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FULL PAPER

Intracranial aneurysms at higher clinical risk for rupture demonstrate increased wall enhancement and thinning on multicontrast 3D vessel wall MRI

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Objective: Identification of aneurysms at risk for rupture is important and challenging. We sought to evaluate if intracranial vessel wall (IVW) imaging characteristics of unruptured aneurysms correlate with clinical risk factors for rupture.

Methods: Patients with unruptured intracranial aneurysms were prospectively recruited and underwent a multi contrast 3D IVW protocol between April 6, 2016 and August 29, 2017. Two independent raters, blinded to aneurysm vulnerability, evaluated each aneurysm for wall enhancement, extent of enhancement in terms of the numbers of quadrants enhancing circumferentially, intensity of enhancement, and qualitative wall thinning. PHASES score was calculated for each aneurysm. Univariate logistic regression analysis was used to compare IVW characteristics between aneurysms at higher clinical risk for rupture (PHASES score > 3) and lower clinical risk for rupture (PHASES score ≤ 3).

Results: 45 patients with 65 unruptured aneurysms were analyzed; 38 aneurysms with PHASES score > 3 (58%) and 27 aneurysms with PHASES score ≤ 3 (42%). Aneurysms with PHASES score > 3 were more likely to demonstrate enhancement (42.1% *vs* 14.8%, $p = 0.022$), greater extent of enhancement (mean: 2.9 *vs* 2.2 quadrants, $p = 0.063$), and wall thinning (9.2% *vs* 0%, $p = 0.044$). Inter-reader agreement was moderate-to-good for the presence ($\kappa = 0.64$), extent ($\kappa = 0.64$), and intensity of enhancement ($\kappa = 0.60$) but relatively low for wall thinning ($\kappa = 0.25$).

Conclusion: Aneurysms at higher risk of rupture by PHASES score are more likely to demonstrate wall enhancement, more diffuse enhancement, and wall thinning on IVW.

Advances in knowledge: This study prospectively compares IVW-detected wall enhancement and thinning between unruptured aneurysms stratified into high and low risk groups by clinical scores (PHASES) of vulnerability.

INTRODUCTION

Intracranial aneurysms affect 2–4% of the population.[1–3] Recent advancements in intracranial vessel wall (IVW) MRI have improved our ability to characterize intracranial vascular diseases[4–6] including aneurysms, particularly with the use of 3D Variable Refocusing Flip Angle (VRFA) techniques.[7,8] Vasa vasorum, not normally present in intracranial arteries, is thought to develop in larger aneurysms, which may leak, resulting in inflammation, aneurysm enlargement, and wall thinning. It has been suggested that enhancement of the vessel wall is due to the presence of vasa vasorum or associated inflammation,[9] and prior studies have shown that enhancement is readily detectable on IVW, and seen more frequently in ruptured or vulnerable aneurysms.[10–15] Wall thinning may also be an important factor in aneurysm rupture,[16] and IVW can qualitatively evaluate aneurysm wall thickness.[17,18]

Aneurysm rupture is associated with devastating consequences,[19–21] but both endovascular and surgical treatments pose their own risks[22–24]—therefore optimized patient selection is critical. Treatment algorithms for unruptured aneurysms have traditionally focused on size,[25] however, natural history studies of unruptured aneurysms have described a 5-year risk of rupture of 4.5% for aneurysms smaller than 10 mm, as well as reporting rupture in

4.1% of patients with aneurysms smaller than 5 mm in a cohort followed for an average of 4.3 years.[26] Therefore, with size alone a limited predictor of rupture, this necessitated the development of more complex predictive models such as the PHASES score,[27] which incorporates size as well as location and clinical data to stratify risk of rupture. However, this score requires clinical data which are not always available or reliable, and while it makes use of luminal imaging, it does not take into account physiological/morphological changes of the vessel wall. Therefore, in order to determine if aneurysmal wall enhancement and thinning detected on IVW may correlate with clinical predictors of aneurysm vulnerability, we sought to compare these IVW characteristics between unruptured aneurysms at higher risk of rupture against those at lower risk of rupture, as determined by PHASES score.

