Scaling laws of vascular trees: of form and function

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BIOLOGICAL TREES are used to conduct fluids such as blood, air, bile, or urine. Energy expenditure is required for the conduction of fluid through a tree structure because of frictional losses. The frictional losses are reduced when the vessel branches have larger diameters. This comes with a cost, however, for the metabolic construction and maintenance of the larger volume of the structure. Eighty years ago, Murray (29) proposed a compromise between the frictional and metabolic cost expressed as a cost function. The formulation of the minimum energy hypothesis led to the well-known Murray’s law, which can be expressed as

\[ Q = kD^3 \]  

where \( Q \) and \( D \) are the volumetric flow rate and diameter of a vessel segment, respectively, and \( k \) is a proportionality constant.

Murray’s law predicts a universal exponent that is invariant (3.0) for all trees whose internal flows obey laminar conditions. Fifty years later, Uylings (38) argued that the exponent can vary in the range of 2.33–3.0 depending on whether the flow is turbulent (2.33) or laminar (3.0). Numerous papers have been published in the past 80 years on Murray’s law and on the validation of the exponent. The studies show support but with significant scatter. In a review of the literature, Sherman (33) concluded that Murray’s law is not obeyed in the most proximal bifurcations of aorta, the pulmonary trunk, the vena cavae, and the pulmonary veins. Interestingly, a recent paper on the applicability of Murray’s law to botanical trees suggests that animals and plants have reached similar solutions for efficient conduction of fluid (28).

Both Murray’s formulation and Uylings’ modification are focused on a particular vessel segment. The flow rate through a vessel branch, however, depends not only on the resistance of that branch but also on the total resistance of the tree distal to that branch. Hence, the formulation of an optimization principle requires the treatment of a tree structure as an integrated whole. Zhou, Kassab, and Molloi (47) (ZKM model) generalized the “minimum energy hypothesis” to an entire coronary arterial tree. In the process, a vessel segment was defined as a stem and the entire tree distal to the stem was defined as a crown (39). Obviously, the entire tree consists of many stem-crown units down to the capillary vessels as shown in Fig. 1. At each bifurcation, there is a unique stem-crown unit that continues down to the smallest unit: an arteriole with two capillaries for an arterial tree or a venule and two capillaries for a venous tree. Functionally, each stem supplies or collects blood from the crown for an arterial or venous tree, respectively. The details of the capillary network (nontree structure) beyond the first bifurcation are excluded from the present analysis. Hence, the present analysis applies strictly to a tree (arterial or venous) structure down to the first capillary bifurcation.

If \( A \) and \( Q \) represent the mean cross-sectional area and blood flow rate of a stem, respectively, and \( V \) and \( L \) represent the cumulative arterial volume and length of a crown, respectively, the ZKM model predicts the following relationships:

\[ V/V_{\text{max}} = (L/L_{\text{max}})^{5(\epsilon - 1)/\epsilon} \]  

\[ D/D_{\text{max}} = (L/L_{\text{max}})^{(3\epsilon - 2)/(4\epsilon - 1)} \]  

\[ Q/Q_{\text{max}} = (D/D_{\text{max}})^{(4\epsilon - 3)/(4\epsilon - 1)} \]

where \( D_{\text{max}}, Q_{\text{max}}, V_{\text{max}}, \) and \( L_{\text{max}} \) correspond to the diameter and flow rate of the most proximal stem, the volume of the entire crown, and the cumulative arterial length of the crown, respectively. The parameter \( \epsilon \) relates to the crown flow resistance and is equal to the ratio of metabolic to viscous power dissipation as described below.

These relationships have been determined and validated for the coronary arterial trees in the following three ways. 1) A hemodynamic analysis of coronary arterial blood flow rate based on detailed anatomic data yields these relationships over the entire arterial network (16). 2) A generalization of Mur-
corresponding to an arteriole-capillary or venule-capillary unit.

**METHODS**

Ray's cost function and conservation of energy predicts the same result over the entire coronary arterial tree (47). In vivo data on coronary stem flow rate, crown length, and volume from digital subtraction angiography (46) verifies the relationships for vessels proximal to 0.5 mm in diameter as observed in an angiogram. The form of Eq. 4 is equivalent to Murray's law, with the important distinction that the exponent depends on the parameter $\epsilon'$. Equations 2 and 3 are novel and together with Eq. 4 represent a major advancement since Murray's formulation in 1926 (29).

