Association between aneurysm hemodynamics and wall enhancement on 3D vessel wall MRI

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OBJECTIVE Aneurysm wall enhancement (AWE) on 3D vessel wall MRI (VWMRI) has been suggested as an imaging biomarker for intracranial aneurysms (IAs) at higher risk of rupture. While computational fluid dynamics (CFD) studies have been used to investigate the association between hemodynamic forces and rupture status of IAs, the role of hemodynamic forces in unruptured IAs with AWE is poorly understood. The authors investigated the role and implications of abnormal hemodynamics related to aneurysm pathophysiology in patients with AWE in unruptured IAs.

METHODS Twenty-five patients who had undergone digital subtraction angiography (DSA) and VWMRI studies from September 2016 to September 2017 were included, resulting in 22 patients with 25 IAs, 9 with and 16 without AWE. High-resolution CFD models of hemodynamics were created from DSA images. Univariate and multivariate analyses were performed to investigate the association between AWE and conventional morphological and hemodynamic parameters. Normalized MRI signal intensity was quantified and quantitatively associated with wall shear stresses (WSSs) for the entire aneurysm sac, and in regions of low, intermediate, and high WSS.

RESULTS The AWE group had lower WSS ($p < 0.01$) and sac-averaged velocity ($p < 0.01$) and larger aneurysm size ($p < 0.001$) and size ratio ($p = 0.0251$) than the non-AWE group. From multivariate analysis of both hemodynamic and morphological factors, only low WSS was found to be independently associated with AWE. Sac-averaged normalized MRI signal intensity correlated with WSS and was significantly different in regions of low WSS compared to regions of intermediate ($p = 0.018$) and high ($p < 0.001$) WSS.

CONCLUSIONS The presence of AWE was associated with morphological and hemodynamic factors related to rupture risk. Low WSS was found to be an independent predictor of AWE. Our findings support the hypothesis that low WSS in IAs with AWE may indicate a growth and remodeling process that may predispose such aneurysms to rupture; however, a causality between the two cannot be established.

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INTRACRANIAL aneurysms (IAs) occur in 4% of the general population but are usually asymptomatic unless rupture occurs.³⁸ For unruptured IAs, the risks associated with treatment and subsequent outcomes can often exceed the natural risk of rupture, and thus determining

patient-specific criteria for predicting instability is critical for therapeutic decision-making. Recently, high-resolution vessel wall MRI (VWMRI) enhancement has been used to assess IA wall pathology as a surrogate marker of wall inflammation, which is an important risk factor for rup-

ABBREVIATIONS AComA = anterior communicating artery; AIC = Akaike information criterion; AR = aspect ratio (ratio of aneurysm dome height to neck width); AUC = area under the ROC; AWE = aneurysm wall enhancement; BNF = bottleneck factor (ratio of aneurysm dome to neck width); CFD = computational fluid dynamics; HW = height to width parameter (ratio of aneurysm height to width); IA = intracranial aneurysm; ICA = internal carotid artery; ISUIA = International Study of Unruptured Intracranial Aneurysms; MCA = middle cerebral artery; MRI-SIF = MRI-SI factor; NSI = nonsphericity index; OSI = oscillatory shear index; PComA = posterior communicating artery; ROC = receiver operating characteristic; SI = signal intensity; SPI = spectral power index; SR = size ratio (ratio of aneurysm size to average diameter of the parent arteries); VWMRI = vessel wall MRI; WSS = wall shear stress; WSS* = WSS normalized to the parent artery WSS.

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ture.²⁴ Hemodynamic forces are thought to play a key role in IA wall deterioration but are difficult to reliably assess through current imaging modalities.

