

Hemorrhage in the Atherosclerotic Carotid Plaque: A High-Resolution MRI Study

Baocheng Chu, MD, PhD; Annette Kampschulte, MD; Marina S. Ferguson, BS; William S. Kerwin, PhD; Vasily L. Yarnykh, PhD; Kevin D. O'Brien, MD; Nayak L. Polissar, PhD; Thomas S. Hatsukami, MD; Chun Yuan, PhD

Background and Purpose—High-resolution, multicontrast magnetic resonance imaging (MRI) has developed into an effective tool for the identification of carotid atherosclerotic plaque components, such as necrotic core, fibrous matrix, and hemorrhage/thrombus. Factors that may lead to plaque instability are lipid content, thin fibrous cap, and intraplaque hemorrhage. Determining the age of intraplaque hemorrhage can give insight to the history and current condition of the biologically active plaque. The aim of this study was to develop criteria for the identification of the stages of intraplaque hemorrhage using high-resolution MRI.

Methods—Twenty-seven patients, scheduled for carotid endarterectomy (CEA), were imaged on a 1.5-T GE SIGNA scanner (sequences: 3-dimensional time of flight, double-inversion recovery, T1-weighted (T1W), PDW and T2W). Two readers, blinded to histology, reviewed MR images and grouped hemorrhage into fresh, recent, and old categories using a modified cerebral hemorrhage criteria. The CEA specimens were serially sectioned and graded as to presence and stage of hemorrhage.

Results—Hemorrhage was histologically identified and staged in 145/189 (77%) of carotid artery plaque locations. MRI detected intraplaque hemorrhage with high sensitivity (90%) but moderate specificity (74%). Moderate agreement in classifying stages occurred between MRI and histology (Cohen $\kappa=0.7$, 95% CI: 0.5 to 0.8 for reviewer 1 and 0.4, 95% CI: 0.2 to 0.6 for reviewer 2), with moderate agreement between the 2 MRI readers ($\kappa=0.4$, 95% CI: 0.3 to 0.6).

Conclusion—Multicontrast MRI can detect and classify carotid intraplaque hemorrhage with high sensitivity and moderate specificity. (*Stroke*. 2004;35:1079-1084.)

Key Words: atherosclerosis ■ carotid arteries ■ magnetic resonance imaging ■ hemorrhage

Intraplaque hemorrhage occurs frequently during the development of atherosclerotic lesions. Virmani et al has suggested that coronary intraplaque hemorrhage could lead to increase in plaque burden, in addition to being a reflection of the overall biological activity of the lesion.¹ Although association between intraplaque hemorrhage and symptoms is still a subject of controversy, the presence of intraplaque hemorrhage very likely distinguishes the biologically active, fragile plaque from a more stable lesion.²⁻⁷

Acute hemorrhagic incidents rarely happen in isolation, especially in the atherosclerotic plaque.^{6,7} Microscopic examination of endarterectomy specimens often demonstrates evidence of a series of microhemorrhages into the necrotic core and into the tissue surrounding the core. Under the best of circumstances, a chain of events resulting in production of interstitial collagen in the attempt to repair damaged areas follows intraplaque hemorrhage. This process may be disrupted by inflammatory mediators that stimulate the expression of matrix metalloproteinases.⁸ Metalloproteinase in-

duced degradation of extracellular matrix, and the subendothelial basement membrane of plaque microvasculature may in turn lead to repeat rupture events, as evidenced by intraplaque hemorrhages of various ages seen in excised specimens.⁹⁻¹⁰

A noninvasive imaging technique that is capable of identifying not only the presence but also the stage of intraplaque hemorrhage would be invaluable. Such a tool would permit in vivo studies to establish the significance of intraplaque hemorrhage in the development of ischemic complications. In addition, the detection of intraplaque hemorrhage would alert the clinician to the possibility of plaque instability. Hence, better characterization of the plaques may be useful for treatment. Although computed tomography (CT) can detect plaques and assess carotid stenosis, there are currently no CT criteria for staging intraplaque hemorrhage.

