Prevalence of Compositional Features in Subclinical Carotid Atherosclerosis Determined by High-Resolution Magnetic Resonance Imaging in Chinese Patients With Coronary Artery Disease

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Background and Purpose—Previous studies have reported that carotid atherosclerosis frequently can be seen in coronary artery disease (CAD) patients. This study sought to determine the prevalence of compositional features in subclinical carotid atherosclerosis by MRI in CAD patients.

Methods—Ninety-six subjects with suspected CAD but free of neurological symptoms underwent coronary CT angiography and carotid MRI including 3-dimensional time-of-flight, T1-weighted, T2-weighted, and proton density-weighted sequences at 3 T within a 2-week interval. The coronary artery calcium score (CACS) and degree of stenosis were measured. Areas for carotid lumen, wall, total vessel, and percent wall volume (wall volume/total vessel volume) were measured. The prevalence of carotid calcification, lipid-rich necrotic core, intraplaque hemorrhage, and surface disruption in coronary stenosis and CACS categories were determined.

Results—Carotid percent wall volume was correlated with CACS (P=0.001). Both coronary stenosis and CACS were significantly associated with presence of carotid calcification (OR=5.79 for 1%–49% vs 0% stenosis; OR=10.23 for >50% vs 0% stenosis; OR=10.65 for CACS 1–399 vs CACS 0; and OR=20.28 for CACS 400 vs CACS 0; all P<0.05) and lipid-rich necrotic core (OR=10.29 for 1%–49% vs 0% stenosis; OR=4.66 for >50% vs 0% stenosis; OR=8.23 for CACS 1–399 vs CACS 0; and OR=11.87 for CACS 400 vs CACS 0; all P<0.05). High prevalence of lipid-rich necrotic core was found in low-grade coronary stenosis (75.6% in 1%–49% stenosis) and CACS (73.5% in CACS 1–399).

Conclusions—Carotid plaque burden and compositional features are significantly associated with CAD severity. The finding of high prevalence of lipid-rich necrotic core in patients with low-grade coronary stenosis and CACS suggests the need for early monitoring of carotid atherosclerosis in CAD patients. (Stroke. 2010;41:1157-1162.)

Key Words: carotid artery ■ coronary artery disease ■ magnetic resonance imaging ■ plaque composition ■ subclinical atherosclerosis

Atherosclerosis is a systemic, chronic, progressive disease frequently involving multiple vascular territories in the same patient with a long asymptomatic phase.1 It has been shown that the progression of subclinical atherosclerosis can lead to cardiovascular and neurovascular events. Patients with coronary atherosclerosis are at risk for myocardial infarction.2 Individuals with carotid atherosclerotic disease tend to have transient ischemic attack or stroke.3 Therefore, identification of subclinical coronary and carotid atherosclerotic lesions is clinically significant to reduce risk for myocardial infarction or stroke.

A number of studies demonstrated that carotid atherosclerosis is highly associated with the presence or severity of coronary artery disease (CAD).4,5 However, for identification of subclinical carotid atherosclerosis, the majority of studies were conducted using intima-media thickness measurements by ultrasound, which limits information on plaque compositions. MRI has been validated by histology to accurately characterize atherosclerotic tissue compositions.6,7 The size of lipid-rich necrotic core (LRNC) and presence of intraplaque hemorrhage (IPH) and surface disruption were found to be significantly associated with transient ischemic
attack or stroke. Nevertheless, the prevalence of compositional features in carotid subclinical atherosclerosis determined by MRI in CAD patients remains unknown. In this study, we sought to determine the prevalence of compositional features in subclinical carotid atherosclerosis, such as calcification, LRNC, IPH, and surface disruption, determined by MRI in CAD patients.

Materials and Methods

Study Population
The institutional review board approved the protocol before study initiation and informed consent was obtained from all participants. Subjects with suspected CAD attributable to presentation of either acute or effort chest pain were referred for coronary CTA and were recruited in this study. The exclusion criteria are as follows: (1) severe respiratory or cardiac failure; (2) allergy to iodine-containing contrast material; (3) history of compromised renal function (glomerular filtration rate <40 mL/min/1.73 m²); (4) history of transient ischemic attack and stroke; (5) pregnancy; and (6) contraindication to MRI. All subjects were informed of the risk associated with the radiation exposure before CT examination. MRI for carotid arteries was performed within 2 weeks after coronary CTA examination.

