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Computational fluid dynamics in brain aneurysms

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SUMMARY

Because of its ability to deal with any geometry, image-based computational fluid dynamics (CFD) has been progressively used to investigate the role of hemodynamics in the underlying mechanisms governing the natural history of cerebral aneurysms. Despite great progress in methodological developments and many studies using patient-specific data, there are still significant controversies about the precise governing processes and divergent conclusions from apparently contradictory results. Sorting out these issues requires a global vision of the state of the art and a unified approach to solving this important scientific problem. Towards this end, this paper reviews the contributions made using patient-specific CFD models to further the understanding of these mechanisms, and highlights the great potential of patient-specific computational models for clinical use in the assessment of aneurysm rupture risk and patient management.

Keywords

cerebral aneurysm; computational fluid dynamics; hemodynamics; initiation; growth; rupture

1. INTRODUCTION

The natural history of intracranial aneurysms consists of three stages: genesis, enlargement, and rupture. It is generally accepted that the pathogenesis results from the fragmentation or degradation of intramural elastin, with subsequent loss of medial smooth muscle cells. Enlargement of aneurysms appears to depend primarily on the balance between collagen synthesis and degradation in response to changing mechanical stimuli. Finally, rupture occurs when wall stress exceeds wall strength. Each phase of the natural history of intracranial aneurysms depends on cell-matrix processes and material properties of the wall. However, the role of shear-induced destructive remodeling and tissue production upon morphology, growth, and rupture of brain aneurysms is not well understood.

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There is significant controversy regarding the mechanisms responsible for growth and ultimate rupture of cerebral aneurysms. The controversy can be divided into two main schools of thought: high flow effects and low flow effects [1]. In each theory, the hemodynamic environment within the aneurysm interacts with the cellular elements of the wall to result in a weakening of the wall. Therefore, aneurysm growth is thought of as a passive yield to blood pressure and reactive healing and thickening of the wall with increasing aneurysm diameter. The distinguishing feature between the two schools of thought is in the mechanisms responsible for wall weakening. The high flow theory focuses on the effects of elevation of wall shear stress (WSS), which can cause endothelial injury and thus initiate wall remodeling and potential degeneration. On the other hand, the low flow theory points to low flows within aneurysms as causing localized stagnation of blood flow against the wall in the dome, which causes a dysfunction of flow-induced nitric oxide and triggers inflammation processes that lead to wall degradation.

The importance of considering patient-specific geometries in studies of the mechanisms of formation, progression, and rupture of cerebral aneurysms has been pointed by a number of researchers [2, 3]. This paper reviews investigations on the hemodynamics role in these mechanisms based on patient-specific computational fluid dynamics (CFD).

2. INITIATION

Studies based on clinical observations and animal models of cerebral aneurysms have demonstrated that cerebral aneurysms tend to occur at sites of complex arterial geometries such as curved vessels and bifurcations. *In vitro* and computational models of curved cerebral arteries and bifurcations based on idealized geometries have demonstrated increased hemodynamic stresses at these sites.

With the development of image-based CFD techniques to model blood flows in patient-specific geometries, a variety of studies have focused on the analysis of the hemodynamic environment at locations where cerebral aneurysms commonly form. For instance, using patient-specific information from normal subjects, models of the cerebral circulation at the level of the circle of Willis have been constructed [4, 5]. These models demonstrated high WSS levels at locations where aneurysms are typically found such as the apex of asymmetric bifurcations or arteries with high curvatures. More recently, Baek *et al.* [6] constructed four patient-specific models of supraclinoid internal carotid arteries with posterior communicating artery infundibulae or aneurysms. They observed that typically the flow impinges at the distal wall of the infundibulum and creates a region of elevated pressure surrounded by a band of high WSS. At the proximal end of the infundibulum, another stagnation area is formed characterized by low WSS and high oscillatory shear index (OSI) (Table I). They suggested that the impingement region seems to coincide with the locations of the rupture of infundibulae or progression to aneurysms. In a series of studies using a combination of animal modeling, histopathology, and CFD, Meng *et al.* found that a combination of high WSS and high positive WSS gradient were associated with vascular and molecular changes that predispose the arterial wall for aneurysm development [7].

