Objective quantification of contrast enhancement of unruptured intracranial aneurysms: a high-resolution vessel wall imaging validation study

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OBJECTIVE High-resolution vessel wall imaging (HR-VWI) has emerged as a valuable tool in assessing unruptured intracranial aneurysms (UIAs). There is no standardized method to quantify contrast enhancement of the aneurysm wall. Contrast enhancement can be objectively measured as signal intensity (SI) or subjectively adjudicated. In this study, the authors compared the different methods to quantify wall enhancement of UIAs and determined the sensitivity and specificity of each method as a surrogate of aneurysm instability. They also compared SI quantification between scanners from different manufacturers.

METHODS The University of Iowa HR-VWI Project database was analyzed. This database compiles patients with UIAs who prospectively underwent HR-VWI using a 3T MRI scanner. The mean and maximal SI values of the aneurysm wall, pituitary stalk, and genu of the corpus callosum were used to compare 3 different measurement methods: 1) aneurysm enhancement ratio AER = (SIwall post − SIwall pre)/SIwall pre; 2) aneurysm-to–pituitary stalk contrast ratio CR stalk = SIwall post/SIstalk post; and 3) aneurysm enhancement index AEI = ([SIwall post/SIbrain post] − [SIwall pre/SIbrain pre])/(SIwall pre/SIbrain pre) (where “pre” indicates precontrast images and “post” indicates postcontrast images). Size ≥ 7 mm was used as a surrogate of aneurysm instability for receiver operating characteristic (ROC) curve analysis. To determine if the objective quantification of SI varies among scanners from different manufacturers, 9 UIAs underwent the same HR-VWI protocol using a 3T General Electric (GE) scanner and a 3T Siemens scanner. Three UIAs also underwent a third scanning procedure on a unit with a different magnet strength (7T GE).

RESULTS Eighty patients with 102 UIAs were included in the study. The mean age was 64.5 ± 12.2 years, and 64 (80%) patients were women. UIAs ≥ 7 mm had significantly higher SIs than smaller UIAs (< 7 mm): AER = 0.82 vs 0.49, p < 0.001; CR stalk = 0.84 vs 0.61, p < 0.001; and AEI = 0.81 vs 0.48, p < 0.001. ROC curves demonstrated optimal sensitivity of 81.5% for CR stalk ≥ 0.60, 75.9% for AEI ≥ 0.50, and 74.1% for AER ≥ 0.49. Intermanufacturer correlation between 3T GE and 3T Siemens MRI scanners for CR stalk using mean and maximal SI values was excellent (Pearson coefficients > 0.80, p < 0.001). A similar correlation was identified among the 3 UIAs that underwent 7T imaging.

CONCLUSIONS CR stalk using maximal SI values was the most reliable objective method to quantify enhancement of UIAs on HR-VWI. The same ratios were obtained between different manufacturers and on scans obtained using magnets of different strengths.


KEYWORDS high-resolution vessel wall imaging; magnetic resonance imaging; aneurysm; circumferential enhancement; validation; aneurysmal subarachnoid hemorrhage; vascular disorders

Unruptured intracranial aneurysms (UIAs) pose a therapeutic dilemma, as the risk-benefit of therapeutic interventions has to be balanced against the natural history of the disease. Early recognition of brain aneurysms with a high risk of rupture is key when deciding treatment. Unfortunately, there is no biomarker of aneurysm instability that has been prospectively validated. High-resolution vessel wall imaging (HR-VWI) has...
emerged as a valuable tool in assessing unstable UIAs.3 There are promising observations in the characterization of aneurysm wall enhancement as a biomarker of aneurysm wall inflammation, growth, and rupture.19

However, there is significant heterogeneity among the imaging protocols used to characterize UIAs with HR-VWI.28 Furthermore, there is no consensus on the standard definition of wall enhancement.23 Most studies have classified wall enhancement subjectively into strong/avid versus faint/no enhancement, or focal versus circumferential wall enhancement, based on the assessment by 2 or more adjudicators. Other studies have used objective data generated from the quantification of signal intensity (SI) in the aneurysm wall to define enhancement. Several formulas have been used to standardize enhancement measurements, including ratios generated through comparisons with the pituitary stalk15,16 and those considering SI measurements in pre- versus postcontrast sequences.26,27

We aimed to compare the different methods of aneurysm wall enhancement measurement to determine the most sensitive and specific measurements. Moreover, our goal was to validate these measurements between scanners from different manufacturers and magnet strengths.

