ORIGINAL RESEARCH

Hemodynamic characteristics of large unruptured internal carotid artery aneurysms prior to rupture: a case control study

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Received 10 December 2014
Revised 8 January 2015
Accepted 13 January 2015

ABSTRACT

Objective Post-ruptured intracranial aneurysm geometry models have been widely used in computational fluid dynamic studies to assess hemodynamic parameters associated with aneurysm rupture. However, their results may not be valid due to the morphological changes of the aneurysm after rupture. Our aim was to identify the hemodynamic features of aneurysms prior to rupture in comparison with unruptured aneurysms.

Materials and methods We retrospectively identified three large unruptured internal carotid artery (ICA) aneurysms (pre-ruptured group) with adequate image quality just before rupture. Matched with the same location and similar size, eight unruptured aneurysms (unruptured group) were selected as controls during the same time period. Flow simulations for these aneurysms were performed to compare differences in hemodynamics.

Results Compared with unruptured aneurysms, pre-ruptured aneurysms had a significantly more irregular aneurysm shape, a higher aspect ratio, and lower aneurysm averaged wall shear stress (WSS) ($p=0.024$, $p=0.048$, and $p=0.048$, respectively). Although pre-ruptured aneurysms had a lower low WSS area and higher Oscillatory Shear Index, these were not statistically significant.

Conclusions For large unruptured ICA aneurysms, low WSS, higher aspect ratio, and irregular shape were indicators of fatal rupture. Early treatment for such lesions with flow diverter and coils may be the best therapeutic option.

INTRODUCTION

Rupture of intracranial aneurysms (IAs) is associated with high mortality and morbidity rates.[1,2] With the rapid advancements in cerebral vascular imaging technology, more and more asymptomatic IAs are being detected. Treatment decisions for unruptured IAs are still very difficult for both patients and surgeons. Rupture predictions for unruptured asymptomatic IAs remain challenging. Larger aneurysm size was regarded as an important indicator for aneurysm rupture. However, not all large IAs left untreated will eventually rupture and many small ones may rupture.[3,4]

Computational fluid dynamics (CFD) has been widely used in assessing hemodynamic parameters to stratify the rupture status of IAs. However, their results are controversial, and both high and low wall shear stress (WSS) were found to be associated with aneurysm rupture.[5–8] Morphological changes after aneurysm rupture, which leads to alteration in hemodynamic features, may be one reason. Some researchers believe that results based on post-ruptured geometric models may not be valid.[9,10] To understand the association between IA rupture and hemodynamic factors, it is important to demonstrate the hemodynamic characteristics of IAs just before rupture.

Obtaining adequate three-dimensional (3D) geometry data of IAs hours or days before rupture are difficult. There are only a few studies on the hemodynamic characteristics of IAs just before rupture, and most are single case reports. Furthermore, the results are not consistent.[9,11–14]

The aim of this study was to identify the hemodynamic features of IAs prior to rupture from our IA database.

METHODS

Patient selection

This study was approved by the ethics committee of our hospital. We retrospectively reviewed the medical records and image data in our aneurysm database. Five patients had sufficient 3D digital subtraction angiography (DSA) images a few days before their aneurysm rupture. Two aneurysms were excluded because of inadequate image quality for computational simulation and dissecting aneurysm features. The remaining three patients, who suffered a subarachnoid hemorrhage a few days after the diagnostic DSA procedures (2, 3, and 5 days, respectively), were included in this study as the pre-ruptured group.

