Carotid intraplaque hemorrhage detected by magnetic resonance imaging predicts embolization during carotid endarterectomy

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Background: Microembolization detected during the dissection phase of carotid endarterectomy (CEA) is associated with plaque instability and might be associated with perioperative morbidity. Intraplaque hemorrhage is found in unstable plaques and is detectable using magnetic resonance imaging (MRI). We aimed to ascertain whether intraplaque hemorrhage as seen on carotid MRI predicts particulate embolization in the dissection phase of CEA.

Methods: Patients with high-grade symptomatic carotid stenosis undergoing CEA were prospectively enrolled. All underwent preoperative MRI assessment of the carotid arteries for intraplaque hemorrhage and transcranial Doppler scanning during the dissection phase of the CEA to assess the presence of microembolic signals. Associations between intraoperative hemorrhage and intraoperative microembolic signals were studied.

Results: Analysis was undertaken on 60 participants; of these, 36 (60%) showed ipsilateral carotid MRI intraplaque hemorrhage, and 24 (40%) did not. Microembolic signals were detected during the dissection phase in 23 (38.3%) participants, and 19 had MRI-detected intraplaque hemorrhage. The association between carotid intraplaque hemorrhage and the presence of dissection phase microembolic signals was significant (odds ratio [OR], 5.6; 95% confidence interval [CI], 1.6 to 19.7, \( P = .007 \)), even after controlling for age, sex, individual surgeon, degree of stenosis, and delay from symptom to CEA (adjusted OR, 5.8; 95% CI, 1.1 to 30.4, \( P = .037 \)).

Conclusion: Intraplaque hemorrhage as detected by carotid MRI predicts particulate embolization during the dissection phase of CEA. This imaging technique can be used to identify patients with increased intraoperative thromboembolic risk, and this could influence preventive strategies. (J Vasc Surg 2007;46:31-6.)

Ischemic strokes and transient ischemic attacks (TIAs) are frequently caused by thromboembolism from an unstable or ruptured atheromatous carotid plaque. Trials have shown the benefits of performing carotid endarterectomy (CEA) in groups of patients with recently symptomatic high-grade carotid stenosis, but the individual likelihood (CEA) in groups of patients with recently symptomatic high-grade carotid stenosis,1,2 but the individual likelihood may allow improved risk stratification for patients considered for carotid endarterectomy.

Intraplaque hemorrhage is commonly seen in atheromatous plaques, the presence of intraplaque hemorrhage was associated with plaque rupture and other features of plaque instability.11,12 In a recent large pathology study of carotid plaques, the presence of intraplaque hemorrhage was associated with plaque rupture and other features of plaque instability.14

Carotid intraplaque hemorrhage can be detected non-invasively by using MRI. A T1-weighted MRI technique is able to detect methemoglobin, a breakdown product of hemoglobin, and thus detect areas of hemorrhage.14 In a pathoradiologic slice-by-slice comparative study, carotid plaque hemorrhage was identified using this MRI technique with a high sensitivity and specificity.15 Moody et al16 demonstrated that the T1 signal hyperintensity seen on MRI was able to predict the complicated carotid plaque as classified by the American Heart Association in a group of 63 symptomatic patients who underwent CEA. Further studies have shown that the presence of intraplaque hem-
Intraplaque hemorrhage, as detected by MRI, causes progression of carotid atherosclerotic disease and is predictive of recurrent short-term ischemia in patients with recently symptomatic as well as those with asymptomatic carotid disease. The aim of this study was to ascertain whether the presence of intraplaque hemorrhage, detected by a T1-weighted MRI technique, was able to identify an active thromboembolic carotid plaque as evidenced by increased microembolization detected by transcranial Doppler during the dissection phase of the CEA.

