A Mathematical Model for the Formation of Cerebral Aneurysms

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Cerebral aneurysms are hypothesized to be acquired lesions resulting from a loss of static equilibrium in the apical region of the bifurcation, which causes the opening angle of the bifurcation to change during the cardiac cycle. Repeated dynamic cycling may disrupt wall elements in a manner analogous to a wire breaking with repeated bending and result in the formation of an aneurysm. A mathematical model that predicts the geometry of arterial bifurcations is proposed. The model predicts that the transmural pressure in the smaller branch is greater than or equal to that in the larger branch and that the larger branch makes a smaller angle with the direction of the parent artery. Bifurcations with smaller area ratios (the sum of the luminal areas of the branches divided by the luminal area of the parent artery) have smaller opening angles. When the area ratio is 1.0, the opening angle is about 90°. The model concludes that the opening angle is constant during the cardiac cycle if the fractional change in the radii of the daughter and parent arteries is the same for any increase in blood pressure and if the ratio of transmural pressures in the parent and daughter branches does not change during the cardiac cycle. Otherwise, the bifurcation is considered predisposed to the development of an aneurysm. (Stroke 1991;22:619–625)

Ruptured berry aneurysms are a cause of significant mortality and morbidity. Cerebral aneurysms are not present in neonates and are rare in children and adolescents. Since the mean age of presentation with a subarachnoid hemorrhage is 50 years,1,2 aneurysms are likely an acquired lesion. Stehbens3 has recently reviewed the evidence for an acquired etiology of cerebral aneurysms.

Saccular aneurysms arise at the apex of bifurcations but are rare in systemic arteries other than the cerebral circulation,4 suggesting that there is some factor at cerebral branching sites that predisposes to aneurysm formation. Therefore, one must understand why most systemic arterial bifurcations are stable and what is peculiar to cerebral bifurcations to render them unstable.

The knowledge of bifurcation geometry is critical in the analysis of the hemodynamics and elastic properties at arterial branches. Roach et al5 have demonstrated the importance of geometry on flow in glass model studies of bifurcations of the circle of Willis. Ferguson7 has proposed that hemodynamic forces at the apex cause degeneration of the internal elastic lamina and result in aneurysmal outpouching. Macfarlane et al8 have found that the geometry of cerebral bifurcations may change with changes in transmural pressure. These authors proposed that changes in bifurcation shape could modify flow patterns. Macfarlane et al9 have shown that the flow divider of cerebral arteries flattens with increases in transmural pressure. Concomitant thinning of the arterial wall at the apex with increased transmural pressure would contribute to stress concentration at the apex and facilitate the formation of an aneurysm. Common to these authors' arguments is the dynamic interaction of hemodynamics and the elastic properties of the arterial wall.

Berry aneurysms are hypothesized to be acquired lesions resulting from a loss of static equilibrium in the apical region of a bifurcation. I propose a mathematical model that predicts the geometry of bifurcations. Due to geometry changes during the cardiac cycle, bifurcations are more susceptible to aneurysm formation. The predilection of the cerebral circulation to aneurysm formation is discussed.

Theoretical Model

Figure 1a defines the simplified geometry of a bifurcation. Flow is from the parent artery of radius \( r_0 \) into daughter branches of radii \( r_1 \) and \( r_2 \). The larger branch has a radius \( r_1 \) and makes an angle \( \theta \) with the direction of the parent artery. Figure 1b indicates the longitudinal tensile forces \( T_L \) in each branch and in
FIGURE 1. Geometry of bifurcation. (a) Daughter branches of radii \(r_1\) and \(r_2\) make angles \(\theta_1\) and \(\theta_2\), respectively, with direction of parent artery of radius \(r_0\). (b) Vector diagram showing longitudinal tensile forces \(T\) about apex \(A\) of bifurcation.

