Branching Exponent Heterogeneity and Wall Shear Stress Distribution in Vascular Trees

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Branching Exponent Heterogeneity and Wall Shear Stress Distribution in Vascular Trees

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Abstract
A bifurcating arterial system with Poiseuille flow can function at minimum cost and with uniform wall shear stress if the branching exponent \( z = 3 \) [where \( z \) is defined by \( (D_1)^z = (D_2)^z + (D_3)^z; D_1 \) is the parent vessel diameter and \( D_2 \) and \( D_3 \) are the two daughter vessel diameters at a bifurcation]. Because wall shear stress is a physiologically transducible force, shear stress-dependent control over vessel diameter would appear to provide a means for preserving this optimal structure through maintenance of uniform shear stress. A mean \( z \) of 3 has been considered confirmation of such a control mechanism. The objective of the present study was to evaluate the consequences of a heterogeneous distribution of \( z \) values about the mean with regard to this uniform shear stress hypothesis. Simulations were carried out on model structures otherwise conforming to
the criteria consistent with uniform shear stress when \( z = 3 \) but with varying distributions of \( z \). The result was that when there was significant heterogeneity in \( z \) approaching that found in a real arterial tree, the coefficient of variation in shear stress was comparable to the coefficient of variation in \( z \) and nearly independent of the mean value of \( z \). A systematic increase in mean shear stress with decreasing vessel diameter was one component of the variation in shear stress even when the mean \( z = 3 \). The conclusion is that the influence of shear stress in determining vessel diameters is not, per se, manifested in a mean value of \( z \). In a vascular tree having a heterogeneous distribution in \( z \) values, a particular mean value of \( z \) (e.g., \( z = 3 \)) apparently has little bearing on the uniform shear stress hypothesis.

Shear stress on the vascular endothelial surface is a physiologically transducible force that influences vascular function in several ways. In the short term, shear stress affects vessel tone, and, in the longer term, it affects the vascular architecture generated during the vasculo- and angiogenesis and vascular remodeling associated with vascular adaptation and disease. Thus there has been considerable interest in the concept that the form of a vascular network reflects shear stress optimization operating during the network construction and maintenance. The complexity of vascular tree structures, in terms of both the branching network and the local contour of the vessel wall, contributes to the difficulty in evaluating this concept. One simplification that has been used as a reference point in such evaluations is “Murray's Law,” which provides a vascular design criterion for minimizing the power required to operate a distribution network constructed of cylindrical vessels with convective transport via Poiseuille flow. According to Murray's Law, power is minimized if flow throughout the network is proportional to the cube of the vessel diameters. This is also a condition that can produce uniform shear stress throughout the network. Thus shear stress control over vessel diameter would appear to be a means of developing and/or maintaining optimal vascular structure.

One implication of Murray's Law is that, for a bifurcating tree having a parent vessel diameter \((D_1)\) and daughter diameters \((D_2)\) and \((D_3)\) at each bifurcation, power is minimized if the branching exponent \((z)\) in

\[
(D_1)^z = (D_2)^z + (D_3)^z
\]

Equation 1

is 3 at each bifurcation of the tree. With regard to shear stress on the vessel walls, it can also be shown that, under certain conditions, if \( z = 3 \) at each bifurcation, the wall shear stress is uniform and independent of vessel diameter. Thus if deviations from a wall shear stress set point were to provide an error signal in the feedback control of vessel diameter, one might expect that this optimal tree structure would develop and be maintained. Given these consequences of Murray's Law, there have been several investigations carried out to determine \( z \) in various vascular beds. The average values have generally fallen between 2 and 3, and various ideas as to how the values other than 3 might be consistent with the overall concept have been suggested, including alternatives to the assumption of Poiseuille flow. Also, the values of \( z \) within a given vascular tree are widely and asymmetrically distributed. Consideration has been given as to which statistical average best represents the large number of bifurcations comprising a vascular tree, but there has been relatively little attention given to the impact of the variance of the distribution about the mean. In the present study, we use a heterogeneous arterial tree model to gain insight into the implications of the distribution of \( z \) values with regard to the uniform shear stress hypothesis.

