A human acinar structure for simulation of realistic alveolar plateau slopes

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Dutrieue, Brigitte, Frederique Vanholsbeck, Sylvia Verbanck, and Manuel Paiva. A human acinar structure for simulation of realistic alveolar plateau slopes. J Appl Physiol 89: 1859–1867, 2000.—We simulated the intra-acinar contribution to phase III slope ($S_{acin}$) for gases of differing diffusivities (He and SF₆) by solving equations of diffusive and convective gas transport in multi-branch-point models (MBPM) of the human acinus. We first conducted a sensitivity study of $S_{acin}$ to asymmetry and its variability in successive generations. $S_{acin}$ increases were greatest when asymmetry and variability of asymmetry were increased at the level of the respiratory bronchioles (generations 17–18) for He and at the level of the alveolar ducts (generations 20–21) for SF₆, corresponding to the location of their respective diffusion fronts. On the basis of this sensitivity study and in keeping with reported acinar morphometry, we built a MBPM that actually reproduced experimental $S_{acin}$ values obtained in normal subjects for He, N₂, and SF₆. Ten variants of such a MBPM were constructed to estimate intrinsic $S_{acin}$ variability owing to peripheral lung structure. The realistic simulation of $S_{acin}$ in the normal lung and the understanding of how asymmetry affects $S_{acin}$ for different diffusivity gases make $S_{acin}$ a powerful tool to detect structural alterations at different depths in the lung periphery.

multi-branch-point models; multiple-breath washout; gas mixing; diffusion-convection interdependence; airway asymmetry; helium; SF₆

PHASE III SLOPE OF THE SINGLE-BREATH washout, which is generally referred to as a marker of small airway alterations, can be generated by various mechanisms. In the human lung, two major mechanisms can be distinguished (10). One is thought to be operational at the level of the intra-acinar airways, where the balance of diffusion and convection establishes a quasi-stationary diffusion front during inspiration. At this level, the asymmetry of the acinar structure generates intra-acinar concentration differences that cause a phase III slope upon expiration. The other mechanism involves purely convective gas transport, generating concentration differences between lung units on inspiration and sequential emptying during expiration, also leading to a sloping phase III. The most familiar example of the latter mechanism results from sequential emptying between top and bottom lung regions with different specific ventilation. However, such a convection-dependent mechanism can also be operational within small lung regions. In recent years, several studies have been aimed at assessing the convective component of the phase III slope, in particular the contribution from gravity (4, 12). The present study focuses on the intra-acinar part of the phase III slope ($S_{acin}$).

By using a multiple-breath washout analysis that was initially developed for physiological studies of ventilation distribution (2) and was adapted in recent years for clinical application (14, 15), it is possible to isolate $S_{acin}$. The purpose of the present work was to quantitatively reproduce the experimental $S_{acin}$ values obtained from the existing literature simply by using equations that describe diffusive and convective gas transport in a realistic structure of the human acinus.

Previous simulation studies of gas transport at the acinar level (8) have indicated that intra-acinar concentration differences occur when 1) transport due to convection and diffusion are of the same order of magnitude and 2) the acinar structure is asymmetrical. The initial model geometries for simulation of intra-acinar gas transport (9, 11) were based on the morphometric data reported by Hansen and Ampaya (6) that accounted, to some extent, for intra-acinar asymmetry. A more detailed description of the human acinus by Haefeli-Bleuer and Weibel (5) prompted the development of a more realistic model of intra-acinar transport (13). All these studies highlighted the complex interactions between serial and parallel branch points and confirmed the principle of the diffusion convection mechanism by which a phase III slope could be generated, also mimicking the dependence of phase III slope on lung volume, inspired volume, flow, and gas diffusivity (11). However, these studies did not actually succeed in quantitatively reproducing the experimental phase III slope, and the degree of underestimation...
of absolute $S_{\text{acin}}$ depended on the diffusivity of the gas. For He, $N_2$, and $SF_6$, phase III slopes were underestimated by 85%, 74%, and 28%, respectively (13). The present study reexamines the intra-acinar morphometry, makes a quantitative evaluation of the critical characteristics of the intra-acinar branching pattern, and quantitatively reproduces the experimental $S_{\text{acin}}$, i.e., the acinar contribution to the phase III slope, for gases with different diffusivities.

