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ORIGINAL PAPER

Association between age and progression of carotid artery atherosclerosis: a serial high resolution magnetic resonance imaging study

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Abstract

This study aimed to investigate the association between age and progression of carotid atherosclerotic plaques using serial high resolution magnetic resonance imaging (MRI). Symptomatic patients who had carotid atherosclerosis with 30–70% stenosis were enrolled in this study. Carotid MRI was performed at baseline and follow-up time point (≥ 6 months after baseline), respectively. The characteristics of carotid plaque progression among different age groups (> 75 years old, 60–75 years old and < 60 years old) were compared. Logistic regression was performed to relate age with carotid plaque progression. Of recruited 84 patients, 73 (mean age, 66.5 ± 11.4 years old; males, 82.2%) with 96 plaques were included in the final analysis. Compared with younger patients, older ones had significantly higher incidence of calcification in carotid plaques (> 75 years old: 91.3%, 60–75 years old: 65.7% and < 60 years old: 55.3%, $p = 0.013$), greater annual change of carotid wall volume (> 75 years old: 39.0 (4.3–104.6) mm^3, 60–75 years old: 28.7 (− 28.0 to 73.7) mm^3 and < 60 years old: 4.8 (− 27.1–31.9) mm^3, $p = 0.032$) and maximum carotid wall area (> 75 years old: 6.1 (− 3.5 to 17.2) mm^2, 60–75 years old: 2.4 (− 4.7 to 15.1) mm^2 and < 60 years old: 1.4 (− 5.8 to 6.9) mm^2, $p = 0.046$). Age (OR 1.44; 95% CI 1.10–1.89; $p = 0.009$) and hypertension (OR 4.61; 95% CI 1.41–15. 02; $p = 0.011$) were independent predictors in discriminating upper quartile of annual change of carotid wall volume after adjusting for all clinical factors. Older patients have faster progression rate in carotid plaques than younger ones and age is independently associated with carotid plaque progression. Our findings suggest that the carotid plaques of older patients need to be monitored more frequently.

Keywords Carotid atherosclerosis · Disease progression · Risk factors · Magnetic resonance imaging

Introduction

It is well established that progression of carotid plaque was associated with the subsequent cerebrovascular events [1–3], such as stroke and transient ischemic attack (TIA). Previous evidences showed that many modifiable factors, such as hypertension [4], diabetes [5, 6], high-density lipoprotein

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cholesterol [7], smoking [8] and statin use [9] could promote or slow the progression of carotid plaque. Age, as an unmodifiable factor, has been found to be associated with the increase of internal media thickness (IMT) [10]. However, previous study utilized ultrasound imaging to assess the progression of early atherosclerotic plaques. It is still challenging for ultrasound to monitor the change of carotid plaque within a certain time course because of its poor intra-and inter-operator reproducibility [11], even although its usefulness in characterizing baseline features of carotid atherosclerosis. Furthermore, the increase of IMT measured by ultrasound may not represent the comprehensive progression of carotid plaque, particularly for advanced lesions.

Previous studies have shown that multi-contrast magnetic resonance imaging (MRI) had excellent reproducibility and accuracy in evaluating the changes of carotid plaque [12, 13]. This technique has been largely utilized to monitor the regreession or progression of carotid atherosclerotic plaques either in clinical trials with statin therapy [13] or cohort studies investigating natural history [12]. The aim of this study was to determine the association between age and the progression of carotid artery atherosclerotic plaques using serial multi-contrast MRI.

Materials and methods

Study population

Consecutive patients with recent cerebrovascular symptoms (< 2 weeks) who had atherosclerosis with 30–70% stenosis in at least one side of carotid artery determined by ultrasound were enrolled in this study. The exclusion criteria were as follows: (1) plan to undergo carotid endarterectomy (CEA); (2) brain tumor; (3) history of radiotherapy at neck; (4) claustrophobia; (5) contraindication to MR examination. MR vessel wall imaging was performed for bilateral carotid arteries at baseline and follow-up time point (≥ 6 months after baseline), respectively. The clinical information including age, gender, body mass index (BMI), hypertension, diabetes, hyperlipidemia, smoking, and history of coronary heart disease was collected from clinical record. Hypertension is defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Diabetes mellitus was diagnosed when fasting blood sugar level ≥ 126 mg/dL, 2-h oral glucose tolerance test result ≥ 200 mg/dL, or hemoglobin A1c ≥ 6.5%. Hyperlipidemia is defined as low density of lipoprotein (LDL) > 1.58 mmol/L, total cholesterol (TC) > 2.26 mmol/L, or triglycerides (TG) > 1.69 mmol/L. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by Institution's ethics committee on research on humans. All participants provided the written consent forms.

