Structure-Function Relationships in the Pulmonary Arterial Tree

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Structure-Function Relationships in The Pulmonary Arterial Tree

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Abstract
Knowledge of the relationship between structure and function of the normal pulmonary arterial tree is necessary for understanding normal pulmonary hemodynamics and the functional consequences of the vascular remodeling that accompanies pulmonary vascular diseases. In an effort to provide a
means for relating the measurable vascular geometry and vessel mechanics data to the mean pressure-flow relationship and longitudinal pressure profile, we present a mathematical model of the pulmonary arterial tree. The model is based on the observation that the normal pulmonary arterial tree is a bifurcating tree in which the parent-to-daughter diameter ratios at a bifurcation and vessel distensibility are independent of vessel diameter, and although the actual arterial tree is quite heterogeneous, the diameter of each route, through which the blood flows, tapers from the arterial inlet to essentially the same terminal arteriolar diameter. In the model the average route is represented as a tapered tube through which the blood flow decreases with distance from the inlet because of the diversion of flow at the many bifurcations along the route. The taper and flow diversion are expressed in terms of morphometric parameters obtained using various methods for summarizing morphometric data. To help put the model parameter values in perspective, we applied one such method to morphometric data obtained from perfused dog lungs. Model simulations demonstrate the sensitivity of model pressure-flow relationships to variations in the morphometric parameters. Comparisons of simulations with experimental data also raise questions as to the “hemodynamically” appropriate ways to summarize morphometric data.

Knowledge of the relationship between structure and function of the normal pulmonary arterial tree is necessary for understanding normal pulmonary hemodynamics and the functional consequences of the vascular remodeling that accompanies pulmonary vascular diseases. It is also a step in the process of developing hypotheses regarding pulmonary arterial tree morphogenesis. As improved imaging techniques are applied to the pulmonary vasculature, the means for interpreting the morphometric data will become more important as well.

The complexity of the pulmonary arterial tree structure can make it difficult to recognize the functional significance of the quantifiable morphometric and biomechanical variables. One approach to clarifying relationships between structure and function has been to develop mathematical models that take advantage of data on the geometric and viscoelastic properties of the vessels and arterial tree to link structure and function with a much smaller number of parameters than the number of individual vessels comprising the tree. There are several examples of this approach, with a progression of models with increasing ability to predict the complexity of the hemodynamic behavior of the vascular tree while minimizing the complexity of mathematical expression. The latter is valuable insofar as it allows for a more intuitive understanding of the quantitative contribution of different variables to system function than do more detailed representations. The present study is a further attempt to find efficient ways of expressing the influence of vascular geometry, vessel mechanics, and blood rheology on mean pressure-flow relationships within the intrapulmonary arterial tree.

One approach to this problem has been to apply Poiseuille’s law for flow through fixed-diameter or distensible cylindrical tubes arranged in a symmetrical pattern with vessel dimensions based on morphometric measurements summarized according to a particular ordering scheme. Each order is characterized by a separate set of parameters, and then the equations for each order are concatenated. An alternative is to use a continuum model, which attempts to express the tree structure-function relationships with global parameters, minimizing the emphasis on particular ordering schemes. In the present study we present some further attempts toward maximizing the efficiency of expression of the pulmonary arterial structure-function relationships, and we explore
some model predictions. There is no expectation that the approach will provide model expressions that accommodate all the details of the pulmonary arterial tree function. Instead, the objective is to provide expressions that demonstrate aspects of the sensitivity of the hemodynamic function of the pulmonary arterial tree to tree geometry and vessel mechanics in a similar sense that Poiseuille’s law is useful for that purpose for individual vessels or that the sheet flow model of Fung and Sobin\textsuperscript{14,15} is useful for the pulmonary capillary bed. As is the case for those models, the expressions may also serve as building blocks for more comprehensive model development in the future.

To help put parameter values used in model simulations in perspective, we also include some morphometric and hemodynamic measurements carried out on isolated dog lungs.

Glossary

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a_1$</td>
<td>Antilog of intercept of log $N_j$ vs. log $D_j$, also defined by Eq. 1</td>
</tr>
<tr>
<td>$a_2$</td>
<td>Antilog of intercept of log $L_j$ vs. log $D_j$, also defined by Eq. 2</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Fractional change in vessel diameter per mmHg change in intravascular pressure</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>Slope of log $N_j$ vs. log $D_j$, also defined by Eq. 1</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>Slope of log $L_j$ vs. log $D_j$, also defined by Eq. 2</td>
</tr>
<tr>
<td>$D$</td>
<td>Vessel diameter</td>
</tr>
<tr>
<td>$D_v$</td>
<td>Diameter of vessels in which viscosity is midway between $\mu_p$ and $\mu_b$</td>
</tr>
<tr>
<td>$D_T$</td>
<td>Terminal arteriolar diameter</td>
</tr>
<tr>
<td>$D(x,P)$</td>
<td>Arterial diameter-pressure relationship</td>
</tr>
<tr>
<td>$D(0)$</td>
<td>Inlet diameter (i.e., at $x = 0$) at zero pressure</td>
</tr>
<tr>
<td>$D(0,0)$</td>
<td>Inlet diameter (i.e., at $x = 0$) at zero pressure</td>
</tr>
<tr>
<td>$D_j$</td>
<td>Diameter of vessels in order $j$</td>
</tr>
<tr>
<td>$D_1$</td>
<td>Diameter of parent vessel at a bifurcation</td>
</tr>
<tr>
<td>$D_2$</td>
<td>Diameter of the larger of two daughter vessels at a bifurcation</td>
</tr>
<tr>
<td>$D_3$</td>
<td>Diameter of the smaller of two daughter vessels at a bifurcation</td>
</tr>
<tr>
<td>$D_{in,j}$</td>
<td>Diameter at inlet of vessel of order $j$</td>
</tr>
<tr>
<td>$D_{out,j}$</td>
<td>Diameter at outlet of vessel of order $j$</td>
</tr>
<tr>
<td>$G$</td>
<td>Defined by Eq. 31</td>
</tr>
<tr>
<td>$K$</td>
<td>Defined by Eq. 31</td>
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<tr>
<td>$L_j$</td>
<td>Length of vessels in order $j$</td>
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<td>$\mu$</td>
<td>Blood viscosity</td>
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<td>$\mu_b$</td>
<td>Large vessel blood viscosity</td>
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<td>$\mu_p$</td>
<td>Plasma viscosity</td>
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<tr>
<td>$N_j$</td>
<td>Number of vessels in order $j$</td>
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<td>$P$</td>
<td>Intravascular pressure</td>
</tr>
<tr>
<td>$P_{in,j}$</td>
<td>Intravascular pressure at inlet of order $j$</td>
</tr>
<tr>
<td>$P_{out,j}$</td>
<td>Intravascular pressure at outlet of order $j$</td>
</tr>
<tr>
<td>$Q$</td>
<td>Cumulative blood volume upstream from all locations at distance $x$ from inlet</td>
</tr>
<tr>
<td>$Q_j$</td>
<td>Volume in order $j$</td>
</tr>
<tr>
<td>$Q(0)$</td>
<td>Total flow rate entering arterial tree</td>
</tr>
</tbody>
</table>
METHODS

Model

We begin with the observation, noted previously\textsuperscript{12, 32}, that for the intrapulmonary arterial tree the available morphometric data summaries, such as previously presented\textsuperscript{17, 22, 25, 26, 37, 54}, can be well approximated by

\begin{equation}
N_j = a_1 D_j^{-\beta_1}
\end{equation}

Equation 1

and

\begin{equation}
L_j = a_2 D_j^{\beta_2}
\end{equation}

Equation 2

where \(N\) is the number of vessels in order (or generation) \(j\); \(D\) and \(L\) are the average diameter and length, respectively, of the vessels in order \(j\), and \(j\) increases from inlet artery \((j = 1)\) to terminal arteries; and \(a_1, \beta_1, a_2, \text{ and } \beta_2\) are parameters summarizing the tree morphometry. As discussed previously\textsuperscript{12, 31, 32}, these morphometric parameters are apparently insensitive to the various ordering systems that have been applied to pulmonary arterial morphometric data to group vessels into order \(j\). The values of \(\beta_1, \beta_2, \text{ and } a_2\) characterize the tree structures, whereas \(a_1\) scales for the different-sized arterial trees from different species or the individuals of a species.