**Methods**

**Patient Population and Data Collection**

After obtaining IRB approval, we analyzed the University of Iowa HR-VWI Project database. This database is prospectively acquired and includes patients with UIAs from January 2015 to August 2019. At our institution, every patient with a UIA undergoes 3T HR-VWI. The IRB was amended to obtain an additional image in a subset of patients using a scanner from a different manufacturer and sometimes a third scan using a scanner with a different magnet strength (7T). Demographics and clinical information, including age, sex, and comorbidities, were obtained from electronic medical records.

**Imaging Acquisition**

Images are routinely acquired using a 3T Siemens MRI scanner (MAGNETOM Skyra, Siemens). The HR-VWI protocol included a 3D T1-weighted SPACE FSE (3D sampling perfection with application-optimized contrasts using different flip-angle evolutions fast spin echo) and a 3D T2-weighted sequence. Five minutes after an intravenous injection of 0.1 mmol/kg gadolinium-based contrast agent (Gadavist, Bayer Pharmaceuticals), a postcontrast 3D T1-weighted SPACE FSE sequence was obtained, and contrast-enhanced MR angiography (CE-MRA) was performed. The reproducibility of results was tested on a 7T GE MRI scanner (GE Healthcare) in 9 UIAs that underwent additional HR-VWI. Three UIAs underwent a third scan on a 7T GE MRI scanner (GE Healthcare). Technical parameters used for imaging acquisition on each scanner are described in Supplemental Tables 1–3.

**HR-VWI Assessment**

All images were analyzed with the Picture Archiving Communication System (PACS, version 12.1.6.1005, Carestream Vue). Aneurysm size (diameter and neck) was measured on CE-MRA images. After 6-fold magnification and autocorrection of viewer windowing, the aneurysm was manually coregistered on both pre- and postcontrast T1-weighted sequences in all 3 planes (axial, coronal, and sagittal). A 2D region of interest (ROI) of the aneurysm wall was drawn at the level of the maximal aneurysm diameter. A combination of CE-MRA and 3D T1-weighted SPACE (precontrast) images were used as a reference to exclude the aneurysm lumen and delineate the inner surface of the aneurysm wall, while both 3D T2-weighted sequences and 3D T1-weighted SPACE (postcontrast) were collectively used to distinguish artifacts such as cerebrospinal fluid, meninges, and veins. ROIs were visually and statistically analyzed to determine that they encompassed the same aneurysm wall area on pre- and postcontrast T1-weighted images (Fig. 1).

Three different methods of the aneurysm wall enhancement measurement were compared: the aneurysm enhancement ratio (AER), the aneurysm enhancement index (AEI), and the aneurysm-to–pituitary stalk contrast ratio (CRstalk). Table 1 summarizes the different formulas and SI measurements used for each method.

As proposed by Wang et al.,27 SI values measured in the aneurysm wall from each projection (SIwall) on pre- and postcontrast T1-weighted images were used to calculate the AER as follows: (SIwall_post – SIwall_pre)/SIwall_pre. Then, following a similar method described by Omodaka et al.,16 SI was quantified in coregistered ROIs of 20 mm2 sampled throughout the pituitary stalk on the sagittal postcontrast T1-weighted images (Fig. 2). The AEI was calculated adjusting SIwall values measured from the aneurysm wall on the postcontrast T1-weighted sequence (SIwall_post) divided by the SI of all sampled points over the pituitary stalk to calculate the CRstalk as follows: SIwall_post/SIstalk_post.

