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Detection and Characterization of Atherosclerotic Fibrous Caps with T2-Weighted MR

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PURPOSE: **We assessed the performance of T2-weighted MR imaging in detecting atherosclerotic fibrous caps and in depicting their integrity.**

METHODS: **Twenty atherosclerotic lesions removed by carotid endarterectomy were imaged on a 1.5-T system using T2-weighted spin-echo sequences. The MR images were reviewed independently by four blinded interpreters for fibrous caps and ruptures. The results obtained from the observers were then graded against histologic findings by using receiver-operating characteristic (ROC) curve analysis.**

RESULTS: **The area under the ROC curve for fibrous cap detection was 0.80, indicating that T2-weighted MR imaging was a good but not definitively diagnostic test for detecting ex vivo fibrous caps. The ROC curve for fibrous cap characterization yielded an area of 0.75, indicating that T2-weighted MR imaging was a fair but not highly diagnostic test for depicting fibrous cap integrity. A definite reading for detection of fibrous caps or rupture was fairly specific (90% and 98%, respectively) but not very sensitive (37% and 12%, respectively).**

CONCLUSIONS: **T2-weighted MR imaging of ex vivo atherosclerotic plaques aided in the detection and evaluation of fibrous caps. In both cases, MR imaging proved more useful for ruling out disease than for confirming its presence.**

Atherosclerosis is the leading cause of morbidity and mortality in the Western world. Over 50% of deaths in the United States are directly attributable to atherosclerotic disease (1). Current imaging approaches, which rely on sonography and X-ray angiography, are able to locate regions of arterial stenosis and thus assist with the identification of atherosclerotic plaques. These techniques, however, are limited by their inability to differentiate the tissue components of atherosclerotic lesions and are therefore less than ideal for distinguishing stable fibrous plaques from high-risk atheromatous lesions. Magnetic resonance (MR) imaging, with its ability to depict soft tissues in exquisite detail, is ideally suited for just such a task.

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Advanced atherosclerotic plaques typically contain a fibrous cap, a layer of tissue composed primarily of smooth muscle cells and collagen, which separates the vessel lumen from an atheromatous core. Histologic examination of carotid arterial plaques at autopsy suggests that rupture of this fibrous cap places patients at higher risk for future complications, particularly distal embolization and local thrombus formation (2, 3). Noninvasive differentiation of stable from unstable plaques would provide physicians with invaluable information as they consider the wide variety of treatment alternatives for atherosclerosis.

Recent research indicates that T2-weighted MR imaging holds significant potential for differentiating the tissue components of complex atherosclerotic plaques (4–7). Our preliminary observations using fast spin-echo data acquisition with T2 contrast weighting as our standard imaging protocol seem to support these findings. Since our pilot research indicated the potential of MR imaging in the characterization of vascular disease, we sought to quantify the accuracy of T2-weighted sequences in the detection and characterization of fibrous caps. Our objective was to use receiver-operator characteristic (ROC) analysis to test the accuracy of MR imaging in the identification and characterization of fibrous caps in ex vivo atherosclerotic plaques.

