Carotid Plaque Composition Differs Between Ethno-Racial Groups

An MRI Pilot Study Comparing Mainland Chinese and American Caucasian Patients


Objective—Ethnicity-based research may identify new clues to the pathogenesis of atherosclerotic disease. Therefore, we sought to determine whether carotid lesions differ between 20 Chinese and 20 Caucasian Americans by MRI.

Methods and Results—Inclusion criteria were >50% stenosis as measured by duplex ultrasound and recent symptoms attributed to carotid artery disease. The patients were imaged in 2 centers (Beijing, China and Seattle, Wash) using a standardized protocol. Both carotid arteries were reviewed quantitatively (lumen, wall, outer wall, tissue components) and morphologically (lesion types, fibrous cap status). Significant differences between the Chinese and Americans were found for the mean size of the lipid/necrotic core (13.6 versus 7.8 mm²; \(P = 0.002\)), percentage of slices with calcified type VII lesions (1.6 versus 12.4%; \(P = 0.03\)), and percentage of slices with early type III lesions (19.3 versus 9.3%; \(P = 0.02\)). Furthermore, the mean outer wall area in the common carotid artery was larger in the Chinese population (\(P = 0.007\)).

Conclusions—This pilot study suggests that composition and morphology of atherosclerotic lesions in symptomatic carotid disease differ between ethno-racial groups. Quantitative MRI-based review of carotid atherosclerosis comparing plaque morphology and composition between ethno-racial groups is feasible, and future MRI studies may improve our understanding of the pathophysiology of this disease. (*Arterioscler Thromb Vasc Biol.* 2005;25:611-616.)

Key Words: atherosclerosis ■ carotid arteries ■ epidemiology ■ MRI

Ethnicity-based research can identify new clues to the pathogenesis of a disease because the populations under study are heterogeneous in genetic and lifestyle characteristics.

Phenotypic differences in atherosclerosis imaging are known to exist between races, although for many modalities, the extent and implications of these differences are yet to be fully defined. This has been most clearly demonstrated in coronary computed tomography (CT) imaging. After an adjustment for cardiovascular risk factors, blacks have less prevalent and less severe coronary calcium¹ but a proportionately greater number of coronary events than do whites.² Although the biologic foundation for this finding is unclear, it indicates the need for ethnic-specific data. In a carotid intima media thickness (IMT) study by Anand et al³ with 985 patients of Chinese, European, or South Asian origin, the authors concluded that ethnicity is independently predictive of cardiovascular disease. Although carotid IMT was thickest in Europeans, thinnest in Chinese, and intermediate in South Asians, the prevalence of cardiovascular disease was highest among South Asians, intermediate in Europeans, and lowest in Chinese. Although ethnicity seems to be an independent risk factor for atherosclerosis, differences in plaque composition and plaque morphology across distinctive ethno-racial groups have not been systematically studied.

Recent human studies showed that MRI can characterize the composition of human carotid atherosclerotic plaque, such as fibrous tissue, lipid-rich/necrotic core (LR-NC), calcium, hemorrhage, and thrombus.⁴⁻⁷ It has also been shown that MRI is able to provide quantitative information of plaque components ex vivo⁸ and in vivo⁹ with high reproducibility in individual¹⁰ as well as in multiple institutions.¹¹ Furthermore, MRI is able to accurately and reproducibly determine lesion types¹²,¹³ and the status of the fibrous cap.¹⁴,¹⁵ Among other applications, these high-resolution MRI techniques hold great promise for in vivo studies of carotid plaque biology. In this cross-sectional study, by using MRI, we sought to determine whether mainland Chinese...
patients with symptomatic carotid disease would have carotid plaque characteristics different from those of a comparable group of Caucasian Americans.

