Formation of Saccular Cerebral Aneurysms May Require Proliferation of the Arterial Wall: Computational Investigation*

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Abstract
We have performed numerical simulations to examine saccular cerebral aneurysm formation at the outer curve of a bent artery. A U-shaped arterial geometry with torsion, which was modeled on part of the human internal carotid artery, has been employed. A new numerical model was proposed to take into account proliferation as well as degradation of the arterial wall. Proliferation of the arterial wall was modeled by surface area expansion in high wall shear stress region. Based on wall shear stress distribution on the artery, we have investigated aneurysm formation for the following three conditions: (a) strength degradation of the wall, (b) proliferation of the wall, and (c) both strength degradation and proliferation of the wall. A saccular aneurysm shape was not observed when considering only arterial wall degradation up to 90%. However, the saccular shape formed when proliferation of the arterial wall was also taken into consideration. The resultant shape was consistent with clinical observations. Our findings have suggested that a saccular aneurysm may not be formed by degradation of the arterial wall alone, but also require its proliferation.

Key words: Cerebral Aneurysm, Growth, Modeling, Wall Shear Stress, Numerical Analysis

1. Introduction
Cerebral aneurysms are an important cerebrovascular condition because aneurysm rupture is the most common cause of subarachnoid hemorrhage, which has a high mortality rate and a poor prognosis. Recent developments in medical imaging techniques have made it possible to detect cerebral aneurysms non-invasively at considerable frequencies. Rinkel et al. reported that between 3.6 and 6% of the population had unruptured cerebral aneurysms1. As the mechanism of cerebral aneurysm pathogenesis is not well understood, the only treatment currently available for unruptured aneurysms is surgery; however, the morbidity of such surgery can exceed 10%2,3. On the other hand, the annual risk of rupture of cerebral aneurysms is only about 1.9%4. Consequently, it is difficult to judge whether a patient with an unruptured cerebral aneurysm, when it is detected, should undergo surgery. Thus, it is important to develop a better understanding of the mechanism of cerebral aneurysm formation.
aneurysm pathogenesis, because this may lead to more therapeutic options.

Hemodynamic factors are thought to be important in the pathogenesis of cerebral aneurysms. Among them, high arterial wall shear stress has been suggested to be a major factor, based on experimental studies in animals\(^4\), \(^5\), \(^6\). However, the measurement of hemodynamic quantities, such as arterial wall shear stress and blood pressure, remains difficult \textit{in vivo}, particularly in the cerebral arteries. Recently, a number of computational studies on cerebral aneurysm hemodynamics have been reported. Steinman \textit{et al.}\(^7\) presented the first prospective analysis of patient-specific cerebral aneurysm hemodynamics using 3D angiography and computational fluid dynamics (CFD). Computed flow patterns within the aneurysm were highly complex, and were consistent with the results of cineangiography. Cebral \textit{et al.}\(^8\) constructed a total of 62 patient-specific models of cerebral aneurysms from 3D angiography and performed CFD simulations under pulsatile flow conditions, measured in a healthy subject. The 62 models consisted of 25 ruptured and 34 unruptured aneurysms, and 3 cases with unknown histories. Valencia \textit{et al.}\(^9\) presented a numerical investigation of the hemodynamics in idealized cerebral aneurysm models. The effects of aneurysm shape, asymmetry, and Newtonian/non-Newtonian fluid modeling were examined with respect to flow patterns and the spatial and temporal distributions of arterial wall pressure and shear stress. Although these studies demonstrated hemodynamic fields in cerebral aneurysms in detail, they have not discussed how high arterial wall shear stress induces cerebral aneurysm growth. To understand the growth of cerebral aneurysms, it is important to address not only hemodynamics, such as arterial wall shear stress, but also the biological behavior of the arterial wall.

Some previous studies\(^10\), \(^11\), \(^12\) have proposed theoretical models for arterial biological features, such as growth or remodeling, and have provided useful information. However, these studies did not analyze cerebral aneurysm formation. Kroon \textit{et al.}\(^13\) developed a theoretical model for the growth of a cerebral aneurysm, incorporating collagen fiber remodeling. Although these theoretical models are valuable, hemodynamic factors, such as arterial wall shear stress, were not included in their analyses. To develop a better understanding of the mechanism of cerebral aneurysm pathogenesis, it is important to develop a model that describes how hemodynamics and biological reactions of the artery are related.

