

RESEARCH ARTICLE

Association of severity between carotid and intracranial artery atherosclerosis

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Abstract

Objective: This study sought to investigate the relationship of atherosclerosis between intracranial and extracranial carotid arteries using three-dimensional multicontrast magnetic resonance (MR) vessel wall imaging. **Methods:** Patients with recent cerebrovascular symptoms in anterior circulation were recruited and underwent MR vessel wall imaging for intracranial and extracranial carotid arteries. The plaque burden, including maximum wall thickness (Max WT) and stenosis, and presence of intraplaque hemorrhage (IPH) were assessed. The correlation of the plaque characteristics between intracranial and extracranial carotid arteries was determined. **Results:** In total, 107 patients (mean age: 57.0 ± 11.1 years, 69 males) were recruited. In discriminating intracranial severe stenosis ($\geq 50\%$ stenosis), the odds ratio (OR) of Max WT of extracranial carotid arteries was 1.41 (95% confidence interval [CI], 0.94–2.11, $P = 0.095$) and 1.72 (95% CI, 1.04–2.83, $P = 0.034$) before and after adjusting for confounding factors, respectively. The OR of stenosis of extracranial carotid arteries with increment of 10% was 1.26 (95% CI, 0.99–1.60, $P = 0.054$) and 1.37 (95% CI, 1.03–1.82, $P = 0.033$) before and after adjusting for confounding factors, in discriminating intracranial severe stenosis respectively. Receiver operating characteristic analysis revealed that the area under the curve (AUC) of Max WT, stenosis, and IPH of extracranial carotid artery plaques was 0.641, 0.605, and 0.603 in discriminating intracranial severe stenosis, respectively. After adjusting for confounding factors, the AUC of Max WT, stenosis, and presence of IPH in extracranial carotid artery plaques increased to 0.812, 0.817 and 0.781, respectively. **Interpretation:** Carotid artery plaque burden is significantly associated with severe intracranial artery stenosis, suggesting that extracranial carotid plaque burden might be an independent indicator for severity of intracranial artery atherosclerosis.

Introduction

It has been shown that intracranial atherosclerotic disease (ICAD) is one of the major causes of ischemic stroke in Chinese population.¹ Clinically, angiography is the major approach for diagnosis of ICAD. However, the angiographic techniques will underestimate plaque severity due

to the lack of vessel wall information and arterial positive remodeling effect.^{2,3} Recently, magnetic resonance (MR) vessel wall imaging has been largely utilized to characterize ICAD.^{4,5} However, using vessel wall imaging to evaluate ICAD is challenging because of the limited spatial resolution and insufficient suppression of cerebral spinal fluid.

As a systemic disease, atherosclerosis commonly involves multiple vascular beds simultaneously and the co-existing atherosclerosis in the intracranial and extracranial carotid arteries has been found to be prevalent in stroke patients.^{6,7} Investigators have found that there was correlation of atherosclerotic stenosis between carotid artery and intracranial arteries.^{8,9} However, the major measurement for ICAD in previous studies is luminal stenosis which may not be the ideal indicator for disease severity due to the lack of vessel wall information.

Recently, three-dimensional (3D) multicontrast MR vessel wall imaging techniques have been proposed and utilized for comprehensively characterizing intracranial and extracranial carotid artery atherosclerosis simultaneously.^{10,11} We hypothesized that extracranial carotid artery atherosclerosis might be an indicator for assessing the ICAD. The purpose of this study was to investigate the relationship of atherosclerotic disease between intracranial and extracranial carotid arteries by using 3D multicontrast MR vessel wall imaging techniques.

Methods

Patients

Patients who had cerebrovascular symptoms within 2 weeks in the anterior circulation were recruited in this study. All the patients were Asian. The exclusion criteria were as follows: (1) cardiogenic stroke; (2) hemorrhagic stroke; and (3) contraindications to MR imaging. All the subjects underwent MR vessel wall imaging for intracranial and extracranial carotid arteries. The clinical characteristics such as age, gender, body mass index, history of hypertension, diabetes mellitus, smoking, hyperlipidemia, stroke, transient ischemic attack, and coronary heart disease, the levels for cholesterols, and the blood pressure were collected from the clinical record. The study protocol was approved by the institutional review board prior to the initiation of this study and all patients provided written consent forms.

