the concentration in the airways within the defect. This difference in concentration indicates back-diffusion of air into the defect during exhalation (we find that back-advection remains very small in comparison to the expiration length), and is indicative of a markedly decreased contribution to the washout by the poorly ventilated regions. This result clearly illustrates the potential for a disconnect between the global S_{cond} index and the severity of asthma as indicated by the number and extent of ventilation defects. There is further potential for disconnect with S_{cond} when units are so poorly ventilated that they do not communicate with the mouth, which is supported by the current model.

Inert gas dilution is inaccurate in predicting the lung volumes of patients with severe asthma and airway closure (Woolcock and Read, 1966); it is theoretically possible that S_{cond} has a similar disconnect to the severity of physiological impairment if the volume of trapped gas is significant. Table 3 lists estimates of FRC from the N₂ washout simulations. At 60% constriction it takes more TOs to washout (LCI higher) and the FRC volume is over-predicted. At 80% and 90% constriction the FRC estimate is lower and the TOs to washout

decreases (LCI lower). In these highly constricted cases the under-prediction of FRC by 110 – 130 mL (~9 – 11% of FRC) is consistent with the ~10% of the model that has poor communication with the mouth (i.e. 10% of a generation was constricted). While these estimations of FRC are sensible, they correlate only weakly with Scond ($R = 0.30$), supporting the notion of disconnect. In contradiction to this Scond has been shown to be correlated with the volume of trapped gas at FRC (King et al., 2005). This is clearly an area for further investigation.

4.1 Limitations of study approach

The levels and locations of airway constriction were chosen for systematic study of their effect on Scond and not to directly mimic the extent of imaged ventilation defects or their dynamic development, therefore they are not likely to represent a specific realistic physiological state. For example, in the intact lung the spatial distribution of defects is influenced by posture (hence gravity acting on the lung tissue (Harris et al., 2009)) and the defect volumes are not likely to be as similar to each other as in the model. Furthermore, intact airways are thought to constrict in a bimodal manner (Anafi and Wilson, 2001). That is, they are thought to be in either an open or nearly closed state. Hence it is likely that some of the constriction levels simulated here represent physiologically unrealistic states. This could explain the model predicting significant elevation of Scond at e.g. the 80 % constriction level followed by significant decrease at the 90 % constriction level: the 90 % level is essentially 'closed', whereas the 80 % level would be unlikely to occur under the bimodal hypothesis.

Models such as Anafi and Wilson (2001) and its derivatives assume dynamically changing airway calibre. In contrast our model assumed rigid airways that maintained the same level constriction throughout a washout simulation. Neglecting phasic oscillations in airway size associated with breathing has minor effect on the model gas washout, however if airways were to intermittently open and close during washout this would not be adequately represented by the model.

The model under-predicts the LCI at baseline (4.94 TO), compared with measurements from normal subjects (6.7 ± 0.4 TO, Horsley et al. (2008)). The model does not include several mechanisms that are likely to be important in predicting a longer time for washout: intermittent airway opening and closure (the model airways are rigid), exchange of respiratory gases and N_2 with the blood, and collateral ventilation.

The model assumed that variability in the acinar compliance was only a function of the acinar volume. That is, variability in the material properties was not included. It is not yet clear what degree of material variability is valid to assume in this type of model. When the lung model is simulated in zero gravity, Scond reduces to zero. This contradicts experimental studies in microgravity that have noted the persistence of Scond (Prisk et al. 1995). Under conditions of zero gravity the flow asynchrony in the model disappears, which is essential for increasing S_n with breath number. However, when we introduce randomness in the c parameter of Equation 5 (results not shown) the model can predict increasing S_n that is of similar magnitude to the experimental results of Prisk et al. (1995).

4.2 Summary

Our model demonstrates that elevation in Scond is consistent with the presence of ventilation defects. The current work supports a previous modelling study that suggested that all airways within a ventilation defect are severely constricted (Tgavalekos et al., 2005). We find that 'effective' airway closure within a defect (such that the time constant of the units are too large to enable ventilation) reduces the model prediction of Scond.

Acknowledgments

The authors thank Dr Alona Ben-Tal of Massey University, Albany, NZ for advice and assistance on the implementation of equations. This work was supported by NIH grants HL064368 and HL103405.

