Investigation of characteristic hemodynamic parameters indicating thinning and thickening sites of cerebral aneurysms

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Received 30 May 2014

Abstract
Cellular and animal experiments and computational fluid dynamics (CFD) have revealed that mechanisms of the initiation, growth and rupture of a cerebral aneurysm are related to hemodynamics. By direct observation of a cerebral aneurysm during craniotomy, thinning or thickening sites can be found on the aneurysmal wall. The thinning site of a cerebral aneurysm is considered to be at high risk of rupture. In addition, the thickening site of a cerebral aneurysm is not necessarily in a stable state since arteriosclerosis may have occurred. Hence, information on wall conditions, i.e., thinning and thickening, of a cerebral aneurysm is beneficial for clinical diagnosis and treatment. In this study, a hemodynamic parameter to effectively estimate the thinness or thickness of cerebral aneurysmal walls was investigated. CFD of hemodynamics in cerebral aneurysms developed at the anterior communicating artery (ACoA), a common site of cerebral aneurysms, was performed, and characteristic distributions of hemodynamic parameters were investigated by comparing the computational results with clinical images. As a result, a high value of the time-averaged wall shear stress (TAWSS) was found to be present at thinning sites, while a low TAWSS and a high relative residence time (RRT) of an indicator of blood retention were observed at thickening sites. Thinning and thickening sites each have their own characteristics distribution of hemodynamic parameters.

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

1. Introduction

A subarachnoidal hemorrhage is fatal or causes severe sequelae, with the result that only one-third of patients can be rehabilitated using currently available advanced medical treatment. The major cause of subarachnoidal hemorrhage is a rupture of a cerebral aneurysm. With regard to the mechanisms of initiation, growth and rupture of a cerebral aneurysm, various studies, including animal experiments (Costalat et al., 2011; Meng et al., 2007), cellular experiments (Cucina et al., 1998; Malek and Izumo, 1995) and computational fluid dynamics (CFD), have been performed. In particular, the mechanisms have been discussed based on the low or high values of wall shear stress (WSS) (Cebrol et al., 2010; Hassan et al., 2005; Mantha et al., 2006; Meng et al., 2013; Omodaka et al., 2012; Shojima et al., 2004), and the hemodynamic parameters derived by WSS, such as the WSS gradient (WSSG) (Meng et al., 2007), the oscillatory shear index (OSI) (Omodaka et al., 2012), the gradient oscillatory number (GON) (Shimogonya et al., 2009), and the relative residence time (RRT) (Sugiyama et al., 2013). However, hemodynamic parameters have still not been applied in clinical diagnosis
since it has not been completely understood what causes and conditions lead to aneurysmal rupture. Consequently, medical doctors usually determine the necessity and procedure of surgery considering empirical information such as the location, shape, and size (the diameter or aspect ratio) of the cerebral aneurysm.

Observation of a cerebral aneurysm during craniotomy sometimes shows thinning or thickening sites of the aneurysmal wall. The existence and the distribution of those sites differ among patients. A rupture of a cerebral aneurysm is generally believed to occur at a thin wall. On the other hand, a thick wall of a cerebral aneurysm is not necessarily stable since arteriosclerosis has progressed. Therefore, information on wall conditions, i.e., thinning and thickening, of the cerebral aneurysm is useful in clinical diagnosis and treatment. As for hemodynamics at thinning and thickening sites of cerebral aneurysms, impingement (Yagi et al., 2013) and retention (Sugiyama et al., 2013) of blood flow, respectively, have been pointed out. However, to the best of our knowledge, there has been no investigation of hemodynamic parameters to simultaneously evaluate both thinning and thickening sites of a cerebral aneurysm.

In this study, a hemodynamic parameter to effectively estimate thinning and thickening sites of a cerebral aneurysm was investigated. CFD study of blood flow in cerebral aneurysms developed in the anterior communicating artery (ACoA), which is a common site of cerebral aneurysms, was performed using patient-derived boundary conditions. Characteristic hemodynamics and distributions of hemodynamic parameters were then investigated by comparing the computational results with the clinical images.

