Prevalence of Complicated Carotid Atheroma as Detected by Magnetic Resonance Direct Thrombus Imaging in Patients With Suspected Carotid Artery Stenosis and Previous Acute Cerebral Ischemia

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Background—It is recognized that complicated plaque largely accounts for the morbidity and mortality from atherosclerosis. Ideally, investigation of symptomatic and asymptomatic patients would identify atheromatous plaques independently of stenosis. We have previously shown that a magnetic resonance direct thrombus imaging (MRDTI) technique demonstrates complicated atheroma as high signal within the carotid arterial wall. We used this technique to examine the prevalence of complicated carotid plaque in vivo in the ipsilateral arteries of recently symptomatic patients with suspected carotid artery stenosis and to compare this with their contralateral arteries and with those of healthy age- and sex-matched controls.

Methods and Results—The carotid arteries of 120 patients with suspected severe carotid artery stenosis and previous acute cerebral ischemia were imaged using MRDTI, as were 28 control arteries. High signal was not seen in any control artery. However, there was a 60% prevalence of high signal, suggestive of complicated plaque in the patients’ ipsilateral arteries. The prevalence of high signal was significantly greater in the patients’ ipsilateral vessels compared with the contralateral, asymptomatic side (60% versus 36%, \( \chi^2 P<0.001 \)), particularly for vessels of only moderate stenosis.

Conclusions—MRDTI high signal suggestive of complicated plaque is prevalent in the ipsilateral carotid arteries of patients with carotid stenosis and recent cerebral ischemic events. MRDTI has a potential role in identifying “at risk” plaque, studying atherogenesis and the effects of plaque-modifying strategies. (Circulation. 2003;107:3053-3058.)

Key Words: plaque ■ carotid arteries ■ magnetic resonance imaging ■ cerebral ischemia

Complicated plaque largely accounts for the morbidity and mortality from atherosclerosis and is defined by the presence of intraplaque hemorrhage, thrombus, and surface disruption. We have developed a magnetic resonance direct thrombus imaging technique (MRDTI) that shows high signal in the carotid arterial wall of patients with recent cerebrovascular ischemia. Examination of carotid endarterectomy specimens demonstrated that this MRDTI high signal is an in vivo marker of carotid complicated plaque. 1a MRDTI high signal represents met-hemoglobin, an intermediate breakdown product of blood, and the sequence highlights the intraplaque hemorrhage component of complicated plaque. One application of such a technique is to ascertain the prevalence of carotid complicated plaque in vivo.

Much of what is known about the prevalence of complicated plaque is from specimen collection at interventional procedures, such as coronary, aortic, and carotid surgery or postmortem series looking at vessel atherosclerosis. Imaging studies have attempted to characterize complicated atheromatous lesions to look at the prevalence of these “dangerous” plaque morphologies in symptomatic and asymptomatic populations. Assessment of complicated plaque prevalence in vivo requires a reliable, noninvasive, well-tolerated imaging procedure that is low risk. Many techniques used are invasive, such as coronary and carotid angiography and transesophageal echocardiography for aortic complicated plaque. 2-4 B-mode ultrasound can noninvasively characterize carotid atherosclerotic lesion morphology using echogenicity, defined as the reflectance of the ultrasound signal. However, at present there is much subjectivity in ultrasound diagnosis of vessel surface, wall, and plaque features, 5 which makes applicability to prevalence studies difficult.
MRDTI is a technique that can noninvasively image carotid plaque morphology in vivo. MRDTI high signal was a marker of complicated plaque in our endarterectomy study, with a positive predictive value of 93% (Moody et al, unpublished data). The technique highlights the pathology as bright signal against a suppressed background, and scan interpretation is therefore relatively simple. The scan takes <5 minutes, and the sequence can be added to most commercially available scanners. These features mean that MRDTI is ideal as a noninvasive technique that could be applied to an in vivo prevalence study of carotid complicated plaque.

The aim of the present study was to use MRDTI to ascertain the prevalence of complex plaque in vivo in the carotid arteries of patients with suspected severe carotid artery stenosis after acute cerebral ischemic events. We then aimed to test the hypothesis that MRDTI-defined complex plaque is associated with previous recent ipsilateral cerebral ischemic events in a group of patients with carotid stenosis. This would be achieved by comparing the patients’ symptomatic artery with their nonsymptomatic side and with the arteries of a small group of control patients.