We proposed a simulation model for the genesis and development of cerebral aneurysms\(^14\). In this model, it was hypothesized that high arterial wall shear stress exceeding a threshold value would lead to strength degeneration of the arterial wall and this effect would continue even after the arterial wall shear stress had dropped below the threshold. Chatziprodromou \textit{et al.}\(^15\) also proposed a simulation model for investigating a hypothesis of aneurysm growth involving a combination of two mechanisms: strength degradation of the arterial wall, because of apoptosis of medial smooth muscle cells, assumed to be caused by high wall shear stress; and arterial wall remodeling, resulting in the canceling of internal stress values and the establishment of a stress-free state. Although the results obtained from these studies are important, they did not represent clinical observations of cerebral aneurysms, characterized by saccular expansion of the arterial wall. Thus, some other mechanism should be considered to represent these saccular cerebral aneurysms.

In this paper, we propose a new simulation model for saccular cerebral aneurysm formation, developing a hypothesis that describes the relation between arterial wall shear stress and biological reactions of the constituents of the wall. In this hypothesis, we focus on the biological reactions of the arterial wall, such as proliferation of smooth muscle cells or extracellular matrix, as candidates for the mechanisms of cerebral aneurysm formation. The details of the hypothesis are provided in the next section. We performed simulations of cerebral aneurysm formation for a cerebral artery model, and showed that the resultant
2. Hypothesis

Kamiya et al.\(^{(16)}\) reported that an arteriovenous shunt between the canine common carotid artery and the external jugular vein caused increased flow rate, and thus led to an increase in the flow-induced wall shear stress. Over time, the arterial internal radius was shown to increase with increased flow rate. The arterial wall shear stress, which was initially proportional to flow rate, recovered to its homeostatic value of about 1.5 Pa. Similar results have been observed in other studies\(^{(17, 18, 19)}\). These results showed that the artery has the ability to adapt to changes in the mechanical environment. At the micro-level, such adaptation was accompanied by growth or remodeling of the arterial wall constituents\(^{(20)}\). The wall shear stress increase was produced experimentally via increased flow rate. In the process of human growth, however, changes in the wall shear stress field commonly occur via altered overall arterial geometry. The geometry of cerebral arteries becomes more complicated with age. For example, the cerebral arteries have much more tortuous geometries in the elderly than in young people. In some cases, complicated cerebral arteries may result in an abnormal wall shear stress field, with a locally high wall shear stress value that exceeds the homeostatic value. Thus, an abnormal wall shear stress field is not an unrealistic condition in the process of human growth.

We assumed that the length of an artery increases with aging, generating more bending and torsion in the arterial geometry. In this study, we employed a simple arterial model with bends and torsion mimicking this geometry change. If high wall shear stress exceeding the threshold value appears at some parts of the artery, we hypothesized that the endothelial cells would be dysfunctional, leading to abnormally persistent growth or remodeling of the arterial wall constituents, referred to here as “over-adaptation.” Such a threshold value has been suggested in some previous studies\(^{(16, 21, 22)}\). In the present study, high wall shear stress was taken to be a factor responsible for induction of arterial dysfunction\(^{(6)}\). High wall shear stress does not always cause over-adaptation, but it may trigger dysfunction and may lead to over-adaptation in combination with genetic and other factors. In the present study, we performed a computational investigation of the resulting arterial shape according to the hypothesis, and sought to establish a numerically tractable model.

Our hypothesis can be summarized as follows. With aging, an artery tends to show increased bending and torsion within a short period of time. High wall shear stress that exceeds the threshold value may result in such an artery, possibly causing over-adaptation. Such over-adaptation includes over-proliferation of smooth muscle cells (SMCs) and/or extracellular matrix (ECM) synthesis. Indeed, proliferation of SMCs and ECM synthesis have been observed in the aneurysmal wall\(^{(23, 24, 25)}\). Moreover, we hypothesized that the surface area of the arterial wall may be continually expanded because of over-adaptation, without marked changes in wall thickness, and this process may lead to cerebral aneurysm formation. In this way, we can translate the cerebral aneurysm formation process into a computationally tractable problem.

3. Modeling and Methods

3.1 Geometry of the artery model

Recently, many researchers have employed arterial geometries based on clinical image data. Such studies are informative and have provided detailed information on flow fields specific to a given patient. In discussing the mechanism of aneurysm formation, however,
patient-specific analysis provides information that is only valid for the patient in question. It has been proposed that there may be several different causes of cerebral aneurysms, including hemodynamic stress, hypertension, and heredity\(^{(26)}\). Thus, we feel that it is more appropriate to employ a simple geometric model to discuss a general hypothesis based on which we can determine the basic properties of aneurysm growth.