Magnetic resonance imaging (MRI) can accurately detect and stage cerebral hemorrhage using multicontrast MR images. The stages of cerebral hemorrhage are defined as

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From Department of Radiology (B.C., A.K., M.S.F., W.S.K., V.L.Y., C.Y.), Department of Medicine (K.D.O.), and Department of Surgery (T.S.H.), University of Washington; and Mountain-Whisper-Light Statistical Consulting (N.L.P.), Seattle, Wash.

Correspondence to Chun Yuan, Department of Radiology, 1959 NE Pacific St, Box 357115, Seattle, WA 98195. E-mail cyuan@u.washington.edu
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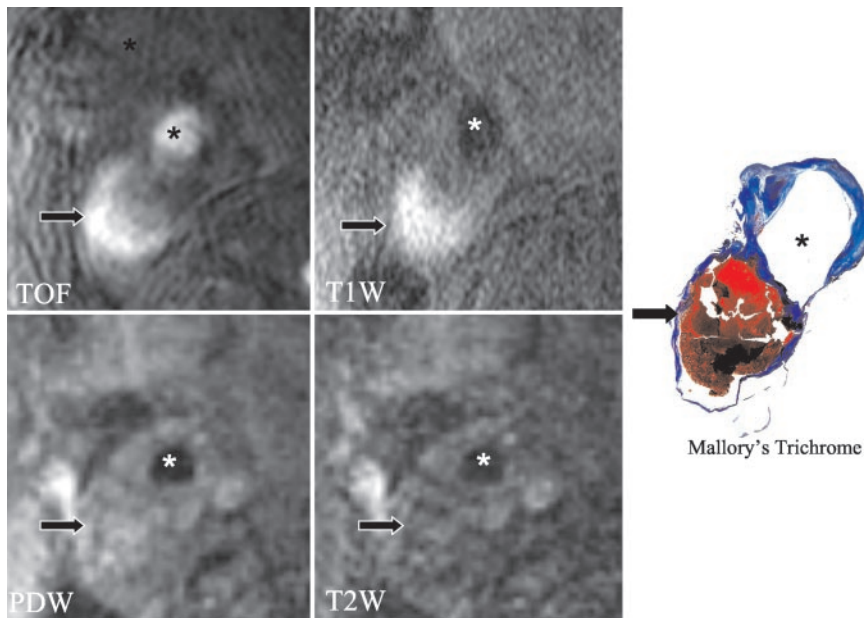


Figure 1. Fresh hemorrhage (arrows) identified by hyperintensity on the TOF and T1W images and isointensity on the T2W image (averaged IQ=3). Mallory trichrome-stained section confirms the presence of intraplaque hemorrhage. Fibrin and erythrocytes stain orange-red. Asterisks show the location of the lumen.

Mallory's Trichrome

hyperacute, acute, early subacute, late subacute, and chronic and are based on red blood cell content and the oxygenation of hemoglobin.^{11,12} MRI studies of extracranial hemorrhage have shown good correlation with signal patterns of cerebral hemorrhage.^{13,14}

Yuan et al¹⁵ have shown that MRI can detect carotid lipid-rich necrotic cores and intraplaque hemorrhage with good accuracy. The accuracy of intraplaque hemorrhage alone by MRI has yet to be defined. Moody et al¹⁶ have demonstrated that a T1-weighted (T1W) magnetization-prepared three-dimensional (3D) gradient echo sequence can detect methemoglobin within intraplaque hemorrhage. The sensitivity and specificity for this technique was 84%, with a positive predictive value of 93% and negative predictive value of 70%. The limitation of this study was lack of separation between thrombus and hemorrhage and all but 1 stage of hemorrhage.

Despite well-defined criteria for staging cerebral hemorrhage, no such MRI criteria has existed for intraplaque hemorrhage. In this study, we classify intraplaque hemorrhage stages and correlate our findings with histology.

Materials and Methods

Study Population

Twenty-seven patients (21 males, 6 females, aged 55 to 82) scheduled for carotid endarterectomy at the University of Washington Medical Center or VA Puget Sound Health Care System were recruited for the study after having given informed consent. Institutional review boards of each facility approved consent forms and study protocols. Thirteen patients had a history of transient ischemic attack or stroke 90 days before surgery. Fourteen patients were asymptomatic with a carotid stenosis >70% by duplex ultrasound. All patients underwent MRI within 1 week before surgery to reduce potential errors in the correlation between images and histology.