METHODS

**Recruitment.** Patients considered for CEA were prospectively identified between January 2004 and August 2006 from the hospital TIA clinic. Eligibility criteria included a high-grade carotid stenosis on Duplex scanning (60% to 99%), using established ultrasound criteria adapted from the angiographic measurements of the North American Symptomatic Carotid Surgery Trial as used in the Carotid and Vertebral Artery Transluminal Angioplasty Study. All patients had ipsilateral symptoms (stroke, TIA, and amaurosis fugax) to the index stenosed artery in the previous 6 months. All participants gave informed consent, and the local research ethics committee approved the study. Exclusion criteria were contraindication for MRI or when waiting for MRI would have delayed CEA. Diagnostic work-up and therapeutic management of the patients and its timing was not affected by this study.

**Magnetic resonance imaging scanning and analysis.** After a baseline assessment at the clinic, all participants underwent MRI scanning of the carotid arteries to determine the presence and extent of intraplaque hemorrhage. MRI was performed on one of three 1.5T scanners: Vision (Siemens Medical, Erlangen, Germany), Intera (Philips, Best, Netherlands), or Signa (General Electric, Waukesha, Wis). All participants were scanned using a receive-only quadrature neck array cervical spine coil. Carotid imaging was performed using a coronal T1-weighted magnetization-prepared three-dimensional gradient echo sequence with a water excitation pulse to remove signal from fat in the Siemens and Philips scanners; and fat suppression was achieved by using the Spectral Inversion at Lipids (SPECIAL) option in the GE scanner: Siemens (TR 10.3 ms, TE 4.0 ms, FA 15°, effective TI 740 ms, voxel size 1.17 × 1.17 × 1.14 mm, acquisition matrix 256 × 256 with 62.5% rectangular FOV, 140 partitions, acquisition time 235 seconds); Philips (TR 8.4 ms, TE 3.1 ms, FA 10°, effective TI 740 ms, voxel size 1.1 × 1.1 × 1.1 mm, acquisition matrix 256 × 256 with 72.5% rectangular FOV, 140 partitions, acquisition time 255 seconds); and General Electric (TR 5.8 ms, TE 1.5 ms, FA 15°, TI 19 ms, interpolated voxel size 0.66 × 0.66 × 1 mm, acquisition matrix 256 × 256 [interpolated to 512 × 512] with 100% rectangular FOV, 72 partitions, acquisition time 251 seconds).

Image analysis was performed using standard image reconstruction techniques as provided by JAVA Imaging software (Xinapse Systems Ltd, Thorpe Waterville, UK) to assess axial reformats and perform signal intensity assessments of the intraplaque hemorrhage signal. The investigators were blinded to the clinical and the transcranial Doppler data.

Intraplaque hemorrhage was identified by two trained experienced researchers if the maximal signal intensity within the carotid plaque was >150% of the maximum adjacent muscle intensity. The presence or absence of a high signal was recorded in the arteries by the researchers blinded to the symptomatic artery and microemboli findings. The researchers considered six scans were equivocal, and a consensus was then reached between the two trained researchers and an experienced neuroradiologist blinded to the clinical data. Intraobserver and interobserver variability assessed on 60 arteries using this procedure has excellent agreement (Cohen κ = 0.88 and 0.81, respectively).

**Transcranial Doppler imaging.** One of two commercially available transcranial Doppler scanners (QVL 842X, SciMed, New York, NY; EmboDop, DWL, Singen, Germany) was used to insonate the ipsilateral middle cerebral artery with a 2-MHz probe by the transtemporal route between the depths of 44 and 56 mm continuously throughout the dissection phase of the CEA. The dissection phase of the operation was defined as the time from skin incision to the time of clamping of the carotid arteries. Any embolization that occurred after the clamping was not analyzed because it was considered unrelated to carotid plaque instability.

The Doppler audio signals were recorded and analyzed by one experienced investigator blinded to the MRI findings. Microembolic signals were defined by established criteria and signal characteristics: (1) duration <300 ms, (2) amplitude at least 7 dB higher than of the background blood flow signal, (3) unidirectional, and (4) a “snap,” “chirp,” or “moan” on the audible output.

The plaque was considered to be positive for a microembolic signal when one or more microemboli were detected in the ipsilateral middle cerebral artery during the dissection phase of the operation.