Methods

Patients

Patients with symptomatic carotid disease who were undergoing assessment for carotid endarterectomy were targeted for recruitment. All patients gave informed consent, and the local ethics committee approved the study. Patients were identified through the surgical “one-stop” vascular clinics. At these clinics, patients undergo a duplex ultrasonographic assessment of the carotid arteries. Patients were referred for MRI if they had 60% to 100% carotid artery stenosis ipsilateral to the affected cerebral hemisphere. The subset of patients imaged who had 70% to 99% stenosis ipsilateral to the affected cerebral hemisphere underwent carotid endarterectomy and have been reported previously. The time taken from the patients’ first symptoms to the MRI scan was calculated for the group as a whole as well as separately for patients with ipsilateral positive scans and patients with ipsilateral negative MRDTI scans.

Controls

We also imaged age- and sex-matched subjects with the MRDTI sequence to act as external controls. The subjects were patients undergoing cervical spine imaging and were selected to reflect, as much as possible, the age distribution in the patient population. The notes of the matches were examined to ensure there was no carotid or other vascular disease. Local ethical committee approval was obtained, and the patients gave informed written consent to have the MRDTI and MR angiography scans performed. Time of flight MR angiography was used to determine whether there was carotid vessel stenosis.

Magnetic Resonance Imaging

MRI scanning was performed on a 1.5T scanner (Siemens, Erlangen) using a receive-only quadrature neck array cervical spine coil. Patients underwent MRDTI and MR angiography. The MRDTI sequence used a T1-weighted magnetization-prepared 3D gradient-echo sequence, acquired in the coronal plane. The sequence included a selective water-excitation radio frequency pulse to abolish fat signal, and the effective inversion time was chosen to null the blood signal. The pixel size and effective slice thickness were 1.2 mm. The resulting acquisition time was 3.5 minutes. Assessment of the images involved reading of coronal source data together with standard image reconstruction techniques.

A positive scan was diagnosed if high signal material (brighter than the adjacent muscle) was seen within the wall or lumen of the carotid artery in the region and 1 cm to either side of the stenosis. The presence or absence of high signal was recorded in both the ipsilateral (symptomatic) artery and the contralateral (asymptomatic) artery for each patient (Figure 1). The prevalence of high signal in the ipsilateral and contralateral arteries in the patient group was ascertained for the patient group as a whole, patients with ipsilateral severe stenosis (70% to 100%), and those with ipsilateral stenosis <70%. Vessel stenosis measurements used were the clinic ultrasound measurements, which were calculated by NASCET criteria.6

Figure 1. A, High signal material within right internal carotid artery (symptomatic side) as well as a smaller volume of asymptomatic complicated plaque on the left. B, Extensive unilateral right internal carotid disease. No high signal is seen on the left (asymptomatic) side.
Contrast MR angiography was used to confirm or refute suspected arterial occlusion on ultrasound, and in these cases MR assessment of vessel stenosis was taken as the measurement. A 3D rapid contrast enhanced angiography sequence was acquired in the coronal plane. Four volumes, taking 10 seconds each, were acquired from the point of intravenous gadolinium injection. This allowed the subtraction of the arterial phase from background. The pixel size was 1 mm, and effective slice thickness was 1.88 mm. Postprocessing used maximum intensity projection to visualize the vessel bifurcation in any plane. For controls, a time of flight angiography sequence was used using a multiple overlapping thin slab angiography technique acquired in the axial plane. The pixel size was 0.8 mm, and the slice thickness was 0.9 mm. The scan duration was 10 minutes 40 seconds. Postprocessing visualized the carotid bifurcation and enabled stenosis calculation by NASCET criteria. Stenosis was dichotomized into greater or equal to 70% and <70%.

Statistical Analysis
All analysis was carried out using the Statistical Package for Social Sciences (SPSS) version 9 for Windows. \( \chi^2 \) test was used to assess differences between the prevalence of high signal in patients' ipsilateral and contralateral arteries, between high signal at severe (70% to 100%) and lesser (<70%) ipsilateral stenoses in patients, and in comparing high signal in patients' arteries overall with controls' arteries. Symptom to scan time was found to have a nonparametric distribution when analyzed with a histogram on SPSS. Therefore, a log transformation of the data was performed, and the independent samples' \( t \) test was then used to seek any differences between the time taken for scan in MRDTI-positive and -negative symptomatic patient groups. A significance level of \( P<0.05 \) was used.

Results
A total of 120 patients and 14 controls (Table 1) were recruited as outlined in Figure 2. All patients had previous focal neurological symptoms in the cerebral hemisphere ipsilateral to the stenosis. Because no patient had bilateral symptoms, the contralateral arteries acted as internal controls for the relationship of MRDTI high signal to symptoms.

