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【Review Paper】

Computational and experimental studies into the hemodynamics of cerebral aneurysms

Yuji SHIMOGONYA* and Shunichi FUKUDA**
*Frontier Research Institute for Interdisciplinary Sciences, Tohoku University
6-3 Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan
E-mail: yujish@pfsl.mech.tohoku.ac.jp
**Department of Neurosurgery, National Hospital Organization Kyoto Medical Center
1-1 Mukaihata-cho, Fukakusa, Fushimi-ku, Kyoto 612-8555, Japan

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Abstract
Rupture of cerebral aneurysms (CAs) is a major cause of life-threatening subarachnoid hemorrhage. It is still difficult to predict CA rupture since little is known about the risk factors. Although the mechanism of development, enlargement and rupture of CAs remains unclear, a series of pioneering investigations using animal models of experimentally induced CAs have revealed that hemodynamics are significant in the development of CAs. There have been a number of investigations into the hemodynamics of CAs, which have provided insight into the mechanisms of CA formation. Here, we review experimental and computational work in this field. We first introduce animal models of experimentally induced CAs and studies into the role of hemodynamic stress in the formation of CAs. We also discuss the animal model-based studies on biochemical contributors to CA induction at the cellular and molecular level. We go on to describe hemodynamic studies of CAs using computational fluid dynamics (CFD), including patient-specific CFD models of blood flow, the non-Newtonian viscous nature of blood, and the elastic properties of vessel walls, as well as boundary conditions for CFD simulations. Finally, we review computational studies into risk factors for the development, enlargement and rupture of CAs, and discuss endovascular treatments.

Key words : Cerebral aneurysm, Hemodynamics, Wall shear stress, Animal model, Computational fluid dynamics

1. Introduction

Rupture of cerebral aneurysms (CAs) is a major cause of life-threatening subarachnoid hemorrhages. CAs occur in approximately 1.9–5.2% of adults (Thompson et al., 2015), and the annual rate of CA rupture is approximately 1% (The UCAS Japan Investigators, 2012), and it appears that there may be a subgroup of CAs that are particularly prone to rupture. There are no effective therapeutic drugs to treat CAs, and the only effective treatments are more invasive surgical interventions; i.e., surgical clipping with craniotomy and endovascular coil embolization. It is therefore important to identify aneurysms that are prone to rupture. However, predicting CA rupture is still a difficult task, in part due to a lack of information on the risk factors. According to American Heart Association Guidelines for unruptured CAs, PHASES score, and the Unruptured Cerebral Aneurysm Study of Japan (UCAS Japan), the risk factors for the development, enlargement and/or rupture of CAs are as follows: smoking, hypertension, a prior history of subarachnoid hemorrhage, a family history of CAs, genetic diseases (including autosomal dominant polycystic kidney disease), multiple CAs, ethnicity (including Japanese and Finnish), the site and size of the CA, a tendency toward enlargement, and the existence of a daughter sac (Greving et al., 2014; The UCAS Japan Investigators, 2012; Thompson et al., 2015). Most of these risk factors may be closely associated with an enhancement of vulnerability of the cerebral artery, or with an increase in the hemodynamic stress in the circle of Willis (or both). For example, hypertension may contribute to both via direct damage to the arterial wall, increased hemodynamic stress due to increased blood pressure, and accelerated asymmetry of the circle of Willis because of atherosclerotic changes. Hereditary diseases and a family

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history of CAs may be involved in congenital vulnerability of the cerebral artery (Schievink et al., 1994). The relationships between the rate of rupture and location and size of the aneurysm, as well as bleb formation, appear to depend on the spatial distribution of hemodynamic factors.

Hemodynamic involvement in CA formation has been empirically observed. CAs are usually located at the bifurcation of the circle of the Willis, and are most commonly induced in the asymmetric circle of Willis (Kayembe et al., 1984). Unilateral internal carotid artery (ICA) occlusion may lead to aneurysm of the anterior communicating artery (Acom) due to a compensatory increase in blood flow (Waga et al., 1978). Asymmetrical geometries of the anterior cerebral arteries are closely associated with Acom aneurysm formation (Kaspera et al., 2014). Furthermore, increased hemodynamic values due to the existence of arteriovenous malformations often lead to CA induction in the feeder of the malformation and surgical removal of the malformation resulting in hemodynamic normalization can resolve a CA (Redekop et al., 1998). CAs that are difficult to treat with common surgical therapies can be cured with flow reduction of the parent artery (Miyamoto et al., 2010). Therefore, in addition to a systemic rise in hemodynamics (i.e., hypertension), a local increase in hemodynamic stress due to a disturbance of the asymmetric circle of Willis is a key factor in the development of CA.

