

Vessel Wall Imaging of Unruptured Intracranial Aneurysms: Ready for Prime Time? Not so Fast!

There are differing viewpoints on the utility of vessel wall imaging (VWI) assessment of unruptured aneurysms within the neuroradiology community. Many authors, including us, have interpreted their data to indicate it offers clinical value. This enthusiasm undoubtedly arises from a sincere viewpoint that the current literature assessing it is compelling enough to positively impact patient care. Vessel wall imaging of intracranial aneurysms is already being used at dozens, if not hundreds, of institutions across the world and may seem ready for prime time. However, despite our initial optimism, we have now concluded that radiologists and clinicians should exercise some caution in their interpretation of the utility of aneurysm wall enhancement (AWE) in the evaluation of intracranial aneurysms as well as some judiciousness when interpreting the existing data.

First, the evaluation of the sensitivity and specificity of AWE in detecting unstable aneurysms is severely limited because to date, there have been few longitudinal studies demonstrating the presence of AWE prior to an unruptured aneurysm growing or rupturing. None of these longitudinal studies have enough follow-up data to reliably assess the natural history of unruptured intracranial aneurysms. Demonstrating that aneurysms that have recently grown, become symptomatic, or ruptured have wall enhancement and concluding that AWE is thus a generalizable biomarker to predict aneurysm instability is a logical fallacy. What came first? The enhancement or the instability? The chicken or the egg? Furthermore, these categories of unstable aneurysms can all be detected with other clinical or radiologic methods, whereas unruptured aneurysms without these features are the group in which VWI might have the greatest potential to impact management. Thus, few meaningful conclusions on the clinical utility of AWE in unruptured aneurysms can be made until we have longitudinal studies comparing the natural history of unruptured aneurysms with or without wall enhancement.

Our group has also purported that AWE is a reliable biomarker of aneurysm instability. For example, we recently published a meta-analysis finding that AWE is sensitive (95%), but not highly specific (62.7%), for unstable aneurysms with a high negative predictive value.¹ The numbers are correct in context, but to analyze the available data, we had to group several definitions of wall enhancement

(circumferential, partial, thick, strong, and so forth) and several definitions of unstable (growing, changing, symptomatic, ruptured, and so forth). Subsequent articles have continued to use similar methods, and the associated limitations have become clear. Any thorough reader of the AWE literature is likely frustrated by the variability of the study designs of prior investigations (Table). Furthermore, the inclusion of ruptured aneurysms and grouping of these aneurysms with “other unstable” is not necessarily helpful. Specifically, the mechanism of enhancement in ruptured aneurysms is likely different and may reflect the ruptured status itself rather than that of any inflammatory precursor condition. Overall, standardization of definitions and logical inclusion criteria would allow fair comparison between study findings.

In addition to all the variability in study design, definitions, and outcomes, one should consider that there are so many confounding variables in our analysis of AWE and aneurysm natural history. In 1 study by the group in Utrecht, there was a more-or-less linear correlation between aneurysm size and the prevalence of wall enhancement.² While this association has been inconsistently demonstrated, it seems to be a recurring theme in the AWE literature. If there is truly a correlation of AWE to size, then the added value of VWI to size alone may be diminished because aneurysm size is already a well-established risk factor for future growth and rupture.

Furthermore, we do not even really know what AWE really means. Although some data correlating AWE to inflammation on histopathology are emerging from clinical data and a rabbit study, mechanisms beyond wall inflammation, including slow flow near the wall (particularly in larger aneurysms), vasa vasorum, thrombotic lining, and increased permeability due to endothelial dysfunction, remain possible alternate or additional etiologies.^{3,4} Additionally, the histology of vulnerable aneurysm walls has been shown to be variable, including some aneurysms with extremely thin hypocellular walls and others with thickened walls. Additional correlation of VWI findings to various histologic aneurysm wall patterns would be useful.

The existing studies are meritorious and lay solid groundwork for initial assessment of this topic, but many questions remain. These include the optimal methods of AWE assessment, long-term diagnostic accuracy in asymptomatic unchanging aneurysms, the added value of VWI luminal size and morphologic data alone, and a more complete understanding of the pathogenic mechanism. Given the high morbidity and mortality of an aneurysm rupture, the proce-