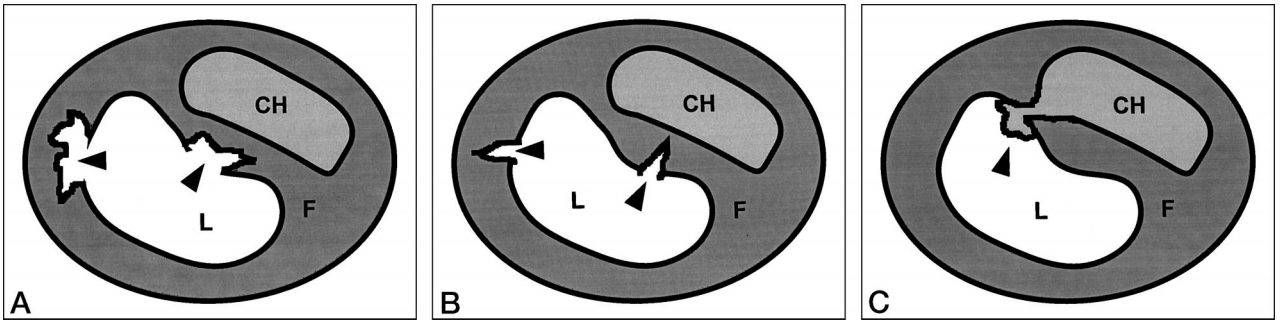

FIG 1. Schematic representations of ulcers (*arrowheads, A*), fissures (*arrowheads, B*), and a rupture (*arrowhead, C*). Histologists were instructed to record only fibrous cap ruptures, defined as discontinuities that allowed the lipid core (*CH*) to come in contact with the vessel lumen (*L*). Therefore, the ulcers in *A* and the fissures in *B* would not be recognized as fibrous cap ruptures, but the lesion represented in *C* would. *F* represents fibrous plaque.

Methods

Study Design

To avoid the biases and pitfalls usually encountered in the evaluation of a diagnostic test, we incorporated the following concepts into the study protocol:

- Histologic and diagnostic determinations would be made independently; that is, without knowledge of corresponding results.
- Imaging parameters (such as contrast weighting and sample temperature) would be reasonably consistent among samples.
- The sample set would not be polarized into clear examples of intact and/or ruptured caps.
- The sample size would be adequate to ensure a difference between observers' determinations and random diagnoses in differentiating cap from rupture, if such a difference existed.
- All observers would possess a minimum level of knowledge of vascular histology and of the principles of vascular MR imaging.
- The sequence of images viewed by the observers would be randomized to protect against order effects.
- A reliable location system that orients the specimen and the images by reference to identifiable landmarks would be used so that both the histologist and the radiologist would be describing the same region of interest (ROI).

Sample Procurement

Twenty atherosclerotic plaques were obtained from patients undergoing carotid endarterectomy for symptomatic cerebrovascular disease. Once removed from patients, the plaques were immediately placed in nutrient media (RPMI medium 1640, Life Technologies Inc, New York, NY) for preservation. The MR study was conducted at body temperature (37°C) within 4 hours of surgery to preserve the relaxation parameters of in vivo tissue and to preserve the tissue for histologic processing. After the first series of MR images were obtained, the specimen was fixed in a 10% neutral buffered formalin solution. Of the 20 MR sequences included in the study, 12 were taken with the plaque in nutrient solution. The eight remaining sequences were acquired within 4 hours of fixation.

Imaging Protocol

MR images were obtained with a 1.5-T unit (Signa, GE Medical Systems). A polyethylene container was built to accommodate the mounted plaque specimen, a quantity of solution for preservation, and a custom-made surface coil (single turn, 4.5 cm long and 3 cm wide) (8). A tube passing through the container allowed for circulation of externally heated water, used to raise the temperature of the plaque specimen to body temperature (37°C). The temperature of the RPMI solution was calibrated before imaging began. The MR imaging protocol included an axial fast spin-echo T2-weighted sequence (3183/100/1 [repetition time/echo time/excitations]) with section thicknesses of 1 mm. The initial nine samples were imaged with an echo train length of 24 in an effort to shorten imaging time. The rest of the samples were imaged with an echo train length of eight to enhance image quality. These images were obtained by using a field of view of 8 cm, a matrix size of 256 × 256 pixels, yielding in-plane resolution and voxel volume to approximately 310 μm and 0.00010 mL, respectively.

The ROI for our study was designated as the 4 mm of plaque at and proximal to the bifurcation of the common carotid artery. This allowed us to use the bifurcation of the carotid artery as a common reference point as well as to target a region prone to plaque rupture and ulceration (2). Four consecutive MR images from the ROI of each carotid plaque were designated for evaluation.