Carotid artery MR imaging

The MR imaging was conducted on a 3.0-T MR scanner (SignaHDx, GE Medical System, Milwaukee, WI, USA) with a 4-channel dedicated phase-arrayed surface coil. A standard carotid MR vessel wall imaging protocol including three dimensional time-of-flight (3D TOF), 2D T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI) was acquired with the following parameters: 3D TOF: 3D gradient echo (GRE), repetition time (TR)/echo time (TE) = 29 ms/2.1 ms, flip angle 20°; T1W: fast spin echo (FSE), TR/TE = 800 ms/7.5 ms; and T2W: FSE, TR/TE = 3000 ms/57 ms. All MR images were acquired with the same field of view of 140 mm × 140 mm, matrix size of 256 × 256, and slice thickness of 2 mm. The MR scan was centered at the bifurcation of carotid artery corresponded to clinical symptoms or with the most severe stenosis.

MR image analysis

The MR images were analyzed by two radiologists with > 3 years' experience in cerebrovascular imaging using custom-designed software (CASCADE [14], Vascular Imaging Lab, University of Washington). The image quality was rated for each axial slice with a 4-point scale (1 = poor, 4 = excellent) [15]. The lumen and outer wall boundaries were outlined and the morphological characteristics of carotid artery including lumen area, wall area and maximum wall thickness were measured. The volume for lumen/wall was calculated by 2 mm × lumen/wall area of slices with plaque (Fig. 1). The presence or absence of plaque compositions [calcification, lipid-rich necrotic core (LRNC), and intraplaque hemorrhage (IPH)] and fibrous cap rupture (FCR) was identified using the published criteria [16]. The luminal stenosis of carotid arteries was measured on the 3D TOF MR angiographic images after maximum intensity projection using NASCET (North American symptomatic carotid endarterectomy trial) criteria [17].

Reproducibility

Twenty subjects were randomly selected to test the inter-observer and intra-observer reproducibility in measuring carotid plaque morphology. All 73 patients were used for determining the inter-observer and intra-observer reproducibility in identification of the presence of carotid plaque compositions. A time interval of 2 months was set for testing the intra-observer agreement to minimize the memory bias. The scan-rescan reproducibility [intraclass correlation coefficient (ICC), 0.87–0.99] has been demonstrated to be

