Determining the Presence of Thin-Walled Regions at High-Pressure Areas in Unruptured Cerebral Aneurysms by Using Computational Fluid Dynamics

Tomoaki Suzuki, MD*‡
Hiroyuki Takao, PhD*§
Takashi Suzuki, MS§
Yukinao Kambayashi, MD*
Mitsuyoshi Watanabe, MD*
Hiroki Sakamoto, MD*
Issei Kan, MD*
Kengo Nishimura, MD*
Shogo Kaku, MD*
Toshihiro Ishibashi, MD*
Satoshi Ikeuchi, MD*
Makoto Yamamoto, PhD¶
Yukihiko Fujii, PhD‡
Yuichi Murayama, MD*

*Department of Neurosurgery, Jikei University School of Medicine, Tokyo, Japan; ‡Department of Neurosurgery, Brain Research Institute, Niigata University, Niigata, Japan; §Graduate School of Mechanical Engineering and ¶Department of Mechanical Engineering, Tokyo University of Science, Tokyo, Japan

Correspondence:
Yuichi Murayama, MD,
Department of Neurosurgery,
The Jikei University School of Medicine,
3-25-8 Nishi-Shinbashi,
Minato-ku, Tokyo 105-8461, Japan.
E-mail: ymurayama@jikei.ac.jp

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BACKGROUND: Thin-walled regions (TWRs) of cerebral aneurysms are at high risk of rupture, and careful attention should be paid during surgical procedures. Despite this, an optimal imaging technique to estimate TWRs has not been established. Previously, pressure elevation at TWRs was reported with computational fluid dynamics (CFD) but not fully evaluated.

OBJECTIVE: To investigate the possibility of predicting aneurysmal TWRs at high-pressure areas with CFD.

METHODS: Fifty unruptured middle cerebral artery aneurysms were analyzed. Spatial and temporal maximum pressure (Pmax) areas were determined with a fluid-flow formula under pulsatile blood flow conditions. Intraoperatively, TWRs of aneurysm domes were identified as reddish areas relative to the healthy normal middle cerebral arteries; 5 neurosurgeons evaluated and divided these regions according to Pmax area and TWR correspondence. Pressure difference (PD) was defined as the degree of pressure elevation on the aneurysmal wall at Pmax and was calculated by subtracting the average pressure from the Pmax and dividing by the dynamic pressure at the aneurysm inlet side for normalization.

RESULTS: In 41 of the 50 cases (82.0%), the Pmax areas and TWRs corresponded. PD values were significantly higher in the correspondence group than in the non-correspondence group ($P = .008$). A receiver-operating characteristic curve demonstrated that PD accurately predicted TWRs at Pmax areas (area under the curve, 0.764; 95% confidence interval, 0.574-0.955; cutoff value, 0.607; sensitivity, 66.7%; specificity, 82.9%).

CONCLUSION: A high PD may be a key parameter for predicting TWRs in unruptured cerebral aneurysms.

KEY WORDS: Aneurysm, Computational fluid dynamics, Pressure, Thin-wall region

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Cerebral aneurysms carry a risk of life-threatening rupture and are associated with high rates of mortality and morbidity.[1] Aneurysm rupture is thought to occur at thin-walled regions (TWRs) caused by degeneration resulting from abnormal hemodynamic stress.[2-4] These TWRs have the potential risk of rupture during surgical treatment and are frequently observed on the daughter sacs of aneurysms. Although imaging modalities for evaluation of cerebral aneurysms have improved recently,[5,6] these methods do not directly evaluate the condition of the aneurysm wall. Contrary to expectations, thick-walled regions may be observed on the daughter sac and may not have a high risk for rupture. Thus, evaluation of the wall condition may be important for predicting the risk of rupture during surgical treatment. Computational fluid dynamics (CFD) analyses have been applied for risk analysis of rupture or growth mechanisms in cerebral and unruptured

ABBREVIATIONS: CFD, computational fluid dynamics; **MCA,** middle cerebral artery; **Pave,** average pressure; **PD,** pressure difference; **Pmax,** maximum pressure; **TWR,** thin-walled region; **WSS,** wall shear stress

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intracranial aneurysms. Several parameters such as wall shear stress (WSS), pressure, and energy loss have been studied with regard to anticipation of eventual rupture of unruptured intracranial aneurysms.[7-9] Pressure, a basic hemodynamic parameter within the aneurysm wall, is directed perpendicularly to the wall surface, and although previous studies have reported pressure elevation at TWRs, this finding has not been fully evaluated.[10,11] This study aimed to evaluate aneurysmal TWRs using CFD modeling.

