

Mathematical model of the rupture mechanism of intracranial saccular aneurysms through daughter aneurysm formation and growth[§]

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Objectives: Daughter aneurysms have been strongly associated with saccular aneurysm rupture. We constructed a mathematical model to help explain this association as a possible hemodynamic mechanism for intracranial saccular aneurysm rupture.

Methods: Our model is based on the assumption that when an aneurysm reaches a state of imminent rupture, the weakest area of the aneurysm wall responds passively to a surge of intraneurysmal pressure by forming a daughter aneurysm that will be the site of the eventual rupture. The daughter and parent aneurysms were assumed to be spherical. Using mathematical modeling, the growth of the daughter aneurysm was observed. To obtain the change in tensile stress in the daughter aneurysm wall under constant pressure and changing geometry, the Law of Laplace was applied to the parent and the daughter aneurysms.

Results: The model reveals that the stress factor, i.e. tensile stress in the daughter aneurysm wall relative to the wall strength (rupture point), is dependent on two geometric parameters: the orifice factor (μ), which represents the relative size of the daughter aneurysm orifice radius to the parent aneurysm radius; and the aspect ratio (λ), which represents the height-to-orifice ratio of the daughter aneurysm. As the daughter aneurysm develops, the stress factor first decreases to protect against rupture. Minimal stress is attained at an aspect ratio (λ) of 0.577 regardless of the orifice factor. This is a relatively stable state. Further growth of the daughter aneurysm results in an increase of stress above the minimum, eventually leading to rupture at a stress factor of 1. A smaller orifice factor μ allows this aneurysm to grow to a higher aspect ratio λ before rupture.

Discussion: Daughter aneurysm formation is a likely path to aneurysm rupture. The formation of a daughter aneurysm temporarily decreases the tensile stress within a parent aneurysm in which rupture is imminent, indicating a temporary protective role of daughter aneurysm development. Aneurysms harboring daughter aneurysms are at a more advanced stage of development, hence at a greater risk for rupture. The severity of the rupture risk can be estimated on the basis of daughter aneurysm geometry; aspect ratio $\lambda > 0.577$ indicates a greater risk of rupture. Furthermore, daughter aneurysms with larger orifices are associated with a greater risk of rupture. [Neurol Res 2005; 27: 459–465]

Keywords: Aspect ratio; daughter aneurysm; mathematical model; intracranial saccular aneurysm; orifice factor; rupture risk

INTRODUCTION

Despite advances in our understanding of intracranial aneurysms, the exact mechanism of aneurysm rupture remains elusive¹. Although it is known that larger aneurysm size and decreasing aneurysm wall thickness

influence aneurysm rupture^{2–4}, there is still no index or scale available to predict either the risk or the imminence of aneurysm rupture.

Daughter aneurysms are surface bubbles on a parent aneurysm wall. They are commonly observed and have been intuitively associated with intracranial saccular aneurysm rupture. Besides the term 'daughter aneurysm'^{3,5,6}, other terms used to describe this phenomenon include 'surface bubble'³, 'loculation'^{7,8}, 'lobulation'^{9,10}, 'secondary loculus'^{7,11}, 'bleb'^{12–15}, 'daughter sac'¹⁶, or 'multichamber'⁷. These reports all suggest that daughter aneurysms are associated with aneurysm

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rupture. The angiographic presence of a daughter aneurysm is considered an ominous sign, encouraging neurosurgeons to act quickly to prevent hemorrhage¹⁷.

Hemodynamic parameters are known to play an important role in all stages of the intracranial aneurysm 'life cycle'¹⁸. Hemodynamic forces, in conjunction with a series of complicated biological responses, are believed to determine aneurysm pathophysiology¹⁹. We attempted to provide insight into a possible mechanism of aneurysm rupture by the application of mathematical modeling based on first-order mechanical principles. We used this model to support our premise that saccular aneurysm wall stress is a mechanism for the growth of a daughter aneurysm arising from the weakest area of the parent aneurysm wall. This model attempts to describe the hemodynamic pressure forces leading to daughter aneurysm formation and growth while minimizing assumptions related to associated biological factors.