Materials and Methods

Study Population
Between April 1998 and February 2003, 40 patients with neurological symptoms (recent transient ischemic attack, stroke, or amaurosis fugax) attributable to carotid artery disease and with >50% stenosis as measured by duplex ultrasound were recruited for the study after informed consent was obtained. All patients underwent a duplex scan of the carotid arteries. The percent stenosis was calculated depending on the peak systolic velocity. The time of the most recent symptoms before the MRI scan was documented. Patients were considered symptomatic if they had a history of transient ischemic attack, stroke, or amaurosis fugax appropriate to the distribution of the index carotid artery within 36 months before carotid endarterectomy. Patients’ medical records were reviewed and risk factors were recorded. These factors included age, sex, hypertension, diabetes mellitus, coronary artery disease, smoking status, and serum total cholesterol. Chinese patients (n=20; mainland Chinese) were scanned at the People Liberation Army General Hospital in Beijing, China, and American patients (n=20; white Caucasian) were scanned at the University of Washington Medical Center in Seattle. Institutional review boards of each facility approved the consent forms and study protocols. All patients were scanned as part of National Institutes of Health (NIH)-funded research grants. Therefore, the number of patients that are scanned per year is relatively small. The strict inclusion criteria for this study limited accrual to a relatively low rate.

MRI Scanners
Patients were imaged using identical 1.5T MRI scanners (Signa Horizon EchoSpeed; General Electric (GE) Healthcare) and phased-array carotid coils (Pathway MRI Inc). Both MRI scanners are maintained by GE service engineers on a regular basis (every 2 to 4 weeks) to ensure that the scanners perform according to GE standard. The operator who performed the MRI scans in China was trained in Seattle, Wash. All technical equipment, including hardware and software (and the imaging protocol), remained unchanged during the 5-year course of the study. Both participating institutions have 1 MRI scanner (GE Signa; 1.5T), which is dedicated to carotid plaque imaging for several hours per week.

MRI Protocol
Four different contrast-weighted images (T1-weighted [T1W], proton density–weighted [PDW], T2W, and time-of-flight [TOF]) of the right and left carotid arteries were obtained using a previously published standardized protocol. All images were obtained with field-of-view of 13 cm, matrix size of 256, slice thickness of 2 mm, and 2 signal averages. A 0-filled Fourier transform was used to reduce pixel size (to 0.25×0.25 mm²) and minimize partial-volume artifacts.

Image Review
Both carotid arteries were reviewed and an image-quality rating (5-point scale: 1 worst; 5 best) for each imaging location was assigned by a radiologist (T.S.) before the review. Imaging locations with an image quality <3 were excluded. For each imaging location, there were 4 images available to be reviewed (TOF, T1, PD, and T2). The mean coverage was 2.1 cm. All MR images were examined by a radiologist (T.S.) blinded to the clinical information and country by removing the patient identifiers from the MR images. Carotid lesions of 10 randomly selected patients were re-evaluated 12 months after the initial review by 2 reviewers (T.S. and N.T.).

Plaque Composition/Quantitative Measurements
Area measurements of the lumen, outer wall, LR-NC, calcium, loose fibrous matrix, and hemorrhage were obtained using QVAS, a custom-designed image analysis tool. The outer wall boundary included lumen, intima, media, and adventitia. Wall area was calculated as the difference between outer wall boundary and lumen area. The LR-NC and hemorrhage were identified using previously established criteria. Calcium is characterized by defined areas with a hypointense signal on all 4 weightings. Loose fibrous matrix is very bright on T2 and PD, isointense to hypointense on T1, and isointense on TOF. All signal intensities are relative to the adjacent sternocleidomastoid muscle.

Plaque Morphology

Lesion Type
Lesion type was determined according to a modified American Heart Association (AHA) classification scheme.

Luminal Surface Condition
The status of the fibrous cap was determined using previously published criteria and labeled as thick, thin, or ruptured. A total of 16% of the locations of the American patients and 9% of the locations of the Chinese patients were excluded from the analysis of the fibrous cap because the image quality on TOF was <3. Locations with luminal calcification in conjunction with juxtaluminal hemorrhage/thrombus were reported. Luminal calcium appears as a hypointense signal on all 4 weightings without clear distinction from the lumen on the black blood images but clearly distinguishable from the bright lumen in the TOF images. Hemorrhage/thrombus was considered juxtaluminal if the region of interest was adjacent to the lumen and the dark juxtaluminal band was absent on TOF images.

