Original Research

In Vivo Accuracy of Multisequence MR Imaging for Identifying Unstable Fibrous Caps in Advanced Human Carotid Plaques

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Purpose: To evaluate the in vivo accuracy of a multisequence MRI technique for prospectively identifying one feature of the vulnerable plaque—an unstable fibrous cap—in human carotid atherosclerosis.

Materials and Methods: The carotid arteries of 18 endarterectomy patients were preoperatively imaged in a 1.5T scanner using a multisequence protocol that generated four contrast weightings (3D time of flight (ToF), T1, proton density (PD), and T2) at each slice location. With the use of previously published MR criteria, the images of the vessel wall were first examined for evidence of an unstable fibrous cap. The imaging findings were then correlated with the histology from the surgical specimens.

Results: A blinded review of the MR findings with the histologic state of the fibrous cap revealed that 1) assessing the preoperative appearance of the fibrous cap has a high test sensitivity (0.81) and specificity (0.90) for identifying an unstable cap in vivo; and 2) the availability of different contrast weightings facilitated image interpretation when intimal calcifications or flow artifacts obscured the lumen surface.

Conclusion: Multisequence MRI can accurately characterize the in vivo state of the fibrous cap. This finding supports the use of these noninvasive techniques to prospectively identify vulnerable plaques.

Key Words: magnetic resonance imaging; plaque rupture; atherosclerosis; carotid arteries; vulnerable plaque
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HISTOLOGIC STUDIES suggest that acute ischemic events, such as stroke and transient ischemic attack (TIA), are related to plaque rupture, and that morphologically the symptomatic lesion often contains a region wherein a thin or disrupted fibrous cap overlies a large necrotic core. Such findings have led to the concept of the vulnerable plaque, which associates these morphologic features of instability with lesions that are at risk of rupturing and causing clinical symptoms (1–3).

A growing body of research is also demonstrating that magnetic resonance imaging (MRI) can be used to characterize human atherosclerotic plaque morphology and identify important intraplaque structures such as the fibrous cap. Although early investigations noted anecdotally that T2-weighted images could differentiate fibrous from lipid-rich regions of plaque (4,5), the accuracy of identifying unstable fibrous caps based on a single T2-weighted sequence tested with ex vivo specimens was only marginal (sensitivity = 0.12, specificity = 0.98) (6). Improved characterization of the cap was achieved in a subsequent study (7) that showed that the axial source images from a 3D multiple-overlapping thin slab carotid angiogram (MOTSA) could be used to distinguish intact thick fibrous caps from unstable caps. Together, these studies provided the basis for recent work (8) that revealed that the in vivo detection of an unstable fibrous cap by MRI was highly associated with the history of a recent TIA or stroke (odds ratio > 10). This important result suggests that MRI can enable detection of a vulnerable plaque prior to the development of an acute ischemic event.

While the development of a noninvasive means of assessing plaque stability could have a tremendous impact on the management of atherosclerotic vascular disease, the accuracy of these MRI techniques for plaque characterization in vivo must be determined before they can be applied clinically (9). Given the important relationship between the state of the fibrous cap and plaque rupture risk, the following investigation was performed to assess the diagnostic performance of a multisequence MR technique in noninvasively detecting unstable fibrous caps in human carotid plaques.

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MATERIALS AND METHODS

Patient Selection

The carotid arteries of 18 consecutive patients, who were scheduled for carotid endarterectomy, were preoperatively imaged after the study was explained to them and informed consent was obtained. The use of human subjects, the consent forms, and the study protocols were approved by the appropriate institutional review boards. All patients were scanned within 1 week of the surgical procedure to reduce potential errors in image–pathological correlation that could result from healing of plaque fissures or ulcers (10).

MRI Protocol

The patients were imaged with specially designed phased-array surface coils (11) in a 1.5T GE Signa Scanner (Horizon EchoSpeed, version 5.8; GE Medical Systems, Milwaukee, WI) using a standardized protocol (12). Slice levels were centered about the carotid bifurcation of the operative side in each patient, and four different contrast-weighted axial images were obtained at each slice location: 3D time of flight (ToF), T1-weighted, proton density (PD)-weighted, and T2-weighted. Typical parameters for the three sequences used to generate the images were: 1) double inversion recovery, T1-weighted, 2D fast-spin-echo (FSE) (TR/TE = 800/9.3 msec, FOV = 13 cm, thickness = 2 mm, 256 × 256 matrix, NEX = 2); 2) cardiac-gated, shared echo-FSE (SHARE) for the PD- and T2-weighted images (TR = 3 R-to-R intervals, first echo TE = 20 msec, second echo TE = 40 msec, FOV = 13 cm, thickness = 2 mm, 256 × 256 matrix, NEX = 2); and 3) 3D-ToF (TR/TE = 23/3.8 msec, flip angle = 25°, FOV = 13 cm, thickness = 2 mm, 256 × 256 matrix, NEX = 2). A zero-filled Fourier transform was used to minimize partial volume artifacts. The best voxel size achieved was $0.25 \times 0.25 \times 2.0$ mm^3, and the total length of each examination, including set-up and localizers, averaged 40 minutes.