CONCEPT AND METHODS

Formation of a daughter aneurysm

We speculate that the formation of a daughter aneurysm is a result of the existence of a weak area in the aneurysm wall with a compromised stress limit, referred to as wall strength (S_0). A pressure surge in the aneurysm can cause the tensile stress (S_p) in the wall to approach this stress limit. To reduce the tensile stress within the aneurysm wall, the parent aneurysm responds passively to this pressure surge by forming a daughter aneurysm. The immediate result is a reduced tensile stress (S_d) in the weak area of the wall, now the daughter aneurysm. We propose that this process provides an early protection against aneurysm rupture. This passive response mechanism can be observed when a thin membrane (like a balloon) with a weakening defect is pressurized. The weakened area bulges out in a manner similar to the formation of a daughter aneurysm.

An indication of the weak area is the reduced thickness of the wall. The structure of an aneurysm wall varies along the sac from a thin layer of fibrous tissue and endothelium to areas containing fibromuscular tissue²⁰. Mizoi *et al.*²¹ reviewed intra-operative videotape recordings of 78 cerebral aneurysms and found that 50% of these aneurysms had a partially thinned wall at the dome.

The weakening of the aneurysm wall may be caused by numerous pathophysiological or hemodynamic factors. Local filtration of white blood cells and fibrin^{3,22} as well as discontinuity of the elastic membrane and collagen layer^{10,23} are reported to be responsible for such weakening. Intra-aneurysmal turbulence has been observed by several authors and implicated in the degeneration of the internal elastic laminae^{11,24}. The jet of blood flow through the aneurysm orifice impinging on the aneurysm wall may cause localized fatiguing of the wall²⁰. High pressure also appears to weaken the internal elastic laminae of the cerebral arteries²⁵.

An intra-aneurysmal pressure surge is possible under certain pathological circumstances. Higher intra-aneurysmal

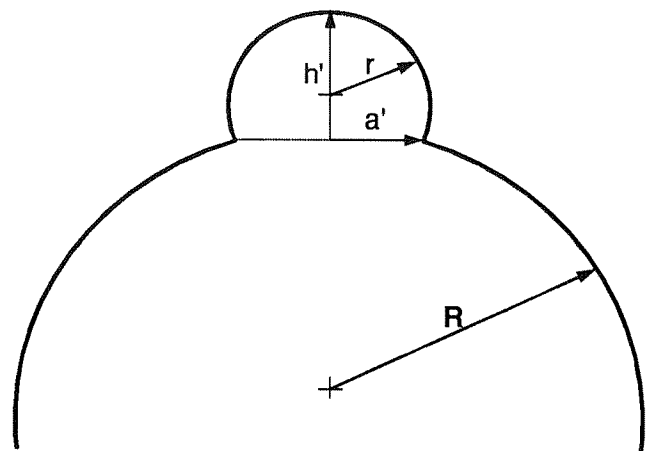


Figure 1: Schematic depiction of a parent aneurysm with a daughter aneurysm. r , daughter aneurysm radius; a' , daughter aneurysm orifice radius; h' , daughter aneurysm height; R , parent aneurysm radius

pressures may be induced by stenosis in the parent vessel distal to the aneurysm. In an experimental model of saccular aneurysms, Sekhar *et al.*²⁶ found that intra-aneurysmal pulse pressures increase as a cubic relationship with mean arterial pressures after the induction of 50% stenosis distal to the aneurysm²⁷. Austin *et al.*^{28,29} postulated that a small increase in the systemic pulse pressure or the pulse rate can lead to sudden increases in flow velocity and turbulence within an aneurysm ("jump phenomenon").