In the present investigation we take the continuum point of view\textsuperscript{32, 48}, from which vessel ordering is of minimal importance. For the continuum point of view expressed by Suwa et al.\textsuperscript{48}, any route the blood follows from pulmonary artery to a terminal arteriole may be visualized as being confined within a tapering tube through which the blood flow decreases with distance from the inlet to account for flow drawn off at the many bifurcations along the route. An alternative visualization leading to the same development might be to think of the vascular tree as branching continuously, such that \(N\) or \(j\) need not be thought of as having only integer values. Figure 1 is a diagrammatic representation of one such route through the tree depicted as a trunk with side branches pruned to emphasize the taper of the trunk. The taper is quantified by \(\beta_1, \beta_2, \text{ and } a_2\).
Fig. 1. Diagrammatic representation of a pulmonary arterial tree trunk with pruned side branches. Taper of trunk, expressed as diameter (D) as a function of distance (x) from inlet, is specified by 3 parameters: $\beta_1$, $\beta_2$, and $a_2$. Aspect (diameter-to-length) ratio was chosen for diagrammatic purposes.

We begin with the examination of a route through a symmetrical, bifurcating tree. After Suwa et al. and noting that, for a bifurcating tree, $N_j = 2^{(j-1)}$, each vessel segment may be considered to be a frustum of a cone having diameter $D_{\text{in},j} = D_{\text{in},1}/2^{(j-1)/\beta_1}$ at the inlet to the vessel segment and $D_{\text{out},j} = D_{\text{in},1}/2^{j/\beta_1}$ at its exit with $D_{\text{in},j} = D_{\text{out},j-1}$. We define $x$ as the cumulative length of a route from the arterial inlet to, but not including, the vessel having diameter $D_{\text{in},j}$. If the route is visualized as consisting of discrete vessel segments, the cumulative length at the inlet would be $x(D_{\text{in},1}) = 0$. At the end of order 1, $x(D_{\text{out},1}) = L_1 = a_2 D_{\text{in},1}^{\beta_2}$. At the end of order 2, $x(D_{\text{out},2}) = L_1 + L_2 = a_2 D_{\text{in},1}^{\beta_2} (1 + 2^{-\beta_2/\beta_1})$, and at the end of order $j$

$$x(D_{\text{out},j}) = L_1 + L_2 + \ldots + L_j = a_2 D_{\text{in},1}^{\beta_2} [1 + 2^{-\beta_2/\beta_1} + \ldots + 2^{(1-j)\beta_2/\beta_1}]$$

$$= \left(a_2 D_{\text{in},1}^{\beta_2}\right) \sum_{k=0}^{j-1} (2^{-\beta_2/\beta_1})^k = \left(a_2 D_{\text{in},1}^{\beta_2}\right) \frac{2^{-j\beta_2/\beta_1} - 1}{2^{-\beta_2/\beta_1} - 1} = \left(a_2 D_{\text{in},1}^{\beta_2}\right) \frac{(D_{\text{out},j}/D_{\text{in},1})^{\beta_2} - 1}{2^{-\beta_2/\beta_1} - 1}$$
Equation 3

To make the transition to the continuum visualization of the tree, we replace $D_{\text{out},j}$ with $D$, and thus one can view

$$x(D) = (a_2 D_{\text{in},1}^\beta_2) \frac{(D/D_{\text{in},1})^\beta_2 - 1}{2^{-\beta_2/\beta_1} - 1}$$

Equation 4

as the distance upstream from diameter $D$ to the arterial inlet. Inverting Eq.4, we obtain

$$D(x) = D_{\text{in},1}(1 - Gx)^{1/\beta_2}$$

or simply

$$D(x) = D(0)(1 - Gx)^{1/\beta_2}$$

Equation 5

Where $D(0) = a_1^{1/\beta_1}$ and $G = (1 - 2^{-\beta_2/\beta_1})/[a_2 D(0)^{\beta_2}]$. The concept of order or generation is thus replaced by establishing a relationship between the diameter $D$ at any location along a route through the tree at distance $x$ from the arterial inlet.

If the morphometric measurements were available for a given steady flow and terminal arterial pressure and under the assumption that the pressure-flow relationship is governed by Poiseuille’s law, the vascular pressure ($P$) at any $x$ could be calculated as follows

$$\frac{dP}{dx} = -\frac{128\mu \hat{Q}(x)}{\pi D(x)^4} = -\frac{128\mu \hat{Q}(0)(1 - Gx)^{\beta_1/\beta_2}}{\pi D(x)^4}$$

Equation 6

where

$$\hat{Q}(x) = \hat{Q}(0) \left[\frac{D(x)}{D(0)}\right]^{\beta_1} = \hat{Q}(0)(1 - Gx)^{\beta_1/\beta_2}$$

Equation 7

With use of Eq. 5

$$\frac{dP}{dx} = -\frac{128\mu \hat{Q}(0)(1 - Gx)^{\beta_1/\beta_2}}{\pi [D(0)(1 - Gx)^{1/\beta_2}]^4} = \frac{-128\mu \hat{Q}(0)(1 - Gx)^{\beta_1-4}/\beta_2}{\pi D(0)^4}$$

Equation 8

Thus

$$- \int_{P(0)}^{P(x)} dP = \int_0^x \frac{128\mu \hat{Q}(0)(1 - Gx)^{\beta_1-4}/\beta_2}{\pi D(0)^4} dx$$
Equation 9

\[ P(x) = P(0) - \frac{128\mu\dot{Q}(0)}{\pi D(0)^4} \left[ \frac{1 - (1 - Gx)\left(\beta_1 + \beta_2 - 4\right) / \beta_2}{G(\beta_1 + \beta_2 - 4) / \beta_2} \right] \]

Equation 10

It will also be useful to keep track of the relationship between vascular pressure and cumulative vascular volume \([Q(x)]\), the volume of the entire tree upstream from distance \(x\) into the tree\textsuperscript{12, 31}, which can be obtained as follows

\[ Q(x) = \int_0^x \frac{\pi}{4} N(x)D(x)^2 \, dx \]

Equation 11

With use of the morphometric relationship

\[ N(x) = \left[ \frac{D(x)}{D(0)} \right]^{-\beta_1} = (1 - Gx)^{-\beta_1 / \beta_2} \]

Equation 12

the cumulative arterial tree volume \((Q)\) as a function of length from the arterial inlet \((x)\) is then given by

\[ Q(x) = \int_0^x \frac{\pi D(0)^2}{4} (1 - Gx)^{2 - \beta_1 / \beta_2} \, dx = \frac{\pi D(0)^2}{4} \left[ \frac{1 - (1 - Gx)^2 - \beta_1 + \beta_2 / \beta_2}{G(2 - \beta_1 + \beta_2) / \beta_2} \right] \]

Equation 13

Thus the pressure at a distance \(x\) in a vessel having diameter \(D(x)\) at cumulative volume \(Q(x)\) can be determined.