2. Methods

2.1 Objectives

This study was conducted in accordance with and under the approval of the ethics review board of Kohnan Hospital, Japan. Cerebral aneurysms which developed in the ACoA were dealt with in this study. The ACoA is located in a complex cerebral vascular system where blood meets from bilateral anterior cerebral arteries (ACAs). In this study, to simplify the settings of boundary conditions in CFD, cerebral aneurysms, to which the blood flow was supplied by one of the ACAs, were chosen (see Fig. 1). Aplastic ACA parts were confirmed by internal carotid artery (ICA) compression and magnetic resonance (MR) angiography. Perioperative clinical images of four cases of cerebral aneurysm are shown in Fig. 2, and information on the patients, the cerebral aneurysms, and the vascular systems is summarized in Table 1. The characteristics of aneurysms were separately evaluated by three persons for objectivity. The red wall observed in the clinical image of Fig. 2(a) is a thinning site (indicated by a gray dotted circle), and a yellowish white wall in Fig. 2(b) is a thickening site (indicated by a black dotted circle). The cerebral aneurysmal wall in Fig. 2(c) has a red thinning site at the upper left side (a gray dotted circle) as well as a yellowish white thickening site at the lower right side (a black dotted circle). The cerebral aneurysm of Fig. 2(d) has neither thinning nor thickening sites, but a pink aneurysmal wall is observed similar to the parent artery.

Fig. 1  Schematic diagram of cerebral artery system dealt with in this study. The dashed part indicates an aplastic blood vessel. ICA: Internal Carotid Artery, MCA: Middle Cerebral Artery, ACA: Anterior Cerebral Artery, ACoA: Anterior Communicating Artery, L-: Left side of blood circulatory system, R-: Right side of blood circulatory system.
Before surgery, conventional digital subtraction and three-dimensional rotational angiography (3D-RA) were performed by standard transfemoral catheterization with a biplane unit (Innova 3131, GE Healthcare Japan, Japan) (Sugiyama et al., 2013). The images were obtained during a 6-second injection of a contrast agent and a 200 rotation with imaging at 30 frame/s for 5 s. The 150 projection images were reconstructed into a 3D data set of 512 × 512 isotropic voxels covering a field of view of 200 mm in all three directions. The 3D data set obtained from 3D-RA was exported to a personal computer to form a 3D isosurface model of the aneurysms. The 3D vessel morphology of each patient was reconstructed by using open source software, Vascular Modeling Toolkit (VMTK, www.vmtk.org), based on the above-mentioned 3D-RA data. The data were output in a stereolithography (STL) format. The results of segmentation were validated by two-dimensional (2D) conventional angiograms and intraoperative videograms of aneurysms during surgery. The vascular system adjacent to the cerebral aneurysm was then extracted using commercial software for modification and editing of the STL data (Magics 16.0, Materialise, Belgium). Here, in order to consider the effect of

| Case | 1    | 2    | 3    | 4    |
|------|------|------|------|------|
| Age  | 58   | 61   | 62   | 60   |
| Sex  | M    | M    | M    | F    |
| Thinning | +  | -    | +    | -    |
| Thickening | -  | +    | +    | -    |
| Major axis [mm] | 6.8 | 10.9 | 7.3  | 4.1  |
| Minor axis [mm] | 5.3 | 6.7  | 5.4  | 3.3  |
| Height [mm] | 4.5 | 7.8  | 4.8  | 3.2  |
| Blood supply | R-ICA | L-ICA | L-ICA | L-ICA |
| Inlet (ICA) [mm²] | 11.7 | 15.1 | 12.6 | 10.9 |
| Outlet (MCA) [mm²] | 5.75 | 5.95 | 5.86 | 4.54 |
| Outlet (L-ACA) [mm²] | 2.47 | 3.19 | 2.66 | 2.86 |
| Outlet (R-ACA) [mm²] | 2.78 | 2.98 | 2.61 | 3.15 |
| Cardiac cycle, T [s] | 0.88 | 1.03 | 0.84 | 0.85 |
| Mean inflow volume, \(Q_0\) [ml/s] | 5.82 | 4.74 | 3.92 | 3.50 |
| Ratio of outflow, \(Q_{L-ACA} : Q_{R-ACA}\) | 47 : 53 | 52 : 48 | 50 : 50 | 48 : 52 |
blood vessel shape near the inlet on computed hemodynamics in the cerebral aneurysm, the extraction domain was set, including a bifurcation from the ICA to an ACA and middle cerebral artery (MCA) and their bends (Castro et al., 2006).