Over the past decade, computational fluid dynamics (CFD) has emerged as a promising tool to noninvasively evaluate the hemodynamic forces to which the IA wall is exposed, leading to IA wall deterioration, particularly wall shear stress (WSS), and thus CFD can be used to investigate the underlying biomechanical phenomena involved in aneurysm pathophysiology.^{6,39} Although CFD studies have retrospectively characterized hundreds of aneurysms according to their rupture status, the use of CFD is not without criticism. Skepticism has been aimed toward CFD modeling assumptions and uncertainties,^{20–22} sensitivity of reconstructed geometry to imaging modality,^{13,16} segmentation variability,^{3,34} impact of rigid rather than compliant walls,^{1,9} and disagreement over whether low or high WSS is correlated with aneurysm rupture.^{6,39} Despite these controversies, CFD has recently begun to move beyond predicting association with rupture status and toward linking WSS to wall inflammation measured through histology^{4,24} and VWMRI.⁴⁰

In recent years, aneurysm wall enhancement (AWE) measured through VWMRI has been shown to be a marker of rupture-prone walls. We hypothesized that abnormal hemodynamic conditions may be associated with the presence of AWE. In this study, we investigated possible correlations between AWE and CFD-derived metrics to understand the role of hemodynamic forces in aneurysm wall degradation.

Methods

Patients

This study was approved by the institutional review board of the University Hospital Düsseldorf (study number 6186R). From September 2016 to September 2017 (1 year), 22 patients with 25 unruptured IAs were included. All patients underwent both DSA and VWMRI within 6 weeks. IAs were considered unruptured on the basis of clinical presentation (no history of subarachnoid hemorrhage, absence of recent or past acute headaches) and imaging data.

Imaging Protocol

VWMRI was acquired on a 3T MR scanner (Magnetom Skyra, Siemens) with a 20-channel head coil. The protocol included a vendor-supplied isometric 3D T1 sampling perfection with application-optimized contrasts using different flip angle evolution (SPACE) turbo spin echo (TSE) sequences with spectral attenuated inversion recovery (SPAIR) and blood suppression (field of view 179 × 230, repetition time/echo time 939/18 msec, matrix 200 × 256, spatial resolution 0.9 × 0.9 × 0.9 mm) before and after administration of gadoteridol (0.2 ml/kg body weight, maximum 20 ml; ProHance, Bracco Imaging). The “black blood” effect, i.e., the suppression of signal of the flowing blood, was achieved by the normal flow void effects of fast-flowing blood in TSE sequences, i.e., the excited molecules leaving the imaging plane before signal recording. To further minimize artifacts and even suppress the signal of slow-flowing blood, the signal of flowing blood was fur-

ther attenuated using a pair of nonselective and selective inversion radiofrequency pulses. In principle, the imaging was optimized so that inflowing blood had no transverse magnetization and thus yielded no signal during readout. The scan time for the sequence was 7 minutes and 55 seconds.

Digital Subtraction Angiography

Informed consent for diagnostic, clinical, and biplanar procedures was obtained from all study participants. DSA was performed and standard projections (posterior-anterior, lateral, and oblique) were obtained during manual injection of an 8- to 10-ml bolus of a contrast-enhancing agent (Accupaque 300 mg J/ml, GE Healthcare). 3D rotational angiograms (88 kV, 200 mAs, 180°, rotation time of 4.1 seconds, 122 images, manual injection of up to 20 ml contrast-enhancing agent during the whole rotation) were obtained for the anterior circulation and on an as-needed basis for the posterior circulation.

VWMRI Analysis

The images were independently reviewed by 2 readers (R.M. with 8 and B.T. with 20 years of experience in vascular neuroimaging) who determined the presence or absence of complete or partial AWE on postgadolinium VWMRI. Multiplanar oblique reconstructions were obtained from precontrast- and postcontrast-enhanced 3D VWMRI and analyzed after coregistration. In case of disagreement among the 2 readers, a consensus was reached through a joint review and discussion of the cases.

Morphological Parameters

Morphological parameters were defined and computed as previously reported.^{10,12} Briefly, the size of the aneurysm was defined as the maximum diameter of the aneurysm dome, and aspect ratio (AR) was defined as the ratio of dome height to neck width, where height is the longest dimension from the neck to dome tip and width is measured perpendicular to dome height. Size ratio (SR) was measured as the ratio of aneurysm size to average diameter of the parent arteries. The bottleneck factor (BNF) was defined as the ratio of dome to neck width, and the height to width parameter (HW) was defined as the ratio of aneurysm height to width.¹² To qualitatively measure the aneurysm shape, a nonsphericity index (NSI) was computed as defined previously.¹⁰ Two observers, a neurosurgeon (A.K.P.) and a neuroradiologist (B.T.), made the analysis independently of each other, and both had more than 18 years of clinical experience. The interobserver variability was minimal, and thus further statistical analysis of this variable was not performed.