Other authors have created patient-specific models of cerebral arteries with aneurysms from three-dimensional (3D) images and then artificially deleted the aneurysm to represent the parent artery before the formation of the aneurysm. This has allowed them to study the local hemodynamic environment at the exact location where an aneurysm is known to have formed. Using this approach Mantha *et al.* [8] studied the hemodynamics at the location of three paraclinoid aneurysms and observed relatively low and rotating WSS at the aneurysmal sites. On the basis of these observations they proposed an aneurysm formation indicator (AFI) related to the angle between the instantaneous WSS vector and the time-averaged WSS direction (Table I). A different index called the gradient oscillatory number (GON) (Table I) was later proposed by a different group as a marker for aneurysm initiation [9]. This factor attempts to quantify the temporal fluctuations of the spatial gradient of the WSS vector. Using the patient-specific geometry of a side wall paraclinoid aneurysm, Shimogonya *et al.* [10] studied the hemodynamic conditions at the aneurysm location after removal of the aneurysm. In addition to their proposed factor (GON) they considered peak systole WSS, time-averaged WSS, time-averaged WSS gradient, oscillatory shear index (OSI), and AFI, and found that only elevated GON correlated with the aneurysm formation site. Subsequently, Ford *et al.* [11] proposed an objective method to artificially remove aneurysms from patient-specific models, and used it to study five side-wall cerebral aneurysms. In this study they observed an association between elevated GON and the site of aneurysm formation in four of the five aneurysms. However, they also observed elevated values of the GON factor at nonaneurysmal sites. Additionally, they pointed out that it remains to be demonstrated that this approach yields a faithful representation of the parent artery before the formation of the aneurysm. More recently, Singh *et al.* [12] used a similar approach to investigate the effect of smoking on the hemodynamic conditions at two aneurysmal sites after aneurysm removal. They observed that under physiologic conditions corresponding to hypertension or smoking (higher blood viscosity), the regions of elevated WSS found at aneurysmal sites increased their area and maximal WSS, while OSI did not change. Thus, they suggest that this may explain the increased risk of aneurysm development in the smoker population.

A more recent contribution on the study of aneurysm initiation by Kulcsar *et al.* [13] included three cases of patients subjected to three-dimensional digital subtraction angiography (3D DSA) prior to developing an aneurysm (i.e., *de novo* aneurysms). This provided the opportunity to analyze flow conditions on vessel geometries before the actual development of the aneurysm (although in one case there was a small lobe that eventually developed to an 8-mm aneurysm). They found that the regions where the aneurysms eventually emerged were subjected to significantly increased WSS compared with the parent artery average, accompanied by an increased positive spatial wall shear stress gradient. This suggests that the combination of these two hemodynamic factors may play a role in aneurysm initiation. However, the authors conceded that the small sample size and the lack of comparison to similar geometries on healthy vessels limit the generality of their observations.

3. GROWTH

Only a few studies of the patient-specific hemodynamics in growing cerebral aneurysms longitudinally followed with 3D imaging have been carried out. This is a challenging task because typically most aneurysms are preventively treated and only a few, which are considered to carry a low rupture risk, are conservatively observed. In one such studies, Jou *et al.* [14] analyzed two fusiform basilar artery aneurysms of similar sizes that were followed for 2 years with MRI. One grew significantly over the observation period while the other remained stable. The regions of aneurysm growth were identified by manually coregistering consecutive vascular models and computing the distance between them. They reported abnormally low WSS values in the area of aneurysmal growth and that the flow patterns did not change during the observation period. Similarly, Bousset *et al.* [15] analyzed seven growing cerebral aneurysms also longitudinally followed with MRA. To quantitatively compare the wall deformation and WSS, they regularly distributed 100 square patches of 1 mm² on the surface of each aneurysm and computed the average aneurysm deformation and mean WSS over each patch. Then, they correlated the mean deformation and the inverse of the mean WSS of all patches from all aneurysms, and again concluded that aneurysm growth occurs at regions of abnormally low WSS. In contrast, Sforza *et al.* [16] presented a preliminary study of a series of five growing intracranial aneurysms longitudinally followed with computed tomography angiography (CTA), in which they observed that in general the aneurysm regions that grew had on average larger WSS than the nongrowing regions. In addition, they demonstrated that contacts with different types of tissue and/or bone structures neighboring the aneurysm (i.e., the perianeurysmal environment) can significantly affect its evolution by changing not only the geometry of the aneurysm but also of the parent artery, which in turn can substantially alter the aneurysmal hemodynamics. They concluded that studies of aneurysmal evolution must consider possible contacts with extra-vascular structures of the surrounding environment.

