Original Contribution

Association of Progression of Carotid Artery Wall Volume and Recurrent Transient Ischemic Attack or Stroke

A Magnetic Resonance Imaging Study

Mingming Lu, MD; Peng Peng, MSc; Yuanyuan Cui, MD; Huiyu Qiao, MD; Dongye Li, MSc; Jianming Cai, MD, PhD*; Xihai Zhao, MD, PhD*

Background and Purpose—This study aimed to investigate the association between carotid plaque progression and subsequent recurrent events using magnetic resonance imaging.

Methods—Sixty-three symptomatic patients with ipsilateral carotid atherosclerotic stenosis (30%–69% stenosis) determined by ultrasound underwent first and second carotid artery magnetic resonance imaging for carotid artery at baseline and ≥6 months after the first scan, respectively. All the patients had clinical follow-up after the second magnetic resonance scan for ≤5 years until the onset of recurrent transient ischemic attack or stroke. Presence/absence of carotid plaque compositional features, particularly intraplaque hemorrhage and fibrous cap rupture was identified. The annual progression of carotid wall volume between 2 magnetic resonance scans was measured. Univariate and multivariate Cox regression was used to calculate the hazard ratio and corresponding 95% confidence interval of carotid plaque features in discriminating recurrent events. Receiver-operating-characteristic-curve analysis was conducted to determine the area-under-the-curve of carotid plaque features in predicting recurrent events.

Results—Sixty-three patients (mean age: 66.5±10.0 years old; 54 males) were eligible for final statistics analysis. During a mean follow-up duration of 55.1±13.6 months, 14.3% of patients (n=9) experienced ipsilateral recurrent transient ischemic attack/stroke. The annual progression of carotid wall volume was significantly associated with recurrent events before (hazard ratio, 1.14 per 10 mm^3; 95% confidence interval, 1.02–1.27; P=0.019) and after (hazard ratio, 1.19 per 10 mm3; 95% confidence interval, 1.03–1.37; P=0.022) adjusted for confounding factors. In discriminating the recurrence of transient ischemia attack/stroke, receiver–operator curve analysis indicated that combined with annual progression of wall volume, there was a significant incremental improvement in the area-under-the-curve of intraplaque hemorrhage (area-under-the-curve: 0.69–0.81) and fibrous cap rupture (area-under-the-curve: 0.73–0.84).

Conclusions—The annual progression of carotid wall volume is independently associated with recurrent ischemic cerebrovascular events, and this measurement has added value for intraplaque hemorrhage and fibrous cap rupture in predicting future events. **(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.117.019422.)**

Key Words: atherosclerosis ■ carotid artery ■ carotid stenosis ■ ischemic attack, transient ■ magnetic resonance imaging

Stroke is a leading cause of death in Chinese population and its first-year recurrent rate has been reported to be ≤11.2%.[1] Investigators found that carotid plaque progression and surface disruption are associated with not only the first but also the recurrent ischemic cerebrovascular events.[2–5] Therefore, it is important to accurately evaluate the baseline characteristics and progression of carotid plaque in stratifying the risk of future ischemic events for stroke patients.

The baseline features and progression of carotid atherosclerosis can be characterized by multiple imaging modalities, such as ultrasound, computed tomographic angiography, and magnetic resonance imaging (MRI). Although ultrasound is a cheap and widely available imaging tool for screening carotid plaque, poor intra- and inter-operator reproducibility[6] limits its application to serial monitoring carotid plaque change within a certain time course. Computed tomographic angiography has been largely used to determine carotid luminal stenosis, but

Received September 17, 2017; final revision received November 18, 2017; accepted December 15, 2017.

From the Department of Radiology, PLA General Hospital, Beijing, China (M.L., Y.C., J.C.); Center for Biomedical Imaging Research, Department of Biomedical Engineering, Tsinghua University School of Medicine, Beijing, China (H.Q., D.L., X.Z.); and Department of Radiology, The Affiliated Hospital of Logistics University of Chinese People's Armed Police Force, Tianjin, China (M.L., P.P.).

*Drs Cai and Zhao contributed equally.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.117.019422/-/DC1.

Correspondence to Jianming Cai, MD, PhD, Department of Radiology, PLA General Hospital, Beijing 100853, China, E-mail beili12345@sina.cn or Xihai Zhao, MD, PhD, Center for Biomedical Imaging Research, Department of Biomedical Engineering, School of Medicine, Tsinghua University, Beijing 100084, China, E-mail xihaizhao@tsinghua.edu.cn

this approach provides less information of plaque compositions except calcification. In addition, computed tomographic angiography is not an ideal imaging tool for serially evaluating carotid plaque progression or regression because of the ionizing radiation. In contrast, it has been shown that MRI has excellent reproducibility and accuracy in qualifying carotid plaque characteristics and progression.[7–9] Using MR plaque imaging techniques, investigators found that carotid plaque characteristics at baseline enabled predicting subsequent ischemic events.[3,10–12] However, the predictive value of progression of carotid plaque determined by MRI for recurrent stroke has not been studied.

This study sought to evaluate the usefulness of carotid plaque progression determined by MRI in predicting subsequent recurrent ischemic cerebrovascular events and test the hypothesis that carotid plaque progression could improve the predictive value of baseline MR characteristics for recurrent events.