CFD Modeling

DSA images were segmented and reconstructed into a 3D model using the open-source Vascular Modeling Toolkit (<http://www.vmtk.org>). Variable density volumetric meshes were generated with the highest mesh density in the aneurysm sac, where the tetrahedron side length was 0.12 mm on average, previously shown through a 320-fold mesh-refinement study to accurately model IA hemody-

namics.²² The number of tetrahedral elements was 4.1 million on average, ranging from 1.3 to 8.7 million, reflecting the variability in IA sizes and extent of CFD model domains.

A representative older adult internal carotid artery (ICA) flow waveform shape¹⁴ was scaled to the mean cycle-averaged cross-sectional velocity of 0.27 m/sec, which was applied to the ICA inlet. The resulting mean ICA flow rate was 4.7 ml/sec, which is comparable to the in vivo measured flow rate of 4.3 ± 0.8 ml/sec.⁴¹ For middle cerebral artery (MCA) and anterior communicating artery (ACoM) aneurysms, the inlet flow waveform was dampened by 10% to account for the transit from cervical to cavernous segments. A fully developed Womersley profile was imposed at the ICA inlet, and the flow division to the outlet segments was scaled based on the area.

CFD simulations were performed using a minimally dissipative and energy-preserving solver,³² previously verified and validated to accurately model aneurysmal flows^{2,22} and cardiovascular flows in general.¹⁸ We assumed rigid walls, blood viscosity of 0.0035 m²/sec, and blood density of 1060 kg/m³. All simulations were run for 3 cycles, with 10,000 time steps per cardiac cycle, and the last cycle was used for postprocessing. For all cases, we computed sac-averaged values for the following variables: time- and sac-averaged WSS, oscillatory shear index (OSI), and spectral power index (SPI), a recently introduced metric for quantifying high-frequency flow instabilities.¹⁹ Since WSS could have uncertainties due to CFD modeling assumptions, we normalized the WSS to the parent artery WSS (WSS*) to dampen these effects.

Image Registration and Quantification of VWMRI Enhancement

CFD models were registered to postcontrast VWMRI using an in-house landmark-based image registration tool. To quantify the AWE on postcontrast VWMRI, we projected the MRI signal intensity (MRI-SI) onto the CFD model and normalized it according to the nominal intensity of the image volume (Fig. 1). More specifically, we quantified MRI-SI along a line that was normal to each mesh node. The MRI-SI was then averaged along the length of the line and normalized to the mean MRI-SI of the entire VWMRI volume (MRI-SI factor [MRI-SIF]). As seen in Fig. 1C, the maximum MRI-SIF corresponded to the region that showed notable AWE on postcontrast VWMRI. Similar to hemodynamic parameters, we computed sac-averaged MRI-SIF as a quantitative measure of AWE. In addition, we computed MRI-SIF in low-, intermediate-, and high-aneurysm WSS regions of the sac, which were defined as regions with < 10%, 10%–30%, and > 30% of parent artery WSS, respectively.

Statistical Analysis

Univariate Analysis of Differences Between the AWE and No-AWE IA Groups

Since there were only 25 observations, a Shapiro-Wilk test was performed to determine if a parameter was normally distributed. For nonnormally distributed parameters, normality was achieved by appropriate nonlinear

transformation (square root or natural logarithm). In subsequent analysis, the parameter form (i.e., the raw parameter or its transformation) with the highest p value (the one most likely to be normally distributed) was used. The statistical significance of the observed mean differences was assessed using a 2-tailed independent Student t-test, and a p value < 0.05 was considered statistically significant. Frequency ratios for nominal variables (hypertension, sex, location, smoking, hyperlipidemia, diabetes, and side of aneurysm) were compared using the Fisher's exact test.