The goal of the present study was to show that the design of all vascular trees for which there exist morphometric data in the literature obeys the scaling laws conveyed in Eqs. 2–4. Specifically, we show that the proposed design laws extend beyond the coronary arterial trees as they are found to predict the morphological data of vascular trees of various species in the lung, various skeletal muscles (e.g., sartorius, retractor, and skin muscles), omentum, mesentery, and bulbular conjunctiva. The major significance of the present study is the reduction of all morphometric data on vascular trees of different organs and species to a set of laws derived on the basis of the minimum energy hypothesis under steady-state conditions.

**THEORETICAL FORMULATION**

The point of departure between Murray's law and the ZKM model is the fact that the former treats the tree one vessel segment at a time, whereas the latter analyzes the tree as an integrated system of stem-crown units. Hence the former view is local, whereas the latter is a global systems point of view. In both formulations, Murray's cost function consists of two terms: viscous and metabolic power dissipation. For a stem-crown unit, the cost function has the form:

$$ F(L,V) = Q^2(L)R_c(L,V) + K_mV $$

(5)

where $R_c$ is the crown resistance defined as the ratio of pressure difference (between inlet and outlet of crown) and flow rate into the crown and $K_m$ is a metabolic constant of blood. Although it is easy to define the resistance of a single vessel segment in Murray's formulation, it is much more difficult to analytically express the equivalent resistance of the entire tree in the ZKM model because the vascular system is composed of millions of vascular segments coupled in series and in parallel. The first break came when we validated a scaling relationship between the equivalent crown resistance $R_c$, the crown volume $V$, and the crown length $L$ as:

$$ \frac{R_c}{R_{max}} = \left( \frac{L}{L_{max}} \right)^5 \left( \frac{V}{V_{max}} \right)^{\epsilon'} $$

(6)

where $R_{max}$, $L_{max}$, and $V_{max}$ are the resistance, length, and volume of the entire tree. The parameter $\epsilon'$ ($\epsilon'$ is related to $\epsilon$ in Ref. 47 as $\epsilon' = 2 - \epsilon$) is determined empirically by fitting Eq. 6 to the experimental data on morphometry of the vascular tree (length and volume) and a network analysis of flow distribution (resistance). It has a unique value for each vascular system and reflects the functional specialization of each organ. The physical significance of this parameter will become apparent below.

The cost function was expressed in terms of equivalent scaling resistance of the tree as given by Eq. 5 similar to Murray's vessel segment. To eliminate the dependence of cost function on flow rate, we propose a proportional relationship between stem flow rate and crown length as:

$$ \frac{Q}{Q_{max}} = \frac{L}{L_{max}} $$

(7)

Equation 6 was validated by hemodynamic simulations (47) and in vivo experimental measurements (46). If we combine Eqs. 5–7 and divide by the maximum metabolic power consumption, we obtain a nondimensional cost function as:

$$ f = F(L,V) \frac{Q_{max}^2 R_{max}}{K_m V_{max}^2} \left( \frac{L}{L_{max}} \right)^5 \left( \frac{V}{V_{max}} \right)^{\epsilon'} = 1 $$

(8)

Next, we minimize the cost function for a given blood volume, i.e.,

$$ \frac{\partial f}{\partial \left( \frac{V}{V_{max}} \right)} = 0 $$

(9)

and yield the desired relation:

$$ \left( \frac{L}{L_{max}} \right)^5 \left( \frac{Q_{max}^2 R_{max}}{K_m V_{max}} \right) \left( \frac{V}{V_{max}} \right)^{\epsilon' - 1} = 1 $$

(10)

Two important results follow from Eq. 9: the crown volume-length relation as expressed by Eq. 2 and the following equation for the crown resistance parameter as:

$$ \epsilon' = \frac{K_m V_{max}}{Q_{max} R_{max}} $$

(11)

Hence, $\epsilon'$ represents the ratio of maximum metabolic to viscous power dissipation for a given tree.