MR imaging

MR imaging was performed on a Philips 3.0T MR scanner (Achieva TX, Philips Healthcare, Best, the Netherlands) with a custom-designed 36-channel neurovascular coil.¹⁰ Joint MR vessel wall imaging for intracranial and extracranial carotid arteries was performed for all the patients. The MR imaging parameters were as follows: 3D MERGE: fast field echo (FFE), repeat time (TR)/echo time (TE) 9.2/4.3 msec, flip angle 6°, field of view (FOV) $4 \times 16 \times 25 \text{ cm}^3$, and spatial resolution $0.8 \times 0.8 \times 0.8 \text{ mm}^3$; T2-VISTA: turbo spin echo, TR/TE 2500/278 msec, flip angle 90°, FOV

$4 \times 16 \times 25 \text{ cm}^3$, and spatial resolution $0.8 \times 0.8 \times 0.8 \text{ mm}^3$; and Simultaneous Non-contrast Angiography and intraPlaque hemorrhage (SNAP): FFE, TR/TE 9.9/4.8 msec, flip angle 11/5°, FOV $4 \times 16 \times 25 \text{ cm}^3$, and spatial resolution $0.8 \times 0.8 \times 0.8 \text{ mm}^3$. Specifically, the intracranial arteries were also imaged with 3D time-of-flight angiography with the following parameters: FFE, TR/TE 25/3.5 msec, FOV $4.5 \times 20 \times 20 \text{ cm}^3$, and spatial resolution $0.7 \times 0.7 \times 1.4 \text{ mm}^3$.

Image interpretation

All MR images were read by four reviewers with >5 years' experience in neurovascular imaging with consensus using MR workstation (Extended MR WorkSpace 2.6.3.4, Best, the Netherlands). Extracranial carotid artery MR images were analyzed by two reviewers blinded to intracranial artery MR images. Another two reviewers interpreted the intracranial artery MR images blinded to extracranial carotid artery MR images. Presence or absence of atherosclerotic plaque at each artery was determined. The atherosclerotic plaque is defined as the eccentric thickening of the vessel wall. The maximum wall thickness (Max WT) and stenosis of each plaque were measured. The degree of arterial luminal stenosis was measured by using the NAS-CET¹² and WASID¹³ criteria for carotid artery and intracranial arteries, respectively. The presence of intraplaque hemorrhage (IPH) in each plaque was identified when hyperintense on SNAP images present (signal intensity ≥ 1.5 times of adjacent muscle or cerebral parenchyma).

Statistical analysis

The continuous variables were presented as mean value and standard deviation and the categorical variables were described as percentage. The plaque burden including Max WT and stenosis and prevalence of IPH in intracranial and extracranial carotid arteries were calculated. Univariate and multivariate logistic regressions were performed to determine the odds ratio (OR) and corresponding 95% confidence interval (CI) of extracranial plaque measurements in discriminating intracranial artery severe disease which is defined as atherosclerotic lesions with $\geq 50\%$ stenosis or IPH. The probability of extracranial carotid artery plaque measurements in predicting intracranial artery severe disease before and after adjusted for confounding factors was calculated using C-statistical analysis. Receiver operating characteristic curve (ROC) was utilized to calculate the area under the curve (AUC) of extracranial carotid artery measurements in discriminating presence of severe intracranial artery atherosclerosis. A $P < 0.05$ was considered as statistically significant. All statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL).