Multivariate Logistic Regression on Significant Variables

The parameters found to be significant ($p < 0.05$) in the univariate analysis were further analyzed using logistic regression to predict AWE. Potential predictor variables were forward selected based on the p value from the univariate t test. Variables with $p > 0.1$ were discarded. Remaining variables were ranked in ascending order based on p value and introduced one by one into the multivariate model, starting with the one with the lowest p value. At each step, the Akaike information criterion (AIC) and the significance of the coefficients were checked. A predictive model relying on raw, nontransformed variables was also developed. The performance of both models for accuracy and the AUC (area under the receiver operating characteristic [ROC] curve) were assessed. Lastly, both models were internally validated and calibrated using bootstrapping with 1000 resamples.

Correlation Between MRI-SIF and WSS in the AWE Group

MRI-SIF sac-averaged means and standard deviations and MRI-SIF in low-, intermediate-, and high-WSS* regions were computed. Linear correlations and Pearson chi-square test were used to evaluate the relationship between MRI-SIF and WSS* in the AWE group.

Results

Qualitative Hemodynamic Characteristics

A total of 25 unruptured IAs were visible in 22 patients, of which 9 aneurysms showed AWE and 16 showed no AWE. Table 1 shows patient clinical characteristics and IA locations, which were not found to be associated with AWE (all p values > 0.05). Figure 2 shows WSS and OSI maps, along with the pre- and postenhanced images, ranked from lowest to highest WSS. These qualitative maps indicate that IAs in the AWE group had larger size and lower WSS compared with those in the no-AWE group. Moreover, IAs with the lowest WSS appeared to have notable AWE, particularly in the cases of the P₄ ACoM, P₅ MCA, and P₅ ACoM.

Univariate Analysis of Differences Between the AWE and No-AWE Groups

Results of the univariate analysis for morphological and hemodynamic factors are summarized in Table 2. For hemodynamic factors, the AWE group had significantly lower WSS (3.88 vs 11.69 Pa, $p = 0.00287$), WSS* (0.33 vs 0.90, $p < 0.001$), and average velocity (0.13 vs 0.27 m/sec, $p = 0.00287$), while OSI (0.04 vs 0.03, $p = 0.0694$) and SPI (0.10 vs 0.12, $p = 0.613$) showed no statistically

FIG. 1. Pipeline to register the CFD model to postcontrast VWMRI and quantify AWE. **A:** CFD model registered to the VWMRI using landmark-based image registration. **B:** Vectors pointing normal to the aneurysm surface, which were used to compute MRI-SI at each point on the surface. The MRI-SI was then normalized to the nominal intensity of the image volume. **C:** Normalized MRI-SI maps where the maximum intensity corresponds to the region that showed AWE. Figure is available in color online only.

significant differences between the 2 groups. Among morphological factors, the AWE group IAs had larger dome size (7.22 vs 3.61 mm, $p = 0.00462$) and SR (4.26 vs 2.33, $p = 0.0251$). Other morphological factors, including AR (1.65 vs 1.48, $p = 0.613$), BNF (1.48 vs 1.43, $p = 0.926$), HWR (1.10 vs 0.92, $p = 0.0698$), and NSI (0.13 vs 0.06, $p = 0.0695$), showed no significant differences between the AWE and no-AWE groups.

Multivariate Logistic Regression on Significant Variables

Figure 3A and B shows a univariate logistic predic-

TABLE 1. Demographic information of the studied cohort

Parameter	AWE	No AWE	p Value
Mean age (yrs)	50.8	56.7	0.29
Hypertension	50%	63%	0.99
Sex			1
Female	4	8	
Male	4	3	
IA location			
MCA	3	11	0.12
ACoMA	5	5	0.4
PCoMA	1	0	0.36
Total	9	16	0.12
Smoking	33%	44%	0.69
Hyperlipidemia	11%	13%	0.88
Diabetes	0%	0%	NA
IA side			
Left	1	4	
Right	3	6	
Both	0	1	

NA = not applicable.

