

Carotid Magnetization-Prepared Rapid Acquisition With Gradient-Echo Signal Is Associated With Acute Territorial Cerebral Ischemic Events Detected by Diffusion-Weighted MRI

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Background—Carotid intraplaque hemorrhage has been associated with symptomatic stroke and can be accurately detected with magnetization-prepared rapid acquisition with gradient-echo (MPRAGE). Currently, there are no studies analyzing carotid MPRAGE signal and territorial ischemic events defined by diffusion restriction in the acute setting. Our aim was to determine the association of carotid MPRAGE signal with acute territorial ischemic events using carotid MPRAGE and brain diffusion tensor imaging.

Methods and Results—After the addition of the MPRAGE sequence to the neck MR angiographic protocol, 159 patients with suspected acute stroke were evaluated with both brain diffusion tensor imaging and carotid MPRAGE sequences over 2 years, providing 318 carotid artery and paired brain images for analysis. Forty-eight arteries were excluded due to extracarotid sources of brain ischemia and 4 were excluded due to carotid occlusion. Two hundred sixty-six arteries were eligible for data analysis. Carotid MPRAGE-positive signal was associated with an acute cerebral territorial ischemic event with a relative risk of 6.4 ($P < 0.001$). The relative risk of a diffusion tensor imaging-positive territorial ischemic event with carotid MPRAGE-positive signal was increased in mild, moderate, and severe stenosis categories (10.3, $P < 0.001$; 2.9, $P = 0.01$; and 2.2, $P = 0.01$, respectively).

Conclusions—In the workup of acute stroke, carotid MPRAGE-positive signal was associated with an increased risk of territorial cerebral ischemic events as detected objectively by brain diffusion tensor imaging. The relative risk of stroke was increased in all carotid stenosis categories but was most elevated in the mild stenosis category. (*Circ Cardiovasc Imaging*. 2012;5:376-382.)

Key Words: carotid MRI ■ intraplaque hemorrhage ■ MRI ■ plaque ■ stroke

Each year >690 000 individuals in the United States are diagnosed with new or recurrent ischemic stroke, and approximately 20% to 30% of these are attributed to carotid atherosclerotic disease.¹ From 2005 to 2007, 358 058 carotid endarterectomies (CEAs) and 46 198 carotid artery stents were performed on patients with carotid stenosis, of which 92.0% were asymptomatic.² Prospective randomized studies have found that only 10% to 12% of these asymptomatic patients will have a symptomatic stroke within 5 years, and the significant majority will never have a cerebrovascular event.^{3–6} Thus, thousands of operations could be eliminated if highly stenotic but stable plaques could be accurately identified. Conversely, if unstable plaque components can be accurately detected, many patients who are asymptomatic or

have only mild or moderate carotid stenosis may benefit from early intervention.

Clinical Perspective on p 382

Intraplaque hemorrhage (IPH), lipid and necrosis, ulceration, and fibrous cap disruption contribute to carotid plaque instability. These components comprise the American Heart Association Type VI carotid plaque and have recently been associated with ipsilateral acute ischemic events.⁷ Of particular importance, hemorrhage has been shown to be a primary factor in plaque instability. Dating back to 1982, retrospective studies on CEA specimens have shown an increased incidence of IPH in symptomatic versus asymptomatic individuals.⁸ CEA specimens from symptomatic plaques have dem-

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onstrated a series of microhemorrhages within the necrotic core.^{9,10} These microhemorrhages within plaque are thought to represent precursors of plaque growth, instability, rupture, and subsequent embolization.¹¹

MRI has demonstrated unparalleled sensitivity and unmatched specificity in detecting IPH compared with ultrasound, CT angiography, and digital subtraction angiography.¹² Murphy and colleagues¹³ were the first to report that a MR direct thrombus imaging technique demonstrates complex atheroma as a high signal within the carotid wall. Previously, controversy has existed concerning the specificity of T1-weighted sequences in detecting hemorrhage, because other plaque components such as lipid/necrosis can also be T1-hyperintense.^{14,15} Far more accurate detection of IPH is now accomplished using advanced, heavily T1-weighted techniques including the magnetization-prepared rapid acquisition with gradient-echo (MPRAGE) sequence. Compared with conventional T1-weighted or time-of-flight sequences, the MPRAGE sequence has demonstrated significantly higher sensitivity (80%) and specificity (97%) in detecting IPH using histological confirmation.¹⁶ Although MPRAGE hyperintense plaque has been associated with clinically detected ipsilateral stroke,^{17,18} no studies have investigated the association between carotid MPRAGE signal and ischemic event distribution and acuity as determined objectively with brain diffusion tensor images (DTIs).