METHODS

Source of the Data and Imaging

This retrospective study included 50 unruptured middle cerebral artery (MCA) aneurysms in 32 women and 18 men (mean age, 62.7 ± 8.73 years; mean aneurysm size, 5.99 ± 1.97 mm) treated by neck clipping at our institution between March 2009 and May 2015; in all cases, operators could observe the aneurysm wall surface directly and clearly. Only patients with unruptured saccular aneurysms and available intraoperative video files, 3-dimensional digital subtraction angiography, or 3-dimensional computed tomography angiography data were included. Aneurysms that were dissecting, fusiform, or clipped after coil embolization were excluded. Ruptured aneurysms were also excluded because of the impaired visualization of the aneurysm wall.

The study protocol was approved by the local ethics committee of our institution.

CFD Modeling

Blood vessel geometry was extracted from computed tomography angiography and digital subtraction angiography images of the head via manual cropping and image thresholding. This information was subsequently converted to a triangulated surface with Real Intage (Cybernet Systems, Tokyo, Japan), which was then used to generate an unstructured computational volumetric mesh. This mesh mainly comprised tetrahedrons and several prism element layers near the wall surface to increase the analytic precision of the boundary layer. After a pulsatile laminar flow, no pressure at the blood vessel outlet, newtonian fluid dynamics, and rigid blood vessel walls with nonslip conditions were assumed, blood flow along the computational mesh was simulated with Navier-Stokes equations. A commercial software package (ANSYS ICEM CFD 14.5, ANSYS Inc, Canonsburg, Pennsylvania) was used to generate mesh and fluid dynamics. Additional details of the CFD modeling are provided in Figure 1. The fluid meshes were composed of 997 311 elements and 486 217 nodes. The analysis domain encompassed the aneurysm inlet side to the outlet side, including the aneurysm dome. The grid independence test was performed on aneurysm models (see **Figures and Table, Supplemental Digital Content**, http://links.lww.com/NEU/A847, which demonstrate the results of grid independence test).

Analysis of Hemodynamic Parameters of the Aneurysm Wall

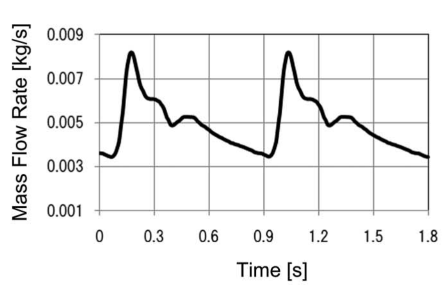
Maximum pressure (Pmax) was calculated as the highest area of pressure at the aneurysm wall, both spatially and temporally. Average pressure (Pave) was also calculated as the mean value of pressure in the domain. For comparisons of aneurysms, the pressure difference (PD) was defined as the degree of pressure elevation at the aneurysm wall at the Pmax area by subtracting Pave from Pmax. This value was divided by the dynamic pressure at the aneurysm inlet side for normalization.

$$PD = \frac{Pmax - Pave}{\frac{1}{2}\rho Vin^2}$$

where Pmax is in Pascals, Pave is in Pascals, ρ is 1100 kg/m^3, and Vin is mean velocity of the aneurysm inlet in meters per second.