Quantifying the spatial and temporal patterns of hemodynamic stress, such as wall shear stress (WSS), may improve our understanding of the role of hemodynamics in the pathogenesis of CAs. However, animal models remain problematic for measuring the WSS due to their small sizes. Recently, progress has been made in phase-contrast magnetic resonance imaging (PC-MRI) as a tool to analyze the dynamics of blood flow, and it has been applied to visualize *in-vivo* intra-aneurysmal flow and even WSS distributions (Naito et al., 2012). However, it remains challenging to use this novel technique to quantify accurately the WSS at the aneurysmal wall. The combination of medical image-based geometry construction techniques and computational fluid dynamics (CFD) has recently emerged as a powerful tool to quantify hemodynamics in large arteries, and can be used to investigate the pathogenesis of CAs.

In this review, we focus on hemodynamics and their association with the development, enlargement and rupture of CAs. We first briefly outline animal models of experimentally induced CAs, indicating the involvement of hemodynamics in CA formation, and then introduce related hemodynamic studies using the animal models. We also discuss the animal model-based studies on biochemical contributors to CA induction at the cellular and molecular level. Recent advances in computational hemodynamic studies of CAs using CFD are then introduced. We discuss the standard methods, assumptions, and limitations of CFD applied to hemodynamic problems. Finally, CFD applications to investigate hemodynamic risk factors for the development, enlargement and rupture of CAs are reviewed, as well as endovascular treatment of CAs.

2. Experimental approaches

2.1 Animal models of experimentally induced CAs

There have been reported a few animal models of experimentally induced CAs. Animal models typically accomplish experimentally induced CAs either by drug-induced vulnerability in the cerebral artery, or an increase in the hemodynamics in the circle of Willis, or both.

Hashimoto et al. first developed an animal model of experimentally induced CAs, which remains the most popular technique (Hashimoto et al., 1978). To make the cerebral vessels vulnerable, beta-aminopropionitrile (BAPN) was administered to rats, which can selectively diminish connections between vascular collagen and elastin. Renal hypertension, a systemic enhancement of hemodynamics, was induced by drinking water including 0.5% NaCl, and via ligation of the posterior branch of both renal arteries. Ligation of the unilateral common carotid artery may induce an increase in blood flow in Acom and bifurcation of the ipsilateral side of the anterior cerebral artery and olfactory artery (i.e., a local increase in the hemodynamics in the circle of Willis), which may induce a CA in these areas. Hashimoto et al. reported that renal hypertension and ligation of the carotid artery (even without BAPN) led to CA development, although BAPN increased the frequency of aneurysm induction (Hashimoto et al., 1979a). Therefore, CAs can be induced in normal animals only via enhanced hemodynamic stress, suggesting that an increase in hemodynamic stress due to disturbed hemodynamics in the asymmetric circle of Willis is a key aspect of CA development. Since these induced CAs resemble the pathophysiology of human CAs, as well as the location (Hashimoto et al., 1979b), they have been accepted as good models for the study of the pathogenesis of human CAs. It has also been reported that CAs could

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be experimentally induced in monkeys, which have greater anatomical similarity to humans (Hashimoto et al., 1987).

Meng et al. developed a rabbit model of experimentally induced basilar artery (BA) aneurysms via bilateral common carotid artery ligation, and reported a series of work on the mechanism of CA formation, including CFD investigations (Meng et al., 2007; Gao et al., 2008). A mouse model of experimentally induced CAs was developed via stereotaxic injection of elastase into the cerebrospinal fluid at the basal cistern together with hypertension induced by angiotensin-II infusion (Nuki et al., 2009). Since the most common locations of CAs induced via this method differ from those in human saccular CAs, this model is of questionable merit for studies into CA development. However, it is useful for research into CA rupture because of the high rate of rupture of induced CAs. These authors suggested that the local renin–angiotensin system is involved in CA rupture, and that this is independent of a rise in blood pressure (Tada et al., 2014). There exist several animal models of experimentally induced extracranial saccular aneurysms due to elastase injection or via surgery, which are commonly used in the development of endovascular devices (Shi et al., 2016).