| Table 1. Ratios and indexes used to objectively quantify aneurysm wall enhancement |
|----------------------------------|-------------------------|
| Method                           | Formula*                | Authors & Year |
| AER                              | (SIwall_post – SIwall_pre)/SIwall_pre | Wang et al., 2018 |
| AEI                              | (SIwall_post/SIbrain_post – SIwall_pre/SIbrain_pre)/(SIwall_post/SIbrain_pre) | Omodaka et al., 2016 |
| CRstalk                          | SIwall_post/SIstalk_post | Omodaka et al., 2019 |

* Each formula was computed using the mean and maximal SIwall.
Some UIAs show a pattern of focal enhancement, while others demonstrate uniform circumferential aneurysm wall enhancement (CAWE) on HR-VWI. To define whether the maximal SI on the aneurysm wall should be achieved with CR stalk using the maximal and mean SIs on both pre- and postcontrast T1-weighted images. Consequently, a total of 6 different objective approaches to measure SI were analyzed (Table 1).

### Statistical Analysis
Continuous variables are presented as mean ± SD, and categorical variables are presented as frequency and percentage. Differences in aneurysm enhancement were statistically assessed using the Student t-test. A 2-sided p < 0.05 was considered significant. Based on results from the ISUIA (International Study of Unruptured Intracranial Aneurysms) and other observational studies, UIAs ≥ 7 mm located in the anterior communicating artery (ACoA), posterior communicating artery (PCoA), and basilar artery (BA) are more likely to rupture and were categorized as unstable. We used these variables (size and location) to perform area under the curve receiver operating characteristic (AUC-ROC) analysis. All statistical analyses were performed using IBM SPSS Statistics (version 25.0, IBM Corp.).

### Results
A total of 80 patients with 102 UIAs were included. The mean age was 64.5 ± 12.2 years, and 64 (80%) patients were women (Table 2). Most aneurysms had saccular morphology (96 aneurysms, 94.1%). Correlation statistics demonstrated high agreement for areas covered by ROIs in the axial, coronal, and sagittal projections for both pre- and postcontrast T1-weighted images (Pearson coefficients > 0.92, p < 0.001).

The Student t-test showed that aneurysms ≥ 7 mm had significantly higher maximal SI measurements for AER (0.84 vs 0.61, p < 0.001), CR stalk (0.84 vs 0.61, p < 0.001), and AEI (0.81 vs 0.48, p < 0.001) than did smaller aneurysms. An analysis of aneurysms located in the ACoA, PCoA, and BA, regardless of size, also reported increased maximal SI values for AER (0.71 vs 0.59, p = 0.154), CR stalk (0.73 vs 0.72, p = 0.955), and AEI (0.71 vs 0.58, p = 0.135) compared with aneurysms in other locations. However, the differences for location were statistically nonsignificant.

The best AUC in subsequent ROC analyses was achieved with CR stalk using the maximal SI (0.776), followed by AER (0.738) and AEI (0.730) (Fig. 3). Setting the specificity of all ratios to 60% or more, curve point coordinates demonstrated an optimal sensitivity of 81.5% for CR stalk ≥ 0.60, 75.9% for AEI ≥ 0.50, and 74.1% for AER ≥ 0.49. The cutoffs for all the ratios using maximal and mean SI are summarized in Supplemental Table 4.

Finally, similar HR-VWI protocols were used for both 3T Siemens and 3T GE MRI scanning of 9 UIAs (Table 4).

