

# Identification of Fibrous Cap Rupture With Magnetic Resonance Imaging Is Highly Associated With Recent Transient Ischemic Attack or Stroke

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**Background**—High-resolution MRI has been shown to be capable of distinguishing intact, thick fibrous caps from thin and ruptured caps in human carotid atherosclerosis in vivo. The aim of this study was to determine whether MRI identification of fibrous cap thinning or rupture is associated with a history of recent transient ischemic attack (TIA) or stroke.

**Methods and Results**—Fifty-three consecutive patients (mean age, 71 years; 49 male) scheduled for carotid endarterectomy were recruited after obtaining informed consent. Twenty-eight subjects had a recent history of TIA or stroke on the side appropriate to the index carotid lesion, and 25 were asymptomatic. Preoperative carotid MRI was performed in a 1.5-T GE Signa scanner that generated T<sub>1</sub>-, PD-, and T<sub>2</sub>-weighted and three-dimensional time-of-flight images. Using previously reported MRI criteria, the fibrous cap was categorized as intact-thick, intact-thin, or ruptured for each carotid plaque by blinded review. There was a strong and statistically significant trend showing a higher percentage of symptomatic patients for ruptured caps (70%) compared with thick caps (9%) ( $P=0.001$  Mann-Whitney test for cap status versus symptoms). Compared with patients with thick fibrous caps, patients with ruptured caps were 23 times more likely to have had a recent TIA or stroke (95% CI=3, 210).

**Conclusions**—MRI identification of a ruptured fibrous cap is highly associated with a recent history of TIA or stroke. Ongoing prospective studies will determine the predictive value fibrous cap characteristics, as visualized by MRI, for risk of subsequent ischemic events. (*Circulation*. 2002;105:181-185.)

**Key Words:** magnetic resonance imaging ■ atherosclerosis ■ carotid arteries ■ stroke

Rupture of the fibrous cap that overlies the thrombogenic necrotic core is presently believed to play an important role in acute ischemic events, such as stroke, transient ischemic attack, myocardial infarction, and unstable angina.<sup>1-4</sup> Several histological studies have revealed that lesions associated with the development of ischemic symptoms typically contain a large necrotic core that is separated from the lumen by a fibrous cap that is thin or disrupted.<sup>5,6</sup> Because the detection of these morphological features could identify the plaques that represent a higher risk for thromboembolic complications, the development of a noninvasive method capable of assessing the state of the fibrous cap would not only improve patient stratification to medical or surgical treatment but would also provide a means of monitoring disease progression or evaluating the efficacy of therapeutic interventions.

Of the clinical imaging modalities presently used to study atherosclerosis, MRI is unique because it is noninvasive,

capable of identifying plaque tissue components with submillimeter resolution, able to provide quantitative measures of disease severity, and suitable for serial investigations.<sup>7-14</sup> Recent studies demonstrated that high-resolution MRI is capable of distinguishing intact, thick fibrous caps from thin or ruptured caps in human carotid atherosclerosis in vivo. Thick fibrous caps appear as a juxtaluminal band of low signal in time-of-flight (TOF) MR images. In plaques with thin fibrous caps, this dark juxtaluminal band is absent. In plaques with fibrous cap rupture, the dark band is absent and there is a region of hyperintense signal adjacent to the lumen.<sup>15</sup>

Using a multiple contrast-weighted, high-resolution MR carotid artery imaging protocol,<sup>16</sup> we evaluated the relationship between carotid plaque fibrous cap characteristics and their association with the patient's neurological symptoms. The aim of this study was to test the hypothesis that if a patient has a carotid plaque with a thin or ruptured

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fibrous cap, as identified by MRI, then the patient is more likely to have had a recent transient ischemic attack (TIA) or stroke, appropriate to the side of the index carotid lesion.

## Methods

### Patient Selection

Fifty-three consecutive patients (49 male, mean age 71) scheduled for carotid endarterectomy at the University of Washington Medical Center or VA Puget Sound Health Care System underwent preoperative MRI of their carotid arteries after obtaining informed consent. The institutional review boards of each facility approved the consent forms and study protocols. All subjects had a high-grade proximal internal carotid artery stenosis (50% to 99% by duplex ultrasonography, defined as a peak systolic velocity  $>125$  cm/sec, measured at a 60-degree Doppler angle). A detailed general physical and neurological examination was performed before surgery and MRI examination to determine whether the patient had any hemispheric ischemic neurological symptoms that could be attributed to the index carotid lesion. The patients were screened for other potential causes for TIA and stroke, and additional workup, including echocardiography, Holter monitoring, and consultation with the Cardiology and Neurology departments, was performed as indicated. Patients were considered symptomatic if they had a history of transient ischemic attack or stroke appropriate to the distribution of the index carotid artery within 90 days before carotid endarterectomy.

