Vascular Dimensions of the Cerebral Arteries Follow the Principle of Minimum Work

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Background and Purpose: The principle of minimum work is a parametric optimization model for the growth and adaptation of arterial trees. It establishes a balance between energy dissipation due to frictional resistance of laminar flow (shear stress) and the minimum volume of the vascular system, implying that the radius of the vessel is adjusted to the cube root of the volumetric flow. The purpose of this study is to verify whether the internal carotid artery system obeys the principle of minimum work.

Methods: Measurements of the radius of parent and branch segments of the internal carotid, anterior, and middle cerebral arteries were performed on analog angiographs chosen at random from a set classified as normal. The branch angles were measured from lateral projections in bifurcations of the anterior cerebral artery. The relation of the calibers of parent and branch vessels was analyzed.

Results: The area ratio of the bifurcations (N=174) was 1.2±0.4 (mean±SD). The equation \((r_0)^n=(r_1)^n+(r_2)^n\) was solved for \(n\), resulting in \(n=2.9±0.7\) (mean±SD, \(N=157\)). Optimum proportions between the radii of parent \((r_0)\) and branch \((r_1, r_2)\) vessels in the internal carotid artery system were verified in normal carotid angiographs up to four branch generations, according to the theoretical equation \(r_0^2=r_1^2+r_2^2\) (\(r=0.989, N=174\)). No clear correlation was found between the measured branch angles, the relative branch cross-sectional area, and the theoretical optimum angles.

Conclusions: This study demonstrates that the process of branching of the internal carotid artery system obeys the principle of minimum work, as the diameter exponent approximates 3. The principle of minimum work establishes strict functional relations between volumetric flow, flow velocity, and vessel radius. This model was extended to parametric optimization of branch angles, which has proved irrelevant in terms of functional optimization. Our results corroborate this finding. Shear stress–induced endothelial mediation seems to be the regulating mechanism for the maintenance of this optimum vessel design. The magnitude of wall shear stress is the same at every point in a vascular network obeying the principle of minimum work, because the flow rate influences the shear stress proportionally to the third power of the vessel radius. This observation has implications for understanding the remodeling of the cerebral vascular network in the presence of arteriovenous malformations and for the pathogenesis of saccular aneurysms. (Stroke 1993;24:371–377)

KEY WORDS • cerebral aneurysms • cerebral arteries • cerebral arteriovenous malformations • hemodynamics

The development and maintenance of optimum geometric properties of the cerebral arterial network are essential to provide a stable blood flow to the brain over a wide range of body and mind activities and simultaneously to avoid abnormally increased hemodynamic stresses. Optimum design of biological structures is an established theoretical principle of biology based on the environmental pressure exerted by natural selection on almost every aspect of the structure and function of biological systems. Every system requires expenditure of energy to build and maintain its infrastructure as well as to perform its physiological tasks. The optimum structure is the one that involves the least metabolic cost, or work.\(^1,2\) The vascular system has a vital physiological significance, and therefore natural selection probably has a powerful influence on vessel design. A common premise of optimum modeling is to assume that each subsystem tends to optimize itself with regard to its specific variables.\(^2\) The efficiency of the vascular system is determined by the arrangement of narrow and wide vessels in a branching hierarchy, the design of which maintains the continuity of flow at a low energy cost, minimizes the volume of the system, and simultaneously avoids increased hemodynamic stresses. Therefore, theoretical studies of optimality of the vascular system have traditionally concentrated on parametrical optimization of the relative calibers of parent and branch vessels and of the angles between them.\(^1-10\)

In the present study we verified an optimum relation between the calibers of parent and branch vessels in the internal carotid artery system of the living human in its conducting portion, i.e., proximal to the regulator or resistance vessels, according to the principle of minimum work.\(^3,9,10\) This is a parametric optimization model for the growth and adaptation of arterial trees, establishing a balance between the radius of the vessel and...
the cube root of the flow through the vessel, implying that the radii of parent \( r_0 \) and branch \( r_1 \) and \( r_2 \) vessels are related as \( r_0^{1/3} = r_1^{1/3} + r_2^{1/3} \) (see "Appendix").

