A Parameter to Identify Thin-walled Regions in Aneurysms by CFD

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Objective: Thin-walled regions of cerebral aneurysms are areas of risk for rupture, particularly during surgical procedures. Prediction of thin-walled regions before surgery can lead to safer treatment, avoiding interactions with thin-walled regions. It is considered that blood flow influences aneurysm wall thickness reduction. The objective of this study was to establish a parameter to accurately identify thin-walled regions using computational fluid dynamics (CFD) analysis.

Methods: The surgical field was photographed during craniotomy in 50 patients with unruptured middle cerebral artery aneurysms and red regions of the aneurysm wall were compared with the color of the parent vessel and defined as a thin-walled region. CFD analysis was performed and the distribution map of wall shear stress divergence (WSSD*) was compared to the surgical image of the cerebral aneurysms.

Results: The WSSDmax region and thin-walled region were coinciding in 41 (82.0%) of the 50 patients. There was a significant difference (P = 0.00022) between the patients with and without coincidence between the WSSDmax and thin-walled regions, and the threshold, sensitivity, specificity, and area under the curve (AUC) on receiver operating characteristic (ROC) analysis of WSSDmax were 0.230, 0.900, 0.875, and 0.883, respectively.

Conclusion: High-WSSD regions tended to be coinciding with thin-walled regions, suggesting that WSSDmax is useful to identify thin-walled regions of cerebral aneurysms.

Keywords ▶ computational fluid dynamics, thin-walled regions, wall shear stress divergence

Introduction

Subarachnoid hemorrhage caused by cerebral aneurysm rupture is a serious disease accounting for 45% of all-cause mortality at 1 month after rupture.1 According to preceding histological studies on the vascular wall, a cerebral aneurysm may rupture when a thin region of the aneurysm wall becomes unable to sustain the tensile force.2 A high correlation between the ruptured point of an aneurysm and a thin region of the aneurysm wall3 and the presence of a thin-walled region in general in most ruptured cerebral aneurysms3–5 have been reported. These studies suggest that thin-walled regions are at high risk of cerebral aneurysm rupture. Cerebral aneurysms with a risk of rupture require surgical treatment, but manipulation of thin-walled regions with surgical instruments during surgery may cause intraoperative rupture. That is particularly important in endovascular neurosurgery, when the aneurysm is not directly visualized. If thin-walled
regions can be predicted before surgery, safe surgery avoiding stimulation of thin-walled regions can be planned.

It has been reported that strong inflammation is induced in the wall of cerebral aneurysms that subsequently become thinner and ruptured.\textsuperscript{3–5} Kataoka et al. stated that the influence of blood flow was the cause of this,\textsuperscript{3} suggesting the association of blood flow with aneurysm wall thickness reduction. If a hemodynamic characteristic of this process could be clarified, it is highly probable that thin-walled regions can be identified by investigating the characteristic of specific wall areas of interest.

Studies on blood flow analysis using computational fluid dynamics (CFD) analysis have recently been performed in the medical field. A preceding study pointed out the association between a parameter related to blood flow pressure on the aneurysm wall, pressure difference ($PD$), and thin-walled regions.\textsuperscript{6} These investigations of hemodynamic parameters may be useful to elucidate the hemodynamics causing aneurysm walls becoming thinner. In addition, development and discovery of a highly accurate parameter for identification of thin-walled regions may increase the possibility of predicting of such regions in the future. Since thin-walled regions could not be identified in some patients using $PD$ reported by preceding studies; in this study, a parameter for evaluating the cerebral aneurysm wall-extending force, wall shear stress divergence ($WSSD$), aiming at the establishment of a non-$PD$ based hemodynamic parameter for thin-walled regions identification, was investigated.