MRI Protocol

Patients were imaged with a custom-designed phased-array surface coil in a 1.5-T Scanner (Signa Horizon EchoSpeed; GE Medical Systems). A standardized protocol was used to obtain 4 different contrast-weighted images of carotids in the transverse plane: (1) T1W; (2) proton density-weighted (PDW); (3) T2-weighted (T2W); and (4) 3D time-of-flight (TOF) MR angiography. Parameters for the imaging follow; T1W: black-blood (double-inversion recovery) 2-dimensional fast-spin echo (FSE), TR/TE=800/9.3 ms, echo train length (ETL)=8; PDW/T2W: FSE, cardiac-gated, TR=3 or 4 heart beats (2500 to 3000 ms, depending on heart rate), effective TE=20 ms for PDW and 40 ms for T2W, ETL=8; and 3D TOF: TR/TE

TABLE 1. MRI/Histology Criteria: Intraplaque Hemorrhage

	Histology		MRI		
	Erythrocytes	Histology Criteria	T1W	T2W/PDW	TOF
Fresh	Intact RBC with intracellular methemoglobin	Lymphocytes and polymorphonuclear cells with scattered macrophages	Hyperintense	Hypointense/Isointense	Hyperintense
Recent	Lytic RBC with extracellular methemoglobin	Macrophage clusters, occasional giant cells, cholesterol crystals, and peripheral angiogenesis, MT=red to brown	Hyperintense	Hyperintense	Hyperintense
Old*	Amorphous	No inflammatory reaction, amorphous debris with hemosiderin, MT=blue	Hypointense	Hypointense	Hypointense

*Old hemorrhage may have focal areas of organizing components giving a distinct speckling of isointense or hyperintense signals on T1- and T2-weighted images. MT indicates Mallory trichrome; RBC, red blood cells.

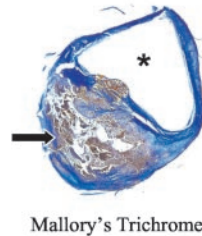
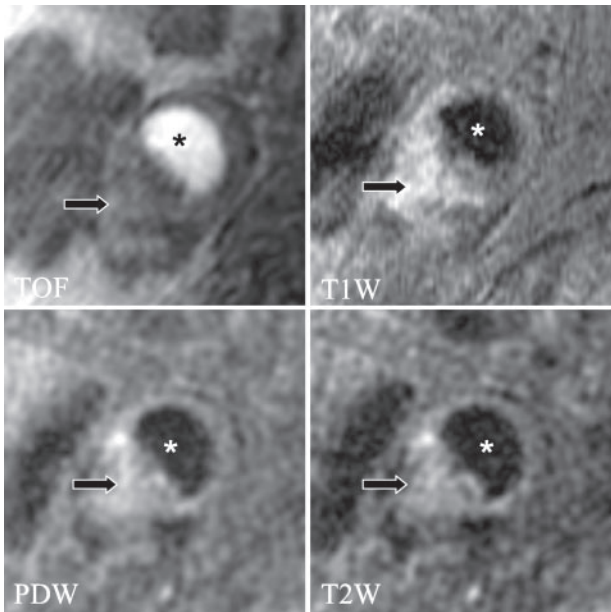


Figure 2. Recent hemorrhage (arrows) identified by hyperintensity in all contrast weightings (averaged IQ=3). Mallory trichrome matching histology section shows degradation products of hemorrhage staining a muddy brown. Asterisks are placed in the lumen.

23/3.5 ms, flip angle 25°. Field-of-view was 16 cm, matrix size was 256, slice thickness was 2 mm (1 mm for 3D TOF), and 2 NEX (number of excitations). Fat suppression was used for T1W, PDW, and T2W images. In-plane resolution was 0.5 mm. The longitudinal coverage of each artery was 24 mm (12 slices) for T1W, 36 mm (18 slices) for PDW and T2W, and 32 mm (32 slices) for 3D TOF.

MR Image Review and Criteria

Image quality (IQ) was rated for each contrast weighting on a 5-point scale (1=poor, 5=excellent) dependent on the overall signal-to-noise ratio and the clarity of the artery wall.¹⁵ Images with an IQ ≤2 were excluded from the study. Each imaging location resulted in 4 contrast weightings, examined by 2 readers blinded to histology.