We investigated how an aneurysm was formed in a model cerebral artery, with curvature and torsion. There are many examples of cerebral aneurysms formed in cerebral arteries with curvature and torsion\(^{(26)}\). Figures 1(a) and (b) show the initial geometry of the artery used in this study, modeled on part of the internal carotid artery. The artery model has a diameter of 3.0 mm, a curvature radius of 3.6 mm, a length of 30 mm along the central axis, and a torsion angle of 15°; these are typical values observed in clinical studies.

![Fig. 1  Geometry and computational mesh of the model artery.](image)

3.2 Blood flow simulation

For the calculation of blood flow, blood was assumed to be an incompressible and Newtonian fluid with density, \(\rho = 1.05 \times 10^3\) kg/m\(^3\), and viscosity, \(\mu = 3.5 \times 10^{-3}\) Pa·s. Governing equations for the flow of such blood are the equation of continuity:

\[
\nabla \cdot \mathbf{u} = 0
\]  
(1)

and the Navier-Stokes equation:

\[
\frac{\partial \mathbf{u}}{\partial t} = -(\mathbf{u} \cdot \nabla)\mathbf{u} - \nabla p + \frac{1}{Re} \nabla^2 \mathbf{u}
\]  
(2)

where \(\mathbf{u}\) is the three-dimensional velocity vector and \(p\) is the pressure. The parameter \(Re\) is the Reynolds number, defined as \(Re = \rho \mathbf{u}_{\text{ave}} D / \mu\), where \(D\) is the diameter of the artery and \(\mathbf{u}_{\text{ave}}\) is the average velocity at the inlet boundary. As the Womersley number in the cerebral artery is less than 3.0\(^{(27)}\), we assumed steady blood flow. Thus, we solved the steady flow at the averaged Reynolds number in human cerebral arteries (\(Re=200\))\(^{(28)}\), and discussed the over-adaptation, based on the wall shear stress distribution. In a real human body, however, the blood flow is pulsatile. Since the pulsatility of the blood flow affects wall shear stress (WSS) distribution, we also performed a trial computation with pulsatile flow condition. In the trial computation, spatial distribution of WSS varied during a pulsation. However, the maximum WSS appeared in almost the same region as the steady state computation, since the Womersley number in the cerebral artery is as low as less than 3.0\(^{(27)}\).
Boundary conditions were a parabolic velocity profile at the inlet, zero pressure at the outlet, and a no-slip condition on the wall. The blood flow calculation was accomplished using an in-house three-dimensional flow solver, based on a MAC algorithm. The total number of grid points was 52,065. The accuracy of our numerical code was checked by a three-dimensional circular tube flow simulation. In addition, the grid convergence was confirmed by comparing with 103,329 and 205,857 grid points.

3.3 Modeling of arterial wall and its growth

The arterial wall was discretized using triangular elements. The computational grid generated on the arterial wall is shown in Fig. 1(c), where 16,384 triangular elements (8,256 nodal points) were generated. The spring network model \( S_i \) was used to mechanically model the arterial wall. In this model, the mechanical behavior of the arterial wall was expressed with two types of spring: \( S_i \) corresponding to the side of a triangular element indicating the resistance to stretch/compression of the membrane, and \( B_i \) indicating the bending resistance of the membrane (Fig. 2). Thus, the effects of wall thickness can be approximated by the bending spring. The reason why we used such a simple discretization method is that the accuracy of the wall deformation is strongly limited by the growth model, which will be explained later by Eq. (3). We think, therefore, the spring model is good enough to discuss aneurysmal growth as a first step.