In addition, quantitative MR velocimetry was performed with a 3T MRI scanner (Signa HDxt, GE Healthcare Japan, Japan) before the surgical treatment to acquire blood flow volume waveforms of each patient for CFD (Sugiyama et al., 2013). The protocol entails standard cranial 3D time-of-flight MR angiography to select a slice orientation for the arterial blood flow measurements. The optimal perpendicular scan plane was determined from the acquired time-of-flight images. The coordinates obtained specified the position of an oblique fast 2D phase-contrast sequence that was then performed on the basis of these coordinates using a peripheral gated 2D phase-contrast sequence with the following imaging parameters: repetition time/echo time/number of excitations, 25 ms/5.4 ms/1; field of view, 160 × 160 mm; matrix, 512 × 512; voxel size, 0.3 × 0.3 mm; velocity encoding, 100 cm/s; imaging time, about 5 min; direction, transaxial; peripheral gated with ECG; and phases, 30. The acquired phase-contrast images were transferred to the workstation for flow quantification with dedicated software (CV Flow, GE Healthcare Japan, Japan). A region of interest was placed semiautomatically on the phase-contrast images over a cardiac cycle. The velocities at all of the pixels inside the vessel border were integrated to calculate the blood flow volume, and these values were used to obtain the quantitative waveform over the cardiac cycle.

2.2 Computational methods

A computational grid was generated with general-purpose computational mesh generation software (ICEM CFD 14.0, ANSYS, USA). Figure 3 represents the computational mesh and coordinate system of each patient. Approximate
positions of thinning and thickening sites are indicated by gray and black dotted circles, respectively. The size of the computational grid was between 0.1 mm and 0.5 mm, and five prism layers were created near the wall. The total number of computational elements was between 300,000 and 600,000, depending on the patients. Commercial thermal fluid analysis software (FLUENT 14.0, ANSYS, USA) was employed for CFD, in which 3D unsteady Navier-Stokes equations for incompressible fluid flow and equation of continuity were solved. As for the computational algorithm, the SIMPLE method was used. The Green-Gauss node-based gradient method was applied for the differential and gradient calculations, and the PRESTO! method and QUICK method were used for pressure completion and convection discretization, respectively.

Among the boundary conditions in CFD, patient-specific blood flow waveforms derived from quantitative MR velocimetry were applied at the inlet, ICA, and one of the outlets, MCA (see Fig. 1). Figure 4 shows the time-dependent blood flow volume in one cardiac cycle at the ICA and the MCA with a linear interpolation of the measured flow data by quantitative MR velocimetry. The waveforms were normalized by the cardiac cycle \( T \) and the mean inflow volume \( Q_0 \) (see Table 1). The inflow velocity profile was set to be a uniform parallel flow. Regarding boundary conditions for the remaining arteries of bilateral ACAs, a flow dividing ratio \( \frac{Q_{L-ACA}}{Q_{R-ACA}} \) was defined based on the ratio of the cross sections since it is difficult to measure the blood flow waveform simultaneously (Table 1). The cross-sectional areas of ACAs were computationally calculated at five points at intervals of 0.5 mm from the downstream boundary. CFD was performed by dividing one cardiac cycle into 100 time steps. Density and viscosity of the blood were assumed to be 1,050 kg/m\(^3\) and 3.5 \times 10^{-3} \text{ Pa}\cdot\text{s}, respectively. The convergent criteria were set as 1 \times 10^{-5} and 450 for the residual of convergence and for the maximum iteration, respectively, after test computations. Unsteady computation in each case was performed for four cardiac cycles to obtain a periodic solution, and the computational result in the last cycle was used for later evaluation of hemodynamics and hemodynamic parameters.