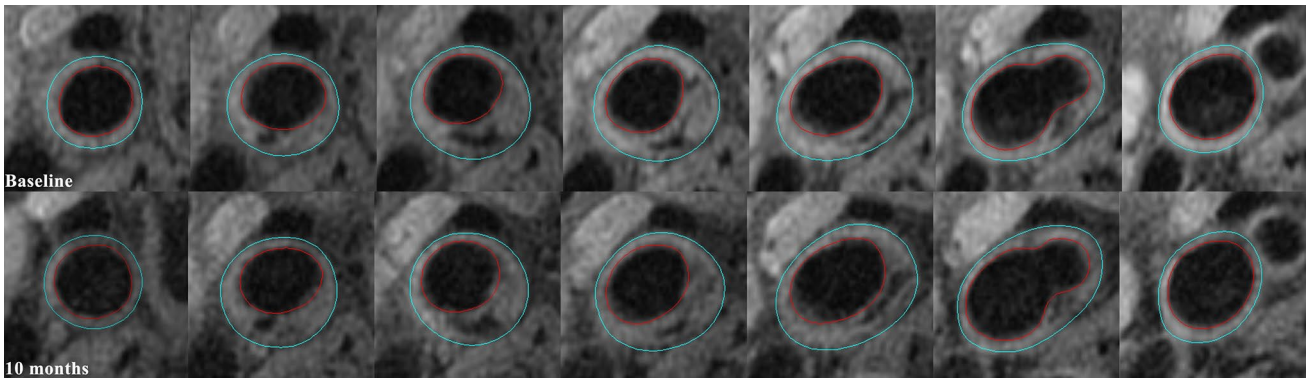

Fig. 1 Example for morphological measurements of carotid artery. The picture shows that the lumen in red and outer wall boundary in blue of the carotid artery are identified and outlined on T1-weighted images. Carotid wall volume is calculated by multiplying the slice thickness (2 mm) by the sum of the areas between the red and blue circles. Carotid lumen volume is calculated by multiplying the slice thickness (2 mm) by the sum of the areas circled in red color

excellent in measuring the morphology of carotid plaques [18, 19].

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (25–75% quartile) and categorical variables were presented as percentage. The patients recruited in our study were divided into three groups as follows: > 75 years old, 60–75 years old and < 60 years old. According to the annual change of carotid wall volume, all participants were divided into quartiles. Logistic regression analysis with generalized estimating equation correction was used to calculate the odds ratio (OR) and corresponding 95% confidence interval (CI) of clinical characteristics at baseline in discriminating the upper quartile of annual change of carotid wall volume. Models of logistic regression included univariable model, stepwise multivariable model with only the significant parameters and multivariable model with all clinical parameters. A value of $p < 0.05$ was defined as statistically significant. All analysis was performed using the statistical software of SPSS 22.0 (IBM, Chicago, IL).

Results

In total, 84 patients with 143 plaques were recruited in this study from November 2005 to February 2012. Of these, 11 patients were excluded because of the following reasons: (1) underwent CEA after the baseline MR scan (6 patients); and (2) poor image quality (5 patients). The mean time interval between baseline and follow-up MR scans was 13.4 ± 8.9 months. The clinical characteristics are summarized in Table 1. Of all 73 patients, mean age was 66.5 ± 11.4 years old, 60 (82.2%) were males, 52 (71.2%) had hypertension, 17 (23.3%) had diabetes, 42 (57.5%) had hyperlipidemia, and 30 (41.1%) had history of smoking.

Association between age and baseline carotid plaque characteristics

Of the included 73 patients, 96 atherosclerotic plaques were detected and had accepted image quality. Of all 96 carotid plaques, 73 (76.0%) had LRNC, 24 (25.0%) had IPH, 65 (67.7%) had calcification, and 28 (29.2%) had FCR (Table 2). The mean luminal volume, wall volume, maximum wall area, stenosis, and maximum wall thickness of carotid arteries at baseline were 794.3 (582.8–969.4) mm^3, 916.5 (646.8–1152.2) mm^3, 77.7 (59.6–90.4) mm^2, 53.7% (41.3–65.1%) % and 5.2 (4.1–5.9) mm, respectively (Table 2). Compared with younger patients, older ones had significantly higher incidence of calcification in carotid plaques (> 75 years old: 91.3%, 60–75 years old: 65.7% and < 60 years old: 55.3%, $p = 0.013$). No significant differences were found in carotid artery morphological measurements and prevalence of LRNC, IPH, and FCR among all age groups (all $p > 0.05$, Table 2).

Association between age and changing of carotid plaques

The annual change of carotid luminal volume, wall volume, maximum wall area, stenosis, and maximum wall thickness was 3.6 (− 22.1 to 31.6) mm^3, 14.6 (− 19.7 to 72.4) mm^3, 2.8 (− 5.1 to 12.2) mm^2, 0.7% (− 1.5 to 5.6%), and 0.2 (− 0.5 to 0.6) mm, respectively. The differences in annual change of carotid plaques among all age groups were presented in Table 2. Compared with younger patients, older ones had greater annual change of carotid wall volume (> 75 years old: 39.0 (4.3–104.6) mm^3, 60–75 years old: 28.7 (− 28.0 to 73.7)

Table 1 Baseline clinical characteristics among different age groups (n = 73)

