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A Volumetric Metric for Monitoring Intracranial Aneurysms: Repeatability and Growth Criteria in a Longitudinal MR Imaging Study

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ABSTRACT

BACKGROUND AND PURPOSE: The reliability of contrast-enhanced MRA in monitoring serial volumetric changes of unruptured intracranial aneurysms has not been established. We aimed to determine the coefficient of variance of contrast-enhanced MRA in measuring aneurysm volumes, thus establishing criteria for aneurysm growth and permitting identification of variables predictive of growth.

MATERIALS AND METHODS: Aneurysm volumes were measured from serial contrast-enhanced MRA studies of patients with untreated intracranial aneurysms who underwent >2 sequential MR imaging evaluations. After coregistering all sequential studies in 3D space for each aneurysm and signal intensity normalization, aneurysm volume was determined across all time points. A linear mixed effects model was built to estimate the coefficient of variance of the measurement as well as to determine predictive variables. Growth was defined as relative growth exceeding 2 times the measurement coefficient of variance (sudden growth, as 4 times the coefficient of variance).

RESULTS: A total of 95 patients with 112 aneurysms were included (5.9 scans during 4.0 years on average, 616 scan measurements in total). The coefficient of variance was 5.5% of the aneurysm volume, and the relative growth rate was dependent on the location: anterior cerebral artery, 4.52% per year; vertebral artery, 2.46% per year; middle cerebral artery, 2.74% per year; basilar artery, 2.36% per year; internal carotid artery, 1.14% per year. Thirty-six of 112 (32%) aneurysms were characterized as growing, and 11/36 of them had an episode of sudden growth.

CONCLUSIONS: Volume measurement of unruptured intracranial aneurysms by contrast-enhanced MRA seems a reliable metric for tracking the growth trajectory of aneurysms. Furthermore, the aneurysm growth rate differs among different locations.

ABBREVIATIONS: ACA = anterior cerebral artery; CE-MRA = contrast-enhanced MRA; CV = coefficient of variance; UIA = unruptured intracranial aneurysm

It is estimated that approximately 3%–5% of the population may have unruptured intracranial aneurysms (UIAs).¹ The most acute complication of UIAs is rupture, which has a high rate of mortality and morbidity.² However, only a small percentage of aneurysms ever rupture.³ Small UIAs are often followed with repeat imaging, with the intention to treat the aneurysm after it has demonstrated growth.⁴ Although multiple studies have explored the natural history of UIAs, current clinical evaluation relies heavily on traditional factors such as UIA diameter, diameter growth on serial imaging, hemorrhagic history, and clinical

symptoms.^{5,6} UIA diameter growth is of particular clinical concern because previous studies have shown it to be a key risk factor for intracranial aneurysmal rupture.^{7–9} However, intracranial aneurysms can present with irregular and complicated geometries, and the accurate and reproducible measurement of aneurysmal diameter is challenging.¹⁰ Volume has been proposed as a more sensitive and comprehensive parameter for evaluation of aneurysm size compared with diameter measured on a 2D plane.^{11–13} While various methods have been developed for aneurysm volume calculation,¹⁴ they lack validation and little is currently known about the growth trajectory of UIAs when assessed by volumetric metrics.

The choice of imaging technique for monitoring UIAs requires careful consideration. Although providing excellent and robust

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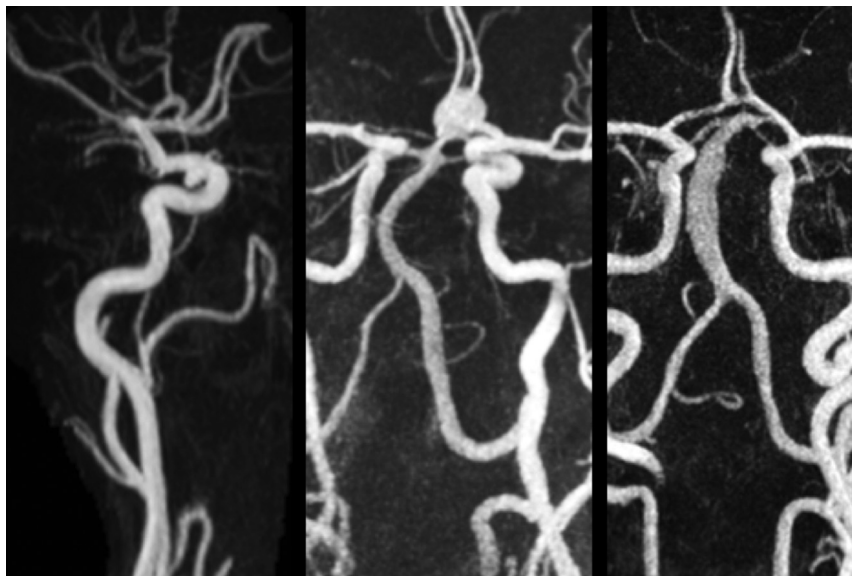