2.2 Studies on hemodynamic stress in CA formation using animal models

It has been shown that vascular endothelial cells sense blood flow, rather than blood pressure. For example, the vascular endothelial cells sense the WSS caused by blood flow, and in response changes in the vascular structure occur, along with the release of various substances in response to WSS, which regulates blood flow (Davies, 1995). Pathophysiological examinations by Hashimoto et al. indicated that early phase CA development (such as endothelial degeneration and disappearance of internal elastic lamina) occurs almost exclusively at the distal side of the major branch adjacent to the apex, and aneurysmal bulging was observed in this area (Hazama et al., 1986). Moreover, their hemorheological studies, which included numerical analyses of latex particle paths and used experimentally induced CA in rat specimens and in living rats, showed that the WSS increased and was greatest in the same area during the early phase of CA development (Nakatani et al., 1991, 1993). Thus, these data suggest the importance of an increase in WSS in CA formation.

Accordingly, it appears that vascular endothelial cells may sense excessively high levels of WSS-related hemodynamic stress (i.e., above normal physiological limits), which initiates several mediators that damage vascular wall components, leading to arterial wall degeneration and subsequent development of CA. In this manner, WSS mechanotransduction mechanisms in the vascular endothelium may trigger CA formation. Inducible nitric oxide synthase (iNOS) is induced by various stimuli and leads to high levels of NO, which is associated with tissue degeneration (Geng et al., 1992). Fukuda S. et al. reported that iNOS is induced in both rat and human aneurysm neck in the early phase of CA development, and that either iNOS inhibition or WSS reduction (or both) can decrease the incidence of CA formation following aneurysm-inducing surgery in rats (Fukuda S. et al., 2000).

Several other studies have also suggested that increased WSS may be important in the initiation of CAs. Nam et al. suggested using a microfluidic system whereby morphological variations in the circle of Willis contribute to CA formation resulting from increased WSS (Nam et al., 2015). CA susceptibility is correlated with the magnitude of the WSS, as well as with a positive WSS gradient (Alfano et al., 2013). Metaxa et al. suggested that high WSS and a positive WSS gradient are important using CFD and experimentally induced BA aneurysms in rabbits (Metaxa et al., 2010). They found that damage to the internal elastic lamina occurred 100% of the time at locations where the WSS was > 122 Pa and the WSS gradient was > 530 Pa/mm. These data suggest the existence of normal physiological limits for the magnitude of the WSS.

Small WSS (below normal physiological levels) appears to prevent normal bioactivity of vascular wall cell components, leading to an increase in vulnerability of the wall, such as atherosclerotic changes (Davies, 1995). In contrast to high WSS at the distal side of the major branch adjacent to the apex and at the neck of CA, which leads to arterial degeneration during progression from normal arterial wall to CA development, low WSS at the dome of CA may make the CA wall more vulnerable, leading to CA enlargement and bleb formation, and eventually to rupture. There may well exist at least these two stages, and WSS-associated disturbed flow may be significant in both.

2.3 Studies on biochemical contributors to CA development using animal models

Morimoto et al. and Hashimoto et al. established an animal model of experimentally induced CAs in mice, which

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enabled them to examine the role of specific genes on the development of CAs via the use of genetically modified animals (Morimoto et al., 2002). P2X4 purinoceptor is a vascular endothelial shear stress sensor, and is a major contributor to ATP- and flow-induced Ca^{2+} influx in endothelial cells (Yamamoto et al., 2006). Here, Ca^{2+} activates signal transduction pathways that evoke several cellular responses, including NO-dependent vascular dilatation. Fukuda M. et al. indicated that the frequency of aneurysm induction following CA-inducing surgery in P2X4 purinoceptor knockout mice was significantly lower than that in wild type mice. They also found that the expression levels of biochemical contributors to CA induction, including iNOS, monocyte chemoattractant protein-1 (MCP-1), cathepsin L and COX-2, in the arterial wall were significantly reduced in P2X4 purinoceptor knockout mice (Fukuda M. et al., 2014). This strongly suggests that disruption of the shear-sensor suppresses WSS mechanotransduction, leading to reduced expression of the biochemical contributors and reduction of CA development. Inhibitors of the shear-sensor may therefore be targets for clinical prophylaxis against CA formation.