Using an approach similar to the studies of aneurysm initiation, an investigation of the hemodynamic conditions at sites of secondary aneurysm lobulations or blebs (a lobe or daughter sac with a well defined neck protruding from the main aneurysmal sac) was carried out using a total of 20 patient-specific aneurysm models harboring 30 blebs [17]. The blebs were artificially deleted from the aneurysm to approximate its geometry prior to the development of the blebs. The results indicate that most blebs tend to occur at or adjacent to regions previously exposed to high WSS associated to the impaction of the inflow jet and typically aligned with the main aneurysmal flow stream. They also showed that once the blebs form they progress to a state of low WSS and develop counter circulation vortices. The authors then suggested that locally elevated WSS may contribute to focalized wall damage leading to the formation of the blebs and possibly rupture.

Because previous studies have shown that aneurysm rupture is not a purely mechanical process, but the result of an insult on the aneurysmal wall by abnormal hemodynamic factors leading to its weakening [1,18], several researchers have focused on the development of computational models of aneurysmal growth. Some researchers [19–21] have developed multicomponent models of the vascular wall coupled to models of wall degradation, growth, and remodeling. Others have focused on coupling the wall biomechanics to different

hemodynamic quantities (typically abnormally high or low WSS or WSS gradients) through models of wall degradation, growth and remodeling [22–24]. The majority of these models have been tested on idealized arterial geometries to demonstrate their ability to develop aneurysms. Only recently, Shimogonya *et al.* [25] conducted a study of aneurysm formation and growth in a patient-specific geometry and concluded that saccular aneurysms can develop if the GON factor is linked to proliferation mechanisms but not when assuming only strength degradation of the wall.

4. RUPTURE

As mentioned in the introduction, the patient-specific vascular geometry has been recognized as a key factor determining the aneurysmal hemodynamics. In particular, Castro *et al.* [26] emphasized the importance of properly modeling the geometry of the proximal parent artery. They showed that if the vascular models are truncated too close to the aneurysm, the secondary swirling flows that determine the inflow pattern into the aneurysm may not be properly captured. This can result in shifting the flow impaction zone and associated region of high WSS from the aneurysm body or dome towards the neck, as happens in most idealized geometries. This can have important implications for mechanisms of aneurysmal rupture.

Several studies have focused on the analysis of a series of aneurysms using image-based CFD to compare hemodynamic characteristics between ruptured and unruptured aneurysms with the objective of identifying possible hemodynamic variables that could be used to stratify rupture risk, and at the same time improve our understanding of the mechanisms leading rupture. On the basis of observations made during some of these studies, some authors seem to favor the low flow theory of aneurysm growth and rupture, while others seem to favor the high flow theories.

For instance, Shojima *et al.* [27] conducted a study of 20 middle cerebral artery aneurysms based on computed tomography angiography (CTA) data and made some interesting observations: the maximum WSS tended to be located at the neck of the aneurysms, and was on average four times larger than the average WSS in the parent artery, but the mean aneurysmal WSS was lower than the average WSS in the parent artery. They also reported that the WSS at the tip of ruptured aneurysms were markedly low, and concluded that in contrast with the pathogenic effects of high WSS, low WSS may facilitate growth and trigger aneurysm rupture. Later, Valencia *et al.* [28] carried out a study using 34 patient-specific models of saccular aneurysms. They observed a wide range of flow structures, and found a relationship between the mean aneurysmal WSS and the aneurysm area index (aneurysm area divided by area of inflow artery) for both ruptured and unruptured aneurysms. They also reported that the area of the aneurysm under low WSS was on average larger for ruptured than unruptured aneurysms. Likewise, Jou *et al.* [29] studied the hemodynamics in 26 patient-specific geometries of internal carotid artery aneurysms. They compared the WSS at end diastole of 8 ruptured and 18 unruptured aneurysms and found that both groups had similar maximum WSS, but ruptured aneurysms had a larger portion under low WSS, and concluded that for aneurysms in this location, the area of low WSS is associated with rupture. They also showed that the mean aneurysmal WSS is a function of

the aneurysm area. More recently, Tremmel *et al.* [30] created patient-specific models of one sidewall and one terminal aneurysm, which were modified to study the relationship between aneurysm-to-parent vessel size ratio and hemodynamics patterns. They found that aneurysms with small size ratio consistently demonstrated simple flow patterns with a single aneurysmal vortex, while aneurysms with larger size ratios presented multiple vortices and complex flow patterns. They also showed that the aneurysm area that was exposed to low WSS increased with increasing size ratio, and concluded that these results provide support to a previously reported correlation between size ratio and rupture risk.