METHODS AND MATERIALS

Patients

After institutional review board approval, luminal imaging was used to prospectively identify adult patients (>18 years of age) with unruptured, untreated intracranial aneurysms. Patients were then consented and underwent MRI with a 3D multi contrast IVW protocol. Previously ruptured or treated aneurysms were not included in the analysis. Patients were excluded if they had any contraindication to MRI or gadolinium contrast, or if their IVW study was of poor quality.

Magnetic resonance imaging

Scanning was performed on a 3T Philips Ingenia MRI system (Philips Healthcare, Best, the Netherlands) with a 32-channel head coil or Siemens Prisma MRI system (Siemens Healthineers, Erlangen, Germany) using a 64-channel neurovascular coil. Patients underwent a multi contrast variable flip-angle turbo spin-echo three-dimensional (3D) IVW protocol on both Siemens and Philips platforms. VRFA techniques with 3D T_1 sampling perfection with application optimized contrast using different flip angle evolutions [SPACE] were obtained on Siemens and volumetric isotropic turbo spin echo acquisition (VISTA), (0.56 mm^3 acquired resolution) was obtained on Philips. The protocol included pre- and post-contrast 3D T_1 SPACE or VISTA, together with MRA and 3D T_{12} SPACE or VISTA.[28] 3D time-of-flight MRA was performed as well as contrast enhanced MRA. Sequence parameters are available in Supplementary Material 1.

Clinical information

Clinical and demographic data were collected from each patient's electronic medical record including age, gender, race, hypertension (diagnosed as systolic blood pressure over 140, diastolic pressure over 90, or the use of antihypertensive medications), diabetes mellitus, hyperlipidemia, vitamin B12 deficiency, sleep apnea, history of or current tobacco use, illicit drug use and type of drug (if ever indicated in patient's chart), any prior ruptured intracranial aneurysm with subarachnoid hemorrhage, current aneurysm size and location, and the total number of aneurysms in each patient. For patients with multiple aneurysms, each was analyzed separately, and a PHASES score (Population, Hypertension, Age, Size, Earlier subarachnoid hemorrhage, Site) was calculated for each individual aneurysm.

Image analysis

Two raters underwent training in evaluation of intracranial aneurysms with IVW through an iterative literature and case review process (using five cases not included in the current analysis), with creation of a set of criteria for defining what represented enhancement and wall thinning.

By the criteria of this training, enhancement was defined as exceeding normal arterial wall enhancement, and was required to match the presumed location of the aneurysm wall between pre-contrast IVW, post-contrast IVW, and MRA. For cavernous sinus lesions or lesions adjacent to the cavernous sinus, enhancement was required to clearly differ in signal from cavernous sinus enhancement, with the aneurysm wall clearly delineated from the surrounding environment. Because aneurysm rupture is a focal process, the evaluation of wall thinning concentrated on focal wall thinning rather than global characteristics. Wall thinning was defined as being evident on both T_1 pre- and post-contrast IVW, appearing as the absence or marked thinning of aneurysm wall within a quadrant, tapering of the wall to a region of non-visualization of the wall or significant wall thinning, and without apposition of brain tissue in the region of apparent wall non-visualization. In cases where enhancement or wall thinning extended across quadrants, both quadrants were counted as abnormal.

Raters then independently reviewed IVW sequences of each aneurysm. Aneurysms were rated independently in patients with multiple aneurysms. Raters selected a single slice which best demonstrated aneurysm wall enhancement and wall thinning. Both readers used the same plane of review, which was recorded. The raters evaluated each aneurysm for the presence of wall enhancement above normal wall enhancement (y/n), intensity of enhancement relative to the pituitary infundibulum (0 = none or enhancement equivalent to expected for normal arterial wall, 1 = less than infundibulum, 2 = equal or greater than infundibulum), and qualitative presence of wall thinning (as described above). The circumferential extent of enhancement and wall thinning was also recorded in terms of the number of quadrants involved. Raters were blinded to relevant clinical data and each other's ratings.