FIG 1. Maximum intensity projections of CE-MRA studies from 3 subjects. A, Subject with a saccular aneurysm of the internal carotid artery. B, Subject with a saccular aneurysm of the anterior communicating artery. C, Subject with a fusiform vertebral artery aneurysm.

results, conventional angiography and CT angiography are unsuited for serial monitoring due to invasiveness and the associated radiation dose, respectively. While contrast-enhanced MRA (CE-MRA) is minimally invasive and provides volumetric data, the reliability of CE-MRA has been verified using DSA.¹⁵ However, the repeatability of this technique has not been established for UIAs.

A reliable and well-characterized metric of change in aneurysm dimensions would help to differentiate important features of the underlying growth trajectory. For example, most previous studies have assumed a linear and continuous aneurysm growth pattern and used only the baseline and final time points to calculate the growth rate.^{3,7,16} This feature obscures cases in which aneurysms exhibit periods of intermittent rapid growth following a period of relative stability. Sudden aneurysmal growth could implicate a more acute pathologic process such as inflammation that requires more aggressive clinical management, whereas the conventional evaluation would underestimate recent rapid growth, diluting it by the overall growth rate calculation.

This study aimed to establish the coefficient of variance (CV) of volumetric measurement by CE-MRA to establish a criterion for likely aneurysm growth and, further, to identify variables predictive of growth.

MATERIALS AND METHODS

Patient Population

This prospective study was conducted under institutional review board approval of the UCSF Medical Center. All subjects gave written informed consent for study participation. Patients with UIAs were recruited between April 2001 and July 2019 for serial MR imaging monitoring studies. Although initially recruited as part of a National Institutes of Health–funded study, this study was later implemented as part of the clinical routine, and despite

the lengthy enrollment period, informed consent was always obtained for use of the image data. Inclusion criteria were the following: 18–100 years of age; diagnosed with at least 1 UIA that was not scheduled for surgical or endovascular treatment; and having undergone >2 follow-up imaging sessions. Exclusion criteria were the following: metal implants, claustrophobia, or allergy to MR contrast agents. Subjects were asked to return every 6 months for CE-MRA. Patient demographic data and cardiovascular risk factors were recorded. Study end points included operative repair, aneurysm rupture, loss to follow-up, or death.

MRA Surveillance Protocol

In the first years of the study, imaging was performed on a 1.5T scanner (Achieva; Philips, Healthcare) and in later years on a 3T scanner (Skyra; Siemens).

A weight-adjusted single dose of Gd-DTPA, diluted with saline to a 22-mL volume, was injected at 2 mL/s through an intravenous catheter placed in the antecubital vein. The delay between contrast injection and arrival at the aneurysm, T_{delay} , was determined by using a 2-mL bolus and visual inspection of the resulting dynamic series of images collected at 1-second intervals. A CE-MRA was then acquired using a 3D paracoronal slab with data acquisition initiated at a T_{delay} of 3 seconds following the start of a 20-mL injection. Representative images are shown in Fig 1.

At 1.5T, imaging was performed with either a 6-channel head coil or a 16-channel head/neck coil. Imaging included contrast-enhanced angiography (3D spoiled gradient-echo: FOV = 240 × 180 × 54 mm, matrix = 400 × 286 × 45, TR/TE = 5.0/1.8 ms, flip angle = 30°, sensitivity encoding factor = 2, bandwidth = 302 Hz/pixel, scanning time = 34 seconds). Elliptic-centric k -space with time to center was 6 seconds. The resultant resolution was 0.6 × 0.6 × 1.2 mm.