On the other hand, in a study that included 62 patient-specific models of cerebral aneurysms Cebal *et al.* [31] proposed a qualitative characterization of intra-aneurysmal hemodynamic patterns. They observed a wide variety of flow characteristics and suggested that ruptured aneurysms were more likely to have concentrated inflow jets, small flow impingement regions, and complex and unstable flow patterns than unruptured aneurysms. However, only small impingement reached a statistically significant association with rupture. Interestingly, a recent study explored the relationship between WSS and flow impingement [32] in a patient-specific CFD model of a giant aneurysm at the internal carotid artery. The authors define an impingement index related to the WSS gradient to evaluate the timing and size of flow impingement. They found the maximum WSS to be proportional to the impingement index, but the area of high wall shear was not proportional to the size of impingement. In another study, Hassan *et al.* [33] analyzed the hemodynamics in 53 patient-specific aneurysm geometries. Wide-necked aneurysms or those with wide-caliber draining vessels were found to be high-flow lesions that tended to rupture at larger sizes. In contrast, small-necked aneurysms or those with small-caliber draining vessels were found to be low-flow lesions that tended to rupture at smaller sizes. They argued that in high-flow aneurysms the corresponding high WSS may be the predominant contributing factor to aneurysmal growth and subsequent rupture. In low-flow aneurysms, however, blood velocity and WSS may not be the dominant factors for rupture. Instead, they argue, intra-aneurysmal pressure and gradual wall expansion together with flow stasis may be the main factors contributing to growth and rupture. Additionally, they compared the CFD results to surgical observations of the rupture point, and concluded that the ruptured area corresponded to the area facing the blood flow that enters the aneurysm. This area is characterized by high maximal WSS in the area hit by the stream, which may be one cause of aneurysm rupture at this location. Subsequently, Chien *et al.* conducted two studies, one [34] using six and the other [35] using eight patient-specific models of aneurysms of similar sizes occurring at a single location (origin of the ophthalmic artery in the internal carotid artery). They observed that most ruptured aneurysms had complex flow structures while all unruptured aneurysms had a single vortex. They also found higher and more inhomogeneous WSS distributions in ruptured aneurysms. They concluded that flow characteristics may change even if aneurysm sizes and locations are similar. In another study that included 24 aneurysms at different locations [36] they showed that WSS and aneurysmal inflow rate changed with location, being higher in middle cerebral arteries and lower in basilar and anterior communicating arteries.

In another study, Ohshima *et al.* [37] constructed two patient-specific terminal aneurysms, and showed that slightly shifting the aneurysm offline towards one branch created a region of intra-aneurysmal flow separation, and that this type of slightly asymmetric placement of the aneurysm was more commonly found within ruptured aneurysms in a series of 46 angiograms. Later, two studies were carried out using 26 patient-specific models of anterior communicating artery aneurysms [38] and 42 models of terminal aneurysms [39], respectively. Both studies showed that on average ruptured aneurysms had higher maximal WSS than unruptured aneurysms, and that asymmetric flow patterns splitting from the parent artery into the aneurysm and daughter arteries were more common among ruptured aneurysms and produced higher WSS than more symmetric flow structures.

As in studies relating geometric indices and aneurysm rupture, all these studies suffer from a common limitation: the geometries of ruptured aneurysms are reconstructed from images obtained after the ruptures. The geometry of an aneurysm may change after rupture; however, all these studies assume that the changes are small enough so that hemodynamic characteristics derived from these geometries are representative of the hemodynamics environment immediately prior to rupture. To test this assumption, two cases studies were carried out on two cerebral aneurysms that were imaged immediately prior to their rupture. In one case the aneurysm was a fusiform basilar artery aneurysm [40], and the other was a terminal saccular aneurysm at the basilar tip [41]. It was found that both aneurysms had flow patterns consistent with characteristics previously associated with aneurysm rupture, namely, they had concentrated inflow jets, small impingement regions, complex and unstable flow structures, and in the case of the terminal aneurysm, asymmetric flow division.