Histologic Assessment and Definitions

Cross-sectional serial sections with a thickness of 10 μm or less were obtained at 0.5-mm intervals from each plaque specimen. These sections were stained with hematoxylin-eosin and examined under the microscope with the assistance of a pathologist who was blinded to the MR results. All fibrous caps and ruptures were recorded on digitized photographs created from each slide. A fibrous cap was defined as a layer of tissue consisting of predominantly smooth muscle cells and collagen fiber overlying a core of lipid-rich or necrotic tissue. For the purpose of this study, a rupture was defined as a discontinuity in a fibrous cap such that the vessel lumen was placed in contact with the contents of the lipid core. An ulcer was defined as any lesion producing a defect in the arterial epithelium and intima. Fibrous caps with ulcers or fissures that did not expose atheromatous or necrotic material to the vessel lumen were not considered ruptured (see Fig 1). Pathologists were consulted on the classification of complex or ambiguous plaques.

Sample Set

Four consecutive images proximal to the bifurcation of the carotid artery were selected from each of the 20 plaques, yielding a total of 80 images/histologic section pairs. Four sections could not be evaluated histologically, owing to fixation artifacts; the corresponding images/section pairs were discarded from the study, resulting in 76 images/histologic pairs available for study.

To ensure a proper number of regions without fibrous caps in this selected, advanced lesion population, and to maximize the efficiency of radiologic and histologic comparisons, each image was divided in half to produce two ROIs. Each histologic ROI was matched with its corresponding radiologic ROI by

using the surgical incision in the plaque made during endarterectomy as a marker. We understood that with this correspondence between analyses on the same specimens, we could not assume independence of the readers' responses for each of the ROIs of a given plaque. Of the 152 ROIs used in the study, 81 were found to have fibrous caps at histologic examination. Of the 81 ROIs with fibrous caps, 37 contained a cap rupture. Five ROIs were discarded from the study because a histologic determination as to the presence or absence of a rupture could not be made. Such a situation arose when the surgical incision produced by the endarterectomy procedure was made through a region that contained a fibrous cap.

Image Interpretation

Four board-certified radiologists with MR experience ranging from 2 to 10 years participated as observers in the study. Each radiologist received a packet containing articles, instructions, and a series of standardized forms. Before participating in the study, the observers were asked to read the articles to refresh their knowledge of vascular imaging and of the histology of atherosclerosis. The instructions contained an overview of the study, histologic definitions, directions for using the standardized forms, and a table of relative T2-weighted contrast values for the variety of soft-tissue components found in atherosclerotic lesions. Before reviewing the images, each observer was familiarized with the workstation (GE Medical Systems, Independent Console) and shown examples of T2-weighted images of plaques along with digitized photographs of the corresponding histologic cross sections.

A standardized form was used to record information from the MR images. Four images at each carotid artery were presented serially. A total of 80 images (from 20 plaque specimens) were magnified by a factor of three and filmed. These were presented in a random sequence for each observer so as to offset possible order effects. A line representing the contour of the arterial lumen was drawn on the standardized form for each of the images. The observers then used these diagrams to record the location of all perceived fibrous caps and fibrous cap ruptures.

After recording the presence of a fibrous cap, observers were asked to rate their confidence in the diagnosis and the perceived integrity of the cap on separate five-point scales, as follows: definite fibrous cap, probable fibrous cap, possible fibrous cap, or probably no fibrous cap; regions in which no fibrous cap was suspected were labeled definitely no fibrous cap. Plaque integrity was classified as definitely intact, probably intact, possibly ruptured, probably ruptured, or definitely ruptured. The observers were provided with representative sketches as examples of each classification.

Accuracy Analysis

The blinded readings were graded against the standard of reference provided by histologic findings. Axial MR images were paired and aligned with slides of the same specimen by matching corresponding cross sections. Data from the individual observers were pooled together with the rationale that standardized observer preparation would produce similar results among the interpreters. Assuming a binomial model and using the maximum likelihood method employed by the FORTRAN program ROCFIT (used by permission of C. E. Metz, University of Chicago [Ill]) receiver-operator curves with asymmetric 95% confidence intervals were calculated for fibrous cap detection and characterization (9). ROCFIT was also used to calculate the area under each ROC curve, with a standard deviation.