### Table 2. Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall†</th>
<th>Enhancing UIAs (n = 64)</th>
<th>Nonenhancing UIAs (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yrs ± SD</td>
<td>64.5 ± 12.2</td>
<td>66.6 ± 11.9</td>
<td>59.9 ± 10.3</td>
</tr>
<tr>
<td>Women</td>
<td>64 (80)</td>
<td>50 (78.1)</td>
<td>32 (84.2)</td>
</tr>
<tr>
<td>Currently smoking</td>
<td>42 (52.5)</td>
<td>33 (51.6)</td>
<td>22 (57.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45 (56.3)</td>
<td>36 (56.3)</td>
<td>23 (60.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12 (15)</td>
<td>10 (15.6)</td>
<td>4 (10.5)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>34 (42.5)</td>
<td>25 (39.1)</td>
<td>16 (42.1)</td>
</tr>
<tr>
<td>Family history of IAs</td>
<td>7 (8.75)</td>
<td>5 (7.8)</td>
<td>5 (13.2)</td>
</tr>
<tr>
<td>Mean aneurysm size, mm (range)</td>
<td>8.7 (3–31)</td>
<td>10.8 (3–31)</td>
<td>5.1 (3–11)</td>
</tr>
<tr>
<td>≥7</td>
<td>54 (52.9)</td>
<td>44 (68.8)</td>
<td>10 (26.3)</td>
</tr>
<tr>
<td>&lt;7</td>
<td>48 (47.1)</td>
<td>20 (31.3)</td>
<td>28 (73.7)</td>
</tr>
</tbody>
</table>

### Table 3. SI measurements on pre- and postcontrast T1-weighted images in 9 UIAs using different MRI units from manufacturers

<table>
<thead>
<tr>
<th>MRI Scanner</th>
<th>Mean SI pre</th>
<th>Max SI pre</th>
<th>Mean SI post</th>
<th>Max SI post</th>
<th>CR stalk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>3T Siemens</td>
<td>155.9</td>
<td>267.7</td>
<td>247.9</td>
<td>437.8</td>
<td>0.71/0.42</td>
</tr>
<tr>
<td>3T GE</td>
<td>121.3</td>
<td>194.9</td>
<td>183.9</td>
<td>288.3</td>
<td>0.68/0.41</td>
</tr>
<tr>
<td>7T GE†</td>
<td>232.2</td>
<td>402.3</td>
<td>378.8</td>
<td>671.0</td>
<td>0.79/0.45</td>
</tr>
</tbody>
</table>

Max = maximal; SI = signal intensity; CR = cranial ratio; SI pre = precontrast SI; SI post = postcontrast SI.

† Only 3 UIAs underwent 7T GE MRI.

* The CR stalk is included for comparison: maximal CR stalk/mean CR stalk.
3). Absolute SI values were significantly lower on the GE scanner than on the Siemens scanner (mean $\text{SI}_{\text{wall pre}}$: 121.3 vs 155.9; maximal $\text{SI}_{\text{wall pre}}$: 194.9 vs 287.7; mean $\text{SI}_{\text{wall post}}$: 183.9 vs 247.9; maximal $\text{SI}_{\text{wall post}}$: 288.3 vs 437.8, $p < 0.001$). However, Pearson coefficients demonstrated an excellent correlation between the two scanners for CR stalk using mean SI values (Pearson coefficient $= 0.975$, $p < 0.001$) and maximal SI values (Pearson coefficient $= 0.814$, $p = 0.008$). A similar correlation pattern for CR stalk was established in the 3 UIAs that underwent 7T GE MRI (Pearson coefficients $> 0.95$). On the other hand, the intermanufacturer correlation using AER and AEI was negligible and statistically nonsignificant (Pearson coefficients $< 0.40$, $p > 0.20$).

Discussion

Clinical and histological correlations have suggested that increased contrast enhancement of the aneurysm wall is a surrogate of aneurysm instability and increased risk of rupture.\textsuperscript{24,28} Enhancement quantification has been performed mostly subjectively by experienced adjudicators.\textsuperscript{2,12} Several objective methods have been described to quantify enhancement and SI. This study compared all the different objective methods and demonstrated that $\text{CR}_{\text{stalk}}$ using maximal SI is the best predictor of aneurysm instability. Moreover, we demonstrated the reproducibility of this technique between scanners made by different manufacturers, which would be pivotal in a multicenter prospective clinical trial.

