Morphological and Hemodynamic Differences Between Ruptured and Unruptured Vertebral Artery Dissecting Aneurysms: A Two-Center Retrospective Study

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Abstract

Purpose

The morphological and hemodynamic features of patients with vertebral artery dissecting aneurysms (VADAs) are yet unknown. This study sought to elucidate morphological and hemodynamical features of patients with ruptured and unruptured VADAs.

Methods

This study recruited 31 patients with unruptured VADAs and 21 patients with ruptured VADAs who were treated at two hospitals. We collected data on their clinical, morphological, and hemodynamic characteristics. After reconstructing a patient-specific model, computational fluid dynamics (CFD) was performed. Binary logistic regression was used to analyze significant parameters and identify independent risk factors. Receiver operating characteristic (ROC) analysis identified cut-off values separating ruptured from unruptured aneurysms for each parameter.

Results

Three hemodynamic parameters were observed to be significantly different between ruptured and unruptured VADAs: intra-aneurysmal pressure (IAP), wall shear stress (WSS), and normalized pressure (NP). However, no morphological parameters had a significant difference between ruptured and unruptured VADAs. Binary logistic regression analysis revealed that IAP (AUC = 0.9662, 95% CI 1.014–1.068) and WSS (AUC = 0.7873, 95% CI 1.124–16.859) were independently significant variables in the hemodynamics model.

Conclusion

This study indicated significant hemodynamic differences but no significant morphological difference between ruptured and unruptured VADAs. Hemodynamic parameters of IAP and WSS are important in discriminating VADAs rupture status. These results should be confirmed through future larger studies.

Introduction

Vertebral artery dissecting aneurysms (VADAs) refer to a tear in the vertebral artery that results in an intramural hematoma and/or an aneurysmal dilatation, accounting for an average annual incidence rate of approximately 0.97–1.5 cases per 100 population¹. At present, the etiology of VADAs remains unclear, most literature believes that they occur spontaneously, while other reports speculate that a potentially fatal arterial injury causes them to occur during sports^{2,3}. VADAs present with symptoms of posterior

circulation ischemia due to vertebrobasilar artery ischemia and brain stem compression or with subarachnoid hemorrhage, resulting in high morbidity and mortality rates⁴. Therefore, some researchers suggest that early treatment of VADAs is necessary because rebleeding after rupture is very common⁵. Given the not-insignificant risk of treating unruptured VADAs as well as the known severe morbidity of aneurysm rupture, deciding on those aneurysms that require prophylactic treatment can be a quandary.

Numerous researches have been conducted on the risk of aneurysm rupture, but prediction accuracy remains not ideal⁶. There were some researches on the relationship between the morphological parameters and rupture risk of saccular aneurysms, but they have not been reported in VADAs. More recently, several publications have focused on the relationship between hemodynamics and IAs. Hemodynamics have been demonstrated to be crucial in development, growth, and rupture of saccular IAs⁷. However, there are no report on hemodynamics with the rupture risk of VADAs.

This study aimed to identify morphological and hemodynamic risk factors of rupture among patients with VADAs to guide the treatment strategy of unruptured VADAs.

Material And Methods

Protocol

This study was approved by Clinical Research Ethics Committee of Renmin Hospital of Wuhan University, all methods were carried out in accordance with the guidelines and regulations for the Ethical Review of Biomedical Research involving Human beings issued by the National Health Commission of China in 2016. All the patients signed the informed consent form after admission and before operation.

Patient selection

All patient's data were retrospectively reviewed including imaging data and medical records from the electronic medical record system in two medical research centers. 52 consecutive patients who were diagnosed with VADAs were collected from March 2015 to May 2021. Cerebral Digital subtraction angiography (DSA) was used to diagnose all aneurysms. The clinical and serial imaging data of all patients were completed. Two neurosurgeons with over 10 years of experience in the interpretation of cerebral angiograms and the endovascular treatment of IAs confirmed the findings.

Inclusion criteria: (1) aneurysm located in the intracranial segment of the vertebral artery (V4 segment); (2) dissecting aneurysm. Exclusion criteria: (1) saccular aneurysms; (2) aneurysm located in the extracranial segment of the vertebral artery (V1-V3 segment); (3) patients with malignant tumors, malignant hypertension, and severe systemic disease; (4) combined with moyamoya disease or vascular malformations, traumatic aneurysms, multiple aneurysms; (5) abundant thrombosis in the sac of aneurysm; (6) 3D-DSA images with poor quality for CFD.