It is conceivable that data in this regard are relevant for the understanding of flow-related pathological changes of the cerebral vasculature, such as the high-flow angiopathy associated with arteriovenous fistulas, and of the development of intracranial saccular aneurysms, which are now recognized as acquired degenerative vascular lesions.\(^{11}\)

**Materials and Methods**

We used analog angiographs of high quality chosen at random from a set classified as normal from the archives of the Department of Neuroradiology, Sahlgrenska Hospital, Gothenburg, Sweden. The films were reviewed, and the absence of pathological changes or congenital anomalies was verified. Measurements of the diameter of parent and branch segments of the internal carotid, anterior, and middle cerebral arteries in 12 internal carotid angiographs of 10 adult patients were performed using a scale and hand lens. The measured parameters are summarized in Figure 1. The measurements of 174 bifurcations up to the fourth branch generation were approximated to the nearest 0.1 mm. Care was taken to avoid measurements very close to the branching points, where the cross-sectional area of the vessels is known to increase.\(^{12}\) No correction was made for the magnification effect of the divergent x-ray beam. The penumbra effect, or unsharpness of edge determination due to diminishing of contrast resolution as the vessel boundary is approached, was minimized by choosing the picture with the best contrast resolution for every vessel from the angiographic series and by avoiding measurements of bifurcations the parent vessel of which had an angiographic diameter of <1 mm. The branch angles \( \theta_1 \) and \( \theta_2 \) were determined from lateral projections in 80 bifurcations of the anterior cerebral artery system, which lie approximately in the sagittal plane, in this way minimizing the measurement error. The branching points were traced on a transparent plastic sheet, and the angles were measured after photostatic magnification.

**Figure 1. Schematic representation of an arterial bifurcation.** Parent artery of radius \( r_0 \) divides into two branches of radii \( r_1 \) and \( r_2 \), presenting angles \( \theta_1 \) and \( \theta_2 \), respectively, with axis of parent vessel.

**Figure 2. Plot shows relation between radii of parent and branch arteries compared according to principle of minimum work.** Equation of regression line is \( r_0^3 = 0.353777 + 1.0602(r_1 + r_2^2) \), and correlation index is \( r = 0.989 \) (N=174).

**Results**

The area ratio of the bifurcations, defined as \( (r_1^3 + r_2^3) / r_0^3 \), was 1.2±0.4 (mean±SD, N=174).

A direct relation between the cube of the radius of the parent arteries and the sum of the cubes of the radii of the daughter arteries, or \( r_0^3 = r_1^3 + r_2^3 \), was determined by linear regression. A remarkable correlation \( (r=0.989, N=174) \) was found (Figure 2).

The equation \( (r_0)^n = (r_1)^n + (r_2)^n \) was solved for \( n \), resulting in \( n = 2.9±0.7 \) (mean±SD, N=157). Seventeen bifurcations were excluded in this analysis because the measured \( r_0 = r_1 \), resulting in very high \( n \)-values despite a relatively small \( r_2 \). In these cases the relation \( r_0^3(r_1^3 + r_2^3)^{-1} \) was 0.87±0.07 (mean±SD, N=17).

The theoretically optimum branch angles were calculated (see Equations 7 and 8 in "Appendix"). The measured angles were found to scatter widely around the predicted optimum angles \( (r=0.275) \) (Figure 3). No clear correlation \( (r=0.396) \) was found between the

**Figure 3. Plot shows relation between relative branch cross-sectional area and branch angle \( (r=0.396, N=80) \).**
Figure 4. Plot shows relation between measured branch angles and predicted optimum angles (r=0.275, N=80).

Discussion

The principle of minimum work is a model for growth and adaptation of arterial trees establishing strict relations between volumetric flow, flow velocity, and vessel radius. This model applies to the arterial and capillary circulation excluding the aorta (which functions also as a blood reservoir, minimizing the high acceleration during the systolic blood ejection from the left ventricle and converting the intermittent blood stream into a continuous one). The same principle was extended to the optimization of branch angles. Initially it assumed that the blood flow is steady and laminar, but further analysis of the model has shown that it applies to all types of steady flow, including complete turbulent and transitional types.