Methods

Study Population

The authors declare that all supporting data are available within the article and its online-only Data Supplement. Patients with recent (<3 months) cerebral ischemic events including transient ischemic attack (TIA) or stroke and index side carotid atherosclerotic 30% to 69% stenosis determined by ultrasound were recruited in this study. All the patients underwent MR vessel wall imaging for bilateral carotid arteries at baseline and follow-up with an interval of >6 months. Patients with the following conditions were excluded: (1) hemorrhagic stroke; (2) cerebral tumor; (3) pregnancy; (4) previous history of carotid endarterectomy; (5) contradiction to MR examination. Demographic and clinical characteristics including age, sex, body mass index, hypertension, hyperlipidemia, diabetes mellitus, coronary artery heart disease, smoking, and treatment were collected from the clinical record. The hypertension was diagnosed when systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg. The hyperlipidemia is defined as elevated concentrations of any or all of the lipids in the plasma, such as low-density lipoprotein >1.58 mmol/L, total cholesterol >2.26 mmol/L, or triglycerides >1.69 mmol/L. Diabetes mellitus is defined as fasting blood sugar level ≥126 mg/dL, 2-hour oral glucose tolerance test result ≥200 mg/dL, or hemoglobin A1c ≥6.5%. The study protocol was approved by institutional review board, and each participant provided the written consent form.

Carotid Artery MR Imaging

Patients underwent MR imaging on a 3.0-T MR scanner (Signa HDx, General Electric Medical System, Milwaukee, WI) with a 4-channel dedicated phase-arrayed carotid coil. A multicontrast MR imaging protocol was conducted to acquire the following imaging sequences: 3-dimensional time-of-flight: 3-dimensional gradient echo, repetition time/echo time=29/2.1 ms, flip angle=20°; 2-dimensional T1-weighted: fast spin echo, repeated time/echo time=800/7.5 ms, flip angle=90°; and T2-weighted images: fast spin echo, repeated time/echo time=3000/57 ms; flip angle=90°. All the imaging sequences were acquired with the same field of view of 140×140 mm^2, matrix size of 256×256, 2 mm of slice thickness, and longitudinal coverage of 24 mm (12 slices). The MR scan was centered to the bifurcation of the index carotid artery, which is defined as the arteries that are associated with the ischemic cerebrovascular symptoms. The same carotid artery MR vessel wall imaging protocol was performed for both baseline and follow-up study.

MR Image Analysis

All MR images were analyzed by 2 radiologists with >2 years' experience in cerebrovascular imaging using custom-designed software CASCADE[13] (Vascular Imaging Lab, University of Washington) with consensus. The radiologists were blinded to the information of outcome and the imaging time point. The image quality was rated per slice on a 4-point scale dependent on the overall signal-to-noise ratio and the contrast between the vessel wall and surrounding tissues: (1=poor; 4=excellent). Images with image-quality grade ≤2 were excluded from the analysis. The boundaries of lumen and wall were outlined to measure the lumen area, wall area, and maximum wall thickness. The lumen and wall volume was calculated. The presence or absence of plaque compositions, such as lipid-rich necrotic core, intraplaque hemorrhage (IPH), and calcification was identified.[14] The presence or absence of fibrous cap rupture (FCR) was also determined.[15] The wall volume was calculated by 2 mm × wall areas of slice with plaque. The degree of carotid artery stenosis was measured on the 3-dimensional time-of-flight MR angiographic images after maximum intensity projection reconstruction using NASCET trial (North American Symptomatic Carotid Endarterectomy) criteria.[16]

Assessment of Outcomes

After the second MR scan, patients were followed ≤60 months to record the recurrence of TIA/stroke. In all cases with event recurrence, the date of ischemic event recurrence was ascertained by face-to-face interviews or telephone interviews and confirmed by review of hospital records. Recurrent ischemic events were defined as an ipsilateral TIA/stroke as the index carotid plaque after the initial TIA/stroke. The follow-up information was collected blinded to the results of the MR images.

Reproducibility

Twenty patients were randomly selected from this study population for testing the inter-reader and intrareader agreement in measuring carotid plaque morphology. All 63 patients were used for testing the inter-reader and intrareader agreement in identification of carotid plaque compositions. The MR images were reviewed by one reader (L.M.) twice with time interval of 2 months to minimize the memory bias. The MR images were independently reviewed by another reader (C.Y.) for testing the inter-reader agreement. The scan–rescan agreement has been demonstrated to be excellent in measuring plaque morphology (intraclass correlation coefficient, 0.87–0.99) in previous studies.[17,18]

Statistical Analysis

The annual progression of wall volume, area, thickness, and stenosis of carotid artery was calculated. According to the annual change of carotid wall volume, participants were stratified into tertiles. The highest tertile was defined as the progression group, and the other two tertiles was defined as the nonprogression group. The Kaplan–Meier survival analysis was performed to estimate the cumulative event-free rates for each group. Univariate and multivariate Cox regression was used to calculate the hazard ratio (HR) and corresponding 95% confidence interval (CI) of carotid plaque features in discriminating recurrent events. Receiver–operator curves analyses were conducted to calculate the area-under-the-curve of baseline MR plaque characteristics and progression of carotid wall volume in predicting presence of recurrent TIA/stroke. The intra-reader and inter-reader agreement in measuring morphology of carotid artery and identifying plaque compositions was calculated by using intraclass correlation coefficient and Cohen κ test, respectively. Statistical analysis was performed using the software of SPSS 22.0 (IBM, Chicago, IL).