Data Analysis
For statistical comparison of the Chinese and American patients, the Mann–Whitney test with correction for ties was used for variables describing frequencies of plaque features, which had skewed distribution. For continuous variables, the Student unpaired t test with equal or unequal variances (as appropriate) was used. To compare clinical demographics between both groups, Fisher’s exact test was used for categorical variables, and the unpaired t test was used for continuous variables. Analyses were performed in SPSS for Windows (version 10) or in Stata (version 8). Only locations/cross-sections with a significant lesion were considered for statistical comparison, and others were excluded from the calculation of areas or frequencies. Categorical variables are described using frequencies, whereas continuous variables are reported as mean (±SD) values per location. The sample mean of the values for continuous variables was calculated per patient (averaging the values of right and left carotid artery across slices) and used to compare the Chinese and American population. For categorical variables, the percentage occurrence of each category across all sections of a patient was calculated and compared between groups. Multiple linear regression analysis was used to accommodate the differences in risk factors. Differences were considered significant at the P<0.05 level. To determine reproducibility measurements, we calculated a modified coefficient of variation as the square root of the mean within-patient variance of a repeated measurement divided by the mean of all observations and multiplied it by 100%. The Intraclass Correlation Coefficient was calculated to measure the level of agreement between 2 measurements repeated within patients compared with the variation in the measurement across patients. Cohen’s kappa (κ) was computed to quantify the intrarater agreement for the presence/absence of plaque components.

Results

Study Population and Risk Factors
In the American group, there were 4 females, and in the Chinese group, there were 2 females. In the American group,
3 patients underwent a previous carotid endarterectomy contralateral to the side of the current symptoms. In these 3 patients, only the side ipsilateral to the symptoms, the so-called index side, was considered for the review. In the Chinese group, 2 exams from the nonindex side (contralateral to the symptoms) were excluded because of insufficient image quality. In all other patients, both carotid arteries were reviewed. No significant differences in the risk factor profile were found (Table 1), although more American patients were on lipid-lowering therapy (45% versus 15%), the Americans were slightly older (71 versus 66 years), and the Chinese patients had diabetes more frequently (15% versus 0%).

<table>
<thead>
<tr>
<th>TABLE 1. Study Population and Risk Factors</th>
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<tbody>
<tr>
<td>Chinese Patients, Mean ± SD or %</td>
</tr>
<tr>
<td>Mean age, years</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>18 male, 2 female</td>
</tr>
<tr>
<td>Elevated cholesterol</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
</tr>
<tr>
<td>Smoker</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Angina</td>
</tr>
<tr>
<td>Previous CEA</td>
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<tr>
<td>Total cholesterol, mg/dL</td>
</tr>
<tr>
<td>Height, m</td>
</tr>
<tr>
<td>Weight, kg</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
</tr>
<tr>
<td>Months between onset of symptoms and MRI</td>
</tr>
</tbody>
</table>

*Unpaired t test; †Fisher exact test.
CFA indicates carotid endarterectomy.

Each duplex category was not significantly different between Chinese and American patients, although American patients, on average, had more stenosis (Table 2).

**Phantom**

In addition to the routine quality control maintenance of the 2 scanners by GE service engineers, identical phantoms (model 2131027-2, DQA Phantom; GE Healthcare) were scanned in Beijing, China, and Seattle, Wash, using the same protocol used for the carotid MRI scan. Area measurements were comparable for the phantom scanned in China and the phantom scanned in the United States (mean area of 6 adjacent slices 531 versus 528 mm²), with extremely small coefficients of variations of 0.5% for TOF images and 0.2%, 0.9%, and 0.3% for T1W, PDW, and T2W images.

**Image Quality**

A total of 38 arteries of Chinese patients (362 locations) with an average image quality of 3.9 and 37 arteries of American patients (371 locations) with an average image quality of 3.6 were reviewed.