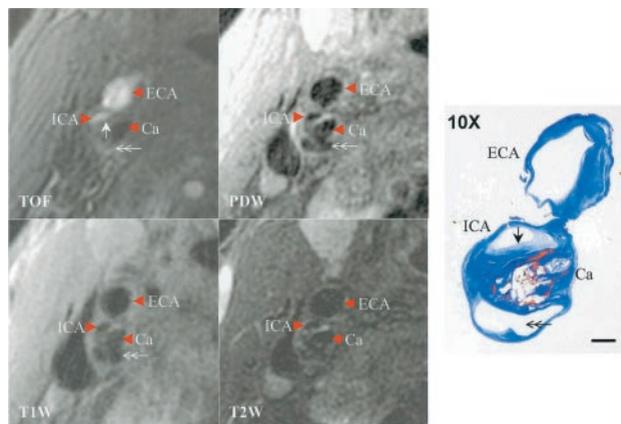
### MRI Protocol

The MRI scans were performed within 1 week before the surgical procedure and neurological examination. Patients were placed in a head holder, which improves comfort and reduces motion artifacts, and were imaged using specially designed phased-array surface coils<sup>17</sup> in a 1.5-T GE Signa scanner (Horizon EchoSpeed, version 5.8, GE Medical Systems).

A standardized protocol was used to obtain 4 different contrast-weighted image sets (three-dimensional [3D] TOF axial source images and T<sub>1</sub>-, proton density [PD]-, and T<sub>2</sub>-weighted images) of the carotid arteries for each patient.<sup>16</sup> The imaging plane was transverse, and the slice readout was in the right to left direction. Fat suppression was used to reduce the signal from the subcutaneous tissues, and a zero-filled Fourier transform was used to reduce the apparent pixel size, thereby minimizing partial volume artifacts. Although the imaging protocol varied depending on patient body habitus, a typical set of parameters for the 3 sequences used to generate the images was as follows: (1) double inversion recovery T<sub>1</sub>-weighted 2D fast spin-echo (repetition time [TR], 800 ms; echo time [TE], 9.3 ms; field of view [FOV], 13 cm; thickness, 2 mm; 256×256 matrix; number of excitations [NEX], 2); (2) cardiac-gated, shared echo and fast spin-echo for PD- and T<sub>2</sub>-weighted images (TR, 3 R-R intervals; first echo TE, 20 ms; second echo TE, 40 ms; FOV, 13 cm; thickness, 2 mm; 256×256 matrix; NEX, 2); and (3) 3D TOF (TR, 23 ms; TE, 3.8 ms; flip angle, 25 degrees; FOV, 13 cm; thickness, 2 mm; 256×256 matrix; NEX, 2). Including set-up time and localizer sequences, the length of each examination averaged 40 minutes. Best voxel size achieved was 0.25×0.25×2.0 mm<sup>3</sup>. The slice levels prescribed were centered around the carotid bifurcation on the operative side in each patient.

### Review of MRI

For each artery, images of the 4 contrast weightings from 12 locations (centered at the bifurcation) were matched and filmed (2.4-cm total longitudinal extent of coverage). The appearance of the fibrous cap was categorized as intact and thick (rating I), intact and thin (rating II), or ruptured (rating III) on the basis of the following definitions: intact and thick cap: a uniform, continuous dark band adjacent to the lumen on the TOF image and a smooth lumen surface on TOF and T<sub>1</sub>-, PD-, and T<sub>2</sub>-weighted images; intact, thin cap: no visible dark band adjacent to the lumen on the TOF image and a smooth lumen surface on TOF and T<sub>1</sub>-, PD-, and T<sub>2</sub>-weighted



**Figure 1.** Example of a thick intact fibrous cap as seen on MRI along with the corresponding matched histological cross-section. TOF image taken immediately distal to the bifurcation shows a distinct hypointense band completely surrounding the narrowed lumen, indicating the presence of a thick fibrous cap (arrow). T<sub>1</sub>-weighted (T1W), PD-weighted (PDW), and T<sub>2</sub>-weighted (T2W) images show the same region to be hyperintense and smooth, in concordance with an intact and thick cap. A Mallory's Trichrome-stained matching histology section confirms the presence of the continuous thick fibrous cap (arrow). The red arrowheads indicate the location of the internal carotid artery (ICA) lumen and external carotid artery (ECA) lumen and an area of dense calcification within the plaque (Ca), seen as a hypointense region on the TOF, T1W, PDW, and T2W images. There is a second internal carotid luminal flow channel, indicated by the double arrows on the histological and MRI cross-sections. The dual internal carotid lumen appearance occurs because of a cul de sac in the flow channel in longitudinal access, as seen with a web-like stenosis or with large ulceration of the plaque (bar=1 mm).