Mechanical principles involved in daughter aneurysm formation

Tensile stress (S) in the aneurysm wall is the predominant force responsible for aneurysm growth and rupture^{9,11}. In our model, we studied the effect of the change in tensile stress on the initiation and growth of a daughter aneurysm. For the purpose of mathematical modeling, the following assumptions were adopted:

- (1) both the parent aneurysm and the daughter aneurysm are spherical;
- (2) the parent aneurysm wall is thin (compared with its radius) so that the Law of Laplace can be applied;
- (3) the volume of the aneurysm wall does not change during the development of the daughter aneurysm. (A modification of this assumption to include vascular growth is discussed later in this section.)

In *Figure 1*, R is the radius of the parent aneurysm, r is the radius of the daughter aneurysm, a' is the radius of the daughter aneurysm orifice, and h' is the height of the daughter aneurysm.

Based on the constant volume of the aneurysm wall, the following geometric relationship between the parent and daughter aneurysm wall dimensions can be applied:

$$2\pi R \cdot (R - \sqrt{R^2 - a'^2}) \cdot t_p = 2\pi r h' \cdot t_d \quad (1)$$

where t_p is the thickness of the parent aneurysm wall, and t_d is the thickness of the daughter aneurysm wall. In this equation, the left side represents the volume of the

aneurysm wall before the development of a daughter aneurysm, whereas the right side represents the volume of the wall after the development of a daughter aneurysm. The parent aneurysm radius, R , and wall thickness, t_p , as well as the daughter aneurysm orifice radius, a' , are all held constant. As the daughter aneurysm bulges, h' increases; and the wall thickness, t_d , must therefore decrease.

By applying the Law of Laplace to the parent aneurysm, we obtain:

$$S_p = PR / (2t_p) \tag{2}$$

where S_p is the tensile stress in the parent aneurysm wall and P is the pressure. Just before daughter aneurysm formation, S_p equals the local wall strength, S_0 , at this weak area. The Law of Laplace can also be applied to the daughter aneurysm, after it has formed, yielding:

$$S_d = Pr / (2t_d) \tag{3}$$

where S_d is the tensile stress in the daughter aneurysm wall.

Within the context of this model, we define the stress factor, η , as the ratio of the tensile stress in the daughter aneurysm (S_d) to the wall strength of this part of the tissue (S_0). We will show below that η can serve as a rupture index for an aneurysm harboring a daughter aneurysm.

Combining Equations 1-3, we obtain:

$$\eta(\lambda, \mu) = \frac{\mu(1 + \sqrt{1 - \mu^2})}{4} \cdot \frac{(1 + \lambda^2)^2}{\lambda} \tag{4}$$

where $\mu = a'/R$ is the orifice factor, which represents the relative size of the daughter aneurysm orifice radius to the parent aneurysm radius, and $\lambda = h'/a'$ is the aspect ratio, which represents the height-to-orifice ratio of the daughter aneurysm. Equation 4 shows that the stress factor (η) only depends on two geometric parameters: orifice factor (μ) and aspect ratio (λ).

Accounting for growth of the aneurysm wall

It is known that the volume of the aneurysm wall may grow thicker through collagen deposition or other vascular remodeling^{3,14,30}. To account for this effect, assumption (3) needs to be modified. We have found that the same results shown in Equation 4 can be obtained by adopting the following assumption: the wall volume of the daughter aneurysm increases at a rate equal to that of an equivalent area of the parent aneurysm¹¹.

RESULTS

Using Equation 4, we can model the stress factor (η) of the daughter aneurysm during its growth cycle. As will be elaborated on later, the stress factor represents the degree to which a daughter aneurysm has advanced and hence is an estimate of the imminence of rupture. From modeling based on Equation 4, it is possible to estimate the rupture risk of a daughter aneurysm through