Results

In total, 80 patients were recruited from November 2005 to November 2011. Of the recruited 80 patients, 17 patients were excluded because of the following reasons: (1) underwent carotid endarterectomy during follow-up (n=8); (2) 4 patients were lost to follow-up (n=4); (3) 3 had poor image quality (n=3); and (4) died because of other diseases (n=2). Of the remaining

63 patients (mean age: 66.5±10.0 years old) who were qualified for final statistical analysis, 47 (74.6%) had hypertension, 24 (38.1%) had history of smoking, 14 (22.2%) had diabetes mellitus, and 36 (57.1%) had hyperlipidemia. The baseline clinical characteristics of population are shown in Table 1, and baseline characteristics and progression of carotid plaque are shown in Table 2. The mean time interval between the 2 MR scans was 15.4±9.4 months. No statistical differences were found in the baseline clinical risk factors between patients in progression group and nonprogression group (all $P>0.05$).

Baseline Characteristics and Changing Information of Carotid Plaques

Of 63 patients, 53 (84.1%) had lipid-rich necrotic core, 14 (22.2%) had IPH, 47 (74.6%) had calcification, and 18 (28.5%) had fibrous cap rupture. No significant differences were found in the prevalence of all plaque compositional features at baseline between progression group and nonprogression group (all $P>0.05$). The annual change of carotid wall volume, stenosis, maximum wall area, and maximum wall thickness was 10.2±69.8 mm^3, 1.8±7.2%, 2.0±11.9 mm^2, and 0.1±1.0 mm, respectively. Additionally, 6 developed new IPH, 2 developed new fibrous cap rupture, and none developed new calcification and lipid-rich necrotic core. Of the 6 patients developed new IPH, 5 had IPH and 1 did not have IPH at baseline.

Recurrent Ischemic Events After the Second MR Scan

During 55.1±13.7 months (range, 2–60 months) of follow-up, 9 participants (14.3%) experienced recurrent ischemic events (6 strokes and 3 TIA) ipsilateral to the initial TIA/stroke.

Table 1. Baseline Clinical Characteristics (n=63)

	Mean±SD or n (%)		
	Carotid Plaque With Nonprogression (n=42)	Carotid Plaque With Progression (n=21)	*P* Value
Sex, male	35 (83.3)	19 (90.5)	0.455
Age, y	66.0±10.2	67.3±9.8	0.640
BMI, kg/m^2	23.7±2.8	23.9±3.2	0.708
Hypertension	30 (71.4)	17 (80.9)	0.413
Hyperlipidemia	24 (57.1)	12 (57.1)	1.000
Diabetes mellitus	10 (23.8)	4 (19.01)	0.668
CHD	13 (31.0)	6 (28.6)	0.846
LDL cholesterol, mmol/L	2.3±1.3	2.4±1.3	0.524
HDL cholesterol, mmol/L	1.1±0.6	1.1±0.7	0.801
Total cholesterol, mmol/L	4.1±1.4	4.3±1.2	0.447
Triglyceride, mmol/L	1.7±0.9	1.5±1.1	0.814
Antiplatelet agent	31 (73.8)	17 (81.0)	0.863
Statin	17 (40.5)	12 (57.1)	0.329
Smoking	14 (33.3)	10 (47.6)	0.386

BMI indicates body mass index; CHD, coronary heart disease; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

Table 2. Baseline Characteristics and Changing Information of Carotid Plaques (n=63)

	Mean±SD or n (%)		
	Carotid Plaque With Nonprogression (n=42)	Carotid Plaque With Progression (n=21)	*P* Value
Lumen volume, mm^3	817.2±376.1	766.9±403.4	0.624
Lumen volume change, mm^3	3.4±58.0	−3.9±74.9	0.666
Wall volume, mm^3	952.4±354.4	1001.2±457.4	0.640
Wall volume change, mm^3	−29.2±50.1	83.6±30.6	<0.0001*
Maximum wall area, mm^2	77.3±24.4	75.1±19.2	0.727
Maximum wall area change, mm^2	0.3±13.6	5.2±6.9	0.119
Stenosis, %	52.8±12.6	55.8±13.1	0.368
Stenosis change, %	2.0±7.2	1.4±7.4	0.732
Maximum WT, mm	5.2±1.3	4.8±1.0	0.251
Maximum WT change, mm	0.02±1.0	0.2±1.1	0.539
Presence of calcification	32 (76.2)	15 (71.4)	0.643
Presence of LRNC	35 (83.3)	18 (85.7)	0.727
Presence of IPH	8 (19.0)	6 (28.5)	0.488
Presence of FCR	11 (26.2)	7 (33.3)	0.682

FCR indicates fibrous cap rupture; LRNC, lipid-rich necrotic core; IPH, intraplaque hemorrhage; and WT, wall thickness.
*The result is only because of the patients' stratification.

The mean time interval between the second MR scan and the recurrent event in these 9 participants was 26.0±18.3 months (minimum: 2 months; maximum: 58 months).

Association Between MR Plaque Features and Recurrent Events

Cox regression analysis showed that the presence of FCR (HR, 5.51; 95% CI, 1.37–22.03; $P=0.016$), the presence of IPH (HR, 5.06; 95% CI, 1.36–18.88; $P=0.016$) and annual progression change of wall volume (HR, 1.14 per 10 mm^3; 95% CI, 1.02–1.27; $P=0.019$) were significantly associated with the recurrence of ischemic cerebrovascular events (Table 3). Multivariate Cox regression analysis revealed that the associations of presence of FCR (HR, 6.72; 95% CI, 1.37–32.95; $P=0.019$) and IPH (HR, 6.05; 95% CI, 1.44–25.51; $P=0.014$) and annual change of wall volume (HR, 1.19 per 10 mm^3; 95% CI, 1.03–1.37; $P=0.022$) with recurrence of ischemic cerebrovascular events remained statistically significant after adjusting for age, sex, body mass index, hypertension, hyperlipidemia, diabetes mellitus, coronary artery heart disease, smoking, statin treatment, and antiplatelet treatment. No significant associations can be found between other carotid plaque characteristics and recurrence of ischemic cerebrovascular events before and after adjusted for above confounding factors (all