Our aim was to determine the relationship of carotid MPRAGE signal with objective evidence of acute ischemic events confined to the ipsilateral carotid territory. To accomplish this, the MPRAGE sequence was used in patients with suspected acute stroke undergoing MRI/MR angiography (MRA). Synchronous brain DTI was used to determine the relative risk of concurrent acute territorial ischemic events.

Methods

Clinical Study Design

A clinical protocol was instituted in November 2009 to determine the risk of acute ischemic events associated with MPRAGE-positive carotid arteries. The carotid MPRAGE sequence was added to standard MRI/MRA protocols used to evaluate patients with suspected acute stroke. Patients presenting with suspected acute stroke were scanned within 24 hours of presentation. The standard MRI/MRA protocol for these patients included brain MRI (axial DTI with apparent diffusion coefficient map, axial T2-weighted, axial fluid-attenuated inversion recovery, and sagittal T1-weighted images), brain MRA (axial time of flight), and neck MRA (axial time of flight, coronal precontrast T1-weighted, coronal postcontrast arterial, and coronal postcontrast venous phase images). Coronal postcontrast MRA neck images extended from the aortic arch through the circle of Willis. Total scan time was approximately 45 minutes of which the 3-dimensional MPRAGE sequence required approximately 5 minutes. Images of the carotid artery for this clinical study were obtained on a Siemens 1.5-T MRI with standard neck coil. Institutional Review Board approval was obtained and all subjects gave informed consent. From November 2009 to November 2011, 159 patients who underwent MRA/MRI acute stroke workup were imaged with the additional MPRAGE sequence. Because the MPRAGE sequence imaged both carotid arteries in each patient, this provided 318 carotid arteries with paired carotid MPRAGE and territorial brain DTI data for potential analysis.

Of the 318 carotids scanned, 48 arteries were excluded for potential extracarotid sources of ischemia, including documented cardiac embolic source of symptoms (38 arteries) and vasculitis on

digital subtraction angiography (10 arteries). Another 4 arteries were excluded because of carotid occlusion. Although there were 13 of 266 carotids with stenosis involving the distal internal carotid artery, in each case, the stenosis measured <50% and the arteries were therefore not excluded from analysis. Distal stenosis was determined by concurrent contrast MRA through the circle of Willis in the vast majority of cases (251 of 266). In cases when renal insufficiency precluded intravenous contrast (15 of 266), percent stenosis of the intracranial internal carotid artery was determined by noncontrast time of flight. Although a few scans exhibited mild motion artifacts primarily from swallowing, these artifacts were not sufficient to exclude any carotid MPRAGE images from interpretation.

MPRAGE Sequence

A 3-dimensional MPRAGE sequence was used in this study. In this sequence, segmented acquisition was performed with the sequence repetition time, the inversion preparation time (TI), and the phase encoding order of the MPRAGE sequence adjusted to optimally identify IPH as hyperintense. Image parameters were as follows: repetition time/TE/TI=6.39/2.37/370 ms, flip angle=15°, field of view=130×130×48 mm³, matrix=256×256×48, voxel=0.5×0.5×1.0 mm³. MPRAGE images were obtained from 20 mm below the bifurcation to 20 mm above the bifurcation at 1.0-mm slice thickness. The TIs of intraluminal blood and hemorrhage were assumed to be approximately 1200 ms and 350 ms at 1.5 T. To produce 3-dimensional images, a secondary phase encoding gradient was used in the slice select direction and measurements for all slice selection phase encodings were performed with rapid acquisition in each segment. The TI time was chosen relative to the phase encoding acquisition to maximize contrast between hemorrhage and inflowing blood. The TI time was found to sufficiently suppress the blood signal at 1.5 T. Chemical fat saturation was used.