### 2.3 Hemodynamic parameters

To evaluate the hemodynamic stress acting on a cerebral aneurysm, WSS, \( \tau \), was calculated by the product of the blood viscosity and computed velocity gradient at each location on the blood vessel wall. The time-averaged WSS (TAWSS) in one cardiac cycle and the magnitude of the time-averaged WSS vector (TAWSSV) were defined at each location by the following equations, respectively.

\[
\text{TAWSS} = \frac{1}{T} \int_0^T |\tau| dt, \tag{1}
\]

\[
\text{TAWSSV} = \frac{1}{T} \int_0^T \tau dt. \tag{2}
\]

The values of both TAWSS and TAWSSV are scalar. Moreover, the OSI (Ku et al., 1985), which represents the degree of oscillation of the WSS vector in one cardiac cycle, was calculated by the following equation:

\[
\text{OSI} = \frac{1}{2} \left( 1 - \frac{\text{TAWSSV}}{\text{TAWSS}} \right). \tag{3}
\]
OSI is a non-dimensional parameter, which takes the value of $0 \leq OSI \leq 0.5$. In the case of $OSI = 0$, it represents that the direction of the WSS vector does not change in one cardiac cycle. When $OSI = 0.5$, the integration of the WSS vector in one cardiac cycle is zero ($TAWSSV = 0$). Furthermore, the RRT (Himburg et al., 2004), which indicates particle retention near the wall, was used for the evaluation.

$$RRT = \frac{1}{(1 - 2 \times OSI) \times TAWSS}.$$  \hspace{1cm} (4)

The unit of RRT is Pa$^{-1}$. The high value of RRT indicates that blood flow remains near the wall for a long time. In this study, the characteristics of hemodynamic parameters at sites of both thinning and thickening of cerebral aneurysms were investigated by comparing the distribution of the above-mentioned four hemodynamic parameters and visually observed wall conditions.

3. Results

Streamlines of blood flow in each cerebral aneurysm at the maximum flow volume are shown in Fig. 5. For the visualization of computational results, the position and orientation of each computational blood vessel model were adjusted to match those in the corresponding clinical image, referring to the characteristic shapes of cerebral aneurysms and locations of the parent arteries as much as possible. The streamlines are colored according to the magnitude of the blood flow velocity. The patterns of streamlines did not largely change during a cardiac cycle. In Case 1 of the cerebral aneurysm with a thin wall (Fig. 5(a)), streamlines indicate that the blood flow is spread throughout the entire aneurysm, forming a large vortex and that the regions with decreased flow velocity are relatively small. On the other hand, those in Case 2 of the cerebral aneurysm with a thick wall (Fig. 5(b)) show a slow vortex formed in the vicinity of the thickening site (Fig. 2(b)). In the result of the cerebral aneurysm with both thin and thick walls (Case 3) shown in Fig. 5(c), streamlines form a vortex at the thinning site, while the number of streamlines is few and the flow velocity decreases at the thickening site. These characteristics are similar to the findings at the thinning and thickening sites in Cases 1 and 2.
respectively. The streamlines in the cerebral aneurysm with neither thinning nor thickening sites (Case 4) display a relatively high-speed stable vortex, by which blood flowing in the cerebral aneurysm is divided between the bilateral ACAs.