**Distensibility.**

In general, the morphometric measurements have been obtained under some arbitrary set of conditions, usually with no flow, i.e., with the pressure constant throughout the tree. Thus the effects of the relationship between vessel diameter and vascular pressure would have to be included to predict, e.g., \(P(x)\), for any other set of conditions of flow \([\dot{Q}(0)]\) and terminal arteriole pressure. In addition, an expression including the effects of vessel distensibility would be more generally useful for the purpose indicated in the introduction.

Over the range of vascular pressures in normal lungs, the arterial diameter-pressure relationship can be approximated by

\[ D(x, P) = D(x, 0)[1 + \alpha P(x)] \]
Equation 14

as indicated elsewhere\(^3,\) \(53\). In addition, under these conditions the value of \(\alpha\) has been found to be essentially constant, independent of vessel diameter\(^3\). Thus more general expressions accounting for the distensibility of the vessels can be developed by taking the point of view that the morphometric data summarized by \(a_1, \beta_1, a_2,\) and \(\beta_2\) are available for some arbitrary pressure. For example, in what follows they are assumed to be measured at \(P(0) = 0\).

For this development, \(D(x)\) can be replaced in Eq. 6 by \(D(x, P)\) by using Eq. 14. Thus

\[
\frac{dP}{dx} = -\frac{128\mu \dot{Q}(x)}{\pi D(x, P)^4} = -\frac{128\mu \dot{Q}(0)(1 - Gx)^{\beta_1/\beta_2}}{\pi D(x, 0)^4[1 + \alpha P(x)]^4}
\]

\[
= \frac{-128\mu \dot{Q}(0)(1 - Gx)^{\beta_1/\beta_2}}{\pi [D(0,0)^4(1 - Gx)^{4/\beta_2}][1 + \alpha P(x)]^4}
\]

\[
= \frac{-128\mu \dot{Q}(0)(1 - Gx)^{(\beta_1-4)/\beta_2}}{\pi D(0,0)^4[1 + \alpha P(x)]^4}
\]

Equation 15

and

\[
[1 + \alpha P(x)]^4dP = \frac{-128\mu \dot{Q}(0)(1 - Gx)^{(\beta_1-4)/\beta_2}}{\pi D(0,0)^4} dx
\]

Equation 16

and

\[
-\int_{P(0)}^{P(x)} [1 + \alpha P(x)]^4dP = \int_{0}^{x} \frac{128\mu \dot{Q}(0)(1 - Gx)^{(\beta_1-4)/\beta_2}}{\pi D(0,0)^4} dx
\]

Equation 17

or

\[
\frac{1}{5\alpha} \left\{ [1 + \alpha P(0)]^5 - [1 + \alpha P(x)]^5 \right\} = \frac{-128\mu \dot{Q}(0)}{\pi D(0,0)^4} \left[ \frac{1 - (1 - Gx)^{(\beta_1+\beta_2-4)/\beta_2}}{G (\beta_1 + \beta_2 - 4)/\beta_2} \right]
\]

Equation 18

Thus, solving for \(P(x)\)

\[
P(x) = \frac{1}{\alpha} \left[ \left( [1 + \alpha P(0)]^5 - \frac{640\mu \dot{Q}(0)\alpha}{\pi D(0,0)^4} \left[ \frac{1 - (1 - Gx)^{(\beta_1+\beta_2-4)/\beta_2}}{G (\beta_1 + \beta_2 - 4)/\beta_2} \right] \right)^{1/5} - 1 \right]
\]
Equation 19
For this distensible vessel model, the \( P(Q) \) can be found as follows

\[
Q(x) = \int_0^x \frac{\pi}{4} N(x) D[x, P(x)]^2 dx
\]

Equation 20
and

\[
N(x) = \left[ \frac{D(x, 0)}{D(0, 0)} \right]^{-\beta_1} = (1 - Gx)^{-\beta_1/\beta_2}
\]

Equation 21

\[
Q(x) = \int_0^x \frac{\pi D(0, 0)^2}{4} \times (1 - Gx)^{-\beta_1/\beta_2} (1 - Gx)^{2} [1 + \alpha P(x)]^2 dx
\]

Equation 22
With \( P(x) \) obtained from Eq. 19

\[
Q(x) = \int_0^x \frac{\pi D(0, 0)^2}{4} \times (1 - Gx)^{2} \left\{ a - b \left[ \frac{1 - (1 - Gx)^c}{Gc} \right] \right\}^{2/5} dx \quad a = [1 + \alpha P(0)]^5, b
\]

\[
= \frac{640 \dot{Q}(0)a}{\pi D(0, 0)^4}, c = \beta_1 + \beta_2 - 4/\beta_2
\]

Equation 23
which can be integrated numerically.

*Fahraeus-Lindqvist effect.*
To this point, the blood viscosity \( \mu \) has been a constant independent of vessel diameter. However, the blood viscosity is also dependent on the vessel geometry (Fahraeus-Lindqvist effect)\textsuperscript{13, 18}. For vessels larger than the terminal pulmonary arteriole diameter of \( \sim 20 \mu m \), \( \mu(D) \) can be approximated by Eq. 24

\[
\mu(D) = \mu_p + \frac{(\mu_b + \mu_p)D}{D_F + D}
\]

Equation 24
where \( \mu_p \) is the plasma viscosity, \( \mu_b \) is the blood viscosity in large vessels, and \( D_F \) is the vessel diameter in which the viscosity is \( (\mu_b + \mu_p)/2 \). Thus with use of \( D = D(x, P) \) in Eq. 24
\[
\frac{dP}{dx} = \frac{-128\mu[D(x, P)]\dot{Q}(x)}{\pi D(x, P)^4}
\]

Equation 25

and by a development analogous to that above

\[
P(x) = P(0) - \frac{128\dot{Q}(0)}{\pi D(0,0)^4} \times \int_0^x \left[ 1 + \alpha P(x) \right]^{-4} (1 - Gx)^{\beta_1 - 4/\beta_2} \times \left\{ \left( \mu_b - \mu_p \right) D(0,0) \left[ 1 + \alpha P(x) \right] (1 - Gx)^{1/\beta_2} \div \left( D_F + D(0,0) \left[ 1 + \alpha P(x) \right] (1 - Gx)^{1/\beta_2} + \mu_p \right) \right\} \, dx
\]

Equation 26

Equation 26 can be numerically integrated to calculate \( P(x) \) by solving the equivalent nonlinear ordinary differential Eq.25, and \( Q(x) \) can then be calculated from Eq. 22.

Cylindrical vessels.

Zhuang et al.\(^{55}\) utilized a distensible vessel model to express the influence of geometry and vessel distensibility on the pressure-flow relationship in each vessel order of the cat pulmonary arterial tree. To put the expressions derived in the present study in perspective, it will be useful to compare the continuum model predictions with those of a model similar to that of Zhuang et al. as a model representative of concatenated order models. That model will be referred to as the “ordered” model to distinguish it from the continuum model. For such comparisons, the ordered model can be written as follows

\[
P_{\text{in},j} = \frac{1}{\alpha} \left\{ \left( 1 + \alpha P_{\text{out},j} \right)^5 + \frac{640\mu_j \alpha \dot{Q}_j L_j D_j(0)/D_j(0)^{\frac{\beta_2}{2}}}{\pi D_j(0)^4 2^{[1-(4/\beta_2)](j-1)}} \right\}^{1/5} - 1
\]

Equation 27

\[
P_{\text{in},j} - P_{\text{out},j} = \frac{\dot{Q}_j 640\pi^{-1} \mu_j L_j 2^{1-j}}{\left[ D_j(\text{in},j)^4 + D_j(\text{in},j)^3 D_j(\text{out},j) + D_j(\text{in},j)^2 D_j(\text{out},j)^2 + D_j(\text{in},j) D_j(\text{out},j)^3 + D_j(\text{out},j)^4 \right]^{1/5}}
\]

Equation 28

\[
D_j(x) = \left\{ D_j(\text{in},j)^5 - \left[ D_j(\text{in},j)^5 - D_j(\text{out},j)^5 \right] \frac{x}{L_j} \right\}^{1/5}
\]

Equation 29

\[
Q_j = \frac{5\pi L_j 2^{1-j} \left[ D_j(\text{in},j)^7 - D_j(\text{out},j)^7 \right]}{28 \left[ D_j(\text{in},j)^5 - D_j(\text{out},j)^5 \right]}
\]
To calculate the pressure-flow relationship for the whole arterial tree with this model, $P_{in,n}$ is calculated for a given $P_{out,n}$ and by using Eq. 27. Then $P_{in,n-1}$ is calculated using $P_{out,n-1} = P_{in,n}$ and so on to $P_{in,1}$.