Table 3. Cox Regression Hazard Models of Risk Factors for Ipsilateral Recurrent TIA/Stroke

	Recurrence of Ischemic Events					
	Univariate Regression			Multivariate Regression		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Carotid plaque characteristics at baseline						
Lumen volume*	1.01	0.99–1.03	0.228	1.12	0.92–1.35	0.256
Wall volume*	1.12	0.96–1.29	0.152	1.09	0.92–1.30	0.330
Maximum wall area†	1.06	0.79–1.41	0.708	1.01	0.755–1.36	0.926
Maximum stenosis‡	1.00	0.95–1.05	0.952	0.99	0.93–1.06	0.732
Maximum WT§	1.04	0.93–1.12	0.812	1.10	0.84–1.45	0.492
Presence of calcification	1.10	0.22–5.29	0.906	1.16	0.21–6.39	0.863
Presence of LRNC	1.53	0.19–12.19	0.691	1.90	0.19–19.33	0.589
Presence of IPH	5.06	1.36–18.88	0.016	6.05	1.44–25.51	0.014
Presence of FCR	5.51	1.37–22.03	0.016	6.72	1.37–32.95	0.019
Progression of carotid plaque						
Lumen volume change*	0.91	0.81–1.01	0.102	0.87	0.75–1.02	0.079
Wall volume change*	1.14	1.02–1.27	0.019	1.19	1.03–1.37	0.022
Maximum wall area change†	1.02	0.97–1.06	0.473	1.04	0.98–1.11	0.188
Maximum WT change§	1.13	0.62–2.04	0.677	1.25	0.58–2.56	0.612
Stenosis change‡	1.02	0.93–1.12	0.613	1.05	0.93–1.19	0.432

Multivariate regression was adjusted for age, sex, BMI, hypertension, hyperlipidemia, diabetes, CHD, smoking, statin treatment, and antiplatelet treatment. BMI indicates body mass index; CHD, coronary heart disease; CI, confidence interval; FCR, fibrous cap rupture; HR, hazard ratio; IPH, intraplaque hemorrhage; LRNC, lipid-rich necrotic core; and WT, wall thickness.

*Increment: 10 mm^3.

†Increment: 10 mm^2.

‡Increment: 1%.

§Increment: 1 mm.

P>0.05). Kaplan–Meier curves for the recurrence of ischemic cerebrovascular events showed that event-free survival was significantly higher for patients in the nonprogression group than ones in the progression group (*P*=0.022; Figure 1). Of 9 patients who experienced recurrent TIA or stroke, 6 were in progression group and 3 were in nonprogression group, respectively. Of the 3 patients with recurrent events in nonprogression group, 2 were in patients with plaque regression (n=27) who experienced recurrent event at 25th and 47th months, respectively. Of 27 patients with plaque regression, 40.7% and 74.1% received long-term lipid-lowering and antiplatelet therapy, respectively. In discriminating the recurrence of ischemic cerebrovascular events, receiver–operator curve analysis indicated that combined with annual progression of wall volume, there was incremental improvement in the area-under-the-curve of FCR (area-under-the-curve from 0.73 to 0.84; Figure 2A) and IPH (area-under-the-curve from 0.69 to 0.81; Figure 2B).

Reproducibility

We found that the intraclass correlation coefficient for plaque morphological measurements was ranging from 0.88 to 0.98 for intrareader agreement and from 0.88 to 0.97 for inter-reader agreement, respectively (Table I in the online-only Data Supplement). For the intrareader agreement in identification of carotid plaque compositions, the κ value was 0.92, 0.88, 0.95, and 0.96 for calcification, LRNC, IPH, and FCR, respectively. For the inter-reader agreement in identification of carotid plaque compositions, the κ value was 0.88, 0.83, 0.91, and 0.92 for calcification, LRNC, IPH, and FCR, respectively.

Discussion

This study investigated the association between the progression of carotid plaque and recurrent ischemic cerebrovascular events. We found that the annual change of carotid wall volume was an independent predictor for recurrent events. In addition, we found that the annual change of carotid wall volume could improve the predictive value of intraplaque hemorrhage and fibrous cap rupture for recurrent ischemic events. Our findings indicate that serial MR examinations of carotid plaque may provide additional information for risk stratification of recurrent ischemic events in symptomatic patients.

In the present study, we found that the annual change of carotid wall volume was superior to maximum wall area and maximum wall thickness in predicting recurrent ischemic events. Our findings are consistent with previous ultrasound imaging studies. Wannarong et al[19] demonstrated that the change of total plaque volume measured by 3-dimensional ultrasound imaging was significantly associated with subsequent ischemic events. In contrast, the associations of intima–media thickness, plaque area, and stenosis determined by ultrasound with future