Carotid MRI Evaluation

MPRAGE-positive plaque was defined by at least 1 image slice with at least 2-fold higher signal intensity compared to sternocleidomastoid muscle as previously described.¹⁸ Two radiologists experienced in MRA determined MPRAGE status in this objective manner independent of brain DTI results. Interobserver variability was determined between the 2 radiologists (J.S.M. and H.C.Y.). Intraobserver variability was obtained for 1 of the radiologists (J.S.M.) by repeat analysis of the scans at least 2 months after the scan was performed with blinding to prior results. Consensus interpretation was used for the final analysis when interpretation differed. In the vast majority of cases (251 of 266), stenosis was determined using contrast MRA according to North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria¹⁹ and categorized into mild (0%–29%), moderate (30%–69%), and severe (70%–99%) categories of stenosis. In 15 of 266 carotid arteries, renal insufficiency precluded contrast administration and percent stenosis of the cervical internal carotid artery was determined by carotid duplex scan either before or after the MRI.

Diffusion-Weighted Imaging Parameters

Diffusion-weighted images were obtained using the DTI technique as part of the standard clinical protocol. Scan parameters were 2-dimensional, 128×128 matrix, 3-mm slice thickness, B value=2000, 22 directions. Both DTI trace images and the apparent diffusion coefficient map were generated as part of the clinical scan.

Acute Territorial Ischemic Event Detection

Although all patients were suspected of an acute cerebral ischemic event by the referring clinician, only objective data from brain DTI were used to determine if an acute ischemic event was present. DTI positivity was defined as hyperintense signal on DTI trace with associated decreased signal on the apparent diffusion coefficient map, corresponding to an acute ischemic event at the time of the scan.^{20,21} Acute territorial ischemic events were first classified based on distribution (ipsilateral internal carotid artery [ICA] territory, ipsilateral basal ganglia, and posterior circulation). Only DTI-

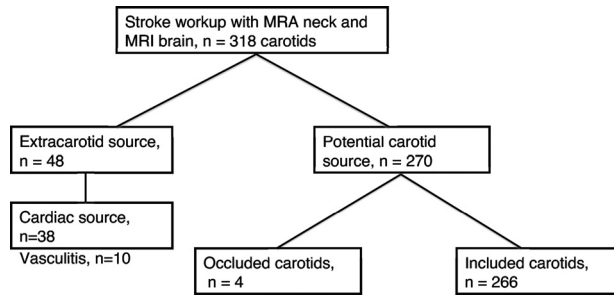


Figure 1. Study algorithm for MR workup of stroke. One hundred fifty-nine patients undergoing evaluation for acute stroke were enrolled in the study providing 318 carotid arteries and paired brain images for analysis. Forty-eight arteries were excluded due to extracarotid sources and 4 arteries were excluded due to occlusion, leaving 266 arteries included in the study.

positive events in the ipsilateral ICA territory were placed in the DTI-positive category. Acute territorial ischemic events were also classified by size. For all ICA territorial embolic infarcts, size was graded on a scale of 1 to 5 (1=0–1 cm, 2=1–3 cm, 3=3–6 cm, 4=6–9 cm, 5= \geq 9 cm). Brain MRI images were interpreted by a subspecialty trained neuroradiologist blinded to the carotid MPRAGE results.

Statistical Analysis

For the population analysis, 2-sided Fisher exact tests and unpaired *t* tests were used for comparison of stroke risk factors (male sex, age, hypertension, diabetes, smoking, and dyslipidemia). A logistic regression analysis was performed to test the interaction of ipsilateral and contralateral MPRAGE signal and found that contralateral MPRAGE signal was not an important predictor of DTI positivity ($P=0.40$) nor was the interaction of ipsilateral and contralateral MPRAGE signal ($P=0.43$). Therefore, carotid artery MPRAGE signal and its associated ipsilateral brain territory DTI signal was assumed to be independent of the contralateral carotid MPRAGE signal. Statistical analysis of carotid MPRAGE signal and brain DTI stroke status was performed using 2-way analysis of variance with a Tukey post hoc test. Likelihood ratios from the 2 \times 2 table were used to determine relative risk of a cerebrovascular ischemic event in MPRAGE-positive plaque with a 95% CI. Sensitivity was defined as the proportion of DTI-positive ICA territorial ischemic events with