Inflammation of the aneurysm wall, usually initiated by a hemodynamic insult, may result in dysfunction of endothelial and vascular smooth muscle cells, local activation of cytokines, degradation of the extracellular matrix, aneurysm remodeling, and rupture.\textsuperscript{4} Several studies have correlated enhancement of the aneurysm wall on HR-VWI with inflammatory histopathological changes: increased inflammatory cells,\textsuperscript{8,9,22} myeloperoxidase activity, and vasa vasorum proliferation.\textsuperscript{10,13,22,25} A histopathological study performed by our group demonstrated that UIAs with avid enhancement had increased macrophage infiltration and cellularity in comparison with aneurysms with a mildly enhancing or no enhancing wall.\textsuperscript{9} This sug-
gests that weakened arterial walls of unstable UIAs exhibit increased contrast enhancement on HR-VWI, and these changes might be explained by an active inflammatory/vasculopathic reaction in the aneurysm wall.

Edjlali et al. analyzed 108 UIAs with HR-VWI and introduced the concept of CAWE as the presence of “circumferential aneurysmal wall enhancement.” CAWE was more commonly seen in unstable than stable UIAs (27/31 [87%] vs 22/77 [28.5%], respectively; p < 0.0001). Omodaka et al. proposed two different standardized tools to objectively assess wall enhancement: 1) CR stalk on post-contrast imaging, and 2) AEI using matched volumes on pre- and postcontrast T1-weighted images in the right frontal lobe as reference.

Later on, the same group compared CR stalk in 69 stable UIAs, 26 evolving UIAs, and 67 ruptured aneurysms, reporting significantly higher CR stalk values in evolving UIAs than in stable UIAs (0.54 vs 0.34, p < 0.0001), but lower than those in ruptured aneurysms (0.54 vs 0.83, p < 0.0002).\(^{15}\) Wang et al.\(^{27}\) showed significantly lower enhancement values in UIAs compared with ruptured aneurysms (0.63 vs 0.90, p < 0.001) using AER.

In this study, we compared all of these objective modalities for quantification of wall enhancement in UIAs. Omodaka et al.\(^{15}\) reported an optimal cutoff value for CR stalk ≥ 0.39 to distinguish evolving from stable UIAs (AUC = 0.80), with a sensitivity of 88% and a specificity of 63%. Our analysis suggested the same cutoff value for CR stalk using mean SI values. In a different publication, Omodaka et al.\(^{16}\) used maximal SI ratios to distinguish ruptured aneurysms (n = 28) from UIAs (n = 76). The authors reported that CR stalk ≥ 0.64 achieved a sensitivity of 75% and specificity of 83% (AUC = 0.84), whereas AEI ≥ 0.53 achieved a sensitivity of 96% and specificity of 43% (AUC = 0.75). We also found similar cutoffs for CR stalk (0.60) and AEI (0.50) using maximal SI values. Using a cutoff value for AER ≥ 0.615 to differentiate ruptured intracranial aneurysms (n = 19) from UIAs (n = 87), Wang et al.\(^{27}\) achieved an AUC of 0.798, sensitivity of 89.5%, and specificity of 63.2%. Although we found lower cutoffs for AER (≥ 0.49), our predictive measurements were lower for sensitivity (74%) but similar for specificity (approximately 60%). Overall, the cutoffs found in our study for each enhancement ratio/index correlate with those reported in previous studies. Minor differences in predictive measurements might be explained by the sample size, heterogeneity of the samples, and statistical power of each study.

Our study determined that the best predictor of aneurysm instability is CR stalk using maximal SI (≥ 0.60; sensitivity of 81.5% and specificity of 61%). HR-VWI is a relatively new biomarker of aneurysm instability; therefore, there is no consensus about the best approach in quantifying aneurysm enhancement. Some studies have used the mean versus maximal SI.\(^{13,15,16,27}\) Saccular aneurysms with focal enhancement will have a lower mean SI as the ROI values are averaged and dilute focal enhancement. Even aneurysms with CAWE will have a higher mean SI. These
The image contains a page from a neurosurgical journal. The content discusses the use of HR-VWI (high-resolution vascular wall imaging) for characterization of UIAs (unruptured intracranial aneurysms). It highlights the importance of reproducibility and consistency in imaging protocols, as well as the potential limitations of using specific structures for reference. The text also mentions future directions and conclusions related to the clinical use of HR-VWI.