Early studies have shown some degree of agreement between the actual and the optimum vessel caliber according to this principle in corrosion casts or radiographs after contrast perfusion of diverse portions of the arterial tree of humans and other mammals. Similar diameter exponent laws have been found in other biological branching duct systems, such as the large airways of the lungs, the branching of trees, the diffusion system of insects, and the duct systems of several species of sponge stromatoporoids. Moreover, studies in vivo with animal models demonstrated that the blood flow in arteries is approximately proportional to the cube of the diameter of the vessel, e.g., in the canine carotid artery (including progressive remodeling after establishment of an arteriovenous fistula), the microvasculature of the rat cremaster muscle, and the feline pial arteries. However, the fact that data on branch angles were disappointingly found to scatter considerably around the theoretical optimum, as verified also in the present study, has hindered a general acceptance of the principle of minimum work. The parametric optimization of branch angles has otherwise proved to be irrelevant in terms of functional optimization. The true measure of departure from optimality is the difference of energy expenditure, or work, of the system, not the difference between the predicted optimum and the measured parameters. Thus, the energy cost increases up to only 5% in most measured vascular bifurcations compared with their so-called optimum values.

The physical mechanism responsible for achieving such a vascular design is probably optimization of the shear stress acting on each unit area along the endothelium, pulling it downstream. The magnitude of wall shear stress is the same at every point in a vascular network obeying the principle of minimum work, because the flow rate influences the shear stress proportionally to the third power of the vessel radius (see “Appendix”). As mentioned above, this blood flow/vessel caliber relation has been demonstrated in vivo and in animal models. Therefore, every local change in the system, either in volume or flow, propagates through all ramifications of the network and imposes a reorganization of the system to maintain an optimum blood flow/vessel diameter relation. Remodeling of whole arterial networks, in the form of increase or diminishing of the vessel diameter, is known to occur after local changes in either the volume of the vascular system (surgical resection, tissue growth, or atrophy) or the blood flow (changes of metabolic demand of the irrigated tissue or increased flow due to an arteriovenous fistula). Recently, increases in blood flow velocities in the microcirculation per se have been demonstrated to provoke increases in the caliber of skeletal muscle arterioles through endothelial mediation. This process is probably regulated by continuous release of endothelium-derived relaxing factor (EDRF). EDRF is also a potent inhibitor of platelet adhesion. In this way, EDRF may reduce the wall shear stress both by vaso-dilation and possibly by influencing the blood viscosity. The assumption that EDRF is identical with nitric oxide (NO) or a nitroso compound that liberates NO seems not to be the case in the cerebral circulation. Release of EDRF is thought to be induced by shear stress on the endothelium and by deformation of the vessel wall. The microvascular blood flow is influenced by EDRF according to a fourth-power dependence on arteriolar caliber. In this way, continuous release of EDRF likely provides the functional signal in long-term regulation of arterial caliber, being inhibited when the blood flow/vessel caliber relation reaches a third-power ratio.

Despite its apparently optimum geometry, the cerebrovascular bed seems peculiarly liable to degenerative changes. Cerebral arteries are thinner than extracranial arteries of correspondent diameter, their walls contain very little elastin, and, lying in the subarachnoidal space, they are poorly supported by surrounding tissue. Local failures of the above described optimum design of the cerebral arteries in avoiding increased shear stress, or intrinsic limitations of the regulating mechanisms, are particularly evident in two disease conditions, namely saccular aneurysms and arteriovenous malformations (AVMs) of the brain.

There is strong evidence against the congenital theory regarding the etiology of intracranial saccular aneurysms, which are most likely hemodynamically induced degenerative vascular lesions. In this process, aging, arterial hypertension, atherosclerosis, and certain connective tissue disorders, inter alia, seem to be aggravating rather than causal factors. Saccular aneurysms arise at the apex of bifurcations,
which as a result of impact and deflection of the blood flow streamlines is the site of maximum hemodynamic stress in a vascular network. Change in the shape of the bifurcations during the cardiac cycle, resulting in loss of static equilibrium at the apex of the bifurcation and disruption of the vessel wall elements, has been proposed as the mechanism of aneurysm formation.\textsuperscript{34} The present study demonstrates that the branch angles may vary widely in the cerebral arteries. Therefore, the apex of the bifurcation may lie in a nonoptimum position relative to the dividing streamline of the flow in the parent vessel, leading to turbulence, vibrations, and increased shear stress on the vessel wall at the apical region, despite the fact that the blood flow/vessel radius relation is optimum.