Likelihood ratios were calculated to determine the utility of each of the five diagnostic categories used by the observers. These ratios (produced by dividing the number of images positive for disease by the number of images negative for disease within each category) tell how strong the association is between a category and the disease state in question (10). Ratios approaching infinity indicate that a category is strongly associated with the presence of disease, while ratios approaching zero indicate that a category is strongly associated with the absence of disease. Categories with likelihood ratios close to one are less helpful in constructing a diagnosis, since they are associated with neither the presence nor the absence of the disease in question.

TABLE 1: Sensitivity and specificity of T2-weighted MR imaging for detection of a fibrous cap

	Sensitivity, %	Specificity, %	Likelihood Ratio
Definite fibrous cap	37	90	3.8
Probable fibrous cap	60	78	2.0
Possible fibrous cap	73	71	1.9
Probably no fibrous cap	82	65	1.4
Definitely no fibrous cap	100	0	0.3

Results

The sensitivity and specificity of T2-weighted MR imaging as a test for fibrous cap detection varied depending on the cutoff point used to determine a positive finding. If "definite fibrous cap" was used alone, the study found a true-positive rate (ie, sensitivity) of 37% with a false-positive rate of 10%. If the definition of a positive test was expanded to include "probable fibrous cap," the sensitivity increased to 60%, but the false-positive rate increased to 21%. For a region designated by the observers as "definitely not fibrous cap," a true-negative rate of 65% and a false-negative rate of 18% were calculated. Sensitivities and specificities for other possible cutoff points are detailed in Table 1. The area of 0.799 (SD ± 0.0193) underneath the ROC curve as calculated by ROCFIT (Fig 2) indicates that T2-weighted MR imaging is a good although not a definitive test for detecting ex vivo fibrous caps.

The study found similar results for the accuracy of MR imaging for characterizing fibrous cap integrity. For regions labeled as "definitely ruptured" by the observers, a sensitivity of 12% and a false-positive rate of 2% were found. When the cutoff point was expanded to include "probably ruptured" caps, the sensitivity increased to 35% and the false-positive rate increased to 8%. T2-weighted MR imaging proved much more useful for ruling out fibrous cap ruptures; for regions labeled "definitely intact," the true-negative rate was 60% and the false-negative rate 25%. These results indicate that MR imaging shows more utility when used to rule out rather than confirm the presence of fibrous cap ruptures. The sensitivity and specificity of other cutoff points are provided in Table 2. An area of 0.748 (SD ± 0.0266) underneath the ROC curve in Figure 3 indicates that T2-weighted MR imaging is a fair but not highly diagnostic test for detecting ex vivo fibrous cap ruptures.

Although the standard deviation of the ROC curve areas using the combined observer data was slight (SD ± 0.0193 and SD ± 0.0266 for fibrous cap de-

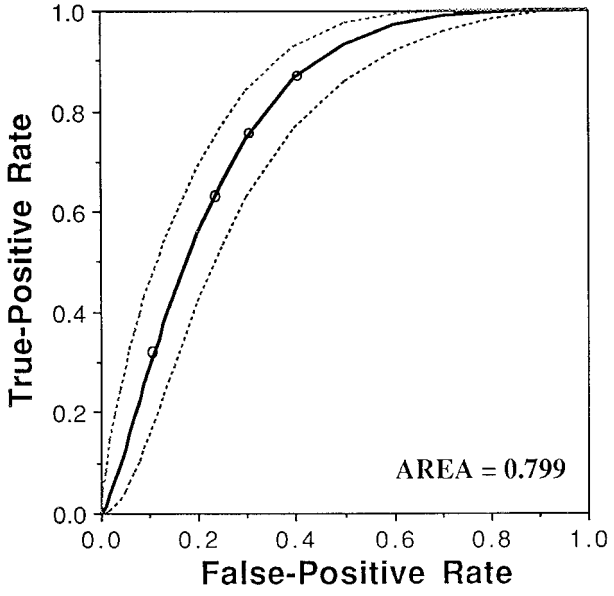

FIG 2. ROC curve for T2-weighted MR imaging for detection of a fibrous cap. The true-positive rate is analogous to sensitivity, while the false-positive rate is calculated as 1−specificity. The *solid line* is the ROC curve calculated by ROCFIT based on combined observer data. The *dashed lines* are the 95% confidence bands. The *circles* represent the operating points from which the curve was calculated. The total area underneath the ROC curve is 0.799 (SD ± 0.0193).