At the Pmax area, we also assessed the WSS, frictional force of blood flow along the aneurysm wall. Calculations included the minimum WSS

A



B

Density, ρ	1100 [kg/m^3]
Viscosity	0.0036 [Pa·s]
Computational model	Laminar (Re is approximately 500)
Simulation time step	0.0005 [s]
Inlet condition	Cardiac beat condition (Mass flow rate)
Outlet condition	Fixed static pressure (0 [Pa])

C

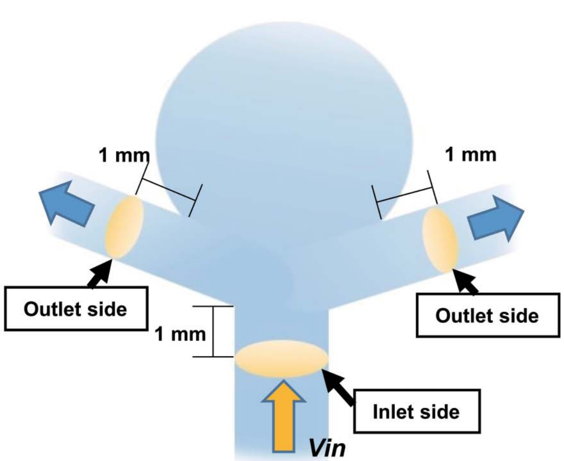


FIGURE 1. *Computational fluid dynamics (CFD) model. Inlet mass flow rate (A) and CFD analysis condition (B) and domain (C).*

as the lowest WSS value, time-averaged WSS as the mean WSS value, and normalized WSS as the minimum WSS value divided by the mean WSS of the vessel wall at the inlet side.

Semiquantitative Assessment of TWRs of Aneurysms

Clipping was performed with the use of the Zeiss OPMI PENTERO 900 surgical microscope (Zeiss, Oberkochen, Germany) or Olympus OME-8000 microscope (OLYMPUS, Tokyo, Japan) to treat all MCA aneurysms. Intraoperative video recording was performed in all cases. On the basis of previous studies,[3,10,12] the thin-walled surfaces of the aneurysms were defined as a region having red color, translucence, and extreme wall thinness compared with healthy areas of the MCA. Five neurosurgeons reviewed the intraoperative videos and scored the aneurysm walls on a 5-point scale to compare the Pmax point of the aneurysm dome with those of normal MCAs (Figure 2). The observers were not provided the CFD maps. They only noted the intraoperative view and the Pmax point, which is indicated by an asterisk. We defined thin-walled areas as those having average scores of ≥4 points.

Statistical Analysis

Continuous data are shown as mean ± SD. Statistical analysis was performed with R version 3.1.3 (R Project for Statistical Computing, Vienna, Austria). An overall significance level of $P < .05$ was adopted. We evaluated the normality of all parameters using the Kolmogorov-Smirnov test. We used the *t* test to analyze parameters for which the normality assumption could not be rejected at a significance level of 0.05 and the Mann-Whitney *U* test to analyze parameters for which normality could not be established. To assess the accuracy of TWR predictions, a receiver-operating characteristic analysis was performed to determine the area under the curve, cutoff value, sensitivity, and specificity.

RESULTS

In 41 of 50 cases (82.0%), the Pmax area corresponded to the TWRs (Figures 3A and 3B); in 9 cases, the Pmax area did not correspond to the TWR (Figure 4). Comparisons of sex, age, size, and hemodynamic aneurysm parameters between the correspondence and noncorrespondence groups are shown in the Table. The PD of the correspondence group was significantly higher than that of the noncorrespondence group ($P = .008$; Figure 5A); however, the minimum WSS, time-averaged WSS, and normalized WSS did not significantly differ. The receiver-operating characteristic curve demonstrated that the PD value could accurately predict TWRs (area under the curve, 0.764; 95% confidence interval, 0.574-0.955; cutoff value, 0.607; sensitivity, 66.7%; specificity, 82.9%; Figure 5B).

DISCUSSION

Our study focused on pressure, a basic hemodynamic parameter of the aneurysm wall. Most CFD studies have attempted to elucidate the involvement of WSS in aneurysm rupture. However, information on this involvement remains unclear because few studies have evaluated pressure in the aneurysm wall.[10,11]