To compare the ordered model with the continuum model, note that $D_1(0)$ does not equal $D(0,0)$. $D(0,0)$ is the inlet diameter of a frustum, whereas $D_1(0)$ is the diameter along the entire length of a cylinder. Suwa et al.\textsuperscript{48} demonstrated that in order for $P(x)$ for a model in which the vessels are represented by right cylinders to be equivalent to that of the continuum tapered tube model, $D_1(0) = KD(0,0)$, where

$$K = \left\{\frac{\left(1 - 2^{-\beta_2/\beta_1}\right)\left(\beta_1 + \beta_2 - 4\right)}{\beta_2\left[1 - 2^{-\beta_1 + \beta_2 - 4/\beta_1}\right]}\right\}$$

Equation 31

$D_1(0)$ is then the inlet artery diameter for an ordered cylindrical vessel model having the same resistance as a continuum tapered vessel model of similar length, with the fact taken into account that, to have equal flow resistance, the inlet and outlet diameters of a frustum must be larger and smaller, respectively, than those of the cylinder of equal length. Because, for physiological values of pressure and $\alpha$, the distortion in shape due to flow through the distensible vessel models is small, $D_1(P) = KD(0, P)$ provides a useful approximation for the relationship between $D_1(P)$ and $D(0, P)$ for the distensible vessel model as well.

To examine the implications of Eqs. 10, 19, and 27 in results, we present a series of simulations. To help put those simulations in perspective, we include Table 1, which provides morphometric data from the lungs of various species summarized by the morphometric parameters indicated. The parameters in Table 1 were either reported as such in the referenced studies or they can be estimated by linear regression from the data available in those references. We also provide additional morphometric data for the pulmonary arterial tree of the dog lung as indicated below.

<table>
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<th>Species</th>
<th>Ref.</th>
<th>$\beta_1$</th>
<th>$z$</th>
<th>$\beta_2$</th>
<th>$a_2$</th>
<th>$D_T$, $\mu$m</th>
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<td>0.89</td>
<td>5.13</td>
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<td>1.16</td>
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<td></td>
<td></td>
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<tr>
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\begin{tabular}{|c|c|c|c|c|c|}
\hline
Species & Number & D & \(a_2\) & \(\beta_2\) & \(D_T\) \\
\hline
Cat & 54 & 2.35 & 1.03 & 7.59 & 21 \\
Cat & 46 & & & 14.5 & \\
Cat & 43 & & & 30 & \\
Rat & 26 & 2.15 & 1.03 & 2.60 & 13 \\
Rabbit & 7 & 2.76 & & & \\
Rabbit & 38 & & & 20 & \\
\hline
\end{tabular}

\(\beta_1\), Defined by Eq. 1; \(z\), defined by Eq.32; \(\beta_2\), defined by Eq. 2; \(a_2\), defined by Eq. 2; \(D_T\), diameter of terminal (precapillary) arterioles.

Experimental Methods

Most of the data in Table 1 were obtained from plastic casts of the pulmonary vasculature made under conditions providing good casts but not necessarily representative of those in the normal in vivo state. To complement those data, we carried out morphometric measurements on arteries in isolated left lower lobes of dog lungs using radiographic images collected under a standard set of perfusion conditions that are closer to the mean pressure and flow conditions normally extant in vivo. The experiments were actually carried out for different purposes\(^2, 3, 8\), but in each experiment, images were available under the standard set of conditions before any subsequent experiments were carried out on the lung lobe.

Experiments were performed using an isolated dog lung lobe preparation that has been described previously\(^3\). Each of 32 dogs [19.7 ± 2.1 (SD) kg body wt] was anesthetized with pentobarbital sodium (30 mg/kg), heparinized (1,250 IU/kg), and exsanguinated via a carotid artery catheter. During the exsanguination procedure, 250 ml of saline solution containing 10% dextran (Rheomacrodex, 40,000 mol wt) were infused. Approximately 1 liter of the autologous blood [hematocrit (Hct) 37.7 ± 1.6% (SD)] was used to prime the perfusion system. After exsanguination the chest was opened and cannulas were placed in the left lower lobe artery, bronchus, and vein. The lobe, removed from the dog, was either vertically suspended by the bronchus or placed horizontally on its ventrolateral surface. The arterial cannula was attached to the temperature-controlled (36–37°C) perfusion system, which included a Masterflex roller pump that pumped the blood at a constant rate of 6.78 ± 1.82 (SD) ml/s from a reservoir into the lobar artery. The blood then drained from the lobar vein back into the reservoir. The height of the reservoir was adjusted to set the venous pressure at 3.6 ± 1.3 (SD) mmHg. The lobar arterial and venous pressures were referenced to approximately the level of the measured vessels. The pressure measured at the lobar arterial inlet was 10.4 ± 3.7 (SD) mmHg.

The lobar bronchus was attached to the ventilation system, and between measurements the lobe was ventilated using a piston respirator with a gas mixture containing \(\sim 15\%\) \(O_2\)-5.6\% \(CO_2\)-79.4\% \(N_2\). This resulted in average \(PO_2\) of 105 ± 23 (SD) Torr, \(PCO_2\) of 40 ± 4 (SD) Torr, and pH of 7.35 ± 0.05 (SD) in the blood in the recirculating perfusion system. The tidal volume was 75–100 ml at \(\sim 10\) breaths/min, and the end-expiratory airway pressure was set at 3.3 ± 0.6 (SD) mmHg by using a water overflow valve.

The inflow tubing included a previously described\(^3\) injection loop that allowed the introduction of a bolus of 4–5 ml of radiopaque contrast medium, 61\% iopamidol (Isovue 300), into the lobe inflow tubing by activating a solenoid valve to redirect the inflow through the bolus-containing loop so that
the bolus could be introduced without changing the pressure or flow. The contrast medium was maintained at the same temperature as the perfusion system.

The lung lobe was situated between the X-ray source and the image train of one of two X-ray imaging systems. One was a Nicolet NXR-200 X-ray imaging system with a 40-μm focal spot X-ray source and an X-ray-sensitive videocamera, as previously described. The other system included a Fein-Focus FXE-100.50 X-ray tube with a 3-μm focal spot, a North American Imaging AI-S830-HP 9/7/5 in. image intensifier, and a Sony (model AI-01-CCD) charge-coupled-device camera. The lobes were situated horizontally and vertically, respectively, in the two systems. The video images were recorded as the bolus passed through the lobar vasculature with a videocassette recorder (model S-VHS). Before the injection of a bolus, the ventilator was stopped at end expiration.