High blood flow conditions in localized portions of the cerebral arterial network associated with a high incidence of saccular aneurysms are related to anatomic variations of the circle of Willis, ligation of vessels, and AVMs.\textsuperscript{11,32–34} That high intravascular pressure is not necessary for the development of aneurysms is evident from the common occurrence of these lesions at branching points of feeder arteries of high-flow AVMs of the brain.\textsuperscript{11,35,36} These vessels characteristically have relatively low intravascular pressure, high flow velocity, large diameter, and thin walls as a result of rarefaction of muscle fibers in the tunica media, sometimes with fenestration of the endothelial cell layer.\textsuperscript{35,36} Shear stress–induced endothelialmediation might also be responsible for the progressive remodeling\textsuperscript{35–37} of the cerebral vascular network in the presence of an AVM and the reversion of these changes after removal of the malformation. Shear stress influences endothelial cell structure and function.\textsuperscript{38} Fluid-imposed shear stress on bovine cerebral endothelial cell monolayers was demonstrated to modify cell adhesion, monolayer permeability, and composition of the extracellular matrix.\textsuperscript{39} Increased wall shear stress has been related to profound vascular damage in high-flow vascular states.\textsuperscript{38,40} Vasodilation has a limited efficacy in avoiding damage, as scaling up a vessel signifies that its volume increases by a third-power factor ($x^3$) while its cross-sectional area and the vessel wall surface increase by a squared factor ($x^2$), in this way increasing the tension of the vessel wall (by a factor $x$). Thus, the efficacy of vasodilation is limited by the strength of the vessel wall.

Conclusions

Obviously, optimum models are abstractions of biological systems; they are not expected to fit these systems with absolute accuracy. This study demonstrates that in the process of branching of the internal carotid artery system there is a good agreement between the cube of the radius of the parent arteries and the sum of the cubes of the corresponding daughter arteries. A real tree structure cannot be fully constructed according to a diameter exponent of 3 on all scales, because this would correspond to the limit of infinitely thin ducts; because arteries are not infinitely thin, the best diameter exponent may only approximate 3.\textsuperscript{17} To our knowledge, this is the first time that such measurements have been performed in the cerebral arterial tree of the living human. The relative simplicity of the methods required does not detract from the relevance of the results in establishing a norm for the cerebral circulation. This observation has implications for understanding the remodeling of the cerebral vascular network in the presence of AVMs and for understanding the pathogenesis of saccular aneurysms.

Appendix

Theoretical Foundations of the Principle of Minimum Work

The principle of minimum work is a parametric optimization model for the growth and adaptation of the arterial tree. It proposes a functional interrelation between vessel radius, flow rate, flow velocity, and wall shear stress that establishes a balance between minimum energy dissipation due to frictional resistance of laminar flow and the minimum volume of the duct system. The present description of the principle of minimum work is based on its original derivation by Cecil D. Murray\textsuperscript{3,4} and on further studies of its theoretical basis.\textsuperscript{5,10,17}

The continuity of flow in the cardiovascular system is given by $f=vA$, where $f$ is the volumetric flow, $v$ is the flow velocity, and $A$ is the lumen area. The volumetric flow in a given heart cycle is the same in the aorta and in the capillaries. The heart pumps a single stream of blood that passes through a process of continuous bifurcation before it reaches the capillary bed. To maintain a stable volumetric flow in a given artery, the velocity increases if the diameter of the vessel decreases. Increasing the velocity in a narrow vessel increases the energy expenditure to circulate the blood, the shear stress on the vessel wall, and the dissipation of energy as heat as a result of the internal resistance of the blood to deformation and flow. At the same time, the increased flow speed impairs the diffusion of metabolites in the microcirculation. Flow in narrow vessels implies a high energy cost. Therefore, the arterioles, capillaries, and venules must be as short as possible, whereas wider vessels conduct blood over longer distances, and the flow velocity in these narrow vessels must be markedly lower than in the wider ones. This is possible because the total cross-sectional area of the capillaries considerably exceeds that of the aorta. However, because the energy cost also increases in proportion to the volume of the system, the diameters of the vessels must be the smallest possible. Therefore, the efficiency of the vascular system is determined by the arrangement of narrow and wide vessels in a branching hierarchy, the design of which maintains the continuity of flow such that in every segment of the vessel flow is achieved with the least possible biological work. The wider the vessel, the smaller is the power $P_f$ required for flow, but the metabolic cost for maintenance of the blood and vessel wall tissue $P_m$ becomes higher. The total power $P_f+P_m$ is minimized by an equilibrium between $P_f$ and $P_m$.

