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Estimation of fusiform intracranial aneurysm growth by serial magnetic resonance imaging

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Running Title: MR estimation of aneurym volume

ABSTRACT

Purpose: Intracranial aneurysm (IA) growth is associated with increased morbidity. We sought to establish a quantitative computational method based on contrast enhanced MR angiography (CE-MRA) for estimating aneurismal volume changes over time.

Materials and Methods: Computational volume calculations were tested against a distensible phantom. Untreated patients with IA were followed longitudinally with annual MRIs. Maximal linear dimensions along the longitudinal axis and two transverse axes were determined by visual review of maximum intensity projection (MIP) data; aneurysm volume was approximated as (length x width x height)/2. Averages of the visual approximations were compared to the luminal volume as determined with a computational algorithm using the MRI data.

Results: MRI-based measurements accurately represented volume changes in the phantom ($R^2=0.97$, $Y=1.06x+271 \text{ CM}^3$). In the clinical study, there were a total of 11 intervals of one-year follow-up in 6 patients (mean $\pm$ SD age 53 $\pm$ 20). The raw one-year growth using computational volume was 9 $\pm$ 17%. The corresponding value for the averaged measurement of the reviewers was 8 $\pm$ 14%. Neither the mean values nor the standard deviations were different ($P=.51$).

Conclusion: MRI-based measurement of aneurysm volume appears feasible for longitudinal studies of aneurysm natural history.

Keywords: MR, aneurysm, longitudinal study

INTRODUCTION

Treatment of unruptured intracranial aneurysms requires balance between intervention risk and natural history rupture risk (1). Presence of symptoms and aneurysm growth often prompts recommendation for treatment. For patients not selected for treatment, serial imaging may be used to monitor aneurysm size. A retrospective study found that 48% of vertebrobasilar non-saccular intracranial aneurysms enlarged over 11 years; growth was associated with morbidity and death (2). There is, however, a striking lack of prospective longitudinal data on aneurysm growth.

Measurement of changes in aneurysm size could provide valuable information to guide clinical decision-making. The ideal diagnostic tool should be minimally invasive and provide three-dimensional images data sets with high contrast between the lumen and the vessel wall. The use of magnetic resonance angiography (MRA) is well suited for serial studies. In particular, contrast-enhanced MRA (CE-MRA) is well suited for serial studies of aneurysms, where conventional time-of-flight MRA fails because of saturation effects that occur in regions of slow recirculating flow. Modeling of flow dynamics in aneurysms may also provide an estimation of biophysical forces in the vascular lumen that may be associated with aneurysm growth (3, 4).

Traditionally, aneurysm size is estimated from x-ray angiograms by visual measurement of linear dimensions, typically the largest diameter. Those studies usually only provide projection data and do not have an absolute distance scale, a measurement that is difficult to obtain given the variability in zoom factors and imaging geometries. Further, x-ray angiograms do not delineate the presence of intraluminal thrombus. The

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4 presence of calcification, the sole indication of the location of the vessel wall, is
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6 visualized only occasionally and cannot be used to accurately delineate the vessel wall.

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8 Alternatively, 3D methods that have intrinsically established measurement scales can
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10 be used to obtain luminal volume measurements. The essential step in that process is
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12 defining luminal boundary. This can either be done by manual tracing by an expert
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14 reader on all slices in the 3D data set, or by signal intensity thresholding.
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18 We report the first study of quantitative changes over time in aneurismal volume in
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20 subjects with untreated aneurysms in whom we obtained longitudinal MR images in
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22 treatment-free yearly intervals. Changes in aneurysm size were determined using a
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24 Computer-segmented approach, and were compared to estimates of change assessed
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26 by expert human observer readers. The primary objective of this work was to
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28 demonstrate the feasibility of a semi-automated, quantitative method that may be
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30 applied to longitudinal studies of aneurysm growth.
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MATERIALS AND METHODS

In vitro Volume Model

As an initial step in method development, a physical model (phantom) was created to assess the reliability of computer-segmented volumes under controlled conditions. Rubber latex tubing with an inner diameter of 6mm and a length of 160mm was placed within an acrylic open-top container, with the ends passing through opposite walls. The distal end of the tubing was clamped shut, and the proximal end was connected to a 3 way plastic stopcock. The remaining two ports of the stopcock were connected to syringes, one a 60 ml syringe and the other a 10 ml syringe. The container was then filled with water, completely immersing the rubber tube. A volume of saline was doped with GdDTPA to provide signal intensity approximating that within arterial structures during clinical CE-MRA(5) . The solution was injected from the 60 ml syringe into the tubing which bulged out at a location of local weakness (Figure 4).