At 3T, imaging was performed with a 20-channel head/neck coil. Imaging included contrast-enhanced angiography (3D spoiled gradient-echo: FOV = 223 × 181 × 84 mm, matrix = 320 × 260 × 120, TR/TE = 3.7/1.4 ms, flip angle = 20°, generalized autocalibrating partially parallel acquisition factor = 3, bandwidth = 505 Hz/pixel, scanning time = 30 seconds). Elliptic-centric k -space with time to center was 6 seconds. The resultant images had an isotropic resolution of 0.7 × 0.7 × 0.7 mm.

Longitudinal Analysis of the Aneurysm Volume

Analysis of the aneurysm volume was performed with 2 thresholding iterations. The threshold for the baseline study was selected using the same windowing techniques as in clinical practice to maximize luminal volume while excluding extraluminal

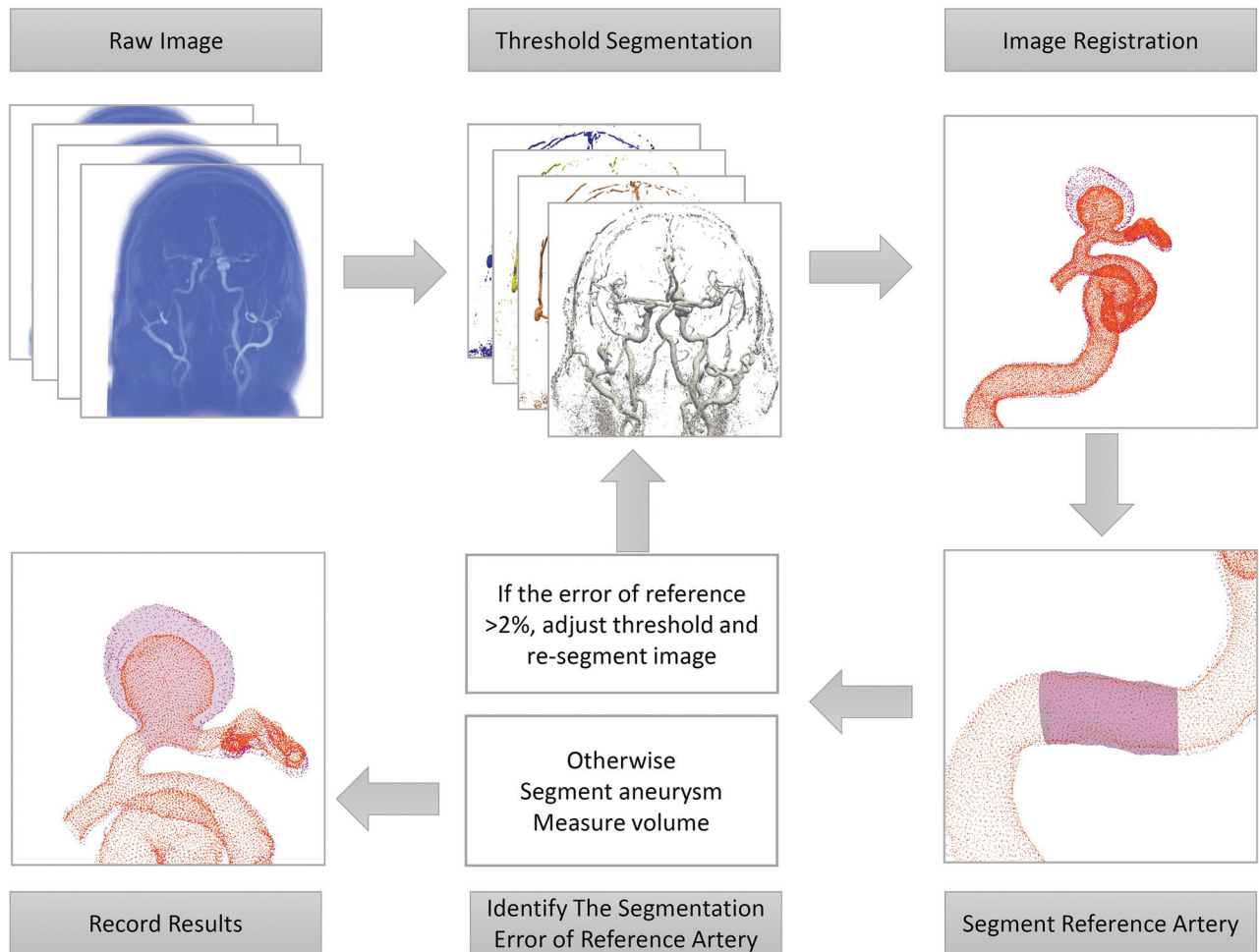


FIG 2. Diagram of the pipeline of aneurysm volume measurement.