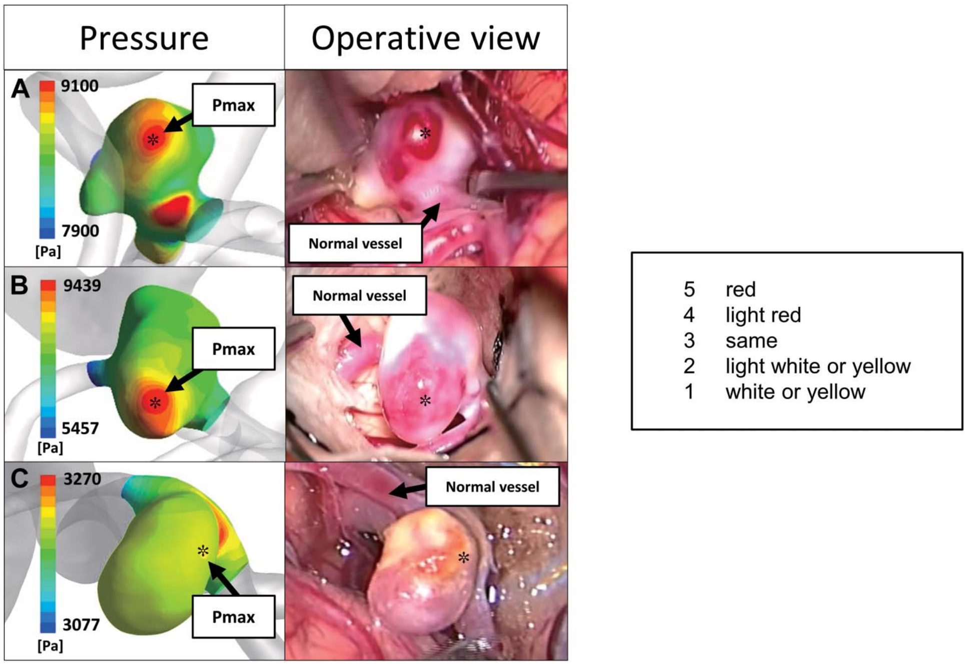


FIGURE 2. *Three examples of analytical computational fluid dynamics.* **Left**, *the maximum pressure (Pmax) point of the aneurysm dome is indicated by an asterisk.* **Right**, *intraoperative view. Neurosurgeons scored the area indicated by an asterisk on a 5-point scale relative to the normal, healthy vessel. The average aneurysm wall scores are (***A***) 5.0, (***B***) 3.4, and (***C***) 2.6.*