From the 18 patient exams, 101 matched image sets were selected, with a minimum of 4 mm separation between slices to reduce correlations between image findings. With four different contrast weightings (ToF, T1, PD, and T2) at each slice location, there were a total of 404 axial carotid images. Because images of poor quality are not reliably interpreted, a subjective five-point rating of image quality (5 = best) was employed as a guide to exclude locations with suboptimal images from the study. Using this scale, the signal-to-noise ratio (SNR) and conspicuity of the vessel wall were evaluated (by C.Y.), and a particular location was not included in the study if two or more of the images at that slice level were rated lower than 3 (12).

The images were examined and scored by two reviewers (C.Y. and L.M.M.) who were blinded to the clinical status of the patient and the histologic findings. A consensus decision was then made regarding the presence and location of the following image features: 1) interruptions or irregularities in a juxtaluminal hypointense band on the ToF images; 2) absence of intimal tissue between the lumen and deeper structures, such as calcifications, necrotic cores, and intraplaque hemorrhages; and 3) focal contour abnormalities of the luminal surface. The presence of any one or a combination of these findings was considered to be an indication of an unstable cap at that location. The results were then recorded and filmed to facilitate subsequent comparisons with histology.

Histological Processing and Interpretation

The endarterectomy specimens were fixed in formalin, decalcified in 10% formic acid, and paraffin-embedded en bloc. Fifteen serial (10 μ) sections were collected at 1.0-mm intervals in the common carotid artery (CCA), while 0.5-mm intervals were used through the bifurcation and internal carotid artery (ICA). All sections were stained with hematoxylin and eosin (H&E). Selected sections were additionally stained with Mallory's trichrome for matrix proteins and Verhoeff Van Gieson's stain for elastic fibers (13). The histological slides were independently evaluated by a reviewer (M.S.F.) who was blinded to the clinical information and was unaware of the imaging results. Histologically, the fibrous cap was defined as the compact subendothelial region containing layered smooth muscle cells and connective tissue (10,13,14). A cap was considered microscopically unstable if it was ulcerated, fissured, or disrupted, or had a minimum thickness of <0.25 mm (7).

MR Image–Histological Correlation

To account for fixation-related shrinkage, the relative distance of the histology section from the carotid flow divider and the gross morphological features (lumen shape, and the appearance and location of large calcifications) of the vessel wall were used to assist in matching the sections with each MR image location. A finding on the MR images was considered to be histologically confirmed only if a corresponding feature on the representative histology slides was also present in the same location of the vessel wall (12).

Statistical Analysis

Because multiple image locations from each patient would be used for the statistical evaluation, the independence of histology findings between adjacent locations was assessed using a Kappa statistic. A value of one was assigned to each slice level that contained an unstable fibrous cap on the corresponding histology section. A zero value was given to the remaining locations that had a stable cap. Each location was then paired to the next adjacent (more proximal) level, and a Kappa statistic was calculated to assess the similarity of the histological state of the cap between the paired slices. For this application, a Kappa value < 0.4 indicates a low level of interdependence (15).

Using the histology results as the gold standard, general test performance statistics (sensitivity and specificity) were calculated to evaluate the in vivo accuracy of the multisequence MR technique for detecting an unstable fibrous cap. All calculations were made using SPSS for Windows (version 7.5.1).

RESULTS

Of the 101 image locations obtained from the 18 patient exams, 10 were excluded from the analysis because of poor image quality or severe specimen distortion that occurred during histologic processing. Calculation of the independence of the histology findings from the remaining 91 locations produced a Kappa value of 0.27, which indicates no significant interdependence between the sections obtained from each artery.

A blinded review of the images from these 91 carotid locations revealed a strong correlation between the appearance and intactness of a juxtaluminal band of low signal identified in the ToF images with the histological state of the fibrous cap. A stable fibrous cap is reflected by a relatively thick, intact band of low signal seen adjacent to the lumen on the ToF images (Figs. 1 and 2). Note that the subendothelial region of the vessel wall, which is hypointense on the 3D-ToF sequence, is predominantly isointense to skeletal muscle on the T1-weighted images and is of mixed intensity when visible on the PD- and T2-weighted images. On the FSE sequences (T1, T2, and PD) the fibrous cap often could not be differentiated from other intimal structures located deeper in the plaque.

Compared to an intact fibrous cap, the presence of luminal irregularities or interruptions in the hypointense, juxtaluminal band on the ToF images agreed well with the histological findings of a ruptured, ulcerated, or thin cap (Figs. 3 and 4).

While the fibrous cap was not consistently visualized in the T1-, T2-, or PD-weighted images, the availability of these additional contrast weightings facilitated the interpretation of the state of the cap at 17 of the 91 (19%) available locations. As shown in Figure 5, slow or turbulent flow produces areas of low signal within the lumen on the ToF images that could create pseudolesions or blur the hypointense juxtaluminal band that represents the fibrous cap. In these situations, the lumen surface was often better visualized on the corresponding T1- or PD-weighted images, which enabled the identification of luminal irregularities associated with an unstable cap. Similarly, intimal calcifications created large amorphous regions of low signal on the ToF images that sometimes obscured the fibrous cap and lumen surface. For these cases, the FSE images (T1, T2, and PD) were used to determine whether fibrocellular tissue was present between the intimal calcifications and the lumen to support the presence of an intact and stable fibrous cap (Fig. 6).

