Atherosclerotic plaque size and composition are not symmetrically distributed. Predominance of intraplaque hemorrhage in left-sided carotid plaques suggests a greater vulnerability as opposed to right-sided plaques, which are more calcified and therefore considered more stable. (Stroke. 2014;45:3226-3230.)

Key Words: atherosclerosis ■ carotid arteries ■ magnetic resonance imaging

Atherosclerotic disease in the carotid arteries is a major cause of ischemic cerebrovascular events. In patient-based series, a significantly higher proportion of ischemic events is diagnosed in the left hemisphere than in the right. Infarctions in the left hemisphere are more likely to be recognized because most people have a dominant left hemisphere for language processing, whereas infarctions in the right hemisphere may be accompanied by a more easily overlooked cognitive deficit or apraxia. Yet, an alternative hypothesis for the higher incidence of events in the left hemisphere may be related to a higher prevalence, severity, or vulnerability of atherosclerotic disease in the left carotid artery. Although atherosclerosis is considered a systemic disease, its distribution across the vascular system is not uniform, and it is thought to depend on several factors, including vessel geometry. Furthermore, it is feasible that not only plaque severity but also plaque composition vary according to location. Some plaque components, such as intraplaque hemorrhage (IPH), are presumed to enhance vulnerability of the plaque, whereas calcification may promote plaque stability. Asymmetry in plaque characteristics between the left and right carotid artery has been poorly investigated, in particular, with respect to vulnerable plaque components. Most studies that focused on plaque asymmetry were conducted within clinical or patient-based settings and are, therefore, often subject to selection bias. A population-based study with asymptomatic individuals is, therefore, the best setting to study the natural history of plaques.

In this study, we assessed the prevalence, severity, and composition of atherosclerotic carotid plaque and investigated whether these characteristics differed between the left and right carotid artery in 1414 stroke-free individuals using MRI.

**Methods**

**Study Population**

The Rotterdam Study is a prospective population-based cohort study in subjects aged ≥45 years, as detailed elsewhere. All study participants routinely undergo carotid ultrasonography to assess carotid intima-media thickness (measured as maximum distance between the near and far wall). Of 10073 participants with carotid ultrasound, 3795 participants (38%) had wall thickness ≥2.5 mm in ≥1 carotid. Participants who passed away, moved out of the study area or were physically disabled (n=701), or had known MRI contraindications (n=428) could not be invited. In total, 2666 participants were invited for carotid MRI scanning. Subsequently, 684 participants did not undergo MRI scanning because of claustrophobia (n=57), physical

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restrictions (n=191), contraindications (n=115), refusal to participate (n=272), and no show or lost to follow-up (n=49). The remaining 1982 participants (74% of those initially invited) underwent MRI of both carotids. Scans were excluded if image quality was bad (n=95), if no plaques ≥2 mm were observed on both sides (n=41), or if scanning was incomplete because of claustrophobia (n=106). Furthermore, we excluded 87 participants with a history of transient ischemic attack or stroke. For 238 scans, analyses were not completed at the time of this study. This resulted in 1414 complete carotid MRI scans. The Medical Ethics Committee approved the study, and all participants gave written informed consent.

MRI Acquisition
Scans were obtained with a 1.5-Tesla scanner (GE Healthcare, Milwaukee, WI) with a bilateral phased-array surface coil (Machnet, Eelde, the Netherlands). Two-dimensional (2D) time-of-flight MR angiography covered the carotid bifurcation on both sides, ranging from 15 mm caudally to 30 mm cranially from the bifurcation. All examinations were found to have sufficient coverage bilaterally. A standard scanning protocol was used and included proton density-weighted (PDw)-fast spin echo-black blood sequence; PDw-echo planar imaging (EPI) sequence; T2w-EPI sequence; 3D-T1w-gradient echo sequence, and 3D phased-contrast MR angiography. Total scanning time was ≈30 minutes.