METHODS

Model of the human acinus. The equations used to describe gas transport in the human acinus are given in the Appendix. The anatomic basis for all acinar model geometries considered here is the morphometric study by Haefeli-Bleuer and Weibel (5), who measured airway dimensions from generation 15 (first respiratory bronchiole) down to the alveolar sacs with the longest pathways extending into generation 27. These authors also provided the branching pattern of a single acinus that was previously used to construct a multi-branch-point model (MBPM) (13) that will be considered here as a reference model, MBPM$_{ref}$. The branching pattern of MBPM$_{ref}$ is depicted in Fig. 1A, and the volume asymmetry at each branch point of the model is plotted in Fig. 1B. Each branch point subtends two intra-acinar units of volume, $V_1$ and $V_2$, respectively. Assuming $V_1 \leq V_2$, the asymmetry (Asym) at any given branch point is defined as

$$\text{Asym} = 1 - \frac{V_1}{V_2} \quad (1)$$

In such a way, Asym = 0 corresponds to a symmetrical branch point, i.e., subtending two units of identical volume.

For the purpose of the present study, we developed an algorithm to build different MBPM geometries, following predefined Asym patterns distributed over serial and parallel branch points. The algorithm starts by subtracting the volume of the parent duct from the total acinar volume and partitioning the remaining volume into two subunits so as to obtain the predefined Asym value for that first branch point. In the next branching generation, each subunit undergoes the same procedure, and subdivision continues until all pathways end in subunits that fall within the range of alveolar sac volume. The number of intra-acinar generations imposes a constraint on the range of Asym values that can be achieved to obtain a realistic MBPM of the human acinus. For instance, if one assumes a constant Asym = 0.7 throughout the acinar branching tree, this would require subdivisions down to generation 28. In fact, considering a MBPM with a constant asymmetry in generations 15 through 23, the maximum asymmetry that can be achieved is Asym = 0.6.

Most MBPM branching patterns presented here are obtained by assigning to each successive MBPM generation a normal distribution of Asym values over all parallel branch points of that generation. The MBPM can then be characterized in terms of the mean and standard deviation ($\mu_{\text{Asym}}$, SD$_{\text{Asym}}$) of the asymmetry distribution attributed to each generation. One example of a MBPM with an Asym distribution characterized by $\mu_{\text{Asym}} = 0.4$ and SD$_{\text{Asym}} = 0.3$ in each successive intra-acinar generation is shown in Fig. 2A; the individual Asym values are plotted in Fig. 2B.

The acinar volume of all MBPM constructed here was set to $187 \times 10^{-3}$ ml, i.e., the mean acinar volume measured by Haefeli-Bleuer and Weibel (5) with a lung inflated to 5.5 liters (corresponding to 90% of its total lung capacity). The conductive airway dimensions from Weibel’s symmetrical model A (17), between generations 0 and 14, were rescaled isotropically from 4.8 to 5.5 liters (5) to obtain a conductive airways volume of 119 ml. The remainder of the 5.5-liter lung volume was considered to be in the acini, and, with an acinar volume of $187 \times 10^{-3}$ ml, this resulted in 28,785 acini $(5,500 - 119 \text{ ml})/(187 \times 10^{-3} \text{ ml})$. Finally, an additional dead space of 50 ml was added to account for the pharyngolaryngeal and mouth cavity volume (7).