In the ZKM model (47), conservation of energy imposed on a stem-crown system under steady-state and isothermal conditions that neglect the elasticity of the vessel wall and gravitational potential energy results in

$$ \int q \rho u dA = K_m V $$

(12)

where $\rho$ and $u$ are the blood density and the axial velocity, respectively. The flow speed $q$ is the magnitude of the flow velocity, which
is, in general, a vector with three components, u, v, and w in the x, y, and z directions, respectively, i.e., \( \mathbf{q} = u^2 + v^2 + w^2 \). Equation 11 is a balance between the rate of kinetic energy flowing into a stem (\( A_s \) is area of stem) and the metabolic dissipation power of the crown. For a uniaxial, fully developed flow, q and u are equivalent and the integral reduces to

\[
ap \frac{Q^3}{A_s} = K_m V
\]

(12)

where \( a \) is a numerical constant that depends on the shape of the velocity profile. Equations 2, 7, and 12 can be combined to yield Eq. 3. Equation 4 can be obtained by simply combining Eqs. 3 and 7. Finally, Eqs. 2 and 5 lead to an analytical expression for the nondimensional cost function under optimal conditions, i.e., minimum power, as

\[
f_{\text{min}} = \frac{Q_{\text{max}}}{\epsilon^3 + \epsilon^2} \left( \frac{L}{L_{\text{max}}} \right)^{\delta + 1}
\]

(13)

It can be verified that the second derivative of the cost function is positive; thus Eq. 13 represents a local minimum for the power dissipation.

Existing morphometric data on vascular trees. The branching pattern (node-to-node connectivity) and vascular geometry (diameter and length of each vessel segment) of arterial and venous vascular trees of many organs have been measured. Once the tree structure was reconstructed, order numbers were assigned to the vessel branches by the Strahler system (37). In this method, the capillary blood vessels are referred to as order 0. Two vessels of order 0 meet to form a larger vessel of order 1. When two arterioles of order 1 meet, the confluent vessel is given an order number 2 and so on. But if a vessel of order 2 merges with a vessel of order 1, the resulting vessel is assigned the highest order, i.e., order 2, and so on.

Singhal et al. (34, 35) and Horsfield and Gordon (10) used Strahler’s system to study the pulmonary arteries and veins of humans, whereas Yen et al. (42, 43) used it to study cat pulmonary arterial and venous trees. Strahler’s system has also been used to study the microcirculation of cat sartorius muscle (22), hamster retractor muscle (5), hamster skin muscle (2), rat mesenteric microvessels (24), rabbit omentum (6), and human bulbar conjunctiva microvessels (6). Kassab et al. (17) modified Strahler’s method with a diameter criterion (diameter-defined Strahler system) and used it to describe the right coronary, left anterior descending, and left circumflex arterial trees. Huang et al. (11) used the diameter-defined Strahler system to model the human pulmonary arterial and venous trees, whereas Jiang et al. (13) used it to describe the rat pulmonary arterial tree.

**Hemodynamic analysis.** To validate Eqs. 6 and 7, we carried out a network flow analysis that required the specification of a definitive vascular circuit. We adapted a simple symmetric model for analysis of blood flow in the present study. The symmetric model simulates the mean statistical data of the trees described in the previous section. Physically, the symmetric model is equivalent to assuming that all the vessel elements in any order are of equal diameter and length and are arranged in parallel and that the blood pressures at all of the junctions between specific orders of vessels are equal (16).

In this simplified circuit, the flow rate in each element of order \( n \) is \( Q_{\text{max}}/N_n \), where \( Q_{\text{max}} \) is the total flow rate into the coronary arterial tree and \( N_n \) is the total number of vessels at order \( n \). \( Q_{\text{max}} \) is determined as the ratio of pressure drop and equivalent resistance of the entire tree (16). The resistance, \( R \), is computed with Poiseuille’s equation \( R = \rho l/D^4 \), where \( \rho \) represents viscosity of blood and \( l \) and \( D \) represent length and diameter of a vessel segment). The equivalent resistance of a crown or the entire tree is then determined by the summation of the vessel segment depending on the series or parallel arrangement. The apparent viscosity of blood is a function of vessel diameter, hematocrit, and shear strain rate. Pries et al. (30) provided a validated model of the dependence of blood viscosity on the diameter and shear rate of flow to describe the Fahraeus-Lindqvist effect and the non-Newtonian properties of blood, which was used in the present study. Appropriate boundary conditions were imposed on the pressure of systemic and pulmonary vessels (100 and 35 mmHg, respectively). The pressure at the inlet of the capillary vessels was taken as 25 mmHg. The postcapillary pressure and venous outlet pressures were taken as 15 and 5 mmHg, respectively. The outlet pressure conditions were considered uniform in all simulations. The data files (morphometric data from literature and computed stem and crown parameters) are made available to the public via the website http://cvbiomech.eng.uci.edu.