Because disruption of P2X4 purinoceptor did not completely inhibit CA formation in mice, there may exist other endothelial shear sensors associated with CA development. Based on our CFD analyses, as well as a high magnitude of WSS, WSS-associated disturbed flow may be important in vascular endothelial mechanotransduction (Fukuda S. et al., 2014). However, the mechanism of sensing disturbed flow remains unclear. In addition to WSS, stretch is also reported to be an important vascular mechanosensing mechanism (Chatterjee et al., 2015), which may be involved in CA formation.

Aoki et al. used Hashimoto et al.'s animal model of experimentally induced CAs in rats and mice, and reported a series of work on the expression of various kinds of biochemical contributors to CA induction, including tumor necrosis factor (TNF)-α, nuclear factor-κB, matrix metalloproteinase-2 and -9, prostaglandin E2, MCP-1, interleukin-1beta, cathepsin B, K and S (Aoki et al., 2007, 2008a, 2008b; Fukuda M. et al., 2015). They found active inflammatory responses in the human CA, including macrophage infiltration and expression of various cytokines, and proposed that CAs may be regarded as a chronic inflammatory disease (Fukuda M. et al., 2015). They reported that nuclear factor-κB is activated in the arterial walls during early phase CA formation, leading to the induction of MCP-1 and subsequent recruitment of macrophages. The macrophages produce large quantities of cytokines and proteinases, and exacerbate the inflammation associated with CA formation. Other authors suggested that localized matrix degradation and cell apoptosis during the early phase of CA development results from intrinsic mural cells, but not inflammatory cells (Kolega et al., 2011). Recently, deficiency of the transcription factor Sox17 was suggested as a potential genetic factor for CA formation (Lee et al., 2015).

Statins have a pleiotropic anti-inflammatory effect (i.e., anti-NF-κB). Aoki et al. reported that the statin simvastatin prevented CA formation in rats (Aoki et al., 2008a). On the basis of their experimental results, a case-control study was undertaken to investigate the association between statin use and CA rupture risk in Japan, suggesting an inverse relation between use of statins and CA rupture (Yoshimura et al., 2014).

3. Computational approaches

3.1 Patient-specific CFD modeling of blood flows

Over the past decade, remarkable progress has been made in the hemodynamic study of CAs using CFD, including both idealized and anatomically realistic models. A large number of hemodynamic CFD studies have been reported, and here we focus on CFD studies with anatomically realistic vessel geometries, which are extracted from medical images.

The combination of image-based geometry construction techniques and CFD has been widely accepted as a powerful tool to investigate blood flow phenomena and arterial diseases in the human circulatory system that are related to hemodynamics. Such patient-specific CFD modeling techniques for blood flow simulations were pioneered in the late 1990s and early 2000s (Milner et al., 1998; Taylor et al., 1999; Steinman et al., 2003). Milner et al. reported a noninvasive MRI protocol that can be used to reconstruct three-dimensional (3D) models of the carotid bifurcation lumen and to acquire patient-specific flow rate waveforms (Milner et al., 1998). The carotid bifurcation models were reconstructed from serial black-blood MRI images, and the flow rates at the common and internal carotid artery were determined from PC-MRI to impose patient-specific velocity boundary conditions. The velocity field, WSS magnitude, WSS oscillation, WSS temporal gradient and WSS spatial gradient were then computed using an in-house CFD solver. The results showed that the WSS patterns computed using patient-specific carotid bifurcation models markedly differed