Patient groups

Patients were divided into rupture group and non-rupture group based on the presence of SAH. SAH were confirmed by computed tomography (CT) of brain and clinical condition. Lumbar puncture was considered mandatory to confirm the diagnosis in cases where SAH was suspected clinically but brain CT was negative. The results were confirmed by two neurosurgeons with over 10 years of experience in diagnosis and treatment of aneurysms.

Imaging

Standard transfemoral artery catheterization was used for all catheter angiographies. All 3D images were obtained through DSA using a Siemens Artis device (Siemens Healthineers, Forchheim, Germany), whereas rotational angiograms were performed 2 sec after 5-sec contrast injection, with a 18 ml contrast agent at a rate of 3 ml/s and a 360° rotation. The corresponding images were reconstructed into 3D modeling on the workstation and then exported in Digital Imaging and Communications in Medicine (DICOM) format.

Aneurysm modeling

DICOM format image data imported into the software Mimics medical 21.0 (Materialise, Leuven, Belgium) to segment geometries and obtain the preliminary 3D models, and then import into the software 3-matic medical 13.0 (Materialise, Leuven, Belgium) in STL format for model repair and smoothing. Simulations were based on the finest grid with a maximum element size of 0.1 mm, resulting in grids of roughly 7–12 million elements, dependent on particular vessel model. The software ANSYS Fluent 2021 R2 and CFD-post 2021 R2 (ANSYS Inc., USA) was used for simulations of hemodynamics and for generating the solution. The blood vessel was modelled as a rigid wall, and the blood flow was modelled as an incompressible Newtonian fluid with constant temperature and laminar flow, resulting in a Navier–Stokes equation approximate blood flow. A density of 1060 kg/m³ and a dynamic viscosity of 0.0035 Pa/s were specified for each simulation. A pulsatile Womersley velocity profile was prescribed at the inlets. Zero-pressure boundary conditions were set at all outlets. Finally, the calculation time was set to last for three cardiac cycles, with the result of the third cycle reaching a stable state after 200-time steps. Three pulsatile cycles were simulated to ensure that numerical stability had been reached, and the last cycle was taken as output. All data presented are time-averages over the third pulsatile cycle of flow simulation.

Morphology analysis

The 3D model of the aneurysm and parent vessels could be tumbled freely and measured on our workplace system, the observers found the best view angle to measure morphological variables. The morphological parameters used in this study including aneurysm maximum length (L_{max} , maximum length of the aneurysm), aneurysm maximum width (W_{max} , maximum diameter of the aneurysm), the average value of vessel diameters at the proximal aneurysm ($Dp1$) and vessel diameters at the distal aneurysm ($Dp2$), diameter of parent artery ($Dp = (Dp1 + Dp2) / 2$). We also analyzed the following ratios related to the aneurysm shape, including L/ W ratio (L_{max} / W_{max}), Size ratio (SR). SR included SR1

(Lmax/ Dp) and SR2 (Wmax/ Dp). The parameters were calculated by two Interventional physician who were blinded to the patient information and stability status. Discordance between the two evaluators was resolved by a third evaluator who has more than 10 years of experience in neuroradiology.

Hemodynamic analysis

Nine hemodynamic parameters defined on the aneurysm surface and volume used to characterize the aneurysm hemodynamics were calculated: WSS, IAP, normalized wall shear stress (NWSS), wall shear stress gradient (WSSG), Low shear area (LSA), oscillatory shear index (OSI), relative residence time (RRT), normalized pressure (NP), and combined hemodynamic parameters (CHP). WSS, WSSG, NWSS, IAP, OSI, NP, RRT and CHP were calculated the average value. WSS represents the pulling force acting tangential to the vascular wall; IAP is the force energy with which blood hits the inner wall of the aneurysm sac; NWSS represents the ratio of the aneurysm wall shear force to the mean value of the parent artery wall shear force; WSSG indicates the amplitude of variation along the wall shear force direction; LSA was described by the area of aneurysm wall exposed to the WSS below 10% of the mean WSS of the parent artery; OSI indicates the drastic change in the direction of wall shear force during a cardiac cycle; RRT characterizes the stagnation time of blood flow around the vascular wall; NP represents the ratio of the pressure in the aneurysm sac to the pressure in the parent artery and was used to compare the IAP of different aneurysms; CHP was the weighted average value of WSS and OSI. All the hemodynamic parameters were computed using the methods of previous reports ⁸⁻¹⁰.