From Hagen-Poiseuille's law we have:

$$f=(\pi r^4 p)/(8\eta l)^{-1}$$

where $r$ is the radius and $l$ is the length of the vessel, $\eta$ is the viscosity of the blood, and $p$ is the pressure gradient. $P_f$ is given by:

$$P_f=pf=(8\eta sl^2)/(\pi r^4)^{-1}$$
For unit length of vessel:

\[ P_f = (8\eta f^2)(\pi r^4)^{-1} \]

We see that \( P_f \) is exponentially reduced by small increases of the vessel radius.

As \( P_m = m \text{ Volume} \), where \( m \) is a metabolic coefficient, we have:

\[ P_m = mr^2 \]

For unit length of vessel:

\[ p_m = m\pi r^2 \]

Thus, \( P_m \) is exponentially increased by small increases of the vessel radius. Consequently, 1) the total power \( P_t \) is:

\[ P_t = P_f + P_m = (8\eta f^2)(\pi r^4)^{-1} + m\pi r^2 \]

and 2) the total power \( p_t \) per unit length of vessel is:

\[ p_t = p_f + p_m = (8\eta f^2)(\pi r^4)^{-1} + m\pi r^2 \]

For a given viscosity \( \eta \) and metabolic level \( m \) the total power \( p_t \) required for flow in a unit segment of vessel depends only on the flow and the radius of the vessel. In this way, the optimum radius for a desired flow rate at the minimum total cost is the one where \( dp/dt = 0 \) and \( d^2p/dt^2 > 0 \). The optimum vessel radius is found by:

\[ dp/dt = d[(8\eta f^2)(\pi r^4)^{-1} + m\pi r^2]/dr = 0 \]

\[ (-32\eta f^2)(\pi r^4)^{-1}2\pi mr = 0 \]

and

\[ d^2p/dr^2 = d[(-32\eta f^2)(\pi r^4)^{-1} + 2\pi mr]/dr = 160\eta f^2 r^6 + 2\pi m \]

Since \( \eta, m, f, \) and \( r \) are positive, \( d^2p/dr^2 \) is positive and \( dp/dr = 0 \), the minimum \( p_t \) occurs when:

\[ (-32\eta f^2)(\pi r^4)^{-1} + 2\pi mr = 0 \]

\[ (16\eta f^2)(\pi r^4)^{-1} = \pi mr \]

\[ f^2 = [(\pi^2 m)(16\eta)^{-1}] r^6 \]

\[ f = Kr^3 \]

Consequently, \( f = K (\Sigma r^3) \) for the whole arterial tree in consideration. \( K \) remains constant as far as the blood viscosity and the metabolic rate of blood and vessel tissues are constant. In the smallest arteries the decrease in blood viscosity changes \( K \).

From Equation 4 and the principle of continuity of flow, we have:

\[ v = Kr \]

In individual branches:

\[ f_0 = f_1 + f_2 \]

\[ Kr_0^3 = Kr_1^3 + Kr_2^3 \]

\[ r_0^3 = r_1^3 + r_2^3 \]

or

\[ r_0 = \sqrt[3]{r_1 + r_2} \]

Figure 5. Relation between radius of parent artery (y axis) and its branches (x and z axes) in vascular network constructed according to principle of minimum work. Area ratio of bifurcations \((r_0^2 + r_1^2 + r_2^2)/r_0^2\) may vary from 2^{1/3} in the case of a symmetrical bifurcation to near 1.0 in the case of a very small branch from the main trunk.

\[ r_0^3 = \Sigma r_n^3 \]

for a given segment of the arterial tree distal to a given point, where \( r_0 \) is the radius of the parent artery and \( r_1 \) and \( r_2 \) are the radii of its branches. An alternative statement for the principle of minimum work is: "an optimum vascular system must have its vessels connected in such a way that the total flow of the system, wherever that flow is intercepted, is carried by a set of vessels whose radii cubed sum to a constant value." See Figure 5. However, a tree structure with diameter exponent of 3 on all scales would fill all the available space. The best arterial trees can achieve is to obey this bifurcation rule over a limited range of branch generations with a diameter exponent of \( \approx 3 \).