Comparison between simulations and experimental results. The experimental data used for actual comparison with simulations were those obtained from three subjects performing multiple-breath washout tests including He and $SF_6$ tracer gases (12). These washout maneuvers involved 12 breaths with a mean tidal volume of 1.23 liters (flow rate was $\sim 0.5 \text{ l/s}$), starting from functional residual capacity that averaged 3.33 liters. The original He, $SF_6$ washin, and $N_2$ washout tracings were reanalyzed to fully comply with the method of phase III slope analysis for $S_{\text{acin}}$ computation. The detailed description and underlying theory for the computation of $S_{\text{acin}}$ can be found elsewhere (15). Briefly, inspired gases (He, $SF_6$) are first rescaled to represent lung resident gases (such as $N_2$) to obtain positive phase III slopes for all gases under study. Then, phase
III slopes are computed by linear regression on $N_2$, He, or $SF_6$ concentrations between 0.7 and 1.2 liters expired volume and normalized by the corresponding mean expired concentration in all 12 expirations. By plotting these normalized slopes as a function of lung turnover (TO, cumulative expired volume divided by the subject’s functional residual capacity), the conductive component to ventilation inhomogeneity can be determined. By defining the conductive component as the regression slope of the normalized slope vs. TO for $TO > 1.5$, its contribution to the normalized slope of the first breath can be subtracted (in proportion to TO of the first breath) to obtain $S_{acin}$. In this way, the following experimental $S_{acin}$ values were obtained for He, $N_2$, and $SF_6$ gases (means ± SD): 0.054 ± 0.009 liter$^{-1}$ (He), 0.080 ± 0.007 liter$^{-1}$ ($N_2$), and 0.109 ± 0.005 liter$^{-1}$ ($SF_6$), representing, respectively, 91.3, 91.6, and 92.0% of corresponding phase III slopes of the first breath. These $S_{acin}$ values constitute the experimental basis for comparison with simulations.

RESULTS

Intra-acinar asymmetry and diffusion front. Figure 3 shows simulated He and $SF_6$ diffusion fronts (mean gas concentrations) at the end of a 1.23-liter inspiration using a flow equal to 0.5 l/s and diffusion coefficients 0.6 cm$^2$/s and 0.1 cm$^2$/s for He and $SF_6$, respectively. Dashed lines are the He and $SF_6$ concentrations for a symmetrical MBPM ($\mu_{Asym} = 0$; $SD_{Asym} = 0$ in all generations), whereas solid lines correspond to the most asymmetrical MBPM ($\mu_{Asym} = 0.6$; $SD_{Asym} = 0$ in generations 15–23). Note that the asymmetrical MBPM extends into four more peripheral generations than the symmetrical MBPM. The steepest slope in concentration curves, indicating the branch points contributing the most to the phase III slope generation, are located, respectively, for He and $SF_6$ in generations 17 and 19, irrespective of MBPM asymmetry (at least in the $\mu_{Asym}$ range 0–0.6).

Sensitivity of phase III slope to intra-acinar asymmetry. We conducted a systematic study of He and $SF_6$ phase III slope sensitivity to $\mu_{Asym}$. First, a set of simulations was considered in which $\mu_{Asym} = 0.4$ was imposed individually in successive branching generations of the MBPM by considering $\mu_{Asym} = 0i$ in all MBPM generations, except for one generation in which $\mu_{Asym} = 0.4$ and $SD_{Asym} = 0$. An example of the resulting Asym distribution in MBPM generations is shown in Fig. 4A, in which $\mu_{Asym} = 0.4$ was imposed in generation 18. For each successive generation $i$ in which the asymmetry was introduced ($i = 15–23$), this led to a slope $S_{\mu=0.4,i}$. A corresponding slope increase $\Delta S_{\mu=0}(i)$ with respect to the symmetrical MBPM (with simulated slope $S_{\mu=0}$) was then defined as

$$\Delta S_{\mu=0}(i) = S_{\mu=0.4,i} - S_{\mu=0}$$ (2)

Figure 4B shows the slope increases $\Delta S_{\mu=0}$ as a function of $i$, indicating that maximal He and $SF_6$ phase III slope increases were obtained when the branching asymmetry $\mu_{Asym} = 0.4$ was introduced in generations 18 and 21, respectively.