Coronary CT Imaging and Image Interpretation
All subjects underwent coronary CT imaging on a dual-source CT scanner (Somatom Definition; Siemens Medical Solutions) using low-dose coronary artery calcium score and clinical CTA protocols (Supplemental Methods, available online at http://stroke.ahajournals.org). Coronary calcifications were quantified with the Agatston algorithm (350 HU threshold). According to the well-established association between CACS and a higher frequency of myocardial infarction, the CACS was divided into 3 categories: CACS=0, CACS=1 to 399, and CACS >400. The coronary artery was segmented according to a modified American Heart Association 15-segment model. Luminal stenosis is visually estimated using the proximal normal arterial segment as a reference for each segment and graded into the following categories: 0%, normal tapering luminal diameter from proximal to distal segments of artery without detectable lesions; 1% to 49%, luminal reduction <50% attributable to detectable lesions; and >50%, luminal reduction >50% attributable to detectable lesions. The most severe degree of stenosis across all coronary segments was evaluated for each subject.

Carotid MRI Protocol
All the subjects underwent bilateral carotid MRI on a 3.0-T MR scanner (Signa Excite; GE Medical Systems) using a multisequence standardized protocol with the following parameters: quadruple inversion pulse T1-weighted sequence with repetition time (TR) 500 ms and echo time (TE) 7.5 ms; proton density-weighted sequence with TR 3000 ms and TE 10.8 ms; T2-weighted sequence with TR 3000 ms and TE 61.2 ms; and time of flight sequence with TR 29 ms, TE 2.1 ms, and flip angle 20°. All the MR axial images were acquired with a slice thickness of 2 mm, a field of view 139 mm, and a matrix size of 256×256. The longitudinal coverage of black blood (T1-weighted, proton density-weighted, and T2-weighted) and bright blood (time of flight) sequences were 32 mm (16 slices) and 44 mm (22 slices), respectively. Fat saturation was applied to the acquisition of black blood sequences to enhance the contrast between the carotid vessel wall and surrounding tissues.

Table 1. Clinical Characteristics Categorized by Coronary Stenosis and CACS

<table>
<thead>
<tr>
<th>Coronary Stenosis</th>
<th>CACS</th>
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<tbody>
<tr>
<td>0% (n=17)</td>
<td>1%–49% (n=45)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>53.7±8.3</td>
</tr>
<tr>
<td>Body mass index</td>
<td>26.8±2.3</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>188.7±35.3</td>
</tr>
<tr>
<td>High-density lipoprotein, mg/dL</td>
<td>51.8±25.7</td>
</tr>
<tr>
<td>Low-density lipoprotein, mg/dL</td>
<td>94.8±32.2</td>
</tr>
<tr>
<td>Male</td>
<td>58.8%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>41.2%</td>
</tr>
<tr>
<td>Smoking</td>
<td>29.4%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5.9%</td>
</tr>
</tbody>
</table>

Carotid MRI Interpretation
The MR images of bilateral carotid arteries were reviewed by 2 trained radiologists with consensus opinion using a custom-designed software (CASCADE). The luminal and outer wall boundaries were traced manually. The lumen area (LA), wall area (WA), and total vessel area (total vessel area=LA+WA) were measured for each location. For each subject, the mean value of each morphological measurement for bilateral carotid arteries was calculated. The percent wall volume (wall volume/tot vessel volume) was also calculated for each subject. In this study, we use percent wall volume to measure carotid plaque burden because it fully exploits the 3-dimensional data acquisition inherent to carotid MRI and is the most reproducible measure of plaque burden across all the morphological measurements by MRI. Presence/absence of carotid compositional features, including calcification, LRNC, IPH, or surface disruption for each subject were identified using published criteria: (1) LRNC without hemorrhage shows hypointensity on T2-weighted, shows isointensity or slight hyperintensity on T1-weighted images, and shows isointensity on proton density-weighted and time of flight images; (2) IPH shows hyperintensity on time of flight and T1-weighted images and hyperintensity/hypointensity (depending on the stage of IPH) on T2-weighted and proton density-weighted images; (3) CA shows hypointensity on all contrast weightings; and (4) surface disruption is defined as fibrous cap rupture that shows discontinuous fibrous cap on T2-weighted images with juxtaluminal hemorrhage on time-of-flight images or ulcer formation with an irregular luminal surface on all contrast weightings. Good to excellent intrarater and inter-rater reproducibility have been obtained for all tissue components (Intraclass correlation coefficient, 0.73–0.95) using CASCADE and published criteria.