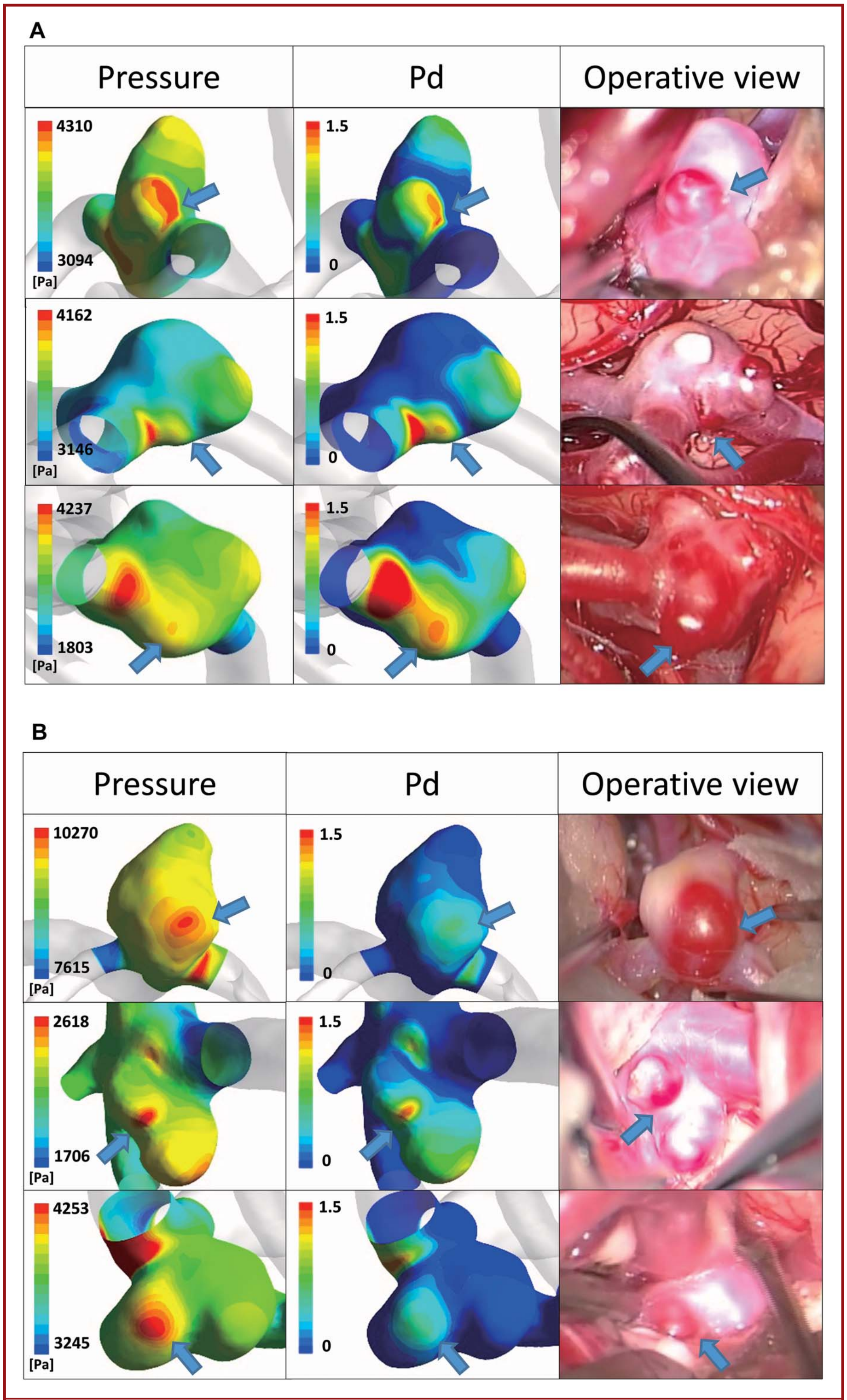


FIGURE 3. A *and* B*, pressure distributions (*left*), pressure difference (PD;* middle*), and intraoperative views (*right*) of 6 representative aneurysms. The maximum pressure areas (Pmax;* arrow*) correspond to thin-walled regions of the aneurysm domes.*