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Appendix A. MBNW indices

In the MBNW the subject inhales multiple breaths of 100 % oxygen (O_2) at a controlled tidal volume (V_T), and the expired nitrogen (N_2) concentration and gas volume are recorded during each exhalation. To normalise for variance between subjects, MBNW data is usually considered relative to lung turnover (TO), which is the cumulative expired volume divided by FRC. Each breath is analysed to determine the slope of phase III of the washout, which represents alveolar gas. The phase III slope is normalised by the mean concentration of nitrogen in the exhalate to produce a normalised slope (S_n) and plotted against TO. This curve can be further broken down into two indices: Sacin and Scond. Scond is the linear approximation to the curve between lung turnovers 1.5 and 6. Sacin is the S_n of the first breath less the contribution of Scond to that breath. The Sacin and Scond components are assumed to be separable, and theoretically the MBNW can be reconstructed by addition of the two components (Verbanck et al., 1997). Sacin represents the contribution of intra-acinar inhomogeneity, or inhomogeneity between units that are situated close enough together so that diffusive flow between them can occur. Scond arises due to differences in inter-regional concentrations that develop due to differences in the specific ventilation (ventilation/per unit lung volume) and sequencing of the contribution of these units to the exhalate (Verbanck and Paiva, 1990). Inter-regional sequencing occurs because of regional variations in the resistance and compliance which result in phase differences in the flow (Otis et al., 1956).

Appendix B. Imaging-based model

Image acquisition

Imaging was acquired at the University of Iowa Comprehensive Lung Imaging Center (I-Clic) under the Human Lung Atlas project (NIH grant: RO1-HL-064368, E.A. Hoffman PI). Imaging of all subjects in the Human Lung Atlas database has been approved by the University of Iowa Institutional Review Board and Radiation Safety Committees. The images used in this study consisted of a spiral scan of the full lung in the supine posture with inflation level held at either 95 % vital capacity (VC, here assumed to represent total lung capacity, TLC) or at functional residual capacity (FRC). Images were acquired using a Siemens Sensation 64 MDCT scanner. Scan parameters were: 120 kV, 100 mA, a pitch of 1.2, scan collimation of 0.6 mm, and slice thickness 0.6 mm.

The subject was female, 34 years old, with a BMI of 21.8 (height 172.8 cm, weight 65.1 kg). The subject's lungs were classified as normal based on a radiologist's read of the subject's CT imaging, and pulmonary function tests (PFTs). Relevant volumes from PFT's performed when seated were residual volume (RV) 2.22 L, FRC 3.36 L, TLC 6.19 L, and forced expiratory volume in 1 second (FEV1) 3.51 L. Left lung volumes when supine (reconstructed from the volumetric imaging) were FRC 1.17 L, and TLC 2.06 L. The subject's mean tissue density (including air, parenchyma, blood, and extra-vascular fluid) in the supine left lung at FRC was 0.298 g.cm^{-3} .

An anatomically-based model of the left lung of a single subject was derived from the MDCT imaging. The lungs and airways were segmented from the subject's MDCT imaging using the image analysis software Pulmonary Workstation 2.0 (PW2, www.vidadiagnostics.com, Vida Diagnostics, Iowa City, IA, USA). A FE volume mesh was geometry fitted to the lung shape. 1D FE elements and nodes were placed along the centre of the segmented airways, to create a tree-like initial model. Supplemental airways to the level of the terminal bronchioles were generated from the initial airway mesh into the geometry-fitted lung volume mesh using a volume-filling branching algorithm (Tawhai et al., 2004). The diameters of elements in the MDCT-based part of the airway tree mesh were defined

using measurements of cross-sectional area (calculated in planes orthogonal to the branch centrelines) from the MDCT imaging, and assuming a circular cross-sectional area. In the supplemental airways the diameters were initialised based on their rate of reduction with Horsfield order (Horsfield et al., 1971).

A single path symmetric model for the acinus was attached to each terminal bronchiole. This model geometry was adopted in preference to an asymmetric geometry because of its compact size. The single path model had dimensions per generation as described by (Haefeli-Bleuer and Weibel, 1988) for the mean acinus pathway.

Appendix C. Ventilation model

The classic ‘equation of motion’ for the lung is:

$$I_A \frac{d^2 V_A}{dt^2} + (R_A + R) \frac{dV_A}{dt} + \frac{1}{C} (V_A - V_0) = P_m - P_{pl} \quad (2)$$

where I_A is inertance, R_A is lung resistance, R is the airway resistance to flow, V_A is the volume of the lung, V_0 is the initial lung volume, C is lung compliance, P_m is the pressure at the proximal end of the entrance airway, and P_{pl} is the pleural pressure.