Figure 5 extends the results of Fig. 4B by applying any given $\mu_{Asym}$ value ranging between 0 and 0.6 to all generations between 15 and 23 simultaneously. In this case, one global slope increase with respect to...
slope sensitivity to Asym variability between parallel branch points (i.e., nonzero SDAsym) in another set of MBPM simulations. In this case, we considered \( \mu_{\text{Asym}} = 0.4 \) in all MBPM generations, and SDAsym = 0 was imposed on all intra-acinar generations except for one generation \( i \) in which SDAsym = 0.3 (variable asymmetry only among branch points of generation \( i \)). An example of the resulting Asym distribution in MBPM generations is shown in Fig. 6A, in which the variability of asymmetry was imposed in generation \( i = 18 \). For each MBPM simulation with SDAsym = 0.3 in generation \( i \), a corresponding slope increase \( \Delta S_{\text{SD}=0}(i) \) was defined, this time with respect to a MBPM with constant asymmetry (\( \mu_{\text{Asym}} = 0.4 \)), as

\[
\Delta S_{\text{SD}=0}(i) = S_{\text{SD}} = 0.3, i - S_{\text{SD}} = 0
\]

where \( S_{\text{SD}=0.3,i} \) is the simulated slope in a MBPM with SDAsym = 0.3 in generation \( i \) (SDAsym = 0 in all other generations and \( \mu_{\text{Asym}} = 0.4 \) in all generations) and \( S_{\text{SD}=0} \) is the simulated slope in a MBPM with \( \mu_{\text{Asym}} = 0.4 \) and SDAsym = 0 in all generations between 15 and 23. Both for He and SF6, the resulting \( \Delta S_{\text{SD}=0}(i) \) are shown in Fig. 6B for \( i = 16–23 \) (generation 15 has only one branch point). Maximal phase III slope increases were obtained when the variability in asymmetry (SDAsym = 0.3) was introduced in generations 17 and 20, for He and SF6, respectively. Figure 7 extends the results of Fig. 6B by applying any given SDAsym value ranging between 0 and 0.35 to all generations between 15 and 23 simultaneously (while \( \mu_{\text{Asym}} \) remains 0.4 throughout). In this case, a global slope increase with respect to the MBPM with constant asymmetry (SDAsym = 0.3) is obtained for each SDAsym value and plotted against SDAsym in Fig. 7. Note that, in this figure, the He and SF6 simulated data points corresponding to SDAsym = 0.3 were obtained with the MBPM shown in Fig. 2 (SDAsym = 0.3 and \( \mu_{\text{Asym}} = 0.4 \) in all generations).

**Fig. 4.** Simulations of phase III slope sensitivity to \( \mu_{\text{Asym}} \) imposed at different levels of a MBPM, in the absence of variability in asymmetry at any MBPM level (see text for details). A: example of MBPM Asym distribution. In this case, a constant Asym of 0.4 is imposed in generation \( i = 18 \), with \( \mu_{\text{Asym}} = 0 \) in all other generations. Solid lines, \( \mu_{\text{Asym}} \). B: Phase III slope increases (\( \Delta S_{\mu=0} \)) with respect to the symmetrical MBPM (Eq. 2) as a function of generation \( i \) in which \( \mu_{\text{Asym}} = 0.4 \) is imposed (\( \mu_{\text{Asym}} = 0 \) in all other generations; SDAsym = 0 in all generations at all times). Triangles, He; circles, SF6; open symbols correspond to the MBPM described in A.

The symmetrical MBPM (\( \Delta S_{\mu=0} \)) is obtained for each \( \mu_{\text{Asym}} \) value. The resulting \( \Delta S_{\mu=0} \) values for He and SF6 are plotted as a function of the \( \mu_{\text{Asym}} \) in Fig. 5, showing an exponential-like increase with \( \mu_{\text{Asym}} \) in the range 0–0.6. By comparison of selected data points in Figs. 4B and 5, it can be inferred that the He and SF6 phase III slope increases obtained by imposing \( \mu_{\text{Asym}} = 0.4 \) on all MBPM generations simultaneously roughly correspond to the summation, over all generations, of He and SF6 phase III slope increases obtained by imposing \( \mu_{\text{Asym}} = 0.4 \) in each individual generation (considering all data points in Fig. 4B). Indeed, the \( \Delta S_{\mu=0} \) value for \( \mu_{\text{Asym}} = 0.4 \) in Fig. 5, yielding 0.022 liter\(^{-1}\) (He) and 0.031 liter\(^{-1}\) (SF6), almost equals the sum of \( \Delta S_{\mu=0}(i) \) for \( i = 15–23 \) (open data points in Fig. 5), which amounts to 0.021 liter\(^{-1}\) (He) and 0.028 liter\(^{-1}\) (SF6).