	Age groups (Mean ± SD or n (%))			*p*
	< 60 years old n = 28	60–70 years old n = 25	> 75 years old n = 20	
Gender (male)	24 (85.7%)	20 (80.0%)	16 (80.0%)	0.825
Age	54.3 ± 4.7	69.5 ± 5.3	79.8 ± 2.9	< 0.001
BMI, kg/m^2	23.6 ± 3.2	23.6 ± 2.7	24.7 ± 3.3	0.370
Hypertension	16 (57.1%)	19 (76.0%)	17 (85.0%)	0.089
Hyperlipidemia	15 (53.6%)	16 (64.0%)	11 (55.0%)	0.719
LDL, mmol/L	2.2 ± 1.5	2.4 ± 1.1	2.3 ± 1.4	0.427
HDL, mmol/L	1.0 ± 0.8	0.9 ± 0.7	1.0 ± 0.5	0.664
TC, mmol/L	4.1 ± 1.2	4.3 ± 1.7	4.2 ± 1.4	0.147
TG, mmol/L	1.5 ± 1.0	1.6 ± 0.9	1.6 ± 1.0	0.765
Statin use	12 (42.9%)	12 (48.0%)	11 (55.0%)	0.708
Diabetes	3 (10.7%)	7 (28.0%)	7 (35.0%)	0.115
Smoking	13 (46.4%)	11 (44.0%)	6 (30.0%)	0.488
Antiplatelet agent	19 (67.9%)	20 (80.0%)	17 (85.0%)	0.341
Coronary heart disease	5 (17.8%)	12 (48.0%)	11 (55.0%)	0.016

LDL low density of lipoprotein, *HDL* high density of lipoprotein, *TC* Total cholesterol, *TG* triglycerides

Table 2 Baseline characteristics and progression of carotid plaques

	Median (25–75% quartile) or n (%)			*p*
	< 60 year old (n = 38)	60–75 years old (n = 35)	> 75 years old (n = 23)	
Baseline characteristics of carotid plaque				
Lumen volume, mm^3	845.9 (605.0–1135.7)	698.3 (507.0–873.2)	827.8 (674.3–947.4)	0.225
Wall volume, mm^3	900.9 (637.9–1181.6)	931.4 (643.2–1213.5)	921.6 (649.7–1004.6)	0.857
Maximum wall area, mm^2	78.0 (57.3–85.4)	79.2 (62.9–93.5)	76.3 (59.4–92.5)	0.513
Stenosis, %	49.8 (39.7–64.0)	58.9 (45.4–67.8)	47.2 (37.4–59.4)	0.151
Maximum wall thickness, mm	4.7 (3.7–5.7)	5.3 (4.4–6.1)	4.8 (3.8–5.7)	0.122
Calcification	21 (55.3)	23 (65.7)	21 (91.3)	0.013
Lipid-rich necrotic core	27 (71.1)	29 (82.9)	17 (73.9)	0.480
Intraplaque hemorrhage	8 (21.1)	11 (31.4)	5 (21.7)	0.544
Fibrous cap rupture	9 (23.7)	13 (37.1)	6 (26.1)	0.420
Annual change of carotid plaque				
Lumen volume, mm^3	5.2 (−6.3 to 31.6)	7.4 (−22.9 to 32.5)	−6.3 (−55.8 to 32.6)	0.375
Wall volume, mm^3	4.8 (−27.1 to 31.9)	28.7 (−28.0 to 73.7)	39.0 (4.3 to 104.6)	0.032
Maximum wall area, mm^2	1.4 (−5.8 to 6.9)	2.4 (−4.7 to 15.1)	6.1 (−3.5 to 17.2)	0.046
Stenosis, %	0.8 (−1.5 to 4.5)	1.2 (−1.4 to 6.2)	0.33 (−2.1 to 7.2)	0.940
Maximum wall thickness, mm	0.2 (−0.4 to 0.6)	0.2 (−0.6 to 0.6)	0.3 (−0.5 to 0.8)	0.727

mm^3 and < 60 years old: 4.8 (−27.1–31.9) mm^3, $p = 0.032$) (Fig. 2) and maximum carotid wall area (> 75 years old: 6.1 (−3.5 to 17.2) mm^2, 60–75 years old: 2.4 (−4.7 to 15.1) mm^2 and < 60 years old: 1.4 (−5.8 to 6.9) mm^2, $p = 0.046$). Figures 3 and 4 represent examples showing that the older patients had faster progression rate of carotid plaque compared with younger patients.