The arterial wall expansion in the hypothesis may be expressed by natural length elongation of a stretch/compression spring. The hypothesis is that the natural length increases with increasing excess amount of wall shear stress (WSS) on a stretch/compression spring element. In this study, we formulated the degree of the elongation as follows:

\[
\frac{l_i - l^0_i}{l^0_i} = \alpha (\tau_i - \tau_{th}) \quad \text{if} \quad \tau_i > \tau_{th},
\]

where \( l^0_i \) and \( l_i \) are the natural length of the stretch/compression spring element \( i \) before and after proliferation of the wall, respectively, \( \tau_i \) is WSS due to blood flow on the element \( i \), and \( \tau_{th} \) is the threshold for WSS. \( \tau_i \) and \( \tau_{th} \) are non-dimensionalized by \( \rho u_{ave}^2 \), where \( \rho \) is the blood density and \( u_{ave} \) is the average velocity at the inlet. \( \alpha \) is a dimensionless parameter for the degree of proliferation of the wall. This equation is applied only to the stretch/compression element in which \( \tau_i > \tau_{th} \). We employed the simple linear Eq. (3). As the details of the relationship are still unclear, it is worthwhile starting from a simple model as a first step.

![Fig. 2 Schematic of the spring network model.](image)

3.4 Wall deformation simulation

We performed the following process to solve the deformation of the arterial wall due to changes in the natural length of the springs: (i) initially change the natural length of the springs without any deformation (i.e., in the same geometry as Fig. 1(c)), (ii) calculate forces acting on each node, (iii) move each node during a small time step, and (iv) continue (ii) and (iii) until the convergence criteria are satisfied.
The natural length elongation of a stretch/compression spring without any deformation results in an imbalance between the blood pressure force and the internal force of the wall. It is necessary to calculate these forces to simulate the formation of a new equilibrium shape of the artery. We assumed a uniform transmural blood pressure difference of 100 mmHg. The blood pressure force acting on a triangular element was then divided equally among three nodes of the element and we expressed the pressure force acting on node \( j \) as \( F_{p,j} \).

In this study, spring forces were calculated on the basis of the principle of virtual work. We considered two types of arterial elastic energy, stretch/compression and bending, and the spring force acting on node \( j \) was expressed as follows:

\[
F_{s,j} = -\frac{\partial(E_s + E_b)}{\partial r_j},
\]

where \( E_s \) and \( E_b \) are the stretch/compression elastic energy and the bending elastic energy stored in the arterial wall, respectively, and \( r_j \) is the position vector of node \( j \).

The stretch/compression elastic energy \( E_s \) was expressed as:

\[
E_s = \frac{1}{2} \sum_{i=1}^{N} k_{s,i} (L_i - l_i)^2,
\]

where \( i \) is a stretch/compression spring element number, \( N \) is the total number of elements, \( k_{s,i} \) is the stretch/compression spring constant of element \( i \), \( L_i \) is the present length of the element, and \( l_i \) is the natural length given by Eq. (3).

The bending elastic energy \( E_b \) was given as:

\[
E_b = \sum_{i=1}^{N} k_{b,i} \tan^2 \left( \frac{\theta_i}{2} \right),
\]

where \( k_{b,i} \) is bending spring constant of element \( i \), and \( \theta_i \) (Fig. 2) is the bending angle between two neighboring triangular elements. In this equation, we have used tangent function to avoid the folding of the triangle elements.

The resultant nodal movement is governed by a set of motion equations for each node,

\[
\kappa \frac{dr_j}{dt} = F_{s,j} + F_{p,j},
\]

where \( \kappa \) is the virtual drag coefficient, to control the velocity of the nodes. We should note that the resultant shape is not affected by \( \kappa \) because it controls only the speed of numerical convergence. The new equilibrium shape of the artery can be obtained by solving the steady solution of Eq. (7), because the steady solution satisfies the equilibrium condition:

\[
F_{s,j} + F_{p,j} = 0.
\]

### 3.5 Estimation of spring constants

We estimated the bending spring constant so that the bending elastic energy given by Eq. (6) was consistent with that given by the shell theory. It was assumed that the arterial wall was an incompressible isotropic elastic media with Young’s modulus \( E \) of 2 MPa, Poisson ration \( \nu \) of 0.5, and wall thickness \( h \) of 0.2 mm. As a result, the bending spring constant was estimated at \( k_{b,ij} \approx 1.0 \times 10^{-6} \) N⋅m. One way to estimate the stretch/compression spring constant was to calculate the variation in the arterial diameter when the artery was loaded with transmural pressure, and to compare that with experimental results. We adjusted the stretch/compression spring constant by trial-and-error method so that the arterial diameter variation calculated in the transmural pressure range 80-120 mmHg was approximately consistent with the experimental result for human internal carotid artery, i.e. stiffness parameter of 11.15. In this calculation, we used the initial diameter of 3 mm and the bending spring constant \( k_{b,ij} = 1.0 \times 10^{-6} \) N⋅m as described above. Eventually, the stretch/compression constant was estimated at \( k_{s,ij} = 1.0 \times 10^2 \) N/m.