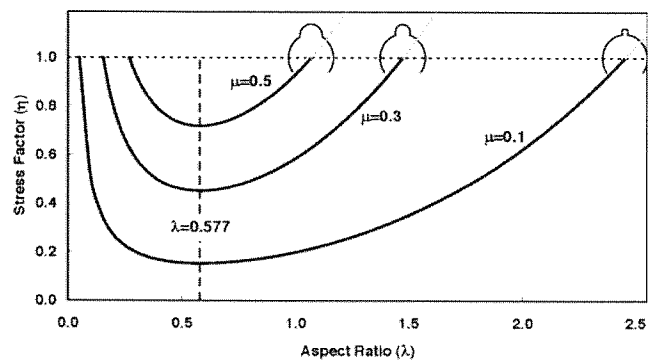


Figure 2: The stress factor (η) as a function of the aspect ratio (λ) of the daughter aneurysm for several different orifice factors (μ). The stress in the daughter aneurysm rapidly decreases as the aspect ratio increases until reaching a minimal value. Regardless of the orifice factor (μ), minimal stress in the daughter aneurysm wall is reached at an aspect ratio of $\lambda=0.577$. Further growth eventually leads to rupture ($\eta=1$). Daughter aneurysms with larger orifices reach the $\eta=1$ rupture point sooner

geometric measures, i.e. the orifice factor (μ) and the aspect ratio (λ).

The modeling results are illustrated in Figure 2 in which the stress factor (η) is plotted as a function of the aspect ratio (λ) for several different orifice factors (μ). All curves start with an initial stress factor, η , value of 1, which is consistent with the assumption that a daughter aneurysm forms when the tensile stress reaches the local wall strength, as a means to temporarily protect the parent aneurysm wall from imminent rupture. As shown in Figure 2, the development of the daughter aneurysm first reduces the stress factor (in this weak area of the wall) to a minimum value much below 1, which represents a relative stable state. If the daughter aneurysm continues to grow beyond this point, the stress factor then increases.

The physics of the stress reduction process in the model accompanying the growth of a daughter aneurysm can be explained as follows. As the daughter aneurysm bulges (with an increasing aspect ratio, λ) and the orifice size remains constant, its spherical radius (r) first decreases until the bulge reaches a hemispherical shape ($\lambda=1$). Beyond this point, further growth of the daughter aneurysm is accompanied by an increase in the spherical radius. Because stress (S_d) is proportional to the spherical radius (r) according to the Law of Laplace in Equation 3, we expect an initial reduction of the stress in the daughter aneurysm followed by an eventual increase of the stress. Furthermore, the stretching of the daughter aneurysm wall requires a continuous reduction in wall thickness, t , from the mechanical point of view. Again from Equation 3, a reduction in thickness contributes to an increase in stress. Combining the effects of both r and t , the stress, S_d , or its normalized version, $\eta = S_d/S_0$, first decreases, reaching a minimum, and then increases. As a result of the reduction in wall thickness, the minimum stress value is attained before the daughter aneurysm becomes a hemisphere (at aspect ratio $\lambda=1$). By taking the derivative of η with respect to λ and requiring $\partial\eta/\partial\lambda=0$,