Statistical Analysis
Descriptive statistics were conducted for patients’ demographic and clinical characteristics. Continuous variables were presented with mean±standard deviation (SD), and discrete variables were presented by count and percentage. Correlation coefficients were calculated to determine the correlation of carotid quantitative measurements with coronary stenosis (Spearman correlation) and CACS as continuous variable (Pearson correlation). The multiple linear regression model was used to assess the association between continuous dependent variables in carotid artery and coronary stenosis and
CACS categories adjusting for confounding factors (eg, age, gender). The logistic regression model was utilized to evaluate the association between binary dependent variables in carotid artery and coronary stenosis and CACS categories adjusting for confounding factors. The overall significance of the associations was evaluated with partial likelihood ratio test. P<0.05 was considered statistically significant and presented probability values were unadjusted for multiple comparisons. All analyses were performed using SPSS for Windows (version 12.0; SPSS).

Results

Of the total recruited 99 subjects, 3 subjects were excluded from this study because of poor image quality of carotid MR images. Of the remaining 96 subjects, the mean age was 57.1±9.4 (range, 45–84) years and 77 (80.2%) were male. The clinical characteristics in different coronary stenosis and CACS categories were detailed in Table 1. The subjects with coronary stenosis >50% had markedly larger WA, total vessel area, and percent wall volume than those with 0% and 1% to 49% coronary stenosis. On average, the subjects with coronary stenosis >50% had similar size LA as the subjects with coronary stenosis 1% to 49%, but both groups had slightly larger LA than 0% coronary stenosis. Carotid calcification and LRNC were found to be present across all categories of coronary stenosis (Figure 1). The subjects with >50% coronary stenosis had the highest prevalence of carotid calcification among the 3 categories of coronary stenosis, followed by those with 1% to 49% coronary stenosis and those with 0% coronary stenosis. Interestingly, subjects with 1% to 49% coronary stenosis had highest prevalence of carotid LRNC among 3 coronary stenosis categories, followed by subjects with >50% coronary stenosis and 0% coronary stenosis. Carotid IPH or surface disruption was not present in coronary 0% stenosis category. The subjects with 1% to 49% coronary stenosis and >50% coronary stenosis had similar prevalence of IPH or surface disruption (11.1% vs 8.8%).

The mean CACS for all 96 subjects was 227.8±500.6 (range, 0–3992.7). Table 2 shows that subjects with CACS of 0 and CACS of 1 to 399 had similar size LA, and the LA in both categories was smaller than CACS >400. The subjects with CACS >400 showed the largest WA, total vessel area, and percent wall volume among 3 CACS categories, followed by those with CACS of 1 to 399 and CACS of 0 (Table 2). Calcification and LRNC in carotid artery were present through all CACS categories (Figure 2). Among 3 CACS categories, CACS >400 showed the highest prevalence of carotid calcification and LRNC. Both CACS >400 and CACS of 1 to 399 had markedly larger prevalence of carotid calcification and LRNC as compared to CACS of 0 category (Table 2). There was no carotid IPH or surface disruption in subjects with CACS of 0. Subjects with CACS of 1 to 399 and CACS >400 had very similar prevalence of IPH or surface disruption (12.2% vs 11.8%).