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from those obtained from a conventional idealized model. Steinman et al. were the first to demonstrate a patient-specific computational simulation of the blood flow dynamics of the CA (Steinman et al., 2003). The lumen geometry of a giant internal carotid artery-posterior communicating artery aneurysm was reconstructed from computed rotational angiographic data using a 3D discrete dynamic contour, which was based on an analogy with an expanding balloon. Pulsatile flow rates acquired at the right internal carotid artery of another volunteer were used to impose the inlet boundary conditions for CFD simulation, because of the lack of patient-specific flow rate measurements. Flow simulations using an in-house CFD solver revealed high-speed flow entering the aneurysm and dynamic patterns of WSS. The features of the flow that were calculated using CFD were consistent with the configuration of subsequent coil compaction. These authors successfully presented the first prospective CFD study on patient-specific aneurysm hemodynamics, creating a trend followed by many researchers in this field. Moreover, Antiga et al. also developed medical image-based modeling tools for patient-specific CFD simulations; i.e., the vascular modeling toolkit (VMTK) (Antiga et al., 2008), which has been applied in numerous analyses in this field (Ford et al., 2009; Piccinelli et al., 2011).

3.2 Non-Newtonian viscous nature of blood and elastic material properties of vessel walls

There are several important characteristics that should be considered when simulating arterial blood flow. These include the non-Newtonian viscous nature of the blood, and the elastic material properties of the vessel walls. Two of the most frequently used non-Newtonian blood models are the Casson model and the Carreau–Yasuda model. A number of studies on the effect of the non-Newtonian viscous nature on the large-artery hemodynamics have been carried out by comparing computed results between non-Newtonian and Newtonian models (Perktold et al., 1991; Cebral et al., 2005; Lee et al., 2007). The results show that the use of a Newtonian model appears to be reasonable for simulating blood flow in large arteries.

According to the treatment of the vessel walls, simulation models of blood flow in large arteries can be categorized as either rigid or deformable. In rigid models, the vessel wall is assumed to be rigid and is treated as only a boundary surface with zero thickness. In deformable models, the vessel wall is treated as a structure with a finite thickness, and its material properties (such as elasticity) are taken into account. The use of the deformable models requires additional formulations and implementations to describe the fluid–structure interaction (FSI), leading to greater computational expense. The FSI should be taken into account to investigate the hemodynamics of the heart and cardiovascular system (Sugiura et al., 2012), which exhibits large deformations of the vessel wall. Rigid models have been widely used for investigating the hemodynamics in the cerebrovascular system. This is reasonable because, in the cerebrovascular system, radial changes due to deformation of vessels as a result of pulsation are relatively small. It has been reported that the overall hemodynamics of CA do not change significantly when incorporating wall deformation (Dempere-Marco et al., 2006); however, some authors have applied FSI algorithms to blood flow problems of CAs (Oshima et al., 2006; Torii et al., 2007; Takizawa et al., 2013), and the differences in computed hemodynamic metrics between rigid and deformable models were also quantified. Bazilevs et al. reported that rigid wall simulations overestimated the WSS magnitude of CAs compared with deformable wall simulations (Bazilevs et al., 2010). Note, however, that it is still difficult (and sometimes impossible) to obtain patient-specific information regarding the vessel wall (such as wall thickness and elasticity), and that this is required as input data in a deformable model. FSI simulations with realistic patient-specific wall properties will enable us to further discuss the impact of deformation of the vessel walls on the simulated hemodynamics.

3.3 Boundary conditions

For realistic blood flow simulations, in addition to the patient-specific arterial geometries, the patient-specific flow velocity or flow rate is also important to impose the physiological boundary conditions required for CFD simulations. The arterial geometry of each patient is closely related to its hemodynamic circumstances, since a shift in hemodynamic stress is associated with CA formation (especially disturbed hemodynamics in the heterogeneous-shaped circle of Willis (see section 2.2)). However, most hemodynamic cohort studies with CFD have substituted assumed boundary conditions rather than used patient-specific data, due to the lack of flow measurements (Shojima et al., 2004; Cebral et al., 2011; Qian et al., 2011; Xiang et al., 2011; Takao et al., 2012; Miura et al., 2013). The assumed velocity is

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usually taken from the literature or acquired from healthy volunteers.