**METHODS**

Versions of the vascular tree modeling approach used have been described previously. The model is referred to as “arterial” because, in the simulations, flow proceeds from a single large inlet vessel to many small terminal outlet vessels. The model algorithm produces bifurcating trees with varying degrees of asymmetry in structure but constructed in a way that ensures that the log of the number of vessels \([N(j)]\) in a Strahler order \( j \) versus the
log of the mean diameter \([\bar{D}(j)]\) of the vessels in order \(j\) is approximately linear with a slope equal to the negative geometric parameter \((-\beta)\). Strahler ordering\(^{38}\) begins with the terminal (precapillary) arterioles as order 1, with the order number increasing as the inlet artery is approached. When two daughter vessel segments of the same order meet, they form a parent vessel segment of the next higher order. When two daughter vessel segments of different orders come together, the parent order number is the higher of the two daughter orders. Once the vessel segment orders have been assigned, contiguous segments of a common order are combined into vessels having the mean diameter and sum of the lengths of the contiguous segments. The number, mean diameter, and mean length of the vessels in each order then comprise the morphometric summary of the tree. Once this ordering has been accomplished, it is often convenient to reverse the order numbers so that they start with the inlet artery as order 1. This has been referred to as reversed Strahler ordering\(^{42}\), and in what follows, \(j\) refers to the reverse Strahler order.

The near linearity of the log \(N(j)\) versus log \([\bar{D}(j)]\) relationship is apparently a universal geometric property of pulmonary arterial trees that has been observed in every species for which the appropriate measurements are available\(^6\). It is a reflection of the self-similar or fractal-like pulmonary arterial tree structure. To this extent, the model may be considered a model of the pulmonary arterial tree. On one hand, it is a gross simplification of a real pulmonary arterial tree; on the other hand, in the context of the specific problem addressed in this study, the primary conclusion that it evokes is probably applicable to vascular trees in general.

Assignment of vessel dimensions.

To construct an asymmetrical model tree, the problem is to generate a range of vessel segment dimensions (diameters and lengths) and then connect the segments so that they satisfy the linear log \(N(j)\) versus log \([\bar{D}(j)]\) rule. Furthermore, it is desirable that the magnitude of the log \(N(j)\) versus log \([\bar{D}(j)]\) slope, the geometric parameter \(\beta\), be predetermined. In other words, the \(\beta\) obtained from Stahler ordering should be an input. To achieve these objectives, we begin with the assumption that no two vessel segments have exactly the same diameter. Each vessel segment that will comprise the tree is assigned a number (or rank) \(N_{cum}\), which is 1 plus the number of vessels having diameter larger than \(D(N_{cum})\). The diameter \(D\) of vessel \(N_{cum}\) is then assigned by Eq. 2

\[
D(N_{cum}) = D(1) \left( \frac{N_{cum} + 0.5}{1.5} \right)^{-3/\beta}
\]

Equation 2

Equation 2 has the following heuristic derivation and has been empirically verified\(^6\). Consider the relationship between \(N(j)\) and \(N_{cum}\) for a bifurcating tree having an equal number of bifurcations along all pathways from inlet to terminal vessels and in which the \(N_{cum}\) are sequentially assigned to order \(j\). That is, the \(N_{cum}\) in order \(j\) range from \(2^{j-1}\) to \(2^j - 1\). For such a tree, if we define \(N_{cum}(j)\) to be the average value of \(N_{cum}\) in order \(j\) [i.e., \((2^{j-1} + 2^j - 1)/2\)], then \(N_{cum}(j) = 2^{j-2} + 2^{j-1} - 0.5 = 1.5N(j) - 0.5\). From the linearity of log \(N(j)\) versus log[\(\bar{D}(j)\)] relationship

\[
N(j) = [\bar{D}(j)/D(1)]^{-\beta}
\]

Equation 3

Thus

\[
N_{cum}(j) = 1.5 \left( \frac{\bar{D}(j)}{D(1)} \right)^{-\beta} - 0.5
\]
Equation 4