There was statistically significant correlation between coronary artery stenosis and carotid WA \((r=0.242; P=0.018)\) and percent wall volume \((r=0.260; P=0.011)\) during Spearman correlation analysis. After adjusted for age, gender, body mass index, history of diabetes, and smoking status, no significant correlation was found between coronary stenosis

Table 2. Carotid Plaque Burden and Compositional Features Categorized by Coronary Stenosis and CACS

<table>
<thead>
<tr>
<th>Carotid Features</th>
<th>0% (n=17)</th>
<th>1%–49% (n=45)</th>
<th>&gt;50% (n=34)</th>
<th>0 (n=30)</th>
<th>1–399 (n=49)</th>
<th>&gt;400 (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumen area, mm²</td>
<td>53.2±11.8</td>
<td>53.8±15.2</td>
<td>53.7±16.4</td>
<td>53.2±9.6</td>
<td>52.0±15.4</td>
<td>59.4±20.2</td>
</tr>
<tr>
<td>Wall area, mm²</td>
<td>23.2±3.6</td>
<td>26.1±7.6</td>
<td>31.0±17.5</td>
<td>22.6±3.1</td>
<td>27.0±8.6</td>
<td>36.6±22.0</td>
</tr>
<tr>
<td>Total vessel area, mm²</td>
<td>76.4±13.2</td>
<td>80.0±19.8</td>
<td>84.6±30.2</td>
<td>75.8±11.0</td>
<td>79.0±20.7</td>
<td>96.0±37.0</td>
</tr>
<tr>
<td>Percent wall volume, %</td>
<td>30.8±4.6</td>
<td>33.0±6.1</td>
<td>35.8±7.6</td>
<td>30±3.7</td>
<td>34.5±6.3</td>
<td>37.2±8.8</td>
</tr>
<tr>
<td>Calcification</td>
<td>11.8%</td>
<td>42.2%</td>
<td>55.9%</td>
<td>10%</td>
<td>53.1%</td>
<td>64.7%</td>
</tr>
<tr>
<td>LRNC</td>
<td>17.6%</td>
<td>75.6%</td>
<td>61.8%</td>
<td>26.7%</td>
<td>73.5%</td>
<td>82.4%</td>
</tr>
<tr>
<td>IPH or surface disruption</td>
<td>0%</td>
<td>11.1%</td>
<td>8.8%</td>
<td>0%</td>
<td>12.2%</td>
<td>11.8%</td>
</tr>
</tbody>
</table>
and carotid quantitative measurements during multivariate linear regression analysis (Table 3). In addition, coronary stenosis was found to be significantly associated with presence of carotid calcification and LRNC (Table 3).

Pearson correlation analysis revealed that there was statistically significant correlation between CACS as a continuous variable and carotid LA ($r=0.244$; $P=0.017$), WA ($r=0.585$; $P<0.001$), total vessel area ($r=0.461$; $P<0.001$), and percent wall volume ($r=0.394$; $P<0.001$). After adjusted for the confounders, the CACS (categorical variable) remained significant correlation with WA, total vessel area, and percent wall volume during multivariate linear regression analysis (Table 3). CACS was significantly associated with presence of carotid calcification and LRNC after adjusting for the confounders (Table 3).

## Discussion

This cross-sectional study is one of the first to investigate the prevalence of compositional features in subclinical carotid atherosclerosis determined by high-resolution MRI in CAD patients. We found that carotid plaque burden and compositional features, particularly LRNC, are significantly associated with CAD severity, as measured by degree of stenosis and CACS. A high prevalence of LRNC can be seen even in subjects with low-grade coronary stenosis (75.6% in 1%–49% stenosis) and CACS (73.5% in CACS of 1–399). Our results indicate that carotid plaque burden and the probability of having compositional features, particularly for LRNC, increase with the CAD severity. Our findings of association between carotid atherosclerosis and CAD severity and the high prevalence of LRNC in patients with low-grade coronary stenosis and CACS suggest that early monitoring of subclinical carotid atherosclerosis may be needed for CAD patients.