**Data analysis.** We used the mean diameters, lengths, and total number of vessels for each order of vessels for the various vascular tree systems described above to determine the ratios \( D/D_{\text{max}}, L/L_{\text{max}}, V/V_{\text{max}}, Q/Q_{\text{max}} \), and \( R/R_{\text{max}} \). Initially, the flow model was set up in a Strahler form, and once the hemodynamic parameters were determined, the various quantities were related directly. For example, \( Q \) was determined as a function of order number \( n \), and because \( D \) is also a function of \( n \), \( Q \) and \( D \) were then related directly for each order \( n \). The determination of these quantities for each stem-crown unit at every bifurcation allowed the test of validity of Eqs. 2–7.

**RESULTS**

**Crown resistance.** The validity of Eq. 6 for the crown resistance was examined as illustrated in Fig. 2 for the various organs and species. The conformity of data to the scaling power law relation expressed by Eq. 6 is excellent. This implies that the equivalent resistance of a complex arterial tree can be described by a relatively simple scaling expression. The values of \( \epsilon' \) along with the correlation coefficients of the least-squares fit for each organ are listed in Table 1.

**Flow-length relation.** Figure 3 verifies the linear flow-length relationship hypothesized by Eq. 7 (\( R^2 = 0.998 \pm 0.0066 \)). The data are shown on a log-log plot to highlight the large span of flow rate and length (9 orders of magnitude) for the various vascular systems ranging from small microcirculatory units to entire arterial or venous vascular organs.

**Design scaling laws.** The crown volume-length relationship for the various vascular organs is reduced to a power law relation predicted by Eq. 2 as shown in Fig. 4, and the exponents are summarized in Table 1. Similarly, the flow-length diameter relationship of a stem is dictated by Eq. 4 as shown in Fig. 5, and the exponents are summarized in Table 1. Also listed in Table 1 are the exponents for the stem diameter-crown length relationship (Eq. 3).

**Scaling exponents.** The exponents \( \beta, \chi, \delta \) for the relationships \( V/V_{\text{max}} = (L/L_{\text{max}})^{\beta} \) (Eq. 2), \( D/D_{\text{max}} = (L/L_{\text{max}})^{\chi} \) (Eq. 3), and \( Q/Q_{\text{max}} = (D/D_{\text{max}})^{\delta} \) (Eq. 4), respectively, were determined by least-squares fit of the data. It is clear that our theoretical formulation predicts a dependence of the exponents on the resistance parameter \( \epsilon' \) (i.e., \( \beta = 5/(\epsilon' + 1), \chi = (3\epsilon' - 2)/(4(\epsilon' + 1)), \) and \( \delta = (4\epsilon' + 1)/(3\epsilon' - 2) \)). Hence, the regression values can be compared with the theoretical predictions. The means (±SD) of the exponents determined by curve fits of measurements and those predicted from theory are 1.26 ± 0.12 and 1.28 ± 0.086 (\( \beta, P = 0.832 \)), 0.37 ± 0.082 and 0.43 ± 0.021 (\( \chi, P = 0.508 \)), and 2.63 ± 0.65 and 2.33 ± 0.11 (\( \delta, P = 0.799 \)), respectively. We did not find any statistically significant differences between the exponents determined from experiment and theory as indicated by the P-values by paired Student’s t-test. The root mean square
errors (RMS) for $\beta$, $\chi$, and $\delta$ are 0.10 (8.2% of mean predicted value), 0.099 (23.1% of mean predicted value), and 0.71 (30.7% of mean predicted value), respectively. Interestingly, the three outliers in the data set are the rat mesentery arteries (MA; 4 orders), cat sartorius muscle arteries (SMA; 4 orders), and human bulbular conjunctiva arteries (BCA; 5 orders). If those data are excluded, the RMS becomes 10% of the mean predicted value for all three exponents.

**Constraints on scaling exponents.** An inspection of Eqs. 2–4 reveals two sets of constraints for the three exponents $\beta$, $\chi$, and $\delta$, namely, $\chi\delta = 1$ and $\beta + 4\chi = 3$. The first constraint is implied from Eqs. 3 and 4, whereas the second relation follows from Eqs. 2 and 3. These two quantities can be computed from Table 1, and their mean values over all organs and species are $0.93 \pm 0.079$ and $2.74 \pm 0.42$, respectively. The RMS for the first and second constraints are 0.10 (10.3% of mean predicted value) and 0.48 (16.1% of mean predicted value), respectively. If the same three sets of data are excluded (rat MA, cat SMA, and human BCA), the RMS becomes <10% of the mean predicted value for both constraints. Hence, there is good agreement with theory.