An evaluation of the carotid images at the 91 exam locations (for the features of an unstable fibrous cap) revealed 19 locations that contained an interruption/irregularity in the juxtaluminal hypointense band, five locations at which no intimal tissue was seen between the lumen and deeper plaque structures, and seven caps that contained a focal contour abnormality. Of these possible 31 unstable caps, 25 were confirmed histologically (Table 1). These results statistically equate to a sensitivity of 0.81 and specificity of 0.90.

The test performance table (Table 1) shows that there were six false-positive (FP) and six false-negative (FN) cases. Of the FPs, four were related to flow artifacts in the proximal ICA or distal to high-grade stenoses that were not resolved by the FSE images. One FP error was attributed to an ICA with a steep posterior course that resulted in an imaging plane that was not orthogonal to the vessel lumen. The last FP is believed to represent an artifact created by the volume averaging of the lumen of the CCA with the smaller lumen of the proximal ICA. Volume averaging of the two lumens in the ToF image of the bifurcation produced a focal concavity on the luminal surface that was misinterpreted as an ulceration in the fibrous cap. Two of the FN cases were related to motion artifacts (images were of marginal image quality, grade 3) that blurred the luminal margins. Two FN errors were due to small ulcers (cross-sectional areas $< 1.0\ mm^2$ on the histology sections), and one error was related to a short segment (2 mm) of cap thinning. Although it was initially missed, one of the ulcers was identified retrospectively when the images were viewed with the histology specimens. The final FN error was caused by an apparent misregistration between the MR images and the histology slide.

DISCUSSION

The ability to detect atherosclerotic plaques that are at risk of rupturing prior to the development of ischemic sequelae would be of tremendous clinical importance. While a number of clinical imaging modalities are currently used to study atherosclerosis (3,9), most can not reliably depict features of the vulnerable plaque, or are not suited for serial studies of disease progression. X-ray angiography, for example, provides no information about the structure or composition of the arterial wall, and therefore is limited in its ability to evaluate rupture risk (16). Electron-beam computed tomography (CT) provides a measure of coronary artery calcification, but the amount of calcium in the vessel wall is not clearly related to plaque instability or clinical risk (17). To date, CT angiography has not been able to accurately depict the fibrous cap or plaque ulceration (18). Angioscopy and intravascular ultrasound permit interrogation of the luminal surface and can demonstrate plaque ulceration or rupture in vivo, but the potential of catheter-related complications limit their use in large serial studies and on low-risk patients (19,20). Although studies using high-resolution B-mode ultrasound suggest that the echogenicity of a plaque reflects lesion morphology, the technique does not satisfactorily assess the state of the plaque surface, and the finding of an echolucent region within the plaque is not specific for intimal lipid collections (21).

Of the available clinical imaging modalities, MRI is unique because it is noninvasive, is capable of achieving submillimeter resolution, can provide quantitative measures of disease severity, and is suitable for serial investigations (22–24). Furthermore, the ability of MRI to generate images with different contrast weightings has proved advantageous for tissue characterization and has been used in both ex vivo and in vivo studies of human atherosclerosis (4–7,12,25).

This study showed that the in vivo MR appearance of the fibrous cap can be used to prospectively identify unstable caps, and that a multisequence protocol facil-

