Abstract A cerebral aneurysm is a vascular condition characterized by local ballooning of an artery in the brain. Although aneurysm formation and growth are thought to be the result of destruction of the blood vessel wall, the details of the etiology are unclear. We review the formation and growth of cerebral aneurysms as follows. In the first part, we summarize the history of theories on the pathogenesis of cerebral aneurysm in chronological order from epidemiological and pathological viewpoints and based on data obtained from animal models of experimentally induced cerebral aneurysms, with a focus on the involvement of hemodynamic stress on the arterial wall. In the second part, we review computational fluid dynamics (CFD) studies on the initiation of cerebral aneurysms with a brief overview of the history of CFD in hemodynamics analysis. Of the hypotheses presented, strong emphasis is placed on that of high wall shear stress and a high wall shear stress gradient. Other leading hypotheses involving hemodynamics-related parameters are also reviewed. In the third part, we review CFD studies on the growth of cerebral aneurysms, in which hemodynamic parameters were compared between growing and stable aneurysms, to highlight the hemodynamic characteristics associated with their growth.

Keywords cerebral aneurysm, formation, growth, pathology, animal model, computational fluid dynamics

1. Introduction

A cerebral aneurysm is a local bulge in or ballooning of a blood vessel in the brain. Rupture of the aneurysm causes internal bleeding such as a subarachnoid hemorrhage and intracranial hematoma, which can lead to death. Most cerebral aneurysms, however, do not rupture. Instead, they occasionally cause health problems or symptoms—compression of surrounding nerves and brain tissue by aneurysms results in nerve paralysis, headache, and vomiting.

Aneurysm formation begins with extrusion of the locally weakened wall of an artery. Why an artery becomes locally weakened is unclear. Some aneurysms stay the same size while others grow continuously. Koffijberg et al. found that intracranial aneurysms do not grow constantly [1]. The growth rate of aneurysms varies; several years can be required for an aneurysm to increase in size by 1 mm and be visually recognized on angiogram [2].

Here we review the formation and growth of cerebral aneurysms as follows. In the first part, we summarize the history of theories on the pathogenesis of cerebral aneurysm in chronological order from epidemiological and pathological viewpoints and based on data obtained from animal models of experimentally induced cerebral aneurysms, with a focus on the involvement of hemodynamic stress on the arterial wall.
The second part summarizes research on the initiation of cerebral aneurysms, in particular, by means of computational fluid dynamics (CFD). Following a brief review of the history of studies of blood flow analysis, hemodynamics-based hypotheses on the initiation of cerebral aneurysms are summarized. Of the hypotheses presented, strong emphasis is placed on that of high wall shear stress (WSS) and a high WSS gradient (WSSG). Other leading hypotheses involving hemodynamics-related parameters are also reviewed. In the third part, we review CFD studies on the growth of cerebral aneurysms, in which hemodynamic parameters were compared between growing and stable aneurysms, to highlight the hemodynamic characteristics associated with their growth.

2. Epidemiology, Pathology, and Animal Experiments

In the past, the etiology of cerebral aneurysm was asserted to be “congenital”, “acquired”, or “both congenital and acquired” [3–5]. It is now thought that cerebral aneurysms are caused mainly by acquired factors, with some contribution by congenital factors, such as genetic diseases, that increase vascular wall vulnerability. Below we summarize the history of theories on the pathogenesis of cerebral aneurysm in chronological order from epidemiological and pathological viewpoints and based on data obtained from animal models of experimentally induced cerebral aneurysms (Fig. 1).

2.1. Hypotheses based on pathological factors: Disruption of the media and degeneration of the inner elastic lamina

In 1930, Forbus et al. claimed that cerebral aneurysm is a congenital disorder involving medial defects, which are sometimes observed in the cerebral arterial bifurcation [3]. In contrast, in 1940, Glynn et al. argued that cerebral aneurysm is an acquired disease caused by local degenerative changes of the internal elastic lamina [4]. In 1950, Carmichael et al. combined the above two theories, and proposed a “congenital and acquired” theory, in which degenerative changes of the inner elastic lamina accidentally occur at a site with a medial defect [5]. In 1961, Hassler et al. first focused on hemodynamic stress, and argued that cerebral aneurysm is induced because the inner elastic lamina is overstretched due to hemodynamic stress at an area with a medial defect [6]. In 1963, Stehben and colleagues focused on acquired elements—such as hypertension, hemodynamic stress, and cerebral arteriosclerosis—and denied the existence of congenital medial defects, proposing that cerebral aneurysm is acquired [7].