This aneurismal bulge volume was used as the baseline; the phantom was scanned using the same parameters that were used in our *in vivo* CE-MRA studies (detailed below). Following baseline scanning, sequential aliquots of approximately one ml of contrast-containing solution were extracted from the tube thereby reducing the size of the bulge. Following each extraction, the amount of fluid withdrawn was recorded and a MR scan was obtained. Since fluid is incompressible, the change in volume within the aneurismal lumen was identical to that collected in the syringe.

The native DICOM data were transferred to a Dell™ Precision 650 workstation, and Amira™ Version 3.0 a commercially available software package (Mercury Computer Systems; Berlin, Germany) was used to segment the lumen information. Examples of similar object renderings performed using patient data are shown in Figure 1. After segmenting the structure (model or vessels) of interest (**Figure 1A**), we exported the polygonal objects (**Figure 1B**) to Rapidform™ 2004 (INUS technology, Seoul, South Korea). After importation into Rapidform™ also a commercially available software package, surface smoothing was performed to remove any noise from the previous process (**Figure 1C**), and a surface mesh was generated to fit the luminal surface. Laplacian smoothing was done by averaging of neighboring vertices iteratively with the volume preservation option enabled. Fiducial markers on either end of the rubber tubing appeared in the scans and were used as location markers for defining the volume of interest. The luminal volume at each of the sequential scans was then calculated using Rapidform™. The luminal volume is calculated in Rapidform™ using volume integrals (6) which simply sums the product of the cross-sectional intra-luminal area with the slice thickness over the length of the vessel segment of interest.

In vivo Studies

Patients with unruptured fusiform intracranial aneurysms followed with conservative medical management were enrolled in this study after IRB approval and informed consent. A clinical decision not to offer surgical or interventional treatment options was based on factors such as an unfavorable anatomy and/or high operative risk, and was independent of this study. After a baseline MR evaluation, patients underwent follow-up MR evaluation at approximately one-year intervals. The time period of the study was

between 2001 and 2005. One subject had a total of four imaging sessions, three had three studies, and two had two studies, resulting in eleven observations of annual interval change.

We used CE-MRA to acquire a para-coronal 3D slab over the vessels of interest. Intravenous injection of 20 ml GdDTPA was delivered at 2ml/s and followed by 15ml of saline also at 2ml/s. The arrival of contrast agent was monitored using a real time, low resolution, fluoroscopic imaging mode. Once contrast arrival was detected, the full MR angiography study was initiated. MR studies were performed on a 1.5T Intera MR System (Philips Medical Systems, Best, Netherlands). The CE-MRA sequence used elliptic-centric phase reordering (7) and data was acquired using parallel imaging with an acceleration factor of 2. Primary imaging parameters were: TR/TE/flip angle = 5/2/30°. Images were acquired from a 54mm paracoronal slab, with an FOV of 240mm and an acquisition matrix of 400x380x39 zero-filled to 512x512x78. The resultant images had acquired resolution of 0.6x0.63x1.2 mm³ and were interpolated to 0.47x0.47x0.6 mm³. Total acquisition time was of the order of 30s. MIPs were generated at 15° intervals around the head-foot axis. A scale bar was included on each image, and the MIPs were printed onto film for radiologist review.

In all our studies, an initial threshold value was set using the same criterion: namely, the mean, M_b , and standard deviation, σ_b , of the background signal were determined by selecting ROIs that excluded vessels. The threshold value was then set equal to $M_b + 3.5 \times \sigma_b$, a value that was empirically determined to retain vessel edges while eliminating stationary tissue signal (Figure 5). Minor adjustment of the threshold value

was performed by an experienced reader to achieve a level that was considered to best delineate the vessel lumen. On subsequent serial studies for the same patient, threshold values were set in by requiring a value that provided identical volume measurements to the baseline study in vessel segments that were thought to remain unchanged over time, i.e., segments that were deemed by visual inspection to be undiseased and that were remote from the aneurysm. This procedure also makes the determination of serial changes relatively insensitive to individual operator variability.