Values are presented as number or percentage of patients unless otherwise indicated.

tive model, using only the square root of the WSS as the predictor for the AWE, which was found to be a significant predictor ($p = 0.01$, AIC = 22.7) along with WSS*. As shown in Fig. 3C, introducing the log(size) reduced the AIC to 17.6, at the cost of making the square root of WSS insignificant and showing only a trend for log(size) ($p = 0.078$). For comparison, Fig. 3D shows a predictive model relying on raw, nontransformed variables, which was found to be similar to the nonlinear model.

The performance of both models was assessed for their accuracy and AUC. As shown in Fig. 3E, the univariate model reached an accuracy of 0.84, with an AUC of 0.9 on the training data. On the other hand, the bivariate model, shown in Fig. 3F, with log(size) as the second predictor, had an accuracy of 0.92 and an AUC of 0.95. We internally validated and calibrated both models using bootstrapping with 1000 resamples. The accuracy was 0.78 for the univariate model and 0.84 for the bivariate one. For both models, a Hosmer-Lemeshow test showed no significant deviations between the model predictions and grouped relative frequencies ($p = 0.62$ and $p = 0.98$ for the univariate and bivariate models, respectively). McFadden's R^2 values were 0.43 and 0.64, respectively.

Correlation Between MRI-SIF and WSS in the AWE Group

There was a qualitative correlation between regions of maximum MRI-SIF and regions of low WSS* (Fig. 4). In particular, we observed that 2 cases in which IAs showed distinct and focal enhancement in Fig. 1, namely P₅ ACoMA and P₂ ACoMA, were those with IA blebs. From Fig. 4 we noted that the focal enhancement was located within the bleb region, and interestingly, also coincided with the location of lowest WSS* on the aneurysm dome.

As shown in Fig. 5A and B, we observed a weak correlation of MRI-SIF with WSS ($r^2 = 0.23$, $p = 0.019$) and a moderate correlation with WSS* ($r = 0.47$, $p = 0.041$). To further explore this association, we computed MRI-SIF in regions of low, intermediate, and high WSS*. The means $\pm$

FIG. 2. Hemodynamic maps of aneurysms with and without AWE, arranged in ascending order from lowest to highest WSS. **A:** The first 2 columns show pre- and postcontrast images of aneurysms with AWE, where the region of enhancement is marked with an arrow. The next 2 columns display WSS and OSI maps, respectively. **B:** WSS and OSI maps for aneurysms without AWE. For brevity, pre- and postcontrast images are not displayed. Note that case names identify the aneurysm location: anterior communicating artery (Acom), MCA, or posterior communicating artery (Pcom). Figure is available in color online only.

standard deviations of low-, intermediate-, and high-WSS* regions were 0.063 ± 0.027 , 0.18 ± 0.020 , and 0.56 ± 0.16 , and the corresponding MRI-SIF values in these regions were 1.41 ± 0.61 , 1.17 ± 0.28 , and 1.15 ± 0.31 , respectively. As shown in Fig. 5C, MRI-SIF values in the low-WSS* re-

gions were statistically different from those in the regions of intermediate ($p = 0.018$) and high ($p < 0.001$) WSS*, but there were no statistically significant differences between the MRI-SIF values in the intermediate- and high-WSS* regions ($p = 0.085$).

TABLE 2. Results from univariate statistical analysis for all parameters examined in the AWE and no-AWE groups

Parameter	AWE (n = 9)	No AWE (n = 16)	p Value
Hemodynamics			
WSS (Pa)	3.88 ± 3.09	11.69 ± 6.15	0.00287
WSS*	0.33 ± 0.20	0.90 ± 0.43	0.000071
OSI	0.04 ± 0.03	0.03 ± 0.02	0.0694
SPI	0.10 ± 0.10	0.12 ± 0.08	0.613
Mean velocity (m/sec)	0.13 ± 0.07	0.27 ± 0.09	0.00287
IA morphology			
Size (mm)	7.22 ± 3.63	3.61 ± 1.24	0.00462
AR	1.65 ± 0.68	1.48 ± 0.49	0.613
SR	4.26 ± 2.42	2.33 ± 0.81	0.0251
BNF	1.48 ± 0.73	1.43 ± 0.46	0.926
HW	1.10 ± 0.23	0.92 ± 0.17	0.0698
NSI	0.13 ± 0.08	0.06 ± 0.03	0.0695

Values are presented as mean ± SD unless otherwise indicated. Boldface type indicates statistical significance.