regions. This selection was repeated on all consecutive datasets, and the 3D volumes were then placed into spatial coregistration.

The second thresholding step was performed using a reference length of vessel that was considered disease-free and presumed to have an unchanged volume during all time points. Interstudy calibration was enforced by adjusting the intensity threshold of each subsequent session to yield a measured volume of the reference artery that matched that of the baseline study to within $\pm 2\%$. Identification of the reference vessel varied with the location of the aneurysm. In general, a branch-free, relatively straight segment of the parent vessel was selected a few centimeters proximal to the aneurysm. For the most common aneurysm type, the ICA, this was typically in the petrous portion of the ICA.

The processing pipeline is illustrated in Fig 2. DICOM images were exported in the Visualization ToolKit format. Isosurfaces for baseline and follow-up studies were imported into the 3D modeling software Geomagic Design X (3D Systems) and were coregistered to the baseline study using a picked point, landmark-based registration. The volume of the reference length was measured. If it differed from that in baseline, the threshold was adjusted and a new isosurface was generated. This process was repeated iteratively until volume matching was achieved for the reference length. Cut planes were then prescribed transverse to the arteries at the proximal and

distal ends of the aneurysmal segment, and the volume contained within the isosurfaces between those planes was calculated.

Statistical Methods

The data were analyzed in R statistical and computing software (Version 3.61; <http://www.r-project.org/>) using linear mixed effects modeling (`lmerTest`¹⁷ for a linear mixed effect model; <https://cran.r-project.org/web/packages/lmerTest/index.html>). Homoscedasticity was obtained by log-transforming the aneurysm volumes, and time was centered for each patient. Time was included as a fixed effect, and the intercepts and slopes of the log-volume for patients and aneurysms were included as random effects. First, it was determined whether a quadratic time component was needed (Satterthwaite method, $P < .05$). Second, whether the residual differed between 1.5T and 3T (Levene test, $P < .05$) was investigated. The CV was obtained from the variance of the residuals as

$$CV = (\text{SD of Original Scale}) / (\text{Mean of Original Scale}) = \sqrt{\exp(\text{Variance of Log-Transformed Residuals}) - 1}.$$

Predictive variables were identified using a stepwise forward selection followed by a backward elimination (Satterthwaite method, $P < .05$).

Noticeable growth was defined as relative growth > 2 times the CV (compared with the initial volume). Sudden growth

was defined as relative growth larger than 4 times the CV per year in consecutive follow-up measurements with no growth before and subsequent to that time interval.

RESULTS

A total of 101 patients who underwent >2 MR imaging scans were included in this longitudinal study. For any subject in whom there was an apparent decrease in aneurysm volume, true FISP images were examined to see whether there was any wall thickening

encroaching on the lumen, indicating thrombus layering in the aneurysm rather than simply measurement error that accounted for this volume change. Six aneurysms were noted to layer intraluminal thrombus during follow-up and were excluded from analysis. Hence the statistical analysis was performed on the basis of 95 patients with 112 aneurysms, and a total of 616 measurements (Figs 3–4).

The average maximal diameter of 112 aneurysms was 6.1 mm. The mean follow-up time for this cohort was 4.0 years, and the mean number of imaging sessions was 5.9. Detailed patient and aneurysm characteristics are presented in Table 1.