Assuming that \( N_{\text{cum}}(j) \) is close to the \( N_{\text{cum}} \) of the vessel having the diameter closest to \([\bar{D}(j)]\), the inverse of Eq. 4 provides a relationship between \([\bar{D}(j)]\) and \( N_{\text{cum}}(j) \) such that

\[
\bar{D}(j) \sim D(1) \left( \frac{N_{\text{cum}}(j) + 0.5}{1.5} \right)^{-1/\beta}
\]

Equation 5

Equation 2 follows from the assumption that the relationship between \([\bar{D}(j)]\) and \( N_{\text{cum}}(j) \) in Eq. 5 sought to hold for the individual vessels as well. Equation 2 differs from its counterpart in Ref. 6 and results in a slightly less accurate approximation to Eq. 3 for the largest vessels. The latter disadvantage is considered to be outweighed by the relative simplicity of form and derivation of Eq. 2.

To assign lengths to the vessel segments whose diameters are determined by Eq. 2 and in a manner consistent with conditions under which Murray’s Law results in uniform shear stress when there is a common outflow pressure; the segment length \( (L) \) is set proportional to the diameter \( (D) \) and, in that sense, segment length is also determined by Eq. 2. This length assignment is also consistent with the pulmonary arterial tree data wherein \( L/D \), although variable, is nearly independent of vessel diameter\(^5,6\).

Connecting vessels into a tree structure.

The next step is to connect the vessel segments into a tree structure. This description may be facilitated by recognizing two types of asymmetry occurring in the tree structures. One is asymmetry in the daughter diameters at a bifurcation (i.e., \( D_1 \neq D_2 \)). The other kind of asymmetry is a variation in the numbers of bifurcations (or branches) along each pathway through the tree. Accordingly, all model trees constructed of vessels whose diameters are assigned by Eq. 2 are asymmetrical. However, they can be more or less asymmetrical depending on the range of variability in the \( D_1 \)-to-\( D_2 \) ratios and in the numbers of branches along each pathway. Both types of asymmetry (bifurcation asymmetry and pathway asymmetry) are controlled during the process of connecting the vessel segments by a parameter \( \phi \) as follows. The algorithm begins with vessel segment \( N_{\text{cum}} = 1 \) and proceeds through \( N_{\text{cum}} = (N_{\text{tot}} - 1)/2 \) (where \( N_{\text{tot}} \) is the total number of segments comprising the tree). Each vessel segment is randomly assigned one daughter (which will ultimately be the larger of the two daughters) from the unattached segments left in the sequence \( N_{\text{cum}} - 1 \) to \( 2 N_{\text{cum}} \). After each \( N_{\text{cum}} \) through \( (N_{\text{tot}} - 1)/2 \) vessel has had one daughter attached, the remaining vessel segments (each of which will be the smaller of the two daughters at a bifurcation) are assigned to parents in the sequence of largest remaining daughter attached to largest remaining parent. To vary the asymmetry of the tree, limits are placed on the initial daughter assignment so that the choice of the largest daughter is among vessel segments having \( N_{\text{cum}} \leq 2 \) times the parent \( N_{\text{cum}} \) but larger than the closest integer \( \leq \varphi \) times the parent \( N_{\text{cum}} \), where \( 1 \leq \varphi < 2 \). Thus as \( \varphi \) approaches 1 or 2 the tree will be, respectively, more or less asymmetrical. For this particular study, \( \varphi \) was set at 1 or near 2 to achieve maximum and minimum asymmetry, respectively.

Regardless of the degree of asymmetry, the terminal vessels are from the \( N_{\text{cum}} \) sequence from \( (N_{\text{tot}} + 1)/2 \) to \( N_{\text{tot}} \). In other words, the terminal arterioles (those connecting to the capillaries) are the smallest vessel segments in the tree. This is a general characteristic of arterial trees that ultimately have to connect to capillaries having diameters that are virtually the same compared with the range of arterial diameters.