## Materials and Methods

### Materials and surgical images

Between March 2009 and May 2015, 119 unruptured cerebral aneurysms of the middle cerebral artery (MCA) were treated with craniotomy and clipping in 107 patients at the Jikei University School of Medicine. Of these, thin-walled regions of the cerebral aneurysms could be photographed during craniotomy and the cerebral aneurysm wall could be directly observed on surgical photograph in 50 patients (18 and 32 were males and females, respectively). These 50 cerebral aneurysms were analyzed. The mean age of the patients was $62.7 \pm 8.73$ years old, and the aneurysm size measured by technologists was as follows: mean size, $5.99 \pm 1.97$ mm; maximum size, $12.6$ mm; minimum size, $2.46$ mm.

### Vascular model construction

The cerebral vascular shape in the patients was prepared by 3D reconstruction of images of CTA (SOMATOM Sensation 16, Siemens Healthineers, Erlangen, Germany) or 3D-DSA (Axiom Artis dBA, Siemens Medical Solutions, Forchheim, Germany). CTA images were used in 23 patients and 3D-DSA images were used in 27 patients. In the extracted vascular shape data, smoothing was applied to the surface using Amira5.6 (FEI Company, Hillsboro, Oregon, USA).

### CFD simulation

CFD grids generation and CFD simulations were performed using STAR-CCM+ v10.06.010 (Siemens PLM software, Plano, TX, USA).

### Computational grid

Unstructured volumetric meshes composed of polyhedral elements were created filling the volume of the vessel. To improve the accuracy of boundary layer analysis, six prism mesh layers were generated near the vascular wall. Prism layer total thickness was set at $0.25$ mm. The number of elements ranged from 12873 to 44101, and the mean length of one side of the polyhedral meshes was $2.62 \times 10^{-1} \pm 4.37 \times 10^{-2}$ mm. To avoid non-physical solution associated with the influence of inflow boundary conditions, a $0.15$-m straight tube was connected to the inlet.\textsuperscript{7}

### Computational and boundary conditions

Blood flow was mathematically modeled as an incompressible Newtonian fluid with $1,056$ kg/m$^3$ density and $0.0035$ Pa·s viscosity\textsuperscript{7} and was assumed to be laminar. Referring to preceding studies, unsteady calculation for two cardiac cycles was performed in each patient and the value at the second pulse peak was adopted.\textsuperscript{6} For the vascular wall, the
assumption of a rigid body with a no-slip boundary condition was applied. The pulsation of the averaged mass flow rate measured from healthy adults at the internal carotid artery (ICA) was referred from Ford et al. and imposed at the inlet boundary condition. The outflow boundary condition was fixed to a static pressure of 0 Pa in all patients.

**Analysis domain**

As shown in Fig. 1, outlet and inlet planes were set at about 1 mm distal and proximal to the end of the aneurysm neck, respectively, and the region surrounded by the cerebral aneurysm dome and inlet and outlet planes was regarded as the analysis domain.

**Parameters**

A hemodynamic parameter found to be associated with thin-walled regions in preceding studies, \( PD \), was defined by Equation (1). \( PD \) was calculated by dividing the deviation of pressure from the mean pressure of the entire analysis domain by the dynamic pressure at the inlet plane shown in Fig. 1:

\[
PD = \frac{\text{Pressure} - \text{Pressure}_{\text{ave}}}{\frac{1}{2} \rho V_{\text{ave}}^2}
\]

Wall Shear Stress (WSS) is a representative hemodynamic parameter on the aneurysm wall. To take both the direction and gradient of WSS into consideration, the WSSD determined by Equation (2) was introduced.

\[
WSSD = \frac{\partial WSS_x}{\partial x} + \frac{\partial WSS_y}{\partial y} + \frac{\partial WSS_z}{\partial z}
\]

To non-dimensionalize WSSD, firstly, WSSx, WSSy and WSSz in Equation (2) were divided by the dynamic pressure at the inlet plane shown in Fig. 1, and in this way defined WSS*\(_x\), WSS*\(_y\) and WSS*\(_z\), shown in Equation (3).