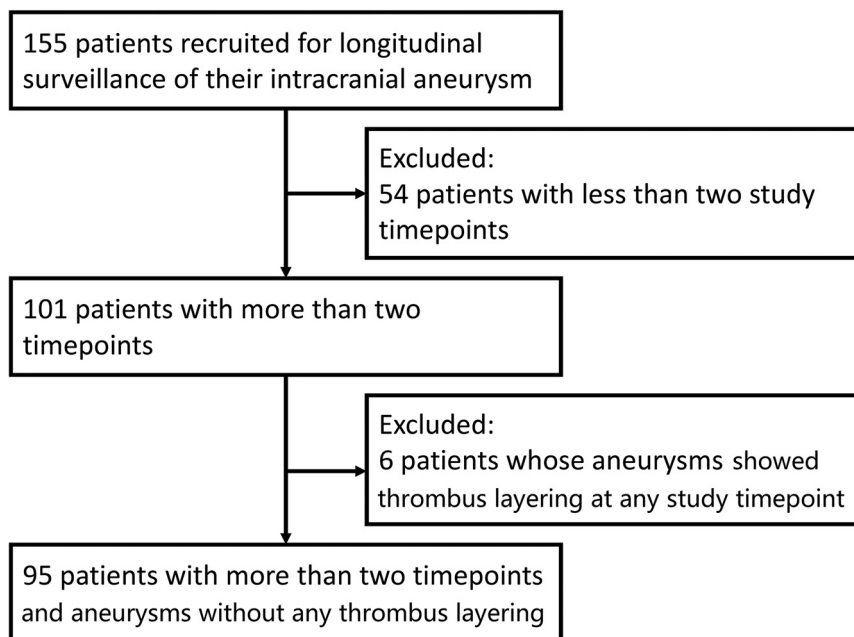


FIG 3. Patient selection flow chart.

Coefficient of Variance and Identification of Predictive Variables of Growth from Linear Mixed Effect Modeling

Including a quadratic time term did not improve the model significantly ($P = .32$). No significant difference of the residuals was found between acquisitions at 1.5T and 3T ($P = .26$). The CV was determined to be 5.5%.

Among the investigated terms (aneurysm location, saccular versus non-saccular aneurysms, sex, hypertension, hyperlipidemia, smoking, diabetes, age, and the presence of multiple aneurysms) as potential fixed effects in the best-fit linear mixed effect model, aneurysm volume growth varied by age and location, with the fastest growth in anterior cerebral artery (ACA) aneurysms, as summarized in Table 2.