an MPRAGE-positive ipsilateral carotid artery. Specificity was defined as the proportion of DTI-negative ICA territories with an MPRAGE-negative ipsilateral carotid artery. Accuracy was determined as the proportion of the total number of cases with DTI-positive ICA territories with MPRAGE-positive ipsilateral carotid or DTI negative ICA territories with MPRAGE negative ipsilateral carotid. Exact binomial 95% CIs were used for sensitivity, specificity, and accuracy. Infarct grades were compared using a Mann-Whitney *U* test. Kappa analysis was used to calculate interobserver and intraobserver agreement.

Results

Risk of Acute Territorial Stroke With Carotid MPRAGE Hyperintensity

One hundred fifty-nine patients presenting with acute focal neurological symptoms were evaluated with brain DTI and carotid MRA with the MPRAGE sequence from November 2009 to November 2011. After exclusion criteria were used, 266 carotid arteries were eligible for data analysis (Figure 1). There were 56 DTI-positive embolic events involving the ipsilateral ICA territory, and these were placed in the DTI-positive category. Although there were 8 ischemic events that involved only the basal ganglia and 13 events involving only the posterior circulation, these were not placed in the DTI-positive category because they did not meet criteria for embolic events in the ICA territory. Furthermore, none of the posterior circulation events were associated with MPRAGE-positive carotid arteries.

The majority of MPRAGE-positive carotid arteries were found in men and in a significantly higher proportion than that of MPRAGE-negative arteries (89.5% versus 54.8%, $P<0.001$; Table 1). A similar result was found in the DTI-positive versus DTI-negative categories (73.2% versus 56.2%, $P=0.02$; Table 1). MPRAGE-positive carotid arteries were on average found in older patients than MPRAGE-negative vessels (75.5 ± 9.9 years versus 66.4 ± 15.5 years, $P<0.001$; Table 1). In the MPRAGE-positive and -negative categories, there were no significant differences in clinical risk factors including hypertension, diabetes, smoking, and

Table 1. Demographics of Patients and Carotid Arteries

	MPRAGE			DTI		
	(+)	(-)	<i>P</i> Value	(+)	(-)	<i>P</i> Value
Patient demographics						
Total carotid	38	228		56	210	
Mean age, y	75.5 \pm 9.9	66.4 \pm 15.5	<0.001*	71.2 \pm 14.2	66.9 \pm 15.4	0.06
Median age, y	74	69		72.5	69	
Age range, y	(57–91)	(21–94)		(36–94)	(21–94)	
Sex (male)	89.5%	54.8%	<0.001*	73.2%	56.2%	<0.02*
Carotid disease risk factors						
Carotids	38	228		56	210	
Hypertension	73.7%	74.6%	1.00	69.6%	75.7%	0.39
Diabetes	36.8%	29.8%	0.45	33.9%	30.0%	0.63
Smoking	26.3%	21.1%	0.52	33.9%	18.6%	<0.02*
Dyslipidemia	71.1%	54.4%	0.08	62.5%	55.2%	0.36

Age, mean values \pm SD. Percent values represent percentage of carotid arteries.

MPRAGE indicates magnetization-prepared rapid acquisition with gradient-echo; DTI, diffusion tensor imaging.

* $P<0.05$.