Discussion

We have used VWMRI to investigate the associations between AWE of unruptured IAs and hemodynamic and morphological factors typically associated with ruptured IAs. The presence of AWE was associated with morphological risk factors, particularly size and SR, and hemodynamic factors such as WSS, but only WSS was found to be an independent predictor of AWE.

Relationship Between AWE and IA Wall Inflammation

Wall inflammation is thought to be a key component in IA wall degradation and rupture. Recently, Larsen et al. performed histological analysis in 13 patients who underwent VWMRI before their IA clipping surgery.²⁴ Five patients showed strong AWE, and histological analysis revealed inflammatory cell infiltrations in 4 of these patients through myeloperoxidase staining and neovascularization in 1 patient. On the other hand, remaining aneurysms without AWE showed no signs of inflammatory cell invasion or neovascularization; thus, AWE occurred only when histological signs of inflammation were present. Cebral et al. demonstrated the association between hemodynamics and histology of tissues resected during

FIG. 3. A: A univariate logistic predictive model using only the square root of WSS as the predictor for AWE. Noise is added to the y-axis for better visualization. For all subplots, blue and red dots refer to the AWE and no-AWE groups, respectively. The green line is the logistic regression curve, and the gray band is the 95% CI. B: The same univariate model shown in panel A visualized as an area. The dashed line indicates 50% probability of AWE. C: A bivariate model, using the square root of WSS and log(size) as the predictors of AWE. Due to nonlinear transformation of variables, the 50% probability boundary (dashed line) is not a straight line. D: An alternative bivariate model, using raw WSS and size values as predictors of AWE. This model is only marginally less accurate than the nonlinear model shown in panel C. E: ROC curve for the univariate predictors. F: ROC curve for the bivariate predictors. The red mark in panels E and F denotes the point where the highest accuracy is achieved. Figure is available in color online only.

FIG. 4. WSS* and MRI-SIF maps of aneurysms that showed AWE. The arrows in the MRI-SIF maps point to the regions that were independently evaluated by 2 neuroradiologists as the regions of postcontrast AWE. Figure is available in color online only.

IA surgery for 9 ruptured and 11 unruptured IAs.⁴ Those authors found that high WSS was correlated with regions of wall inflammation and low flow was correlated with degenerated wall that had lost mural cells, both of which are markers of unstable IAs.

Since the AWE group in our study had low flow and WSS, a mural cell–mediated inflammatory response may have been at play. Previous studies have shown that aneurysms that are missing mural smooth muscle cells are incapable of organizing a luminal thrombus, a condition that may subsequently lead to an increased inflammatory reaction and thus severe wall degradation and aneurysm growth and rupture.²⁸ On the other hand, it is also plausible that AWE may not be a direct marker of structural changes and wall inflammation, but rather could be an epiphenomenon related to growth or other remodeling processes that may predispose IAs to rupture.

Relationship Between Hemodynamics and Aneurysm Remodeling

The majority of the evidence linking WSS to IA rupture is derived from retrospective CFD studies that have compared hemodynamics in unruptured versus already ruptured IAs. In particular, 2 large, retrospective CFD studies independently found low WSS³⁹ ($n = 119$ patients) and high WSS⁶ ($n = 210$ patients) to be associated with rupture status. While there have been other studies of the associations of WSS with rupture, these 2 seminal studies highlight an ongoing controversy in aneurysm literature: is high or low WSS more deleterious? A unifying hypothesis has been proposed whereby both low and high WSS may drive distinct mechanobiological pathways toward aneurysm instability.³¹