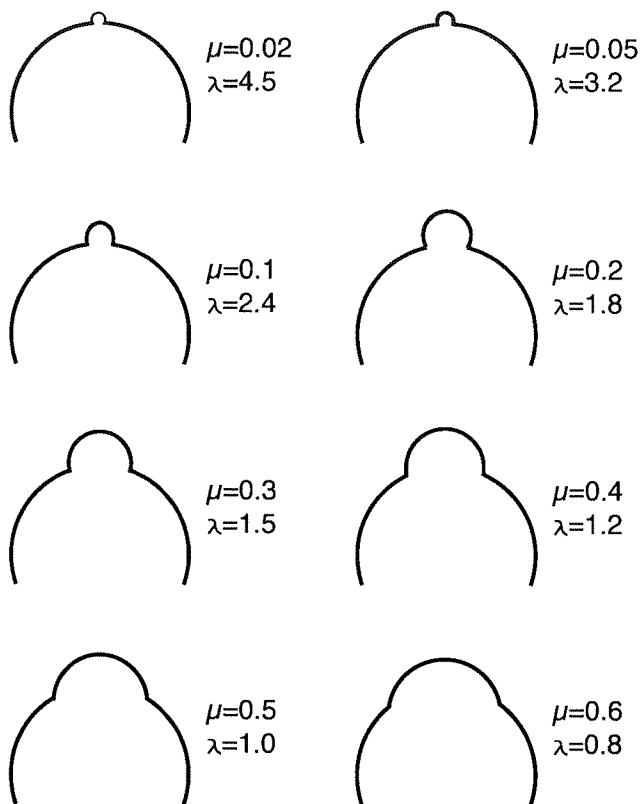


Figure 3: Various daughter aneurysm geometries at rupture, as predicted by $\eta=1$. μ , orifice factor; λ , aspect ratio

we find that the stress reaches its minimum at an aspect ratio of $\lambda=0.577$. This critical aspect ratio value is independent of the orifice factor (μ).

From a mechanical perspective, the minimal stress state is a relatively stable state. However, if the daughter aneurysm is stretched further, the stress factor will increase and eventually return to 1. At this point, the weak area of the wall is once again subject to the same tensile stress limit (S_0) as before the daughter aneurysm was formed. Unless a third-generation aneurysm forms on the daughter aneurysm (which, to our knowledge, has not been reported clinically), rupture will ensue. Hence, the daughter aneurysm stress factor, η , can be used as an index of rupture; and η returning to a value of 1 can be considered a criterion of rupture.

Using $\eta=1$ as a rupture index, we plot aneurysms with different aspect ratios (λ) and orifice factors (μ) that are expected to rupture (Figure 3). The clinical significance of these aneurysm geometries is obvious: aneurysms of such geometries are likely to rupture at any time.

Since in this study the geometry of a daughter aneurysm is characterized by its orifice factor (μ) and aspect ratio (λ), we further explore the relationship between these two geometric parameters and the risk of rupture. In Figure 4, the solid line represents all the daughter aneurysms of $\eta=1$, which represents the borderline of rupture. Below the rupture line is the unruptured zone, in which daughter aneurysms are still

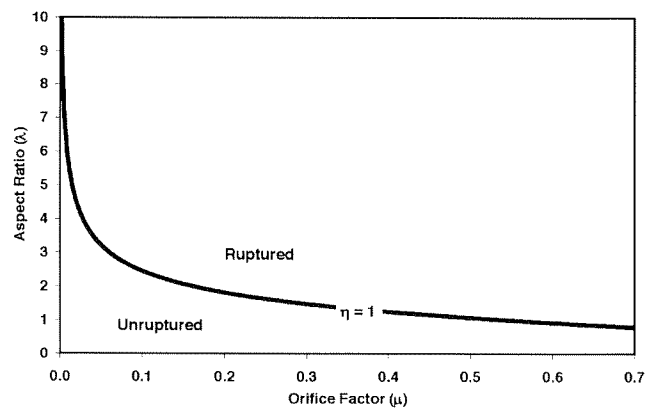


Figure 4: Relationship between aspect ratio (λ) and orifice factor (μ) for daughter aneurysm geometries at rupture (solid line)

unruptured. This plot provides us with a means to assess the rupture risk of a daughter aneurysm by measuring the orifice factor (μ) and the aspect ratio (λ).

DISCUSSION

Biomathematical modeling

Many researchers have used biomathematical modeling to gain insight into the complex process of intracranial aneurysm rupture. In 1963, Jain³¹ postulated a theory of aneurysm rupture based on resonance phenomena. This theory was consistent with the research conducted by Hung and Botwin⁸ in which the properties of a uniform, thin wall were applied to a spherical aneurysm model. The natural frequencies of these thin-walled spheres were found to fall within the range of bruit frequencies that commonly are observed in aneurysms. Canham and Ferguson² estimated the critical size for rupture by applying the Law of Laplace. Nieto and Torres³² constructed a non-linear mathematical model that simulated blood flow within the aneurysm. Austin²⁸ used an electric circuit model and found that an elevated pulse pressure or an increased pulse rate can result in increased turbulence, which is assumed to be a destructive factor on the aneurysm wall, leading to sudden enlargement and potential rupture. Hademenos *et al.* modified the Law of Laplace and established non-linear mathematical models for both saccular³³ and fusiform³⁴ intracranial aneurysms. Chitanvis *et al.*³⁵ developed a non-linear constitutive quasi-static model and studied the dynamic behavior of saccular aneurysms in response to pulsatile blood flow. These mathematical models provide qualitative and/or quantitative information and give us valuable insight into the process of aneurysm rupture.