When such a tree is Strahler ordered, the log \( N(j) \) versus log mean \([\bar{D}(j)]\) is approximately linear, with the model input value of \(-\beta\) as its slope\(^6\). Thus one unique aspect of this method for constructing an asymmetrical tree is that the tree can be constructed with this morphometric relationship predetermined. Figures 1-3 are an attempt to graphically represent the relationship between \( D(N_{\text{cum}}) \) and \([\bar{D}(j)]\) for a given value of \( \beta \) (which
happens to be 2.5 in these simulations). These figures are for the first four to six orders, with different symbol shadings for the vessel segments in each order. Only the first few orders are depicted because once the order number becomes much larger, the $D(N_{\text{cum}})$ and $[\bar{D}(j)]$ simply become parallel lines with the number of vessels in an order so large that the $D(N_{\text{cum}})$ symbols form a continuous line. The average diameter (normalized to the inlet diameter) in an order, $\bar{D}(j)/D(1)$, versus the number of vessels in an order, $N(j)$, which is a form of the data available from several morphometric studies of pulmonary arterial trees, is depicted (triangles on dashed lines in Figs. 1-3). The normalized diameter, $D(N_{\text{cum}})/D(1)$, and rank, $N_{\text{cum}}$, of each individual vessel segment in the tree are also depicted (circular symbols on solid lines in Figs. 1-3). Figure 1 is the most nearly symmetrical tree visualized in the above derivation of Eq. 2. The vessels of a given Strahler order (shaded symbols) are sequential, and their numbers increase as $2^j - 1$. In addition, the arithmetic mean ($\bar{D}$) of the individual diameters within a given order is

$$\bar{D}(j) \sim D(1)N(j)^{-1/\beta}$$

Equation 6

Figure 2 includes the same vessel segments as Fig. 1, but the tree is more asymmetric. In the asymmetric model, an order is not necessarily a continuous sequence of $N_{\text{cum}}$. Thus, in Fig. 2 (in which the shaded symbols indicate the Strahler order to which each vessel segment belongs), the sequence for a given shading is broken. The average number of vessels comprising an order approaches $3^j - 1$ (rather than the $2^j - 1$ in the symmetrical trees), as in the Stahler-ordered morphometric data from the human lung reported by Horsfield.

Fig. 1. The log of the individual normalized vessel diameters $[D(N_{\text{cum}})/D(1)]$ versus the log of the vessel rank ($N_{\text{cum}}$) (circles) or the log of the normalized average diameter $[\bar{D}(j)/D(1)]$ in order $j$ versus the log of the number $[N(j)]$ of vessels in order $j$ (triangles). Dashed line, Eq. 2; solid line, Eq. 5. Each symbol shading gradient represents a different Strahler order. The first five and a fraction of the sixth reverse Strahler orders of a tree are shown, in which each order is a consecutive sequence of $N_{\text{cum}}$ [the least asymmetrical configuration of vessel segments having diameters ($D$) assigned by Eq. 2].
Models relating hemodynamic function and pulmonary arterial tree structure have often employed Strahler-ordered data to construct symmetrical trees wherein all vessels within an order are assigned the mean diameter of the order. To help put Figs. 1 and 2 in perspective, Fig. 3 demonstrates how the diameter versus number relationships would appear for a symmetrical tree wherein all diameters within an order are the same (circles). In Fig. 3, $N_{cum}$ loses its usual meaning for the circular symbols because each vessel in an order has the same diameter. However, it is used by way of analogy with Figs. 1 and 2. Figure 3 is shown only to help guide an
understanding of Figs. 1 and 2. Such trees have been well studied in the past and are, therefore, not included in the simulations carried out in the next sections.

Shear stress calculations.
With the simulated tree being constructed as indicated above, shear stress ($\tau$) was calculated for each vessel segment, assuming Poiseuille flow, as $\tau = \frac{32 f \mu}{\pi D^3}$, where $f$ is the flow rate through a vessel segment having diameter $D$ and $\mu$ is viscosity. The individual vessel segment flow rate was determined by first calculating the Poiseuille resistance of each segment. The total downstream resistance at each branch point was then successively calculated beginning with the subtended terminal vessel segments. For a given total flow and a common terminal vessel outlet pressure, the flow division at each bifurcation was then recursively calculated for each bifurcation from the two total downstream resistances.