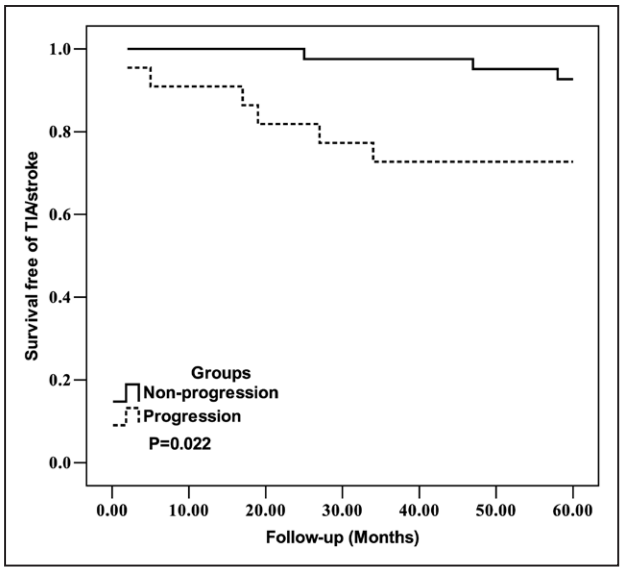

Figure 1. Kaplan–Meier analysis of survival free of recurrent transient ischemic attack (TIA)/stroke in the nonprogression group and progression group over a total of 60-months follow-up. The x-axis represents the time of follow-up in months. The y-axis represents the proportion of patients who were survival free of recurrent TIA/stroke.

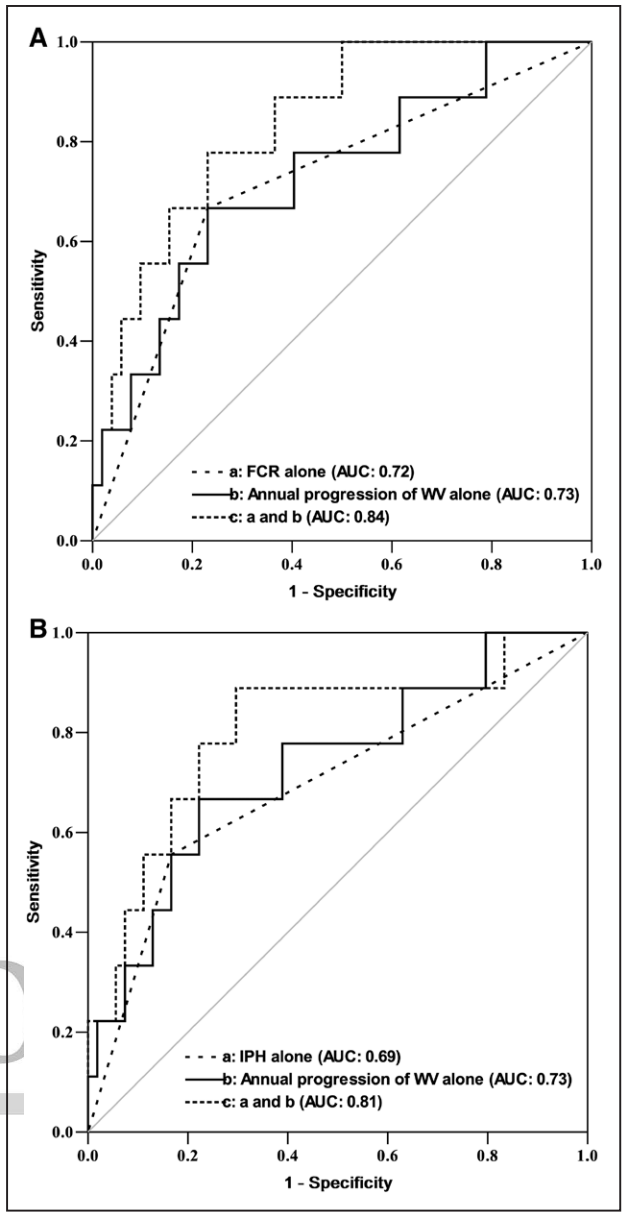

Figure 2. Receiver–operator characteristic curves for predicting recurrent transient ischemic attack (TIA)/stroke using the annual change of wall volume with or without the addition of presence of fibrous cap rupture (FCR; **A**) and intraplaque hemorrhage (IPH; **B**). AUC indicates area-under-the-curve; and WV, wall volume of carotid artery.

ischemic events are controversial. Hirano et al[5] claimed that progression of intima–media thickness can predict future ischemic events and Spence et al[4] showed that progression of plaque evaluated by annual carotid area was a useful measurement to evaluate preventive therapies; however, some investigators documented that there were no significant associations of the change of intima–media thickness and plaque area with subsequent ischemic events.[19,20] These findings indicate that the wall volume that includes 3-dimensional information might be a more sensitive measurement for plaque progression than intima–media thickness and plaque area with only 1-dimensional metrics.

Luminal measurements such as luminal stenosis and lumen volume were found not to be associated with ischemic cerebrovascular events in our study. The associations between progression of carotid stenosis and future events are not uniform in previous studies. Lewis et al[21] claimed that carotid stenosis progression was a poor predictor of neurological events (HR, 1.7; 95% CI, 0.9–2.9; $P>0.05$). However, Mono et al[12] reported that the progression of carotid stenosis was associated with ipsilateral cerebrovascular events (HR, 7.00; 95% CI, 1.13–41.34; $P=0.036$). In the present study, we excluded patients with severe carotid stenosis who may be more vulnerable to the progression of stenosis as result of chronic insufficiency of blood supply. Because of positive remodeling, carotid wall volume can increase substantially without compromising lumen area,[22] suggesting that the progression of wall volume may better reflect the progression of carotid atherosclerosis than lumen stenosis. Generally, ultrasound has poor image resolution and shadowing because of attention of the ultrasound beam of reconstructed 3-dimensional ultrasound images in the measurements of plaque volume.[23] Hence, to more accurately evaluate the progression of carotid plaque, carotid wall volume was applied, which was measured by MR imaging with excellent reproducibility[24] and ability to accurately characterize compositional features and surface status of carotid plaque simultaneously.[25]

Enlarging plaques with a high progression rate may indicate an active inflammatory status in them.[26] The inflammatory macrophages and lymphocytes in plaques will promote the decrease of smooth muscle cells and apoptosis of macrophages, which contribute to the necrotic core enlarging and fibrous cap thinning.[22] Additionally, in a rapidly growing plaque, reduced oxygen diffusion causes hypoxia and the release of angiogenic growth factors, leading to the rupture of intraplaque neovessels and IPH.[22] With the inflammatory mechanism, rapidly enlarging carotid plaque may be more likely to rupture and lead to subsequent ischemic events.