The selected patients were admitted to our hospital between December 2011 and December 2013, and were diagnosed with large unruptured saccular internal carotid artery (ICA) aneurysms (12.3 mm at the ophthalmic segment, 14.7 mm at the ophthalmic segment, and 22.4 mm at the communicating segment, for the three cases, respectively) (figure 1). In our study, aneurysm size was categorized based on the criteria of the International Study of Unruptured Intracranial Aneurysms (ISUIA) (small, <10 mm; large, 10–25 mm; giant, >25 mm).[15] Controls, who presented without a history of subarachnoid hemorrhage, were selected as the unruptured group during the same time period (December 2011–December 2013) using the following four criteria: (1) IAs were from the same location (ophthalmic and communicating segments of the ICA) and had a similar size (10–25 mm); (2) 3D DSA

To cite: Liu J, Fan J, Xiang J, *et al. J NeuroIntervent Surg* Published Online First: [*please include* Day Month Year] doi:10.1136/neurintsurg-2014-011577

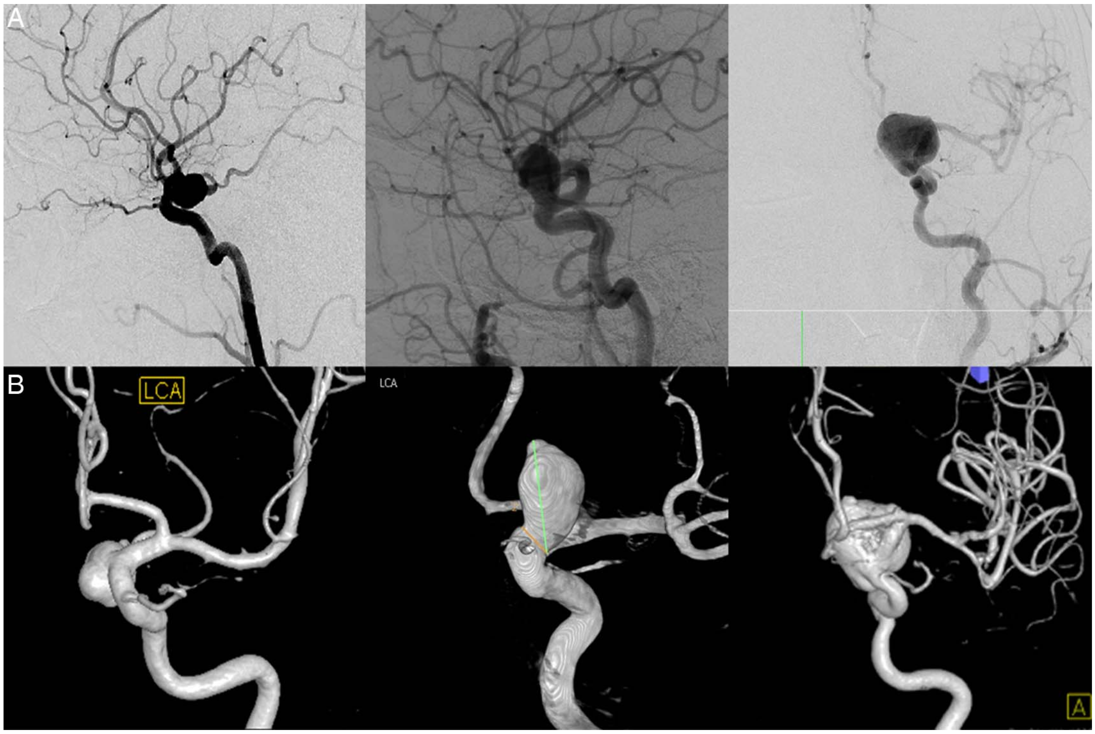

Figure 1 Digital subtraction angiography of the three pre-ruptured cases. (Row A) Conventional angiography of the three aneurysms. (Row B) Three-dimensional rotational angiography of the three aneurysms (case 1, left; case 2, middle; case 3, right).

images of the IAs were adequate for CFD analysis; (3) unruptured IAs were monitored for at least 3 months without rupture; and (4) IAs diagnosed as dissecting aneurysms were excluded. During this period, 894 patients with 985 aneurysms were admitted. Of these, 86 patients had large ICA aneurysms (ophthalmic and communicating segments). According to the above criteria, eight large unruptured ICA aneurysms were finally included in the control group.