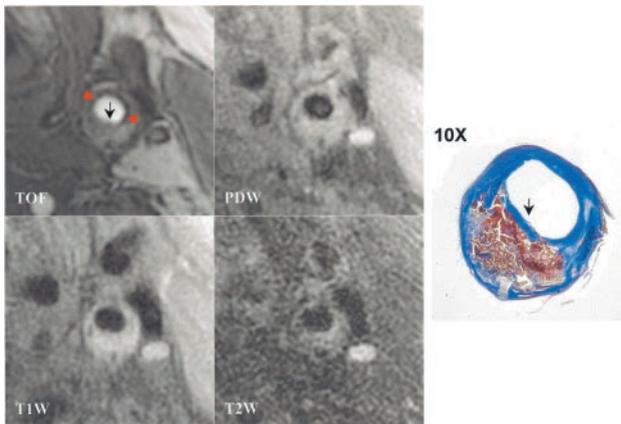
images; and ruptured cap: disrupted or no visible dark band adjacent to the lumen on TOF images, irregular lumen boundary on TOF and T<sub>1</sub>-, PD-, and T<sub>2</sub>-weighted images, and a hyperintense, bright signal adjacent to the lumen (Figures 1 through 3). The fibrous cap state was categorized by a reader who was blinded to the clinical status of the patient. The presence of calcification near the lumen surface, which may also appear as a hypointense region on the TOF images, was distinguished from a thick cap on the basis of its appearance on the T<sub>1</sub>-, PD-, or T<sub>2</sub>-weighted images. Calcification appeared as a dark region on TOF and T<sub>1</sub>-, PD-, and T<sub>2</sub>-weighted images, whereas a thick fibrous cap appeared as a dark band only on the TOF images. All MRI cross-sections for the index carotid artery were reviewed, and a single rating was assigned for the index artery (highest rating).

### Statistical Analysis

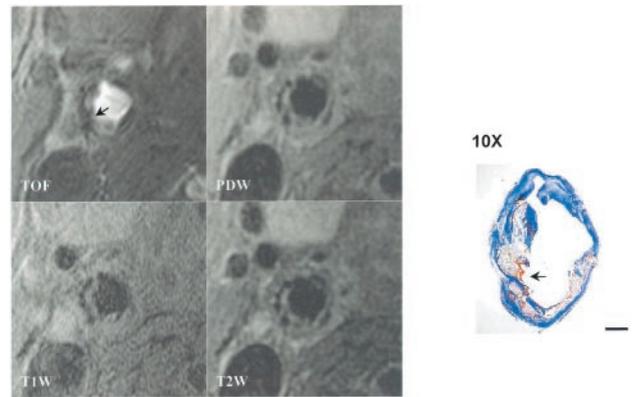
Logistic regression analysis was performed to determine odds ratios for the risk of symptoms by categories of cap status, and the nonparametric (Mann-Whitney test) was performed to compare cap status (ordered as thick, thin, and ruptured) versus presence or absence of symptoms. Student's *t* tests and Fisher's exact test were performed to compare the descriptive characteristics of the symptomatic and asymptomatic groups. All analyses were carried out using SPSS for Windows (version 7.5.1).

## Results

Among all subjects, 28 had a recent (within 90 day) history of TIA or stroke on the side appropriate to the index carotid lesion, and the other 25 were asymptomatic. There was no statistically significant difference in mean age or percent with history of smoking, diabetes, hypertension, hypercholesterol-



**Figure 2.** Example of a thin intact fibrous cap as seen on MRI along with the corresponding matched histological cross-section. A distinct hypointense band (red arrowheads) is clearly visible on a segment of the luminal boundary of an atherosclerotic common carotid artery on the TOF image but is missing on the surface of the bulk of the plaque (black arrow). PD-weighted (PDW), T<sub>1</sub>-weighted (T1W), and T<sub>2</sub>-weighted (T2W) images from the same location show a smooth surface, suggesting an absence of rupture. A Mallory's Trichrome-stained histology section of the area confirms the presence of a large necrotic core covered by a thin fibrous cap (arrow) (bar=1 mm).