the parent artery. The apex \(A\) is the point of zero tension. The conditions for static equilibrium require

\[ T_1 \cos \theta_1 + T_2 \cos \theta_2 = T_0 \]  

\[ T_1 \sin \theta_1 = T_2 \sin \theta_2 \]  

For a homogeneous, isotropic thin-walled vessel subjected to a transmural pressure \(P\), the tensile forces may be calculated from the free-body diagram in Figure 2. This treatment assumes that there are no additional forces such as longitudinal tethering and that there is no tension in the wall when the transmural pressure is 0. The circumferential force distending the artery is \(2\pi r T\), which for equilibrium must equal the circumferential tensile force \(2\pi r T_c\) that constricts the lumen. Consequently, the circumferential tension \(T_c\) is given by Laplace’s law:

\[ T_c = Pr \]  

\[ T_c = \frac{(Pr)}{2} \]  

The longitudinal force is equivalent to the force due to pressure acting on the cross-sectional area of the lumen, \(\pi r^2 P\). The total longitudinal tensile force over the cross-section of the wall is \(2\pi r P L\). At equilibrium these forces are equal, so the longitudinal tension \(T_L\) is given by

\[ T_L = \frac{(Pr)}{2} \]  

On substitution for the longitudinal tensions \(T_L\),

\[ P_1 r_1 \cos \theta_1 + P_2 r_2 \cos \theta_2 = P_0 r_0 \]  

and

\[ P_1 r_1 \sin \theta_1 = P_2 r_2 \sin \theta_2 \]  

The following nondimensional variables are introduced:

\[ \alpha = \frac{r_1}{r_0} (0 \leq \alpha \leq 1) \]  

and

\[ \beta = \frac{(r_1^2 + r_2^2)}{r_0^2} \text{(area ratio)} \]  

Therefore, in terms of these variables, one has

\[ \cos \theta_1 + \frac{(P_2/P_1) \alpha}{(P_1/P_2)} \cos \theta_2 = (P_0/P_2) \left( \frac{1 + \alpha^2}{\beta} \right)^{1/2} \]  

and

\[ \sin \theta_1 = \frac{(P_2/P_1) \alpha \sin \theta_2}{(P_1/P_2)} \]  

From the trigonometric relation \(\sin^2 \theta + \cos^2 \theta = 1\), one can combine Equations 9 and 10 to get

\[ \left[ 1 - \frac{(P_2/P_1) \alpha \sin \theta_2}{(P_1/P_2)} \right] \sin \theta_1 = \frac{\alpha}{(P_1/P_2)} \left( \frac{1 + \alpha^2}{\beta} \right)^{1/2} \]  

For the square root on the left-hand side of Equation 11 to be defined, one has the inequality

\[ \frac{(P_2/P_1) \alpha \sin \theta_2}{(P_1/P_2)} \leq 1 \]  

Since \(0 \leq \alpha \leq 1\) and \(0 \leq |\sin \theta| \leq 1\), this requires that

\[ P_2 \geq P_1 \]  

For the simple case in which the transmural pressures in all vessels are equal, Equations 10 and 11 become respectively

\[ \sin \theta_1 = \alpha \sin \theta_2 \]  

and

\[ \left[ 1 - \alpha^2 \sin^2 \theta_2 \right]^{1/2} + \alpha \cos \theta_2 = \left( \frac{1 + \alpha^2}{\beta} \right)^{1/2} \]  

Equation 15 may be solved for \(\theta_2\) using iterative methods given \(\alpha\) and \(\beta\). The result of \(\theta_2\) can be substituted into Equation 14 to get \(\theta_1\). Consequently, if \(\alpha\) and \(\beta\) are known for a bifurcation, the geometry can be completely specified.
For the special case of a symmetric bifurcation in which the transmural pressures in all vessels are equal, Equation 15 gives the simple relation.

$$\cos \theta = \left[ 1/(2\beta) \right]^{1/2}$$  \hspace{1cm} (16)

and because $\cos \theta \leq 1$, $\beta \geq 0.5$.