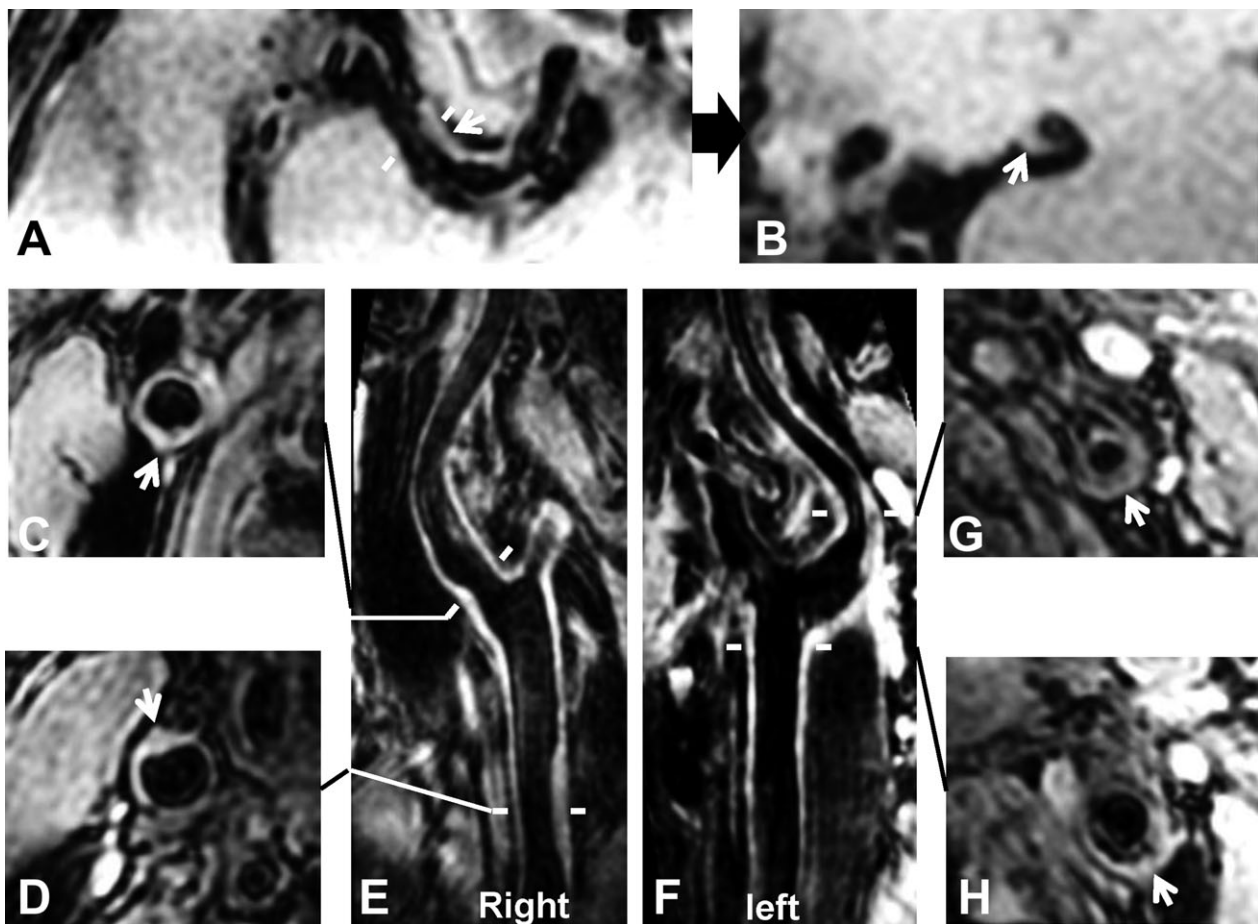


Figure 1. The 3D MERGE images showed an eccentric soft plaque in right middle cerebral artery (A and B, arrows) and multiple atherosclerotic plaques (arrows) in bilateral extracranial carotid arteries (C–E from right carotid arteries; F–H from left carotid arteries) in the same patient.

Results

Of 111 recruited patients, four were excluded from statistical analysis because of poor image quality. Among the remaining 107 patients (mean age, 57.0 ± 11.1 years old) with acceptable image quality, 69 (64.5%) are males, 71 (66.4%) had hypertension, 34 (31.8%) had diabetes, 75 (70.1%) had hyperlipidemia, and 55 (51.4%) had history of smoking. Table 1 summarized the clinical characteristics of all patients and subgroups with extracranial carotid plaque only, intracranial artery plaque only, and co-existing intra- and extracranial plaque.