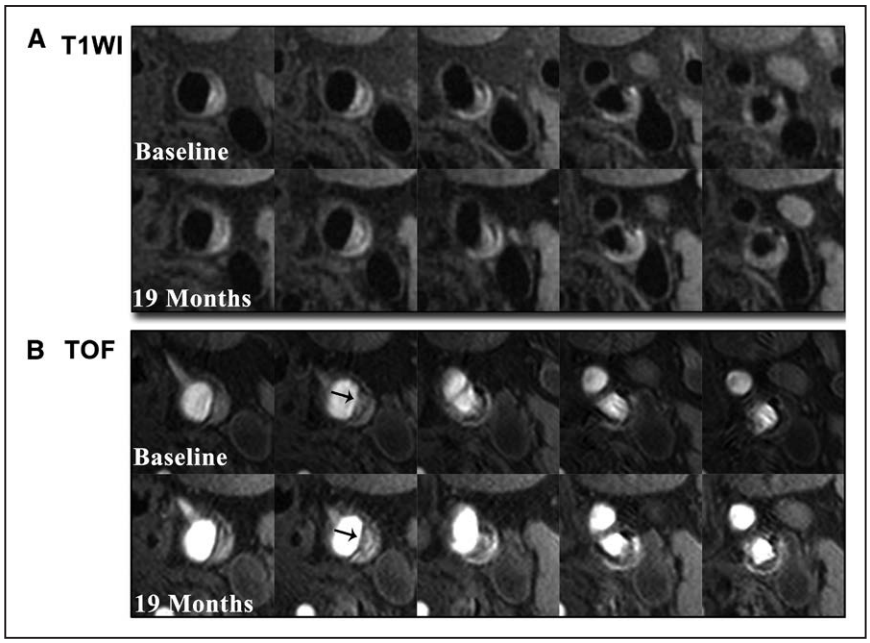

Figure 3. A 62-year-old female patient with carotid plaque progression after 19 months experienced a recurrence of ipsilateral stroke 17 months later since the second MR scan. A high-risk plaque at left carotid bifurcation was depicted on T1-weighted (T1W; **A**) and time-of-flight (TOF; **B**) images in both baseline and follow-up MR imaging. The baseline MR images showed that the carotid plaque had calcification, lipid-rich necrotic core, intraplaque hemorrhage, and fibrous cap rupture (black arrows). On the images of second MR scan, progression in plaque size can be seen.

The Kaplan–Meier survival analysis revealed that there was a high risk of recurrent TIA or stroke for patients in the progression group. Compared with rapidly progressive plaques, stable or enlarging plaques with a lower progression rate may indicate an inactive or weak inflammatory status, and in our study, a low risk of recurrence of TIA/stroke was revealed in Kaplan–Meier curves, even though for patients with vulnerable plaque characteristics at baseline. Additionally, regressive plaques were observed in our study accounting a relatively large proportion (42.8%), which may be because we recruited symptomatic patients with a high proportion of receiving lipid-lowering therapy.

Our data have shown that the progression of wall volume had the added value for the baseline MR characteristics of intraplaque hemorrhage and fibrous cap rupture in predicting subsequent events. Increasing evidences showed that baseline MR characteristics of carotid plaque were significantly associated with the development of subsequent cerebrovascular events. A recent meta-analysis[27] summarized previous prospective studies and reported that thinning/ruptured of fibrous cap (HR, 5.93; 95% CI, 2.65–13.20; $P<0.01$), IPH (HR, 4.59; 95% CI, 2.91–7.24; $P<0.01$) and larger maximum lipid-rich necrotic core (HR, 3.0; 95% CI, 1.51–5.95; $P=0.002$) detected by MRI were strongly associated with a recent ischemic neurological events. The wall volume progression in this study represents the enlargement of atherosclerotic plaque. A rapid progression of carotid plaque with fibrous cap rupture or IPH may increase the risk of developing repeated fibrous cap rupture/IPH, which will lead to subsequent recurrence of cerebrovascular events (Figure 3). Our findings suggest serial MRI examinations to assess the risk of subsequent ischemic events for patients with fibrous cap rupture or IPH.

The present study has several limitations. First, the sample size of this study was small, and future investigations with large sample size are required. Second, we did not quantitatively evaluate the volume change of intraplaque components, which may be more meaningful to assess the progression of carotid atherosclerosis. Third, patients with <30% stenosis or >69% stenosis were excluded from our study. Therefore, future studies that include patients with more broad range of carotid stenosis are warranted. Fourth, the longitudinal extension of carotid plaque was not measured in this present study. Because the MR examination of this study was conducted in an early period when the available vessel wall imaging sequences were 2 dimensional. It will be challenging to measure the longitudinal length of plaque with 2-dimensional imaging because of partial volume effect and limited z-axis spatial resolution (2 mm). Recently, 3-dimensional vessel wall imaging techniques[28,29] have been proposed for characterization of carotid plaques with high isotropic spatial resolution (≤0.8 mm). These 3-dimensional imaging techniques might be appropriate in measuring plaque extension longitudinally.