| Year | Hypothesis Description |
|------|------------------------|
| 1930 | congenital theory, Forbus et al. [3] |
| 1940 | acquired theory, Glynn et al. [4] |
| 1950 | congenital & acquired theory, Carmichael et al. [5] |
| 1961 | hemodynamic theory, Hassler et al. [6] |
| 1978 | rat aneurysm induced model, Hashimoto et al. [13] |
| 1987 | monkey aneurysm induced model, Hashimoto et al. [17] |
| 1991 | role of WSS, Nakatani et al. [18] |
| 2000 | WSS mechanotransduction theory, Fukuda et al. [21] |
| 2004 | CFD analyzes start in earnest |
| 2007 | chronic inflammation theory, Aoki et al. [22] |
| 2008 | rabbit aneurysm induced model, Gao et al. [25] |
| 2014 | mural cell / MMP theory, Meng et al. [27] |
| 2019 | mechanical stretch theory, Koseki et al. [37] |
| 2019 | role of P2X4, Fukuda et al. [34] |

Fig. 1 History of theories on the pathogenesis of cerebral aneurysm in chronological order. WSS; wall shear stress, CFD; computational fluid dynamics.

2.2. Animal model of experimentally induced cerebral aneurysms based on hemodynamic stress

Hemodynamic involvement in cerebral aneurysm development has been empirically observed [8–12], and hypertension, which causes systemic enhancement of hemodynamics, is one of the major risk factors for aneurysm development [10]. Cerebral aneurysms are typically located in the bifurcation of the circle of Willis, where the communicating pathway permits anastomotic circulation if a part of the circulation is occluded. Cerebral aneurysms are more common in patients with an asymmetric circle of Willis [11]. Unilateral internal carotid artery (ICA) occlusion can lead to cerebral aneurysm induction in the anterior communicating artery (Acom), where blood flow is increased in a compensatory way [8], and asymmetrical geometries of the anterior cerebral arteries (ACAs) are closely associated with Acom aneurysm formation [12]. Hence, local increases in hemodynamic stress caused by disturbed hemodynamics in an asymmetric circle of Willis as well as a systemic rise in hemodynamics (e.g., hypertension) may be key requirements for cerebral aneurysm development.

Hashimoto et al. focused on this hemodynamic phenomenon. In 1978 they were the first to induce cerebral aneurysms successfully in rats experimentally, by both stimulating a local increase in hemodynamics in the circle of Willis by unilateral common carotid artery ligation and enhancing systemic hemodynamics by inducing renovascular hypertension, and by administering 3-aminopropionitrile (BAPN), an inhibitor of lysyl oxidase (which catalyzes cross-linking of collagen and elastin), to promote weakening of the arterial wall [13]. The resultant cerebral aneurysms are induced in
the Acom and at the bifurcation of the ACA and the olfactory artery where blood flow is increased consequent to unilateral carotid artery occlusion, similar to the microstructural changes observed in human cerebral aneurysms [13–15]. Furthermore, they showed that cerebral aneurysms can be induced without BAPN in the animal model [16], suggesting that cerebral aneurysm development requires only acquired hemodynamic factors. Later, cerebral aneurysms were induced experimentally in monkeys, which have greater anatomical similarity to humans [17]. The common association of cerebral aneurysms with increased hemodynamic values in rodents, monkeys, and humans suggests that the mechanisms of cerebral aneurysm development are likely to be shared among mammalian species. Therefore, researchers should be able to gain insight into the pathogenesis of cerebral aneurysms in human patients by examining the mechanisms underlying their formation in animal models.

In the animal model by Hashimoto et al., early cerebral aneurysm development, as indicated by endothelial degeneration and disruption of the internal elastic lamina, occurs almost exclusively at the distal side of the major branch adjacent to the apex; aneurysmal bulging was also observed in this area [15]. Interestingly, hemorheological studies involving numerical analysis of latex particle paths in a rat model showed that WSS increased and was greatest in this area during early-phase cerebral aneurysm development [18]. Nakatani et al. in 1991 first suggested that an increased WSS is involved in the development of cerebral aneurysm.