Ben-Tal (2006) showed that if the acceleration and velocity terms are assumed to be small, and if change in alveolar pressure due to volume change is larger than that due to air compressibility, then a ‘simplified’ model can be derived that is valid for flow and volume change in the whole lung and is scalable to the acinus. The simplified model is written:

$$\frac{dP_A}{dt} = \frac{1}{C} \frac{dV_A}{dt} + \frac{dP_{pl}}{dt} \quad (3)$$

where P_A is the terminal airway pressure. Equivalently this is

$$\frac{dP_A}{dt} = \frac{dP_{tp}}{dt} + \frac{dP_{pl}}{dt} \quad (4)$$

where P_{tp} is the transpulmonary pressure ($P_{tp} = P_A - P_{pl}$).

The relationship between P_{tp} and volume in each acinus was described by the following phenomenological equation (Venegas et al., 1998):

$$V = a + b \left(1 + e^{(-P_{tp} - c)/d} \right)^{-1} \quad (5)$$

where V was expressed as a percentage of V_{TLC} . Each of the parameters in this equation has a physiological meaning: V is volume of the terminal ventilation unit (here the acinus), a is RV (%), b is the VC (or the total change in volume between the upper and lower asymptotes of the curve (%)), c (cmH₂O) is the pressure at the inflection point of the sigmoidal curve and also corresponds to the point of highest compliance, d (cmH₂O) is proportional to the pressure range over which most of the volume change takes place. The pressure at which the function rapidly changes slope - the upper (P_{cu}) and lower (P_{cl}) corner points of the P-V curve (cmH₂O) - was determined by the intersection of the tangent to the P-V curve at its point of greatest compliance (c) and the upper and lower asymptotes. The parameter d was defined by the distance along the pressure axis between the point c and the corner points. That is, $P_{cl} = c - 2d$, and $P_{cu} = c + 2d$. The parameters in Equation (5) were chosen to represent a ‘normal’ lung with $a = 10\%$, $b = 90\%$, $c = 6.5$ cmH₂O and $d = 3.8$ cmH₂O. One

criteria for the parameter selection was that the model would produce a baseline S_{cond} that is consistent with a normal healthy lung. That is, selection of a different parameter set will give a different quantitative prediction for baseline S_{cond} . We have quantified the sensitivity of the model to the a, c, and d parameters as the rate of change of S_{cond} with change of parameter (%/%) : -2.15 for a; 3.66 for b; and -0.44 for c.

All acini in the model were assumed equally expanded at TLC, and therefore the maximal volume of the acinus was calculated by dividing TLC volume by the number of acini. Initial (FRC) volumes in the model were distributed by assuming that at FRC the P_p pressure is linearly proportional to height along the gravitational axis.

Compliance in Equation 3 was calculated from Equation (5) as $C = dV/dP$. C was recalculated and updated for each acinus at every 0.01 s during the simulation.

The pleural pressure differential was an input described by a sinusoidal function, and a fixed zero pressure boundary condition was prescribed at the tracheal entrance. The stiffly accurate solver RADAU5 (Hairer et al., 1986) was used to solve the resulting system of ordinary differential and algebraic equations, with adaptive time-step size $\ll 0.01$ s. The peak differential of pleural pressure was converged to using the bisection method. A target tidal volume of 1 L was specified, and the ventilation simulation was considered complete when a tidal volume within the experimental tolerance of 50 mL (5%) was attained in the model.

- We model nitrogen washout in anatomically-representative airway and tissue model
- Ventilation is driven by a nominal pleural pressure change
- Ventilation defects seen on imaging are simulated by narrowing airway geometry
- Multiple breath washout is simulated for the integrated system
- Estimates of asthma severity may differ between using imaging or multiple breath washout

Figure 1.

Regional distribution of flow and washin gas in the model. The raw terminal unit ventilation does not show a strong gravitational distribution of ventilation. The ventilation normalised by volume (specific ventilation) however shows the linear gravitationally dependent distribution expected. The gas distribution in the lungs is similar to that of specific ventilation distribution although there is a greater heterogeneity of distributions in the iso-gravitational plane and some decrease of regional gas concentration in the dependent lung.

Figure 2.

The effect of airway resistance on the distribution of washed in gas after one breath. A) Ventilation distributed according to the tissue compliance (zero resistance). B) Ventilation distribution dependent on both tissue compliance and airway resistance. Scnd is 0.0161 L^{-1} for A, and 0.0278 L^{-1} for B. Note although minor differences can be seen in the simulations the overall distribution of washed in gas is very similar.

Figure 3.

Flow against time for acini in sections of the baseline lung model along the gravitational axis. A small degree of flow asynchrony is evident, as a consequence of the non-uniform time constants of the peripheral acinar units.