None of the controls had MRDTI high signal in their carotid arteries (Table 3). Three control arteries had mild (20%) stenosis, and the rest had no stenosis. The prevalence of MRDTI high signal in the ipsilateral arteries of 120 symptomatic patients was 60%. There was a significant difference in the prevalence of MRDTI high signal between the ipsilateral and contralateral arteries of patients (Table 2). The difference was most marked in the arteries that were <70% stenosed. Thirty-three patients (27%) had bilateral high signal, 39 (33%) had only ipsilateral high signal, and 38 (32%) had neither. Only 10 (8%) had contralateral high signal without ipsilateral high signal. In those patients with <70% stenosis, there were 9 patients (38%) with bilateral high signal, 7 (29%) with only ipsilateral high signal, 6 (25%) with neither, and only 2 (8%) had contralateral high signal without its presence in the ipsilateral artery.

Patients who had ipsilateral high signal had a median time of 12 weeks from first symptom to scan (range, 4 days to 8 weeks). For those with no ipsilateral high signal, this median time was 17 weeks (range, 4 to 109 weeks). There was a significant difference between the time taken from first symptoms to scan between the symptomatic MRDTI-positive and -negative groups (\( P=0.041 \)). Eighteen patients were known to have had recurrent symptoms in the symptomatic artery territory. The median time from last symptoms to scan for patients with ipsilateral high signal was 4 weeks, and that for those with no ipsilateral high signal was 6 weeks. This difference was not significant.

Discussion

Summary of Findings
The aim of the present study was to examine the in vivo prevalence of complicated plaque, as detected by MRDTI high signal, in a group of recently symptomatic patients with suspected severe carotid stenosis. In so doing, we tested the hypothesis that complicated plaque in the ipsilateral artery is related to cerebrovascular symptoms in these patients. The prevalence of MRDTI high signal in the ipsilateral arteries of 120 symptomatic patients scanned was 60%. There was significantly greater prevalence of MRDTI high signal in the ipsilateral compared with the contralateral arteries (60% compared with 27%), suggesting a relationship.
versus 36% prevalence, \( P < 0.001 \)). This difference was most marked in the vessels that were <70% stenosed, where the prevalence of high signal was 67% in ipsilateral and 31% in contralateral arteries (\( P < 0.01 \)). There was no carotid high signal seen in age- and sex-matched controls without history of stroke or other vascular events. MRDTI high signal in the patients’ contralateral artery was associated with the presence of high signal on the ipsilateral side. The time taken from first symptoms to scan was significantly less in the positive ipsilateral signal group than the negative ipsilateral signal group. For those patients in whom the timing of last symptoms was known, there was no difference in these groups.

**Discussion of Findings**

The 60% prevalence of MRDTI high signal in the ipsilateral artery of patients with cerebrovascular ischemia suggests that more than half of the patients in this group have complicated plaque in their symptomatic artery. Because no patient had simultaneous cerebrovascular symptoms referable to both arteries, comparison was made between the patients’ ipsilateral and contralateral arteries. The significantly greater prevalence of high signal in our patients’ ipsilateral arteries compared with their contralateral side suggests that the presence of complicated plaque as identified by this technique is important in the production of their symptoms. This may be particularly so in the patients with a stenosis of <70%, where the prevalence of high signal in ipsilateral arteries was more than two thirds. The mechanism of symptom generation from complicated plaque is likely to be thromboembolism. Previous studies of coronary arteries have shown that coronary occlusion and myocardial infarction most frequently arise from mild to moderate rather than severe stenoses.7,8 In the ECST and NASCET trials, it was shown that there was no benefit of carotid endarterectomy for symptomatic carotid stenoses of <70%.9,10 Although the percentage risk of stroke from these moderate stenoses is less overall, they are more numerous than their severe counterparts, so there is a large stroke burden from stenoses that are presently not recommended for surgery.

The very presence of high signal in 36% of the contralateral, asymptomatic arteries suggests that the production of clinical symptoms is not inevitable when complex plaque is present. The presence of asymptomatic complicated plaque may reflect that many complications undergo healing without causing symptoms or that lesions can still be actively embolizing without clinical manifestations.11 Our findings showed that more than three quarters of patients who had contralateral high signal had ipsilateral signal (33 of 43 patients). This is in keeping with the recognition that atheroma is a systemic disease and is additionally supported by the absence of high signal in the carotid arteries of control subjects who had no history of any vascular events.