Image Review
Image quality was assessed and found sufficient in 95% of scans. In both carotids, PDw-fast spin echo images were used to measure maximum carotid wall thickness, minimal luminal diameter, and the distal luminal diameter. Luminal stenosis was then calculated according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. Plaques were visually reviewed for prevalence of 3 different plaque components: calcification, intraplaque hemorrhage, and lipid core. Intraplaque hemorrhage was defined as a hyperintense region in the atherosclerotic plaque on the 3D-T1w-gradient echo sequence. Calcification was defined as a hypointense region on all sequences but mainly on the magnitude images of the 3D-PC-MRA sequence. Lipid was defined as a region not classified as intraplaque hemorrhage or calcification on PDw-fast spin echo, PDw-EPI, and T2w-EPI images and with a relative signal-intensity drop in the plaque on the T2w-EPI sequence. Prevalence of multiple components was permissible within 1 plaque. Furthermore, one of these components was also selected as the most predominant component, which we defined as a single main component that covered the largest proportion of the plaque based on visual assessment. Hereby, fibrous tissue was added as an additional option if other components were absent or only minimally present.16,17 Plaques were reviewed for plaque characteristics with a standardized evaluation protocol by 1 of 2 trained observers (M.S. and Q.v.d.B.), blinded to all participant characteristics, overseen by a radiologist (A.v.d.L.) with 12 years of experience. In cases of doubt or disagreement, the judgment by the expert was considered definite. Inter-rater agreement for predominant and prevalent component (n=60 carotid arteries) was excellent (κ=0.88–0.94).12

Cardiovascular Risk Factors
Information on cardiovascular risk factors was obtained from the closest research center visit before the MRI scanning and measured as described previously.12 Hypertension was defined as the use of antihypertensive medications or blood pressure of ≥140/90 mm Hg. Serum total cholesterol was measured using standard laboratory techniques. Smoking status was classified as ever or never. Diabetes mellitus was considered present when fasting blood glucose exceeded 7.0 mmol/L, when nonfasting glucose exceeded 11.0 mmol/L, or when antidiabetic medication was used. A history of cardiovascular disease was defined as a history of myocardial infarction until date of MRI.18

Table 1. Baseline Characteristics of the Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>Men</th>
<th>Women</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, ±SD</td>
<td>72.0±9.6</td>
<td>71.4±9.4</td>
<td>72.8±9.7</td>
<td>0.008</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>1057</td>
<td>570 (76.1)</td>
<td>487 (73.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L, ±SD</td>
<td>5.7±1.0</td>
<td>5.4±1.0</td>
<td>5.9±1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ever smoking, n (%)</td>
<td>1047</td>
<td>637 (85.0)</td>
<td>410 (61.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>200</td>
<td>124 (16.6)</td>
<td>76 (11.4)</td>
<td>0.005</td>
</tr>
<tr>
<td>Statin use (%)</td>
<td>375</td>
<td>229 (30.6)</td>
<td>146 (22.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of cardiovascular disease, n (%)</td>
<td>128 (9.1)</td>
<td>91 (12.1)</td>
<td>37 (5.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Categorical variables are presented as no. (%). Continuous variables are presented as mean±SD. P values indicate age-adjusted difference between men and women.

Statistical Analysis
Differences in prevalence, stenosis, thickness, and composition of atherosclerotic plaques between the left and right carotid arteries were tested using paired t tests for continuous variables and McNemar test for categorical variables. A value of zero was substituted for plaque thickness and degree of stenosis if atherosclerotic plaque was absent on 1 side. To adjust for confounders and take into account within-subject correlations between the 2 carotid arteries, we used Generalized Estimation Equation analyses. These analyses were modeled with an unstructured working correlation matrix that included 2 levels per participant (ie, left and right carotid artery). We studied effect modification by age, by entering an interaction term in the model. Odds ratios and corresponding 95% confidence intervals adjusted for age, sex, and carotid wall thickness were estimated per predominant component. All analyses were performed using the Statistical Package for Social Sciences (SPSS) version 20.0 (Chicago, IL).