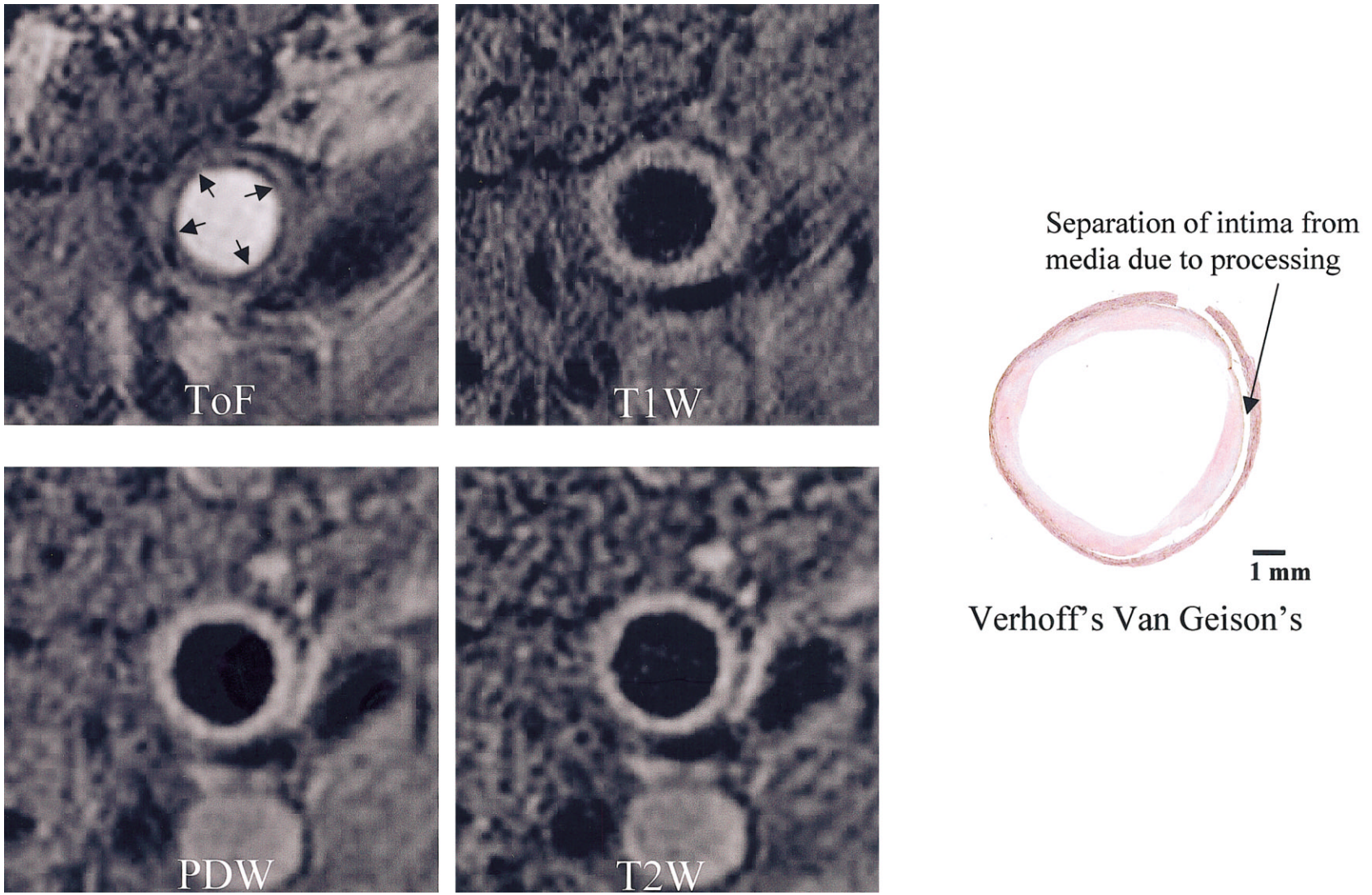

Figure 1. Multisequence (ToF, T1, PD, and T2) appearance of a stable, concentric fibrofatty plaque in a left CCA shown adjacent to the matched histology section. An intact, hypointense juxtaluminal band seen in the ToF image (black arrows) correlates with a subendothelial region of fibrous tissue that is not readily discernable in the T1-, PD-, or T2-weighted sequences.

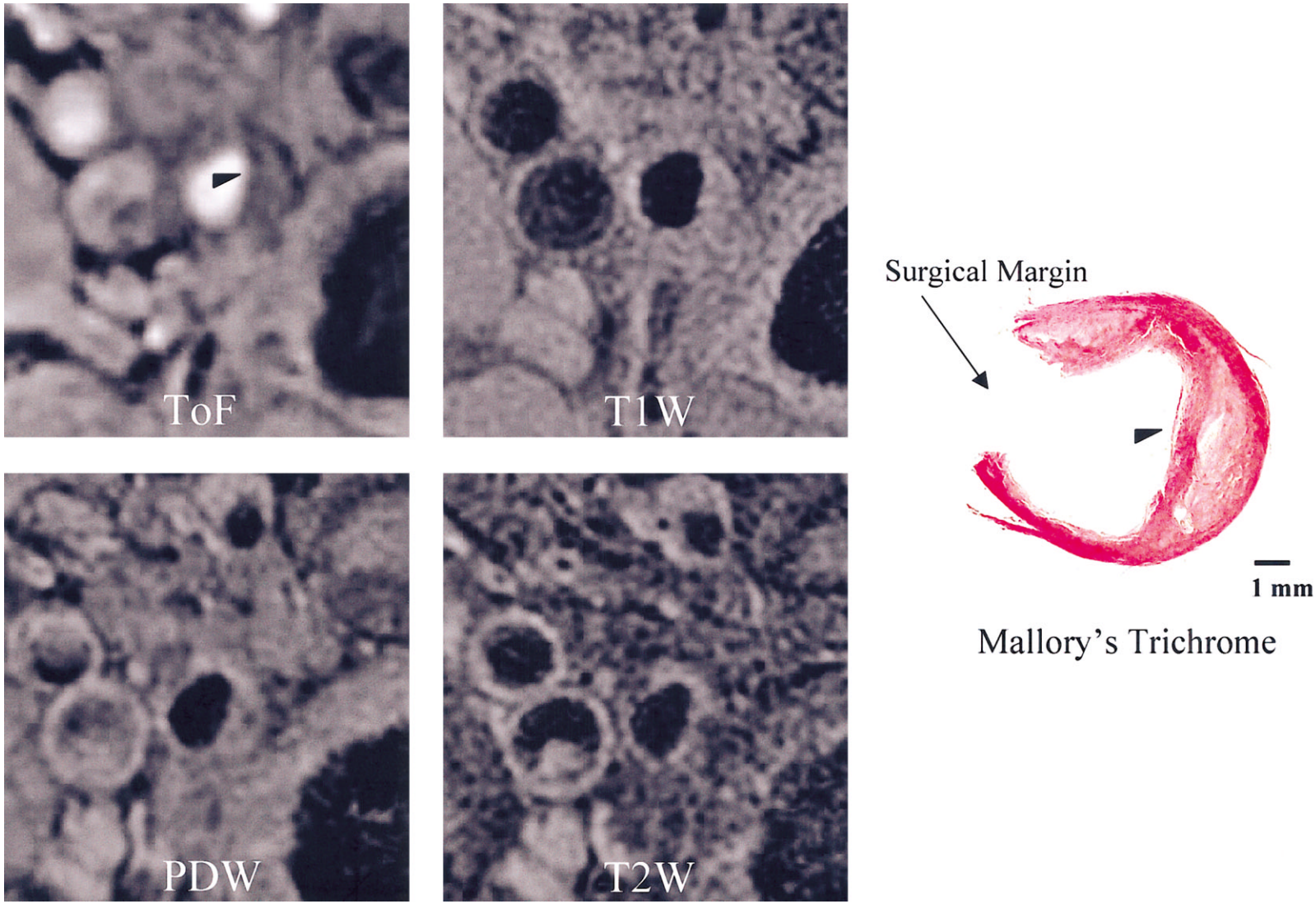

Figure 2. Noninvasive depiction of an intact fibrous cap in a stable, eccentric CCA plaque. The arrowhead highlights the appearance of the hypointense juxlatuminal band overlying an eccentric plaque and the corresponding region of organized fibrous subintimal tissue present on the histological section.