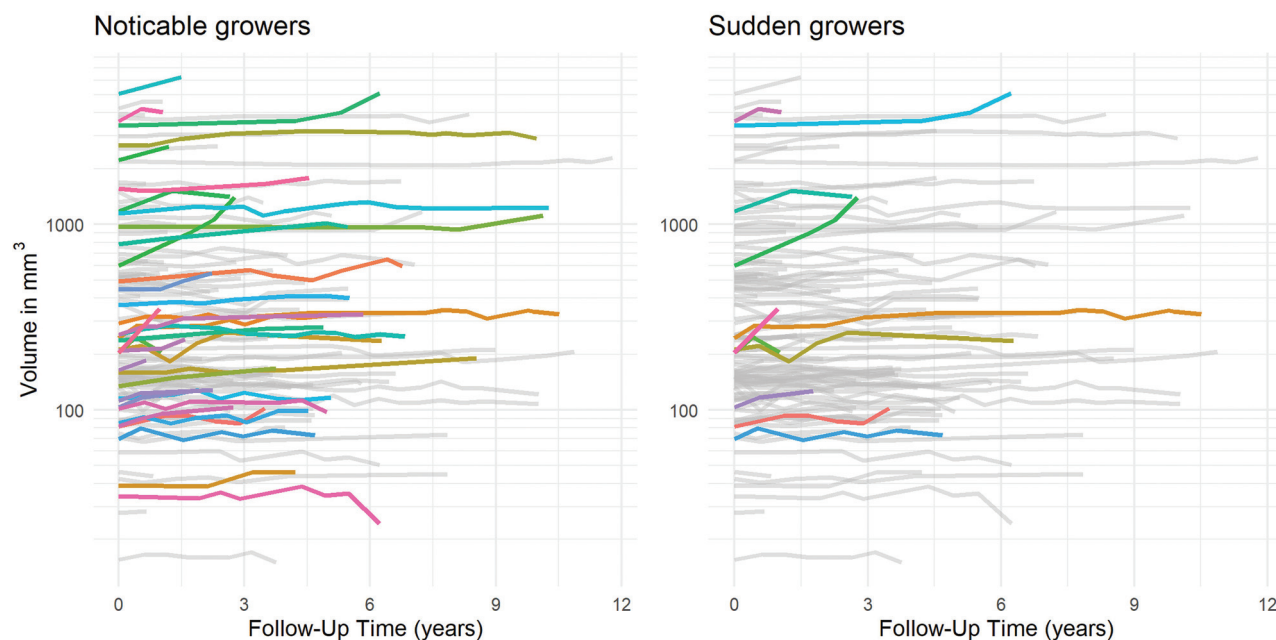


FIG 4. Plots showing evolution across time of volume for each of the 112 aneurysms. Color coding is used to highlight noticeable growers (left) and sudden growers (right).

Table 1: Demographics^a

Variable	Value
No. of patients	95
No. of aneurysms	112
Age (mean) (yr)	61.1 (SD, 17.4)
Female	62 (65.3%)
Male	33 (34.7%)
Hypertension	42 (44.2%)
Hyperlipidemia	20 (21.1%)
Smoking	32 (33.7%)
Diabetes	11 (11.6%)
Fusiform	27 (28.4%)
Nonfusiform	68 (71.6%)
ICA [mean diameter ±SD (mm)]	67 (59.8%) [6.09±4.57]
ACA [mean diameter ±SD (mm)]	10 (8.9%) [4.36±2.37]
MCA [mean diameter ±SD (mm)]	11 (9.8%) [4.74±2.36]
Vertebral artery [mean diameter ±SD (mm)]	6 (5.4%) [5.95±2.83]
Basilar artery [mean diameter ±SD (mm)]	18 (16.1%) [8.09±4.01]
Follow-up time (mean) (yr)	4.0 (SD, 2.8)
No. of imaging sessions per patient (mean)	5.9 (SD, 3.4)
Maximal diameter (mean) (mm)	6.1 (SD, 4.2)
Baseline volume (mean) (mm ³)	246.7 (139.1–663.8)

Note:—SD indicates standard deviation.

^aData are No. (%) unless otherwise indicated.

Table 2: Growth and 95% CI of the relative growth

	Relative Aneurysm Growth per Year (%)	
	Estimates	95% CI
ACA	4.07	2.28–5.87
VA	1.66	–0.44–4.03
MCA	1.41	–0.10–3.22
BA	1.32	–0.21–2.78
ICA	0.47	–0.25–1.19
Change per age (yr)	–0.044	–0.086–0.000

Note:—BA indicates basilar artery; VA, vertebral artery.

Clinical Interpretation Using the Proposed Methodology

By means of the volumetric metric suggested in this study to monitor intracranial aneurysms, noticeable growth would be defined as relative growth of >2 times the CV (11%) compared with the initial volume. Requiring change to be >2 times the CV implies that there is 95% statistical confidence that there has been a true change in aneurysm size and that the perceived change is not just measurement variability. In our study population, 8% of aneurysms had an average growth rate that would have resulted in noticeable growth in 1 year of follow-up.

Sudden growth was defined as 4 times the CV (22%) volume growth in consecutive follow-up intervals. If this methodology were applied to the patients included in this study, it would conclude that 36 of the 112 aneurysms (32%) demonstrated noticeable growth during the course of the study and that 11 of the 36 (31%) aneurysms with noticeable growth had an episode of sudden growth.

DISCUSSION

This study investigated the use of a volumetric measure to monitor UIAs across time in imaging studies with a large number of follow-

up time points. There are 3 key findings: First, the analysis demonstrates that CE-MRA, a relatively noninvasive imaging method, provides volume measurements with a CV of 5.5%. This corresponds, in most intracranial aneurysms, to an error of measurement of less than a voxel in terms of linear measurements, the conventional clinical metric. Most important, this estimate incorporates all potential contributing sources of variance, including: physiologic factors such as cardiac output, which might vary between imaging sessions; acquisition errors related to imperfect timing of contrast injection; and postprocessing errors related to user-dependent choices such as thresholding and cut plane selections. Second, the study showed that the growth rate was dependent on age and the location of the aneurysm, with UIAs of the ACA showing the fastest growth rate of 4.52% per year. Third, 11/112 (9.8%) of the UIAs presented with what appeared to be an episode of sudden growth.