Logistic regression showed that age (OR 1.35; 95% CI 1.09–1.67; $p = 0.006$), hypertension (OR 3.25; 95% CI 1.06–9.90; $p = 0.039$) and smoking (OR 2.69; 95% CI 1.02–7.10; $p = 0.046$) were significantly associated with the upper quartile of annual change of carotid wall volume (Table 3). When above three variables entered into the stepwise multivariate model, the association of age (OR 1.34; 95% CI 1.06–1.70; $p = 0.016$, Table 3) with upper quartile of annual change of carotid wall volume remain statistically significant. After adjusting for all clinical factors, this association still remains statistically significant (OR 1.44; 95% CI 1.10–1.89; $p = 0.009$, Table 3).

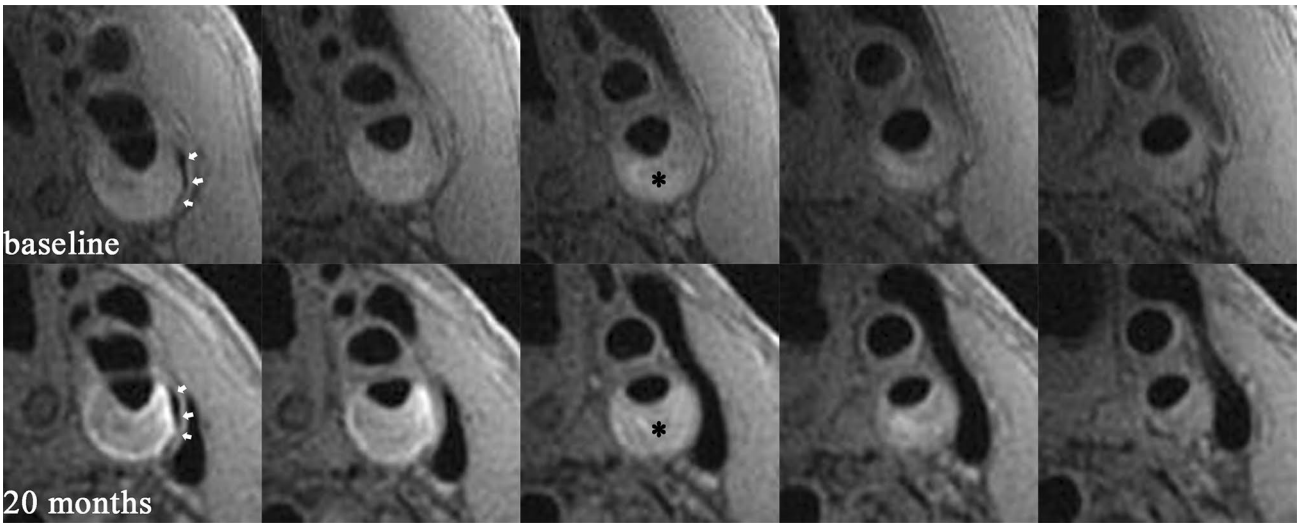

Fig. 2 The images were from a 79 years-old male patient. A progressive plaque with calcification (short arrow) and intraplaque hemorrhage (asterisk) at left carotid bifurcation was depicted on T1W images at baseline and 20 months later