**DISCUSSION**

The task of distribution and collection of nutrients in nature often requires a branching system. The tree structure is prev-

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**Table 1. Parameters $\varepsilon^*$, $\beta$, $\chi$, and $\delta$**

<table>
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<tr>
<th>Species</th>
<th>Vessel (N)</th>
<th>$\varepsilon^*$</th>
<th>$R^2$</th>
<th>$\beta$</th>
<th>$R^2$</th>
<th>$\chi$</th>
<th>$R^2$</th>
<th>$\delta$</th>
<th>$R^2$</th>
<th>Ref.</th>
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<td>0.994</td>
<td>2.18</td>
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<td>0.993</td>
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N, total no. of orders in the respective vascular tree; RCA, right coronary artery; LAD, left anterior descending artery; LCx, left circumflex artery; PA, pulmonary artery; PV, pulmonary vein; SKMA, skin muscle arteries; SMA, sartorius muscle arteries; MA, mesentery arteries; OV, omentum veins; BCA, bulbular conjunctiva arteries; RMA, retractor muscle artery; BCV, bulbular conjunctiva vein.
alent in nature. In biological systems, vascular trees are the rules of architecture for three-dimensional (3D) organs (18). Nontreelike structures such as arcades, however, do exist in biological organs. Interestingly, the existence of arcades seems to be restricted to 2D organs or surfaces of 3D organs, e.g., mesentery and omentum, surface of the heart, inner ear, retina, surface of the small intestine and colon, iris, diaphragm, thin skeletal muscle, surface of uterus, and surface of the elbow (see review in Ref. 18). Analysis of the relevance of the present model to arcade structures remains a task for a future study.

Design of vascular trees. Although the morphogenesis of the vascular tree is likely to be determined by a preprogrammed genetic algorithm, a number of physical, chemical, and biological factors related to the functional needs of a particular tissue determine the subsequent growth and remodeling during postnatal development. The detailed form of tree structures reflects the changes brought about by natural selection and adaptation to the environment, which reflects a survival value of the structure. The design determinants of structure are undoubtedly multifactorial, and an analysis of their effects on structure and function is often nontrivial.

In the present study, the mathematical properties of branching trees were utilized to explore the underlying principles in the design of physiological trees under steady-state conditions and to elucidate the factors that dictate their morphometry. Here we show that all vascular trees examined (coronary,.
pulmonary, vascular systems of various skeletal muscles, mesentery, omentum, and conjunctiva) in various species (rat, hamster, cat, rabbit, pig, and human) obey a set of design rules or scaling laws. Equations 2 and 3 are structure-structure relations, whereas Eq. 4 is a structure-function relation. These relations are a consequence of the minimum energy hypothesis, which implies that the design of vascular trees is such that the power required to pump a volume of blood through the tree structure is a minimum given the constraint of producing and maintaining the metabolic cost of blood volume. Hence, the resulting structure is a consequence of a compromise between two costs: frictional energy of operation and metabolic energy of construction and maintenance. The power law nature of the relations is undoubtedly related to the fractal nature of tree structures (1), albeit we do not directly impose the fractal hypothesis in the present model. The conformity of data of various vascular systems and various species to these power laws is excellent (Table 1). It is interesting to note that Murray’s law (δ = 3.0) does not hold for most of the organs examined (Table 1).

Extension of Murray’s law. Equation 4 is a generalized extension of Murray’s law in which the exponent δ is not a universal constant. Uylings (38) proposed that the value of the exponent may vary depending on whether the flow is turbulent (2.333) or laminar (3.0). It is difficult to predict the state of flow a priori. Hence, it is difficult to validate the physical meaning of Uylings’ exponent. Furthermore, Hutchins et al. (12) reported a value >3.0 (3.2 ± 0.25), as we did in the present study (δ ranged from 2.06 to 4.18). In the present analysis, δ depends on the metabolic-to-viscous dissipation ratio e′, which is specific to the organ system of interest as seen in Table 1. For lower-resistance organs such as human pulmonary arteries and veins, the value of e′ is higher than that of higher-resistance organs (Table 1 and Fig. 2).