\[
WSS^*_x = \frac{WSS_x}{\frac{1}{2} \rho V_{\text{ave}}^2}, \quad WSS^*_y = \frac{WSS_y}{\frac{1}{2} \rho V_{\text{ave}}^2}, \quad WSS^*_z = \frac{WSS_z}{\frac{1}{2} \rho V_{\text{ave}}^2}
\]

Then, using the area of the inlet plane shown in Fig. 1, \( S_{\text{in}} \), and assuming that the inlet plane is a circle, the equivalent diameter, \( D_{\text{in}} \), was defined as the inlet plane diameter by Equation (4).

\[
D_{\text{in}} = 2 \sqrt{\frac{S_{\text{in}}}{\pi}}
\]

\[
X = \frac{x}{D_{\text{in}}}, \quad Y = \frac{y}{D_{\text{in}}}, \quad Z = \frac{z}{D_{\text{in}}}
\]

Using Equations (3)–(5), dimensionless value of WSSD, WSSD*, was defined as Equation (6).

\[
WSSD^* = \frac{\partial WSS^*_x}{\partial x} + \frac{\partial WSS^*_y}{\partial y} + \frac{\partial WSS^*_z}{\partial z}
\]
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mean blood flow velocity at the inlet plane of the analysis domain.

**Qualitative evaluation**

Initially, the $WSSD_{\text{max}}$ and $PD_{\text{max}}$ points were plotted on the surgical image of the cerebral aneurysm to qualitatively investigate coincidence of the regions of interest near these points with the thin-walled regions of the cerebral aneurysm. Next, thin-walled regions were defined as red transparent regions of the cerebral aneurysm wall compared to the color of the parent blood vessel presented as a pentagon on the surgical image. When it was red, the region was regarded as a thin-walled region. $PD$: pressure difference; $WSS$: wall shear stress; $WSSD$: wall shear stress divergence

In addition to $PD$ and $WSSD^*$ for evaluation of the hemodynamic characteristics on the aneurysm wall, $V_{\text{ave}}$ was defined by Equation (7) as a parameter to evaluate the hemodynamic characteristic inside the aneurysm.

$$V_{\text{ave}}^* = \frac{V_{\text{ave}}}{V_{\text{in}}}$$

$V_{\text{ave}}$ represents the mean blood flow velocity in the cerebral aneurysm at the pulsation peak. $V_{\text{in}}$ represents the mean blood flow velocity at the inlet plane of the analysis domain.
with the color of the parent vessel, following the definition in preceding studies.6,9 As a following step, the color of the healthy parent vessel was determined in cooperation with neurosurgeons and presented as a pentagon on the surgical image (Fig. 3). Finally, regions near the WSSD*<sub>max</sub> and PD<sub>max</sub> points were presented as circles on the surgical image, and whether the region surrounded by the circle was reddish compared with the color of the healthy parent vessel was evaluated by two neurosurgeons (Fig. 3). When both neurosurgeons decided a region to be reddish, the WSSD*<sub>max</sub> or PD<sub>max</sub> region was regarded as concordant with a thin-walled region. WSSD*<sub>max</sub> and PD<sub>max</sub> represent the maximum values of WSSD* and PD at the pulsation peak in the cerebral aneurysm.

### Statistical analysis

The patients were classified into those with and without coincidence between the WSSD*<sub>max</sub> and thin-walled regions on the qualitative evaluation, and the WSSD*<sub>max</sub> and V'<sub>ave</sub> values were statistically compared between two groups. PD<sub>max</sub> was similarly analyzed. Statistical analysis was performed using R version 3.4.1 (R Project for Statistical Computing, Vienna, Austria). When normality could not be confirmed by the Kolmogorov–Smirnov test, test for homogeneity of variance (F-test) of the two groups was performed followed by Student’s t-test or Welch’s t-test. When normality could not be confirmed, the Mann–Whitney U test was performed. P values below 0.05 and 0.01 were regarded as statistically significant. To compare the thin-walled region-identifying ability between the parameters, receiver operating characteristic (ROC) curves of WSSD*<sub>max</sub> and PD<sub>max</sub> were prepared and the threshold, sensitivity, specificity, and area under the curve (AUC) were calculated. A ROC curve of V'<sub>ave</sub> was similarly prepared and the threshold, sensitivity, specificity, and AUC were calculated.