Three stages of intraplaque hemorrhage were categorized: fresh, recent, and old. Fresh hemorrhage (<1 week) corresponds to early subacute cerebral hemorrhage and produces hyperintensity on T1W/TOF images and isointensity or hypointensity on T2W/PD images (Figure 1; Table 1). Recent hemorrhage (1 to 6 weeks) corresponds to late subacute brain hemorrhage and produces hyperintensity on all 4 contrast weightings (Figure 2). Old hemorrhage (>6 weeks)

corresponds to the late chronic brain hemorrhage and produces hypointensity on all 4 contrast weightings (Figure 3). The adjacent sternocleidomastoid muscle was used as reference.

Histology Processing and Criteria

After carotid endarterectomy, the specimens were fixed in formalin, decalcified, and embedded in paraffin. Samples were sectioned (10 μm) every 0.5 to 1.0 mm throughout the length of the specimen and stained (hematoxylin and eosin [H&E] and Mallory trichrome¹⁷). The slides were scored by an investigator (M.S.F.) blinded to the imaging results.

This study used the 4 pathologic categories proposed by Lusby et al² for carotid intraplaque hemorrhage.¹ Operative-intact erythrocytes staining bright orange-red with Mallory stain without associated inflammatory response.² Acute, fresh (<1 week), intact erythrocytes were associated with polymorphonuclear infiltrate and focal macrophage activity.³ Recent hemorrhage (1 to 6 weeks) containing hemorrhagic debris staining red to brown with Mallory trichrome and a mixture of intact and degenerating hemorrhage, macrophage engulfment of hemosiderin, giant cell development, cholesterol

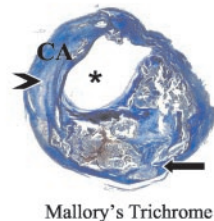
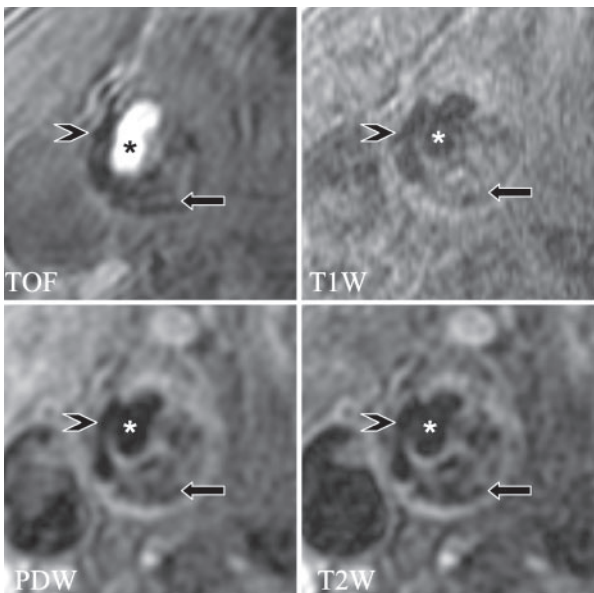


Figure 3. Old hemorrhage (arrow) produces variable hypointensity on MR images (averaged IQ=4). Calcification produces hypointensity with well-demarcated borders on all contrast weightings (chevron). Asterisks are placed in the lumen.

crystal formation, peripheral angiogenesis, and speckled calcification.⁴ Remote or old hemorrhage (>6 weeks) was characterized by amorphous material staining blue with Mallory trichrome, light pink with H&E, and surrounded by dense fibrous or calcified tissue, showing no evidence of inflammatory reaction, occasionally showing dense formation of cholesterol crystals and well-developed angiogenesis. In cases in which fresh or recent hemorrhage occurred in a space containing old hemorrhage, Mallory trichrome facilitated the new from old by staining erythrocytes, fibrin, and fibrin degradation products differing in shades of red to brown.

MRI and Histology Matching

Given the difference in slice thickness between MRI (2 mm) and histological cross sections (10 μ m, every 0.5 to 1.0 mm), comparison was made between 3 to 4 histological sections and 1 MR cross-sectional image on the basis of the relative distance to the bifurcation. To correct for shrinkage of the endarterectomy specimen during histological processing, additional measures were used for matching MRI and histology. Morphological features of lumen, vessel wall, and calcifications were used for co-registration.¹⁵ For a hemorrhage to be considered matched between histology and MRI sections, it had to lie in the same quadrant (or quadrants) in the matched sections.