Prevalence and characteristics of atherosclerotic plaques

Of 107 patients, 29 (27.1%) had only extracranial carotid artery plaques, 8 (7.5%) had only intracranial artery plaques, 60 (56.1%) had plaques in both intracranial and extracranial carotid arteries, and 10 (9.3%) had neither

intracranial nor extracranial carotid plaques. Figure 1 showed an example of co-existing intracranial and extracranial carotid artery plaques in one patient. The prevalence of IPH in intracranial and extracranial carotid artery plaques was 26.5% and 20.2%, respectively. Severe intracranial artery stenosis (stenosis $\geq 50\%$) was found in 14 (13.9%) patients. The quantitative measurements of plaque burden in intracranial and extracranial carotid arteries are detailed in Table 2.

Correlation of atherosclerosis between intracranial and extracranial carotid arteries

Table 3 presents the results on the relationship between plaque characteristics of extracranial carotid arteries and severe stenosis of intracranial arteries. In discriminating intracranial severe stenosis, the OR of Max WT of extracranial carotid arteries was 1.41 (95% CI, 0.94–2.11, $P = 0.095$) and 1.72 (95% CI, 1.04–2.83, $P = 0.034$) before and after adjusting for confounding factors, respectively.

Table 1. Clinical characteristics of study population.

	Mean ± SD or n (%)			
	All subjects (n = 107)	Extracranial carotid plaque only (n = 29)	Intracranial artery plaque only (n = 8)	Co-existing intra- and extracranial plaque (n = 60)
Age, years	57.0 ± 11.1	56.0 ± 12.9	55.0 ± 8.7	59.0 ± 9.1
Gender, male	69 (64.5)	16 (55.2)	6 (75)	40 (66.7)
BMI, kg/m ²	25.3 ± 3.1	26.0 ± 2.7	26.3 ± 2.0	25.0 ± 3.3
Hypertension	71 (66.4)	20 (69.0)	7 (87.5)	40 (66.7)
SBP, mmHg	142.2 ± 24.8	141.2 ± 21.9	143.0 ± 32.8	144.1 ± 25.1
DBP, mmHg	88.0 ± 16.5	85.8 ± 14.6	88.0 ± 21.2	90.3 ± 15.5
Diabetes	34 (31.8)	9 (31.0)	3 (37.5)	20 (33.3)
Smoking	55 (51.4)	14 (48.3)	4 (50)	33 (55)
Hyperlipidemia	75 (70.1)	19 (65.5)	4 (50)	49 (81.7)
Statin use	81 (75.7)	22 (75.9)	7 (87.5)	48 (80)
LDL, mmol/L	2.85 ± 1.13	2.53 ± 0.94	2.32 ± 0.74	3.11 ± 1.26
HDL, mmol/L	1.11 ± 0.35	1.11 ± 0.36	1.01 ± 0.20	1.11 ± 0.38
TC, mmol/L	4.56 ± 1.16	4.32 ± 1.16	4.09 ± 0.86	4.78 ± 1.23
TG, mmol/L	1.61 ± 0.90	1.59 ± 0.87	1.92 ± 1.61	1.58 ± 0.78
History of stroke	62 (57.9)	15 (51.7)	2 (25)	44 (73.3)
History of CHD	15 (14.0)	4 (13.8)	0 (0)	10 (16.7)

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol; TG, total glyceride; CHD, coronary heart disease

Table 2. Characteristics of intracranial and extracranial plaques on magnetic resonance imaging.