In a recent work, Xiang *et al.* [42] studied a large population of 119 intracranial aneurysms to identify significant hemodynamic and morphologic parameters related to rupture. They found that most ruptured aneurysms had complex flow patterns with multiple vortices. On the other hand, most unruptured aneurysms had simple flow patterns with a single vortex. WSS was lower within ruptured aneurysms than in their parent arteries, but there was no difference for unruptured aneurysms. Furthermore, ruptured aneurysms had lower WSS magnitudes and larger areas of low WSS than unruptured aneurysms. In addition, OSI was higher on ruptured aneurysms. The authors identified size ratio [43], WSS, and OSI as independently significant variables to discriminate rupture using multivariate logistic regression analysis.

More recently, Cebal *et al.* [44] conducted a larger study comparing qualitative hemodynamic characteristics of rupture and unruptured aneurysms on a patient population comprising 210 intracranial aneurysms. Extending previous results, they showed that ruptured aneurysms were statistically more likely to have concentrated inflow streams, small impingement regions, complex and unstable flows than unruptured aneurysms. Subsequently, Cebal *et al.* [45] defined a number of hemodynamic measures that attempt to capture these characteristics and showed that ruptured aneurysms were more likely to have higher maximal WSS, more concentrated WSS distributions, and more concentrated inflow patterns. In contrast, they observed that the area under low WSS was not statistically different between ruptured and unruptured aneurysms. Additionally, they showed that these

associations were largely independent from the physiologic conditions. Therefore, this work is in agreement with Xiang *et al.* [42] on complex flows being associated with rupture but disagrees on its relation to WSS. This fact does not necessarily mean there is a profound contradiction. There is no standard definition of ‘low’ and ‘high’ WSS variables, for example Xiang *et al.* defined high WSS as the maximum WSS averaged during the cardiac cycle and normalized by the parent vessel WSS, while Cebal *et al.* defined it as the maximum WSS value at peak systole, which makes very difficult a meaningful comparison of their results.

5. CONCLUSIONS

The development, progression, and rupture of cerebral aneurysms are complex multifactorial processes that are still not well understood. It is generally accepted that hemodynamics plays a fundamental role in these processes. However, there is still no consensus about which hemodynamic variables are implicated in these mechanisms. Because hemodynamics strongly depends on the vascular geometry, better understanding the interaction between hemodynamic loading and mechano-biological wall responses that govern the natural history of cerebral aneurysms requires investigations of the *in vivo* aneurysmal hemodynamics environment. Image-based CFD is capable of realistically representing this hemodynamics environment, and therefore it can be used to relate hemodynamic characteristics and aneurysm initiation, growth and rupture. Thus, patient-specific CFD constitutes a promising approach for studying these complex mechanisms and can potentially be used to assess rupture risk, and therefore has a great potential for clinical use in the diagnosis and treatment of this disease.

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Table I

Definition of different hemodynamic quantities proposed to evaluate possible initiation site of aneurysms. All temporal integrations are calculated over the cardiac cycle T .

Quantity	Definition	Notes
OSI	$\frac{1}{2} \left\{ 1 - \frac{ \int_0^T \mathbf{f}_i dt }{\int_0^T \mathbf{f}_i dt} \right\}$	f_i is the instantaneous wall shear stress
AFI	$\frac{\mathbf{f}_i \cdot \mathbf{f}_{av}}{ \mathbf{f}_i \mathbf{f}_{av} }$	f_{av} is the time averaged wall shear stress
GON	$\frac{1}{2} \left\{ 1 - \frac{ \int_0^T \mathbf{G} dt }{\int_0^T \mathbf{G} dt} \right\}$	$\mathbf{G} = \left(\frac{\partial f_p}{\partial p}, \frac{\partial f_q}{\partial q} \right)$ is the spatial wall shear stress gradient, where the p -direction corresponds to the time-averaged direction of the \mathbf{f} vector over the flow cycle and the q -direction is perpendicular to p .