In conclusion, the annual progression of carotid wall volume is independently associated with recurrent ischemic cerebrovascular events, and this measurement has added value for intraplaque hemorrhage and fibrous cap rupture in predicting future events. Our findings suggest that the evaluation of annual progression of carotid wall volume will be a useful approach to predict recurrent ischemic events, especially combined with baseline MR characteristics.

Disclosures

None.

Sources of Funding

This research was supported by the Beijing Science and Technology Project (D171100003017003) and National Natural Science Foundation of China (81771825 and 81361120402).

References

1. Xu G, Liu X, Wu W, Zhang R, Yin Q. Recurrence after ischemic stroke in Chinese patients: impact of uncontrolled modifiable risk factors. *Cerebrovasc Dis*. 2007;23:117–120. doi: 10.1159/000097047.
2. Yuan C, Zhang SX, Polissar NL, Echelard D, Ortiz G, Davis JW, et al. Identification of fibrous cap rupture with magnetic resonance imaging

is highly associated with recent transient ischemic attack or stroke. *Circulation*. 2002;105:181–185.
3. Kwee RM, van Oostenbrugge RJ, Mess WH, Prins MH, van der Geest RJ, ter Berg JW, et al. MRI of carotid atherosclerosis to identify TIA and stroke patients who are at risk of a recurrence. *J Magn Reson Imaging*. 2013;37:1189–1194. doi: 10.1002/jmri.23918.
4. Spence JD, Eliasziw M, DiCicco M, Hackam DG, Galil R, Lohmann T. Carotid plaque area: a tool for targeting and evaluating vascular preventive therapy. *Stroke*. 2002;33:2916–2922.
5. Hirano M, Nakamura T, Kitta Y, Takishima I, Deyama J, Kobayashi T, et al. Short-term progression of maximum intima-media thickness of carotid plaque is associated with future coronary events in patients with coronary artery disease. *Atherosclerosis*. 2011;215:507–512. doi: 10.1016/j.atherosclerosis.2011.01.014.
6. Corriveau MM, Johnston KW. Interobserver variability of carotid Doppler peak velocity measurements among technologists in an ICAVL-accredited vascular laboratory. *J Vasc Surg*. 2004;39:735–741. doi: 10.1016/j.jvs.2003.12.017.
7. Gao S, van 't Klooster R, van Wijk DF, Nederveen AJ, Lelieveldt BP, van der Geest RJ. Repeatability of in vivo quantification of atherosclerotic carotid artery plaque components by supervised multispectral classification. *MAGMA*. 2015;28:535–545. doi: 10.1007/s10334-015-0495-2.
8. van 't Klooster R, Naggara O, Marsico R, Reiber JH, Meder JF, van der Geest RJ, et al. Automated versus manual in vivo segmentation of carotid plaque MRI. *AJNR Am J Neuroradiol*. 2012;33:1621–1627.
9. Sun J, Balu N, Hippe DS, Xue Y, Dong L, Zhao X, et al. Subclinical carotid atherosclerosis: short-term natural history of lipid-rich necrotic core–a multicenter study with MR imaging. *Radiology*. 2013;268:61–68. doi: 10.1148/radiol.13121702.
10. Saam T, Hetterich H, Hoffmann V, Yuan C, Dichgans M, Poppert H, et al. Meta-analysis and systematic review of the predictive value of carotid plaque hemorrhage on cerebrovascular events by magnetic resonance imaging. *J Am Coll Cardiol*. 2013;62:1081–1091. doi: 10.1016/j.jacc.2013.06.015.
11. Hellings WE, Peeters W, Moll FL, Piers SR, van Setten J, Van der Spek PJ, et al. Composition of carotid atherosclerotic plaque is associated with cardiovascular outcome: a prognostic study. *Circulation*. 2010;121:1941–1950. doi: 10.1161/CIRCULATIONAHA.109.887497.
12. Mono ML, Karameshev A, Slotboom J, Remonda L, Galimanis A, Jung S, et al. Plaque characteristics of asymptomatic carotid stenosis and risk of stroke. *Cerebrovasc Dis*. 2012;34:343–350. doi: 10.1159/000343227.
13. Kerwin W, Xu D, Liu F, Saam T, Underhill H, Takaya N, et al. Magnetic resonance imaging of carotid atherosclerosis: plaque analysis. *Top Magn Reson Imaging*. 2007;18:371–378. doi: 10.1097/rmr.0b013e3181598d9d.
14. Yuan C, Mitsumori LM, Ferguson MS, Polissar NL, Echelard D, Ortiz G, et al. In vivo accuracy of multispectral magnetic resonance imaging for identifying lipid-rich necrotic cores and intraplaque hemorrhage in advanced human carotid plaques. *Circulation*. 2001;104:2051–2056.
15. Hatsukami TS, Ross R, Polissar NL, Yuan C. Visualization of fibrous cap thickness and rupture in human atherosclerotic carotid plaque in vivo with high-resolution magnetic resonance imaging. *Circulation*. 2000;102:959–964.
16. Barnett HJM, Taylor DW, Haynes RB, Sackett DL, Peerless SJ, Ferguson GG, et al. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med*. 1991;325:445–453.
17. Li F, Yarnykh VL, Hatsukami TS, Chu B, Balu N, Wang J, et al. Scan-rescan reproducibility of carotid atherosclerotic plaque morphology and tissue composition measurements using multicontrast MRI at 3T. *J Magn Reson Imaging*. 2010;31:168–176. doi: 10.1002/jmri.22014.
18. Sun J, Zhao XQ, Balu N, Hippe DS, Hatsukami TS, Isquith DA, et al. Carotid magnetic resonance imaging for monitoring atherosclerotic plaque progression: a multicenter reproducibility study. *Int J Cardiovasc Imaging*. 2015;31:95–103. doi: 10.1007/s10554-014-0532-7.
19. Wannarong T, Parraga G, Buchanan D, Fenster A, House AA, Hackam DG, et al. Progression of carotid plaque volume predicts cardiovascular events. *Stroke*. 2013;44:1859–1865. doi: 10.1161/STROKEAHA.113.001461.
20. Chen PC, Jeng JS, Hsu HC, Su TC, Chien KL, Lee YT. Carotid atherosclerosis progression and risk of cardiovascular events in a community in Taiwan. *Sci Rep*. 2016;6:25733. doi: 10.1038/srep25733.
21. Lewis RF, Abrahamowicz M, Côté R, Battista RN. Predictive power of duplex ultrasonography in asymptomatic carotid disease. *Ann Intern Med*. 1997;127:13–20.
22. Alonso A, Artemis D, Hennerici MG. Molecular imaging of carotid plaque vulnerability. *Cerebrovasc Dis*. 2015;39:5–12. doi: 10.1159/000369123.
23. Landry A, Spence JD, Fenster A. Measurement of carotid plaque volume by 3-dimensional ultrasound. *Stroke*. 2004;35:864–869. doi: 10.1161/01.STR.0000121161.61324.ab.
24. Sun J, Zhao XQ, Balu N, Hippe DS, Hatsukami TS, Isquith DA, et al. Carotid magnetic resonance imaging for monitoring atherosclerotic plaque progression: a multicenter reproducibility study. *Int J Cardiovasc Imaging*. 2015;31:95–103. doi: 10.1007/s10554-014-0532-7.
25. Cai J, Hatsukami TS, Ferguson MS, Kerwin WS, Saam T, Chu B, et al. In vivo quantitative measurement of intact fibrous cap and lipid-rich necrotic core size in atherosclerotic carotid plaque: comparison of high-resolution, contrast-enhanced magnetic resonance imaging and histology. *Circulation*. 2005;112:3437–3444. doi: 10.1161/CIRCULATIONAHA.104.528174.
26. Chen H, Ricks J, Rosenfeld M, Kerwin WS. Progression of experimental lesions of atherosclerosis: assessment by kinetic modeling of black-blood dynamic contrast-enhanced MRI. *Magn Reson Med*. 2013;69:1712–1720. doi: 10.1002/mrm.24415.
27. Gupta A, Baradaran H, Schweitzer AD, Kamel H, Pandya A, Delgado D, et al. Carotid plaque MRI and stroke risk: a systematic review and meta-analysis. *Stroke*. 2013;44:3071–3077. doi: 10.1161/STROKEAHA.113.002551.
28. Zhou Z, Li R, Zhao X, He L, Wang X, Wang J, et al. Evaluation of 3D multi-contrast joint intra- and extracranial vessel wall cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2015;17:41. doi: 10.1186/s12968-015-0143-z.
29. Fan Z, Yu W, Xie Y, Dong L, Yang L, Wang Z, et al. Multi-contrast atherosclerosis characterization (MATCH) of carotid plaque with a single 5-min scan: technical development and clinical feasibility. *J Cardiovasc Magn Reson*. 2014;16:53. doi: 10.1186/s12968-014-0053-5.