In addition to the minimum energy hypothesis, the ZKM model is based on Eqs. 6 and 7 and conservation of energy under steady-state conditions. Equation 6 reduces to Poiseuille’s resistance for a single vessel or the equivalent resistance of many vessels arranged in series when e′ = 2. Interestingly, the form of Eq. 6 is similar to the allometric scaling law proposed by West, Brown, and Enquist (WBE model) (40). They showed that an equivalent Poiseuille’s resistance of a fractalike network scales with mass M as 
\[ R_c \propto M^{-3/4} \] or 
\[ R_c \propto V^{-3/4} \] because V \( \propto M \). If we combine Eqs. 2 and 6, we obtain
\[
R_c = V^{\delta - 3/4} \left( \frac{\epsilon + 1}{\epsilon} \right)^{1/2}
\] (14)

If we equate this expression to the allometric scaling relation, we obtain an algebraic equation for the exponent that requires a value of e′ = 27/8 or 3.37. Conversely, if we consider the mean value of e′ to be 3 (it is actually 2.94 ± 0.27 from Table 1), the ZKM model predicts a value of −3/5 rather than the −3/4 given by the WBE model. Hence, although Eq. 6 has the form of a scaling relation, the value of e′ required by the WBE model is not realized by any of the vascular organs examined (Table 1). Accordingly, Eq. 6 is not explicitly based on Poiseuille’s resistance or the fractal branching model.

Equation 7 can also be explained on the basis of allometric scaling. The WBE model predicts a 3/4 power relation between flow rate and mass, i.e., Q \( \propto M^{3/4} \). Seiler et al. (32) obtained data on the relationship between myocardial mass assessed by radiomicrospheres and coronary arterial crown length obtained by angiography. The equation L \( \propto M^{3/4} \) can be used to fit the data as well as their proposed linear relation within the scatter of data (\( R^2 = 0.889 \)). The two results imply a linear flow-length relation as given by Eq. 7.

Optimal power dissipation. The optimal (minimum) power consumption normalized with respect to the metabolic requirements of blood volume is expressed by Eq. 13 and shown in Fig. 6. Appropriately, the power dissipation is strongly dictated by e′, i.e., power dissipation is directly related to the resistive process. Borders and Granger (3) showed previously that power dissipation is related to the flow rate through a power

![Fig. 5. Relationship between normalized stem flow and diameter. A power law relation is observed, consistent with Eq. 4.](http://aijheart.physiology.org/10.1152/ajpheart.00258.2005)
law relation in the microcirculatory bed of normal and hypertensive rat cremaster muscle. Because flow rate is proportional to crown length, their experiments validate the form of our theoretical prediction, Eq. 13. Our results also show that for an entire crown, $L = L_{\text{max}}$, the total dissipation power is proportional to the metabolic power. The proportionality constant is given by $(e' + 1)/e'\left(\text{(metabolic + viscous)/metabolic power dissipation}\right)$, whose mean value for the various organs and species was found to be $1.34 \pm 0.031$. It should be noted that the exponent of the volume-length relation ($\delta$) is also the exponent of the power dissipation-length relation (Eqs. 2 and 13). This is expected because the volume-length exponent is a direct result of the minimum energy principle. It should also be noted that when Murray’s law holds ($\delta = 3$, i.e., $e' = 2$), the optimal minimum power has the highest value but decreases as $e'$ increases beyond 2, as is the case for the organ systems in Table 1.

Comparison between ZKM and WBE models. A discussion of the scaling laws of the ZKM model with those of WBE model is warranted (27). With the following assumptions, 1) a space-filling fractallike branching system, 2) the capillary vessels are size and flow invariant, and 3) the energy required to distribute resources is minimized, West, Brown, and Enquist proposed the following relevant scaling relations: $Q \propto M^{\delta-1}$, $V \propto M$, and $D \propto M^{\delta}$. If we combine the first and third relations, we obtain a universal value for $\delta$ of 2.0. This value holds for some of the circulatory systems summarized in Table 1 but not for most. If we consider the second and third relations, we obtain $V \propto D^{\delta/3}$ for the WBE model. If we combine Eqs. 2 and 3, the ZKM model predicts a scaling relation of the form $V \propto D^{\delta/3}(\delta - 2)$. With the values of $e'$ listed in Table 1, we obtain a mean ($\pm$1SD) value of $2.98 \pm 0.34$ compared with the WBE model’s prediction of 2.67. A plot of experimental data of $V$ vs. $D$ yields values of the exponents with a mean of $3.2 \pm 0.89$ ($R^2 = 0.999 \pm 0.00096$). The experimental exponents were not significantly different from the ZKM model predictions but were significantly larger than the exponent predicted by the WBE model. Finally, the WBE model predicts a $3/4$ scaling between flow rate and volume as per the first and second relations. The ZKM model predicts scaling of $Q \propto V^{(\delta+1)/3}$ (Eqs. 2 and 7) or an exponent of $2/\delta$. The data in Table 1 yield a mean value of $0.79 \pm 0.055$ averaged over all organs and species. A curve fit of raw data yields a mean of $0.77 \pm 0.093$ ($R^2 = 0.999 -1.00$). Although the experimental data are in general agreement with both models, the agreement with the ZKM model is excellent. More recently, the same authors generalized their WBE model on the basis of geometry rather than hydrodynamics of hierarchical structures, which confirmed their previous scaling laws (41).