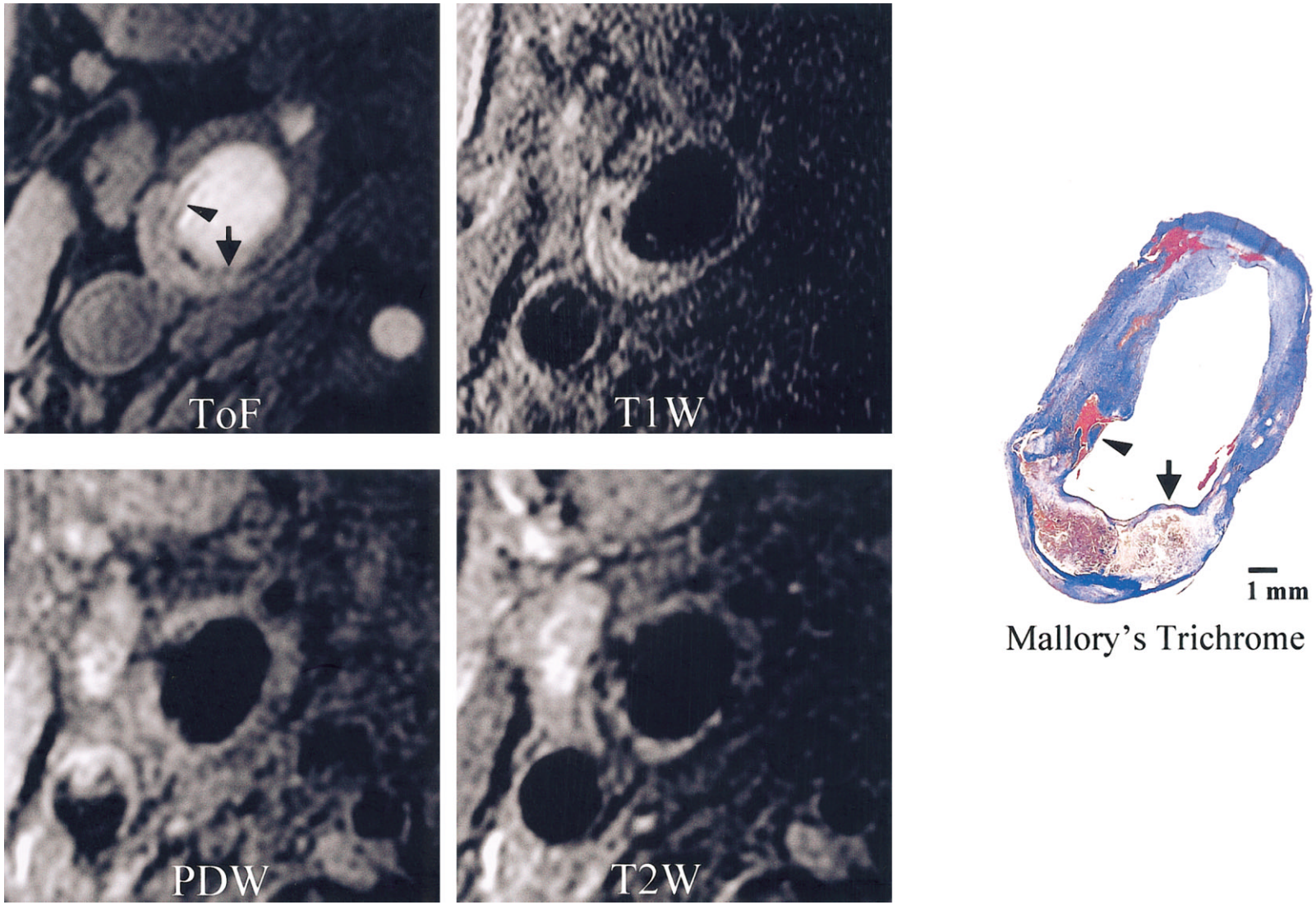

Figure 3. A discontinuity in the hypointense juxtaluminal band (arrowhead) on the ToF image depicts an intimal flap related to a disrupted fibrous cap found in a right CCA on the matched histology section. The 3D-ToF image also demonstrates regions where the juxtaluminal band is indistinct (arrow)—a feature that, in this case, histologically represents a thinned cap separating a hemorrhagic necrotic core from the vessel lumen.