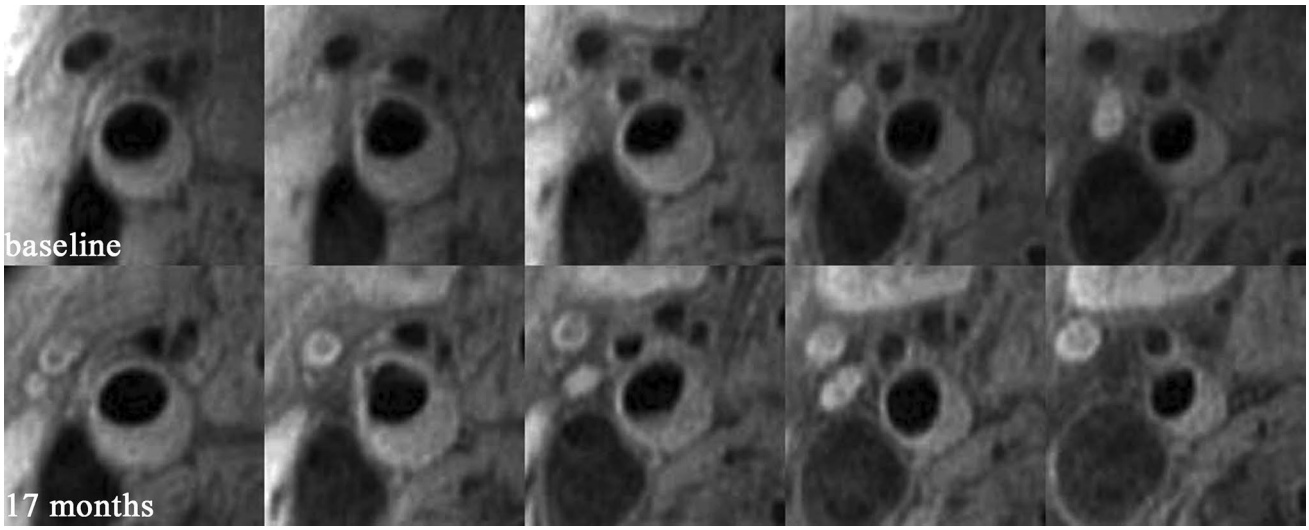

Fig. 3 The images were from a 58 years-old male patient. A plaque at right common carotid bifurcation was depicted on T1W images at baseline and 17 months later. No progression of carotid plaque was observed

Reproducibility

We found the ICC for measuring plaque morphology was ranging from 0.84 to 0.97 for intra-observer agreement (Supplemental Table). For the intra-observer agreement, the Kappa value for identification of the presence of calcification, LRNC, IPH, and FCR was 0.90, 0.87, 0.89, and 0.93, respectively.

For inter-observer agreement in measuring plaque morphology, the ICC was ranging from 0.83 to 0.96(supplemental table). For the inter-observer agreement in assessment of calcification, LRNC, IPH, and FCR, the Kappa value was 0.88, 0.82, 0.86, and 0.91, respectively.

Discussion

This study investigated the association between age and the progression of carotid atherosclerotic plaques in symptomatic patients. We found that compared with younger patients, older ones had significantly more calcified plaques and greater annual change of carotid wall volume and maximum carotid wall area. Logistic regression analysis revealed that age was an independent predictor for annual change of carotid wall volume. Our findings indicate that older patients with carotid atherosclerosis may have faster progression rate in carotid plaque which

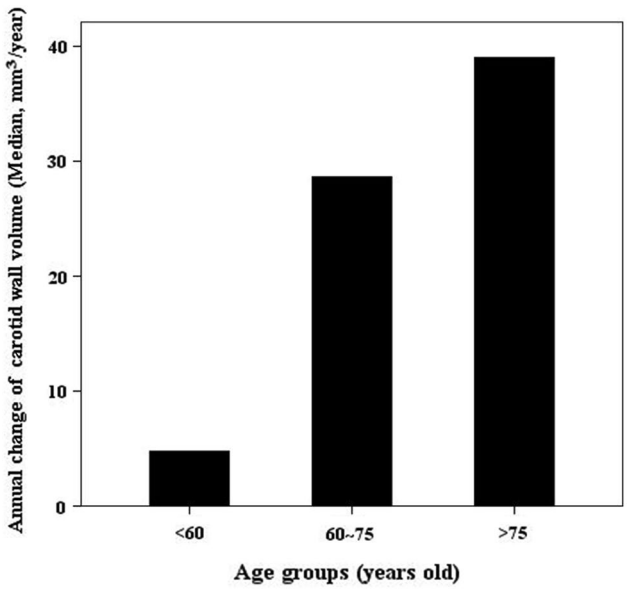

Fig. 4 The image shows the annual progression of carotid wall volume among different age groups (> 75 years old, 60–75 years old and < 60 years old)

may accelerate disruption of vulnerable plaques (Fig. 5), suggesting that the carotid plaques of older patients may need to be monitored more frequently.