Simulations.
The question addressed using these model trees is as follows: What is the impact of heterogeneity in $z$ values on the distribution of $\tau$? Because the model parameters $L/D$, $f$, $\mu$, and $D(1)$ are simply scaling factors, their values are not of particular relevance to this question. The problem is defined by the geometric parameters $\beta$ and $z$. For a symmetrical tree, $z = \beta$. However, when the two daughters at a bifurcation have unequal diameters, the mean $z > \beta$. In fact, the ratio of $z$ to $\beta$ is a measure of that kind of asymmetry. $\beta$ is the geometric input parameter to the model. Therefore, for a given asymmetrical tree simulation, $\beta$ was adjusted until the desired mean value of $z$ was obtained. The individual $z$ values were calculated by iteratively solving Eq. 1. Because the algorithm uses a seeded pseudorandom assignment of the vessels to a given bifurcation, it can generate any number of trees, each different in detail. The results are for individual examples but are representative of all the trees that could be generated in a given category. Comparisons made in this study were of simulations carried out on the most nearly symmetrical trees of the type depicted in Fig.1, wherein the values of $z$ were virtually the same for all bifurcations throughout the tree and, on the most asymmetrical trees of the type depicted in Fig. 2, wherein the values of $z$ were heterogeneously distributed.

RESULTS
To put the model results in context, the Fig.4A is the $z$ distribution obtained from morphometric measurements on dog lungs as previously described. Figure 4B is the distribution for an asymmetric tree constructed as indicated above to provide the same mean $z$ as the dog lung data. The model $z$ values have a right-skewed heterogeneous distribution resembling the dog lung data.
To put the impact of asymmetry in perspective, we begin with the most nearly symmetrical trees obtainable with the model, i.e., with $\phi \sim 2$. The results of these simulations, presented in Fig. 5, show how $\tau$ (normalized to the mean $\bar{\tau}$) is distributed in trees in which the $D_2/D_3$ ratios are as close to 1 as possible for this model algorithm and $z$ is virtually the same at each bifurcation. Figure 5A restates the point that when $z \sim 3$ at each bifurcation, uniformity in $\tau$ is achieved. Figure 5, B and C, is the $\tau$ distributions likewise obtained from nearly symmetrical trees but with the mean $z$ value set at the dog lung value from Fig. 4 (shown in Fig. 5B) or close to the value for the human lung reported by Horsfield and Woldenberg$^{16}$ (shown in Fig. 5C), which also is the geometric mean for the dog lung in Ref. 5. These mean values cover much of the range of mean values previously reported for the lungs$^5$. The key observation from Fig. 5, B and C, is when $z < 3$ in a nearly symmetric tree, even if $z$ is virtually the same at each bifurcation, $\tau$ increases as the vessel diameters decrease.

For the nearly symmetrical model providing the results depicted in Fig. 5 and constructed as depicted in Fig. 1, each of the $\tau$ bin bars includes the vessels of a single order, as would also be the case in a truly symmetrical tree such as represented in Fig. 3. Figure 6 is in the same format as Fig. 5 but depicts maximally asymmetrical trees generated by the algorithm (i.e., $\phi = 1$) having the same mean $z$ values as the Fig. 5 examples. Figure 6 reveals that, for the asymmetrical trees, $\tau$ is widely distributed regardless of the value of $z$. In fact, the coefficients of variation in $\tau$ are not very different for the three mean $z$ values studied. The variation in the Fig. 6 representation includes the increasing trend that occurs simply as the vessels get smaller when $z < 3$ (i.e., the contribution to the $\tau$ variance also observed in Fig. 5B and C) or when the mean value of $z = 3$ but the individual $z$ values are heterogeneous. To evaluate the contribution due to decreasing vessel size, the residual shear stress ($\tau_r$) was determined by removing this diameter-dependent component of the $\tau$ variation.