**Lumen and Wall Area**

The minimal lumen area was comparable between Chinese and American patients (10.0 versus 8.9 mm²; P=0.8), but the Chinese tended to have a larger wall area (51.6 versus 45.4 mm²; P=0.3) and a larger outer wall boundary (86.8 versus 74.5 mm²; P=0.2; Table 3). Separate analysis of internal carotid artery (ICA) and common carotid artery (CCA) showed larger lumen areas (52.5 versus 37.5; P=0.001) and larger outer wall areas (115.0 versus 89.3 mm³; P=0.007) in the CCA of the Chinese population, indicating more outward remodeling.

**Plaque Composition**

The size of the LR-NC was significantly larger in the Chinese population (13.6 versus 7.8 mm²; P=0.002; Figure 1). Separate analysis of CCA and ICA revealed the same trend, with larger LR-NCs in the Chinese population (CCA 15.4 versus 9.2 mm²; P=0.006; ICA 11.2 versus 6.2 mm²; P=0.002). LR-NC as a percentage of the vessel wall was 25.2% in the Chinese population versus 17.7% in the Caucasian patients (P=0.002). Nine of the Caucasian patients but only 3 patients of the Chinese population were on lipid-lowering drugs. To accommodate for the different percentage of patients on lipid-lowering medicine, we performed a multiple linear regression analysis, and the differences between the 2 populations remained highly significant after adjustment for risk factors, such as lipid-lowering therapy or hypercholesterolemia. No other significant differences in plaque composition (Table 3) were found, although there was a trend toward less calcium (1.2 versus 2.7 mm²; P=0.5) and more loose matrix (2.1 versus 1.0 mm²; P=0.1) in the Chinese population.

**Lesion Type Distribution**

The Caucasian population had significantly more calcified type VII lesions (12.4 versus 1.6%; P=0.03; Figure 2), whereas the Chinese population had significantly more early type III lesions (19.3 versus 9.9%; P=0.02; Table 4). The
percentages of slices with complicated type VI lesions (52.9 versus 50%; \( P < 0.7 \)) and type IV/V lesions (26.4 versus 28.2%; \( P < 1.0 \)) were comparable between groups.

**Surface Conditions**

No significant differences in the surface conditions (Table 4) were found, although the Chinese tended to have more locations with a thick cap (30.9 versus 20.2%; \( P < 0.2 \)), and the Caucasians had more locations with luminal calcification in conjunction with juxtaluminal hemorrhage/thrombus (11.1 versus 3.1%; \( P < 0.07 \)). Ruptured caps were found in 32% of the locations in the Caucasian population and in 25% of the locations of the Chinese population (\( P < 0.3 \)).

**Intrareader and Inter-Reader Reproducibility**

Ten randomly selected patients were re-evaluated 12 months after the initial review by 2 reviewers. The intrareader agreement for the absence/presence of tissue components was strong for LR-NC (\( \kappa = 0.77 \)) and calcium (\( \kappa = 0.68 \)) and moderate to strong for loose fibrous matrix (\( \kappa = 0.64 \)) and hemorrhage (\( \kappa = 0.53 \)). Intraclass correlation coefficients for the intrareader reproducibility using mean areas were high for LR-NC (\( r = 0.93 \)), calcium (\( r = 0.91 \)), hemorrhage (\( r = 0.81 \)), and loose fibrous matrix (\( r = 0.71 \)). Intrareader reproducibility for the modified AHA lesion type was good, with a \( \kappa \)-value of 0.68.

The inter-reader agreement for the absence/presence of tissue components was strong for LR-NCs (\( \kappa = 0.71 \)) and calcium (\( \kappa = 0.62 \)) and moderate for loose fibrous matrix (\( \kappa = 0.38 \)) and hemorrhage (\( \kappa = 0.47 \)). Intraclass correlation coefficients for the intrareader reproducibility using mean areas were high for LR-NC (\( r = 0.93 \)) and calcium (\( r = 0.91 \)), hemorrhage (\( r = 0.81 \)), and loose fibrous matrix (\( r = 0.71 \)). Intrareader reproducibility for the modified AHA lesion type was good, with a \( \kappa \)-value of 0.55.