**Operative technique.** All CEAs were performed in conscious patients with locoregional anesthetic techniques in a tertiary referral center in which the perioperative stroke rate was <3%. One of three consultant vascular surgeons...
or a supervised senior specialist trainee performed the procedure.

In brief, after making an incision along the anterior border of the sternocleidomastoid muscle, the platysma was divided, and the facial vein was identified and then divided. The carotid sheath was identified and opened to expose the common carotid artery and its bifurcation. Using gentle, sharp dissection, the external and internal carotid arteries were exposed, and slings were passed around these arteries. Before cross-clamping, an intravenous bolus of heparin (3 to 5000 IU) was administered. The clotting times were not checked and protamine reversal was not used. A shunt was used if there was any loss of consciousness or focal neurology in the patient. Tacking sutures and Dacron patch repairs were performed in all patients. The surgeons were blinded to the MRI findings.

**RESULTS**

Initially, 86 participants were recruited, but six were unable to complete the MRI scan due to claustrophobia and one was withdrawn when a subsequent assessment indicated that his presenting symptoms were unrelated to the carotid artery disease. A further 11 participants did not undergo an operation: five had carotid artery occlusions either at the time of MRI or whilst waiting for carotid endarterectomy, three had large strokes pending the operation, and three opted for conservative management. Details of the clinical outcomes of this cohort are published elsewhere. A further eight patients had a poor temporal acoustic window for transcranial Doppler signal acquisition. The MRI scans of the remaining 60 participants were of suitable quality for assessment of intraplaque hemorrhage and were analyzed. The mean age of this group was 69.8 ± 10.5 years, and 17 (28.3%) were women. MRI signs of intraplaque hemorrhage were found in 36 (60%) of the symptomatic carotid arteries but not in 24 (40%). There were no significant differences in age, atherosclerotic risk factors, and delay between symptom and MRI and CEA dissection time between those who demonstrated intraplaque hemorrhage and those who did not, but the proportion of men was higher in the intraplaque hemorrhage group (Table I).

<table>
<thead>
<tr>
<th>Factor</th>
<th>Present, n (%)</th>
<th>Absent, n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient total</td>
<td>36 (60)</td>
<td>24 (40)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>69.0 ± 8.7</td>
<td>66.9 ± 11.4</td>
<td>.4</td>
</tr>
<tr>
<td>Sex (females)</td>
<td>6 (16.7)</td>
<td>11 (45.8)</td>
<td>.02</td>
</tr>
<tr>
<td>Hypertension</td>
<td>31 (86.1)</td>
<td>12 (50)</td>
<td>.3</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>9 (25)</td>
<td>7 (29.2)</td>
<td>.5</td>
</tr>
<tr>
<td>Previous MI</td>
<td>7 (19.4)</td>
<td>3 (12.5)</td>
<td>.5</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (13.9)</td>
<td>1 (4.2)</td>
<td>.2</td>
</tr>
<tr>
<td>Smoker</td>
<td>10 (27.8)</td>
<td>11 (45.8)</td>
<td>.4</td>
</tr>
<tr>
<td>Statin use</td>
<td>37 (75.0)</td>
<td>20 (83.3)</td>
<td>.3</td>
</tr>
<tr>
<td>Antiplatelet drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>1 (4.2)</td>
<td>.4</td>
</tr>
<tr>
<td>Aspirin</td>
<td>26 (72.2)</td>
<td>13 (54.2)</td>
<td></td>
</tr>
<tr>
<td>Aspirin + dipyridamole</td>
<td>7 (19.4)</td>
<td>5 (20.8)</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>1 (2.8)</td>
<td>1 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>1 (2.8)</td>
<td>1 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Presenting symptom</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>12 (33.3)</td>
<td>7 (29.2)</td>
<td>.8</td>
</tr>
<tr>
<td>TIA</td>
<td>17 (47.2)</td>
<td>9 (37.5)</td>
<td></td>
</tr>
<tr>
<td>Amaurosis fugax</td>
<td>7 (19.4)</td>
<td>8 (33.3)</td>
<td></td>
</tr>
<tr>
<td>CEA dissection time, minutes</td>
<td>41.4 ± 9.7</td>
<td>40.5 ± 9.7</td>
<td>.8</td>
</tr>
<tr>
<td>Time between</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last symptom and MRI</td>
<td>26.0 (12.3 to 62.0)</td>
<td>33 (22.5 to 75.5)</td>
<td>.2</td>
</tr>
<tr>
<td>MRI and CEA</td>
<td>19.0 (8.0 to 34.5)</td>
<td>16.5 (8.3 to 31.3)</td>
<td>1</td>
</tr>
</tbody>
</table>