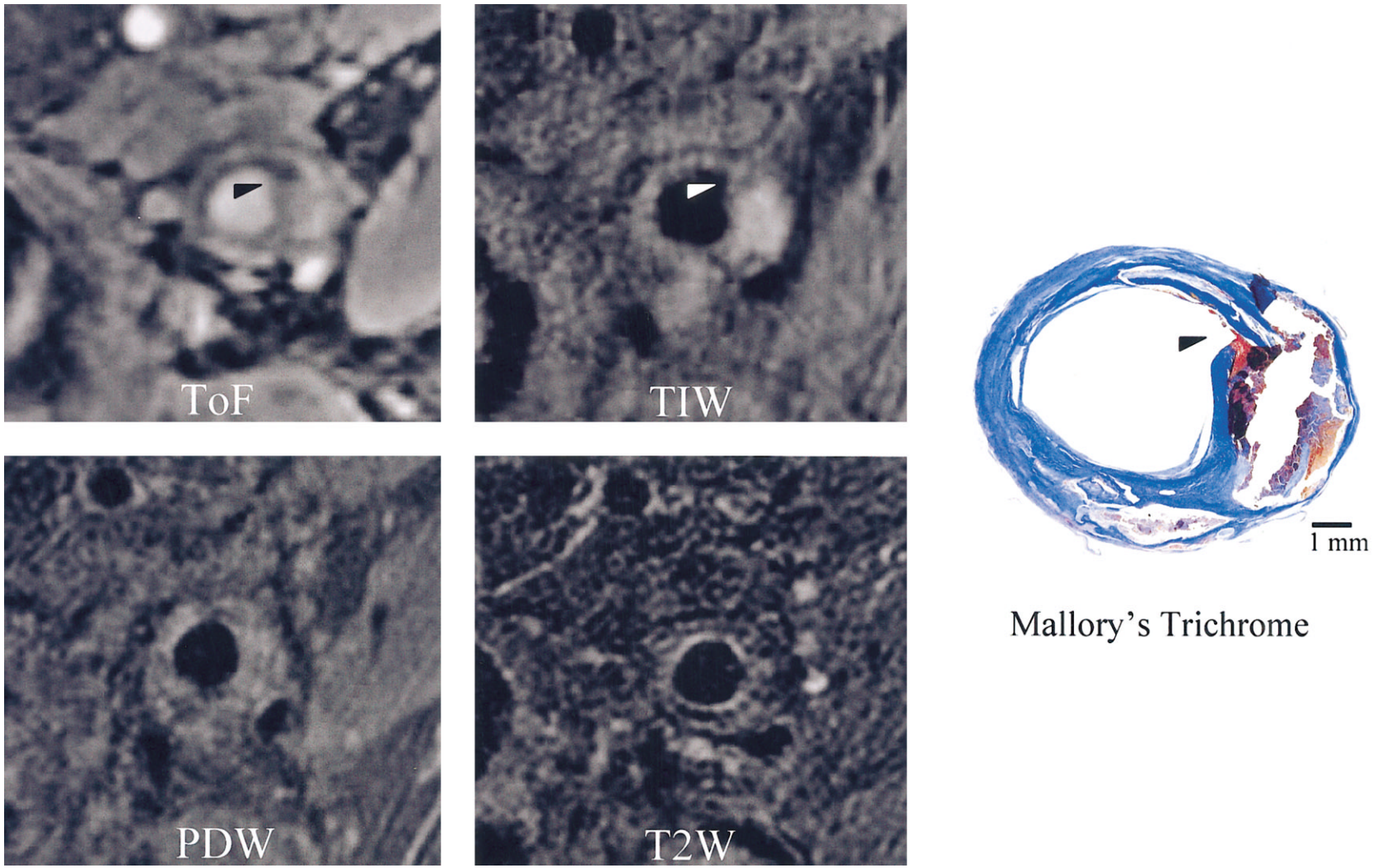

Figure 4. Example of a luminal contour abnormality. A focal concavity of the luminal surface (arrowhead), best depicted on the ToF and T1 images, correlates with an unstable, ruptured cap on the corresponding histologic section.