**Discussion**

To our knowledge, this is the first study using noninvasive MRI to compare quantitative and morphological differences in atherosclerotic carotid lesions between different ethnoracial groups. Identical MRI scanners and identical MRI protocols were used in the 2 study centers in Beijing, China, and Seattle, Wash. MR images in the 2 centers had a comparable image quality. This shows that protocols using high-resolution multicontrast MRI with phased-array surface coils can be implemented internationally in different centers.

To homogenize the 2 groups, only patients with symptomatic carotid disease were included in the study. Risk factor profiles and the degree of stenosis measured by duplex ultrasound were comparable among both groups (Tables 1 and 2). Although the number of patients enrolled was rela-

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**TABLE 3. Area Measurements (in mm\(^2\)) Comparing 20 Chinese Versus 20 Americans**

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Chinese, Area in mm</th>
<th>Americans, Area in mm</th>
<th>( P )-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum lumen area</td>
<td>10.0±15.2</td>
<td>8.9±8.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Wall</td>
<td>51.6±19.1</td>
<td>45.4±15.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Outer wall boundary</td>
<td>86.8±30.4</td>
<td>74.5±22.7</td>
<td>0.2</td>
</tr>
<tr>
<td>LR-NC</td>
<td>13.6±6.9</td>
<td>7.8±3.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>2.7±2.8</td>
<td>2.1±1.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Calcium</td>
<td>1.2±1.7</td>
<td>2.7±5.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Loose matrix</td>
<td>2.1±3.0</td>
<td>1.0±1.0</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*Unpaired \( t \) test.

All areas as mean area per slice per artery±1 SD.
tively small, revealing differences in atherosclerotic disease between mainland Chinese and Caucasian American were identified. This study suggests that MRI is a powerful tool to noninvasively evaluate atherosclerotic disease systematically across different groups of patients and populations.

The minimal lumen area as an indirect measurement of stenosis was similar in both groups. The wall areas and the outer boundary areas were larger in the Chinese population (Table 3), suggesting a higher plaque burden in this group of patients.

The average size of the LR-NC (Figure 1) was 1.8× larger in the Chinese population, and this difference remained significant after adjustment for risk factors. In a study from Virmani et al., the authors suggested that hypertension may increase the size of necrotic cores in atherosclerosis but otherwise may have no impact on intimal thickness. They compared morphological aortic changes in Asian (Chinese) and Caucasian (American and Australian) subjects with aging and showed that the histological atherosclerosis score in 3 of 4 measured locations in hypertensive subjects was significantly different from nonhypertensives but not of intimal thickness. Although hypertension may increase the size of the LR-NC, the prevalence of hypertension in our groups was comparable and, therefore, does not explain the differences in the size of the LR-NC. Cholesterol levels were not significantly different, but the Caucasian population used statins more frequently in their therapy than the Chinese. It is well established in primary and secondary prevention trials that statins can significantly decrease cardiovascular morbidity and mortality, but effects on the size of the LR-NC are less established in primary and secondary prevention trials that other plaque components did not differ significantly between the 2 groups, but a trend was seen toward less calcium and more loose fibrous matrix content in the Chinese population.

Morphological evaluation of the lesion type distribution revealed 8× fewer calcified type VII lesions (P=0.03; Figure 2) but twice as many early type III lesions (P=0.02) in the Chinese population compared with the Caucasians. This reflects a shift of the lesion profile in the Caucasian population toward more calcified lesions compared with the more lipid-driven lesions of the Chinese population. It has been estimated that a large proportion of variation in coronary artery calcification is not attributable to traditional risk factors, and genetic linkage studies have pointed to chromosome 6p21.3. Racial differences in the amount of computed tomographically measured coronary calcium have been best established between blacks and whites, with less prevalent and severe atherosclerotic calcification in blacks than in whites, suggesting ethnic-specific pathways.