The vessel diameters were measured off-line from the videotaped images in one of two ways. Those obtained from the Nicolet system \((n = 570)\) were analyzed as described previously using visual edge detection of background-subtracted images. For those obtained with the Fein-Focus system \((n = 313)\), a region of interest (ROI) was placed over a portion of the image including the vessel, the diameter of which was to be measured. The videotape was automatically advanced frame by frame until the frame having the maximum ROI absorbance during passage of the contrast medium through the ROI was identified by the computer. An average background image was calculated by averaging image pixel intensities for 10 image frames \((0.33 \text{ s})\) before injection of the contrast bolus. This background image was subtracted from the maximum absorbance image. Then the absorbance across the vessel cross section was measured, and the diameter was estimated as a fraction of the total image dimensions by using the cylindrical model-based algorithm described by Al-Tinawi et al. and Clough et al. The diameter-measuring algorithm included a modification, not previously reported, for automatically setting the absorbance line scans used to calculate the vessel diameter orthogonal to the vessel axis. This was accomplished by identifying within the rectangular ROI the lines of pixels that would ultimately need to be parallel to the axis of the vessel. Initially, these lines were oriented at an arbitrary angle relative to the vessel axis as the result of user placement of the ROI in approximately the correct orientation. The SD of all pixel intensities was calculated along each line. If the lines had, in fact, been oriented parallel to the vessel, the SD of pixel intensities along each line would be at a minimum. To find the box position that resulted in that minimum, the box was rotated ±20°, in 0.1° increments, and the SD of pixel intensities along each line was calculated at each angle. Finally, the box was oriented to the angle corresponding to the smallest sum of the SD of pixel intensities along the lines. To calibrate the imaging dimensions, a remotely controlled micrometer was used to move the lung lobe a known distance. The actual distance moved during the calibration displacement was divided by the displacement of the bifurcation on the image to provide a calibration factor for the vessels of that bifurcation.

**Morphometry Methods**

The centripetal ordering systems used for summarizing the morphometric data from plastic casts, in which the vessels are assigned to orders starting with the terminal arteries, are not practical for summarizing the data from X-ray images having limited fields of view and/or limited resolution. Another way that vascular tree morphometry has been carried out is by measuring the diameters of the three vessels comprising a bifurcation for a large number of bifurcations. By designating...
the parent vessel diameter $D_1$ and the two daughter diameters $D_2$ and $D_3$, a value $z$ can be estimated by an iterative method from

$$D_1^z + D_2^z + D_3^z$$

Equation 32

Then the values of $z$ from many bifurcations can be averaged. In a homogeneous symmetrical tree for which the log $N_j$ vs. log $D_j$ is linear, the mean value of $z = \beta_1$. Therefore, $z$ and $\beta_1$ have been commonly interpreted as being equivalent\textsuperscript{4, 24, 48} when the heterogeneity of the tree is not being specifically addressed, and we will not make a distinction between them in the present model analysis. Some consequences of this interpretation will be discussed below. In any real tree the value of $z$ varies from bifurcation to bifurcation. The $z$ values do not have a symmetrical distribution, and various transformations have been used to obtain mean values used in hemodynamic analyses analogous to that described here\textsuperscript{24, 34, 48}. Therefore, the results are reported as arithmetic, geometric, harmonic, and arctan mean values. The morphometric parameters $z$ or $\beta_1$ have received the most attention in such models. This is because the average length-to-diameter ratio throughout the tree tends to be nearly constant, i.e., $\beta_2 \sim 1$ (Table 1), in which case $\alpha_2$ is the average length-to-diameter ratio. Vessel length measurements were not available from the single projection images of the type obtained in this study. Therefore, estimates of $\alpha_2$ or $\beta_2$ were not obtained.

RESULTS

Morphometry

Figure 2 shows the distributions of the $z$ estimates obtained from the diameter measurements of 883 bifurcations by using Eq. 32. The bifurcations are divided into four groups of approximately the same number according to the range of $D_1$. Table 2 gives the mean values of the four groups. The $z$ values were apparently independent of vessel size; i.e., the four individual subgroups were indistinguishable from the entire population (Kruskal-Wallis one-way ANOVA on ranks, $P > 0.05$). The size independence of $z$ is the basis of the model analysis. For 36 of the bifurcations measured, the estimate of $D_2$ was larger than $D_1$; therefore, $z$ could not be calculated. For 12 of those bifurcations, the diameters of the four daughter vessels of the two subsequent downstream vessels could be measured. In those cases, $z$ was calculated as suggested by Suwa et al.\textsuperscript{48} by equating the parent diameter of the upstream bifurcation raised to the $z$ power to the sum of the four daughter vessel segments of the two downstream bifurcations raised to the $z$ power. The arithmetic mean value of $z$ was $2.67 \pm 0.23$ (SE) for these sequential bifurcations and was not significantly different from the mean obtained from the 883 bifurcations as indicated above. Thus there was no indication that bifurcations for which $z$ could not be calculated represented any fundamentally different morphometric pattern propagating through the tree. In addition, to obtain a sense of the precision of the diameter measurements in one lung lobe, nine consecutive boluses were injected under the same experimental conditions. The magnification was set such that within the diameter of the field of view (DVF, 4.6 cm) there was a fairly large range of measurable vessel diameters in one field, from $\sim 0.3$ to 0.05 cm. The coefficient of variation (CV) in vessel diameter estimates among the boluses was $-0.32 \ cm^{-1} \times \ \text{average diameter} + 0.11 \ (r^2 = 0.70)$, where the average diameter is in centimeters. Because the magnitude of the variation depends on the
magnification, the average diameter in this relationship can also be expressed as a fraction of the DVF instead of in centimeters. Thus \( CV = -1.46 \times \text{average diameter}/\text{DVF} + 0.11. \)

Fig. 2. Frequency of \( z \) values for vessels in 4 size ranges; \( n \), number of measured bifurcations in each size range.
Table 2. Mean values of *z* obtained from arterial diameter measurements on dog lung lobes

<table>
<thead>
<tr>
<th>Diameter, μm</th>
<th>30–336 (n = 221)</th>
<th>337–664 (n = 221)</th>
<th>665–1,699 (n = 224)</th>
<th>1,700–7,574 (n = 217)</th>
<th>30–7,574 (n = 883)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arithmetic mean ± SD</td>
<td>2.816 ± 2.242</td>
<td>2.412 ± 1.158</td>
<td>2.921 ± 2.135</td>
<td>2.892 ± 2.325</td>
<td>2.760 ± 2.026</td>
</tr>
<tr>
<td>Mean log ± SD</td>
<td>0.3648 ± 0.2489</td>
<td>0.3424 ± 0.1811</td>
<td>0.3978 ± 0.2216</td>
<td>0.3800 ± 0.2397</td>
<td>0.3713 ± 0.2248</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>2.316</td>
<td>2.200</td>
<td>2.499</td>
<td>2.399</td>
<td>2.351</td>
</tr>
<tr>
<td>Mean arctan ± SD</td>
<td>1.275 ± 0.1808</td>
<td>1.125 ± 0.1494</td>
<td>1.162 ± 0.1555</td>
<td>1.143 ± 0.1663</td>
<td>1.139 ± 0.1638</td>
</tr>
<tr>
<td>Arctan mean</td>
<td>2.106</td>
<td>2.090</td>
<td>2.308</td>
<td>2.190</td>
<td>2.171</td>
</tr>
<tr>
<td>Mean reciprocal ± SD</td>
<td>0.4954 ± 0.2353</td>
<td>0.4935 ± 0.2002</td>
<td>0.4476 ± 0.2012</td>
<td>0.4722 ± 0.2119</td>
<td>0.4771 ± 0.2119</td>
</tr>
<tr>
<td>Harmonic mean</td>
<td>2.019</td>
<td>2.026</td>
<td>2.234</td>
<td>2.118</td>
<td>2.096</td>
</tr>
<tr>
<td>Median</td>
<td>2.050</td>
<td>2.073</td>
<td>2.254</td>
<td>2.079</td>
<td>2.121</td>
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</table>

*n*, Number of bifurcations.
Sources of Input Values for Simulations
The model input parameters for various simulations were generally chosen to be consistent with the range of values available for the dog lung. For example, the morphometric parameters can be compared with those summarized in Tables 1 and 2.