Clinical and morphological factors for all 11 patients (age, sex, smoking history, hypertension (HTN), presenting symptom, aneurysm size, aneurysm shape, size ratio (SR), and aspect ratio (AR)) were collected and calculated. In this study, aneurysm shape was categorized as regular or irregular. Irregular shape was defined as aneurysms with irregularities due to bilobate bleb, polylobate bleb, or intra-aneurysmal thrombosis.[4 16] SR and AR, described by Dhar *et al*,[17] were calculated from 3D images. The characteristics of the two groups are summarized in table 1.

Image reconstruction and CFD modeling

Image reconstruction and CFD numerical simulation of blood hemodynamics was performed as described previously.[4 18] Briefly, we first segmented the 3D images using standard proprietary software and saved the segmented surface geometry into a standard tessellation language format.

Prior to meshing, the aneurysm model was subdivided into the aneurysm sac and the parent artery regions. Each model was imported into the ICEM CFD (ANSYS Inc, Canonsburg,

Table 1 Individual patient characteristics

Patient No	Age	Presenting symptoms	Smoking	HTN	Maximum diameter (mm)	Location*	SR	AR	Shape	Time interval†
P1	70s	Severe headache	No	No	12.3	Lt C7	2.72	1.45	Irregular	5 days
P2	40s	Headache	Yes	No	14.7	Lt C6	4.32	2.72	Irregular	2 days
P3	60s	Dizziness	Yes	No	22.4	Lt C7	4.80	1.96	Irregular	3 days
U1	50s	Headache	No	Yes	10.1	Lt C6	3.58	1.43	Regular	3 months
U2	70s	Headache	No	No	16.0	Lt C6	2.70	1.85	Regular	8 months
U3	60s	Incidental	No	Yes	11.9	Lt C7	3.01	1.44	Irregular	3 months
U4	50s	Headache, dizziness and tinnitus	No	No	10.7	Rt C6	3.07	1.61	Regular	4 months
U5	50s	Transient dizziness	No	No	14.7	Lt C7	3.17	1.27	Regular	18 months
U6	70s	Incidental	Yes	Yes	11.4	Rt C7	2.80	1.10	Regular	5 months
U7	40s	Left blurred vision	No	No	11.5	Lt C6	3.17	1.21	Regular	5 months
U8	30s	Headache	Yes	Yes	10.0	Rt C6	2.56	1.16	Regular	4 months

*The Bouthillier classification of internal carotid artery segments: C4, cavernous; C5, clinoid; C6, ophthalmic; C7, communicating.
†The time interval for pre-ruptured cases indicates the time between angiography and eventual rupture. For unruptured cases, the time interval indicates the monitoring period from diagnosis.
AR, aspect ratio; HTN, hypertension; Lt, left; P, pre-ruptured case; Rt, right; SR, size ratio; U, unruptured case.

Pennsylvania, USA) to create approximately 1 million finite volume tetrahedral element grids with four layers of prism elements for accurate calculation of WSS.

ANSYS CFX 14.0 (ANSYS Inc) was then used to solve the flow governing Navier–Strokes equations with the assumption of laminar, incompressible, and Newtonian blood flow. The density and dynamic viscosity of blood were specified as 1060 kg/m^3 and 0.004 N s/m^2, respectively. The blood vessel wall was assumed to be rigid with no slip boundary conditions. A pulsatile velocity profile obtained by transcranial Doppler was applied for the inflow boundary condition by superimposing the Womersley velocity profile.[18] A traction free boundary condition was applied to all outlets.[19] Initial pressure and velocity were set to zero. Eight hundred time steps (0.001 s/step) were set for each cardiac cycle. Two cardiac cycles were simulated for numerical stability. Results from the second cardiac cycle were collected as output for hemodynamics post-processing.