	Mean ± SD or n (%)	Range
Intracranial artery		
Presence of plaque	68 (63.6)	
Presence of intraplaque hemorrhage	18 (26.5)	
Maximum wall thickness, mm	2.2 ± 0.8	1.0–3.5
Stenosis, %	33.1 ± 25.3	0–100
Extracranial carotid artery		
Presence of plaque	89 (83.2)	
Presence of intraplaque hemorrhage	18 (20.2)	
Maximum wall thickness, mm	3.8 ± 1.3	1.7–8.0
Stenosis, %	19.0 ± 21.0	0–100

The OR of stenosis of extracranial carotid arteries with increment of 10% was 1.26 (95% CI, 0.99–1.60, *P* = 0.054) and 1.37 (95% CI, 1.03–1.82, *P* = 0.033) before and after adjusting for confounding factors in discriminating intracranial severe stenosis, respectively. No significant correlation can be found between extracranial carotid artery IPH and intracranial artery severe stenosis (*P* > 0.05). Similarly, there were no significant correlations between plaque characteristics of extracranial carotid arteries and intracranial artery IPH (all *P* > 0.05, Table 4).

ROC analysis revealed that, in discriminating intracranial severe stenosis, the AUC of Max WT, stenosis, and presence of IPH of extracranial carotid artery plaques were 0.641 (95% CI, 0.472–0.809), 0.605 (95% CI, 0.427–0.783), and

Table 3. Association between carotid plaque characteristics and intracranial artery stenosis.

	Stenosis ≥50% in intracranial artery					
	Univariate regression			Multivariate regression ¹		
	OR	95% CI	<i>P</i>	OR	95% CI	<i>P</i>
Extracranial carotid plaques						
Max WT, mm	1.41	0.94–2.11	0.095	1.72	1.04–2.83	0.034
Stenosis ²	1.26	0.99–1.60	0.054	1.37	1.03–1.82	0.033
IPH	3.14	0.91–10.75	0.069	3.93	0.81–19.04	0.089

OR, odds ratio; Max WT, maximum wall thickness; IPH, intraplaque hemorrhage.

¹The logistic regression was conducted before and after adjusting for the traditional risk factors, including age, gender, body mass index, history of hypertension, smoking, diabetes, and hyperlipidemia.

²With increment of 10%.

0.603 (95% CI, 0.432–0.775), respectively. After adjusting for confounding factors, the AUC of Max WT, stenosis, and presence of IPH of extracranial carotid artery plaques increased to 0.812 (95% CI, 0.683–0.942), 0.817 (95% CI, 0.701–0.932), and 0.781 (95% CI, 0.649–0.913), respectively.

Discussion

This study investigated the correlation between intracranial and extracranial artery atherosclerotic disease in symptomatic patients by using 3D multicontrast MR vessel wall imaging. We found that the Max WT and stenosis

Table 4. Association between carotid plaque characteristics and intracranial IPH.

	IPH in intracranial artery plaque					
	Univariate regression			Multivariate regression ¹		
	OR	95% CI	P	OR	95% CI	P
Extracranial carotid plaques						
Max WT, mm	1.14	0.78–1.65	0.482	0.97	0.61–1.54	0.903
Stenosis ²	1.10	0.88–1.37	0.428	1.15	0.88–1.50	0.308
IPH	1.89	0.59–6.08	0.290	1.61	0.36–7.17	0.535

IPH, intraplaque hemorrhage; OR, odds ratio; Max WT, maximum wall thickness.

¹The logistic regression was conducted before and after adjusting for the traditional risk factors, including age, gender, BMI, history of hypertension, smoking, diabetes, and hyperlipidemia.

²With increment of 10%.

of extracranial arteries were independently associated with intracranial artery severe stenosis but not with IPH. Our findings indicate the carotid artery quantitative measurements might be effective indicators for severe stenotic disease in intracranial arteries.