**Strengths of the Present Study**

The MRDTI sequence is an in vivo technique that is quick (3.5 minutes), well tolerated, and has good interobserver agreement. Any commercially available scanner can be set up for the technique, making it clinically applicable. Inclusion of this sequence in a brain and vessel imaging protocol for patients with cerebrovascular symptoms enables a comprehensive assessment of carotid stenosis, plaque complexity, and cerebral damage in one visit. This technique is well suited for use in large-scale observational studies, setting the scene for natural history and interventional studies.

**Limitations of the Present Study**

The number of patients in the symptomatic moderate stenosis group (<70%) was small at only 24, compared with 96 in the symptomatic severely stenosed group. This is attributable to the inherent bias in selection of patients scanned. The number of control subjects was much lower than that of patients, and it cannot yet be assumed that the prevalence of complicated plaque in a low risk group is zero. The timing from first symptoms to scan was long, and analysis suggested that the presence of MRDTI high signal might be related to this timing. The shorter time to study in the MRDTI-positive group could reflect more frequent or more significant ongoing symptoms causing the patient to seek earlier advice. Some patients continued to have symptoms long after the index

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<th>TABLE 2. Tabulation of MRDTI High-Signal Prevalence (Scan Positive) in Patients</th>
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<td>Total ipsilateral arteries (n=120)</td>
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<td>Total contralateral arteries (n=120)</td>
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<td>Ipsilateral &lt;70% stenosis (n=24)</td>
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<td>Ipsilateral 70% to 100% stenosis (n=96)</td>
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<td>Contralateral 70% to 100% stenosis (n=30)</td>
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<th>TABLE 3. Comparison of High-Signal Prevalence in Patients and Controls</th>
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<td>Patients (n=120 symptomatic vessels)</td>
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<td>Controls (n=28 nonsymptomatic vessels)</td>
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event, and time to scan from this last event was therefore shorter for these patients, but there was no difference in this timing for scan-positive and scan-negative patients.

Relationship to Other Work
The present study provides an estimate of the prevalence (60%) of complicated plaque defined by intraplaque hemorrhage in a selected group of stenosed, symptomatic carotid arteries in vivo. In a histological study of endarterectomy specimens, Lusby et al.12 found an 85% prevalence of intraplaque hemorrhage in symptomatic vessels of >50% stenosis. A recent meta-analysis of carotid endarterectomy studies found this figure was 48%.13 We do not yet know the duration of in vivo MRDTI high signal, and our technique may be detecting different ages of hemorrhage/thrombus. Application of a similar technique in the venous lumen has shown that MRDTI high signal can form in deep vein thrombus within hours and persist for several weeks once formed.14

Assessment of fibrous cap thickness and integrity, and therefore plaque vulnerability, has been achieved using T2-weighted and bright-blood imaging sequences to generate contrast between vessel wall and lumen.15 Full morphological characterization, however, relies on the use of more than one sequence.16 Thrombus and hemorrhage are plaque components previously shown to be detected with the least sensitivity using a variety of MR techniques, such as diffusion-weighted and T1 high spatial resolution imaging.18–20 However, in animal experiments, MRI has accurately identified and aged intra-arterial lumen thrombus.21,22 Recent work with multispectral MRI identified intraplaque hemorrhage and necrotic core with high accuracy in 18 human carotid endarterectomy subjects.23 Later work has demonstrated that in vivo high resolution multicontrast MRI is capable of classifying intermediate to advanced atherosclerotic lesions in the human carotid artery and found a 37% prevalence of histological complicated (type VI) plaque in 52 endarterectomy patients.24 Yuan et al.25 showed that multicontrast MRI identification of a ruptured fibrous cap is highly associated with a recent history of transient ischemic attack or stroke in 53 endarterectomy subjects. Our study has shown a 60% prevalence of MRDTI-defined ipsilateral complicated plaque and a significantly higher prevalence in symptomatic versus asymptomatic arteries.

Implications and Future
This technique has been used for the study of point prevalence of carotid complicated plaque. A natural history study will, however, give information regarding the persistence over time of high signal and its relationship to incident symptoms, and there is the potential to study the relationship of complicated plaque with clinical parameters and blood markers of endothelial cell dysfunction. The pilot data from this study suggest that additional investigation of symptomatic plaques specifically with <70% stenosis would be worthwhile.

Conclusion
Prevalence of MRDTI-defined complicated plaque in the ipsilateral arteries of 120 patients with previous cerebrovascular ischemia was 60%. MRDTI high signal suggestive of complicated plaque was more prevalent in the ipsilateral carotid arteries of patients compared with their contralateral arteries, particularly in arteries of <70% stenosis. The technique may have a role in identifying “at risk” plaque morphology and in natural history studies of plaque behavior.

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References
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