Figure 4.

The effect of constricting only the terminal airways in contiguous regions on the regional distribution of inert gas. Results are illustrated as the distribution of oxygen at the end of the first inspiration normalised by the regional distribution of oxygen under baseline conditions. Note that no significant redistribution of tracer gas is seen until high levels of constriction are imposed on the airways.

Figure 5.

Concentration of washin gas post-bronchoconstriction of 10 % of the named generation airways and all airways distal to them, normalised by washin gas concentration under baseline conditions. In each simulation the radius is decreased by the percentage noted under each column.

Figure 6.

Defect volume determined by measuring the normalised concentration in either the terminal branch or the parent branch at end expiration. Fewer defects are identified when the concentration in the parent branch is considered than when the concentration in the terminal branch is considered.

Figure A.1.

The pressure-volume relationship from Venegas et al. (1998) as used in the current model, demonstrating consistency with other model estimations for the relationship from Pengelly et al. (1977) and Murphy and Engel (1978).

Table 1

Physiological response to constriction of a randomly selected 10% of the airways in generation 12 only. Results are shown for the change in anatomical deadspace, airway resistance, Scond, and LCI.

% constriction	Deadspace (% baseline)	Resistance (% baseline)	Scond (L ⁻¹)	LCI (TO)
0 % (baseline)	100.00	100.00	0.0274	4.94
20 %	98.41	100.38	0.0262	4.94
40 %	98.24	100.88	0.0248	4.94
60 %	98.09	101.52	0.0260	4.94
80 %	97.96	102.26	0.0262	4.94
90 %	97.60	102.63	0.0265	4.94

Table 2

Physiological response to constriction of the terminal bronchioles that subtend a randomly selected 10% of the airways in generation 12. Results are shown for the change in anatomical deadspace, airway resistance, Scond, and LCI

% constriction	Deadspace (% baseline)	Resistance (% baseline)	Scond (L ⁻¹)	LCI (TO)
0 (baseline)	100.00	100.00	0.0274	4.90
20 %	98.01	100.72	0.0261	4.72
40 %	97.53	101.93	0.0260	4.71
60 %	97.15	103.29	0.0268	4.93
80 %	96.86	105.05	0.2698	8.57
90 %	96.79	105.34	0.0268	4.86

Physiological response to constriction of all airways including and below a randomly selected 10% of the airways in generations 10, 11, and 12. Results are shown for the change in anatomical deadspace, airway resistance, Second, LCI, and FRC estimated from gas washout.

Table 3

% constriction	Deadspace (% baseline)	Resistance (%baseline)	Second (L ⁻¹)	LCI (TO)	FRC (L)
Constriction of 10 % of 10 th generation airways and airways below					
20	96.53	103.26	0.0270	4.95	1.18
40	94.89	106.08	0.0277	4.95	1.18
60	93.68	108.04	0.2428	5.25	1.20
80	92.89	109.38	0.0509	4.67	1.11
90	92.66	109.99	0.0292	4.70	1.05
Constriction of 10 % of 12 th generation airways and airways below					
20	97.06	101.66	0.0259	4.97	1.18
40	95.84	103.40	0.0220	4.89	1.18
60	94.96	104.82	0.1276	5.05	1.20
80	94.23	105.82	0.1289	5.33	1.13
90	94.40	106.25	0.0189	4.60	1.07
Constriction of 10 % of 14 th generation airways and airways below					
20	97.26	101.66	0.0352	4.95	1.18
40	96.18	103.41	0.0439	4.95	1.18
60	95.36	104.84	0.1820	5.10	1.19
80	94.81	105.84	0.0928	4.65	1.15
90	94.67	106.25	0.0206	4.70	1.09

Effect of respiratory asymmetry on calculation of Sacin and Scond. Raw values are given in the first two columns. Although the total V_T is constant at 1 L, the regional V_T alters with bronchoconstriction (third column), reflecting redistribution of V_T away from the constricted regions. The indices in the right-most two columns are corrected to a 1 L V_T .

Table 4

	Sacin (L ⁻¹) (raw V_T)	Scond (L ⁻¹) (raw V_T)	V_T (in model) (L)	Sacin (L ⁻¹)	Scond (L ⁻¹)
Baseline					
Symmetric	0.0017	0.0010	0.84	0.0020	0.0012
Asymmetric	0.0821	0.0015	0.84	0.0978	0.0018
80% constriction					
Symmetric	0.0016	0.0242	0.70	0.0023	0.0347
Asymmetric	0.1089	0.0131	0.70	0.1566	0.0188