**Fig. 5.** Simulations of phase III slope sensitivity to constant asymmetry imposed in MBPM generations 15–23 simultaneously (SDAsym = 0 in all generations at all times). \( \Delta S_{\mu=0} \) with respect to the symmetrical MBPM is plotted as a function of the \( \mu_{\text{Asym}} \) value. Triangles, He; circles, SF6; open symbols (\( \Delta S_{\mu=0} \) values for \( \mu_{\text{Asym}} = 0.4 \)) are the summation of the \( \Delta S_{\mu=0}(i) \) values in Fig. 4B for \( i \) between 15 and 23.

Sensitivity of phase III slope to the variability of intra-acinar asymmetry. In analogy to Fig. 4, we conducted a systematic study of He and SF6 phase III
To further explore the role of variability of asymmetry, as evidenced by Figs. 6 and 7, we considered additional sets of simple simulations (Table 1). We considered MBPM that are symmetrical except in one generation in which $\mu_{\text{Asym}} \neq 0$. For He and SF$_6$ simulations, $\mu_{\text{Asym}} \neq 0$ was considered in generations 18 and 21, respectively (because, in these generations, phase III slope of the gas under consideration had been shown to be particularly sensitive to asymmetry). In the generation in which $\mu_{\text{Asym}} \neq 0$, four configurations were considered: a) Asym = 0.4 on all branch points of that generation; b) Asym = 0.6 on half the number of branch points and Asym = 0.2 on the other half; c) Asym = 0.6 on half the number of branch points and Asym = 0 on the other half; and d) Asym = 0.2 on half the number of branch points and Asym = 0 on the other half. The resulting He and SF$_6$ slope increases compared with the symmetrical model ($\Delta S_{\mu=0}$) are also depicted in Table 1 and show that $\Delta S_{\mu=0}$ obtained with $b$ were indeed larger than those obtained with $a$, and that $\Delta S_{\mu=0}$ obtained from MBPM configurations $c$ and $d$ add up exactly to that obtained with $b$.

Table 1. Sensitivity of He and SF$_6$ slope to variability of asymmetry in four simple models

<table>
<thead>
<tr>
<th>MBPM</th>
<th>Asym</th>
<th>$\Delta S$ (He) (liter$^{-1}$)</th>
<th>$\Delta S$ (SF$_6$) (liter$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n/2$</td>
<td>$n/2$</td>
<td>$i = 18$; $n_i = 8$</td>
</tr>
<tr>
<td>$a$</td>
<td>0.40</td>
<td>0.40</td>
<td>0.065</td>
</tr>
<tr>
<td>$b$</td>
<td>0.60</td>
<td>0.20</td>
<td>0.119</td>
</tr>
<tr>
<td>$c$</td>
<td>0.60</td>
<td>0.00</td>
<td>0.113</td>
</tr>
<tr>
<td>$d$</td>
<td>0.00</td>
<td>0.20</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Asym, asymmetry at a given branch point, defined by Eq. 1. MBPM, multi-branch-point model in which a given distribution of asymmetry is imposed on branch points of a particular generation $i$ and Asym = 0 on branch points of all other generations. $n_i$, number of branch points of generation $i$. For He and SF$_6$ simulations, the specified Asym distributions $a$ to $d$ are imposed on generations 18 and 21, respectively; $\Delta S$ are the He and SF$_6$ slope increases with respect to symmetrical MBPM.
The main goal of the present study was to obtain quantitative agreement between $S_{\text{acin}}$ in the normal human lung and phase III slopes simulated with a model of the acinus (MBPM). This was essentially done by modifying MBPM geometry within the constraints of available anatomic data. We successfully reproduced experimental $S_{\text{acin}}$ values for He, $N_2$, and SF$_6$ obtained in healthy subjects. More importantly, the sensitivity study that led up to this final goal provided major insights into the relation between acinar structure and phase III slope. It was shown that, besides the mean volume asymmetry between any two lung units subtended by all parallel branch points of a given intra-acinar generation, the variability in asymmetry among parallel branch points has a crucial impact on phase III slope. The study also confirmed that, even in a complex MBPM structure, phase III slopes of gases with a sixfold difference in diffusivity (He, SF$_6$) can be indexes of airway structural change at different lung depths within the acinus.