Investigating this hypothesis, Cebal et al. recently

FIG. 5. Quantitative correlation of the sac-averaged MRI-SIF with (A) WSS and (B) WSS*. C: MRI-SIF in regions of low, intermediate, and high WSS*. The red line indicates the standard deviation. Figure is available in color online only.

demonstrated that regions visually characteristic of atherosclerotic and hyperplastic walls tended to have focally low flow and WSS while thin-walled regions had high WSS.⁵ In our study, we found AWE to occur at the location of focally low WSS, as shown in Fig. 2. In particular, the 2 IAs that showed distinct and focal enhancement (P₅ AComA and P₂ AComA) coincided with the location of the lowest WSS on the IA sac, and interestingly, were also aneurysms that had blebs. Since bleb regions tend to have slow and recirculating flow,¹⁷ it is plausible that these 2 IAs had atherosclerotic and hyperplastic walls as suggested by the findings of Cebal et al.⁵ Although previous studies have indicated that IA walls that appear atherosclerotic and hyperplastic are thicker, this characteristic does not necessarily imply that such regions are mechanically stronger and not rupture prone. As suggested by Cebal et al.,⁵ it is plausible that the wall structure in these low-WSS regions may be degraded, resulting in an overall weaker IA wall.

Aneurysm Wall Enhancement in Rupture Risk Assessment

Recently VWMRI has been used in patients with IAs, and AWE on VWMRI is considered to be a marker of wall inflammation, and thus aneurysm wall weakening. Matouk et al. showed the presence of AWE in 5 of 5 ruptured aneurysms.³⁰ Similarly, Nagahata et al. investigated 61 ruptured and 83 unruptured IAs and found strong to faint signs of AWE in 98.4% of ruptured and only 18.1% of unruptured IAs.³³ Distinguishing strong from faint enhancement is a subjective process, and thus Wang et al. quantitatively measured enhancement ratios of IA walls, bodies, and necks on pre- versus postcontrast images, with a threshold value of 61.5% to distinguish ruptured from unruptured IAs.³⁶ However, issues such as leaked or stagnant contrast agent and alteration of radiological characteristics postrupture may limit the applicability of these studies to rupture risk assessment.

Edjlali et al. focused instead on unruptured IAs and prospectively found AWE to be present in 87% of 31 unstable and symptomatic IAs and only 28.5% of 77 stable aneurysms.¹¹ Of 108 patients, 46% showed AWE, which is comparable to 36% of the 25 IAs showing AWE in the present study. More recently, Lv et al. also focused on unruptured IAs and found the presence of AWE to be associated with conventional rupture-related risk factors such as larger size and irregular shape, findings consistent with

those of the present study.²⁷ These findings suggest that AWE may be a potential patient-specific biomarker that may be complementary to the conventional risk factors for IA rupture.

Association Between Morphology and Rupture Risk Assessment

The most widely used rupture risk assessment method in clinical practice is the aneurysm size measured from DSA, which was established by the International Study of Unruptured Intracranial Aneurysms (ISUIA).³⁸ However, one major drawback of the size-based ISUIA standard is that small-sized aneurysms may still rupture. Juvela et al. showed that 37% of patients had IAs smaller than 5 mm in diameter,¹⁵ which would be within ISUIA grade 1 (lowest risk score), defined as IA size < 7 mm. In fact, Korja et al. found that during lifelong follow-up of 118 patients with unruptured IAs, 19% were < 7 mm at the time of rupture.²³ Similar findings in ruptured mirror aneurysms were reported by Maslehaty et al., where the average size of ruptured aneurysms was 7 mm.²⁹ In our study, although the average IA size of the AWE group was 7.22 mm, 4 of 9 IAs that showed AWE were smaller than 7 mm, falling under the ISUIA low-risk category despite showing AWE.