Statistical analysis

All data were analyzed using IBM SPSS Statistics version 25.0 (SPSS, Inc., Chicago, Illinois, US). Continuous variables were analyzed using independent t-test or Mann–Whitney U test and are presented as means $\pm$ SD or medians with interquartile range. Categorical variables are expressed as numbers and were analyzed using χ^2 tests. Differences were considered statistically significant if the two-tailed p values were <0.05 (95% confidence). Statistically significant variables in univariate analysis were further evaluated using binary logistic regression analysis to identify independent risk factors and ROC curves was performed to acquire cut off values.

Results

Patient's clinical characteristics

The total of 52 VADAs, 21 were ruptured and 31 were unruptured. The average age of ruptured group (12 males and 9 females) was 55.10 ± 9.24 , and the average age of unruptured group (16 males and 15 females) was 53.74 ± 12.68 . There was no significant difference in age, gender, smoking, drinking, hypertension, diabetes, CHD, hyperlipidemia between the two groups (Table 1).

Table 1

Demographic information and clinical characteristics between ruptured and unruptured VADAs

Variable	Ruptured	Unruptured	P-value
Age	55.10 ± 9.24	53.74 ± 12.68	0.677
Gender			
Male	12	16	0.695
Female	9	15	
Hypertension			
Yes	13	19	0.964
No	8	12	
Diabetes			
Yes	2	2	0.683
No	19	29	
CHD			
Yes	1	1	0.777
No	20	30	
hyperlipidemia			
Yes	2	5	0.494
No	19	26	
Drinking			
Yes	3	2	0.347
No	18	29	
Smoking			
Yes	5	6	0.700
No	16	25	
VADAs, vertebral artery dissecting aneurysms; CHD, coronary heart disease, * <i>P</i> < 0.05 was considered significant			

Morphologic Risk Factors Between Ruptured And Unruptured Vadas

By comparing morphological parameters between ruptured VADAs and unruptured VADAs, we found that Wmax, Lmax, Dp1, Dp, SR1 and SR2 in the ruptured group were lower than the unruptured group, Dp2 and L/W higher than the unruptured group. However, all morphological parameters had no significant difference between the two groups (Table 2).

Table 2
Results of morphological characteristics between ruptured and unruptured VADAs

Variable	Ruptured	Unruptured	P-value
Wmax	7.171 ± 3.306	7.640 ± 2.043	0.530
Lmax	10.075 ± 3.105	10.326 ± 2.655	0.756
Dp1	3.069 ± 0.717	3.175 ± 0.436	0.510
Dp2	3.338 ± 0.486	3.322 ± 0.472	0.906
Dp	3.173 ± 0.524	3.237 ± 0.333	0.589
L/W	1.516 ± 0.402	1.374 ± 0.246	0.119
SR1	3.154 ± 0.780	3.167 ± 0.817	0.952
SR2	2.209 ± 0.798	2.342 ± 0.616	0.501
*P < 0.05 was considered significant			

Hemodynamic Risk Factors Between Ruptured And Unruptured Vadas

Nine hemodynamic parameters of VADAs were analyzed between ruptured group and unruptured group (Fig. 1, Fig. 2). WSS, NP and IAP in ruptured group were significantly higher than unruptured group, while the other six hemodynamic parameters have no significant differences between the two groups (Table 3).

Table 3
Results of hemodynamic characteristics of VADAs

Variable	Ruptured	Unruptured	P-value
WSS	2.822 ± 1.198	1.814 ± 0.927	0.001
NWSS	0.486 ± 0.159	0.572 ± 0.153	0.055
WSSG	123.174 ± 27.088	110.606 ± 26.380	0.102
NP	1.393 ± 0.088	1.244 ± 0.158	<0.001
OSI	0.018 ± 0.007	0.020 ± 0.008	0.400
CHP	0.163 ± 0.043	0.164 ± 0.045	0.952
RRT	0.238 ± 0.159	0.217 ± 0.142	0.621
LSA	0.339 ± 0.157	0.314 ± 0.133	0.533
IAP	394.196 ± 83.930	205.920 ± 66.551	<0.001
VADAs, vertebral artery dissecting aneurysms; WSS, wall shear stress; NWSS, normalized wall shear stress; WSSG, wall shear stress gradient; NP, normalized pressure; OSI, oscillatory shear index; CHP, combined hemodynamic parameters; RRT, relative residence time ; LSA, Low shear area; IAP, intra-aneurysmal pressure. * $P < 0.05$ was considered significant			

Binary Logistic Regression And Roc Analysis

We performed binary logistic regression analysis on the three significant hemodynamic parameters of VADAs and found that IAP and WSS were independent predictive factors for the status of VADAs. The ORs indicated that the ruptured VADAs were 1.050 times (95%CI 1.014 to 1.086, $p = 0.006$) more likely to be higher in IAP than unruptured VADAs, and 4.353 times (95%CI 1.124 to 16.859, $p = 0.033$) (Table 4) more likely to be higher in WSS than unruptured VADAs.