**Results**

Theoretical predictions of the angles $\theta_1$ and $\theta_2$ and the opening angle $\theta_1 + \theta_2$ are plotted as a function of the parameter $\alpha$. Each curve in the plot represents a prediction for a given value of the area ratio $\beta$. Two cases are considered: case 1, in which the transmural pressures in the parent and daughter arteries are equal, and case 2, in which the area ratio $\beta$ is 1.0 and the transmural pressures in the branches do not equal that in the parent artery.

Case 1: $P_0 = P_1 = P_2$

The larger branch makes a smaller angle with the direction of the parent artery (compare Figures 3, top and 3, center). As the area ratio $\beta$ decreases, the angle of the larger branch increases (Figure 3, top), that of the smaller branch decreases (Figure 3, center), and the opening angle decreases (Figure 3, bottom). When $\beta$ is 1.0, the opening angle is about 90° (Figure 3, bottom). Consequently, the opening angle of a bifurcation is stable only if the parameters $\alpha$ and $\beta$ are constant during the cardiac cycle.

This condition requires that the incremental strain (percentage change in radius) in the daughter and parent arteries must be the same for any increment in blood pressure. Note that the changes in opening angles are much greater for a small $\alpha$ if the bifurcation is unstable.

Case 2: $P_1 = P_2 = P_0$, $\beta = 1$

Figure 4 shows the effect on the branching angles of a 10% difference in pressure between the parent and daughter arteries. If the transmural pressure in the daughter branches exceeds that in the parent artery, the opening angle is greater than when the pressures are equal and conversely for lower pressures in the daughter branches. The same result is true for the individual angles of the daughter branches with the direction of the parent artery.

Figure 5 shows the change in angles caused by a 1% difference in pressure between the parent and daughter arteries (i.e., if $P_0 = 100$ mm Hg this corresponds to a 1 mm Hg difference). The change in opening angle ranges from about 10° ($\alpha = 0.05$) to 1° ($\alpha = 1.0$). Similar calculations demonstrate a change in opening angle ranging from about 1° ($\alpha = 0.05$) to 0.1° ($\alpha = 1.0$) for a 0.1% difference in pressure between the parent and daughter arteries (i.e., for $P_0 = 100$ mm Hg this represents a 0.1 mm Hg pressure difference). Therefore, small differences in pressure between the parent and daughter arteries are sufficient to change arterial geometry. Consequently, a bifurcation is stable in geometry only if the ratio of the parent to daughter transmural pressures does not change during the cardiac cycle. This condition prohibits flow reversal.

**Discussion**

Any mathematical model is only as valid as the assumptions employed in its derivation. I emphasize that this model is highly idealized and at present there are no experimental studies to prove or disprove its predictions. The model is strictly applicable to surface membranes whereas arteries may have thick walls relative to their radii. Fung and Oka and Azuma have proposed alternative models for thick-walled vessels that are not dependent on wall isotropy or homogeneity nor on whether the elastic...
behavior is hookean or nonlinear. In those models the circumferential tension $T$ is expressed in terms of the pressures and radii, $P_1$ and $P_0$, and $r_1$ and $r_0$, for the internal and external surfaces, respectively: $T=P_1r_1-P_0r_0=(P_1-P_0)r_1t$, where $(P_1-P_0)$ is the transmural pressure and $t$ is the wall thickness $(r_0-r_1)$. The first term in this expression is Laplace's law, and the second term may be of the same order of magnitude.