However, cerebral aneurysm development is unlikely to be due to direct mechanical stress caused by high WSS [19]. Blood vessels sense the volume of blood flow by sensing not blood pressure but WSS. Vascular endothelial cells sense WSS caused by blood flow and, in turn, regulate blood flow by changing their shape and releasing biochemical mediators [20]. Fukuda et al. proposed the WSS mechanotransduction theory that endothelial cells sense locally enhanced WSS-related hemodynamics in the vessel wall, which initiates the production or activation of biochemical mediators that damage vascular wall components, leading to cerebral aneurysm formation. They reported in 2000 that inducible nitric oxide synthase (iNOS) is expressed in human and rat cerebral aneurysms, and that both a reduction in WSS and inhibition of iNOS reduce aneurysm development in rats after aneurysm induction surgery [21]. Thus, the site of initiation of cerebral aneurysm formation moved from the vascular media and internal elastic lamina to the endothelium, the inner side of the blood vessel. The next stage was to clarify the spatial and temporal patterns of hemodynamic stress in cerebral aneurysms. Due to their small size, animal models are not suitable for such work. Instead, CFD techniques begun to be used around 2004 to clarify the hemodynamics-related factors involved in human cerebral aneurysm development, enlargement, and rupture.

2.3. Cerebral aneurysm as a chronic inflammatory disease and hemodynamic stress

Aoki et al. developed the work of Fukuda et al., and proposed that the inducers that damage the arterial wall and generate cerebral aneurysms are inflammatory factors derived from macrophages [22–24]. They suggested that, during early-phase cerebral aneurysm development under enhanced WSS-related hemodynamics, a positive signaling pathway, consisting of cyclooxygenase-2 (COX-2), prostaglandin E2, and prostaglandin E receptor 2, is formed, followed by induction of monocyte chemotactic protein-1 (MCP-1) expression and subsequent recruitment of macrophages [24]. They aimed to identify pharmacological inhibitors of the development of cerebral aneurysm.

Gao et al. developed an animal model of cerebral aneurysm induction by bilateral carotid artery ligation in rabbits in 2008 [25]. They integrated this animal model and CFD analysis with clinical data. In a study using the rabbit aneurysm model, they suggested that damage to the internal elastic lamina occurred only at locations with a WSS of >122 Pa (a surprisingly high value), and a WSSG of >530 Pa/mm [26]. suggesting that the early changes in cerebral aneurysm development were related to the exceeding of normal physiological WSS. Please see the next section for their hypothesis on the formation of cerebral aneurysm [27].

A cerebral aneurysm disappears or shrinks as the blood flow of the parent artery decreases [28, 29]. Cerebral aneurysms that arise on distal feeding arteries near the nidus of an arteriovenous malformation have a high probability of regressing with substantial or curative therapy of the arteriovenous malformation [28]. A tailored flow-reduction strategy together with bypass surgery can obliterate or shrink giant partially thrombosed basilar artery aneurysms [29]. Thus, the shear stress response of endothelial cells not only triggers an inflammatory response but may also be essential for the continuation of the inflammation required for the maintenance, growth, and eventual rupture of the aneurysm.

Since Fukuda et al. proposed the WSS mechanotransduction theory in 2000 [21], several other investigators have suggested that increased WSS may be involved in cerebral aneurysm development [26, 30–32]. Using a microfluidic system, Nam et al. found that morphological variations in the circle of Willis contribute to cerebral aneurysm formation resulting from increased WSS [30]. Areas enriched in cerebral aneurysms correlated significantly with the magnitude of WSS [31]. CFD analysis in de novo human cerebral aneurysms suggested that high WSS and a high WSSG are associated with cerebral aneurysm development [32]. However, there was no direct evidence that WSS sensing is responsible for cerebral aneurysm formation. P2X4 purinoceptor is involved in the shear stress response of vascular endothelial cells, contributing to vascular remodeling [33]. Fukuda et al. indicated that the incidence of cerebral...
CFD has been used for blood flow analysis since the late 1990s. Due to the limited performance of computers of the time, flow analysis only in pipes of simple geometry was conducted. The increase in computational power in the 2000s enabled flow analysis in anatomically realistic geometrical models of blood vessels and investigation of the hemodynamic stresses on vascular lesions. In particular, due to the improved performance of medical diagnostic imaging equipment, such as magnetic resonance imaging (MRI) and computed tomography (CT), patient-specific blood flow simulations were realized. Researchers then began to devise boundary conditions to individualize the simulation. Typical examples of inlet boundary conditions include those based on literature values, those that refer to measured values such as by phase-contrast (PC) MRI, and those estimated based on hypotheses such as the constant WSS theory [43]. As outlet boundary conditions, some people use pre-distributed flow rates according to hypotheses such as Murray’s law, and others use a reduced dimensional model of the peripheral vessel network based on fractal nature of branching arteries. In addition, fluid-structure interactions are realized by calculating flow and wall motion by treating the wall as an elastic rather than a rigid body. Blood flow analysis has made dramatic progress in the last 20 years. However, there remains doubt as to whether use of complex boundary conditions and implementation of fluid-structure analysis have contributed to identification of the initiation and growth factors of the cerebral arteries. Recent studies have attempted to simplify blood flow simulations without complex boundary conditions, and to identify factors involved in the initiation and growth of cerebral aneurysms from a large set of simulation data by statistical analysis. At present we cannot foresee future developments in blood flow analysis, but it will be likely to involve large-scale data analysis and artificial intelligence.