**DISCUSSION**

The main goal of the present study was to obtain quantitative agreement between $S_{\text{acin}}$ in the normal human lung and phase III slopes simulated with a model of the acinus (MBPM). This was essentially done by modifying MBPM geometry within the constraints of available anatomic data. We successfully reproduced experimental $S_{\text{acin}}$ values for He, $N_2$, and SF$_6$ obtained in healthy subjects. More importantly, the sensitivity study that led up to this final goal provided major insights into the relation between acinar structure and phase III slope. It was shown that, besides the mean volume asymmetry between any two lung units subtended by all parallel branch points of a given intra-acinar generation, the variability in asymmetry among parallel branch points has a crucial impact on phase III slope. The study also confirmed that, even in a complex MBPM structure, phase III slopes of gases with a sixfold difference in diffusivity (He, SF$_6$) can be indexes of airway structural change at different lung depths within the acinus.

**Sensitivity of phase III slope to intra-acinar asymmetry.** A key feature of intra-acinar gas transport is the diffusion front (Fig. 3), which is quasi-stationary over the course of an inspiration and results from a balance of convective and diffusive gas transport. This implies that the diffusion front of the least diffusive gas (SF$_6$) is more peripherally located than that of a more diffusive gas (He). Of particular relevance is the fact that MBPM asymmetry has virtually no impact on the actual location of the diffusion front (Fig. 3), which greatly facilitates interpretation of phase III slope changes for different diffusivity gases. Indeed, diffusion-convection interdependence theory (8) predicts that branch points situated on the steepest part of the diffusion front of a given gas will contribute the most to the overall phase III slope of that gas. The comparison of Figs. 4B and 6B with Fig. 3 confirms that this is applicable to He and SF$_6$ in a MBPM structure. Consequently, structural alterations affecting asymmetry at the level of the respiratory bronchioles (generations 17–18) will preferentially modify He phase III slope, whereas changes in asymmetry at the level of the alveolar ducts (generations 20–21) will preferentially affect SF$_6$ phase III slope.

Sensitivity studies to intra-acinar asymmetry indicate the crucial importance of variable Asym compared with constant Asym in generating a phase III slope. The reason a variable asymmetry produces larger phase III slopes than a constant asymmetry for a given $\mu_{\text{Asym}}$ per generation is that MBPM asymmetry has virtually no impact on the actual location of the diffusion front (Fig. 3), which greatly facilitates interpretation of phase III slope changes for different diffusivity gases. Indeed, diffusion-convection interdependence theory (8) predicts that branch points situated on the steepest part of the diffusion front of a given gas will contribute the most to the overall phase III slope of that gas. The comparison of Figs. 4B and 6B with Fig. 3 confirms that this is applicable to He and SF$_6$ in a MBPM structure. Consequently, structural alterations affecting asymmetry at the level of the respiratory bronchioles (generations 17–18) will preferentially modify He phase III slope, whereas changes in asymmetry at the level of the alveolar ducts (generations 20–21) will preferentially affect SF$_6$ phase III slope.

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**Table 2. Asymmetry characteristics of intra-acinar MBPM**

<table>
<thead>
<tr>
<th>Generation Number</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
<th>21</th>
<th>22</th>
<th>23</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu_{\text{Asym}}$</td>
<td>MBPM$^a$</td>
<td>0.40</td>
<td>0.40</td>
<td>0.40</td>
<td>0.40</td>
<td>0.40</td>
<td>0.40</td>
<td>0.40</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>MBPM$_{\text{ref}}$</td>
<td>0.11</td>
<td>0.13</td>
<td>0.16</td>
<td>0.17</td>
<td>0.26</td>
<td>0.31</td>
<td>0.38</td>
<td>0.60</td>
</tr>
<tr>
<td>$\text{SD}_{\text{Asym}}$</td>
<td>MBPM$^a$</td>
<td>0.00</td>
<td>0.24</td>
<td>0.28</td>
<td>0.33</td>
<td>0.30</td>
<td>0.28</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>MBPM$_{\text{ref}}$</td>
<td>0.00</td>
<td>0.01</td>
<td>0.21</td>
<td>0.07</td>
<td>0.12</td>
<td>0.22</td>
<td>0.17</td>
<td>0.14</td>
</tr>
</tbody>
</table>