Results
Carotid atherosclerotic plaque characteristics on MRI were available for 1414 asymptomatic participants (Table 1), with mean age of 72.0±9.6 years and 749 men (53%). Overall, 1196 subjects (85%) had plaque in both carotid arteries. Among the 218 subjects with unilateral plaque, left-sided plaques were twice as prevalent as right-sided plaques (145 versus 73; P<0.001). This did not differ across men and women (72 left-sided versus 31 right-sided in men; P<0.001 and 73 versus 42 in women; P<0.001). However, individuals with unilateral left-sided plaques were significantly younger than participants with unilateral right-sided plaques (68.3±10.0 versus 71.2±10.4 years; P=0.04). Asymmetry of plaque severity and plaque composition is presented in Table 2. Although overall carotid wall thickness was slightly greater on the left than on the right (3.1±1.2 versus 2.9±1.3 mm; P<0.001), the degree of luminal stenosis did not differ. Also, the degree of clinically relevant stenosis did not differ between sides: 64 (4.5%) participants had stenosis >50% on the left side versus 72 (5.1%) on the right side (P=0.4). Both Lipid and IPH were more frequent in left carotid artery plaque than in the right (lipid, 27.6% versus 23.4%; P=0.006 and IPH, 23.1% versus 19.7%; P=0.01), whereas calcification was equal on both sides.

When we assigned just a single component as the most predominant component, we found that both IPH and fibrous tissue to be more often predominant on the left than on the right (9.1...
Table 2. Asymmetry of Plaque Severity and Plaque Components

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th></th>
<th></th>
<th>Men</th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
<td>PValue</td>
<td>Right</td>
<td>Left</td>
<td>PValue</td>
<td>Right</td>
<td>Left</td>
<td>PValue</td>
</tr>
<tr>
<td>Wall thickness, mm, mean±SD</td>
<td>2.9±1.3</td>
<td>3.1±1.3</td>
<td>&lt;0.001</td>
<td>3.0±1.4</td>
<td>3.2±1.2</td>
<td>0.001</td>
<td>2.7±1.2</td>
<td>3.0±1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stenosis, %, mean±SD</td>
<td>11.9±17.7</td>
<td>11.4±16.7</td>
<td>0.4</td>
<td>12.9±19.3</td>
<td>12.4±17.8</td>
<td>0.5</td>
<td>10.8±15.6</td>
<td>10.3±15.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Prevalent component, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Lipid</td>
<td>331 (23.4)</td>
<td>390 (27.6)</td>
<td>0.006</td>
<td>197 (26.3)</td>
<td>240 (32)</td>
<td>0.01</td>
<td>134 (20.2)</td>
<td>150 (22.6)</td>
<td>0.3</td>
</tr>
<tr>
<td>IPH</td>
<td>279 (19.7)</td>
<td>327 (23.1)</td>
<td>0.01</td>
<td>190 (25.4)</td>
<td>199 (26.6)</td>
<td>0.6</td>
<td>89 (13.4)</td>
<td>128 (19.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Calciification</td>
<td>900 (63.6)</td>
<td>920 (65.1)</td>
<td>0.4</td>
<td>483 (64.5)</td>
<td>496 (66.2)</td>
<td>0.5</td>
<td>417 (62.7)</td>
<td>424 (63.8)</td>
<td>0.7</td>
</tr>
<tr>
<td>Predominant component, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid</td>
<td>113 (8.0)</td>
<td>130 (9.2)</td>
<td>0.2</td>
<td>62 (8.3)</td>
<td>86 (11.5)</td>
<td>0.03</td>
<td>51 (7.7)</td>
<td>44 (6.6)</td>
<td>0.5</td>
</tr>
<tr>
<td>IPH</td>
<td>83 (5.9)</td>
<td>128 (9.1)</td>
<td>&lt;0.001</td>
<td>62 (8.3)</td>
<td>94 (12.6)</td>
<td>0.004</td>
<td>21 (3.2)</td>
<td>34 (5.1)</td>
<td>0.07</td>
</tr>
<tr>
<td>Calciification</td>
<td>529 (37.4)</td>
<td>447 (31.6)</td>
<td>&lt;0.001</td>
<td>265 (35.4)</td>
<td>221 (29.5)</td>
<td>0.008</td>
<td>264 (39.7)</td>
<td>226 (34.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Fibrous tissue</td>
<td>544 (38.5)</td>
<td>636 (45.0)</td>
<td>&lt;0.001</td>
<td>288 (38.5)</td>
<td>317 (42.3)</td>
<td>0.09</td>
<td>256 (38.5)</td>
<td>319 (48.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note that percentages of prevalent components do not add up to 100% because multiple components per plaque could be present. Percentages of prevalent component, expressed as proportion of the 1414 carotid arteries, do not add up to 100% because a proportion of carotid arteries did not have an atherosclerotic plaque. IPH indicates intraplaque hemorrhage.