Figure 7 is a visual representation of how that was accomplished. $\tau$ (normalized to $\bar{\tau}$) for each vessel segment is plotted versus the vessel segment diameter [normalized to the inlet diameter $D(1)$]. Two different sets of simulation data are plotted. Data from the asymmetrical trees (shaded areas in Fig. 7) were used to construct Fig. 6 with the indicated mean $z$ values, and data are shown from the most nearly symmetrical tree ($\phi \sim 2$) having the same value of $\beta$ as its respective asymmetrical tree (solid symbols in Fig. 7) ($A$: $\beta = 2.57$; $B$: $\beta = 2.35$; and $C$: $\beta = 1.98$). The latter symbols run together, appearing as a stair graph, where the length of each step is the range of vessel diameters comprising an order in the nearly symmetrical tree. The variation in the shaded area above and below the stair steps is the residual variation after accounting for the increasing trend.
associated simply with decreasing diameter. Thus subtraction of the nearly symmetrical tree values from the asymmetric tree values removes this vessel size component, and the resulting $\tau_r$ distributions are plotted on Fig. 8, where $\tau_r$ is $[\tau(N_{cum})/(\bar{\tau})]$ for the asymmetrical tree minus $[\tau(N_{cum})/(\bar{\tau})]$ for the respective nearly symmetrical tree. Figure 8 shows that, after eliminating this diameter effect, $\tau_r$ remains widely distributed in the asymmetrical tree even when the mean value of $z = 3$.

Fig. 5. The shear stress ($\tau$) [normalized to mean shear stress ($\bar{\tau}$)] distribution for trees having the smallest possible differences between the diameters of the daughter vessels ($D_2$ and $D_3$) at each bifurcation such that they are the most nearly symmetrical trees generated by the model algorithm. These trees also have the smallest possible variations in the 3 designated $z$ values obtainable with the model. When $z \sim 3$ at each bifurcation, the coefficient of variation in $\tau$ ($CV_\tau$) is negligible. When $z$ is smaller than 3 at each bifurcation, $\tau$ becomes diameter dependent, increasing with decreasing diameter. Therefore, the $CV_\tau$ increases as $z$ gets smaller even though $z$ remains virtually constant throughout the tree. For $z < 3$, each bin bar is made up of vessels from the same order. For each panel, the geometric parameter ($\beta$) = mean $z$. A: when $z \sim 3$ at each bifurcation, uniformity in $\tau$ is achieved. B and C: $\tau$ distributions obtained from nearly symmetrical trees but with the mean $z$ value set at the dog lung value from Fig. 4 (B) or close to the value for the human lung reported by Horsfield and Woldenberg16 (C), which is also the geometric mean for the dog lung in Ref. 5.
**Fig. 6.** \( \tau \) (normalized to \( \bar{\tau} \)) distribution for the maximally asymmetrical trees. A–C: \( \beta \) adjusted to obtain same average \( z \) values as in the respective panels in Fig. 5, i.e., for mean \( z = 3 \), \( \beta = 2.57 \); for mean \( z = 2.76 \), \( \beta = 2.35 \); and for mean \( z = 2.35 \), \( \beta = 1.98 \). \( CV_{\tau} \) is considerably larger than in Fig. 5 even when the mean \( z = 3 \).

**Fig. 7.** \( \tau \) (normalized to \( \bar{\tau} \)) versus the diameter \( D(N_{\text{cum}}) \) [normalized to the inlet diameter \( D(1) \)] for the same asymmetrical trees as in Fig. 6 (gray dots) or for the nearly symmetrical trees with the smallest possible differences between the parent vessel diameter \( (D_1) \) and \( D_2 \) at each bifurcation giving the smallest possible variation in \( z \) in an order obtainable with the model (black dots, appearing as stair steps). The latter trees were
constructed with the same values of $\beta$ as the respective asymmetrical trees (i.e., for mean $z = 3$, $\beta = 2.57$; for mean $z = 2.76$, $\beta = 2.35$; and for mean $z = 2.35$, $\beta = 1.98$) but with $z = \beta$. Thus the stair steps indicate the variation in $\tau$ due to the increase with diameter alone. The step values subtracted from the individual $\tau$ values results in the residual shear stress ($\tau_r$) data plotted on Fig. 8 $[\tau(1)/\bar{\tau} = 0.277, 0.114, \text{and } 0.0163 \text{ for mean } z = 3, 2.76, \text{and } 2.35, \text{respectively}]$. $A$–$C$ have the same meaning as the respective panels in Fig. 6.