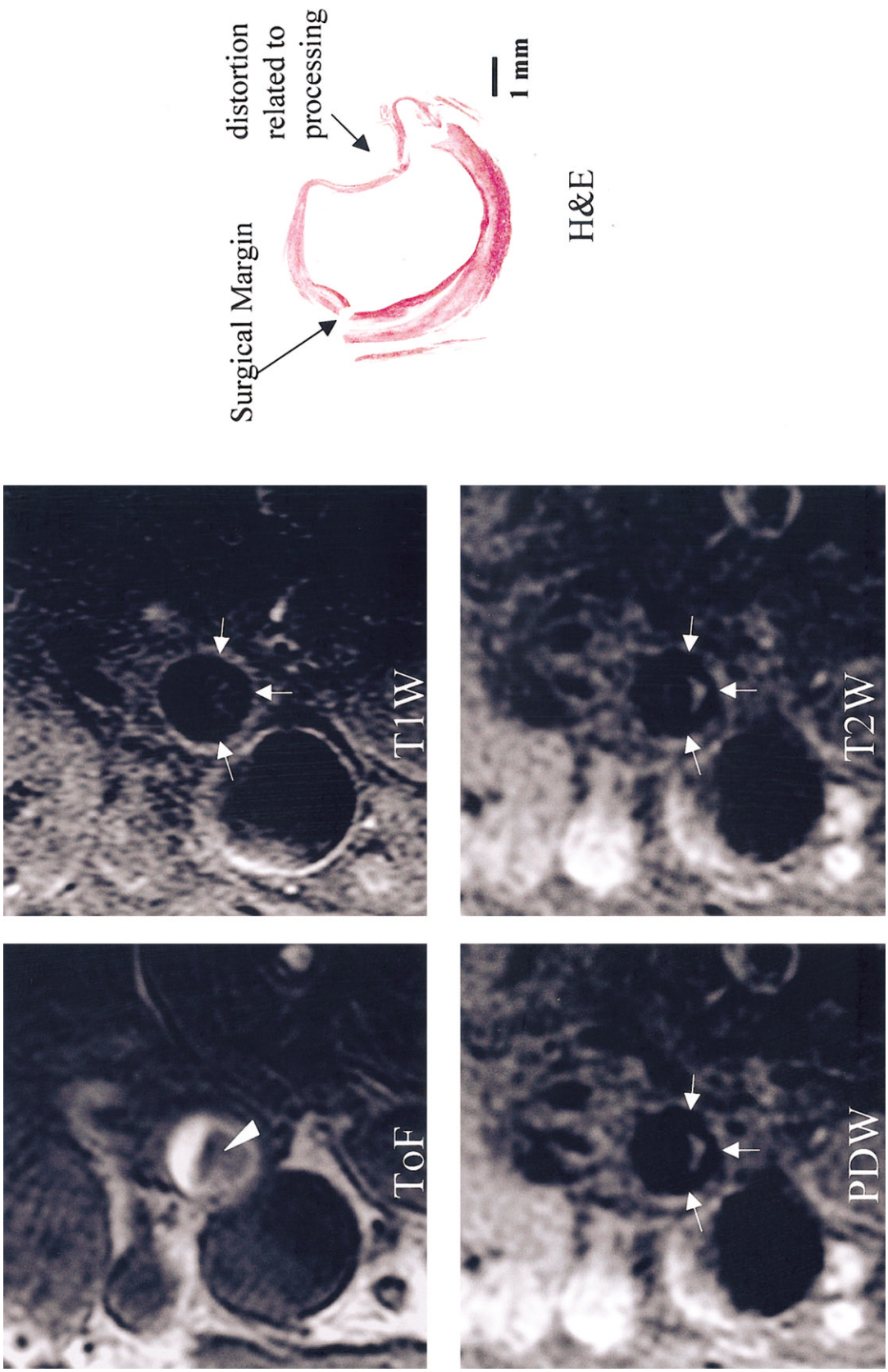

Figure 5. Utility of multisequence imaging in the presence of intraluminal flow artifacts. While the ToF image appears to depict a large eccentric lesion separated from the carotid lumen by a thick hypointense band (arrowhead), evaluation of the FSE images (T1, PD, and T2) reveals the presence of a pseudolesion, which is created by a flow artifact that can occur along the back wall of the carotid bulb. SE (T1, PD, and T2) images are less susceptible to this artifact, and correctly identify the true lumen (arrows) and the minimal intimal thickening that was confirmed by histology.