There have been some hemodynamic studies on comparisons of simulated data between assumed and measured inlet boundary conditions. Marzo et al. examined the sensitivity of computed hemodynamic metrics (such as the WSS) to the choice of assumed or measured inlet boundary conditions (Marzo et al., 2011). The results showed that the WSS obtained under these conditions had qualitatively similar distributions on the aneurysmal wall; however, quantitatively the results differed significantly. They also showed that differences in the simulated WSS between these conditions were smaller when the WSS was normalized by the spatial average of the WSS over the aneurysmal wall, and concluded that the use of assumed inlet boundary conditions provided realistic predictions of CA hemodynamics. Considering that the WSS itself is of more interest than the normalized WSS in hemodynamic cohort studies with CFD, however, the quantitatively large differences in the simulated WSS appears to underscore the importance of using measured inlet boundary conditions. In contrast to Marzo et al., Jansen et al. reported that the choice of assumed or measured inlet boundary conditions can affect the intra-aneurysmal flow significantly, leading to large differences in the simulated WSS (Jansen et al., 2014). They concluded that patient-specific inlet boundary conditions were necessary for CFD simulations of the intra-aneurysmal flow. Moreover, we have recently found a statistically significant association between enhancement of the WSS disturbance and CA development. We observed this association when using measured inlet boundary conditions, but not assumed boundaries, which further underlines the importance of using measured inlet boundary conditions (Fukuda S. et al., 2015).

3.4 Computational studies on the development, enlargement and rupture of CAs

Many authors have continued using CFD simulations to improve our understanding of the role of hemodynamics in the development, enlargement and rupture of CAs.

There have been several studies that aimed to identify the hemodynamic factors related to the development of CAs. Using a combination of CFD and animal models of experimentally induced CAs, high WSS and a positive WSS spatial gradient have been shown to be important during early phase CA development (Meng et al., 2007; Metaxa et al., 2010; Doran et al., 2013). Kulcsár et al. also reported similar results using CFD simulations of three patients (Kulcsár et al., 2011). Shimogonya et al. proposed a potential hemodynamic metric, the gradient oscillatory number (GON), for the development of CAs (Shimogonya et al., 2009a). The GON is defined by temporal fluctuations of the WSS spatial gradient, and was designed to quantify the disturbance of the flow-induced tangential forces on the arterial wall in pulsatile flow. These authors calculated GON for a patient-specific ICA geometry using a technique of virtual CA removal (Yokoi et al., 2005; Mantha et al., 2006; Ford et al., 2009; Chen et al., 2013), which allowed them to reconstruct (approximately) the parent arterial geometry prior to the development of the aneurysm. The results showed that the GON was correlated with the location of formation of the aneurysm, suggesting that the GON may be useful as a hemodynamic metric for the development of CAs. In addition, the GON was shown to be insensitive to the variability in flow input waveform shapes (Shimogonya et al., 2012). Shimogonya et al. also performed a computational analysis of CA formation based on the GON distribution for a patient-specific arterial geometry (Shimogonya et al., 2009b).

Jou et al. reported a correlation between lumenal geometry changes and hemodynamics in fusiform CAs using CFD (Jou et al., 2005). Boussel et al. reported seven patient-specific CA models that were reconstructed from MR angiography images at two different times (Boussel et al., 2008). The local radial displacement of the wall between the two times was measured, and the WSS distributions were computed in the baseline geometries and compared with the radial displacement, which corresponded to the local growth of the aneurysm. The computed mean WSS for the area with a smaller displacement (< 0.3 mm) was 2.55 ± 3.6 Pa, and that with a larger displacement (> 0.3 mm) was 0.76 ± 1.5 Pa ($P < 0.001$). This suggests that aneurysm enlargement is associated with an abnormally small WSS. By contrast, Sforza et al. reported that the hemodynamics of growing aneurysms are characterized by non-uniform WSS distributions with areas of concentrated high WSS and large areas of low WSS (Sforza et al., 2016). In addition to magnitudes of WSS, Fukuda S. et al. suggested the important role of disturbed flow in CA enlargement (Fukuda S. et al., 2016).