Table 4
The results of binary logistic regression analysis

variable	OR (95% CI)	P-value
WSS	4.353(1.124, 16.859)	0.033
NP	0.037(0.000, 836.536)	0.519
IAP	1.050(1.014, 1.086)	0.006
WSS, wall shear stress; NP, normalized pressure; IAP, intra-aneurysmal pressure		
* $P < 0.05$ was considered significant		

The ROC analysis of independent predictors showed that IAP (AUC = 0.9662, $p < 0.001$) and WSS (AUC = 0.7873, $p < 0.001$) had diagnostic value for ruptured. The cut off values of IAP and WSS were 314.1 pa and 2.597 pa (Fig. 3).

Discussion

In this study, by comparing eight morphological and nine hemodynamic parameters of VADAs, no morphological parameters were found to be associated with rupture status, whereas hemodynamic parameters IAP and WSS were linked to VADAs ruptured status. This is the first report to evaluate the rupture risk of VADAs according to hemodynamic parameters.

Unruptured VADAs are frequently attributed to sluggish growth patterns and often achieve good outcomes when medically managed, similarly to extracranial vascular dissections¹¹. Ischemia occurred in approximately 77% of VADAs, with favorable outcomes in 82%¹². However, in bleeding VADAs group, mortality rate was 20% in the treated group and 50% in the untreated group^{13,14}. Because treatment involves a high risk of associated morbidity and mortality, appropriate treatments for unruptured VADAs remain controversial¹⁵. Therefore, it is very important to accurately predict the rupture risk of VADAs.

The morphological parameters of aneurysms are frequently thought to be associated with saccular aneurysm rupture. Previous studies have indicated that size, shape, location, irregularity, height-width ratio (H/W), size ratio, and aspect ratio (AR) of saccular aneurysms are all linked to rupture status^{16–19}. However, the results of these studies were entirely morphological and concerned with saccular aneurysms. Fusiform or dissecting aneurysms were excluded in case selection of these studies. The present study examined the rupture risk of VADAs using eight morphological parameters and discovered that none of morphological parameters correlated with rupture status. These findings imply that it may be inappropriate to quantify the rupture risk of dissecting aneurysms using the common morphological factors previously utilized to calculate saccular aneurysms. Histologically, because media and adventitia of vertebral artery (VA) are weaker than those of internal carotid aneurysm, dissecting aneurysms are easily dilated between the two walls of VA, resulting in aneurysmal SAH²⁰. Some people found that VADAs with pain are a critical predictor of stroke and a critical decision factor for surgical or endovascular treatment^{21,22}. However, other studies have discovered that aggressive interventional treatment may not be necessary for patients with VADAs who only present with pain^{13,23}. As a result, it is necessary to identify more precise predictive parameters suitable for predicting the rupture risk of dissecting aneurysms.

WSS is proposed as an important hemodynamic parameter of CFD-based studies. It represents a frictional force from blood flow tangential to the arterial lumen. Previous research has indicated a correlation between WSS and formation and rupture of aneurysms^{24–26}. In this study, we discovered significantly higher mean WSS associated with rupture risk status of VADAs. Our findings corroborated those of prior research on saccular aneurysms were also applicable to VADAs. Aneurysm ruptured regions

frequently occurred in thin-walled areas^{27,28}. Previous studies revealed that thin regions of aneurysms have higher average WSS and IAP than hyperplastic regions. Moreover, ruptured aneurysms have significantly higher average and maximum WSS^{29,30}. Ruptured aneurysms were characterized by more irregular shapes and were subjected to a more adverse hemodynamic environment, as described by faster flow, higher maximum WSS, higher mean WSS, etc. These associations with rupture status were consistent for different aneurysm locations³¹. Kim et al. also stated that aneurysms with thin areas had a higher WSS, despite their belief that a higher WSS alone might not provide a satisfactory characterization status of aneurysms³². Increased WSS inhibits the activation of endothelial cell receptors such as integrins and mechanically sensitive ion channel sensors, resulting in an increase in matrix metalloproteinase (MMP) secretion, causing degeneration of extracellular matrix (ECM) in vascular wall and injury of endothelial cells (ECs)³³. When ECs layers are not damaged, WSS does not influence smooth muscle cells (SMCs). Once the damage occurred, SMCs initially respond to higher WSS by migrating from the media to the intima, and in response to local signals, they change from a contractile phenotype to a secretory type, increasing nuclear factor kappa beta (NF- κ B), interleukin-1beta (IL-1 β), tumor necrosis factor- α and matrix metals. Protease was produced, and the apoptotic pathway was initiated³⁴. IL-1 β was found to locally act on SMCs in mouse aneurysm model, resulting in apoptosis of SMCs, weakening of elasticity layer, and aneurysm rupture³⁵. Increased WSS stimulates SMC migration and phenotypic alterations, resulting in secreting inflammatory mediators and factors involved in vascular wall degradation, hence encouraging aneurysm rupture.