Below, we summarize the hypotheses involving hemodynamic factors proposed to be involved in the initiation and growth of cerebral aneurysms.
3.1. High WSS and positive WSSG

Meng et al. [44, 45] created a bifurcated blood vessel by end-to-side anastomosis of two ICAs in a dog to intentionally form an aneurysm. They divided the bifurcation area into three (I, collision area; II, acceleration area; III, recovery area) according to hemodynamic parameters. In region I the flow collided with the bifurcation, and the WSS was low to normal. In region I, intimal thickening by growth remodeling was observed and fibronectin production was detected. In region II, immediately adjacent to region I, the inner elastic lamina was destroyed, and destructive remodeling such as loss of smooth muscle cells and endothelial cells occurred. In region II the WSS and WSSG values were abnormally high. Note that the WSS increased from proximal to distal in region II, giving a positive gradient of WSS. These observations suggest that the combination of these hemodynamic stresses induced excessive production of matrix metalloproteinases (MMP) by endothelial cells and smooth muscle cells, thereby devastating the inner elastic lamina. Normally, endothelial cells in arteries undergo proliferative remodeling in response to chronic increases in WSS. The combination of a high WSS and positive WSSG, however, caused endothelial cell dysfunction, which terminated expression of proliferating cell nuclear antigen (PCNA) and caused loss of smooth muscle cells. Based on this, Meng et al. [44, 45] hypothesized that destructive remodeling by the combination of a high WSS and positive WSSG causes thinning of the blood vessel wall, thus initiating cerebral aneurysm.

The hypothesis of a high WSS and positive WSSG was tested by various research groups. Wang et al. [46] studied it from a molecular biology viewpoint, using the same experimental system as Meng et al. [44, 45], and revealed that the combination of a high WSS and positive WSSG led to a decrease in the expression of endothelial nitric oxide synthase (eNOS) and iNOS, which promote nitric oxide (NO) production and, therefore, enhanced MMP production and activation. Moreover, these molecular changes were not detected in the region of a high WSS and negative WSSG, corroborating the hypothesis of Meng et al. [44, 45]. The Meng hypothesis was further supported by Metaxa et al. [26], who observed destructive remodeling at the bifurcation of the basilar artery by ligating the rabbit common carotid artery and increasing flow into the basilar artery.

Meng’s hypothesis, the work for which began in 2011, used human cerebral aneurysms. Kulcsár et al. [32] attempted to correlate hemodynamics and aneurysm formation by observing naturally occurring cerebral aneurysms in the branch vessels of three human patients. An aneurysm was formed in the region of a high WSS and positive WSSG, consistent with Meng et al. [44, 45]. Meng’s hypothesis was also supported by Alfano et al. [31], who investigated blood flow at 114 bifurcations in 31 individuals and Geers et al. [47], who studied wall-type aneurysms. Watanabe et al. [48] compared hemodynamics in groups with and without aneurysms at ICA and found that the aneurysm group had a significantly higher WSS and WSSG compared with the non-aneurysm group.