Distributions of hemodynamic parameters obtained by CFD of each patient are shown in Fig. 6 in comparison with the clinical images. For comparison among the patients, the range of the color bar for each hemodynamic parameter is set to be identical with reference to the calculated values in all cases. Additionally, the positions of the maximum value of TAWSS in the cerebral aneurysms of Cases 1 and 3 and those of the minimum value in Cases 2 and 3 are indicated by black and white stars, respectively (Fig. 6(b)). In case 1 of the cerebral aneurysm with a thin wall (the left-most column in Fig. 6), the position with the maximum TAWSS of 66.75 Pa (a black star in Fig. 6(b)) is located at the thinning site. Moreover, the values of TAWSS in Case 1 are entirely higher than those in the other cases. As for other hemodynamic parameters, the distribution of TAWSSV almost coincides with that of TAWSS, and the values of OSI and RRT are small in the entire domain of the cerebral aneurysm.

![Fig. 6 Comparison of (a) clinical image and distributions of hemodynamic parameters, (b) TAWSS, (c) TAWSSV, (d) OSI, and (e) RRT. Black and white stars represent the positions with the maximum and minimum values of TAWSS, respectively.](image-url)
In contrast, in the result of the cerebral aneurysm with a thickened wall (Case 2), the low TAWSS region with a minimum value of 0.09 Pa (a white star in Fig. 6(b)) corresponds to the thickening site. Distributions of TAWSS and TAWSSV are almost identical, and there is no characteristic distribution of the OSI at the thickening site. The RRT is large at the locations with small values of TAWSS and TAWSSV, showing a large value of 23.54 Pa$^{-1}$ at the position with the minimum value of TAWSS (see the white star in Fig. 6(b)). This suggests a correlation between a high RRT with a thickening site of a cerebral aneurysm.

The result of the cerebral aneurysm of Case 3 with both thinning and thickening sites exhibits tendencies similar to the results observed in Cases 1 and 2. In other words, high and low TAWSS are depicted at the thinning and thickening sites, respectively. The maximum TAWSS of 25.10 Pa is located at the thinning site (a black star in Fig. 6(b)), while the minimum TAWSS of 0.37 Pa is located at the thickening site (a white star mark in Fig. 6(b)). In the distribution of OSI, the locations with TAWSS values of >0.25 locally exist at the thickening site. The value of RRT at the position of the minimum TAWSS is 2.80 Pa$^{-1}$, and RRT becomes slightly large at the thickening site.

In the cerebral aneurysm of Case 4 with neither thinning nor thickening sites (the right-most column in Fig. 6), the values of TAWSSV and TAWSS are almost identical, increasing at the aneurysmal neck where blood flows into the cerebral aneurysm. The values in the aneurysm are intermediate between the other results of the cerebral aneurysms with thinning and thickening sites. The values of OSI and RRT are almost zero in the entire domain of the cerebral aneurysm, implying no characteristic distribution.

Figure 7 shows enlargements of the rectangular domains in the figures of the TAWSSV distribution in Fig. 6(c) with unit vectors obtained by dividing the time-averaged WSS vectors by the values of TAWSSV. Here, though the vectors have the same length, starting from computational grid points on the aneurysmal wall, the length seems to be different due to the 3D morphology. The source of the time-averaged WSS vectors is mainly derived from impingement of the bloodstream, and the small value of TAWSSV around the impingement region implies that the blood flow does not move in one cardiac cycle. In the cerebral aneurysms of Cases 1 and 3 (Figs. 7(a) and (c)), the source of the unit vectors is located at the vicinity of thinning sites (see the black circle). In addition, in the cerebral aneurysm of Cases 2, 3, and 4 (Figs. 7(b) - (d)), low TAWSSV is observed in the source of the unit vectors in contrast with those in the surrounding area. Especially in Case 3, the source of the unit vectors is in the center of the ring-shaped distribution of TAWSSV.
4. Discussion

Among parameters investigated in this study, our results indicate that TAWSS is the most effective hemodynamic parameter to estimate the wall conditions of thinning or thickening of cerebral aneurysms. TAWSS represents a high value at a thinning site of a cerebral aneurysm, whereas it shows a low value at a thickening site. Regarding the other hemodynamic parameters dealt with in this study, TAWSSV is qualitatively the same as TAWSS, and OSI does not show any characteristic distributions related to wall conditions of a cerebral aneurysm. RRT is high at a thickening site, but it does not present a characteristic distribution at a thinning site.