By visual impression, the lesions of the Chinese patients seemed to be more homogenous with clearly distinct areas within the plaque compared with the heterogeneous lesions of the Caucasian patients, with many different small areas of different plaque components at 1 location. In our experience in imaging review, this is most likely attributable to a longer history of lesion evolution in the Caucasian population. This is supported by the finding that luminal calcification in conjunction with hemorrhage/thrombus, a sign of more mature lesions, was 4× more common in the Caucasians (Table 4). Kragel et al. and Virmani et al. showed in coronary arteries that large necrotic cores are more frequently found in ruptured plaques, supporting the concept that a large LR-NC is associated with plaque vulnerability. One can only speculate that the larger size of the LR-NC in the Chinese population makes it more likely that they will develop symptoms in an earlier stage of lesion history. If the natural history of fibrous caps follows the pathway thick-thin-ruptured, the higher prevalence of thick caps in the Chinese population provides further evidence that the lesions of the Chinese were less mature. No other differences in surface characteristics were found.

### Table 4. Lesion Distribution and Surface Status Chinese Versus Americans

<table>
<thead>
<tr>
<th>AHA lesion type</th>
<th>Chinese, % of Locations</th>
<th>Americans, % of Locations</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHA lesion type</td>
<td>19.3±16.5</td>
<td>9.3±11.0</td>
<td>0.02</td>
</tr>
<tr>
<td>III</td>
<td>26.4±17.8</td>
<td>28.2±24.1</td>
<td>1.0</td>
</tr>
<tr>
<td>IV/V</td>
<td>52.9±23.3</td>
<td>50.0±25.6</td>
<td>0.7</td>
</tr>
<tr>
<td>VI</td>
<td>1.6±3.1</td>
<td>12.4±17.6</td>
<td>0.03</td>
</tr>
<tr>
<td>VII</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fibrous cap status</th>
<th>Chinese, % of Locations</th>
<th>Americans, % of Locations</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thick</td>
<td>30.9±26.6</td>
<td>20.2±22.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Thin</td>
<td>44.9±26.2</td>
<td>48.3±26.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Ruptured</td>
<td>25.3±24.6</td>
<td>31.5±23.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Luminal calcium+hemorrhage/Thrombus</td>
<td>3.1±6.1</td>
<td>11.1±13.5</td>
<td>0.07</td>
</tr>
</tbody>
</table>

All values as mean percentage per patient±1SD. *Mann–Whitney test with correction for ties.
Limitations

Although this study shows significant differences in plaque morphology and lesion type distribution between the ethno-racial groups, the number of patients in this study is relatively small, and a larger study performed in multiple centers is necessary to confirm these preliminary findings. Furthermore, we compared only a subgroup of patients who were symptomatic with advanced carotid lesions, and it has yet to be determined whether a comparison of the 2 populations that includes asymptomatic patients or patients with less advanced carotid atherosclerotic disease would show similar differences. Only images with at least average image quality were considered for the review, resulting in exclusion of 2 arteries from analysis. The number of exclusions secondary to poor image quality should decline with improvements in hardware (eg, higher-field MRI) and in pulse sequence design.

These results were based on a single imaging modality: MRI. Information gathered from other well-known imaging techniques, notably measurements of calcifications from x-ray CT, might further illuminate the differences. However, MRI is generally considered to have the broadest sensitivity to plaque components, shows good correlation with histology in quantitative measurements, and does not use ionizing radiation. Given these advantages and the comparative complexity of a multiple modality study, sole use of MRI was the logical choice for this study.

Conclusion

In conclusion, this pilot study showed a remarkable difference in the size of the LR-NC and the lesion type distribution between a Chinese and American Caucasian population with similar risk profiles, who have had recent transient ischemic attacks or strokes. This suggests that the composition of carotid atherosclerotic lesions and the lesion morphology in symptomatic carotid disease differs between ethno-racial groups. Quantitative MRI-based review of carotid atherosclerosis to compare plaque morphology and composition between ethno-racial groups and in different centers in China and the United States is feasible. In the future, follow-up studies by in vivo MRI at multiple institutions with a larger number of patients are needed to confirm these preliminary results.

Acknowledgments

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References