Geometrical factors that induce a high WSS and high WSSG have also been examined. Kono et al. [49] suggested that proximal stenosis induces initiation of one class of cerebral aneurysm. They prepared two pre-aneurysm models: one with and the other without stenosis and compared their hemodynamics. Owing to the jet flow caused by the stenosis, the maximum WSS and WSSG at the aneurysm initiation site were approximately doubled and tripled, respectively. Based on these results, they concluded that proximal stenosis could lead to aneurysm initiation. Similarly, Lauric et al. [50] showed that narrowing of an upstream vessel led to flow acceleration, which accentuated the WSS and spatial gradient at the bifurcation apex, where aneurysms typically form. According to Tutuncu et al. [51] and Zhang et al. [52], a larger bifurcation angle increases the area exposed to direct flow impingement, which leads to abnormally enhanced hemodynamic stresses and thus, possibly, aneurysm initiation. Lauric et al. [53] evaluated the effect of blood vessel curvature on hemodynamics. They focused on the inner carotid siphon and created carotid siphon models with different curvature tightness. The flow simulations demonstrated that a high bend curvature induced fluctuating and high proximal WSS and WSSG values, followed by regions of flow stasis and recirculation. This resulted in local conditions known to induce destructive vessel-wall remodeling and aneurysmal initiation.

3.2. Other hypotheses

Hemodynamic parameters other than a high WSS and normal WSSG influence the formation of cerebral aneurysms. The oscillating shear index (OSI) is the degree to which WSS changes direction during one cardiac cycle. The OSI is expressed as a dimensionless parameter ranging from 0 (steady-state flow with WSS in one direction) to 0.5 (flow with WSS in any direction). The relative residence time (RRT) indicates the residence time of blood near the wall and is caused by the combination of a low WSS and high OSI. The gradient oscillatory number (GON), potential aneurysm formation index (AFI), WSS divergence (WSSD), oscillation velocity index, inflow concentration index, shear concentration index, low shear area (LSA), low shear area ratio, and indices related to kinetic energy and turbulence enable more complex analysis of blood flow. These are summarized in Table 1.