In the vicinity of a thinning site with a high value of TAWSS on a cerebral aneurysm (Figs. 6(a) and (c)), the source of the time-averaged WSS vector field is observed (Figs. 7(a) and (c)), which reflects that blood flow impinges on the aneurysmal wall as observed with streamlines in Figs. 5(a) and (c). This result is consistent with the observation by Yagi et al. (Yagi et al., 2013), who suggested the relationship between the impingement of blood flow and the thinning of a cerebral aneurysm. In contrast, steady state CFD of blood flow by Kadasi et al. (Kadasi et al., 2013) indicated that thin-walled dome regions in unruptured cerebral aneurysms were under low WSS. The unsteady CFD study of blood flow in ruptured cerebral aneurysms by Omodaka et al. (Omodaka et al., 2012) showed that the positions of ruptures had low TAWSS and high OSI. Moreover, Cebral et al. (Cebral et al., 2010) reported that WSS was low in a bleb formed on cerebral aneurysm, the bleb being known to easily rupture. These two results indicate the relationship between a rupture of a cerebral aneurysm and low WSS. However, in this study, a different result was obtained, namely, that TAWSS is high at a thinning site, which is considered to be prone to rupture. In this regard, it is conceivable that a high TAWSS at a thinning site of a cerebral aneurysm forms a bleb, resulting in a decrease of TAWSS, and that the bleb then ruptures due to degeneration of the aneurysmal wall. However, the mechanisms underlying aneurysmal wall thinning, bleb formation, and subsequent rupture remain to be clarified.

At a thickening site of a cerebral aneurysm, a low TAWSS as well as a high RRT were observed (Figs. 6(b) and (c)). The observed results of streamlines at the maximum flow volume (Figs. 5(b) and (c)) indicate that blood hardly flows near a thinning site and remains in the blood vessel. This phenomenon is similar to the characteristics of the hemodynamics at atherosclerosis-prone sites such as a carotid bifurcation (Malek et al., 1999). Moreover, the result agrees with the suggestion by Sugiyama et al. (Sugiyama et al., 2013) that the RRT increases at an arteriosclerotic site of a cerebral aneurysm.

In this study, we dealt with only four cerebral aneurysms developed at ACoA, to which blood flow was supplied by one of the ACAs. The effectiveness of TAWSS as an indicator of thinning and thickening sites of a cerebral aneurysmal wall should be further investigated by performing CFD of blood flow in many patients. Furthermore, a more objective evaluation method is necessary for better investigation of the relationship between wall properties and hemodynamic parameters. For instance, determination of thinning and thickening sites based on RGB values in a clinical image as well as objective matching of position and orientation of aneurysms should be considered in future. It was difficult to completely match aneurysmal shapes of CFD and clinical images: clinical images showed the appearance of aneurysms taken during craniotomy, but the blood vessel shapes dealt with by CFD were lumens reconstructed from the 3D-RA data. In addition, the difference between them might have occurred due to the existence of in vivo tissues around the aneurysms because the clinical images were taken during craniotomy (see Fig. 3). Cerebral aneurysms at ACoA, to which blood is supplied from bilateral ACAs, should be considered since this is the usual case. Furthermore, other hemodynamic parameters should be investigated for better estimation of wall conditions of a cerebral aneurysm.

5. Summary

In this paper, a hemodynamic parameter to effectively estimate thin and thick walls of cerebral aneurysms was investigated. CFD of hemodynamics in cerebral aneurysms developed in the ACoA was performed, and characteristic distributions of hemodynamic parameters were investigated by comparing the computational results with the clinical images. As a result, a high TAWSS was found to be present at thinning sites, while a low TAWSS and a high RRT of an indicator of blood retention were observed at thickening sites. Thinning and thickening sites have their own individual characteristics distributions of hemodynamic parameters.
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