In the present study, we found that intraplaque calcifications were more commonly seen in older patients compared with younger patients. Our findings are consisted with previous studies. Guus et al. [20] found that older patients with carotid atherosclerosis had more calcified plaques as compared with younger patients (OR 1.36; 95% CI 1.16–1.58; p = 0.001). Gils et al. [21] showed that age was independently associated with increased calcification in atherosclerotic plaque (OR 4.6; 95% CI, 1.85–11.49; $p < 0.001$). Histologically, calcifications were more common in advanced plaques [22] which were more frequently seen in the elderly. Furthermore, long-term statin treatment in the elderly patients with carotid atherosclerosis may be contributable to the formation of calcification in plaques [23]. In addition, in the present study, no differences were found in plaque burden among all age groups at baseline. However, previous studies showed that older subjects had thicker carotid IMT [8] or greater total plaque area [24] compared with younger patients. The inconsistency between our study and previous reports might be due to the exclusion of patients with early stage plaques (stenosis < 30%) which are more prevalent in younger patients in our study.

Our study showed that there was greater annual change of carotid wall volume and maximum wall area in older patients and age was an independent predictor for plaque progression. Previous ultrasound study reported that age was significantly associated with the progression of carotid atherosclerosis as measured by IMT [10]. The possible mechanism may be that cellular senescence induced by aging will accelerate the expression of pro-inflammatory cytokines and adhesion molecules, which can promote inflammation and affect the synthesis and maintenance of extracellular matrix

Table 3 Determinants of progression of carotid wall volume

	Progression of carotid wall volume[a]					
	Univariate model		Multivariate model 1[b]		Multivariate model 2[c]	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Age, years[d]	1.35 (1.09–1.67)	0.006	1.34 (1.06–1.70)	0.016	1.44 (1.10–1.89)	0.009
Gender, man	1.43 (0.44–4.60)	0.550			0.82 (0.19–3.62)	0.794
BMI, kg/m^2[e]	1.11 (0.67–1.81)	0.694			1.19 (0.65–2.18)	0.570
Hypertension	3.25 (1.06–9.90)	0.039	3.70 (1.09–12.58)	0.036	4.61 (1.41–15.02)	0.011
Hyperlipidemia	1.40 (0.54–3.66)	0.489			2.20 (0.52–9.33)	0.285
Diabetes	1.57 (0.48–5.12)	0.456			1.40 (0.35–3.50)	0.566
CHD	0.71 (0.26–1.93)	0.502			0.60 (0.16–2.24)	0.444
Antiplatelet therapy	0.71 (0.23–2.18)	0.543			0.50 (0.12–2.12)	0.350
Statin use	0.78 (0.31–1.96)	0.600			0.34 (0.08–1.41)	0.138
Smoking	2.69 (1.02–7.10)	0.046	2.96 (0.97–9.06)	0.057	2.55 (0.83–7.87)	0.103

BMI: body mass index, *CHD* coronary heart disease

[a]The progression of carotid wall volume: upper quintile value of annual change of carotid wall volume

[b]A stepwise multivariable model was performed using generalized estimating equation. Variables with significant level of 0.05 were finally entered into the multivariate model

[c]Model 2 was adjusting for all the clinical factors listed in the table; Increment