![Graph A](image)

$z = 3.00 \pm 1.20 \text{ S.D. } \text{CV}_{\tau_r}=54.42\%$

![Graph B](image)

$z = 2.76 \pm 1.12 \text{ S.D. } \text{CV}_{\tau_r}=47.20\%$

![Graph C](image)

$z = 2.35 \pm 0.96 \text{ S.D. } \text{CV}_{\tau_r}=46.22\%$

**Fig. 8.** The distribution of normalized $\tau_r$ remaining after subtracting the increasing component that is diameter dependent for the same asymmetrical heterogeneous trees as in Fig. 6. $A$–$C$ have the same meaning as the respective panels in Fig. 6. $\tau_r$ is $[\tau(N_{\text{cum}})/(\bar{\tau})]$ for the asymmetrical tree minus $[\tau(N'_{\text{cum}})/(\bar{\tau})]$ for the respective nearly symmetrical tree. The coefficient of variation in $\tau_r$ ($\text{CV}_{\tau_r}$) is somewhat smaller than the total $\text{CV}_{\tau}$ in Fig. 6, but this representation of the results demonstrates that a significant fraction of the $\tau$ variation in Fig. 6 remains over and above that due to the trend toward increasing shear stress with decreasing diameter.

One noticeable feature of Fig. 7 that deserves comment is the discontinuity that occurs between the terminal sequence of vessel segments and the rest of the tree. This apparently results from the fact that the connectivity of the tree is such that the terminal vessels are the smallest sequence of vessels. Thus there is a tendency for shorter pathways to make a more abrupt transition to their respective terminals than longer, more smoothly tapered pathways. The vessel segments that comprise the gray dots in the region to the right of the discontinuity are all terminal vessel segments. They are also all in the same Strahler order, as are the vessel segments comprising the black-dot step in this region of the graph. On the other hand, the vessel segments represented by the gray dots in the region to the left of the discontinuity are not necessarily, and commonly not, in the same order as the vessel segment (black dots in Fig. 7) having the same diameter.

**DISCUSSION**

The key observation from these simulations is that when the values of $z$ were distributed, the shear stress distribution was virtually independent of the mean $z$ value. Thus the simulations suggest that significant heterogeneity in $z$ among bifurcations renders knowledge of the mean and local values of $z$ almost irrelevant to the uniform shear stress hypothesis. Thus the conclusion is that the influence of shear stress on the vascular structure is not, per se, manifested in an average value of the branching exponent $z$. An additional observation is
that the increase in shear stress with decreasing diameter that occurs in symmetrical trees having a common value of $z < 3$ also occurs in asymmetrical trees having a heterogeneous distribution of $z$ about a mean value of 3.

Again, the model is an obviously simplified representation of a real tree both geometrically and hemodynamically. The assumption of Poiseuille flow carries with it several conditions that are not strictly adhered to in the real tree. The impact of some of these conditions with respect to Murray’s Law has been evaluated in other studies. The key feature of the present model for this study is that it provides a means of using the average morphometric parameters, such as those available from Strahler-ordered data, to construct trees with a heterogeneous distribution of $z$ but otherwise conforming to the conditions under which $z = 3$ results in uniform shear stress. Conditions under which uniform shear stress occurs in an asymmetric tree with a uniform Murray’s Law $z$ of 3 include the following: 1) each terminal outlet pressure is determined solely by the Murray’s Law flow partitioning at each upstream bifurcation through which the flow exiting that terminal has passed, or 2) the terminal pressures are influenced by downstream conditions, and the length-to-diameter ratio of each vessel segment is adjusted so that the flow partitioning at each bifurcation is consistent with Murray’s Law as well as any downstream conditions affecting the pressure at each terminal outlet. A special case of the latter is that of the constant $L$-to-$D$ ratio and equal outlet pressures used in the present model simulations. The first condition is apparently that most commonly visualized in linking the uniform shear stress concept with Murray’s Law. It includes the implicit assumption that the terminal pressures are independent of downstream conditions. The second condition has apparently not been previously considered. The special case of the second condition addressed herein includes the implicit assumption that terminal pressures are determined solely by downstream conditions. Neither of these extreme assumptions would appear to be completely consistent with any real vascular tree, although we favor the latter as more appropriately weighing the importance of downstream conditions in the pulmonary circulation. Regardless, there does not appear to be anything obvious in the fairly extensive observations made on vascular tree structures to suggest that there is some additional known structural feature that, if included, would alter the primary conclusion regarding the mean of a heterogeneous $z$ distribution. This conclusion may also be consistent with the observation that, in mathematical modeling studies evaluating the uniform shear stress hypothesis, diameter control dominated by a shear stress set point has resulted in unstable or aberrant structures. One problem is that the effect of changing local diameter on local shear stress depends on the extent to which changing local diameter affects local flow. The latter depends on the entire structure and where the vessel is located within that structure.