TABLE 2: Sensitivity and specificity of T2-weighted MR imaging for characterization of a fibrous cap

	Sensitivity, %	Specificity, %	Likelihood Ratio
Definitely ruptured	12	98	7.2
Probably ruptured	35	92	3.4
Possibly ruptured	54	81	1.9
Probably intact	75	60	1.0
Definitely intact	100	0	0.4

tection and characterization, respectively) the sensitivity and specificity of the individual observers did vary significantly according to their confidence in identifying caps and ruptures. For example, the sensitivity of using either a "definite fibrous cap" or a "probable fibrous cap" designation as a positive test ranged from a low of 48% to a high of 93% among the four observers. The observer with the highest sensitivity also produced the highest number of false-positive scores, however; resulting in a specificity of only 53%.

Discussion

Degree of arterial stenosis is widely used as a clinical indicator of the severity of atherosclerotic disease. Unfortunately, degree of stenosis does not always correlate well with the risk for such clinical events as transient ischemic attack, stroke, and occlusion. Coronary angiographic studies, for example, have shown that plaques that produce only mild to moderate stenosis frequently undergo abrupt disruption (3, 11, 12). Davies and coworkers (3, 13) found

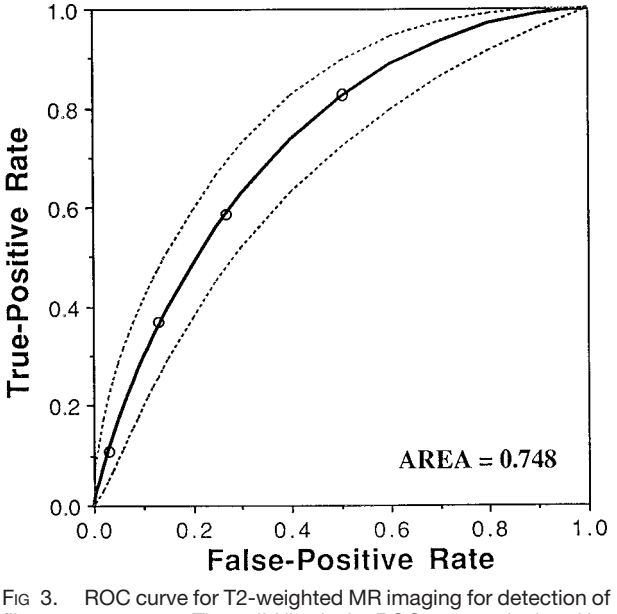

FIG 3. ROC curve for T2-weighted MR imaging for detection of fibrous cap rupture. The *solid line* is the ROC curve calculated by ROCFIT based on combined observer data. The *dashed lines* are the 95% confidence bands. The *circles* represent the operating points from which the curve was calculated. The total area underneath the ROC curve is 0.748 (SD ± 0.0266).

that relatively small plaques with increased lipid content appear more prone to rupture, particularly if the lipid pool is located eccentrically within the intima. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) found that nearly three fourths of all atherosclerotic lesions (more than 70% stenosis) remained clinically silent during a 2-year follow-up period, suggesting that stenosis may not directly correlate with symptoms (14).

Carotid plaque rupture, on the other hand, has been directly implicated in the pathogenesis of acute and subacute cerebrovascular events (15). Acute events caused by the release of necrotic tissue include distal embolization and occlusion. A rupture site may also act as a nidus for subsequent platelet and fibrin aggregation, leading to arterial thrombosis or embolization (16). The pathogenesis of fibrous cap formation and rupture is not fully understood, partly because we lack imaging methods that can detect disease before symptoms develop. It is thought, however, that the formation of a lipid core and subsequent weakening of the overlying fibrous cap predispose the plaque to rupture (17, 18).