Hemodynamic and rheological information used in the simulations, but not obtained from measurements made in the present study, were chosen with reference to values from previous studies based on the following information. In studies in which subpleural arteriole pressures were measured in arterioles with diameters between 20 and 50 μm in the dog lung, the estimated intrapulmonary arterial pressure drop has ranged between \( \sim 20\% \) and 50\% of the total arteriovenous pressure difference\( ^2 \). On the basis of those measurements, for the lung lobes in the present study with a mean arteriovenous pressure difference of \( \sim 6.8 \text{ mmHg} \), the arterial tree pressure drop would be from \( \sim 1.4 \) to 3.4 mmHg. Because of the availability of these pressure data in vessels of \( \sim 35 \mu m \) diameter, the terminal arteriole diameter \( (D_T) \) in the model simulations was generally \( \sim 35 \mu m \). The precapillary terminal pulmonary arteriole diameters, which have been measured, tend to be a little smaller than the average for which most of the pressure measurements are available and are listed in Table 1.

Left lower lobar arterial volume for a 20-kg dog under pressure and flow conditions of the present study was found to be \( \sim 10 \text{ ml} \) by using the ether dilution method\( ^{11} \). Also a morphometric estimate of \( \sim 12 \text{ ml} \) can be calculated from the dog right lung data of Gan and Yen\( ^{17} \) by taking into account the size of the dog on which the measurements were made and the relative sizes of the left lower lobe and right lung\( ^{41} \).

The value of \( \alpha \) for the dog lung has been found to be \( \sim 0.02/\text{mmHg} \) with a range of \( \sim 0.01\text{–}0.04/\text{mmHg} \).

In the present study, \( D(0, P = 10.4 \text{ mmHg}) = 0.757 \text{ cm} \) (i.e., the largest diameter from Fig. 2 and Table 2), which, for \( \alpha = 0.02/\text{mmHg} \), is also equivalent to \( D(0,0) = 0.627 \text{ cm} \).

The lower and upper bounds on \( D_F \) from the summary of blood viscosity vs. tube diameter data presented by Goldsmith et al.\( ^{18} \) are 0.0023 and 0.0050 cm, respectively.

Fitting the equation \( \mu_b = \mu_p \exp(k \text{Hct}) \) to the viscosity vs. Hct data for dog blood from Stone et al.\( ^{47} \), for which \( \mu_p = 0.0119 \) Poise, yields \( k = 0.0267 \). Thus the Hct in the present study (37.7 ml cells per 100 ml large vessel blood volume) gives \( \mu_b \sim 0.033 \) Poise. The Hct of 37.7\% obtained in the present study compares with the normal mean large vessel Hct for the dog reported to be 39.7\% by Rapaport et al.\( ^{42} \).

Model Simulations
In the first set of simulations we compare some predictions of the continuum model as expressed by Eqs.19 and 23 with those of the ordered model, Eqs. 27-30. The model parameter values were chosen to be in relevant ranges to reveal the basic shapes of the distributions. Figure3 F provides a geometric representation of the two models. When \( D \) is plotted vs. \( x \), the distance along a given pathway through the tree, the ordered model appears as a stair graph with logarithmically diminishing step size on the descent. Each step represents an order. Although the treads appear flat, they actually curve slightly downward, because, within an order, the upstream pressure is greater than the downstream pressure
and the vessels are distensible. This is not easily detectable in Fig. 3, because the pressure change along the length of a given vessel segment (tread) is very small in relation to the vessel distensibility ($\alpha$). The risers reflect the differences in diameters between adjacent orders. In contrast, the continuum model $D(x)$ is a smooth curve reflecting the vessel taper along the pathway. Again, for the continuum model, the inlet diameter [$D(0, P)$] is larger than for the ordered model [$D_1(P)$]. The graphs for both models are slightly concave downward in Fig.3 F. In the physiological range of $\alpha$, this concavity is dominated by $\beta_2$. The graph of the simulations appears nearly linear when $\beta_2 = 1$ and changes to concave downward or upward when $\beta_2$ is greater than or less than $\sim 1$, respectively.

The intravascular pressure is presented as a function of diameter for the two models in Fig. 3 B. Again, the stair graph is the ordered model. In this case, the risers, which appear to be vertical, are actually slightly pitched, reflecting the pressure drop through each vessel and the vessel distensibility. The treads are flat, because there is no pressure difference between the outlet of one vessel and the inlet to the next. The continuum model produces a smooth curve. The curvature of the pressure vs. diameter graphs is determined by $\beta_1$, $\beta_2$, and $\alpha_2$. The graphs of the pressure vs. distance $x$ into the tree are indistinguishable between the two models (Fig.3 A). On the other hand, the volume (Q) accumulated through all parallel pathways from the inlet to distance $x$ (Fig.3 D) or the volume upstream from a given diameter (Fig. 3 E) or a given pressure (Fig. 3 C) is larger for the continuum than for the ordered model. These differences again reflect the fact that a frustum and a cylinder of equal length cannot have equal volume and equal resistance and the continuous vs. stepwise progression of the changes in total cross-sectional area of all the pathways with distance $x$ into the tree. Having made these comparisons, subsequent simulations are from the continuum models.
In the model development we distinguished between models that predict the pressure-flow relationship and the longitudinal pressure and volume profile for the vascular tree, given the availability of morphometric parameters obtained under one specific set of conditions (e.g., Eqs. 10 and 13), and a model that can make predictions over a range of conditions (e.g., Eqs. 19 and 23 or 27 and 30). We will refer to the former as fixed-diameter models, because no accommodation for vessel distensibility is included, since the vessel morphometry is assumed to be available for a specific set of relevant pressures and flow. The latter are referred to as distensible-vessel models, because they predict the results under any set of pressure and flow conditions within the range for which Eq. 14 is a useful representation of the diameter-pressure relationship. This distinction can also serve to provide a sense of the sensitivity of the morphometric parameters to the conditions under which they are measured. To obtain morphometric data from the continuum model, ordering was imposed by calculating a length $L_j$ from

$$L_j = a_2 D(0)^{\beta_2} [2^{-(j-1)(\beta_2/\beta_1)}]$$

(33)

and then “measuring” the diameters at $x = \sum L_j$. $N_j$ was set equal to $2^{j-1}$.

Two sets of simulated morphometric data are shown in Fig.4 as plots of log $N_j$ vs. log $D_j$ or log $L_j$ vs. log $D_j$. One set is for the vessels at $P = 0$. The other is that obtained from the distensible-vessel model during the simulated flow (6.8 ml/s) condition. Linear regression of the latter using Eqs.1 and 2 provided the input morphometric parameters for the fixed-diameter model. In this set of simulations, $\beta_1$, $\beta_2$, $a_1$, and $a_2$ input into the distensible-vessel model was 2.560, 1.150, 0.303, and 5.000, respectively. The pressures that resulted from flow (6.8 ml/s) through the model distended the vessels such that when the morphometry was carried out “with flow,” $\beta_1$, $\beta_2$, $a_1$, and $a_2$ were 2.534, 1.139, 0.741, and 3.987, respectively. The largest differences are in $a_1$ and $a_2$, because the vessel diameters increase with pressure ($\alpha = 0.02$/mmHg). Figure5 shows the longitudinal pressure profiles obtained for the two sets of parameters used as input to the distensible-vessel and fixed-diameter models, respectively. The differences in pressure between the distensible-vessel and fixed-diameter models reflect the small differences in the shape of a vessel in the two models. These pressure differences are small enough to suggest that the simpler fixed-diameter model would be useful, in the sense indicated in the introduction, given morphometric measurements made while the lungs are being perfused.
Fig. 4. Simulated number ($N_j$) vs. diameter ($D_j$, in cm) and length ($L_j$, in cm) vs. $D_j$ from distensible-vessel model. •, Diameters at undistended or zero pressure values; ○, diameters with flow through model. Model $\beta_1$, $\beta_2$, $\alpha_1$, and $\alpha_2$, values input into distensible-vessel model (i.e., no-flow values) were 2.56, 1.15, 0.303, and 5.0, respectively. Values obtained by fitting straight lines through ○ were 2.534, 1.139, 0.741, and 3.987, respectively.