There have been a number of hemodynamic CFD studies into CA rupture. Miura et al. performed CFD analysis for 106 middle cerebral artery (MCA) aneurysms (43 ruptured, 63 unruptured) reconstructed from 3D rotational angiography images, comparing morphological and hemodynamic parameters between the ruptured and unruptured groups (Miura et al., 2013). The tested morphological parameters were the aneurysm size and aspect ratio, and the

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hemodynamic parameters included the WSS, the normalized WSS (Jou et al., 2008; Xiang et al., 2011), oscillatory shear index (OSI) (Ku et al., 1985; He and Ku, 1996), WSS spatial gradient (Lei et al., 2001), GON (Shimogonya et al., 2009a) and aneurysm formation indicator (AFI) (Mantha et al., 2006). Multivariate analyses indicated that the WSS was significantly lower in the ruptured aneurysm group than the unruptured group. The other morphological and hemodynamic parameters did not show significant differences between the two groups in the multivariate analyses. Xiang et al. analyzed 119 CAs (38 ruptured, 81 unruptured) using 3D angiographic images and CFD to identify morphological and hemodynamic parameters for discriminating aneurysm rupture status (Xiang et al., 2011). They reported that a high probability of rupture was associated with lower aneurysm-averaged WSS and higher aneurysm-averaged OSI. Takao et al. evaluated hemodynamic differences between 87 unruptured and 13 ruptured CAs formed at the side-wall of the ICA or the MCA bifurcation (Takao et al., 2012). The minimum WSS was significantly lower in the ruptured aneurysms for the ICA cases. The pressure loss coefficient was significantly lower in ruptured aneurysms for both the ICA and MCA cases. Omodaka et al. examined the local hemodynamics at the rupture points of 6 MCA aneurysms. The results suggested that the location of the rupture point was related to low WSS (Omodaka et al., 2012). Cebral et al. compared the hemodynamic environments between ruptured and unruptured groups from a total of 210 CAs in 128 patients (Cebral et al., 2011). The results showed that ruptured aneurysms were more likely to have larger inflow concentrations and a larger maximum WSS, which is in contrast to the trends reported in the above studies. Thus, the results obtained so far appear inconsistent, and hence further work is required in this area.

3.5 Applications to CA therapy

CFD simulations have been successfully applied to studying the hemodynamics of CA therapies. Endovascular stent-assisted coil embolization is widely used as a therapeutic method for wide-neck CAs. Kono et al. performed CFD simulations for a no-stent model and eight different stent models deployed in a patient-specific bifurcation aneurysm geometry, which were all reconstructed from 3D images obtained using micro-computed tomography, and compared the resulting hemodynamics (Kono et al., 2013). They found that, among these configurations, kissing-Y and crossing-Y stents resulted in the largest reduction in the intra-aneurysmal flow velocity. Roszelle et al. also compared the hemodynamics among different stent models (Roszelle et al., 2013). Anzai et al. performed optimization of strut placement in stents for four different CA configurations and showed the relationship between the CA configuration and optimal strut placement (Anzai et al., 2014).

The stent placement itself is expected to affect the recurrence rate of CAs because stenting changes the surrounding arterial geometry, which may alter the hemodynamics of the CA (Kono et al., 2014; Jeong et al., 2014).

Recently, a new endovascular treatment device called a flow diverter (FD) has been reported to treat wide-neck CAs. The deployment of FD can decrease significantly the inflow rate into CA, which leads to changes in the intra-aneurysmal hemodynamic environment, and stabilizes or embolizes the CA. Ma et al. developed a high-fidelity virtual stenting technique, which was able to simulate the FD placement process in detail in patient-specific CAs (Ma et al., 2013). This advanced technique was validated via comparison with experimental data, and was used successfully to evaluate the flow-diversion performance of a dynamic push-pull technique for FDs in patient-specific CA models (Ma et al, 2014).

3.6 Future directions

Over the past decade, there has been remarkable progress in the study of the hemodynamics of CAs using CFD. In closing, we discuss some possible research directions that should be investigated over the coming decade.

Quantifying the differences in simulated hemodynamic metrics between rigid and patient-specific deformable models should be interesting. Technical developments of non-invasive imaging will be required for obtaining patient-specific information regarding the vessel wall, such as the distributions of the wall thickness and elasticity.