A number of previous studies reported that carotid plaque burden is associated with CAD. Consistent with existing literatures, in this study a significant correlation was found between carotid plaque burden, as measured by percent wall volume and the degree of coronary stenosis and CACS. A recent MR study demonstrated that subjects with $>50\%$ coronary stenosis by angiography show larger carotid plaque burdens than those with normal coronary angiograms. In this study, we included subjects with a full range of coronary stenosis and found a significant increasing trend of plaque burden with degree of coronary stenosis. These findings further compel the evidence that carotid and coronary arteries are common targets of atherosclerotic diseases.

Our study showed a greater prevalence of LRNC (61.8%) for subjects with coronary stenosis $\geq 50\%$, as compared to a prevalence of LRNC (29.9%) in a case-control study. The greater prevalence probably can be attributed to 3 factors. First, our study has primarily male participants (80.2%). It has been shown that males have significantly greater prevalence of carotid LRNC (46.9% vs 12.5%) than females with coronary stenosis $\geq 50\%$. Second, all our participants are of Chinese ethnicity. A previous study demonstrated that Chinese participants have significantly larger LRNC as compared to an American population. Finally, our participants have lower percentage of statin use (24%) as compared to 81.4% in a study by Underhill et al. Statins have been established to be associated with a percentage reduction in carotid LRNC. This potential difference of prevalence of carotid LRNC in CAD patients among multiple ethnicities needs to be further investigated using larger study sample.

A substantial number of CAD patients had carotid IPH or surface disruption although they were neurologically asymptomatic in this study. Because IPH is associated with neurovascular events, identification of carotid IPH is clinically important. Patients with carotid surface disruption but without neurological symptoms in this study may be explained by the evidence of prevalence of silent cerebral infarcts in asymptomatic individuals. However, these patients are at risk for future symptomatic stroke. Therefore, identification of carotid IPH and surface disruption may potentially reduce the risk of developing transient ischemic attack or stroke in CAD patients via appropriate therapeutic intervention.

The role of calcification in the vulnerability of atherosclerosis is a subject of debate. Prabhakaran et al demonstrated that presence of carotid calcification is an independent predictor of vascular events. Other investigators established that carotid calcification is a structural marker of plaque stability. Our finding of correlation between coronary and
CACS is in line with a study by Odink et al. The previous inconsistent statements of the correlation between calcification and plaque vulnerability and cerebrovascular events may be partially explained by the evidence that calcification can be present from intermediate to advanced lesions (American Heart Association types IV–VIII). Recently, Li et al demonstrated that calcification at the thin fibrous cap may result in high-stress concentrations that are associated with plaque rupture. As such, for assessing atherosclerotic plaque vulnerability, considering calcification together with the other compositional features and evaluating calcification location are suggested.

In this study, we found that carotid plaque burden and the probability of having compositional features, particularly LRNC, increase with the degree of coronary stenosis and CACS increasing. In addition, we found a high prevalence of LRNC even in low-grade stenosis (75.6% in 1%–49% stenosis) and CACS (73.5% in CACS of 1–399). Previous studies have shown that the size of LRNC is highly associated with future neurological events. Our results suggest that early monitoring of carotid atherosclerosis (burden or composition) in CAD patients may be needed clinically.

Although MRI has been shown to be able to measure carotid plaque burden and characterize compositional features, MRI may not be a suitable routine screening modality because of its high cost and limited availability. Alternatively, ultrasound is largely used for screening and monitoring carotid atherosclerosis because of its low cost and wide availability. For example, carotid intima-media thickness is strongly correlated with vessel wall thickness as measured by ultrasound because of its high cost and limited availability. Alternatively, for assessing atherosclerotic plaque vulnerability, considering calcification together with the other compositional features and evaluating calcification location are suggested.

In conclusion, carotid plaque burden and compositional features, particularly LRNC, are significantly associated with the severity of CAD, as measured by CACS and coronary stenosis. The high prevalence of LRNC in patients with low-grade coronary stenosis and CACS suggests that early monitoring of carotid atherosclerotic disease for CAD patients may be needed.

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Disclosures

None.

References


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