Fig. 5. Pressure vs. distance ($x$) from arterial inlet for distensible-vessel (solid line) with $\beta_1$, $\beta_2$, $\alpha_1$, and $\alpha_2$ set at 2.56, 1.15, 0.303, and 5.0, respectively, and fixed diameter (dashed line) models with input values of 2.534, 1.139, 0.741, and 3.987, respectively, obtained by linear regression of morphometric data from distensible-vessel model simulation data on Fig. 4. Small differences reflect the fact that vessels are not exactly the same shape in the 2 models; i.e., “with flow” data on Fig. 4 do not fall on exactly straight lines.
Another way to examine sensitivity to morphometric parameters is to note that, given the volume of the arterial tree and the pressure drop through it, the combination of values of possible morphometric parameters $\beta_1$, $\beta_2$, and $a_2$ can be specified by the pressure and volume equations, such as Eqs. 26 and 23. In addition, if one of the three morphometric parameters, $\beta_1$, $\beta_2$, or $a_2$, is given, the other two are specified. Given volumes and pressure drops available from independent measurements\textsuperscript{11,21}, one can examine which mean value of $z$, or value of $\beta_1$, is consistent with the total volume and pressure drop. Examples are shown in Figs. 6 and 7, which give the relationships between values of $\beta_1$, $\beta_2$, and $a_2$ that produce a particular total volume and pressure drop for a given set of inlet and terminal diameters, flow, Hct, and $\alpha$. To maintain a given volume and pressure drop, the acceptable values of $\beta_2$ and $a_2$ are negatively correlated with $\beta_1$ and positively correlated with each other. Increasing volume (Fig. 6) or decreasing the pressure drop (Fig. 7) moves the relationships toward increasing values of $\beta_2$ and $a_2$ for a given value of $\beta_1$. In these examples, to have values of $\beta_2$ and $a_2$ in the ranges for the dog lung cited in Table 1, the range in mean values of $z$ that would appropriately represent $\beta_1$ would be from $\sim 2.5$ to 2.7. The parameters for the subsequent simulations were chosen to be consistent with previous volume and pressure drop measurements and the range of morphometric parameters in Tables 1 and 2.

![Graph showing $\beta_2$ and $a_2$ vs. $\beta_1$ compatible with inlet pressure $P(0) = 10.4$ mmHg, arterial pressure drop = 3.4 mmHg, and arterial volumes = 8, 10, or 12 ml. Flow rate = 6.8 ml/s, $\alpha = 0.02$/mmHg, hematocrit (Hct) = 38%, $D(0,0) = 0.627$ cm, $D_T(0) = 0.003$ cm.]

**Fig. 6.** $\beta_2$ and $a_2$ vs. $\beta_1$ compatible with inlet pressure $P(0) = 10.4$ mmHg, arterial pressure drop = 3.4 mmHg, and arterial volumes = 8, 10, or 12 ml. Flow rate = 6.8 ml/s, $\alpha = 0.02$/mmHg, hematocrit (Hct) = 38%, $D(0,0) = 0.627$ cm, $D_T(0) = 0.003$ cm.
Fig. 7. $\beta_2$ and $a_2$ vs. $\beta_1$ compatible with inlet pressure $P(0) = 10.4$ mmHg, arterial pressure drops = 1.7, 3.4, or 5.1 mmHg, and arterial volume = 10 ml. Flow rate = 6.8 ml/s, $\alpha = 0.02$/mmHg, Hct = 38%, $D(0,0) = 0.627$ cm, $D_T(0) = 0.003$ cm.

As another means of demonstrating model behavior and parameter sensitivity, Figs.8-12 show the impact of changing model (Eqs.22 and 26) parameters on the longitudinal pressure profiles. In these simulations, $\beta_1 = 2.63$, $\beta_2 = 1$, $a_2 = 3.64$, $\alpha = 0.02$/mmHg, $D(0,0) = 0.627$ cm, $D_T(0) = 0.003$ cm, large vessel Hct = 38% resulting in $\mu_b = 0.033$ Poise, and $\mu_p = 0.0119$ Poise, $D_F = 0.0037$ cm, flow = 6.8 ml/s, and outlet pressure = 7 mmHg, except when individually varied as indicated. The solid lines in Figs. 8-12 represent the simulation with all the parameter values as indicated above; the dashed lines were obtained when the one indicated parameter was varied above or below its respective common value. A change in each of the parameters, $\beta_1$, $\beta_2$, and $a_2$, has a different effect on the profiles (Figs. 8, 9, and 10, respectively). The total pressure drop and volume are quite sensitive to small changes, particularly in $\beta_1$. Figure 11 shows the effects of changing $\alpha$. The Fahreus-Lindqvist effect was varied by changing the diameter $D_f$, at which the viscosity is midway between inlet blood and plasma (Fig. 12). $D_F = 0$ means that the viscosity was diameter independent. The model is relatively insensitive to such changes.
Fig. 8. Pressure vs. distance ($x$), diameter ($D$), and cumulative volume ($Q$) for range of $\beta_1$. Line types identified in middle panel.

Fig. 9. Pressure vs. distance, diameter, and cumulative volume for range of $\beta_2$. Line types identified in middle panel.

Fig. 10. Pressure vs. distance, diameter, and cumulative volume for range of $a_2$. Line types identified in middle panel.
A common method of expressing pressure-flow relations in the lung is as pressure vs. flow curves\textsuperscript{20,30,55}. Therefore, Fig. 13 is included to provide an example of model simulations in that format. The model parameter $\alpha$ was varied, because $\alpha$ influences the shape of the pressure vs. flow curve, whereas for the other simulations with a constant value $\alpha$, the flow rate is essentially a scaling factor. Thus, for a constant $\alpha$, the pressure vs. flow curves provide little additional information not already provided by the inlet pressures on Figs. 8-12. Figure 13, top, was obtained by holding the terminal arteriole outlet pressure constant and calculating the arterial inlet pressure. Figure 13, bottom, was obtained by holding the arterial inlet pressure constant and calculating the terminal arterial pressure. When $\alpha = 0$, the pressure vs. flow curves are straight lines. Curvature results from the vessel distensibility, i.e., $\alpha > 0$. 

**Fig. 11.** Pressure vs. distance, diameter, and cumulative volume for range of $\alpha$. Line types identified in middle panel.