**Future Directions**

A previous trial that randomized UIAs to coiling versus conservative management failed due to slow recruitment. One of the major drawbacks of this trial was the lack of a biomarker of aneurysm instability. Patients and physicians faced the dichotomy of intervention versus observation. A new trial will have to include HR-VWI as a biomarker of aneurysm instability and may incorporate the following parameters: SI, quantitative susceptibility mapping, wall thickness, and advanced volumetric measurements. Patients and physicians will have to commit to participating in the study and follow through with randomization, even if it involves serial imaging without intervention. Unfortunately, there are no prospective clinical data to determine if a UIA with a CRstalk ≥ 0.60 should be treated. Patients with 3- to 7-mm UIAs may undergo HR-VWI at diagnosis and follow-up. Aneurysm growth, morphological changes, development of new symptoms, or progression to rupture could be prospectively compared with parameters of aneurysm instability on HR-VWI.

**Limitations**

Our relatively small sample size limits the generalizability of the results. HR-VWI may be prone to more artifacts when analyzing smaller aneurysms located in the cavernous and paraclinoid segments of the internal carotid artery. The cavernous/sphenoid sinuses and dural folds of the skull base enhance with contrast and may be confused with the aneurysm wall. In this study, 6 (5.9%) aneurysms were in the cavernous portion of the internal carotid artery.

Additionally, our AUC-ROC curve analyses assumed that UIAs ≥ 7 mm located in the ACoA, PCoA, and BA were unstable. Although such an assumption is widely supported by the ISUIA and the UCAS (Unruptured Cerebral Aneurysm Study), the gold standard would be to evaluate aneurysm instability prospectively. The PHASES (population, hypertension, age, size of aneurysm, earlier SAH from another aneurysm, site of aneurysm) score was not used to define aneurysm instability due to the known limitations of this scale: underrepresentation of patients with familial aneurysms and young smokers, limited long-term follow-up data, and exclusion of the risk of intervention or treatment. Moreover, the PHASES score did not account for aneurysm morphology as a risk factor of rupture. No UIAs ruptured during follow-up in our cohort. A total of 12 patients with 16 UIAs underwent follow-up HR-VWI (mean 7.2 months). These patients will be followed prospectively to determine if there are changes in the degree of aneurysm wall enhancement and whether the UIAs grow or become symptomatic.

Another limitation when comparing SI across different scanners is the effect of manufacturer-specific sequences and techniques for fat suppression and image acquisition, and the associated hardware differences between scanners (32-channel head coil for the GE scanner vs 20-channel coil for the Siemens scanner). Nevertheless, these differences are more reflective of a real-world setting and likely to be encountered as HR-VWI is more frequently utilized.

**Conclusions**

**CRstalk** using maximal SI values was the most reliable reference when defining aneurysm wall enhancement.
objective method to quantify aneurysm enhancement on HR-VWI. Aneurysms \( \geq 7 \) mm located in the ACoA, PCoA, and BA showed increased wall enhancement. Adjusting aneurysm enhancement for SI values measured in the pituitary stalk allows standardization and reproducibility of results between MRI studies with scanners from different manufacturers and achieves higher sensitivity and specificity. These findings may help with standardization of quantifiable parameters of aneurysm enhancement and comparison of results across different manufacturer platforms.

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References

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**Author Contributions**

Conception and design: Samaniego, Roa, Hasan. Acquisition of data: Roa, Osorno-Cruz. Analysis and interpretation of data: Roa, Bathla, Hasan. Drafting the article: Samaniego, Roa, Zanaty, Ishii, Bathla, Ortega-Gutierrez, Hasan. Critically revising the article: Samaniego, Roa, Hasan. Reviewed submitted version of manuscript: Samaniego, Roa. Approved the final version of the manuscript on behalf of all authors: Samaniego. Statistical analysis: Roa. Study supervision: Samaniego.

**Supplemental Information**

Online-Only Content

Supplemental material is available with the online version of the article.


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