When the nature length of a stretch spring becomes \( n \) times longer than the initial geometry, the stretch spring constant is reduced to \( 1/n \) in order to generate equivalent
spring forces per strain of the spring, i.e. $\Delta L_i/L_i$, between before and after the growth.

All basic equations were non-dimensionalized by the initial diameter $D$, the averaged velocity $u_{\text{ave}}$ at the inlet boundary, the blood density $\rho$, and the blood viscosity $\mu$.

4. Results

First, we simulated the steady blood flow of $Re=200$ in the artery model. Figure 3 shows the magnitude of the axial velocity at several cross-sections. The main stream was slanted to the outside of the curvature. Figure 4 shows the distribution of flow-induced WSS. The color contour in the figure shows the magnitude of WSS. As shown in the figure, WSS was relatively high on the bent side, and an especially high WSS region was concentrated on one side of the artery due to arterial torsion.

![Fig. 3 Magnitude of the axial velocity component at several cross-sections.](image)

![Fig. 4 Wall shear stress distribution on the wall.](image)

We performed simulations of aneurysm formation based on the WSS distribution, assuming the following three conditions: (a) only strength degradation of the wall, (b) only proliferation of the wall (surface area expansion), and (c) both strength degradation and proliferation of the wall. The threshold value $\tau_{th}$ in these simulations was assumed to be 0.12, equivalent to 90% of the maximum WSS value. The threshold value 0.12 corresponded to 3.0 Pa in the dimensional form. Since the mean WSS in a real artery is about 1-2 Pa, we assumed the threshold value $\tau_{th}$ to be 3 Pa.
Figure 5(a) shows the resultant shape of the aneurysm formation simulation, assuming only strength degradation of the wall. In this simulation, the stretch/compression constants were decreased uniformly by 30%, 60%, and 90%, in the region where the WSS exceeded the threshold value. A larger expansion was formed as the strength degradation of the wall increased. However, none of the resultant shapes in this simulation were saccular.

Figure 5(b) shows the resultant shape of the aneurysm formation simulation, assuming only proliferation of the wall. In this simulation, the parameter $\alpha$, which expresses the degree of proliferation of the wall, was set to 30, 50, or 100 in the region where WSS exceeded the threshold value. The expansion was greater as the parameter $\alpha$ increased. When $\alpha = 100$, the resultant shape became saccular. We defined the neck diameter $N$, the aneurysm height $H$, and the aneurysm diameter $W$ as shown in Fig. 6 for the case of Fig. 5(b-3). The diameter at the neck was smaller than that in the aneurysm, and the aneurysm shape was almost spherical. These tendencies agreed well with the definition of a saccular aneurysm. In the case of Fig. 5(b-3), $N = 3.1$ mm, $H = 2.3$ mm, and $W = 3.5$ mm.

Finally, we show the resultant shape of the aneurysm formation simulation assuming both strength degradation and proliferation of the wall. In this simulation, the stretch/compression constants were uniformly decreased by 30% in the region where the WSS exceeded the threshold value, and the parameter $\alpha$ was set to 30, 50, or 90. The results in Fig. 5(c-1) and (c-2) showed qualitatively equivalent shape to those assuming only proliferation of the wall (Fig. 5(b-1), (b-2)) under the same $\alpha$ conditions. By considering both the strength degradation and proliferation of the wall, a saccular aneurysm similar to Fig. 5(b-3) appears with smaller value of $\alpha$ ($= 90$), as shown in Fig. 5(c-3).
5. Discussion