$\mu_{\text{Asym}}$ and $\text{SD}_{\text{Asym}}$ are mean and standard deviation of the Asym values (Eq. 1) at parallel branch points of any given MBPM generation; MBPM$_{\text{ref}}$ is the so-called reference MBPM (13), and MBPM$^a$ represents the 10 MBPM models corresponding to this $\mu_{\text{Asym}}$ and $\text{SD}_{\text{Asym}}$ profile that reproduce the experimental acinar contribution to the phase III slopes, $S_{\text{acin}}$, for He, $N_2$, and SF$_6$ (see text for details).
Another interesting feature of the MBPM simulations is that the sum of slopes generated at the MBPM entrance by imposing a given Asym in successive intracinar generations (Fig. 4B) approximately corresponds to the slope generated at the MBPM entrance when the same Asym is imposed on all MBPM generations simultaneously (Fig. 5). Indeed, in relatively simple MBPM examples such as these, the superposition principle holds for phase III slopes generated at serially distributed branch points. The superposition principle holds also for parallel distributed branch points in simple MBPM such as illustrated from simulations with MBPM b–d (Table 1). Indeed, the phase III slopes generated by imposing either Asym = 0.6 (c) or Asym = 0.2 (d) on half the number of branch points of a given generation, and Asym = 0 (symmetry) on the other half, added up to the slope generated with Asym = 0.6 on half the number of branch points and Asym = 0.2 on the other half (b). Both superposition principles, together with results from sensitivity studies, were essential guidelines to build the MBPM* to reproduce experimental $S_{acin}$. 

Simulations of experimental $S_{acin}$ values. The extent of phase III slope increases ($\Delta S$) with $\mu_{Asym}$ (Figs. 4 and 5) or $SD_{Asym}$ (Figs. 6 and 7) suggested that some combination of $\mu_{Asym}$ and $SD_{Asym}$ should yield a MBPM with SDAsym (0.40). This could explain why the underestimation of $S_{acin}$ was more marked for He than for SF6 with MBPMref simulations. In summary, to reproduce experimental $S_{acin}$ for gases of different diffusivity, the Asym distribution in MBPM* with respect to MBPMref was modified in two steps: first, $\mu_{Asym}$ was set to 0.4 uniformly, and, second, it was necessary to increase $SD_{Asym}$ throughout all generations.

The fact that overall asymmetry is an important contributor to phase III slope has previously encouraged simulation studies to artificially increase $\mu_{Asym}$ in models of the acinus to match experimental phase III slope values. For instance, Bowes et al. (1) contended to "have deliberately chosen a model with a degree of asymmetry greater than that demonstrated by a number of studies of acinar anatomy in the human lung." A major problem indicated by these authors was that no detailed anatomic data and branching pattern of an "average" acinus existed at the time. Although the present study provides an interesting new perspective on the role of variability of asymmetry over parallel branch points, it also reiterates the demand for more morphometric data in terms of average asymmetry and variability of asymmetry in successive generations of an average human acinus.

Besides the branching pattern of the single acinus reported in Ref. 5, which led to MBPMref (Table 2), we have checked whether the increased $\mu_{Asym}$ in the first MBPM* generations (with respect to MBPMref) could be accounted for, to some extent, by the available anatomic data. On the basis of the volume distribution of the 209 acini obtained from the human lung study of Haefeli-Bleuer and Weibel (5), we computed Asym values (Eq. 1) for all two-by-two combinations of acinar volume. This yielded $Asym = 0.35 \pm 0.21$ (mean $\pm SD$), which would correspond to a set of $\mu_{Asym}$ and $SD_{Asym}$ values for generation 14. This computation at least provides an indication that $\mu_{Asym}$ values in generations 15 and 16 of MBPMref (Table 2), obtained on the basis of the Asym of, respectively, one and two branch points of a single acinus (5), may have led to a severe underestimation of actual asymmetry in the first acinar generations. Therefore, the Asym distribution chosen for MBPM*, which led to realistic $S_{acin}$, seems reasonable.