Our study attempted to quantify the ability of T2-weighted MR imaging to depict and characterize these fibrous caps in ex vivo atherosclerotic plaques. As prior research has shown (4, 5), this imaging method is effective in differentiating between fibrous and cholesterol-laden plaque tissue. Figure 4 shows corresponding T2-weighted MR and histologic sections of an atheromatous plaque with a well-defined, intact fibrous cap. Fibrous caps rich in calcification were particularly easy for the observers to identify. The signal intensity of a fibrous plaque appears to vary depending on its water content; it is, however, consistently brighter than regions of calcification. Re-

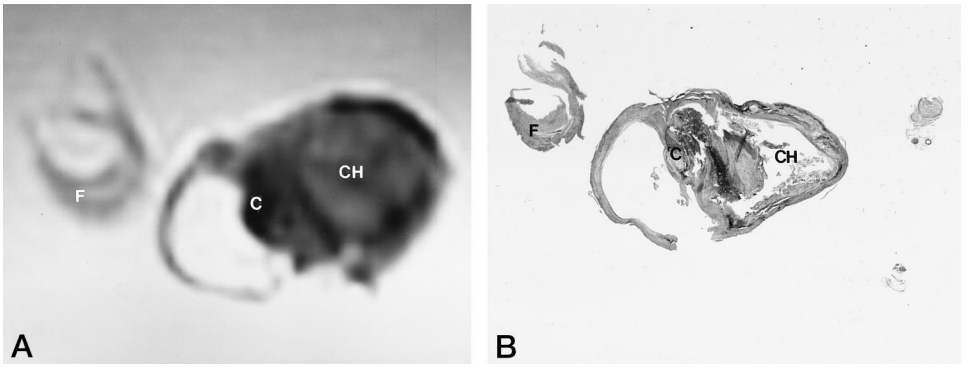

FIG 4. T2-weighted MR image (*A*) and corresponding histologic section (*B*) of an atherosclerotic plaque with intact fibrous cap. The plaque on the right (internal carotid) has a calcified fibrous cap (*C*) and a necrotic core rich in cholesterol crystals (*CH*). The plaque on the left (external carotid) is composed mainly of fibrous tissue (*F*).

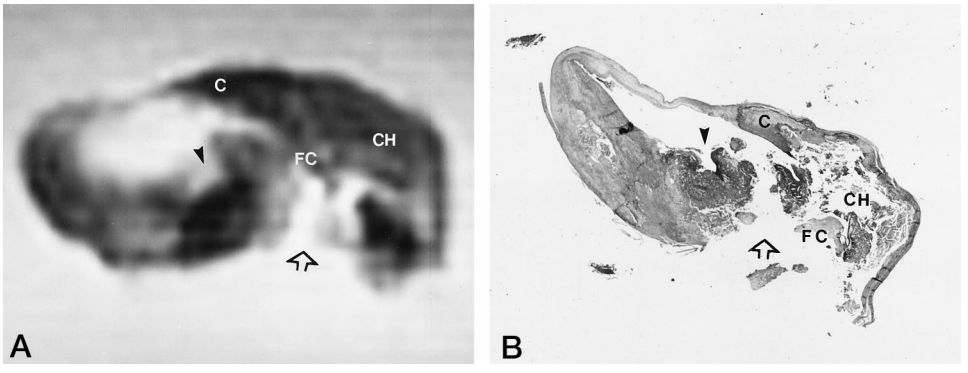

FIG 5. T2-weighted MR image (*A*) and corresponding histologic section (*B*) of an atherosclerotic plaque with ruptured fibrous cap. This specimen shows an ulcer overlying atheromatous tissue (*arrowhead*). *Arrow* indicates the surgical incision produced by endarterectomy. Regions of calcification (*C*), cholesterol (*CH*), and discontinuous fibrous cap (*FC*) are also present.