Hemodynamics analysis

Hemodynamic parameters, including time averaged WSS (TAWSS), Oscillatory Shear Index (OSI), and low WSS area (LSA), were calculated based on the simulated pulsatile flow simulations. In this study, TAWSS distributions were normalized by the parent artery averaged TAWSS in the same patient to allow comparison among different cases. LSA was defined as the area of the aneurysm wall exposed to a TAWSS below the threshold that was 10% of the parent artery TAWSS[4 6] and then normalized by aneurysm sac area. For quantitative comparisons, TAWSS and OSI were further averaged over the aneurysm sac.

Statistical analysis

For continuous parameters, the Mann–Whitney test was performed for statistical analysis between two groups. Fisher's exact test was used appropriately for categorical parameters. A p value <0.05 was regarded as statistically significant. Both tests are robust and suitable for small sample size. SPSS V.17.0 software was used for statistical analysis (SPSS, Chicago, Illinois, USA).

RESULTS

Clinical factors and aneurysm morphology

In our study, mean age of the study population was 58.45 years. Patients in pre-ruptured group were older than the controls. Forty-five per cent (5/11) of the study population were female and all were from the unruptured group. Nine patients showed clinical symptoms and the remaining two from the control group were incidental (table 1). In the pre-ruptured group, the proportion of patients with a history of smoking was higher; however, it was lower for HTN. There were no statistically significant differences in clinical factors (age, gender, symptoms, cigarette smoking, and history of HTN) between the two groups (table 2).

The mean maximum size of the pre-ruptured aneurysms was larger than that of the unruptured aneurysms (16.47 vs 12.04 mm) and there was no significant difference between the two groups (p=0.085). Both SR and AR were higher in the pre-ruptured group. The difference in AR was statistically significant between the two groups (p=0.048). All of the pre-ruptured IAs (100%) were irregular in shape with daughter blebs. In contrast, only one aneurysm (12.5%) from the unruptured group had daughter blebs. The difference in aneurysm shape was significant (Fisher's exact test, p=0.024) (table 2).

Table 2 Patient demographics and aneurysm morphology in the pre-ruptured and unruptured aneurysms

	Pre-ruptured group (n=3)	Unruptured group (n=8)	p Value*
Age (years) (mean±SD)	60.33±16.56	57.75±13.46	0.776
Female sex (n (%))	0/3(0.00)	5/8 (62.50)	0.182
Symptoms (n (%))	3/3 (100.00)	6/8 (75.00)	1.000
Smoker (n (%))	2/3(66.67)	2/8 (25.00)	0.491
Hypertension (n (%))	0/3(0.00)	4/8 (50.00)	0.236
Maximum size (mm) (mean±SD)	16.47±5.28	12.04±2.18	0.085
Size ratio (mean±SD)	3.95±1.09	3.01±0.32	0.279
Aspect ratio (mean±SD)	2.04±0.64	1.38±0.25	0.048
Irregular shape (n (%))	3/3(100.00)	1/8 (12.50)	0.024

*Mann–Whitney test or Fisher's exact test as appropriate. A p value <0.05 was considered statistically significant.

Hemodynamic characteristics

TAWSS distributions are showed in figure 2. In the pre-ruptured group, TAWSS was lower within the aneurysm sac than that in the parent arteries, whereas in the unruptured group they were comparable. Compared with unruptured aneurysms, pre-ruptured cases had lower WSS magnitudes and larger low stress areas.

The results of the hemodynamic parameters from univariate analyses are shown in table 3. Using the Mann–Whitney test, aneurysm averaged TAWSS was significantly lower in the pre-ruptured group than in the unruptured group (p=0.048). In addition to TAWSS, LSA in the pre-ruptured group was twice as large as that in the unruptured group. However, the difference was not statistically significant (p=0.085). In addition, although aneurysm averaged OSI in the pre-ruptured group was higher than that in the unruptured group, the difference was not statistically significant (p=1.000).

DISCUSSION

In most previous CFD studies,[5–8] post-ruptured patient specific IA models were used to perform flow simulations. Evidence showed that the simulation results were altered by the morphologic changes of the IAs after rupture.[9 10] In the current study, we compared hemodynamic parameters between pre-ruptured and unruptured (controls) aneurysm models. Lower WSS in large unruptured ICA aneurysms was found to be a significant hemodynamic characteristic associated with fatal rupture.