Stroke
Journal of the American Heart Association

Association of Progression of Carotid Artery Wall Volume and Recurrent Transient Ischemic Attack or Stroke: A Magnetic Resonance Imaging Study

Mingming Lu, Peng Peng, Yuanyuan Cui, Huiyu Qiao, Dongye Li, Jianming Cai and Xihai Zhao

Stroke. published online January 30, 2018;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

SUPPLEMENTAL MATERIAL

Association of Progression of Carotid Artery wall Volume and Recurrent TIA or Stroke: A Magnetic Resonance Imaging Study

Mingming Lu, MD[1,3*], Peng Peng, MSc[3], Yuanyuan Cui, MD[1], Huiyu Qiao, MD[2], Dongye Li, MSc[2], Jianming Cai, MD, PhD[1†] , Xihai Zhao, MD, PhD[2†]

Supplemental Table. Reproducibility of morphologic measurements of carotid plaque.

	Intra-reader agreement		Inter-reader agreement	
	ICC	95%CI	ICC	95%CI
Lumen volume	0.97	0.96-0.99	0.97	0.95-0.99
Wall volume	0.96	0.91-0.98	0.95	0.89-0.98
Maximum wall area	0.98	0.94-0.99	0.96	0.92-0.98
Maximum WT	0.89	0.75-0.96	0.90	0.82-0.95
Stenosis	0.91	0.82-0.96	0.92	0.85-0.96
Change of lumen volume	0.96	0.92-0.98	0.95	0.87-0.98
Change of wall volume	0.94	0.86-0.98	0.93	0.83-0.97
Change of maximum wall area	0.95	0.85-0.98	0.94	0.85-0.97
Change of maximum WT	0.88	0.72-0.95	0.89	0.76-0.95
Change of stenosis	0.88	0.70-0.95	0.88	0.73-0.96

ICC: intraclass correlation coefficient; WT: wall thickness.