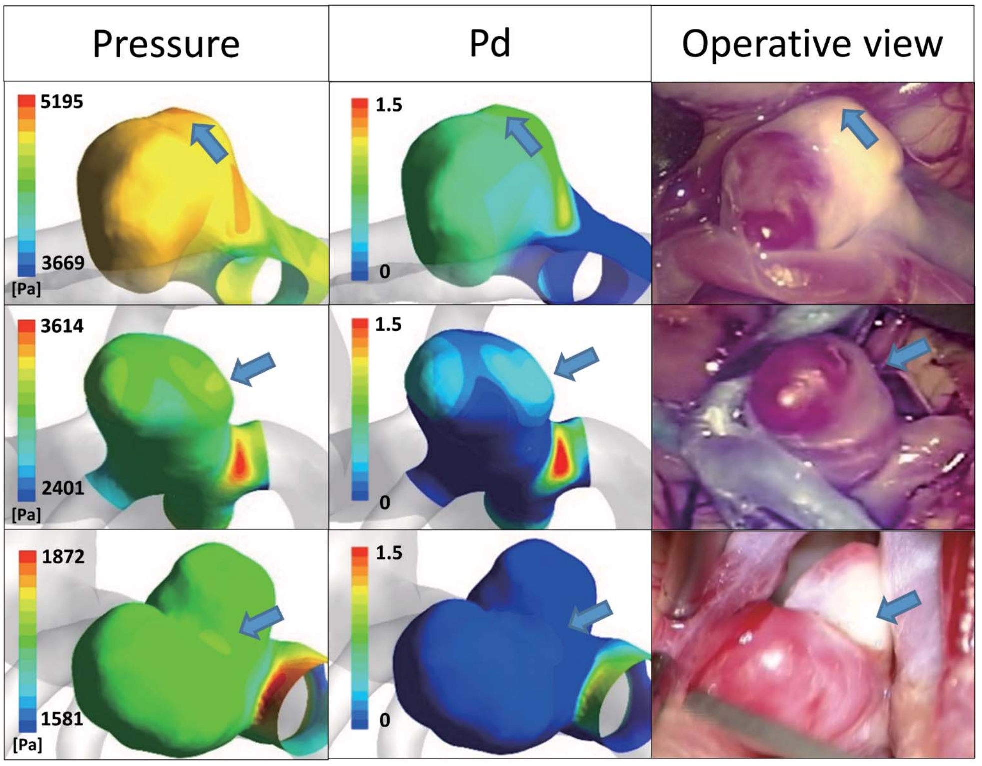


FIGURE 4. *Three representative aneurysms in the noncorrespondence group. The maximum pressure areas (Pmax;* **blue arrow***) do not correspond to the thin-walled regions of these aneurysms.*

Previously, Kadasi et al[10] reported the colocalization of TWRs with areas of low WSS. That study included a small number of cases and reported focal pressure elevation at TWRs. Although aneurysm rupture is thought to occur in TWRs, only a few reports have evaluated these regions.[3,10,12] In our study, we assessed 50 aneurysm wall surfaces using intraoperative videos and investigated the correlation between pressure elevation and TWRs in greater detail. Most Pmax areas (82.0%) corresponded

TABLE. Statistical Comparison of Aneurysms Between the Correspondence and Noncorrespondence Groups[a]

	Noncorrespondence Group (n = 9)	Correspondence Group (n = 41)	P^b
Sex, n (%)			.06
Male	6 (33.3)	12 (66.7)	
Female	3 (9.3)	29 (90.7)	
Age, y	61.5 ± 0.12	63.0 ± 8.52	.66
Size, mm	5.45 ± 1.43	6.11 ± 2.06	.44
Vin, m/s	0.764 ± 0.435	0.863 ± 0.332	.45
Minimum WSS, Pa	2.720 ± 3.870	3.881 ± 3.113	.06
Time-averaged WSS, Pa	6.068 ± 8.904	9.914 ± 11.301	.11
Normalized WSS	0.340 ± 0.326	0.539 ± 0.355	.10
Pave, Pa	3522 ± 2266	3878 ± 2412	.67
Pmax, Pa	3859 ± 2739	4340 ± 2644	.50
PD	0.585 ± 0.377	0.986 ± 0.397	.008

[a]Pave, average pressure; PD, pressure difference; Pmax, maximum pressure; Vin, mean velocity of the aneurysm inlet; WSS, wall shear stress. Values are shown as mean ± SD when appropriate.
[b]The *t* test, Mann-Whitney *U* test; $P < .05$ was considered statistically significant.

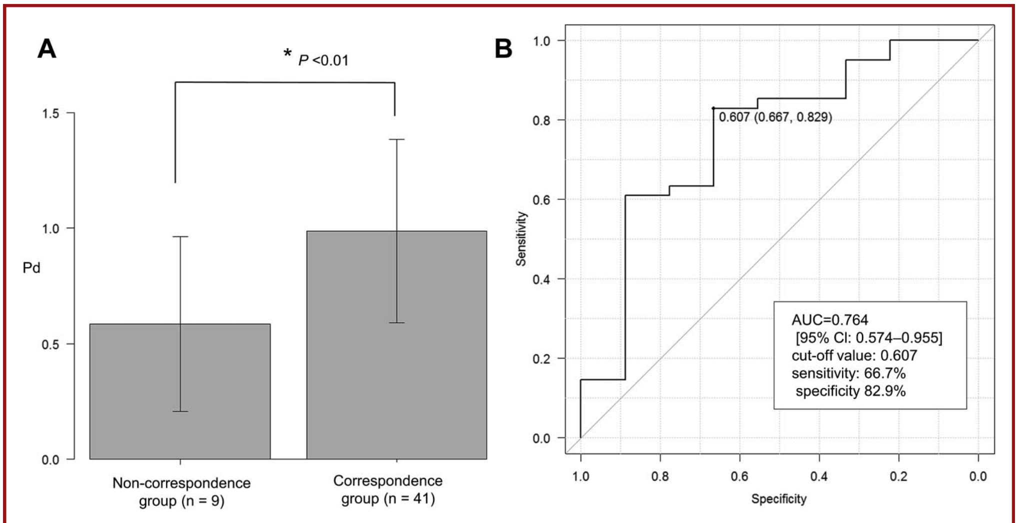


FIGURE 5. **A**, *comparison of pressure difference (PD) values between the correspondence and noncorrespondence groups.* **B**, *receiver-operating characteristic curve of PD for predicting thin-walled regions. AUC, area under the curve.*