From the literature, a few case reports have addressed the hemodynamic features of IAs just before rupture.[11–14 20–22] However, most of the reported cases were rebleeding IAs and the results were inconsistent. Based on a rebleeding IA geometry model, Kono *et al*[11] performed a CFD study to determine the characteristic patterns of hemodynamic parameters that were related to the rupture site. The rupture site was confirmed at one of the blebs and it showed a low WSS at end diastole and high pressure at peak systole. Hodis *et al*[20] also reported a case that spontaneously re-ruptured immediately following 3D rotational angiography. WSS and pressure at peak systole were both maximal near the rupture location. However, our geometric models were based on unruptured IAs that ruptured in the following days. It is possible that the mechanism of aneurysm rupture is not the same in the first rupture and rebleeding procedures.

There are three studies describing multiple pre-ruptured cases and two are case control studies. Based on pre-ruptured imaging

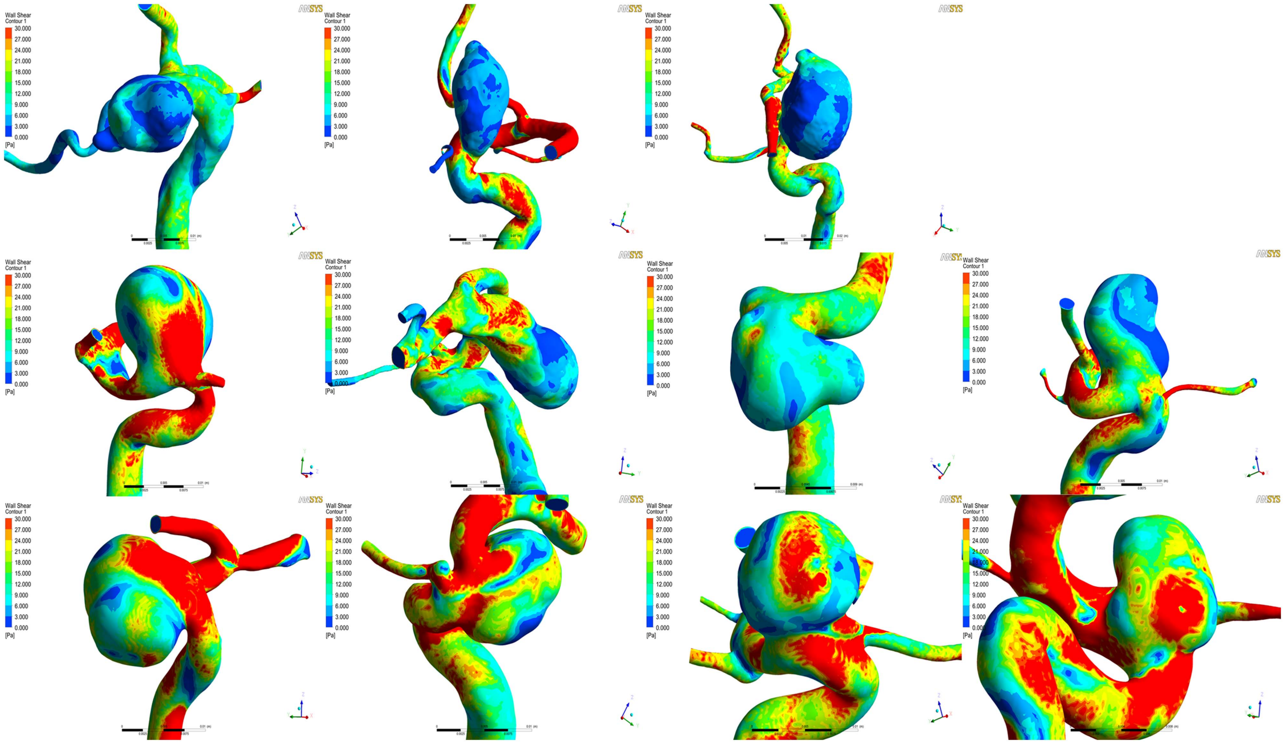

Figure 2 Distribution of wall shear stress for the three pre-ruptured (top row) and eight unruptured (second and third rows) cases. The pre-ruptured aneurysms showed a lower magnitude of wall shear stress.