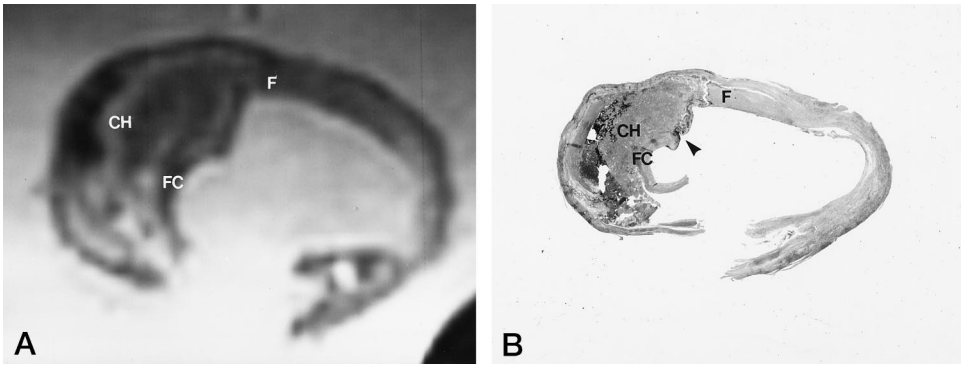

FIG 6. T2-weighted MR image (*A*) and corresponding histologic section (*B*) of an atherosclerotic plaque with undetected rupture. The microulceration seen clearly on the histologic section (*arrowhead*) was not detected by the majority of observers. This specimen clearly shows a fibrous cap (*FC*) overlying an atheromatous core (*CH*) rich in cholesterol crystals. *F* indicates fibrous intima.

gions of necrotic tissue rich in cholesterol appear as brighter regions on the MR image. These findings are consistent with those of previous studies (4, 5).

Figure 5 shows an ulcerated atheromatous plaque with a distinct fibrous cap rupture alongside the surgical incision produced by the endarterectomy procedure. Unfortunately, these surgical artifacts occasionally traversed ROIs within a plaque cross section. For this reason, subsequent to this study, the endarterectomy procedure used to procure ex vivo samples was altered. Atherosclerotic plaques are now cored out, resulting in plaque specimens without an intimal incision.

The rupture in Figure 5 illustrates a number of characteristics that make a fibrous cap rupture more likely to be detected by an observer. First, it is large, measuring 0.4 mm across, and second, it is an open lesion, relatively uncomplicated by thrombus formation. In addition, ruptures formed through regions of a well-defined fibrous cap produced an obvious discontinuity on the MR image. This type of rupture may belong to a category that yields high sensitivity and specificity results.

The plaque shown in Figure 6, however, contains a rupture that all four observers were unable to identify despite a well-defined cap and atheromatous core. The histologic section shows a discontinuity in the fibrous cap, which places the contents of the atheromatous core in contact with the vessel lumen, thus meeting our definition of a fibrous cap rupture. There are, however, two characteristics that make this rupture difficult to detect: first, it is thin and shallow, measuring 0.1 by 0.2 mm. Our observers had difficulty identifying ruptures that were smaller than 0.2 mm across. This was not unexpected. Second, this rupture is complicated by thrombus formation. We did not anticipate the confusion that would be caused by regions of thrombus formation overlying regions of plaque rupture. Coagulating hemorrhage and organizing thrombus were significant sources of false-

positive identification of fibrous caps and false-negative identification of fibrous cap rupture. To confuse the issue further, the signal intensity of thrombus and hemorrhage varied considerably depending on its age and degree of organization.

The sensitivity and specificity of ex vivo plaque characterization may be increased by taking additional steps. First, the performance of the observers should improve as they gain more experience with plaque evaluation. Observer preparation can be optimized by expanding the set of training images and devising a pretest to assure a minimum level of competence. Second, optimal imaging parameters (eg, repetition and echo times) still need to be identified. Alternative image-processing algorithms that enhance contrastbetween fibrous and fat-laden tissues could also prove useful. Finally, use of the new, "incisionless" endarterectomy technique will preserve greater regions of plaque intima, reduce surgical artifacts, and hence improve sensitivity and specificity.

Despite these encouraging findings, it is important to note that ex vivo imaging takes place under special conditions not necessarily equivalent to clinical imaging. Our study design did not have to consider patient movement or arterial pulsation, either of which could cause substantial motion artifacts. In addition, the process of surgical excision and tissue preparation may result in distorted tissue contrast values as compared with in vivo conditions. Extensive comparison of in vivo MR images and histologic sections of excised carotid plaque remains to be done.