Statistical analysis

For analysis, aneurysms were divided into two groups: those with PHASES score >3 (higher risk for aneurysm rupture), and those with PHASES score ≤3 (lower risk for aneurysm rupture), with this threshold selected based on a prior study.[29] Inter-reader agreement was evaluated using unweighted Cohen's κ for binary variables and linearly weighted Cohen's κ for ordinal variables. Logistic regression was used to compare each IVW feature individually between the higher and lower risk groups with an adjustment for reader. The generalized estimating equations approach was used to account for the non-independence between multiple aneurysms from the same patient and two ratings per aneurysm. Permutation tests were used to test for associations with IVW features when this could not be done using logistic regression due to very few or no cases in a group. The permutation tests were clustered by patient to account for non-independence between multiple ratings from

Table 1. Characteristics of 45 patients with 65 aneurysms

Variable		Value[a]
Maximum aneurysm diameter (mm)		4 (1–28)
Maximum PHASES score		Please remove this box and reduce to 1 entry for maximum phases score
		5 (0–12)
Male sex		18 (40.0)
Age, years		57 (21–83)
Race	White	35 (83.3)
	Black	4 (9.5)
	Asian	3 (7.1)
Hypertension		31 (68.9)
Hyperlipidemia		19 (42.2)
Sleep apnea		8 (17.8)
B12 deficiency		4 (8.9)
Ever smoker		26 (57.8)
Illicit drug use		11 (24.4)
Prior Subarachnoid Hemorrhage		3 (6.7)
No. of aneurysms	1	31 (68.9)
	2	9 (20.0)
	3	4 (8.9)
	4	1 (2.2)

[a]Values are no. (%) or median (range);
[b]Race was missing or unknown in three patients.

the same patient. *P*-values were not adjusted for the number of tests. All statistical calculations were conducted with the statistical computing language R (v. 3.1.1; R Foundation for Statistical Computing, Vienna, Austria). Throughout, two-sided tests were used, with statistical significance defined as $p < 0.05$.

RESULTS

Patient population

46 patients with 66 aneurysms were enrolled and imaged between April 6, 2016 and August 29, 2017. Nine patients were scanned on a 3T Philips Ingenia MRI system with a VISTA protocol, and 37 patients were scanned on a 3T Siemens Prisma MRI system (Siemens Healthineers; Erlangen, Germany) with a SPACE protocol. 1 patient was excluded due to poor image quality, therefore, 45 patients with a total of 65 aneurysms were included in the analysis. None of the aneurysms demonstrated visible thrombus adherent to the walls. A majority of patients (68.9%) had only a single aneurysm, while 11.1% had three or more aneurysms. There were 26 (40.6%) aneurysms involving the internal carotid artery, 14 (21.9%) involving the middle cerebral artery (MCA), and 24 (37.5%) involving the anterior cerebral artery (ACA), posterior communicating artery (PcoA), or posterior cerebral artery. See Table 1 for additional patient characteristics.

Inter-reader agreement

Inter-reader agreement is summarized in Table 2. Inter reader agreement was moderate-to-good for the presence of enhancement ($\kappa = 0.64$), extent of enhancement ($\kappa = 0.64$), and intensity of enhancement ($\kappa = 0.60$) while agreement was relatively low for wall thinning ($\kappa = 0.25$).

Vessel wall imaging correlation with PHASES score

Association between PHASES scores and aneurysm characteristics are detailed in Table 3. Data from the two raters were pooled for analysis, resulting in $n = 130$ evaluations of 65 aneurysms.

Table 2. Inter-reader agreement on vessel wall MRI features of aneurysm.

		Reader[a]		Agreement	
Variable		**HW**	**JS**	**κ[b]**	**(95% CI)**
Any enhancement		17 (26.2)	23 (35.4)	0.64	(0.41, 0.83)
No. of quadrants with enhancement	0	48 (73.8)	42 (64.6)	0.64	(0.41, 0.79)
	1	3 (4.6)	5 (7.7)		
	2	5 (7.7)	5 (7.7)		
	3	2 (3.1)	3 (4.6)		
	4	7 (10.8)	10 (15.4)		
Maximum intensity of enhancement	None	48 (73.8)	42 (64.6)	0.60	(0.37, 0.78)
	<infundibulum	10 (15.4)	10 (15.4)		
	≥infundibulum	7 (10.8)	13 (20.0)		
Any appreciable wall thinning		4 (6.2)	3 (4.6)	0.25	(−0.07, 0.79)

CI, confidence interval.
[a]Values are no. (%);
[b]Unweighted Cohen's κ for binary variables and linearly weighted Cohen's κ for ordinal variables.