Data Analysis

Sensitivity, specificity, and Cohen kappa (κ) were computed to quantify the agreement between MRI and histology, and between the 2 MRI reviewers. Because of the multiple locations for each artery within a patient, and the possibility of statistical dependence, the 95% CIs for sensitivity, specificity, and Cohen κ were calculated with the bootstrap method. The 95% CI for each performance statistic was defined as the 2.5th to the 97.5th percentile of the respective bootstrap distribution.¹⁸ A value of $\kappa > 0.75$ was used to indicate a high level of agreement, and $0.40 \leq \kappa \leq 0.75$ denotes moderate agreement.¹⁹ All computations and cross-tabulations were performed using the statistical language R (version 1.6.1).

Results

Three patients were eliminated from this study, 2 because of poor image quality and 1 because of a disrupted histology specimen. Twenty-three of the remaining 24 patients had hemorrhage in their plaques. One patient had no hemorrhage. The 24 patients yielded 180 MRI cross-sectional levels matched to histology (≈ 8 per patient). Each level contained 4 contrast weightings (720 images). Images were divided into quadrants totaling 2880 locations for precise colocalization. Multiple distinct areas of hemorrhage were present in 9 cross sections, giving 189 regions for comparison between histology and MRI.

Hemorrhage was present in 145 and absent in 44 out of 189 regions by histology. The mean sensitivity and specificity for the detection of intraplaque hemorrhage was 90% and 74%, respectively. Moderate agreement was seen between 2 readers and histology in the detection of intraplaque hemorrhage ($\kappa = 0.74$ for reader 1 and $\kappa = 0.52$ for reader 2) (Table 2).

The performance of each reader for classifying the age of intraplaque hemorrhage is presented in Table 3. Moderate agreement was reached between 2 readers and histology ($\kappa = 0.66$ for reader 1 and $\kappa = 0.44$ for reader 2). Reviewer 1 (148 positive regions) and reviewer 2 (136 positive regions) (Table 2) overlapped on 128 of the positive regions and agreed on the staging of hemorrhage in 96 of those regions ($\kappa = 0.4$ [0.3 to 0.6]).

TABLE 2. Sensitivity and Specificity: Each Reviewer Comparing Histology

		Histology+	Histology–	Total
Reviewer 1	MRI+	138	10	148
	MRI–	7	34	41
	Total	145	44	189
Reviewer 2	MRI+	123	13	136
	MRI–	22	31	53
	Total	145	44	189

Reviewer 1: sensitivity and specificity (95% CI) are 95% (91% to 99%) and 77% (57% to 97%), respectively. κ (95% CI)=0.74 (0.55–0.90).

Reviewer 2: sensitivity and specificity (95% CI) are 85% (75% to 93%) and 70% (50% to 88%), respectively. κ (95% CI)=0.52 (0.33–0.67).

Discussion

Increasing evidence from previous studies suggest that clinical symptoms and morbidity resulting from carotid artery disease are related to thrombosis, plaque ulceration, thinned fibrous caps, and intraplaque hemorrhage.^{1–7,20–26} The high prevalence of histologically identified hemorrhage in this study indicates that intraplaque hemorrhage may be common in advanced carotid atherosclerotic plaques and raises the possibility that intraplaque hemorrhage is a major mechanism for carotid atherosclerotic plaque progression. However, the limited number of patients in this study precludes conclusions regarding the clinical relevance of intraplaque hemorrhage. The focus of this study was to verify criteria and demonstrate the accuracy of MRI in locating and staging intraplaque hemorrhage.