Conclusion

Our study found that T2-weighted MR imaging was able to provide valuable assistance in characterizing atherosclerotic lesions removed by endarterectomy. Radiologists determined the presence and integrity of atherosclerotic fibrous caps with reasonable specificity. Our results may also be used to help predict the minimum size of fibrous capsule rupture that is likely to be detectable with clinical MR imaging techniques presently available. If similar imaging techniques can be successfully adapted to in vivo situations, as we believe possible, clinicians will have a valuable tool for identifying high-risk atherosclerotic lesions. Identification of rupture-prone plaques could affect decisions regarding medical versus surgical therapy. In addition, in vivo adaptation of this technique may prove useful for monitoring long-term efficacy of various medical therapies and lifestyle changes in patients with atherosclerosis.

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References

1. Lilly LS. **Pathophysiology of Heart Disease**. Philadelphia, Pa: Lea & Febiger; 1993:84–98
2. Masawa N, Yoshida Y, Joshita T, et al. **Three-dimensional analysis of human carotid atherosclerotic ulcer associated with recent thrombotic occlusion**. *Pathol Int* 1994;44:745–752
3. Davies MJ, Thomas AC. **Plaque fissuring: the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina**. *Br Heart J* 1985;53:363–373
4. Martin AJ, Gotlieb AI, Henkelman RM. **High-resolution MR imaging of human arteries**. *J Magn Reson Imaging* 1995;5:93–100
5. Toussaint JF, LaMurgaglin GM, Southern JF, Fuster V, Kantor HL. **Magnetic resonance images lipid, fibrous, calcified, hemorrhagic, and thrombotic components of human atherosclerosis in vivo**. *Circulation* 1996;94:932–938
6. Pan XM, Saloner D, Reilly LM, et al. **Assessment of carotid artery stenosis by ultrasonography, conventional angiography, and magnetic resonance angiography: correlation with ex vivo measurement of plaque stenosis**. *J Vasc Surg* 1995;21:82–88
7. Gold GE, Pauly JM, Glover GH, et al. **Characterization of atherosclerosis with a 1.5-T imaging system**. *J Magn Reson Imaging* 1993; 3:399–407
8. Yuan C, Tsuruda JS, Beach KN, et al. **Techniques for high-resolution MR imaging of atherosclerotic plaque**. *J Magn Reson Imaging* 1994;4:43–49
9. Metz CE. **ROC methodology in radiologic imaging**. *Invest Radiol* 1986;21:720–733
10. Mushlin AI, Detsky AS, Phelps CE, et al. **The accuracy of magnetic resonance imaging in patients with suspected multiple sclerosis**. *JAMA* 1993;269:3146–3151
11. Ambrose JA, Tannenbaum MA, Alexopoulos D, et al. **Angiographic progression of coronary artery disease and the development of myocardial infarction**. *J Am Coll Cardiol* 1988;12:56–62
12. Little WC, Constantinescu M, Applegate RJ, et al. **Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease**? *Circulation* 1988;78:1157–1166
13. Davies MJ. **A macro and micro view of coronary vascular insult in ischemic heart disease**. *Circulation* 1990;82:1138–1146
14. North American Symptomatic Carotid Endarterectomy Trial Collaborators. **Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade stenosis**. *N Engl J Med* 1991;325:445–453
15. Carr S, Farb A, Pearce WH, Virmani R, Yao JST. **Atherosclerotic plaque rupture in symptomatic carotid artery stenosis**. *J Vasc Surg* 1996;23:755–766
16. Van Damme H, Demoulin JC, Zicot M, Creemers E, Trotteur G, Limet R. **Pathological aspects of carotid plaques: surgical and clinical significance**. *J Cardiovasc Surg* 1992;33:46–53
17. Falk E. **Why do plaques rupture**? *Circulation* 1992;86(Suppl): 30–42
18. Leen EJ, Feeley TM, Colgan MP, et al. **"Haemorrhagic" carotid plaque does not contain haemorrhage**. *Eur J Vasc Surg* 1990;4:123–128