All data was segmented and surface meshed using Amira™ and Rapidform™ as described above. For a representative case of one patient and one time point, a MIP is shown (**Figure 1A**), along with the data after processing by Amira (**Figure 1B**), and finally by Rapidform (**Figure 1C**). At each time point, the model was co-registered to the model from the previous time point to give a visual representation of growth (**Figure 1D**). With both models co-registered, the volumes were uniformly cut proximal to and distal to the aneurysm. The cases are summarized in **Table 1** and in **Figure 2 (A-F)**.

Image Review by Neuroradiologist Panel

Sets of films for each patient, containing 12 MIPs in 15 degree increments were randomized and independently presented to three interventional neuroradiologists (RTH, CFD, VVH). Each radiologist was asked to evaluate each study to determine the maximum linear dimension along the longitudinal axis and two transverse axes of the aneurysm at each given time point. From these linear dimensions, an approximation of aneurysm volume was calculated using the formula: (length x width x height)/2 (8).

Statistical Analyses

In vitro Model

Linear regression was used to relate the percent change in computational volume from MR data to that of the phantom flow model.

Clinical Data

The volume measurement at each time point was computed by both Computer-segmented volumes and three individual reviewers' estimations. The growth rates for each annual interval were calculated, treating each yearly interval as a discrete observation of aneurysm growth. We examined individual human observer volumes as well as the average of the human observer volumes measurements but present only the averaged measurements for clarity. In addition to descriptive statistics (reported as mean±SD) for annual growth rates for each method, we compared the growth rates calculated by each method by paired t-test and tests of equal standard deviation. The one-year volume change by the MRI method was plotted versus the average of reviewers' estimation and the correlation calculated.

We also performed a secondary analysis on the log-transformed volumes using a linear mixed model to estimate percent annual growth in order to adjust for repeated measures and the unequal number of observations per patient.

RESULTS

For the *in vitro* study, computer-segmented volumes change demonstrate strong correlation with the actual measured volume changes in the flow phantom ($R^2=0.97$, $Y=1.06x+271 \text{ CM}^3$).

In the clinical study, there were a total of 11 intervals of annual follow-up in 6 patients (age 53 ± 20). The calculated volumes are shown in **Table 1**. The raw one-year growth using the computational volume method was $9\pm 17\%$. The corresponding value for the averaged measurement of the reviewers was $8\pm 14\%$. Neither the mean values (paired t-test $P=.85$) nor the standard deviations (test of equal variance $P=.51$) were different.

Table 2 summarizes the percent growth changes for the three reviewers and the computational method. The poor agreement between human readers is expected, as the radiologists assessing growth use crude lineal measurements that do not take into account subtleties of a complex 3D structure.

Correspondence between the change in reviewers' volume estimates with that of the computational volume calculations is shown in **Figure 3**. The volume changes by the computer-segmented method and by Human Observer showed high correlation ($R^2=.82$; $y=-119.38+1.64*x \text{ CM}^3$).

After adjusting for between subject effects in a linear mixed model, yearly percent growth rate was estimated to be 12% (95% CI: 3 - 21%) for the computational method and 10% (95% CI: 2 - 19%) for the average of the three reviewers.

Because aneurysm growth has been suggested to correlate with initial aneurysm size (2), we compared one-year percent change in volume as a function of baseline volume; no apparent correlation was observed (data not shown).

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DISCUSSION

This is the first description of a longitudinal study of aneurysm growth using MR angiography combined with a computer aided assessment of aneurysm volume. In all 11 CE-MRA studies, high resolution, high contrast-to-noise data sets rated technically adequate by the reviewing radiologists were acquired of the vasculature of interest. Using our computational method, we found that yearly growth rate was similar to visual assessment by a panel of neuroradiologists.

The main objective of the study was to demonstrate the feasibility of assessing growth computationally. Three-dimensional datasets, such as those available from CE-MRA, lend themselves well to semi-automated analysis of geometric features such as luminal volume. As seen in **Figure 3**, four of 11 intervals showed large changes in volume and agreed with the visual review assessment; one patient developed intraluminal thrombus and had a net decrease in luminal volume. These findings are in general agreement with those reported in a recent Mangrum et al retrospective study, which showed a little under half of patients followed longitudinally displayed aneurysm growth (2). Improved methods to quantitatively monitor changes in aneurysm size should be helpful in patient management as well as designing future studies to identify mechanisms or risk factors responsible for changes.