Although MRI criteria of cerebral hemorrhage provides a framework, direct extrapolation of hemorrhage criteria from cerebral events to intraplaque hemorrhage is difficult because of the complexity of the substrate matrix of the latter. In brain, the underlying matrix is either gray or white matter, both of which give a uniform set of MRI signals. Moreover, the morphology and pathology of cerebral tissues have been well characterized by MRI. Even acute hemorrhage is readily detected in the brain, because of the presence of a tell-tale

TABLE 3. MRI/Histology Hemorrhage Stage Distribution

	Histology			Total
	Fresh	Recent	Old	
Reviewer 1				
Fresh	8	3		11
Recent	1	102	5	108
Old		7	12	19
Total	9	112	17	138
	Histology			Total
	Fresh	Recent	Old	
Reviewer 2				
Fresh	4	8		12
Recent	1	74	3	78
Old	2	17	14	33
Total	7	99	17	123

Reviewer 1: κ (95% CI)=0.66 (0.46–0.82).

Reviewer 2: κ (95% CI)=0.44 (0.23–0.61).

ring of edema and subsequent mass effect and the ability to correlate MRI findings with patient symptoms.

The situation is vastly different in the carotid atherosclerotic plaque. Intraplaque hemorrhage may insudate into preexisting necrotic cores or into spaces between calcifications and matrix. Microscopic examination of these areas shows a history of repeated hemorrhagic incidents. This varied matrix results in MR signal intensities of background substrate that have wide ranges of intensity. Blood entering an established necrotic core may organize and degrade at different rates because of existing degradative enzymes and inflammatory cells. In addition, many intraplaque hemorrhages fail to produce clinical symptoms limiting the ability to time of the hemorrhagic event.^{24,26} The use of a good animal model will greatly facilitate our understanding of the time of onset.²⁷

The first modification to cerebral criteria classifies early subacute hemorrhage into a “fresh” category. Morphologically, this encompasses early clotting mechanisms, macrophage and inflammatory cell infiltration. The low prevalence of large, acute hemorrhage in our advanced atherosclerotic lesions, along with the complexity of background tissues and inability to use patient symptoms to establish exact hemorrhage age made the “acute” category used for intracranial hemorrhage unrealistic.

The second category, “recent,” used late subacute criteria from brain hemorrhage and included the combination of hemorrhagic debris, intact and degenerating red blood cells, and the increased interstitial fluid associated with inflammation and early organization. These components combine to create hyperintense signal patterns in all contrast weightings. Seven false-positives occurred in this category, contributing to the moderate specificity of 74%.

Hypointensity in all 4 contrast weightings is the signal pattern of “old” hemorrhage. This category was responsible for the low Cohen κ in the interreader agreement. Although close examination of the edges of the hypointense signal aided in the differentiation between chronic hemorrhage and calcification, one reader considered these lesions calcification dominant while the other called them chronic hemorrhage-dominant. Stricter criteria are needed to estimate the mixture of components in a heterogeneous substrate.

There were several circumstances in which agreement between the 2 readers was high: when large, areas of hemorrhage $\geq 0.3 \text{ mm}^2$ were present; when medium-sized, area of hemorrhage 0.1 to 0.3 mm^2 occurred in the absence of confounding factors, such as speckled calcification, pockets, invaginations, and neovasculature. The large proportion of disagreement between the 2 readers was found in small areas of hemorrhage and in the presence of the aforementioned confounding factors.

It is important to note that the capability of staging intraplaque hemorrhage is dependent on the use of 4 contrast weightings and the subsequent information available in each weighting. Although a single T1W magnetization-prepared 3D gradient echo sequence can accurately detect methemoglobin within intraplaque hemorrhage,^{5,16} it cannot distinguish methemoglobin contained in erythrocytes from methemoglobin extruded from lysed cells into the surrounding

tissues. The use of PDW and T2W in this study allows for that discrimination by giving hypointense signals in the former and hyperintense in the latter scenarios, creating the opportunity for classification of fresh and recent hemorrhage.

Future work will focus on improving accuracy in the differentiation between lipid and recent hemorrhage. T2*-weighted gradient echo MRI will be studied for use in the detection of hemosiderin and calcifications, thus improving inter-reader reproducibility. Animal work, using a fibrin-targeted contrast agent, may give insights into the degradation of intraplaque incidents.²⁸

Conclusions

The results of this study indicate that in vivo high-resolution MRI can identify and stage intraplaque hemorrhage in advanced atherosclerotic carotid plaques with high sensitivity and moderate specificity. The capability of staging intraplaque hemorrhage may lead to a better understanding of its role in plaque stability and evolution, as well as provide valuable clinical information for patient management.

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