### Results

The WSSD*<sub>max</sub> region was corresponding to the thin-walled region in 41 of the 50 patients (82.0%), and not corresponding in nine patients. Regarding PD, the PD<sub>max</sub> region was corresponding to the thin-walled region in 40 of the 50 patients (80.0%) and not corresponding in 10 patients. For the patients with correspondence of both WSSD*<sub>max</sub> and PD<sub>max</sub> to the thin-walled regions and those without correspondence with each of the parameters, the WSSD* distribution, PD distribution, streamlines, and surgical image of typical cases are shown in Figs. 4 and 5. The Mann–Whitney U test and ROC analysis were performed in the group with (Group a) and without (Group b) coincidence with the thin-walled regions for each of WSSD*<sub>max</sub> and PD<sub>max</sub>. The results are shown in Fig. 6. A very significant difference was noted in the WSSD*<sub>max</sub> value between the groups with and without coincidence of the WSSD*<sub>max</sub> region with the thin-walled region (P = 0.00022), and the threshold was 0.230, sensitivity was 0.900, specificity was 0.875, and AUC was 0.883 on ROC analysis. Regarding PD, a significant difference was noted between the groups with and without coincidence of the PD<sub>max</sub> region with the thin-walled region (P = 0.018), and the threshold was 0.415, sensitivity was 0.600, specificity was 0.900, was AUC was 0.764 on ROC analysis of PD<sub>max</sub>. Of the patients with coincidence of both WSSD*<sub>max</sub> and PD<sub>max</sub> with the thin-walled regions, the WSSD*<sub>max</sub> region and PD<sub>max</sub> region were present at different locations and thin-walled regions were identified in three patients (Fig. 7). When the WSSD* value in the PD<sub>max</sub> region was investigated in these three patients, it was higher than the WSSD* threshold (0.230) determined by ROC analysis in two patients (Fig. 7A and 7B), showing that the thin-walled region identified in the PD<sub>max</sub> region could be identified using WSSD*. Similarly, the PD value in the WSSD*<sub>max</sub> region was investigated, but the value did not exceed the PD threshold (0.415) determined by ROC analysis in any of the three patients. In all, 43 thin-walled regions were identified in regions with a WSSD* value exceeding the threshold (0.230), whereas 40 thin-walled regions were identified in regions with a PD value exceeding the threshold (0.415), showing that thin-walled regions were more sensitively identified through WSSD*.

The V'<sub>ave</sub> value was statistically compared between the groups with (Group a) and without (Group b) coincidence of the WSSD*<sub>max</sub> and the thin-walled regions. The results are shown in Fig. 8A. A significant difference was noted between the two groups (P = 0.003), and the threshold was 0.365, sensitivity was 1.00, specificity was 0.575, and AUC was 0.806 on ROC analysis (Fig. 8C). Similarly, V'<sub>ave</sub> was statistically compared between the groups with (Group a) and without (Group b) coincidence of the PD<sub>max</sub> and the thin-walled region. The results are shown in Fig. 8B. A significant difference was noted between the two groups (P = 0.014), and the threshold was 0.365, sensitivity was 0.909, specificity was 0.564, and AUC was 0.745 on ROC analysis (Fig. 8C).
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**Fig. 5** Patient subgroup with no thin-walled region identified in the WSSD\(_{\text{max}}^*\) or PD\(_{\text{max}}\) region. The WSSD\(^*\) and PD distribution maps, streamlines, and surgical image of three of the patients with no thin-walled region identified in the WSSD\(_{\text{max}}^*\) or PD\(_{\text{max}}\) region are presented. In these patients, the WSSD\(_{\text{max}}^*\) and PD\(_{\text{max}}\) values were low compared with those in the subgroup with thin-walled regions identified. When the streamlines were observed, both the volume and velocity of blood inflow into the aneurysm were markedly lower than those in the subgroup with thin-walled regions identified. PD: pressure difference; WSSD: wall shear stress divergence.