Prospective hemodynamic cohort studies using patient-specific boundary conditions have not yet been reported. Because the results of hemodynamics simulations vary significantly depending on the inlet boundary conditions (Xiang et al., 2014; Fukuda S. et al., 2015), the use of individual physiological data with wide inter-individual variability even among normal subjects (Ford et al., 2005) may affect the conclusions of these simulation studies. Thus, cohort studies using both patient-specific geometries and patient-specific boundary conditions are desirable to examine the details of

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hemodynamics in human CAs, and to investigate hemodynamic risk factors for the development, enlargement and rupture of CAs. To this end, we recently launched the multi-institutional prospective clinical trial "Computational Fluid Dynamics Analysis of Blood Flow in Cerebral Aneurysms: Prospective Observational Study (CFD ABO Study)", which is a National Hospital Organization collaborative clinical study (UMIN000013584). The observation period is 3 years, and 25 institutions participate in this trial. In addition to 3D-computed tomography angiography images, flow velocities are measured using a carotid ultrasound Doppler technique in all cases to obtain patient-specific physiological data.

Further developments in CFD modeling for endovascular coil embolization (Otani et al., 2013; Babiker et al., 2013) and its application to therapies in a clinical setting are expected.

Recently, high-resolution (HR) CFD simulations have revealed that flow instabilities with high-frequency fluctuations can occur at relatively low Reynolds numbers in the intra-aneurysmal blood flow (Valen-Sendstad et al., 2013; Valen-Sendstad and Steinman, 2014; Khan et al., 2015). It would be interesting to see how computed intra-aneurysmal hemodynamics derived from HR simulations are affected by HR-FSI coupling. In addition, further efforts should be made regarding hemodynamic metrics that can better describe the high-frequency fluctuations of the WSS magnitude and direction in disturbed blood flow (Peiffer et al., 2013).

Several CFD Challenges for CAs, which sought to assess the variability of CFD solutions, were organized and the results have been published (Radaelli, et al., 2008; Steinman, et al., 2013; Janiga, et al., 2015). These challenges are especially important, and the accumulated knowledge is expected to drive further progress in hemodynamic studies on CAs using CFD.

Although it is still difficult to predict the development, enlargement and rupture of CAs since we have limited information about the risk factors, there have been a number of evidence that the hemodynamics is a key aspect of CAs. The patient-specific CFD simulations are suitable for quantifying the hemodynamic environments and comparing them between normal and abnormal groups. However, the mechanism of the development, enlargement and rupture of CAs will not be clarified by CFD alone, since the hemodynamics at the blood-wall interface (i.e., vascular endothelial cells), which can be quantified by CFD, acts just as a trigger for CAs. The mechanotransduction processes of vascular endothelial cells are essential for fully understanding the pathogenesis of CAs. Thus, experiments at the cellular and molecular level and the patient-specific CFD simulations should be used in a complementary manner for clarifying the role of hemodynamics in CAs. For example, from our recent studies, a hemodynamic factor related to the pathogenesis of CAs may be localization of disturbed flow. We have indicated the importance of both WSS and flow disturbance in CAs; a high WSS with disturbed flow may be involved in CA development (Fukuda S. et al., 2015), and a low WSS with disturbed flow may be associated with enlargement and rupture of CAs (Fukuda S. et al., 2016). The latter is strongly supported by the *in-vitro* experiments conducted by Aoki et al. in collaboration with us, which show that low WSS with disturbed flow contributes to sustained expression of MCP-1 (a known contributor to CA induction), in cultured vascular endothelial cells (Aoki et al., 2016).

4. Summary

We have reviewed a number of experimental and computational studies on the hemodynamics of CAs. Animal models of experimentally induced CAs show that hemodynamics appear to be significant in the development, enlargement and rupture of CAs, and a number of related experimental studies at the cellular and molecular level have been reported. We then discussed recent advances on computational hemodynamic studies of CAs using CFD. Remarkable progress in patient-specific modeling approaches has enabled us to investigate large-scale complex hemodynamic problems using CFD. However, the hemodynamic risk factors for CA pathogenesis and recanalization in endovascular treatment of CAs remain unclear. Further work is therefore required, and a combination of animal studies and CFD simulations is expected to provide insight into many details of the role of hemodynamics in CA pathogenesis and treatment.

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