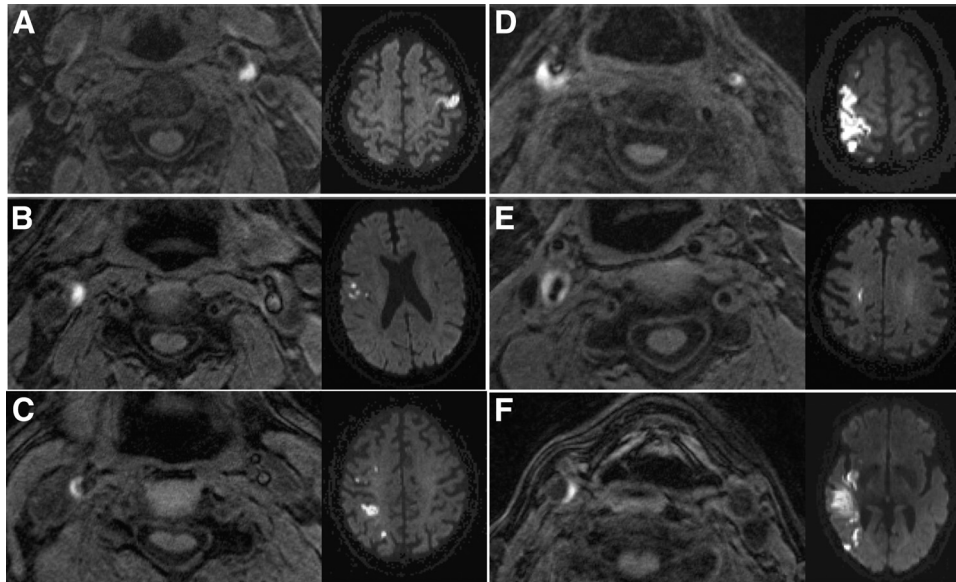


Figure 2. Six separate patients with MPRAGE-positive carotid arteries and associated territorial ischemic events. Images demonstrated MPRAGE-positive carotid arteries (left images) coupled with territorial ischemic events on DTI images (right images). MPRAGE-positive plaque and territorial ischemic events were as follows: (A) left, (B) right, (C) right, (D) bilateral, (E) right, (F) right. MPRAGE indicates magnetization-prepared rapid acquisition with gradient-echo; DTI, diffusion tensor imaging.

dyslipidemia (Table 1). In the DTI analysis, only smoking was associated with increased risk of a DTI-positive ischemic event.

MPRAGE-positive carotids were associated with increased risk of a DTI-positive acute territorial ischemic event as shown in the representative images (Figure 2) and pooled data (Table 2). The relative risk of an acute territorial ischemic event with an MPRAGE-positive carotid artery compared with an MPRAGE-negative carotid was 6.4 ($P < 0.001$; Table 2). MPRAGE positivity was assigned to 38 of 266 (14.3%) carotid arteries. Kappa values for interobserver and intraobserver agreement on MPRAGE signal were 0.862 and 0.918, respectively (very good agreement). For all ICA territorial embolic infarcts, size was graded on a scale of

1 to 5 (1=0–1 cm, 2=1–3 cm, 3=3–6 cm, 4=6–9 cm, 5= ≥ 9 cm). Infarcts with MPRAGE-positive ipsilateral carotids had an average grade of 2.38 ± 1.27 and median grade of 2. Infarcts with MPRAGE-negative ipsilateral carotids had an average grade of 2.78 ± 1.28 and median grade of 3. Using a Mann-Whitney *U* test, the 2-tailed probability value was 0.28 (not statistically significant).

These results were stratified based on percent stenosis. As expected, the incidence of ischemic events increased with percent stenosis of the cervical ICA (12.3%, 29.8%, and 72.7% for mild, moderate, and severe stenosis categories, respectively). The incidence of MPRAGE positivity also increased with higher degrees of carotid stenosis (5.9%, 28.1%, and 50.0% for mild, moderate, and severe stenosis

Table 2. Pooled Data of the Relationship of MPRAGE-Positive Carotid IPH With Territorial DTI-Positive Acute Ischemic Events

Stenosis	0%–29% DTI		30%–69% DTI		70%–99% DTI		Total DTI	
	(+)	(–)	(+)	(–)	(+)	(–)	(+)	(–)
MPRAGE								
(+)	9	2	9	7	11	0	29	9
(–)	14	162	8	33	5	6	27	201
Total carotids	187		57		22		266	
Prevalence of DTI (+)	12.3%		29.8%		72.7%		21.1%	
Prevalence of MPRAGE (+)	5.9%		28.1%		50.0%		14.3%	
Specificity	98.8% (95.7–99.9%)		82.5% (67.2–92.7%)		100.0% (54.1–100.0%)		95.7% (92.0–98.0%)	
Sensitivity	39.1% (19.7–61.5%)		52.9% (27.8–77.0%)		68.8% (41.3–89.0%)		51.8% (38.0–65.3%)	
Accuracy	91.4% (86.5–95.0%)		73.7% (60.3–84.5%)		77.3% (54.6–92.2%)		86.5% (81.8–90.3%)	
Relative risk	10.3 (5.0–13.8)		2.9 (1.2–6.3)		2.2 (1.1–2.2)		6.4 (4.3–8.7)	
<i>P</i> value (2-tailed)	<0.001*		0.01*		0.01*		<0.001*	