MI, Myocardial infarction; TIA, transient ischemic attack; CEA, carotid endarterectomy; MRI, magnetic resonance imaging.

*Continuous variables are presented as mean ± standard deviation or median (interquartile range).
Table II. Univariate logistic regression analysis results of factors affecting the presence of dissection phase microemboli

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.0 (1.0 to 1.1)</td>
<td>.6</td>
</tr>
<tr>
<td>Sex (females)</td>
<td>0.6 (0.2 to 1.9)</td>
<td>.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.2 (0.3 to 4.7)</td>
<td>.8</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>0.9 (0.3 to 3.1)</td>
<td>.9</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.8 (0.1 to 4.7)</td>
<td>.8</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.9 (0.3 to 2.9)</td>
<td>.8</td>
</tr>
<tr>
<td>Degree of stenosis</td>
<td>0.9 (0.5 to 1.9)</td>
<td>.9</td>
</tr>
<tr>
<td>Time from last symptom and TCD recording during CEA</td>
<td>0.99 (0.98 to 1.00)</td>
<td>.1</td>
</tr>
<tr>
<td>Presence of intraplaque hemorrhage</td>
<td>5.6 (1.6 to 19.6)</td>
<td>.007</td>
</tr>
</tbody>
</table>

OR, Odds ratio for embolization; CI, confidence interval; TCD, transcranial Doppler; CEA, carotid endarterectomy.

During the dissection phase (41.1 ± 11.0 minutes), microembolic signals (range, 1 to 64 signals) were detected in the ipsilateral middle cerebral artery in 23 (38.3%) participants. Nineteen of the plaques with intraoperative microembolic signals had MRI intraplaque hemorrhage and four did not (OR, 5.6; 95% CI, 1.6 to 19.6, P = .007). By contrast, none of the patient factors were significantly associated with microembolic signals (Table II). The sensitivity of predicting microembolic signals using the MRI assessment of intraplaque hemorrhage was 82.6%, the specificity was 54.1%, the positive predictive value was 52.8%, and the negative predictive value was 83.3%.

In the multivariate logistic regression analysis, intraplaque hemorrhage conferred a significant independent risk for microembolic signals (adjusted OR, 5.8; 95% CI, 1.1 to 30.4, P = .037) after controlling for age, sex, degree of stenosis, individual surgeon, and delay from symptom to carotid endarterectomy.

In the 36 patients with intraplaque hemorrhage, no additional factors (including age, sex, stenosis, ischemic heart disease and hypertension) significantly altered the risk of microembolization (P varied from .3 to .7).

Postoperatively, only one participant developed a minor stroke. This person had intraplaque hemorrhage and demonstrated intraoperative microembolic signals.

**DISCUSSION**

Patients with high-grade symptomatic carotid stenosis and preoperatively determined carotid intraplaque hemorrhage had an elevated risk of microembolization during the dissection phase of CEA. This relationship remained significant after adjusting for other known risk factors.

The results of this study provide further evidence that carotid intraplaque hemorrhage, as detected by MRI, can identify active thromboembolic plaque. There has been uncertainty over whether and how intraplaque hemorrhage is associated with plaque instability. Lusby et al initially noted that plaque hemorrhage was more prevalent in symptomatic than in asymptomatic carotid plaques. In the largest pathologic study of symptomatic carotid plaques, Redgrave et al demonstrated that intraplaque hemorrhage was associated with morphologic features of plaque instability. Intraplaque hemorrhage has been suggested to stimulate atherogenic activity by being a source of free cholesterol to the necrotic core and macrophage activation. A small study by Sitzer et al stated that plaque ulceration and not intraplaque hemorrhage was associated with significant spontaneous embolization (defined as >5 microembolic signals per hour), but in fact, seven of eight patients in that study with plaque hemorrhage had some microembolization (>1 microembolic signal).