**Figure 3.** Example of a ruptured fibrous cap as seen on MRI along with the corresponding matched histological cross-section. TOF image of a ruptured fibrous cap from a heavily calcified plaque taken proximal to the bifurcation shows a discontinuous hypointense band surrounding the lumen (arrow). A branching collateral artery can be seen at 11 o'clock and was used as an added landmark in matching MR images and histology. The rough lumen boundary and the presence of juxtaluminal calcification can be appreciated in the T<sub>1</sub>-weighted (T1W), PD-weighted (PDW), and T<sub>2</sub>-weighted (T2W) images. The Mallory's Trichrome-stained histology section confirms the ruptured cap (arrow) and also shows a fragile membrane separating necrotic core contents from the lumen (between 4 and 6 o'clock) (bar=1 mm).

emia, or family history of atherosclerosis between the symptomatic and asymptomatic groups (Table 1). Furthermore, there was no statistically significant difference in the mean peak systolic velocity (PSV) on preoperative carotid duplex scan of the index carotid artery between the two groups. The mean PSV ( $\pm$ SD) in the symptomatic group was  $392 \pm 145$  cm/sec, compared with  $429 \pm 95$  cm/sec in the asymptomatic group, which indicates that the degree of luminal stenosis in the asymptomatic group was slightly greater overall, although PSV was quite variable in each group (Table 1). Results from analysis of cap status versus symptoms are summarized in Table 2. MRI showed 11 patients with intact, thick fibrous caps, 12 patients with intact, thin caps, and 30 patients with ruptured fibrous caps. There was a strong and statistically significant trend showing a higher percentage of symptomatic patients among those who had a thin fibrous cap or ruptured

cap by MRI ( $P=0.001$  Mann-Whitney test for cap status versus symptoms). Only 9% of patients with thick fibrous caps were symptomatic compared with 50% of patients with thin caps and 70% of patients with ruptured caps. Furthermore, compared with patients with thick fibrous caps, patients with thin fibrous caps were 10 times more likely to have had a recent TIA or stroke (95% CI=1.0, 104), and those with ruptured fibrous caps were 23 times more likely to have had recent ischemic neurological symptoms (95% CI=3, 210). Although the confidence intervals for the odds ratios are wide, the trend of increasing percent symptomatic as the cap status deteriorates is both strong and highly significant. This trend was still present and statistically significant ( $P=0.03$ ) in a logistic regression analysis controlling for PSV ( $P=0.4$ ).

**TABLE 1. Descriptive Characteristics of Symptomatic and Asymptomatic Patients**

Variable	Symptomatic (n=28) % or mean $\pm$ SD	Asymptomatic (n=25) % or mean $\pm$ SD	P Value
Age, y	69.7 $\pm$ 8.6	73.0 $\pm$ 7.5	0.77*
Male sex, %	93%	92%	1.00†
Smoker, %	78%	88%	0.47†
HCH, %	68%	68%	1.00†
Diabetes mellitus, %	14%	32%	0.19†
Hypertension, %	82%	92%	0.43†
Family history of ASO, %	53%	67%	0.48†
PSV on duplex, cm/sec	392 $\pm$ 145	429 $\pm$ 95	0.3*

\*t test.

†Fisher's exact test.

HCH indicates hypercholesterolemia; ASO, atherosclerosis; and PSV, peak systolic velocity (on preoperative carotid duplex scan of index carotid artery).

**TABLE 2. Status of the Fibrous Cap as Determined by MRI Versus Symptomatic Status of Patient**

Cap Status by MRI	Symptomatic	Asymptomatic	Percent With Symptoms	Odds Ratio for Symptoms	95% CI
Intact thick (I)	1	10	9	1	...
Intact thin (II)	6	6	50	10	1.0, 104
Ruptured (III)	21	9	70	23	3, 210

$P=0.001$  Mann-Whitney test for cap status vs symptoms.

Patients were considered symptomatic if they had a transient ischemic attack or stroke appropriate to the distribution of the index carotid artery within 90 days before carotid endarterectomy.

The odds ratios in the controlled analysis were 6 and 18 for thin and ruptured caps versus thick caps, respectively.