Specificity, sensitivity, and accuracy values are reported with exact binomial 95% CIs. Relative risk values are reported with 95% CIs. MPRAGE indicates magnetization-prepared rapid acquisition with gradient-echo; IPH, intraplaque hemorrhage; DTI, diffusion tensor imaging. * $P < 0.05$.

categories, respectively). The relative risk of cerebral ischemic event with MPRAGE-positive carotids was increased in all categories of stenosis, but this was most prominent in the mild stenosis category (10.3, $P < 0.001$; 2.9, $P = 0.01$; and 2.2, $P = 0.01$ in mild, moderate, and severe stenosis categories, respectively; Table 2).

Discussion

In patients presenting with a suspected acute stroke, clinicians attempt to confirm the presence of cerebral ischemia, identify the extent of the neurological deficit, and determine the etiology of the event. To detect a carotid source, patients usually undergo carotid duplex scan, CT angiography, conventional MRA, or digital subtraction angiography, all of which rely heavily on percent stenosis. Although these methods can detect luminal narrowing to a high degree of certainty, they cannot identify unstable plaque components. The current study and others have shown that stenosis does not fully determine the potential for embolization from the carotid artery. Traditionally, mild and moderate carotid artery stenoses have been overlooked as potential sources for thromboembolic stroke.

Although studies have found that complex carotid plaques (American Heart Association Type VI plaques) are associated with increased risk of subsequent events,⁷ the final common pathway has not been evaluated synchronously with the cerebral event. Parmar⁷ was the first to determine the association of acute ipsilateral neurological events with complex carotid plaques in a noninvasive manner. Although the Parmar study assessed all plaque components to determine American Heart Association plaque type, the evaluation of hemorrhage was limited because the study used a conventional T1-weighted sequence as opposed to the MPRAGE sequence. Our approach used MPRAGE because recent research has shown this sequence has higher sensitivity and specificity in detecting hemorrhage compared with conventional techniques.¹⁶ The MPRAGE sequence is also easier and more practical for many institutions that do not have the ability to measure all components and determine American Heart Association plaque type. Also, although contrast-enhanced MRA was used in the majority of patients in this study, it is not required for MPRAGE carotid analysis. Another major difference between our study and others is the use of DTI imaging to define acute territorial ischemic events. DTI trace images have been shown to be superior to conventional diffusion-weighted sequences in detecting acute ischemic events.²² In addition, many studies including Parmar used not only diffusion-positive events, but also included stroke symptoms such as transient ischemic attacks and aphasia without corresponding evidence of an actual territorial event on MRI. Despite these differences, the Parmar study provided the foundation and basis for much of our analysis.

Studies from CEA specimens have supported the relationship of carotid IPH with acute stroke. Early autopsy studies demonstrated IPH within emboli detected in arterial segments in the circle of Willis.²³ In an investigation on thrombotically active plaques, Spagnoli²⁴ found that hemorrhage in CEA specimens corresponded with a recent clinical stroke or transient ischemic attack based on the presence of neurolog-

ical symptoms. In patients with recurrent ipsilateral carotid symptoms, CEA specimens have demonstrated increased rates of hemorrhage suggesting a temporal association of hemorrhage with ischemic events.²⁵ By showing there is an increased relative risk of acute ischemia with MPRAGE-positive carotid signal, our data further support the hypothesis that IPH plays an important role in plaque instability and embolization.