of four small IAs, Pereira *et al*[21] performed a case control study to evaluate the use of computed hemodynamics and to detect IAs prone to rupture. According to their supplementary data, WSS derived parameters in their cases were lower than those in controls. However, no statistically significant differences were found. This was a good study with description of rare cases, but the cases originated from different locations, which may have influenced the results. Takao *et al*[22] did similar research and found that the minimum WSS was significantly different between ruptured and unruptured ICA aneurysms (0.0222 and 0.0407 pa, respectively; $p<0.001$). However, as there was a relatively long time interval between pre-ruptured imaging and rupture events in these two studies, the unobserved morphological changes could have occurred during the monitoring period. In addition, all of their cases were 5–10 mm in size.

Recently, Duan *et al*[14] published their matched case control study which included six patients with posterior communicating artery aneurysms that eventually ruptured within 7 days. Compared with controls, a lower WSS was significantly associated with rupture of posterior communicating artery aneurysms. Mean aneurysm size was small and it was not clear whether the cases rebled. In our study, these three cases also had a short time interval between 3D angiography and IA rupture. After the CFD simulation, we found that aneurysm averaged TAWSS was significantly lower in these rare cases than in controls. Our results are consistent with these three previous studies. By analyzing all large aneurysms from a single ICA location, we found further support for lower WSS being associated with pre-ruptured aneurysms. Low WSS could trigger inflammatory cell mediated pathways and this process is accompanied by increased inflammatory cell infiltration.[23 24]

Currently, WSS is controversial in stratifying aneurysm rupture status.[5–8] Xiang *et al*[6] reported that low WSS was a risk factor for aneurysm rupture. However, a study from Cebral *et al*[8] showed that ruptured aneurysms were more likely to have a larger maximum WSS. Meng *et al*[23 24] proposed a new concept that both low and high WSS could drive IA growth and rupture via different biological mechanisms. Except for the effect of low WSS, the mural cell mediated pathway induced by high WSS could lead to extracellular matrix degradation and cell death. This mechanism might also be involved in the process of IA growth and rupture. In our unruptured group, the aneurysms showed a relatively high WSS. Although the control cases had remained stable over at least 3 months, the time intervals were still short. Left untreated, we were unsure whether the IAs might undergo growth or rupture in the future.

Morphological assessment of IAs was effective and reproducible in terms of treatment decision. Unruptured IAs with an irregular shape or blebs are strongly advised to undergo treatment.[3 16] Previous studies and the current result support this conclusion.[4 18] Associated with a higher rupture risk, the

Table 3 Univariate analysis results for hemodynamic parameters examined between the two groups

Parameters	Pre-ruptured group (n=3)	Unruptured group (n=8)	p Value*
TAWSS	0.30±0.06	0.48±0.13	0.048
LSA	12.39±4.63	6.28±5.16	0.085
OSI	0.05±0.04	0.04±0.03	1.000

*The Mann–Whitney test was used, and a p value <0.05 was considered statistically significant.
LSA, low wall shear stress area; OSI, Oscillatory Shear Index; TAWSS, time averaged wall shear stress.