Discussion

Within a large cohort of stroke-free individuals, we demonstrated that plaque prevalence, severity, and composition are not equally distributed among the left and right carotid arteries. Although most individuals had bilateral carotid disease, unilateral plaque was more usually located on the left, and left-sided plaques were also thicker than the contralateral side. Although IPH and lipid were most prevalent in left-sided plaques, these plaques were predominantly composed of IPH and fibrous tissue. In contrast, right-sided plaques were predominantly composed of calcification, which is considered more stable and, therefore, less likely to result in thromboembolic complications. These findings suggest that atherosclerotic plaques on the left are more vulnerable than on the right.

Important strengths of this study are its population-based design and the large number of stroke-free individuals who underwent carotid plaque characterization with MRI. Yet, not all participants with atherosclerotic plaque on carotid ultrasound underwent carotid MRI scanning because of both logistical and participant-related reasons. Although this may have led to selection bias, we expect this to be nondifferential. Restricting our study to a stroke-free population allowed us to generalize our findings to asymptomatic individuals. Because of this inclusion criterion, patients with highly vulnerable plaques may have had symptoms and been excluded from the study. Because of the preponderance of left-sided strokes among symptomatic persons, it is thus feasible that we may have underestimated left-sided vulnerable plaques.

Although MRI is currently regarded as the most reliable method for in vivo assessment of plaque composition, small plaques (<2.0 mm) could not be characterized because of constraints in spatial resolution of MRI. Furthermore, we could not apply contrast-enhanced sequences because we are investigating healthy subjects. Hence, distinguishing lipid from fibrous tissue was more difficult, possibly resulting in an underestimation of the presence of lipid or an overestimation of fibrous tissue although we do not expect a predilection for a particular side. A further limitation is that fibrous tissue was defined per exclusion of other components, which may have led to underestimation of this component. Image reviewing was performed by 2 observers, who were not blinded to the side of the carotid artery. We should, therefore, consider potential observer bias although the observers were at time of rating unaware of potential left-right differences and inter-rater reliability was very high.

The higher prevalence of subjects with left-sided unilateral plaques and the significantly younger age of these subjects versus 5.9%; P<0.001 and 45.0 versus 38.5%; P<0.001; Table 2). In contrast, calcification was the predominant component more on the right than on the left (37.4 versus 31.6%; P<0.001). Lipid was distributed equally. Similar trends were found for men and women (Table 2). There was no interaction between plaque characteristics and age (data not shown). An example of asymmetry in predominant plaque components is presented in Figure 1.

Figure 2 shows the odds ratios for the predominance of a specific plaque component on the left side, adjusted for age, sex, and maximal wall thickness. The right side was used as the reference. The odds ratios for IPH or fibrous tissue on the side of the carotid artery. We should, therefore, consider potential observer bias although the observers were at time of rating unaware of potential left-right differences and inter-rater reliability was very high.

The higher prevalence of subjects with left-sided unilateral plaques and the significantly younger age of these subjects...
supports a predisposition of atherosclerotic plaques in the left carotid artery. We found a slight but significant difference in wall thickness between the left and the right carotid artery. This finding is consistent with a previous study that found a thicker intima-media thickness in the left common carotid artery than in the right using B-mode ultrasonography. A greater wall thickness may indicate more plaque growth.