Traditional Magnetic Resonance Angiography methods (such as time-of-flight and phase contrast angiography) have been ineffective in imaging structures, such as aneurysms, that contain complex, swirling flow. This is principally because the magnetization in blood that slowly recirculates within the belly of the aneurysm becomes

saturated. In CE-MRA, saturation effects are eliminated because the contrast agent induces a very short T1 relaxation time in intraluminal blood. This effect is demonstrated in our studies by the uniform and high signal strength that is noted in all cases.

There are a number of limitations in this study Because of the small sample size, we cannot definitively rule out a type II error, however, given the mean values of 8 and 9% for the reviewers and the computational method, a very large sample size would be necessary to demonstrate what would be a clinically insignificant difference. Perhaps the most important underlying technical limitation for using CE-MRA methods for assessing luminal volume for *in vivo* studies is the timing of data acquisition relative to injection of the contrast bolus. Incorrect timing by as little as a few seconds can seriously degrade image quality and could potentially result in mis-estimation of vascular volumes independent of whether the volumes were manually measured or determined using the computational method outlined here. It is difficult to assess this variability in-vivo because one is limited to a single injection following which signal contamination in background tissue degrades any subsequent CE-MRA study. In this situation, we can only rely on a visual inspection of the data set to ensure that none of the tell-tale signs of a poor study are present (such as enhancement of vessel edges or “ringing” of signal outside the vessel).

Although we have seen those effects in past image acquisitions, all of the studies included here were rated technically adequate by the reviewing radiologists. In addition the correct selection of a threshold value in the creation of the MIPs can result in mis-estimation of vascular volumes. Inherent properties of MR imaging (such as variable

signal strength reception from a given tissue between one study and the next) obviate the use of absolute intensity values in segmenting tissue. However, basing threshold settings on relative signal intensity between the flow channel and the background signal was found to be accurate in the physical model, and is expected to be reliable in all cases where there is a high contrast-to-noise ratio between the lumen and surrounding tissue, as is the case in CE- MRA.

Similarly, an effect not assessed in our phantom study is the impact of patient motion, such as gross motion or swallowing. Swallowing can be a problem in the extracranial arteries but is not important for the vessels near the circle of Willis. Acquisition of the 3D CE-MRA data set took less than 30 seconds and patients were instructed to hold very still during that interval. Qualitative inspection indicated that there was little gross motion artifact present. An additional concern is the pulsatile variation through the cardiac cycle. These studies represent the time-average of the luminal contours over 30 seconds, and the final images represent the mean geometry through the cardiac cycle, a measure that is constant from one study to the next.

It is important for clinicians to be able to assess the presence of intraluminal thrombus. We only quantitated the volume of the patent lumen. Although not reported here, we also acquired spin echo images to determine the location of the outside of the vessel wall and correlated that with the luminal location. In all cases except one, the vessel wall was determined to be barely detectable reflecting a very thin wall and the absence of intraluminal thrombus, including case 3, which experienced a symmetrical modest reduction in luminal volume. The exception (case 4) was found to have substantial intraluminal thrombus. The role of mural thrombus in relation to aneurysm growth is

not known, and in this one anecdotal case, the thrombus volume was noted to increase and then decrease over multiple time points, possibly indicating layering and then shedding of thrombus.

With regard to the data analysis, we emphasize that this is primarily a descriptive study and we do not wish to overemphasize the importance of the various calculated parameters of growth, nor the quantitative values given for correlations between computational and visual methods. First, it is a small sample size. Second, the estimated volumes from visual review were simply semi-spherical estimations of aneurysm volume; as can be seen from **Figure 2**, there were a variety of different shapes. Third, the correlations may in fact be non-linear, so that linear regression may not be the ideal way to assess correlations. However, this preliminary study provides a basis for further inquiry.