**Fig. 6** Statistical analysis of WSSD\(_{\text{max}}^*\) and PD\(_{\text{max}}\) values. (A) The WSSD\(_{\text{max}}^*\) value was statistically compared between the groups with (Group a) and without (Group b) coincidence of the WSSD\(_{\text{max}}^*\) and the thin-walled region using the Mann–Whitney U test. (B) The PD\(_{\text{max}}\) value was statistically compared between the groups with (Group a) and without (Group b) coincidence of the PD\(_{\text{max}}\) and the thin-walled region using the Mann–Whitney U test. (C) ROC analyses of WSSD\(_{\text{max}}^*\) and PD\(_{\text{max}}\) were performed. AUC: area under the curve; PD: pressure difference; ROC: receiver operating characteristic; WSSD: wall shear stress divergence.
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Fig. 7  Cases in which the WSSD$_{max}$ and PD$_{max}$ regions were present at different locations and thin-walled regions were identified in both regions. Thin-walled regions were identified in both WSSD$_{max}$ and PD$_{max}$ regions, but these were preset at different locations. In two (A and B) of these patients, the WSSD* value in the PD$_{max}$ region exceeded the threshold determined on ROC analysis, being consistent with the thin-walled region. In the patient (C), the WSSD* value in the PD$_{max}$ region didn’t exceed the threshold determined on ROC analysis, being inconsistent with the thin-walled region.

PD: pressure difference; ROC: receiver operating characteristic; WSSD: wall shear stress divergence

Fig. 8  Statistical analysis of $V^*$ value. (A) The $V^*$ value was compared between the groups with (Group a) and without (Group b) coincidence of the WSSD$_{max}$ and the thin-walled region using the Mann–Whitney U test and a significant difference was noted between the two groups. (B) The $V^*$ value was compared between the groups with (Group a) and without (Group b) coincidence of the PD$_{max}$ region with the thin-walled region using the Mann–Whitney U test and a significant difference was noted between the two groups. (C) $V^*$ compared between the two groups in (A and B) was subjected to ROC analysis. AUC: area under the curve; PD: pressure difference; ROC: receiver operating characteristic; WSSD: wall shear stress divergence.
Discussion

A study on cerebral aneurysm rupture using WSSD has been reported, but to our best knowledge, this is the first study in which WSSD* is applied to evaluate thin-walled regions of cerebral aneurysms. Many histological studies on thin-walled regions of cerebral aneurysms have been reported. Kataoka et al. stated that the cerebral aneurysm wall rapidly expands after structural fatigue and vascular endothelial cell damage leads to wall thickness reduction. The cerebral aneurysm wall is thin and fragile compared to the wall of the healthy parent vessel. Therefore, a high-WSSD* region on the aneurysmal wall can be regarded as a strongly expanded and fragile aneurysm wall region and it is very likely to be associated with a region to be found thin on histological examination. Actually, a thin wall was identified in the WSSD*$_{max}$ region in many patients (82.0% out of the whole cohort) and a significant difference was observed in the WSSD*$_{max}$ value between the patient groups with and without an identified thin-walled region. That clearly suggests the association of aneurysm wall expansion with wall thickness reduction. A high-PD region represents a region in which high pressure is loaded on the vascular wall by collision with blood flow, but it is not a parameter for direct evaluation of the region with an expanding wall. Actually, the WSSD value was not necessarily high in high-PD regions, showing that this is not a parameter of wall expansion. Therefore, if aneurysm wall expansion is the cause of thickness reduction, the WSSD* distribution may be more accurate for identification of thin-walled regions.