Stenosis in the internal carotid artery is an important cause of large-vessel stroke. In asymptomatic subjects with mild stenosis, plaque growth might be accompanied by outward remodeling of the plaque. This may explain why we did not find a difference in (clinically relevant) luminal stenosis between both sides. Yet, it is important to realize that a substantial proportion of strokes results from carotids with only mild stenosis and are probably because of variations in plaque composition rather than lumen narrowing.

About plaque composition, we found that IPH occurred predominantly on the left in men. IPH is considered an important indicator of vulnerable plaques. Vulnerable plaques, and in particular IPHs, are gaining importance because they may lead to plaque rupture and subsequent ischemic stroke. Left-sided plaques have a more vulnerable phenotype, whereas right-sided plaques were predominantly composed of calcification. Calcifications have been suggested to increase plaque stability because they are associated with lower risks of cerebrovascular complications, and therefore considered as a more favorable phenotype of carotid atherosclerosis. Atherosclerotic plaques can remain stable for many years without surface rupture and subsequent cerebrovascular complications. In studies that compared carotid atherosclerotic plaques in symptomatic and asymptomatic subjects, calcified plaques were less likely to be symptomatic than noncalcified plaques and asymptomatic patients had a higher calcification content than symptomatic patients.

We found more predominant fibrous tissue and prevalent lipid on the left, which may also reflect higher vulnerability, although their contributions to plaque instability are less conclusive than IPH. Enlargement of the lipid pool may result in the development of a necrotic core, initiating a cascade with fibrous cap erosion or rupture. However, the role of lipid and fibrous tissue in plaque instability, in health subjects, has not been determined.

Few studies have compared plaque components between the left and right carotid arteries and usually only distinguish between calcified and noncalcified plaques. In 50 pairs of carotid arteries from cadaveric donors, plaque calcification, quantified using electron beam computed tomography, was found to be similarly distributed between both carotid arteries. Although the authors used cumulative volume of calcification for comparison, we assessed the prevalent and predominant component. It should be noted that absolute volumes do not reflect the proportion of specific components within a plaque. We overcame this by defining a predominant plaque component, which can be more easily assessed.

Although sex differences about the severity of atherosclerosis are widely known, studies that assess sex differences in plaque composition are scarce. In a recent MRI study among 96 patients with mild stenosis, vulnerable plaque characteristics, such as a thin or ruptured fibrous cap and IPH, were significantly higher in men than in women. We also found asymmetry in plaque composition across sexes although IPH was more prevalent on the left in women and more predominant on the left in men.

Differences in plaque thickness and composition between both carotid arteries may be explained by geometric factors, such as bifurcation angle, the configuration of the left carotid artery to the aortic arch or because of the direct connection of the left carotid artery to the aortic arch as opposed to the right carotid artery that arises from the brachiocephalic artery. Vessel anatomy in turn influences the hemodynamic forces and as such the left carotid artery may be exposed to higher arterial pressures. Flow models have shown that atherosclerotic plaques preferentially develop in areas with low wall shear stress, such as at bifurcations or inner curves. Wall shear stress and stress inside the vessel wall may affect plaque formation and composition by causing alterations in wall structure and metabolism. The role of these local factors has been scarcely investigated in vivo. However, we think that studying their contributions may help understand the variation between left and right carotid atherosclerosis and should be considered in future studies.

This study was initiated because of the reported high incidence of left-sided strokes and we hypothesized that asymmetry in carotid atherosclerosis may play a role in this observation. Although we found an asymmetry in plaque prevalence and composition between the left and right carotid artery, these side-differences seem to be too small to explain the higher incidence of left-sided strokes, which may primarily be because of left-sided strokes causing more apparent problems. Nevertheless, it is important to identify local or systemic factors underlying these asymmetrical differences in plaque composition, and to gain insight into the factors that lead to development of side-specific vulnerable plaque characteristics. Understanding these pathways could improve risk prediction of stroke and contribute to the prevention of stroke in primary care.

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Disclosures

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References

Atherosclerotic Plaque in the Left Carotid Artery Is More Vulnerable Than in the Right
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