In this study, the prevalence of atherosclerotic plaques in extracranial carotid artery was higher than that in intracranial artery. It has been shown that distribution of atherosclerotic disease in intracranial and extracranial carotid arteries has ethnic differences.^{14–17} A Chinese population-based study showed the prevalence of severe atherosclerotic disease (stenosis $\geq 50\%$) in intracranial artery was significantly higher than that in extracranial carotid artery (46.6% vs. 14.0%).¹ The prevalence of severe atherosclerotic disease (stenosis $\geq 50\%$) in American white population in intracranial artery and extracranial carotid artery was 24% and 33%, respectively.¹⁷ However, these atherosclerotic diseases were determined by angiography approaches which may underestimate the disease severity due to the positive remodeling effect. A histological study reported that the common carotid artery was an elastic artery and the internal carotid artery becomes muscular at a varying distance (0.5–2 cm) from the bifurcation.¹⁸ The more elastic component the vessel contains, the greater compensatory remodeling it has.¹⁹ As such, the positive remodeling effect in carotid artery, particularly in the common carotid artery, may be greater than that in intracranial arteries. This may partially explain the lower prevalence of carotid plaques reported by studies using angiography methods. To minimize the underestimation of angiography, investigators used MR vessel wall imaging to evaluate intracranial arteries in American population and found²⁰ that the prevalence of intracranial artery plaques reaches 32.4% in White people with >60 years old.

In this study, the intracranial artery plaques were found to have similar prevalence of IPH compared with extracranial carotid artery plaques. Previous studies showed that the prevalence of IPH (21.6% vs. 84%) of vulnerable plaques was significantly lower in intracranial artery than that in extracranial carotid artery.^{21–23} The incidence of intracranial IPH has only been occasionally reported in previous studies. This may be due to the inaccessibility of angiography-based imaging approaches which do not provide vessel wall information beyond luminal stenosis. The assessments of IPH by MR T1 imaging in intracranial arteries remained uncertain until a histology validation was performed recently.²⁴ The prevalence of IPH in extracranial carotid artery plaques in this study was lower than previous studies.^{3,25,26} This may be due to our dominant recruitment of patients with mild stenosis (stenosis $<50\%$). It has been proven that the prevalence of IPH will increase with severity of carotid artery stenosis.^{3,27}

In our data, Max WT and stenosis of extracranial carotid plaque were associated with intracranial disease severity determined by stenosis. The association of plaque burden between intracranial and extracranial carotid arteries indicates that the burden of atherosclerosis in these two vascular beds may be parallel. Our results are in line with previous studies. The intima-media thickness measured by ultrasound was found to be significantly associated with presence or severity of ICAD.^{28,29} Investigators have found significant correlation of atherosclerotic stenosis between carotid artery and intracranial arteries ($r = 0.616$, $P < 0.001$).⁸ This correlation may be explained by the hypothesis that intracranial and extracranial carotid arteries may share with the similar risk factors for progression of atherosclerosis, such as hypertension, hyperlipidemia, diabetes, etc.³⁰

We did not find significant correlation in IPH between intracranial and extracranial carotid arteries in this study. Previous studies have shown that the intensity of neovasculature within plaques^{31,32} and the blood pressure³³ were associated with carotid IPH. Beyond these risk factors, investigators demonstrated that local mechanical conditions may play important role in the occurrence of carotid IPH.^{34,35} In contrast, the normal vessel wall of intracranial arteries is lacking of vasa vasorum and the local hemodynamics are complex which may be different from the extracranial carotid arteries.

This study has several limitations. First, the spatial resolution of vessel wall imaging for both intracranial and extracranial arteries was 0.8 mm^3 which is limited for characterization of intracranial plaque components. Recently, the spatial resolution of emerging intracranial MR vessel wall imaging techniques at 3.0 Tesla reaches 0.5 mm^3 .^{20,36,37} Second, gadolinium contrast agent was

not applied to MR vessel wall imaging in this study. This limits the detection and quantification of the lipid-rich necrotic core (LRNC) both in intracranial and extracranial carotid artery plaques. Third, the proportion of subjects with severe cerebral artery stenosis is low in our study population. Future studies recruiting subjects with more broad range of disease severity are warranted.

In conclusion, extracranial carotid artery plaque burden measurements, particularly the Max WT and stenosis, are significantly associated with intracranial artery severe stenosis. Our findings suggest that extracranial carotid plaque burden might be an independent indicator for severity of intracranial artery atherosclerosis.

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Conflict of Interest

All the authors have no conflicts of interest to disclose.

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