Daughter aneurysms and rupture

Our model describes aneurysm wall stress during the growth cycle of a daughter aneurysm. Crompton³ first reported the incidence of daughter aneurysms. He performed a pathological study of 275 ruptured, intracranial aneurysms and found that 57% of the aneurysms had daughter aneurysm "bubbles". In

contrast, only 16% of 112 unruptured aneurysms had daughter aneurysms. In a study by Sampei *et al.*⁵, three out of four unruptured aneurysms with a daughter aneurysm later ruptured between 1 month and 10 years of follow-up review, whereas only two of ten unruptured aneurysms without a daughter aneurysm later ruptured. Austin *et al.*²⁹ reported the formation of one or more loculations, which they interpreted as abrupt enlargements resulting from focal weakening in the wall. In a cerebral angiographic study by Hinshaw *et al.*²³, one-third of the aneurysms were found to be loculated, of which 65% of these patients had subarachnoid hemorrhage. Du Boulay⁷ studied the natural history of intracranial aneurysms and found that one-third of recently ruptured aneurysms had one or more loculations, whereas previously unruptured aneurysms had virtually no loculations. These reports all suggest a strong correlation between the presence of a daughter aneurysm and the probability of aneurysm rupture.

Application of the Law of Laplace

Daughter aneurysms are commonly observed by neurosurgeons. However, little research has been conducted to quantitatively document and track the initiation, growth, and rupture of daughter aneurysms. To the best of our knowledge, Steiger¹⁴ is the only investigator who quantitatively explained the daughter aneurysm phenomenon by applying the Law of Laplace in his computer simulations of aneurysm development.

The Law of Laplace, despite its simplicity, is a powerful tool in modeling vascular biology³⁶. The application of this law requires the aneurysm wall to be a sphere, which is generally a good approximation according to the geometric study of intracranial aneurysms by Parlea *et al.*³⁷. Moreover, Steiger¹⁴ concluded from his computer simulations that non-spherical aneurysms have a tendency to assume a spherical configuration as they enlarge. The Law of Laplace also requires the object to be thin-walled, which is generally true for intracranial aneurysms^{4,14,26,38}.

Minimal stress state and two phases of daughter aneurysm growth

Steiger¹⁴ concluded that daughter aneurysms would rupture if their height exceeded 60% of the base radius, which corresponds to an aspect ratio (λ) of 0.6. Our model, however, shows that $\lambda=0.577\approx 0.6$ represents a minimal stress state in the daughter aneurysm wall, instead of the point of rupture. As the aspect ratio (λ) increases beyond this value, the tensile stress in the daughter aneurysm is expected to increase, but not immediately back to the stress limit or $\eta=1$. Hence, no compelling reason exists to conclude that the daughter aneurysm will rupture immediately after reaching an aspect ratio of 0.6. In fact, elongated daughter aneurysms with aspect ratios exceeding 1 are commonly observed clinically, especially those with small orifice indices (e.g. $\mu=0.1$ in Figure 3).

The minimal stress state at $\lambda=0.577$ marks a turning point that separates the two phases of daughter

aneurysm growth. Before reaching this point, the stress factor, η , decreases as the daughter aneurysm grows, providing a positive feedback mechanism: the more the aneurysm bulges, the lower the wall stress; therefore, encouraging further bulging. After reaching the minimal stress state, further growth of the daughter aneurysm has to overcome the increasing stress, and thus growth is more difficult. Hence, it is reasonable to suggest that an aspect ratio of $\lambda=0.577$ is the most stable state for a daughter aneurysm. The daughter aneurysm could persist at this state, but a pressure surge can push it over to the riskier phase of further elongation to the point of rupture.