The equation for longitudinal tension is similar. For very thick-walled vessels, the second term may exceed the first term so that the vessel is under compressive rather than tensile stress. Even when the transmural pressure is zero, however, their model predicts compressive stresses both circumferentially and longitudinally although cerebral vessels do not shorten, buckle, or collapse at autopsy. Because it is unlikely that arteries are under compressive stress, Laplace's law is considered a reasonable first approximation even for thick vessels. Furthermore, the geometry is much more complex than the junction of three straight tubes. For simplicity, curvature at branch points and the expansion zone in the bifurcation have been ignored. A comparison of model studies by Houle and Roach and by Malcolm and Roach indicates that the curvature may be important in flow division at the apex. Macfarlane et al have shown that there is a linear increase in luminal area of up to 50–60% in the region from the parent artery to the apex. This expansion zone may cause...
deceleration of flow and enhancement of the pressure at the apex. Tethering may introduce additional forces the magnitude and direction of which are unknown, and consequently, the model is not valid if these forces are significant. Future studies may incorporate these complicating factors as the need arises. For the present purposes the simplicity of this model is viewed as a merit rather than a fault.

The mathematical model predicts the geometry of bifurcations caused by the interaction of hemodynamic forces and the elastic properties of the wall. The model is proposed to be applicable to all vasculature, arterial and venous, and not restricted to cerebral vessels.

**Static Predictions**

Experimental measurements in extracranial arteries show that the angle the larger branch makes with the direction of the parent artery is less than that of the smaller branch, in agreement with the model. Bifurcations with smaller area ratios $β$ are predicted to have smaller opening angles. When the transmural pressure in the daughter arteries exceeds that in the parent artery, the opening angle is greater than when the transmural pressures are equal and conversely for lower transmural pressures in the daughter arteries. Different transmural pressures in the parent and daughter vessels imply reflection in the bifurcation.

Verification of these static predictions is easily done in vitro using fresh, unfixed bifurcations. The use of static distending pressure in isolated bifurcations guarantees that the transmural pressures in the parent and daughter vessels are equal. Measurements may be compared with the predictions of Figure 3. If one imposes steady flow in the bifurcation, this necessitates measurement of the pressures in the parent and daughter arteries to assess whether reflection is present in the bifurcation. If reflection is present, the predictions for $θ_1$ and $θ_2$ based on the measured $α$ and $β$ may be derived by solving Equation 11 for $θ_2$ and substituting this result into Equation 10 to get $θ_1$. These results may then be compared with the measured angles. Measurement of bifurcations in vivo may be done radiologically, but corrections are required if the x-rays are not perpendicular to the plane of the bifurcation. Transmural pressures would be unknown in this case.

**Dynamic Predictions**

Any change during the cardiac cycle of the relative luminal areas of the daughter branches to that of the parent artery, $β$, or in the relative diameters of the daughter branches to one another, $α$, requires a change in the opening angle between the branches to maintain the equilibrium of tensile forces at the apex. The opening angle is stable if the incremental strains in the daughter and parent arteries are equal with increments in blood pressure. Similarly, any change in the ratio of parent to daughter artery transmural pressures during the cardiac cycle will cause a change in the angle between the branches. In summary, the stability of the opening angle is dependent on the elastic properties and transmural pressures of the parent and daughter arteries.

Verification of these dynamic predictions requires pulsatile flow and knowledge of the pressure waveforms, amplitude and phase, in the parent and daughter arteries. Measurements of geometry during the pulse cycle necessitate appropriate resolution in the timing of the recording system. The complexity of measurement is more easily managed in vitro than in vivo, but radiologic measurements with appropriate timing resolution may be able to detect changes in bifurcation angle during the cycle. These arguments presume that the change in geometry is large enough to be measured, but it may in fact need be only microscopic to damage the structure. Furthermore, estimates of geometric changes have been based on the instantaneous elastic behavior of the artery wall, but these changes may be attenuated by viscous properties of the wall. Nonlinear elastic properties may also delimit undesirable strains and changes in geometry.