Possible mechanism for minimum energy hypothesis. Numerous other theoretical attempts have been made to explain the design of vascular trees based on the principle of minimum blood volume, minimum lumen surface area, and minimum drag force on the vessel wall (14, 44). Any proposed principle or hypothesis must provide a mechanism for the implementation of the principle. One of the advantages of the minimum energy hypothesis is that it provides a mechanism for the local implementation of minimum energy. It was shown previously that the global requirement of “minimum energy” is consistent with the local condition of “uniform shear” on the vessel wall (15, 23, 45). Hence, the endothelial cells may play an important role in the local enforcement of the global minimum energy, which adds to the huge list of functions of the endothelial cells.

The uniform shear hypothesis, however, implies Murray’s law with an exponent of 3.0 (15). This is certainly not the case for most vascular trees, as seen from the data in Table 1. The uniformity of shear stress throughout the vascular system is not supported experimentally. In the mesentery, it has been found that shear stress is amplified in the microcirculation (vessels $<100 \mu$m in diameter) increasing from $\sim10$ to 60 dyn/cm$^2$ toward the capillary vessels (25, 26). A similar conclusion was made by Pries et al. (31) on the mesenteric microcirculation. They showed that although the variation in shear stress is significant, it is pressure dependent, i.e., the arteriole, capillary,
and venule shear stress variations reduce to a single curve when examined as a function of pressure. In a different organ, Stepp et al. (36) measured the velocity and diameter of epicardial vessels (50–450 µm in diameter) in the dog heart. They computed the wall shear stress and found it to be heterogeneously distributed, where arterioles <160 µm in diameter have increased shear stress relative to the larger vessels. The variation of wall shear stress in baseline and adenosine-dilated vessels was ~10–30 and 10–40 dyn/cm² in the 50- to 450-µm diameter range, respectively.

There is no doubt that for a given blood vessel there appears a “set point” for the wall shear stress that is regulated by the endothelium (21). Murray’s law implies that the set point is exactly the same throughout the vasculature, which has been the prevailing thought. Because Murray’s law does not hold throughout the vasculature, the set point cannot be the same for all blood vessels. This raises a very interesting issue that requires a change in the current paradigm. It may be that the shear stress is not the “sensed” element. The wall shear stress provides the loading on the endothelial cells that causes axial tension and deformation in those cells. Fung and Liu (7) showed previously that the tension in the endothelial cell is proportional to the wall shear stress. They also showed that the transmission of tension from one endothelial cell to the neighboring cells depends on the angle of the cell-cell junction. The higher shear stress in the microcirculation suggests a larger tension on those endothelial cells. The tension will cause some level of deformation depending on the mechanical properties (stiffness) of the cell. Suppose that the endothelial cells regulate deformation rather than shear stress. A set point of strain for the endothelium may exist throughout the entire vascular system provided that the endothelial cells of microvessels are stiffer than those of larger vessels. The changes in stiffness may be locally controlled by cell volume regulation. In summary, we hypothesize that a strain-dependent set point can be locally controlled by endothelial cell volume regulation to adjust the stiffness to the tension imposed by the shear stress. This is a plausible hypothesis for a future investigation.

There is experimental evidence that the circumferential strain is remarkably uniform in the cardiovascular system. Guo and Kassab (8) determined the stress and strain distribution throughout the aorta and coronary arterial tree down to 10-µm vessels. They found that strain (stretch ratio relative to the zero-stress state) and stress varied between 1.2 and 1.6 and between 10 and 150 kPa, respectively. The relative uniformity of strain (50% variation) from the proximal aorta to a 10-µm arteriole implies that the vascular system closely regulates the degree of deformation. Additional support for the uniform strain hypothesis arises from remodeling studies in which the circumferential strain (computed in reference to the zero-stress state) responds faster and recovers more quickly than the shear stress or circumferential stress in flow- and pressure overload, respectively (4, 27).