Despite the limitations in this study, we believe that CE-MRA with computational 3D co-registration can offer a useful means of tracking aneurysm growth over time. Limited data exist on the natural history of fusiform aneurysms which tend to be significantly larger and have a morphology associated with higher treatment risk (2). A non-invasive imaging modality that can provide quantitative information on aneurysm growth for these patients may improve clinical decision-making and understanding of factors associated with aneurysm growth. Development of a reliable modality for longitudinal assessment of aneurysm growth could be applied to other aneurysm subtypes as well as other vascular malformations.

ACKNOWLEDGMENTS

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Table 1. Demographics and Raw Data

							Visually measured estimated volume (mm ³)											
							Reviewer 1				Reviewer 2				Reviewer 3			
Case #	Cohort	Gender	Age	Race	Presentation	Maximal transverse diameter (mm)*	Year 1	Year 2	Year 3	Year 4	Year 1	Year 2	Year 3	Year 4	Year 1	Year 2	Year 3	Year 4
1	Basilar	M	74	Hispanic	Dizziness	18	1251	1366	1765	2159	1497	1691	1979	2276	1157	1182	1215	1251
2	Basilar	M	41	White	Sensorimotor Deficit	20	2005	2143	2555		2165	2467	2901		1829	1883	2005	2005
3	Carotid	F	28	White	Asymptomatic	10	195	190	184		279	202	201		281	214	195	190
4	Basilar	F	75	Hispanic	Gait Disturbance	27	2082	1749	2246		2182	1937	2281		1831	1802	2082	1749
5	Basilar	M	60	African American	Asymptomatic	18	1612	1531			1094	1582			1383	1530		
6	Carotid	F	40	White	Headache & Dizziness	14	618	537			340	327			303	308		

*Obtained by taking the mean of three reviewers' baseline maximal baseline transverse diameter

	Minimum	Maximum	Range	Mean	Standard Deviation
Computational method	-26%	39%	65%	9%	17%
Reviewer #1	-27%	45%	72%	9%	19%
Reviewer #2	-16%	29%	45%	7%	16%
Reviewer #3	-24%	36%	60%	9%	17%
Average of Reviewers	-18%	26%	44%	8%	14%

Table 2. Descriptive Statistics for percent change in volumes

FIGURE LEGENDS

Figure 1.

(A) A CE-MRA (B) Amira™ 3D reconstruction of figure 2A. (C) The surface model as seen in Rapidform™ after surface smooth operation and surface gaps have been filled. (D) A co-registration of two time points where the green surface is the baseline study and the blue is the follow up study.

Figure 2.

CE-MRA for calendar year indicated.

A - Case 1: 2001 through 2004.

B - Case 2: 2001 through 2003.

C - Case 3: 2003 through 2005.

D - Case 4: 2002 through 2004.

E - Case 5: 2004 through 2005.

F - Case 6: 2004 through 2005.

Figure 3. (A-D).

Correlation of computational volume change (MRI) to the estimate of aneurysm volume change using the formula: $[(length \times width \times height)/2]$ for the three reviewers separately (A-C) and averaged (D).

Figure 4.

The in vitro flow phantom in the case enclosure.

Figure 5(A-B).

Thresholding of the CE-MRA data. a) A single partition from a 3D CE-MRA data set shows arterial segments as hyperintense regions. b) Segments are identified as belonging to the vertebro-basilar system if they are connected in 3D space, and voxels within those segments are included if they have signal

intensity above the defined threshold. The boundary of those segments are indicated as a continuous white line.

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Figure 1. (A) A CE-MRA (B) Amira 3D reconstruction of figure 2A. (C) The surface model as seen in Rapidform after surface smooth operation and surface gaps have been filled. (D) A co-registration of two time points where the green surface is the baseline study and the blue is the follow up study.

Figure 2A. CE-MRA for calendar year indicated. A - Case 1: 2001 through 2004

Figure 2B. B - Case 2: 2001 through 2003

Figure 2C. C - Case 3: 2003 through 2005

Figure 2D. D - Case 4: 2002 through 2004

Figure 2E. E - Case 5: 2004 through 2005

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Figure 2F. Case 6: 2004 through 2005

ONLY

Figure 3. Correlation of computational volume change (MRI) to the estimate of aneurysm volume change using the formula: $[(\text{length} \times \text{width} \times \text{height})/2]$ for the three reviewers separately (A-C) and averaged (D).

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