The role of variability of asymmetry also has implications for the use of $S_{acin}$ in lung pathology. Indeed, if mild structural changes occur at a given lung depth,
with marginal influence on $\mu_{\text{Asym}}$ in that generation, these could nevertheless be reflected in an increased $S_{\text{acin}}$ through the effect of increased $SD_{\text{Asym}}$. Mean $S_{\text{acin}}$ values for $N_2$ yielded 0.107 liter$^{-1}$ in hyperresponsive subjects, 0.195 liter$^{-1}$ in asthmatic subjects, and 0.443 liter$^{-1}$ in chronic obstructive pulmonary disease patients (14, 15). In the above studies, only $N_2$ could be used. The importance of using gases of different diffusivity is illustrated by a recent follow-up study of

$$\frac{\partial C_{\text{K1}}}{\partial t} = \frac{D}{\Delta z_{\text{K1}}} \left( \frac{s(K_1) - s(K_2)}{s(K_1) + s(K_2)} \right) \frac{[C(K_1) - C(K_2)]S(K_1)}{\Delta z_{\text{m}(K_1)}}$$

$$+ \frac{D}{S(K_2)} \left( \frac{s(K_2) - s(K_1)}{s(K_2) + s(K_1)} \right) \frac{[C(K_2) - C(K_1)]S(K_2)}{\Delta z_{\text{m}(K_2)}}$$

$$+ \frac{[s(K_1) - s(K_2)]}{\Delta z_{\text{m}(K_1)}} \frac{[C(K_1) - C(K_1)]}{\Delta z_{\text{m}(K_2)}}$$

$$+ \frac{C(K_1) - C(K_1)}{\Delta z_{\text{m}(K_2)}}$$

where subscripts M and T, respectively, refer to entities peripheral and proximal to a given node K, and where $\Delta z_{\text{m}(K)} = [\Delta z(K) + \Delta z(K)/2$ for $i = 1, 2$] and $\Delta z_{\text{T}} = [\Delta z(K) + \Delta z(K) - 1]/2; V_L (t = 0)$ is total lung volume at $t = 0; V_L$ is the total flow at lung entrance, and $\text{Hom}$ is the homogeneous expansion coefficient equaling $1 + V_L \times t/V_L (t = 0)$. Changes with respect to the previously used discretization of Eq. AI over a bifurcation (published in Ref. 16) are highlighted in bold and allow for different lengths of any two daughter ducts (represented by $K_1$ and $K_2$).

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APPENDIX

Gas transport in the human lung was simulated by solving a one-dimensional partial differential equation describing convective and diffusive gas transport along each pathway down to the alveolar sacs (10)

$$\frac{\partial C}{\partial t} = D \frac{s \partial^2 C}{s \partial z^2} + \frac{D \partial s \partial C}{s \partial z} - \frac{V \partial C}{s \partial z} - \frac{C \partial V}{\partial t}$$

(AI)

where $C$ is concentration and $z$ is cumulative longitudinal distance along the airway axes with its origin situated at the lung model entrance (in our simulations, $z = 0$ corresponds to the trachea); $s$ and $S$ are the airway cross sections without and with alveoli, respectively; $D$ is the binary molecular diffusion coefficient; and $V$ is convective flow (piston-type; positive and constant during inspiration; negative and constant during expiration). Finally, all volume changes ($\partial V/\partial t$) were considered isotropic, homogeneous, and in phase (16). Initial condition was $C(z, t = 0) = 0$ and boundary conditions were $C(z = 0, t) = 1$ during inspiration, $\partial C/\partial z (z = 0, t) = 0$ during expiration, and $\partial C/\partial t (z) = 0$ on all peripheral boundaries at all times.

For the purpose of the numerical solution of the gas transport equation, the human lung structure was discretized into nodes, and on a bifurcation node K, as the one depicted in Fig. 9, the finite difference equation corresponding to Eq. AI was
REFERENCES