By using this MRI technique to assess the carotid plaque, we were able to demonstrate a high negative predictive value of microembolization during the dissection phase. The absence of intraplaque hemorrhage therefore seems to be a strong indicator of a carotid plaque that is unlikely to cause embolization during surgery and, hence, is at a lower perioperative risk. Only about half (53%) of carotid plaques with intraplaque hemorrhage had any embolization, however. Presumably, additional factors (such as fibrous cap integrity of the plaque) or platelet/fibrin aggregation may also trigger intraoperative microembolization. Further studies using the more time-consuming technique of multisquence MRI to detect other features of plaque, or using ultrasound scanning, are warranted to see if other factors add to prediction based upon the presence of intraplaque hemorrhage alone. As in the rest of the United Kingdom, the delay from the symptomatic event to surgery in our unit was significant. The MRI findings may have changed in this interim period; however, intraplaque hemorrhage appears to remain stable over some time after a symptomatic event.

Because only one clinical perioperative event occurred in this series, we cannot claim that intraplaque hemorrhage predicts higher perioperative stroke. Perioperative microembolic signals in the dissection phase are known to predict postoperative ischemia, however, and so our findings are likely to be of clinical importance. By being forewarned by the presence of intraplaque hemorrhage of the possibility of perioperative morbidity, appropriate measures can be taken to optimize the management of the patient. Preemptive measures include the use of anticoagulants, combinations of antiplatelet agents, and intravenous dextran, which decrease microembolic signal counts and thereby potentially decrease the preoperative and perioperative risk of stroke.

A technique that allows preoperative identification of those plaques at high risk of embolization could guide the choice of treatment modality and technique. For example, it may be prudent for trainee surgeons not to undertake procedures in patients with intraplaque hemorrhage until they are adequately experienced. For experienced surgeons, earlier clamping of the internal carotid artery before completion of the dissection of the carotid arteries, which increases the carotid clamp time and may increase the risk of iatrogenic cerebral ischemia, may be warranted in those with intraplaque hemorrhage who are at higher risk of...
embolism during the dissection procedure. It remains to be seen whether this technique is of any value in patients undergoing carotid artery stenting, during which microembolization is of some concern.

A change of operative technique might have occurred once the surgeon was alerted to the presence of microembolic signals, but this would influence the number of subsequent microembolic signals and not their presence in the first instance and, hence, does not invalidate our conclusions. In this study we have not reported spontaneous preoperative or postoperative microembolic signals, both of which are also of clinical significance. However, in choosing to report the relationship between MRI intraplaque hemorrhage and microembolic signals during the dissection phase of carotid endarterectomy, we studied outcomes that are both clinically important and sufficiently frequent for statistical testing to be done on the results.

CONCLUSION

Carotid intraplaque hemorrhage, as detected by MRI, is associated with an increased risk of microembolization during the dissection phase of carotid endarterectomy. Determination of intraplaque hemorrhage using MRI may be useful to stratify risk when considering interventions for carotid artery disease and to optimize antithrombotic and other preventive strategies during surgery to reduce operative ischemia.

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AUTHOR CONTRIBUTIONS

Conception and design: NA, SM, AM, JG
Analysis and interpretation: NA, SM, DA, JG
Data collection: NA, AB, SG
Writing the article: NA, SM, DA, SG, AM, JG
Critical revision of the article: NA, JG, AB, AM, SM
Final approval of the article: NA, AB, SG, JG, AM, DA, SM
Statistical analysis: NA, DA, JG
Obtained funding: NA, DA, JG, SM
Overall responsibility: SM

REFERENCES


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