Schreiner et al. examined the shear stress distribution from the point of view of an asymmetrical model tree, with a common value of $z$ at each bifurcation. They demonstrated that constraints such as equal terminal flows and pressures require adjustments in lengths and daughter diameter ratios that result in nonuniform shear stress even with a uniform Murray’s Law $z$ of 3, i.e., even when $z$ is the same at each bifurcation, $z = 3$ is a necessary but not sufficient condition for uniform shear stress.

The distribution of $z$ values obtained in the model has a smaller coefficient of variation than the lung data. This suggests that the model results are a conservative representation of the potential effect of the heterogeneity in $z$. However, the data of Fig.4 and other studies not withstanding, distributions of $z$ in real vascular trees are at least somewhat uncertain. This is because the contribution of measurement errors has not been fully evaluated. Kitaoka and Suki noted that, in the presence of random measurement error, the mean values are overestimated. This is because the sensitivity to measurement error is proportional to the actual value of $z$ and the ratio of $D_2$ to $D_3$ (where $D_3$ is the smaller daughter). Thus any diameter measurement error in the direction that causes an overestimation of $z$ will have a larger effect than an error that causes an underestimation in $z$. When $D_3$ is small compared with $D_2$, small errors can have a large effect. While it is likely
that the actual distributions in real vascular trees are wider than produced by this particular model algorithm, it is also likely that the variance in experimentally determined z values includes a significant contribution resulting from the noise amplification caused by this sensitivity.

Two components of the \( \tau \) distribution can be recognized Fig. 7. One component is a systematic increase in \( \tau \) with decreasing vessel diameter, and the other is the more random variation at any diameter. The former occurred in trees having a common \( z \) value when \( z \) was smaller than 3, as observed in Fig. 5, but it also emerged when \( z \) was heterogeneous even when mean \( z = 3 \). It is interesting that after the diameter effect was eliminated, as in Fig. 8, the coefficient of variation in \( \tau_r \) was actually lower when the mean value of \( z \) was \(< 3 \). The effect was not great, and it would take more extensive study to determine how model specific it is. However, it raises the question as to whether lower mean \( z \) values might actually reflect mechanisms working toward shear stress uniformity within a given diameter range rather than globally. A possibly related phenomenon observed in the heterogeneous vascular structures simulated in Refs. 6 and 18 is that the minimum values of the coefficients of variation in terminal flows or pressures, respectively, also occurred when \( z < 3 \). The narrowing of these distributions may be at least partly a consequence of the fact that a larger fraction of the total pressure drop is concentrated toward the terminal vessels as \( z \) decreases, resulting in a more manifold-like structure\(^6\). Because the efficiency of solute transport between blood and tissue is inversely proportional to the variance in the microvascular flow distribution\(^1\), a mean value of \( z < 3 \) may reflect adaptive pressure toward optimization of microvascular transport. The mean \( z \) values measured in various organs have generally fallen between 2 and 3\(^5\).37 and are commonly well below 3, including those in the lungs\(^5\).

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FOOTNOTES

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