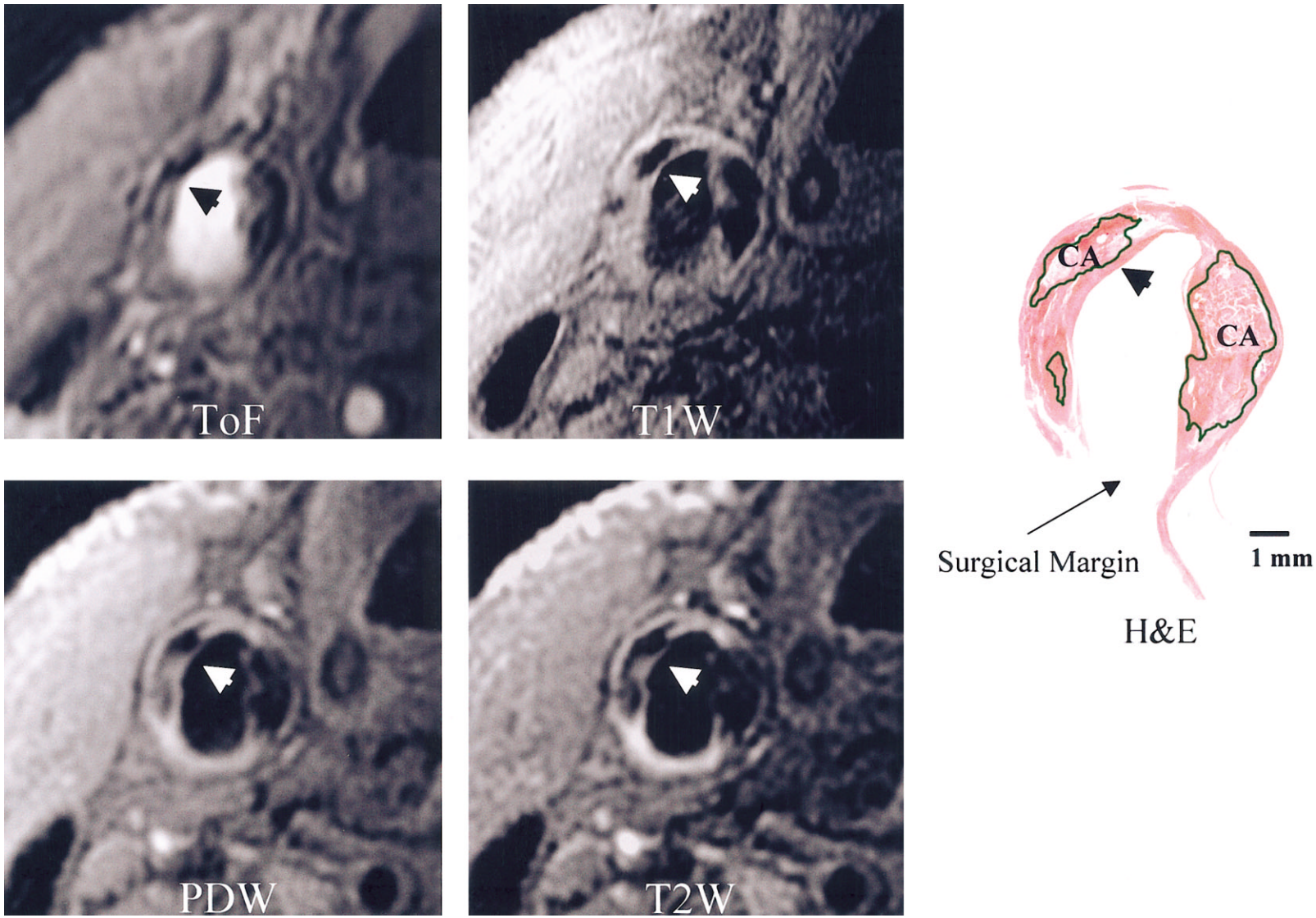

Figure 6. Utility of multisequence imaging in the presence of intimal calcifications. In the ToF image the hypointense juxtaluminal band, which is associated with the fibrous cap, is obscured (black arrow) by amorphous regions of low signal created by large intimal calcifications (labeled and outlined on the histology section). Intimal tissue present between these calcifications and the lumen is visible as an area of increased signal (white arrows) in the T1, PD, and T2 images.

Table 1
Test Performance Table (2 × 2) for the Noninvasive Identification of Unstable Fibrous Caps by MR Imaging Compared to a Histologic Standard

MR appearance of the fibrous cap	Histologic state of the fibrous cap		Row totals
	Unstable	Stable	
Unstable	25	6	31
Stable	6	54	60
Column totals	31	60	91

itates accurate characterization of plaque morphology. In agreement with a previous report by Hatsukami et al (7), the ToF sequence was subjectively found to be the most useful in differentiating the fibrous cap from underlying intimal tissue. The availability of the additional FSE images (T1, PD, and T2), however, did improve image interpretation when the hypointense juxtaluminal band on the ToF (gradient echo) images was obscured by flow artifacts or intimal calcifications.

The juxtaluminal hypointense band seen in the ToF images of the arteries is believed to result from T2* effects caused by the layered organization of the matrix proteins of an intact fibrous cap that restrict the movement of free water in this subintimal region. The creation of bright blood within the lumen, and the T2* sensitivity of the 3D-ToF sequence provide the tissue contrast needed to differentiate this organized subintimal layer from the lumen and deeper intimal structures. Disruption or absence of the collagen layers in the fibrous cap would remove this barrier to molecular motion creating discontinuities in the juxtaluminal band of low signal (8).

As noted above, flow artifacts and intimal calcifications sometimes obscured the lumen surface and the juxtaluminal hypointense band seen in the ToF images. At locations where intraluminal flow disturbances were problematic, the SE sequences reduced turbulence-induced dephasing (26) and improved visualization of the luminal surface. When large intimal calcifications were present, the FSE sequences, also being less sensitive to calcium-related susceptibility artifacts, helped demonstrate the intact lumen of a stable cap.

Although the T2-weighted images from the SHARE sequence presented intraplaque signal characteristics similar to those of the PD images, the second echo images were often less clear, since with their longer TE they are more sensitive to motion and susceptibility artifacts. Similar to ex vivo results (6), the fibrous cap could not be reliably characterized using only the PD- or T2-weighted images. Thus, while a multisequence protocol will likely become the standard for in vivo plaque characterization, the results of this study also suggest the importance of including a ToF (gradient echo) sequence in any protocol designed to assess the state of the fibrous cap.

Although this work demonstrates that the subjective evaluation of the in vivo MR appearance of the fibrous cap reflects the histological state of the ex vivo specimen, the accuracy and reproducibility of image interpretation may be improved by the development of more objective image analysis tools that provide quantitative measures of cap thickness and volume (27). Ongoing work is also being performed to overcome the problems in image interpretation described in the Results section. For example, artifacts caused by flow disturbances could be reduced after the administration of an intravascular contrast agent (28), while the poor image quality created by patient motion could be corrected with faster imaging techniques. Improved 3D data acquisitions or thinner 2D slices would minimize volume averaging artifacts and the registration errors that occur when correlating millimeter-long MR voxels to histology sections that are only 10 μ thick. Continued refinements in postprocessing of MR data may permit construction of reformatted images to create image planes that remain orthogonal to obliquely oriented vessels.

In conclusion, this study demonstrates that a multisequence protocol facilitates characterization of plaque morphology, and that MRI can accurately assess the in vivo state of the fibrous cap. If further work confirms the reproducibility of MR plaque characterization, this modality could provide a serial noninvasive and quantitative means of evaluating atherosclerotic disease that would play an important role in the evaluation of plaque rupture risk and stabilization.

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