Measurements of aneurysms in terms of volume is attractive because of its potential to provide a more sensitive and comprehensive assessment of change.¹⁸ Several software-based methods of volume measurement have been implemented on CTA images.¹⁴ CE-MRA has advantages in the serial monitoring of untreated UIAs because there is no radiation (as in CTA) or arterial catheterization-related risks (as in conventional angiography). CE-MRA also is not subject to flow-related artifacts, specifically saturation effects that are pronounced in slowly rotating intra-aneurysmal blood, and the benefits provided by the increased reliability of this approach are considered, in a high-risk disease condition, to outweigh the known risks of gadolinium administration. However, reliable CE-MRA measurements in longitudinal studies are challenging. They require coregistration in 3D space and also lack an absolute signal calibration for standardized thresholding—unlike CTA, which is measured in Hounsfield units.^{19,20} In this study, surface meshes of thresholded vascular territories from all time points were brought into coregistration using internal fiducials and an affine transformation. Thresholding consistency was enforced by constraining the volume of a reference length of the vessel to remain constant during all time points. Using this in-house software, we found an acceptable CV (5.5%) in the measurement of UIAs.

The existing literature on assessing aneurysm size is principally based on 2D diameter measurements. Reports on the rate of growth and risk factors for growth of UIAs are inconsistent.^{8,21–24} Furthermore, most previous studies used only 2 time points (the first and the last) to evaluate aneurysm growth, thus excluding important information on the growth trajectory in the intervening periods.^{3,7,16,25} Using such datasets, most studies assume that aneurysm growth is linear and steady, though clinical observation or even proposed growth models^{3,16} cause skepticism about this assumption. In this study, we included the often-neglected intermediate events and more sensitively identified a higher percentage of growing aneurysms (32%) than in previous studies (4%~18%).^{3,4,7,8,21,26–29} Further analysis of growth trends revealed that approximately 31% of growing aneurysms presented with a sudden/episodic growth pattern, the presentation of which is of high clinical concern. A better understanding of the growth trajectory and pattern of aneurysms will support a more judicious selection of UIAs for preventative treatment and enable the development of improved follow-up strategies for UIAs.³

Two recent meta-analyses reported aneurysm size, female sex, smoking, cavernous carotid artery location, and nonsaccular shape as independent risk factors for UIA growth. The roles of other risk factors were inconsistent.²⁹⁻³¹ Despite a partial overlap, several of these findings were not replicated in this study. Possible reasons for the discordance were the following: 1) The reported aneurysm sizes were all in terms of 2D diameters, while volumetric measures might display a different dependence; and 2) this cohort for aneurysm monitoring had generally small-sized UIAs, and the results presented here might better reflect the growth behavior of relatively small UIAs.

This study has several limitations. First, there was possible patient selection bias because the preference of patients for participating in a monitoring study could result in an over-representation of patients with relatively smaller UIAs. Also, patients with known risk factors such as a history of subarachnoid hemorrhage were not included because near-term treatment was likely. Second, it is difficult to validate the accuracy of the volume measurement method in serial studies in clinical patients against the current criterion standard of DSA, given the invasive nature of the latter. Third, because the diagnostic criteria for aneurysm sudden growth have not been explored previously, the criteria used here were based on our clinical experience. Finally, in this study, we enrolled all suitable subjects referred to us by referring clinicians. It is apparent that the clinicians were more comfortable referring aneurysms of the ICA for surveillance imaging than aneurysms in other locations where interventional treatment could have been preferred. As a result, the total number of ACA, MCA, and vertebral artery aneurysms was relatively small, and the result that the ACA location was significantly associated with greater volume growth should be interpreted with caution.

CONCLUSIONS

This proposed method of aneurysm volume measurement provides an acceptable CV for longitudinal follow-up studies compared with prior linear metrics. Approximately one-fourth of UIAs showed noticeable growth with time, and approximately one-third of these growing UIAs presented with a sudden/episodic growth pattern. Aneurysm volume measurement appears to be a sensitive and useful tool to depict and identify the growth trajectory and patterns of UIAs.

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