Unfortunately from the point of view of verification of the model, normal bifurcations may be inherently stable. Macfarlane et al8 have shown using static distending pressure in five human cerebral bifurcations that there was no significant difference in incremental strains of parent and daughter arteries with increases in transmural pressure; opening angles were not measured. Testing of the mathematical model should be done using both "normal" bifurcations and bifurcations from subjects with known predisposition to developing cerebral aneurysms but dying of unrelated causes. Predisposing conditions are rare and include Marfan's syndrome, Ehlers-Danlos syndrome, coarctation of the aorta, and polycystic renal disease.3

**Formation of Cerebral Aneurysms**

I propose that repeated dynamic cycling of the opening angle due to an unstable equilibrium may disrupt the wall elements in a manner analogous to a wire breaking with repeated bending and result in the formation of an aneurysm. Special characteristics of the cerebral circulation that may breach the conditions of stability are discussed below.

**Transmural pressure.** The cerebral circulation is subject to an external cerebrospinal fluid (CSF) pressure of 80–180 mm H$_2$O (6–13 mm Hg).16 Intracranial masses may cause CSF pressure to rise as high as 60 mm Hg.17 Straining or coughing may produce transient increases in CSF pressure sufficient to produce venous congestion. Since the same CSF pressure is applied to parent and daughter vessels, the ratio of the transmural pressures (the difference between the intraluminal and CSF pressures) in the daughter and parent vessels will change with any change in CSF pressure unless the parent and daughter intraluminal pressures are equal. Intraluminal pressures in parent and daughter arteries are equal.
only if there is no reflection of the pressure waveform across the bifurcation. To my knowledge no data is available on reflections of pressure waveforms at cerebral bifurcations.

**Structure.** Current belief is that aneurysms arise secondary to degeneration of the internal elastic lamina at the apex of the bifurcation. In humans cerebral arteries differ from other muscular arteries as the former do not have both an external and an internal elastic lamina but only an internal elastic lamina. Animals have medial or adventitial elastin in their cerebral arteries, which may be why aneurysms are rare in animals. The model proposed in this paper suggests that fracture of the internal elastic lamina may be caused by dynamic cycling of the opening angle as a result of an unstable equilibrium in the longitudinal tensile forces. Mechanical fatigue would eventually cause elastin fragmentation at the apex and possibly at the lateral angles, although the location of the latter is less well defined due to curvature.

**Collateral circulation.** The circle of Willis provides a collateral network between the anterior and posterior and between the left and right cerebral circulations. The anastomotic circuit may be important in the redistribution of blood flow due to occlusive disease and as well in the compensation for reduced flow in the vertebral and perhaps the carotid arteries caused by movements of the head. Redistribution of blood flow may allow flow reversal in the circuit and, according to the model, will cause an unstable equilibrium predisposed to the development of an aneurysm. As a further consequence, while the impedance in the bifurcation may be matched under normal flow conditions, reflections may occur when flow enters from one of the daughter branches. Reflection will cause changes in the amplitude and phase of pressure waves in the outgoing branches, which may further promote instability.

Model studies of blood flow in the circle of Willis have demonstrated considerable sensitivity to asymmetries in the dimensions of arteries within the circle. Occlusions of one or more vessels in these model studies cause significant pressure drops and redistribution of blood flow between the right and left and between the anterior and posterior circulations. I propose that congenital or acquired conditions, either intracranial or extracranial, that cause a phase lag or an amplitude difference in pressures within the circle of Willis may promote aneurysm formation. Persons with congenital anatomic variations of the anterior communicating artery and carotid artery have been shown to have a higher predilection for aneurysms than the normal population. Pressure drops caused by atherosclerotic plaque formation in the two carotid bulbs may be sufficient to cause differences in pressure pulse transmission as well as differences in amplitudes of the pressure waves. Aneurysms in the anterior communicating artery have been found following surgical ligation of the carotid artery in humans and in animal models.

In summary, the collateral circulation of the circle of Willis, while preserving blood flow to areas of the brain that would otherwise be compromised by proximal occlusive disease, may unfortunately predispose to aneurysm formation.

**References**


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