Recent advances in MRI have found that heavily T1-weighted inversion recovery sequences such as our MPRAGE sequence aid in the identification of plaque hemorrhage. Zhu²⁶ used an optimized MPRAGE sequence similar to ours and also showed excellent detection of IPH in contrast to necrotic core, although the study was limited in that only 6 matched histology/carotid MRI paired regions of interest were compared. Bitar²⁷ used a similar approach comparing 97 matched histology/carotid MRI pairs but used a spoiled gradient sequence to provide T1-weighted contrast without magnetization preparation. More recently, Ota and colleagues¹⁶ reported using a MPRAGE sequence that offers an advantage over conventional T1 sequences in detecting IPH. Although there was no clear description of TI used in that study, the sequence used is very similar to that of Zhu and the sequence in this study. In the current study, the heavily T1-weighted signal of the MPRAGE sequence was accomplished by a magnetization preparation inversion pulse. From signal simulations that incorporated T1 values of muscle, blood, and hemorrhage, the segment repetition time and TI in the MPRAGE sequence were selected to suppress the inflowing blood signal and enhance tissues with short T1 relative to muscle similar to these prior studies.

The current study has added further support to the concept that carotid MPRAGE signal and presumably carotid IPH is associated with stroke. Using various combinations of MRI sequences, prior studies have linked carotid IPH to the risk of future stroke.^{17,18,25,28,29} These reports have noted that carotid IPH is associated with a higher incidence of subsequent ischemic events. Until now, carotid MPRAGE has not been used in the workup of stroke in an emergent setting. In this study, we used brain DTI to diagnose acute territorial ischemic events. This allowed for objective and accurate characterization of stroke acuity and territorial distribution. The increased risk of acute ischemic stroke in the ipsilateral territory of an MPRAGE-positive carotid artery adds further support to a recent report identifying nonspecific white matter lesions in patients with carotid IPH.³⁰ Our study differs from this work by using MPRAGE to determine plaque vulnerability instead of proton density and T2-weighted imaging. In addition, our study used DTI instead of fluid-attenuated inversion recovery to detect territorial ischemic events. Unlike fluid-attenuated inversion recovery imaging in which hyperintensity is permanent and does not allow temporal determination of event occurrence, DTI ensures the ischemic event occurred within 7 to 10 days of the scan.

A major limitation to carotid plaque characterization with MRI thus far has been motion. The modified MPRAGE sequence used in this study required approximately 5 minutes to perform, which can result in more motion artifact than lumenography performed by contrast MRA, CT angiography,

ultrasound, or digital subtraction angiography. In prior studies, however, 15% to 20% of carotid MRI images have been excluded due to image degradation from motion.⁷ In the current clinical study, no images were excluded due to motion and MPRAGE-positive signal was determined with very good interobserver and intraobserver agreement. Improvements in image acquisition and postprocessing may further reduce motion artifact and allow more accurate assessment of subsequent stroke risk. By using dedicated coils and by using motion-sensitized segmented gradient echo techniques to limit the effects of swallowing, excellent contrast-to-noise ratios can be obtained,³¹ which may allow more accurate carotid IPH volume assessment and likely more accurate carotid embolization risk assessment.

An additional limitation to the current version of our MPRAGE sequence was the restricted coverage from just above the common carotid origin to just below the petrous segment of the ICA that is necessary to limit the duration of imaging. Future studies including these vessel segments in the MPRAGE field of view could potentially detect alternative sources of ischemic stroke and improve the diagnostic use of the MPRAGE sequence. Cardiac gating, by identifying and correcting for cardiac-induced motion artifacts, may also improve MPRAGE imaging of plaques in the thoracic aorta or great vessel origins.

A final limitation of this study is that stroke risk was not further stratified based on hemorrhage age and location within the plaque. Saam²⁸ found that the location of plaque hemorrhage influenced the risk for acute stroke and separated hemorrhage into Type I (intracellular methemoglobin) and Type II (extracellular methemoglobin). This information would potentially improve risk stratification but was not specifically analyzed in our study. A longitudinal study on the ischemic events and hemorrhage acuity would better separate the significance of Type I versus Type II hemorrhage. Nevertheless, our study confirmed that the presence of any MPRAGE-positive lesion (presumably methemoglobin-containing) was strongly associated with increased risk of acute ipsilateral ischemic events.