[d]5 years

[e]One standard deviation

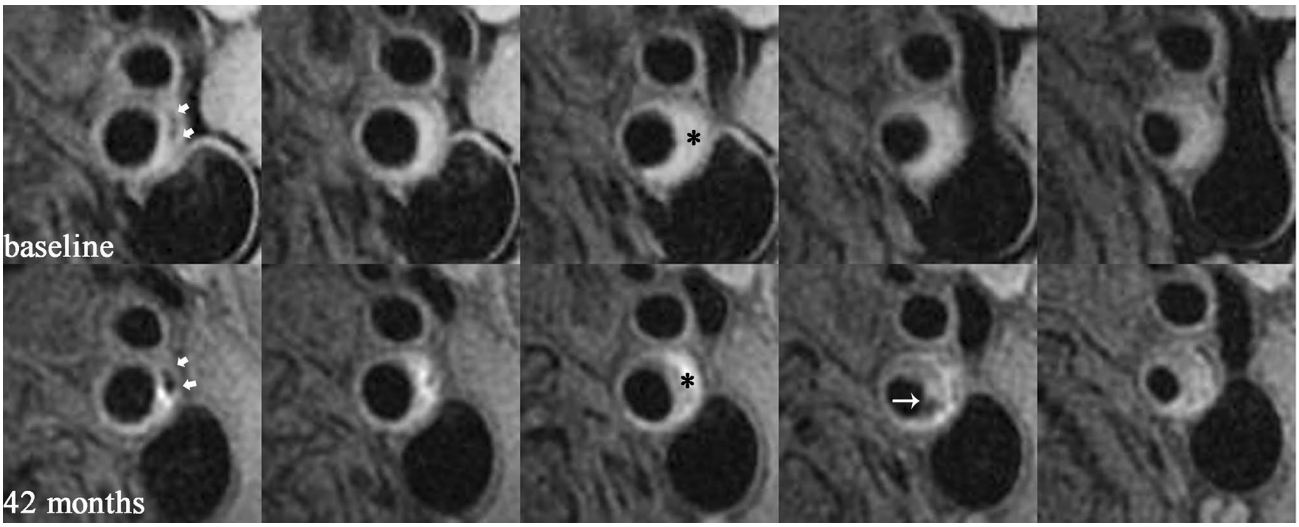

Fig. 5 The images were from an 81 years-old male patient. A plaque with calcification (short arrow) and intraplaque hemorrhage (asterisk) at left internal carotid artery was depicted on T1W images at baseline. Progression of the carotid plaque with new fibrous cap rupture (long arrow) was observed after 42 months

protein [25]. The inflammatory status and insufficient extracellular matrix protein will subsequently stimulate the progression of carotid plaque. Additionally, in the present study, the statistic significance of the association between age and plaque progression was slightly attenuated after adjusting other clinical risk factors, indicating that these clinical risk factors might have synergistic effects on carotid plaque progression. Previous studies have shown that hypertension [4], diabetes [5, 6], high-density lipoprotein cholesterol [7], smoking [8] and statin use [9] were associated with the progression of carotid atherosclerosis. However, in our study, only age and hypertension were found to be the independent predictors for plaque progression. The relationship between carotid plaque progression and cardiovascular risk factors needs to be further investigated in future studies.

Two-dimensional multi-contrast MR vessel imaging techniques had been utilized to assess plaque changes over time. To minimize the mismatch in the MR images at baseline and follow-up MR imaging, consistent landmark such as carotid bifurcation will be used in localization of MR scan. However, it is still challenging to acquire the MR images at the exactly same location and orientation between two time points due to the variation from the differences in the operation of technicians and the neck position. In addition, partial volume effect from two-dimensional (2D) imaging may also introduce substantial bias in quantitative measurements. Recently, three-dimensional (3D) MR vessel wall imaging techniques have been proposed for characterization of carotid plaques. These 3D techniques allow isotropic high resolution acquisition and large longitudinal coverage. The volumetric acquisition of 3D sequences is flexible for localization of technicians during MR scan. The reformat of 3D imaging data can mostly avoid the mismatch in MR images between two time points. Use of 3D MR vessel wall imaging techniques to monitor the changes of carotid plaques over time in future studies is warranted.

The present study has several limitations. First, the sample size of the study was limited and the follow-up intervals of MR imaging scans were relatively short. Future investigations with larger sample size and long-term follow-up were suggested. Second, MR examinations with contrast agent were not performed in the present study. It will be interesting to assess the time course of neovasculature and inflammation in carotid plaques. Third, the changes of carotid plaque components, such as IPH, LRNC and calcification, were not determined in the present study. Previous studies [26, 27] demonstrated that compositional features play important role in plaque vulnerability. As such, it is valuable to evaluate the relationship between cardiovascular risk factors and carotid plaque progression in future studies. Finally, the longitudinal coverage of MR imaging in our study was 24 mm which is not sufficient for carotid plaques with large extent in the longitudinal dimension.

In conclusion, older subjects have faster progression rate in carotid plaques than younger ones and age is independently associated with carotid plaque progression. Our findings suggest that the carotid plaques of older patients need to be monitored more frequently.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by Institution's ethics committee on research on humans.

Informed consent Informed consent was obtained from all individual participants included in the study.

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