Critique of model. Although the linear network model is simple, it captures the salient features of blood flow in the network. We previously (19) modified the Poiseuille equation to account for the elasticity of coronary blood vessels and predicted a quadratic relation between flow and pressure drop compared with Poiseuille’s linear relation. In the in vivo range, the compliance of coronary blood vessels, for example, is relatively small such that this modification does not alter the pressure-flow relation significantly (9, 20). Finally, the Womersley’s number is larger than 1 (3–4) only in the largest one or two generations of blood vessels (16). Hence, in the majority of the vascular networks considered, steady-state flow is reasonable for the smaller vessels. The pulsatile flow is a superposition of two terms: steady-state and oscillatory flow. For the systems of interest (medium- to small-size vessels), the first term dominates. It is reasonable that a steady-state analysis should predict the design features of the system because design is likely a steady-state process that does not change with every pulse of the heart. We opted to pursue the economic and efficient approach in engineering, which is to utilize the simplest model that answers a particular question.

The use of a symmetric branching pattern that is not anatomically accurate warrants some discussion. Kassab et al. (16) showed previously that the distribution of mean flow rate in various orders of tree is not strongly dependent on the asymmetry of the tree. The use of a symmetric tree model is necessitated by the fact that data on the realistic connectivity or asymmetry of most vascular trees considered are lacking. For the coronary arterial trees whose asymmetry has been quantified (17), the proposed design principles lead to nearly identical results for the symmetric and asymmetric models (47). Hence, the use of a symmetric model should not diminish the utility or implications of the present analysis.

It may be argued that the high correlation shown in Fig. 2 is expected because the two variables have a strong covariance with the size (diameter and length) of the stem and crown. Furthermore, the range of variables is very large (it is a log-log plot with 11 decades on the x-axis and 35 decades on the y-axis). In such a plot, even large variations from the proposed scaling would be barely visible. A more appropriate test of a model prediction would be to plot a ratio at each order that is hypothesized to be constant according to the proposed scaling law. In Table 2, we summarize the ratios determined in this way for Eqs. 2 and 6, which have a covariance for the crown length. We determined the ratio at each order and present the

<table>
<thead>
<tr>
<th>Species</th>
<th>Vessel (N)</th>
<th>ε/±SD</th>
<th>β±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pig</td>
<td>RCA (11)</td>
<td>2.83±0.091</td>
<td>1.40±0.038</td>
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<tr>
<td>Pig</td>
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<td>1.43±0.071</td>
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<tr>
<td>Rat</td>
<td>PA (11)</td>
<td>2.75±0.068</td>
<td>1.43±0.049</td>
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<td>Cat</td>
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<tr>
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<td>PV (10)</td>
<td>2.79±0.090</td>
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<td>PA (17)</td>
<td>3.45±0.16</td>
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<tr>
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<td>3.24±0.058</td>
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<td>1.26±0.041</td>
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</table>

Values are the parameters ε/ and β for Eqs. 6 and 2, respectively, determined as means ± SD of the ratios at each order number. N, total no. of orders in the respective vascular tree.
means ± SD of the data compared with the averages determined from the slope of the entire curve as summarized in Table 1. It is clear that the later value is generally within 1 SD of the former. Hence, the validity of the constants and the form of the equations holds.

Significance of study. The significance of the present study is that it unifies the design principles of all vascular trees found in the literature. Hence, we reveal a set of scaling laws that dictate the morphological construction of vascular trees. This provides some insight into the workings of nature and reveals the physical and physiological principles that dictate the great complexity of vascular trees that span many orders of magnitude of spatial dimension. These laws provide the “signatures” of normal vascular trees and may impart a rationale for diagnosis of disease processes. The self-similar nature of these laws implies that the analysis can be carried out on a partial tree as obtained from an angiogram or a computerized tomography scan (46). Hence, these formulations may serve for diagnosis of vascular disease that affect lumen dimension, volume, length (vascularity), or perfusion (flow rate). The application of the present findings to vascular disease is a laudable goal of future investigations. Fundamentally, the proposed structure-function scaling laws provide powerful analytical tools to understand the micro- and macrocirculation as integrated systems in health and disease.

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