The following studies focused on the parameters described in the preceding paragraph. Mantha et al. [62] proposed AFI as a measure to detect flow stagnation zones where the WSS vectors aligned with endothelial cells over the course of the cardiac cycle. They examined AFI in paraclinoid aneurysms with virtual removal of the aneurysms...
| parameter name                              | definition                                                                 | notes                                                                                                                                                                                                 |
|---------------------------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Time-averaged wall shear stress (TAWSS) [47] | \( TAWSS = \frac{1}{T} \int_{0}^{T} WSS \, dt \) \( WSS \): WSS vector at time \( t \) \( T \): the duration of one cardiac cycle | - an average of the absolute value of WSS over one cardiac cycle                                                                                                                                                                                                 |
| WSS pulsatility index (WSSPI) [47]          | \( WSSPI = \frac{WSS_{\text{max}} - WSS_{\text{min}}}{TAWSS} \) \( WSS_{\text{max}} \): maximum WSS over one cardiac cycle \( WSS_{\text{min}} \): minimum WSS over one cardiac cycle | - a normalized difference between the maximum and minimum WSSs                                                                                                                                                                                                     |
| Wall shear stress gradient (WSSG) [54]      | \( WSSG = \left( \nabla \cdot \nabla WSS \right)^{2} + \left( \frac{\partial WSS}{\partial x} \right)^{2} + \left( \frac{\partial WSS}{\partial y} \right)^{2} \) | - High WSSG increases wall permeability [54], and mediates the occurrence of intimal hyperplasia [55]                                                                                                                                                           |
| Temporal wall shear stress gradient (TWSSG) [56] | \( TWSSG = \frac{\partial WSS}{\partial t} \) | - a rate of a change in the WSS vector - strongly associated to calcified plaque [57]                                                                                                                                                                          |
| Oscillatory shear index (OSI) [58, 59]       | \( OSI = \frac{1}{2} \left[ 1 - \int_{t_{0}}^{t_{1}} \frac{WSS_{dt}}{TAWSS} \right] = 1 - \frac{WSS}{TAWSS} \) | - a metric to assess the degree of WSS oscillation - correlated with plaque formation                                                                                                                                                                         |
| Relative residence time (RRT) [60]          | \( RRT = \frac{1}{T} \int_{0}^{T} \frac{WSS_{dt}}{TAWSS} \) \( (1 - 2 \times OSI) \times TAWSS \) | - a single metric of low and high oscillating shear stress                                                                                                                                                                                                       |
| Gradient oscillatory number (GON) [61]      | \( GON = -\frac{1}{\int_{t_{0}}^{t_{1}} WSS_{dt}} \left( \frac{\partial WSS_{p}}{\partial p} \frac{\partial WSS_{q}}{\partial q} \right) \) \( p \): a direction corresponding to the time-averaged direction of the WSS vector over one cardiac cycle \( q \): a direction normal to \( p \) in a wall plane | - a metric to quantify the change in WSSG magnitude and direction over one cardiac cycle for characterizing the degree of temporal fluctuation in hemodynamic tension/compression forces acting on endothelial cells, ranging from 0 to 1                                                                 |
| Aneurysm formation indicator (AFI) [62]     | \( AFI = \cos \theta = \frac{WSS_{\text{ave}} - WSS_{ave}}{WSS_{ave}} \) \( WSS_{ave} \): time-averaged WSS vector | - the degree of a change in the direction of WSS from the average WSS direction - AFI is evaluated at midsystolic deceleration (just after peak systole) in the original article [62]                                                                                                    |
| Inflow concentration index (ICI) [63]       | \( ICI = \frac{Q_{n}}{A_{n}} \times \frac{Q}{A_{a}} \) \( Q_{n} \): the flow rate into the aneurysm \( Q \): the flow rate in the parent artery \( A_{n} \): the area of the inflow region \( A_{a} \): the area of the ostium surface | - the percent of the flow rate of the parent artery that enters the aneurysm divided by the percent of the aneurysm ostium area that corresponds to positive inflow velocity                                                                                         |
| Shear concentration index (SCI) [63]        | \( SCI = \frac{F_{n}}{F_{a}} \times \frac{A_{a}}{A_{n}} \) \( F_{n} \): the total wall shear force over the high WSS region \( F_{a} \): the total wall shear force over the aneurysm sac \( A_{n} \): the area of the high WSS region \( A_{a} \): the area of the aneurysm sac | - the degree of concentration of the WSS distribution with the definition of the high WSS where the WSS is higher than the mean WSS over the “near-vessel” region by 1 standard deviation                                                                 |
| Low wall shear stress area (LSA) [63]       | \( LSA = \frac{A_{l}}{A_{a}} \) \( A_{l} \): the area of the low WSS region | - a measure of the aneurysm that is subjected to an abnormally low WSS, which is defined as the percentage of the area of the aneurysm sac that has WSS below the mean WSS in the parent artery by 1 SD                                                                 |
| Low shear index (LSI) [63]                  | \( LSI = \frac{F_{n}}{F_{a}} \times \frac{A_{a}}{A_{n}} \) \( F_{n} \): the total wall shear force over the low WSS region | - the relative amount of the total shear force applied in regions of abnormally low WSS                                                                                                                                                                               |
and reconstruction of the parent artery. Their simulations revealed an area of relatively low and rotating WSS or large negative AFI at the location of aneurysm development. Shimogonya et al. [61] used virtual removal of aneurysms to explore the hemodynamics in a pre-aneurysmal ICA. Of the hemodynamic parameters examined, GON, but not WSS, OSI, or AFI, was correlated with aneurysm formation. Similarly, Chen et al. [64] simulated blood flow in 22 human sidewall-type aneurysms and reported higher WSS and GON at sites of aneurysm formation. Isoda et al. [65] focused on sidewall-type cerebral aneurysms in the human basilar artery and found that the GON was high at the sites of aneurysms. By contrast, Tanaka et al. [66] examined WSS, WSSG, OSI, GON, and WSSD; of these, only WSSD was correlated with the site of aneurysm formation. A concern of RRT with aneurysm formation was examined by Riccardello et al. [67]. Simulations of hemodynamics in 14 cases of sidewall aneurysm showed a negative correlation between RRT and the occurrence of sidewall aneurysms. However, no hemodynamic factor linked to the occurrence of all aneurysms has been found.

4. CFD studies on the growth of cerebral aneurysms

There have been few computational studies on the growth of cerebral aneurysms. Jou et al. [68] investigated the correlation between cerebral aneurysm growth and hemodynamics by comparing the aneurysm growth pattern with the distributions of hemodynamic variables calculated by CFD simulations. Two patients with basilar aneurysms of similar size were followed; one aneurysm grew significantly (~3 mm/year) while the other remained stable during a 2-year follow-up. The growth pattern of the aneurysm wall was determined by co-registering aneurysm models constructed from MR angiography images at different time points. In the growing aneurysm, the region of growth correlated with that of very low WSS (<0.1 Pa), and a relatively large fraction of the surface of the aneurysm had a WSS of <0.1 Pa. The stable aneurysm had a smaller surface area with a WSS of <0.1 Pa. Both aneurysms showed a relatively uniform pressure distribution over the aneurysm wall. Therefore, a low WSS is more likely to be responsible for the growth of cerebral aneurysm than pressure.