IAP is the kinetic energy of blood transferred as an inertial force perpendicular to the aneurysms wall surface. The local pressure increases at a flow impingement point as fluid kinetic energy is converted to static wall pressure³⁶. Previous research has examined changes in IAP following endovascular embolization with stent implantation for aneurysms and the risk of postoperative rupture. Piasecki et al. found that stent implantation resulted in a significant decrease in IAP ($p = 0.046$) during diastolic. Systolic or mean IAP did not differ significantly³⁷. Yu et al. also found that stent implantation significantly lowered IAP and WSS in a reconstructed model³⁸. IAP was previously measured by inserting a microwire probe such as an arterial pressure transducer into the lumen of an aneurysm, and no significant difference was observed between ruptured and unruptured aneurysms. This measurement yields a value comparable to that of the parent artery pressure³⁹. A study has indicated an obvious linear relationship between aneurysm pressure and radial artery blood pressure⁴⁰. Therefore, we believe that there may be obvious errors in IAP results measured by this method. In our present study, IAP represents the energy perpendicular to the aneurysm wall caused by the impact of blood flow on the aneurysm wall, and it is also vertical to the tension direction represented by WSS⁴¹. It is intimately linked to velocity and blood flow state⁴². Our findings indicate a statistically significant difference in IAP between ruptured and unruptured VADAs, and the AUC = 96.62% ($p < 0.001$). This finding suggest that it may be a more appropriate parameter for predicting VADAs rupture risk.

There were some potential limitations in our study. First, although we selected patients from two centers for the study, the number of cases remains small due to low incidence of VADAs, which may have a deviation from the trial's results. Additional multi-center studies with larger samples are required to corroborate our results. Second, while there are several studies on morphological parameters in saccular aneurysms but few on dissecting aneurysms, morphological parameters we selected may not be comprehensive or precise. Third, this study was a retrospective analysis, using a patient-specific model in CFD simulation, but the entrance boundary conditions were not patient-specific, and the hemodynamic simulation employed assumptions of laminar flow, Newtonian blood, and rigid wall. This may lead to inaccurate trial results. Fourth, some studies demonstrated that morphology of ruptured aneurysms may change⁴³. This may possibly have occurred in hemodynamics before and after aneurysm rupture^{44,45}.

Conclusion

We compared eight morphological and nine hemodynamic parameters between ruptured and unruptured VADAs. We discovered no morphological parameters that can discriminants of VADAs rupture status. Meanwhile, WSS and IAP were found as independently significant variables, which clinically useful discriminants of VADAs rupture status with high AUC values. This shows that there is a correlation between hemodynamics and the ruptured status of VADAs. The ability of WSS and IAP to predict rupture risk need to be assessed in large prospective studies that include follow up of patients with unruptured VADAs.

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Figures

Figure 1

Hemodynamic analysis of ruptured VADAs. (A) combined hemodynamic parameters (CHP). (B) Low shear area (LSA). (C) normalized pressure (NP). (D) normalize wall shear stress (NWSS). (E) oscillatory shear index (OSI). (F) intra-aneurysmal pressure (Pressure, IAP). (G) relative residence time (RRT). (H) wall shear stress (WSS). (I) wall shear stress gradient (WSSG).

Figure 2

Hemodynamic analysis of unruptured VADAs. (A) combined hemodynamic parameters (CHP). (B) Low shear area (LSA). (C) normalized pressure (NP). (D) normalize wall shear stress (NWSS). (E) oscillatory shear index (OSI). (F) intra-aneurysmal pressure (Pressure, IAP). (G) relative residence time (RRT). (H) wall shear stress (WSS). (I) wall shear stress gradient (WSSG).

Figure 3

ROC curves for independent risk factors of WSS and IAP