Table 3. Univariate analysis of associations between the PHASES score and vessel wall MRI features of aneurysms using 130 ratings of 65 aneurysm by two readers

			PHASES score[a]		Univariate model[b]		
Variable	**Group**	**No.**	**0–3 (N = 54)**	**>3 (N = 76)**	**OR**	**(95% CI)**	*p*-value
Any enhancement	All	130	8 (14.8)	32 (42.1)	4.2	(1.2, 14.7)	0.022
No. of quadrants with enhancement (0–4), per 1-quadrant increase	All	130	0.3	1.2	1.7	(1.1, 2.7)	0.020
	With enhancement	40	2.2	2.9	1.6	(1.0, 2.6)	0.063
Maximum intensity of enhancement (0–2), per 1-level increase	All	130	0.2	0.6	2.6	(1.0, 6.9)	0.050
	With enhancement	40	1.4	1.5	2.0	(0.2, 17.6)	0.53
Any appreciable wall thinning	All	130	0 (0.0)	7 (9.2)	∞	-	0.044

CI, confidence interval; OR, odds ratio.
[a]Values are no. (%) or mean;
[b]Logistic regression model containing a single IVW feature for predicting PHASES score, adjusted for reader.

Aneurysms with higher PHASES scores were significantly more likely to demonstrate enhancement [odds ratio (OR) = 4.2, 95% confidence interval (CI) (1.2–14.7), p = 0.022)] (Figure 1). Of those aneurysms with enhancement (n = 40, 30%), the number of quadrants trended toward association with higher PHASES scores (OR = 1.6 per 1-quadrant increase, 95% CI 1.0–2.6, p = 0.063). The intensity of enhancement (when present) was not statistically significantly different between the two groups (p = 0.53). Aneurysms with PHASES >3 were more likely to demonstrate wall thinning (9.2% *vs* 0%, p = 0.044) (Figure 2).

Wall thinning was more common in aneurysms with enhancement (12.5% *vs* 2.2%, p = 0.042), though thinning was not significantly associated with the extent of enhancement (p = 0.62). Of the 38 aneurysms (58.5%) with PHASES >3, 16 had maximum size ≥7 mm (≥3 points in PHASES), 24 were located in the ACA/PcoA/posterior circulation (four points in PHASES) and 5 had both risk factors. Only three had other risk factors that combined exceeded three points. Aneurysms ≥ 7 mm were more likely to demonstrate wall enhancement (75.0% *vs* 16.3%, $p < 0.001$) and wall thinning (21.9% *vs* 0.0%, $p < 0.001$) than aneurysms < 7 mm. However, aneurysms in the ACA/PcoA/posterior circulation had similar rates of enhancement (29.2% *vs* 31.7%, p = 0.85) and wall thinning (6.1% *vs* 4.2%, p = 0.72) compared to aneurysms in other locations. Rates of wall enhancement and thinning did not differ significantly between the other risk factor groups comprising PHASES (Supplementary Material 1).

Overall, 42.1% of higher risk aneurysms and 14.8% of lower risk aneurysms demonstrated any enhancement, resulting in sensitivity of 42.1% and specificity of 85.2%. Wall thinning was only seen in aneurysms with PHASES score greater than 3.

DISCUSSION

In this study we prospectively compared IVW detected wall enhancement and wall thinning between unruptured intracranial aneurysms at high- and low-risk for future rupture. We found that the presence of wall enhancement, more diffuse wall enhancement, and wall thinning were more likely to

Figure 1.Demonstrates a 12 mm anterior communicating artery aneurysm on pre- and post-contrast 3D T_1 SPACE sequences. The post-contrast image (right) demonstrates enhancement in all four quadrants of the aneurysm wall. PHASES score for this aneurysm was 12. 3D, three-dimensional.