These equations were developed assuming that the blood flow in arteries is steady and laminar. Further analysis has extended the principle of minimum work to all types of steady flow. Summarizing, the total power \( p_t \) per unit length of vessel may be expressed as:

\[ p_t = C f^2 r^3 + m\pi r^2 \]

given

\[ C = \frac{g(\pi f^2/2r)^k}{r(4\pi^2)^{-1}} \]

where \( \rho \) is the density of blood and \( g \) depends on the relative roughness of the vessel wall. The term \( k \) depends on the Reynolds number \( (Re) \), assuming values between 1 (in the case of laminar flow) and 0 (complete-
ly turbulent flow). The term $j$ relates to $k$ as $j = 5 - k$, therefore assuming values between 4 (laminar flow) and 5 (turbulent flow).

The optimum radius $r_M$ for which $p_i$ is minimum is achieved by $d_p/dt$ as discussed above, resulting in:

$$r_M = [(jC^f)^{-2}/(2m)]^{1/(j+2)}$$

Substituting the above expression in $f_0 = f_1 + f_2$, we have:

$$r_0^{1+2j/(j-2)^2} = r_1^{(1+j)/(j-2)} + r_2^{(1+j)/(j-2)}$$

Optimization of the branch angles has been attempted. Substituting $f$ from Equation 3 in Equation 1, we have:

$$p_j = 3 \pi m = r^2$$

Given $l_0, l_1$, and $l_2$ as the lengths of parent and branch vessels, $\theta_1$ and $\theta_2$ as the angles between them, and $m$ as constant, by geometric reasons infinitesimal increments $d l_i$ of $l_i$ will increase $P_i$ for the section $l_i$ by $d l_i r_i^2$ and decrease the costs of the branches by $\cos \theta_1 d l_i r_i$ and $\cos \theta_2 d l_i r_i$ for the sections $l_i$, $l_2$, respectively. By using similar constructions for increments in $l_i$ and $l_1$, we obtain the equations:

$$d l_0 r_0^2 = \cos \theta_1 d l_0 r_1^2 + \cos \theta_2 d l_0 r_2^2$$

$$d l_0 r_1^2 = -\cos (\theta_1 + \theta_2) d l_1 r_1^2 + \cos \theta_1 d l_1 r_0^2$$

$$d l_0 r_2^2 = -\cos (\theta_1 + \theta_2) d l_2 r_1^2 + \cos \theta_2 d l_2 r_0^2$$

Dividing these expressions by $l_0, l_1$, and $l_2$, respectively, the optimal branch angles $\theta_1$ and $\theta_2$ are given as:

$$\cos \theta_1 = (r_0^4 + r_1^4 - r_2^4)/(2r_0^2 r_1^2)$$

$$\cos \theta_2 = (r_0^4 + r_2^4 - r_1^4)/(2r_0^2 r_2^2)$$

$$\cos (\theta_1 + \theta_2) = (r_0^4 - r_1^4 - r_2^4)/(2r_0^2 r_2^2)$$

The physical mechanism responsible for such vascular design is probably the minimization of the shear stress ($\tau$) acting on each unit area along the endothelium pulling it downstream. In laminar flow, shear stress is:

$$\tau = (4\eta r) \times (\pi r^3)^{-1}$$

or

$$\tau = (4\eta r) \times (r)^{-1}$$

It is evident from Equations 4 and 10 that in an arterial network modeled on the principle of minimum work the vessel radius, which stabilizes the wall shear stress, is proportional to the cube root of the volumetric flow rate. The wall shear stress probably has the same magnitude in every point of the arterial tree over a wide range of scales, and local changes in the system propagate through all ramifications of the network, imposing a reorganization of the system to maintain the optimum blood flow/vessel diameter relation.

References


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