### Discussion

Previous studies have shown that high-resolution MRI can distinguish thick, thin, and ruptured caps with good sensitivity and specificity *in vivo*.<sup>15,18</sup> In a study comparing the appearance of the fibrous cap on preoperative MRI to 36 matched sections from the excised carotid endarterectomy specimen, we found a high level of agreement between the MRI and histology designation of 3 levels of cap status ( $\kappa=0.83$ , weighted  $\kappa=0.87$ , 89% agreement, Spearman's correlation coefficient=0.88).<sup>15</sup> In a follow-up study, we compared multispectral MR images to 91 matched histological sections. The sensitivity and specificity (95% CI) of MRI for distinguishing thin and ruptured cap from thick fibrous caps was  $81\pm 6\%$  and  $90\pm 2\%$ , respectively.<sup>18</sup>

On the basis of histological examination of excised coronary and carotid artery specimens, studies published by Davies and Thomas,<sup>19</sup> Falk,<sup>20</sup> Fuster et al,<sup>21</sup> Virmani et al,<sup>4</sup> and others have established that an important morphological component of the vulnerable atherosclerotic plaque is the presence of a fibrous cap that is thinned or ruptured. Falk<sup>20</sup> noted that  $>75\%$  of major coronary thrombotic events were precipitated by atherosclerotic plaque rupture. In a study involving 44 carotid endarterectomy specimens (25 asymptomatic and 19 symptomatic), Carr et al<sup>5</sup> noted fibrous cap rupture in 74% of symptomatic plaques, compared with 32% of asymptomatic lesions, and fibrous cap thinning in 95% of symptomatic lesions compared with 48% of asymptomatic plaques.

In concurrence with this histological evidence, this study found a strong and highly significant association between the *in vivo* state of the fibrous cap and patient symptoms using a noninvasive high-resolution MRI technique. Seventy percent of patients with ruptured fibrous caps and 50% with thin fibrous caps had a history of recent TIA or stroke, compared with only 9% of those with thick fibrous caps on MRI. Remarkably, there was an estimated 23-fold increase in the likelihood of having recent ischemic neurologic symptoms if MRI identified a ruptured fibrous cap, compared with a thick cap. The rate of TIA or stroke is much more similar between the thin and ruptured cap groups than between either of these groups and those with a thick fibrous cap. This similarity of the thin and ruptured cap groups suggests that these two categories combined constitute the high-risk cohort of patients, as determined by MRI.

The use of gradient echo-based 3D TOF sequence is critically important to differentiate the fibrous cap from the underlying intimal tissue. Presumably, the visibility of the fibrous cap on the TOF images is attributable to the  $T_2^*$  effects caused by the layered organization of the matrix proteins that are present in the cap<sup>22,23</sup> and the short effective echo time of gradient echo data acquisition.<sup>24,25</sup> The macromolecular structure of the collagen in the cap could create a barrier to molecular motion, thereby creating a  $T_2^*$  mechanism as water molecules traverse across layers.<sup>22,23,26,27</sup> The  $T_2^*$  sensitivity of the GRE-weighted 3D TOF sequence would then allow detection of disruptions or absence of the collagen layers in the fibrous cap that would be caused by plaque rupture or the presence of proteoglycan-rich regions.<sup>28</sup> Because  $T_1$  relaxation is less dependent on the static component of dipole-dipole coupling, this effect is not evident in  $T_1$ -weighted images.<sup>29</sup>

Because the conspicuity of the fibrous cap is dependent on the contrast present at the fibrous cap (lumen interface and between the cap and the underlying intima), the state of the cap was difficult to determine when there were areas of low signal adjacent to the lumen surface. In the present study, the instances where the hypointense juxtaluminous band on the 3D TOF images was obscured were typically related to flow artifacts or juxtaluminous calcifications. In several image locations that contained intraluminal flow disturbances, the double-inversion recovery sequence, which was designed to reduce turbulence-induced dephasing,<sup>30</sup> was found to improve visualization of the luminal surface. When large intimal calcifications were present, the SE sequences were less sensitive than the TOF to the calcium-related susceptibility artifacts.<sup>31</sup> At these locations, the PD-weighted images were able to depict the presence of fibrous tissue immediately adjacent to intimal calcifications.

In conclusion, this study provides strong evidence of the association between the state of the fibrous cap, as detected by MRI, and recent ischemic neurological events. The ability to noninvasively detect atherosclerotic plaques that are at risk of rupturing before the development of ischemic complications *in vivo* has tremendous clinical importance. Ongoing prospective studies are presently underway that will determine the predictive value of fibrous cap characteristics on MRI for risk of subsequent ischemic events.

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