**Fig. 12.** Pressure vs. distance, diameter, and cumulative volume for range of $D_T$. Line types identified in middle panel.
DISCUSSION

The objective of the modeling aspect of this study was to provide a means for examining hemodynamic implications of available morphometric and vessel mechanics measurements and for evaluating the sensitivity of the arterial pressure-flow relationships to geometric and mechanical properties of the tree. The models obviously do not include representations of all features of the pulmonary arterial tree. For example, there is no representation of the heterogeneity of the connectivity of the vessel segments that exists in the real tree. Thus the models predict the longitudinal (inlet artery-to-arteriole) intravascular pressure distribution, but not possible parallel pressure distributions. The pattern of arterial tree connectivity is apparently such that the parallel heterogeneity has little impact on the longitudinal profiles\textsuperscript{12, 31, 45} if the diameter \([D(x)]\) or distance \((x)\) values are thought of as averages and the cumulative volume \([Q(x)]\) is thought of as the total volume upstream of all sites within the arterial tree where the pressures are equal. Similarly, the model assumes Poiseuille flow and would be expected to reflect the mean pressure-flow relationship during, e.g., pulsatile flow, only to the extent that Poiseuille flow does so in a cylindrical tube. As indicated earlier, the distensible-vessel model can

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**Fig. 13.** Pressure vs. flow curves for a range of \(\alpha\). Top: arterial inlet pressure obtained when terminal arteriole outflow pressure was held constant at 7 mmHg. Bottom: terminal arteriole pressure obtained while inflow arterial pressure was constant at 10.4 mmHg.
be expected to be useful for the range of pressures for which Eq. 14 is an adequate representation of
the diameter-pressure relationship\(^3\). In addition, the models are for the range of conditions in which
the changes in kinetic energy with changes in flow velocity through the arterial tree are small enough
to be neglected in computing the longitudinal pressure distribution. To put this in perspective, the data
in Tables 1 and 2 suggest that, for pulmonary arterial trees, \(\beta_1\) is no greater than 3 and not much less
than 2. If \(\beta_1 = 2\), under any set of other conditions, the model blood velocity would be independent of
vessel diameter and the kinetic energy component would be constant. At the other extreme, with \(\beta_1 = 3\),
inlet and terminal diameters of 0.757 and 0.0034 cm, respectively, and experimental flow rate of
6.8 ml/s, the inlet velocity would decrease from \(\sim 15\) cm/s to an outlet velocity of \(\sim 0.07\) cm/s, giving a
total increase in pressure from inlet to outlet due to the decrease in kinetic energy of \(< 0.1\) mmHg.

In keeping with the objective of providing concise expressions that reveal the dominant sensitivities,
we note that the differences in vessel shapes between the fixed-diameter and distensible-vessel
models and the inclusion of the Fahraeus-Lindqvist effect have only small effects on the shapes of the
pressure profiles (Figs. 5 and 12). Thus, of the relationships presented, the algebraic Eqs. 10 and 13 are
the most concise for revealing the dominant consequences of tree geometry on the longitudinal
profiles for a set of morphometric parameters obtained under a particular set of pressure and flow
conditions. It should also be noted that the shapes of the arterial pressure profiles and the relative
changes in the profiles with parameter changes are of most interest in the context of the structure-
function relationships developed here. There is little expectation that either the morphometric
measurements themselves or the morphometric data summarized by parameters such \(\beta_1\), \(\beta_2\), \(a_1\), and
\(a_2\), obtained with various ordering schemes as in Table 1, or mean values of \(z\) estimated as in the
present study will be accurate enough to predict the actual arterial pressure-flow relationship to a
specified degree of accuracy from morphometric measurements alone. The power of the vessel
diameters in the calculation of volumes and pressure-flow relationships appears to vitiate that
possibility.

One reason for interest in this problem is that as imaging technology improves, pulmonary arterial
morphometric data will become available under a broader range of experimental conditions\(^2, 27, 35, 36\).
Table 1 represents all the morphometric data that we have found on luminal dimensions of the normal
pulmonary arterial tree. Most of the data have been collected on only a few plastic casts, and that
technique does not lend itself to comparisons between experimental groups of, e.g., normal lungs and
lungs under the acute influence of vasoactive stimuli or after chronic remodeling. Imaging techniques
have the potential for such comparisons. However, the methods of creating morphometric summaries
using the various ordering schemes applied to the vascular casts are not always practical for image
data. In the present study the images were single-projection images with limited fields of view. Often a
single bifurcation filled the field. Therefore, complete ordering was not an option. Instead, we used the
method of Suwa et al.\(^48\) and others\(^19, 24, 34\), in which measurements of the diameters of the parent and
daughter vessels at a large number of bifurcations are used to obtain a mean value of \(z\). As indicated
above, in a symmetrical tree in which the two daughter vessel diameters are equal, \(z\) and \(\beta_1\) would
also be equal. Otherwise, \(z > \beta_1\), with the difference being a function of the daughter diameter
asymmetry at a bifurcation. Therefore, \(z\) might be better construed as an upper bound on \(\beta_1\). In
addition, \(z\) is not the same at each bifurcation, and the observed distribution is skewed to the right
(Fig. 2). With regard to identifying the relevant experimentally obtained value of \(z\), the rationale behind
choosing a particular transformation has been based on the assumption that a transformation that results in a more symmetrical distribution should provide a more representative mean value than the arithmetic mean. This is emphasized by the fact that the arithmetic mean of the skewed distribution of \( z \) tends to be inordinately sensitive to variations in a small number of high values of \( z \). However, there is not an obvious hemodynamic basis for this assumption. Another complicating factor was demonstrated by Kitaoka and Suki, who showed that random diameter measurement errors result in overestimation of the mean \( z \) value. Limited resolution, which disproportionately reduces the number of measurable bifurcations having one small daughter, can also result in overestimation of \( z \). Further investigation of these issues is outside the scope of the present study, but it does bring into question which, if any, of the mean values of \( z \) reported in Table 2 provides the appropriate estimate for \( \beta_1 \) in this modeling context. Although this point is raised with regard to the value of \( z \), a similar question could be raised with regard to the appropriate mean diameter for a given order in the various ordering schemes. This point is also raised by the work of Kassab et al., who described the “diameter-defined” Strahler ordering system. The data presented in Fig. 2 and Table 2 are apparently unique, in that they were obtained from perfused lungs under relatively physiological conditions rather than from plastic casts. However, model simulations, such as in Figs. 4 and 5, suggest that there is no reason to expect that variations in the filling pressure or pressure profile between morphometric studies would have a major impact on the estimation of \( z \).

Murray’s law [e.g., for Poiseuille flow, minimization of the sum of hydraulic and metabolic work occurs when \( z = 3 \)] is often used as a benchmark for vascular tree design. Given the available data, it is difficult to conceive of any realistic error in diameter measurements or set of “unphysiological” conditions during data collection that if corrected would result in \( z > 3 \) for the pulmonary arterial tree. Similarly, a value much less than 2 seems to be ruled out. To put this range in perspective, it encompasses a large range of longitudinal pressure profiles, as can be seen from Fig. 8, in which a decrease in \( \beta_1 \) of only \( \sim 7\% \) was accompanied by an increase in pressure drop for the entire tree of \( \sim 70\% \). On the other hand, for a single bifurcation with two equal daughter branches, the daughter diameters would be \( \sim 0.794 \) times the parent for \( z = 3 \) and 0.707 times the parent for \( z = 2 \), a difference that is visually hardly perceptible.

In conclusion, we have expanded on previous expressions relating tree structure and function by including distensibility- and diameter-dependent viscosity in the continuum model of Suwa et al. We have used the model to demonstrate some examples of parameter sensitivity in parameter ranges relevant to the pulmonary arterial tree. The unique aspect of the morphometric data presented is that they were obtained under somewhat more physiological conditions than data from plastic casts. The diameter independence of \( z \) is consistent with previously obtained data on plastic casts and is the basis of the continuum model concept. The problem of identifying a hemodynamically appropriate mean value for this kind of modeling approach can be exemplified by examining model sensitivity, with additional information such as the pressure drop and volume of the tree as exemplified in Figs. 6 and 7 taken into account, but resolution of that problem will require additional investigation.

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FOOTNOTES

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AUTHOR NOTES

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