A significant correlation between IA size and the presence of AWE has been reported by several authors. In particular, Liu et al. found aneurysm size to be an independent predictor of AWE.²⁵ These authors found 83% of 36 IAs > 7 mm to have AWE, while only 12% of 25 IAs < 7 mm showed AWE. We similarly found all IAs > 7 mm to have AWE, and only 25% of IAs < 7 mm to have AWE. This higher prevalence of smaller IAs in our AWE group may be due to the small sample size; however, these findings suggest that AWE may provide additional information about aneurysm instability other than size, and thus could be a potential metric to improve the current standards for assessment of rupture risk.

Shape-based metrics have been shown to be better predictors of rupture risk than size alone. Interestingly, we did not find AR to be a statistically significant predictor of AWE. Previous studies have shown AR to be a potential metric to assess rupture risk;³⁷ however, the findings have not been unequivocal³⁹ and are based on retrospective data. On the other hand, a recent longitudinal study of 93 patients showed that in growing versus stable aneurysms,

AR did not show any significance, even when aneurysms were segregated by size (< 3, 3–5, 5–7, or > 7 mm) or location.⁸ The only 2 parameters that enabled consistent detection of growing versus stable aneurysms were NSI and SR, both of which showed significance or a trend toward significance in detecting aneurysms with wall enhancement in our study.

Location of IAs has previously been suggested as a risk factor for rupture. The ISUIA study results suggested that aneurysms located at the posterior circulation have the highest risk of rupture, while both ICA and MCA aneurysms have low to moderate risks of rupture.³⁸ Although we did not evaluate location-specific quantities, whether hemodynamics vary based on location is not clear. In particular, Chien et al. showed higher WSS in MCA than the posterior communicating artery (PComA),⁷ while Varble et al. found no hemodynamic differences in MCA and PComA aneurysms.³⁵

Clinical Implications

With the increasing number of incidental findings of unruptured IAs, patient-specific assessment of rupture risk is gaining importance. Recent efforts have been focused on VWMRI,^{11,30} however, this imaging technique is not available in standard clinical care or may not be feasible due to contraindications. On the other hand, CFD-derived hemodynamic factors, such as WSS and OSI, have shown promise for aneurysm rupture risk assessment. Our study has shown that low WSS is an independent predictor of AWE and thus may serve as an alternative measure to identify high-risk aneurysms in need of immediate treatment.

We have also provided quantitative evidence that AWE on VWMRI can be augmented with CFD-based hemodynamic factors to investigate the degraded state of the vessel wall. While we did not perform a validation of AWE against histological data, there is sufficient evidence in the literature to suggest that AWE is a marker of IA wall degeneration,^{11,24,30} and thus CFD-based hemodynamic factors may provide a quantitative measure to study aneurysmal wall remodeling in vivo by longitudinally following patients who have not been treated.

Although larger aneurysm size is highly correlated with rupture, 25% of small aneurysms also rupture. Toward developing improved predictive markers for small aneurysms, parsimonious models that incorporate our proposed parameters, MRI-SIF with WSS, may allow better assessment of the rupture risk of small aneurysms.

Limitations

One key limitation of the current study is the small sample size. While we have found a correlation between low WSS and the presence of AWE, a larger sample size with radiological follow-up is needed to establish the usefulness of hemodynamics as a biomarker of AWE and rupture risk. Although previous studies have already found AWE to be present in IAs with wall inflammation, the histological data of patients with AWE were not available in our study, and thus direct association of wall pathology with hemodynamic factors could not be investigated. Lastly, we have made conventional assumptions in our CFD

model such as rigid walls, Newtonian rheology, and fully developed inflow. These are commonly accepted assumptions and their effects are now well documented to be of relatively minor importance.

Conclusions

Our results suggest that the presence of AWE in our unruptured IA cohort is associated with conventional hemodynamic and morphological factors. Aneurysms with larger size and SR were more prone to have AWE. However, only low WSS was independently predictive of AWE. Our results support the hypothesis that low WSS in the AWE group may indicate a growth and remodeling process that may predispose such aneurysms to rupture; however, a causality between the two could not be established. VWMRI may be augmented with CFD-based hemodynamic factors to assess patient-specific risk factors.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: all authors. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors.

Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Khan. Statistical analysis: all authors. Administrative/technical/material support: all authors. Study supervision: all authors.

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