Boussel et al. [69] examined the relationship between cerebral aneurysm growth and hemodynamics, in particular the WSS, by comparing the local radial displacement (growth) of the aneurysm wall with the time-averaged WSS (TAWSS) value at that location. Seven patients with aneurysms (three basilar artery, three ICA, and one middle cerebral artery aneurysms) were included; patient-specific models were constructed using MR angiography images at two time points (mean 16.4 ± 7.4 months). The local radial displacement of the aneurysm wall between the two time points was determined by co-registering the models manually and calculating the displacement on a pixel-by-pixel basis. In that study, the radial displacement was considered significant when it was >0.3 mm, which corresponded to half of the MR pixel resolution. The mean radial displacement was 0.19 ± 0.34 mm; 20% of wall-surface patches had a displacement of ≥0.3 mm and 80% a displacement of <0.3 mm. The TAWSS in the baseline geometry calculated by CFD was further averaged spatially over the areas with a displacement of ≥0.3 mm and <0.3 mm. The spatial mean TAWSS values were 0.76 ± 1.51 and 2.55 ± 3.65 Pa, respectively (p < 0.001). The results suggest that growth of cerebral aneurysms occurs in areas of low WSS.

Sforza et al. [70] investigated the hemodynamic characteristics of growing cerebral aneurysms by comparing them with those of stable cerebral aneurysms. A total of 33 patient-specific CFD models of growing (n = 16) and stable (n = 17) cerebral aneurysms were constructed from 3D-CT angiography or rotational angiography images and the hemodynamic characteristics were compared. A growing cerebral aneurysm was defined as an aneurysm that exhibited a displacement of >0.5 mm in any direction on at least 5% of the points on the aneurysm wall during follow-up observations. A stable cerebral aneurysm was defined as an aneurysm that did not exhibit a displacement of >0.5 mm for at least 9 months. The displacement of the aneurysm wall was determined by aligning the parent vessels by minimizing the distance between them. The shear concentration index was significantly higher in the growing than in the stable aneurysm group (p = 0.03). The shear rate ratio (p = 0.01), vorticity ratio (p = 0.01), and viscous dissipation ratio (p = 0.01) were significantly lower in the growing than in the stable aneurysm group. The growing aneurysm group had a larger area under low WSS (LSA) (p = 0.06), where low WSS was defined as 1 SD below the mean WSS of the parent artery, and a larger aspect ratio (p = 0.18) than the stable aneurysm group, although the differences were not significant. The oscillatory shear index showed no significant difference between the growing and stable aneurysm groups (p = 0.35). The results suggest that the hemodynamic environment of growing cerebral aneurysms may be characterized by non-uniform WSS distributions with areas of concentrated high WSS and large areas of low WSS.

As stated above, CFD studies have resulted in remarkable progress in our understanding of the hemodynamics of cerebral aneurysms. However, the hemodynamic factors related to the initiation and growth of cerebral aneurysms are unclear; therefore, further investigation is required.

5. Conclusion

We reviewed the formation and growth of cerebral aneurysms, focusing on the involvement of hemodynamic stress on the arterial wall. First, we summarized the history of
theories of the pathogenesis of cerebral aneurysm in chronological order from epidemiological and pathological viewpoints and based on data obtained from animal models of experimentally induced cerebral aneurysm. Enhanced hemodynamic stress may be a requirement for the formation of saccular cerebral aneurysm. The hemodynamic factors involved in aneurysm formation are unclear, although high WSS and possibly stretching are related. Also unclear is the mechanism of the WSS-induced mechanotransduction that induces the expression of inflammatory factors. Next, we briefly reviewed the history of studies of blood flow analysis by CFD, and summarized hemodynamics-based hypotheses on the initiation of cerebral aneurysms. Finally, we reviewed CFD studies on the growth of cerebral aneurysms, in which hemodynamic parameters were compared between growing and stable aneurysms, to highlight the hemodynamic characteristics associated with their growth. Remarkable progress has been made in CFD studies on the hemodynamics of cerebral aneurysms. Nevertheless, to date, no hemodynamic factors that explain the initiation or growth of cerebral aneurysms have been found. Further hemodynamic CFD studies complemented by animal models will improve our understanding of the initiation and growth of cerebral aneurysms.

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