Many clinical studies have suggested that degradation of arterial wall constituents is a key phenomenon in cerebral aneurysm formation, and consequently the saccular expansion forms due to blood pressure load\cite{30,31}. Steiger et al.\cite{32} reported that the Young’s modulus degradation of the cerebral aneurysmal wall was about 30%. Thus, the strength degradation of 90% in Fig. 5(a-3) may be unrealistically large. Nevertheless, the resultant shape was not saccular. This suggests that strength degradation of the arterial wall is not sufficient to explain the formation of a saccular cerebral aneurysm. On the other hand, saccular expansion can be formed by considering the surface area expansion due to proliferation of the wall (Fig. 5(b-3)). These observations indicate that the key phenomenon in saccular cerebral aneurysm formation may be proliferation of the wall. Although strength degradation in the arterial wall is important, we think it is also necessary to consider proliferation of the wall for a better understanding of the mechanism of saccular cerebral aneurysm formation. Some clinical studies support this suggestion. Masuda et al.\cite{20} reported that flow-induced surface area expansion was accompanied at the micro-level by arterial remodeling, such as cell proliferation and the transformation of internal elastic lamina. A similar result was reported by Sho et al.\cite{33}. Frösen et al.\cite{23} also observed smooth muscle cell proliferation in the cerebral aneurysmal wall. In the histopathological study of an aneurysmal wall, both the degradation of internal elastic lamina and the surface area expansion of the wall were observed. Thus, we presume that both of them occur at the same time during the process of the formation of cerebral aneurysms. (The case of Fig. 5(c) may represent this situation.)

The threshold value 0.12 corresponded to 3.0 Pa in the dimensional form. Since the mean WSS in a real artery is about 1-2 Pa, we assumed the threshold value to be 3 Pa. If we change the threshold value, the size of the aneurysm changes significantly. In extreme cases, the vessel may expand as a whole if we set $\tau_{th} << 1$, or the vessel does not expand at all if $\tau_{th} >> 1$. In this study, the choice of $\tau_{th} = 3$ Pa resulted in a realistic aneurysmal size. However, we think that quantitative discussion on the threshold value will be necessary in future studies.

$\alpha$ is a parameter representing the degree of proliferation of the wall. It means that as the parameter $\alpha$ becomes higher, greater expansion of the arterial surface area occur under the same WSS conditions. The real value of $\alpha$ within the living body, to our knowledge, has not been previously reported. Thus, we changed the parameter $\alpha$ to the extent that a resultant aneurysmal shape became similar to clinical observations.
If we decrease or increase the Reynolds number, the wall shear stress changes
significantly. If we perform the present simulation under such conditions, we may need to
change the value of $\tau_{th}$ and $\alpha$. In a real artery, however, vessel diameter changes
gradually so that the mean wall shear stress recovers to normal physiological condition.
Thus, we think that the wall shear stress after a long time period is eventually returned to
1-2 Pa. If we perform the present simulation after such remodeling of the arterial diameter,
we may use the similar value of $\tau_{th}$ and $\alpha$.

In the present study, we employed a tube with curvature and torsion as a human internal
carotid artery model. The results indicated that a saccular aneurysm was formed outside the
bent side, which was consistent with clinical observations. Valencia et al. (26) reported a total
of 25 patient-specific models of saccular cerebral aneurysms formed on the bent side, most
of which were located outside the bent side.

There have been a few previous numerical investigations of the growth of cerebral
aneurysms. In our previous model (14), we hypothesized that high wall shear stress exceeding
the threshold value would lead to strength degradation in the arterial wall and this
degenerative effect would continue even after the wall shear stress dropped below the
threshold. Although a small expansion of the arterial wall was formed in this simulation,
saccular expansion was not observed. Chatziprodromou et al. (15) also proposed a simulation
model for investigating aneurysm growth. Their hypothesis involved a combination of two
mechanisms: strength degradation of the arterial wall due to apoptosis of the medial smooth
muscle cells, assumed to be caused by high wall shear stress; and arterial wall remodeling,
which resulted in canceling of internal stress values and establishment of a stress-free state.
However, they also did not demonstrate formation of a saccular cerebral aneurysm. Here,
we successfully showed the formation of a saccular cerebral aneurysm by modeling the
surface area expansion due to proliferation of the arterial wall. The resultant shape was
consistent with clinical observations.

6. Conclusion

We have proposed a new simulation model for saccular cerebral aneurysm formation,
developing a hypothesis that describes the relation between wall shear stress and
proliferation of the wall. The model has been applied to the following three cases, i.e.
degradation of the wall, proliferation of the wall, and both degradation and proliferation of
the wall. The results have suggested that proliferation of the wall may play an important
role in saccular cerebral aneurysm formation, whereas many clinical studies have explained
that a predominant player in aneurysm formation is degradation of the wall and the saccular
expansion forms due to blood pressure load. Although further investigation is needed to
verify the hypothesis, proliferation of the arterial wall seems to have a strong correlation
with saccular aneurysm formation. We believe that the methodology described in this paper
is a powerful platform to obtain a better understanding of the mechanism of cerebral
aneurysm formation.

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