with TWRs. Furthermore, we defined PD by using a formula for calculating the degree of pressure elevation in the aneurysm wall at the Pmax area, and when aneurysms were compared, a higher PD value predicted a TWR at the Pmax area. Shojima et al[13] reported that local pressure elevation resulting from a blood-stream-impacting force was not sufficient to contribute to aneurysm rupture. However, in that study, the authors did not appropriately evaluate the aneurysm wall surface. Biologically, pressure elevation has been estimated to induce endothelial damage and to activate inflammatory cascades, hypertrophy, migration, and extracellular matrix imbalances.[14] Accordingly, pressure is a nonnegligible hemodynamic force on the aneurysm wall. Our study presents a preliminary investigation of the correlation between high-pressure areas and TWRs of aneurysms.

According to the results of our study, although no significant correlation was observed between the relevant WSS parameters and TWRs, a relatively higher WSS corresponded with TWRs at the Pmax area. Although we focused only on TWRs in Pmax areas, these results were different from those reported by Kadasi et al.[10] Cebral et al[15] described a high WSS and impingement flow zone at the rupture site. These Pmax areas were almost always observed at the first or second impact zone after the impact at the aneurysm neck, suggesting that the hemodynamic parameters of TWRs observed in our study are similar to those at the rupture site, as described by Cebral et al.[15] Estimating the presence of TWRs is very useful for the treatment of cerebral aneurysms not only during open surgery but also during endovascular surgery, an increasingly common treatment that is performed depending on aneurysm wall surfaces. In the cases in which aneurysm blebs with high PD values were located near the neck, along with a thin, reddish wall, early and careful treatment should be considered[16,17] because these morphological configurations have been associated with a high risk of rupture.

Limitations

The present study has some limitations. First, we evaluated only aneurysms that were located in the MCA because this vessel facilitates complete visualization of the aneurysm dome surface relative to other aneurysm locations such as the anterior communicating artery and internal carotid artery. Future studies should evaluate aneurysms in other locations. Second, the boundary conditions were uniform across all cases, whereas in practice, these conditions may vary among cases. For patient-specific analysis, boundary conditions could be established with magnetic resonance imaging and echocardiographic imaging, if available. Third, the vessel walls were also assumed to be rigid, whereas in practice, they may deform to a different degree during the cardiac cycle.

Fourth, the TWR evaluation method was relatively subjective. The exact wall thickness was not measured because of its aneurysmal nature. Histopathological validation will be needed. Finally, the present study performed retrospective analyses of a limited number of cases. Additional prospective and multicenter studies are warranted to clarify the correlations between hemodynamic parameters and TWRs of aneurysms.

CONCLUSION

Areas of Pmax may be important markers of TWRs in unruptured cerebral aneurysms. Through calculation of the PD value for each aneurysm type with CFD, estimation of the accuracies of predictions of the presence of TWRs may be possible. In the surgical treatment of cerebral aneurysms, high PD provides useful information for avoiding the risk of rupture that may result in fatal outcomes.

Disclosures

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COMMENT

The authors have chosen an interesting approach to the difficult problem of correlating hemodynamic parameters obtained from computational fluid dynamics with physiological effects in unruptured cerebral aneurysms. They were able to demonstrate that thin-walled regions of the aneurysm dome, considered a potential precursor for aneurysm rupture, are exposed to high maximum pressure (Pmax) values. These results indicate that intra-aneurysmal pressures may play a more important role in aneurysm rupture than wall shear stress or energy loss. Despite 2 obvious limitations of the study, the pressure values were calculated from various assumptions and the wall thickness was only visually assessed instead of being directly measured, the authors should be congratulated on their work.

Goetz Benndorf
Odense, Denmark