Likely location of daughter aneurysms

Because most daughter aneurysms are noted to be on the dome of an aneurysm and most intracranial aneurysm rupture sites occur on the dome^{3,6}, a relationship between daughter aneurysms and aneurysm rupture is conceivable¹². Because the parent aneurysm develops from a diseased portion of the vessel wall, its wall is generally weaker than that of the normal vessel. Accordingly, continuous deterioration of the vessel wall from the parent artery to the aneurysmal wall must occur. This deterioration is reflected in the histology of the aneurysm wall: the media is absent, and there are discontinuities in the internal elastic membrane^{5,14}. The dome region is further from the normal artery than are other areas of the aneurysm wall; thus it is most likely to be the weakest part of the aneurysm wall, and hence the preferred site of daughter aneurysm development.

The weak area of the parent aneurysm can also be the result of a previous hemorrhage. Suzuki and Ohara⁴ observed that bleeding may cease soon after intracranial aneurysm rupture, and the aneurysm may form a new protective fibrin layer that is relatively weaker than the original aneurysm wall. It is likely that the aneurysm wall forms another protective layer after the daughter aneurysm ruptures, which would increase the probability of repeated rupture at this site. Because the daughter aneurysm wall is already very weak, the new protective layer cannot exist for long. There is a substantial difference between previously ruptured and unruptured aneurysms^{5,39}; further study is needed to elucidate the history of parent aneurysms before they grow daughter aneurysms.

Unanswered questions

Many questions remain that cannot be answered by this model. For example, which types of aneurysms are likely to grow daughter aneurysms? Does the orifice of a daughter aneurysm expand and, if so, in a continuous or intermittent manner? Why do some daughter aneurysms remain in a stable equilibrium whereas others rupture? What does it take to push a daughter aneurysm over the minimal stress state? Is it a brief but strong pressure surge or a constant pressure increase over a long period of time—days? months? years?

The present study underscores a need to build a clinical database of detailed intracranial aneurysm

geometries to characterize the life cycle of daughter aneurysms. Although it is difficult to directly analyze the focal fragility of the aneurysmal wall, we can estimate this on the basis of the shape of the aneurysm¹⁵. A clinical database could be used to determine the locations and shapes of aneurysms that are predisposed to grow daughter aneurysms and the actual geometries of daughter aneurysms.

CONCLUSIONS

We propose that the formation of a daughter aneurysm is a protective response of a weak area of the aneurysm wall to intra-aneurysmal pressure. Our model shows that a daughter aneurysm can reduce the tensile stress in the weak area. The stress factor (η) of the daughter aneurysm wall is a function of two geometric parameters: the orifice factor (μ) and the aspect ratio (λ) of the daughter aneurysm. As the daughter aneurysm develops, the stress factor first decreases to protect against rupture. The minimal stress is attained at an aspect ratio (λ) of 0.577. Further elongation of the daughter aneurysm results in an increase of stress above the minimum, eventually leading to rupture at a stress factor of 1. The stress factor can thus be used to evaluate the risk of rupture based on the daughter aneurysm geometry. A smaller aneurysm orifice factor (μ) allows the daughter aneurysm to grow to a higher aspect ratio (λ) before rupture.

Angiographic evidence of daughter aneurysms may predict impending hemorrhage. Because daughter aneurysms are formed in response to the imminence of rupture of the parent aneurysm and because the daughter aneurysm provides only a temporary reduction of stress, angiographic evidence of a daughter aneurysm is indicative of a higher risk of imminent rupture. The orifice factor (μ) and aspect ratio (λ) of a daughter aneurysm should alert the treating physician of impending rupture and should guide consideration for surgical or endovascular treatment. Future angiographic studies of daughter aneurysm growth should result in validation of this model.

DISCLOSURE STATEMENT

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