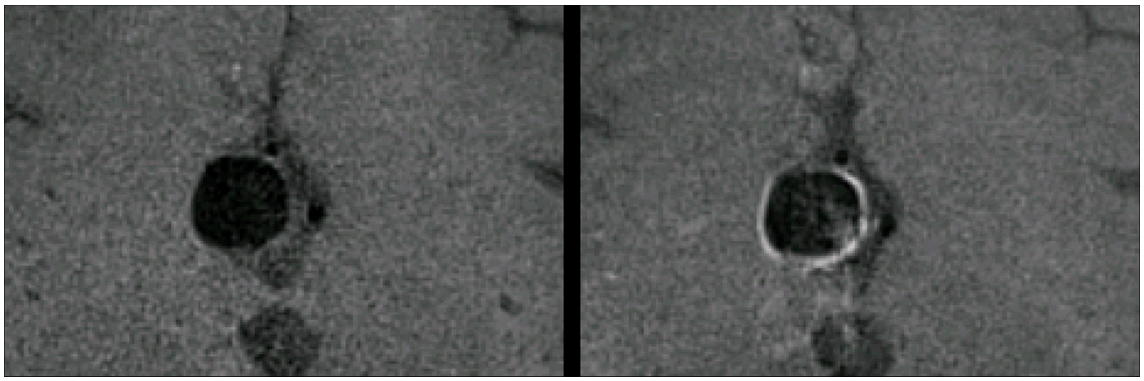
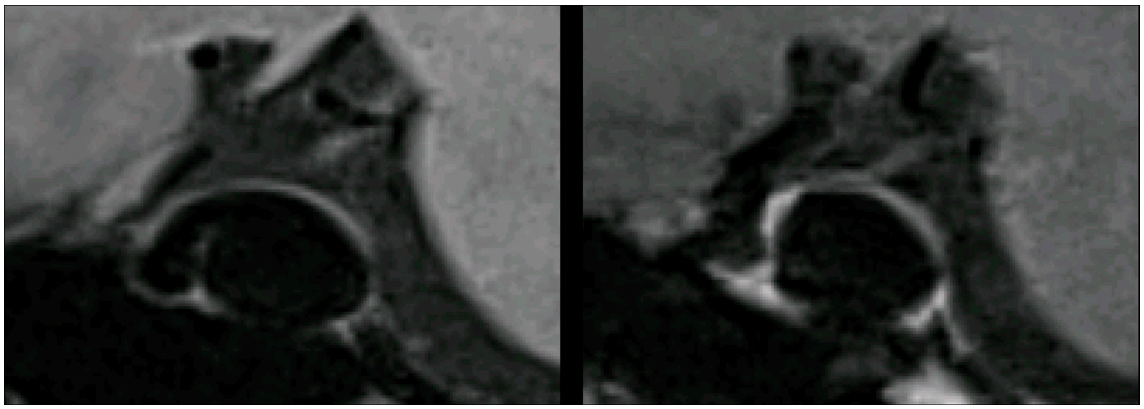


Figure 2.Demonstrates an 18 mm paraclinoid segment right internal carotid artery aneurysm on pre- and post-contrast 3D T_1 SPACE sequences. On pre- and post-contrast images there is thinning of the posterior wall. PHASES score for this aneurysm was 7. 3D, three-dimensional.



occur in aneurysms at higher clinical risk of rupture based on PHASES score. In addition, we also found a significant relationship between wall thinning and the presence of aneurysm wall enhancement. This suggests that these features, if present, may help predict the risk of future aneurysm rupture, and aid in deciding which aneurysms should undergo intervention *vs* observation.

Multiple studies have attempted to predict intracranial aneurysm rupture risk. In 2014, Greving et al[27] incorporated data from multiple prospective cohort studies to develop the PHASES score as a model to predict aneurysm rupture. This score integrates ethnicity (with Finnish and Japanese populations at higher risk), the presence of hypertension, age over 70 years, aneurysm size, prior aneurysmal subarachnoid hemorrhage, and site of aneurysm (with MCA and ACA/Posterior communicating/posterior locations at higher risk). For patients who score 12 points or higher, the 5-year risk of aneurysm rupture is greater than 15%. Subsequent studies have validated the PHASES score, determining that higher scores are associated with aneurysm growth[30] and worse outcomes when aneurysms rupture.[31]