complex flow pattern and larger low WSS area were found more commonly in aneurysms with an irregular shape or blebs.[18 25] Other than aneurysm shape, aneurysm size was another important factor. However, aneurysm size remains conflicting. According to the traditional view, large IAs are more likely to rupture than small ones.[3] However, some small or very small IAs do rupture, and some large or giant IAs remain stable. We have studied rupture of paraclinoid aneurysms and found that ruptured aneurysms were significantly smaller in size.[4] However, the ISUIA reported a rupture rate of 0.05% per year in patients with aneurysms <10 mm in diameter and of about 1% per year for those with aneurysms ≥10 mm in size.[15] However, large aneurysms warrant careful consideration for treatment.[2] For a better assessment, SR and AR were introduced for the assessment of rupture risk. Consistent with previous studies,[17 25] ruptured cases had higher SR and AR values in our study, and AR showed a statistically significant difference. As demonstrated by Ujiie *et al*,[25] complex flow patterns with slow secondary flow were observed in IAs with a higher AR. The reason why SR was not significant in this study may be due to the relative small sample size.

Demographic factors, such as age, gender, smoking history, and HTN, should also be taken into consideration during the treatment decision. Juvela *et al*[1] found that cigarette smoking, younger age, being female, and HTN were associated with a higher rupture risk. Another meta-analysis showed that the factors that had a significant association with an increased risk of rupture of IAs were age older than 60 years, female gender, and Japanese or Finnish descent.[26] Smoking increased the risk of rupture, but this factor was not statistically significant. In our study, none of the demographic factors showed significant differences which may have been due to the small sample size.

Neurologic symptoms for aneurysms have generally been regarded as high risk for future rupture.[2] More commonly, symptomatic aneurysms were larger. However, in our study, only two patients presented with specific symptoms that were considered to be definitively caused by the aneurysm. Pre-ruptured case No 1 presented with onset of severe headache within 4 weeks before rupture, and unruptured case No 7 complained of progressively blurred vision on the left side. These data may be beneficial for clinical management. Therapeutic indications for large aneurysms based on symptoms, location, shape, and size are probably safer than waiting for WSS changes in the control group. Therefore, comprehensive assessment of large ICA IAs, including hemodynamic parameters, morphological factors, and clinical features, should be recommended.

Other than traditional endovascular treatment, the therapeutic options for large aneurysms with an unfavorable morphology normally include flow diverter treatment. Alteration of intra-aneurysmal hemodynamics by flow diverter was significant, and velocity and WSS were greatly reduced.[27–29] More importantly, low WSS was associated with aneurysm rupture.[6] In this instance, using coils in conjunction with a flow diverter may be the optimal treatment. Coils could facilitate the formation of intra-aneurysmal thrombosis and prevent post-procedural rupture.[30]

The present study had some limitations. Firstly, all of the cases came from a single center and the sample size was small. Further studies with a large cohort from multiple centers are required to validate these findings. Secondly, it would be interesting to do a case control study in the same patients based on geometry before and after rupture. However, post-ruptured 3D geometric data in these three cases were not available because of the emergency situation or the treatment strategy. Thirdly, we used control aneurysms to evaluate rupture risk in the near future. Therefore, we believe that 3 months of follow-up may have been enough in this research. However, 3 months of follow-up is too short for common research of rupture risk. Short term follow-up may have influenced the results, and the conclusions may not be valid. Fourthly, rigid wall, laminar flow, and Newtonian blood assumptions were used in our IA models for CFD simulations. Finally, our results may not be applicable to small aneurysms or aneurysms from other locations.

CONCLUSIONS

For large unruptured ICA aneurysms, low WSS, higher AR, and irregular shape were indicators of fatal rupture. Early treatment for such lesions with flow diverter and coils might be the best therapeutic option.

Contributors JL and JF contributed equally to the preparation of the manuscript and data collection. JX contributed to revising the manuscript. YZ contributed to data analysis. XY contributed to the experimental design.

Funding This work was supported by the National Natural Science Foundation of China (grant Nos 81301003, 81171079, 81371315, and 81220108007) and by the Special Research Project for Capital Health Development (grant No 2014-1-1071).

Competing interests None.

Ethics approval This study was approved by the ethics committee of Beijing Tiantan Hospital.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The authors agree to share any data on request. Any data from this study are available by contacting the corresponding author.

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