Major clinical studies characterizing saccular aneurysm wall enhancement on VWI

Study ^a	Aneurysm Categories (Type, Any Enhancement Present) (No.)	Pattern of AWE	Degree of AWE ^b	AWE Association with Size (Range) (mm)	Histopathologic Correlation
Marouk et al. <i>Neurosurgery</i> 2013;72:492–96	Ruptured (5/5) ^c Unruptured (0/3) Total = 8	Thick	Not assessed	Not assessed (2–8)	No
Edjlali et al. <i>Stroke</i> 2014;45:3704–06	Ruptured (16/17) Changing (5/5) Symptomatic (6/9) Other (22/77) Total = 108	CAWE	Not assessed	No correlation to size of entire cohort (4–8)	No
Nagahata et al. <i>Clin Neuroradiol</i> 2014;26:277–83	Ruptured (60/61) Unruptured (15/83) Total = 144	1) CAWE/PAWE grouped 2) Focal	1) Strong 2) Faint 3) Absent Not assessed	No correlation to size in the unruptured cohort (1–18)	No
Liu et al. <i>Interv Neuroradiol</i> 2016;22:501–05	Unruptured (33/61) Total = 61	Present or absent	Not assessed	AWE likelihood increased with size (only 12% of those <7 mm) (2.9–30.5)	No
Omodaka et al. <i>AJNR Am J Neuroradiol</i> 2016;37:1262–66	Ruptured (28) Unruptured (76) Total = 104 (signal intensity cutoff values rather than absolute numbers determined)	1) Circumferential signal intensity 2) Focal enhancement of bleb in some cases	Assessed as a signal intensity ratio	Not reported	No
Hu et al. <i>Neuroradiology</i> 2016; 58:979–85	Ruptured (6/6)	Partial or CAWE	Not assessed	No relationship of AWE to size found Mean size = 11 ± 11.7	Reported for 2 aneurysms (1 giant symptomatic and 1 ruptured) demonstrating inflammatory mediators
Fu et al. <i>Clin Neuroradiol</i> 2017 [Epub ahead of print]	Symptomatic (4/4) Growing (1/1) Other (4/19) Total = 30	CAWE	Not assessed	AWE not correlated to size in entire cohort Mean size = 7.8 ± 4.5 for symptomatic aneurysms	No
Wang. <i>J Neurointerven Surg</i> 2018;10:566–70	Symptomatic (16/23) Asymptomatic (6/22) Total = 45	1) CAWE 2) PAWE	(Quantitative signal intensity analysis)	Not assessed	No
Edjlali et al. <i>Radiology</i> 2018;289:181–87	Ruptured (19/19) Unruptured (64/87) Total = 106	1) Focal thick 2) Thin CAWE 3) Thick CAWE	Not assessed	(Unruptured 7.29 ± 6.60) (Ruptured mean size = 8.4 ± 4.8 for asymptomatic aneurysms) Correlation to size not assessed Median size (5–6)	No
	Total = 333				

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Study ^a	Aneurysm Categories (Type, Any Enhancement Present) (No.)	Pattern of AWE	Degree of AWE ^b	AWE Association with Size (Range) (mm)	Histopathologic Correlation
Lv et al. <i>Neurosurgery</i> 2018 [Epub ahead of print]	Unruptured (82/140) Total = 140	Present or absent	Not assessed	Positive association with size (1.7–36.0)	No
Lv et al. <i>World Neurosurg</i> 2018:e338–43	Unruptured (16/30) Total = 30	Present or absent	Not assessed	Positive association with size (2.5–15.9)	No
Omodaka et al. <i>Neurosurgery</i> 2018;82:638–44	Ruptured (26) ^c	Circumferential signal intensity	Signal intensity ratio of ruptured to unruptured aneurysms	Results adjusted for size, but not formally assessed	No
Backes et al. <i>Neurosurgery</i> 2018;83:719–25	Unruptured (6/89) Total = 89	Present or absent	Not assessed	Ruptured (2.7–11.8) Unruptured (2.0–11.4)	No
Wang et al. <i>J Neurosurg</i> 2019;46:25–28	Unruptured (65/88) Total = 88	Present or absent	Not assessed	Positive association with size (≤7)	No
Larsen et al. <i>AJNR Am J Neuroradiol</i> 2018;39:1617–21	Unruptured (6/13)	None/faint vs strong	None/faint vs strong	Positive association with size 3.6–7.9 Enhancement present in 4/4 aneurysms ≥10 mm but absent in 7/9 <10 mm	Inflammatory mediators, neovascularization and vasa vasorum variably present in aneurysms with strong AWE; absent in those without AWE
Shimonaga et al. <i>Stroke</i> 2018;49:2516–19	Total = 13 Unruptured (5/6)	Present or absent	Not assessed	(4–17) Not assessed	Thickening of the wall with vasa vasorum, inflammatory mediators (n = 5); thin vessel wall with a few macrophages with 3 others with walls not visible on 1.5T VWI
	Total = 6 (additional aneurysms had walls not discernable on VWI)			(5.3–9.0)	

Note:—CAWE indicates circumferential aneurysm wall enhancement; PAWE, partial aneurysm wall enhancement.

^a Reports do not account for any aneurysm with duplicate reports in instances of 2 publications by the same institution/author.

^b Not assessed beyond binary present/absent.

^c All patients had at least 1 ruptured aneurysm.

dural risks with treatment, and the high prevalence of “stable” aneurysms, a very high diagnostic accuracy is necessary for any novel imaging modalities to improve on existing clinical prognostic factors that have been studied in longitudinal multicenter prospective clinical trials. Additional methods to help stratify aneurysms into stable and unstable categories are needed. Continued evaluation of VWI for this purpose may be very useful to better define the potential value for such risk stratification. Given the limitations of the existing literature on VWI, determinations regarding its clinical utility and its added value over standard clinical and radiographic risk factor predictors are premature.

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