Both the WSSD*$_{max}$ and PD$_{max}$ regions were coinciding with the thin-walled regions in 40 of the 50 patients. As shown in Fig. 4, both the WSSD*$_{max}$ and PD$_{max}$ regions were present near the blood flow impingement point in 37 of these 40 patients. Since the vessel wall was extended and pressure was elevated by the blood flow at its impingement point as shown in Fig. 2A and 2B, in MCA aneurysm developing at its bifurcation region, in which strong blood flow impingement usually occurs, thin-walled regions are easily identified in the WSSD*$_{max}$ and PD$_{max}$ regions. In the remaining three patients, the WSSD*$_{max}$ and PD$_{max}$ regions were present at different locations and the thin-walled regions were identified in both regions (Fig. 7). In these cases, the thin-walled region identified in the PD$_{max}$ region could also be identified based on the WSSD* value, but the opposite region identified in the WSSD*$_{max}$ region could not be identified based on the PD value. That suggests that thin-walled regions can be identified more sensitively by WSSD* compared with PD and that stretch of the aneurysm wall is related to its thickness reduction.

No thin-walled region could be identified in the WSSD*$_{max}$ region in 9 of the 50 patients, as shown in Fig. 5. The WSSD*$_{max}$ value was significantly lower in this patient subgroup than in the subgroup where thin-walled regions were identified in the WSSD*$_{max}$ region (Fig. 6). When the streamlines in the first subgroup were observed in Fig. 5, the volume and velocity of blood inflow into the aneurysm was markedly lower than those in the subgroup with an identified thin-walled region. Actually, the $V_{ave}$ value representing the average flow velocity in the aneurysm was significantly lower in this same subgroup than in the subgroup with a thin-walled region identified in the WSSD*$_{max}$ region. That indicates that the flow velocity in the aneurysm in this subgroup was markedly low (Fig. 8A). Similar tendency was also noted for PD. Therefore, when energy of blood flow in the aneurysm is low due to the lower blood flow velocity, no thin-walled regions would be identified in the WSSD*$_{max}$ or PD$_{max}$ region and this may have been the reason for the location inconsistency between WSSD*$_{max}$ and PD$_{max}$, and the thin-walled regions in this subgroup.

Limitations

Our analysis is limited to the data of 50 patients. Moreover, only cerebral aneurysms with MCA location were included in the study because in this location the entire aneurysm can be visualized. The aneurysm wall thickness was not actually measured and red regions of the aneurysm wall on visual observation of the surgical field were defined as thin-walled regions. This was based on a histological study reporting that the wall is thinner in a semitransparent region in which blood flow become visible. In our study, thin-walled regions tended to be identified in regions in which the WSSD value reached its maximum, whereas WSSD was not necessarily at the maximum in thin-walled regions, showing that WSSD$_{max}$ was a sufficient, but not a necessary condition. A method to accurately identify all thin-walled regions remains to be identified. The physical property values and blood flow rate were standardized in all patients for the purpose of our study, but it is necessary to use individual physical property values of the blood for each of the patients. Blood flow was assumed to be Newtonian fluid and the vascular wall was assumed to be a rigid wall. Since location coincidence of the WSSD*$_{max}$ and PD$_{max}$ regions with the thin-walled regions was evaluated...
using a qualitative method, it is necessary to introduce a quantitative method. Furthermore, $WSSD^{\ast\max}$ value and degree of wall-thinning (specific thickness reduction) precise quantitative relations remains to be investigated. Finally, CTA and 3D-DSA images were used and the imaging modality was not uniformed.

## Conclusion

A parameter for evaluating the cerebral aneurysm wall-expanding force of the blood flow, $WSSD^{\ast}$, was proposed and evaluated. The $WSSD^{\ast\max}$ region, in which the $WSSD^{\ast}$ value was at its maximum on the cerebral aneurysmal wall, was coinciding with the thin-walled region at a high rate and the accuracy was higher than those of parameters reported by preceding studies. In addition, it was suggested that calculation of $WSSD^{\ast}$ can be utilized to predict thin-walled regions. $WSSD^{\ast}$ may be useful to identify thin-walled regions of cerebral aneurysms before surgery.

## Disclosure Statement

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## References