While luminal imaging contributes to the PHASES score, multiple studies have suggested that IVW may allow more direct evaluation of pathophysiological predictors of vulnerability, because ruptured, growing, or symptomatic aneurysms are more likely to demonstrate enhancement. Edjlali et al[11] examined 307 unruptured aneurysms with IVW, categorizing wall enhancement as none, focal, thin, or thick. They found that unstable aneurysms (those which were ruptured, symptomatic or changing) were more likely to show wall enhancement, with thick wall enhancement providing the greatest specificity. Texakalidis et al[14] performed a meta-analysis of 6 studies comprising 505 ruptured and unruptured intracranial aneurysms and found that wall enhancement was associated with higher odds of instability and a lack of wall enhancement may predict aneurysm stability. Backes et al[10] examined gadolinium enhancement in unruptured intracranial aneurysms using IVW techniques, and reported that 26/89 aneurysms demonstrated wall enhancement, and that size was the strongest predictor of enhancement.

Our study showed similar findings and expanded on this work. Our study differs from the above studies in that we only evaluated unruptured aneurysms and compared high- and low-risk aneurysms based on PHASES scores. Inclusion of ruptured and unruptured aneurysms in the vulnerable/unstable category presents difficulties, as the presence of enhancement in ruptured aneurysms may be the result of inflammation or vasa vasorum that led to rupture, or inflammation secondary to rupture.

Prior studies have also suggested that wall thinning may be an important factor in aneurysm rupture. Cebral et al[16] examined the wall shear stress distribution of nine ruptured aneurysms using computational fluid dynamics simulations. They tested models with varied wall thickness and stiffness, and ultimately found that wall thinning and stiffness in areas of high wall shear stress correlated with known rupture sites. Tenjin et al[18] evaluated wall thickness of 37 unruptured aneurysms and graded the wall as either thinned (and therefore invisible or almost invisible) or normal, then compared to surgical findings. In 78% of cases the MRI findings correctly matched the surgical findings, demonstrating that high resolution MRI could be employed to identify wall thinning.

Our study differs in that we used PHASES scores to identify which aneurysms were at higher clinical risk of rupture, and subsequently found that these aneurysms were more likely to demonstrate wall thinning. Because quantitative analysis of wall thinning is below the imaging resolution threshold of IVW,[17] we used qualitative assessment of wall thinning, in which the imperceptibly thin wall appears as an imaging gap.

Our study is limited by the use of PHASES scores to identify the future risk of aneurysm rupture, which is an estimate of aneurysm vulnerability and risk of rupture, not a true endpoint, however, other studies have validated the PHASES score.[30,31] Multiple factors for aneurysm vulnerability were considered individually such as aneurysm size and location, however, these criteria contribute heavily to PHASES score, and thus are incorporated in terms of overall risk assessment. It could be considered a limitation that two different MRI systems were used, however we

strove to create nearly identical protocols with similar sequences and parameters on the two platforms, and the heterogeneity of imaging environment further supports the significance of our results, as they survived any minimal introduced noise. The small sample size prevented us from performing a reliable multivariate analysis, and *p*-values were not adjusted for the number of tests, so the results should be considered principally hypothesis-generating. Inter-reader agreement was moderate-to-good for enhancement characteristic evaluations. However, evaluating aneurysms using IVW has a steep learning curve, and this is reflected in our relatively limited inter-reader agreement for the presence of wall thinning. In part this could be because wall thinning was only seen in less than 7% of aneurysms, limiting our analysis of this feature. Additionally, the evaluation of qualitative characteristics is inherently expected to result in lower κ values. The training of raters was brief, which may have contributed to limited agreement, however both raters have extensive experience in IVW review and are expert general reviewers. While these early results are not sufficient to conclude that IVW adds value to the PHASES score, future multicenter, prospective trials correlating pathology and flow simulations with IVW findings would be beneficial to confirm vulnerable features that correlate with imaging findings.

CONCLUSIONS

Unruptured intracranial aneurysms at higher risk of rupture based on PHASES score are more likely to demonstrate wall enhancement, more diffuse wall enhancement, and wall thinning on IVW. Future studies would be helpful to determine if these IVW findings may help supplement or supplant PHASES scores in the pretreatment evaluation of unruptured intracranial aneurysms.

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