Using the MPRAGE sequence, this study demonstrated that carotid MPRAGE signal hyperintensity increased the risk of concurrent ischemic events in all categories of stenosis. Interestingly, the relative risk was most elevated in the mild (<30%) stenosis category, which is considered lower risk and has not been shown to benefit from intervention. These findings have added further support to the concept that IPH is responsible for a large portion of carotid-based acute ischemic events independent of percent stenosis. Although not as marked as a mild stenosis, a high-grade carotid stenosis had a further 2.2-fold increased risk of acute stroke if the lesion was MPRAGE-positive. In addition, some DTI-positive ICA territory ischemic events occurred despite an MPRAGE-negative ipsilateral carotid artery. Clearly not all carotid territory cerebral ischemic events occur in patients with IPH and, in these cases, likely result from a carotid MPRAGE-negative plaque that may have a significant lipid-rich necrotic core, plaque ulceration without hemorrhage, or rupture of a fibrous cap with hyperacute thrombosis. Future new or modified MRI sequences or multicontrast combinations of

sequences may be needed to better determine the clinical importance of other carotid plaque components.

Interestingly, the relative risk of ischemic event with an MPRAGE-positive plaque independent of percent stenosis (relative risk, 6.4) was even greater than that of a severely stenotic plaque not stratified by MPRAGE signal (relative risk, 4.4). Currently, >70% stenosis is an accepted indication for CEA. Because the risk of ischemic event with MPRAGE-positive plaque was similar to >70% stenosis, MPRAGE-positive lesions also represent a high-risk plaque. These patients may benefit from early intervention with aggressive medical therapy and/or CEA.

In summary, MPRAGE-positive carotid plaque was associated with increased risk of acute territorial ischemic events detected by brain DTI. This increased risk was present in all categories of carotid stenosis. This study found that this marker of carotid plaque hemorrhage was present in a high proportion of acute embolic strokes and may be a critical component of many carotid-based cerebral embolic events. Routine use of the MPRAGE sequence may lead to a more accurate stroke risk estimate in patients with carotid disease and more accurate determination of a carotid source of ischemic events.

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Disclosures

None.

References

1. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner MB, Wong ND, Wylie-Rosett J. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. *Circulation*. 2011;123:e18–e209.
2. Eslami MH, McPhee JT, Simons JP, Schanzer A, Messina LM. National trends in utilization and postprocedure outcomes for carotid artery revascularization 2005 to 2007. *J Vasc Surg*. 2011;53:307–315.
3. The CASANOVA Study Group. Carotid surgery versus medical therapy in asymptomatic carotid stenosis. *Stroke*. 1991;22:1229–1235.
4. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA*. 1995;273:1421–1428.
5. The European Carotid Surgery Trialists Collaborative Group. Risk of stroke in the distribution of an asymptomatic carotid artery. *Lancet*. 1995;345:209–212.
6. Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, Thomas D. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet*. 2004;363:1491–1502.
7. Parmar JP, Rogers WJ, Mugler JP III, Baskurt E, Altes TA, Nandalur KR, Stukenborg GJ, Phillips CD, Hagspiel KD, Matsumoto AH, Dake MD, Kramer CM. Magnetic resonance imaging of carotid atherosclerotic plaque in clinically suspected acute transient ischemic attack and acute ischemic stroke. *Circulation*. 2010;122:2031–2038.
8. Lusby RJ, Ferrell LD, Ehrenfeld WK, Stoney RJ, Wylie EJ. Carotid plaque hemorrhage. Its role in production of cerebral ischemia. *Arch Surg*. 1982;117:1479–1488.

9. Burke AP, Koldogic FD, Farb A, Weber DK, Malcom GT, Smialek J, Virmani R. Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. *Circulation*. 2001;103:934–940.
10. Davies AH, Hayward JK, Currie I, Cole SE, Lopatazidis A, Lamont PM, Baird RN. Risk prediction of outcome following carotid endarterectomy. *Cardiovasc Surg*. 1996;4:338–339.
11. Kockx MM, Cromheeke KM, Knaapen MW, Bosmans JM, De Meyer GR, Herman AG, Bult H. Phagocytosis and macrophage activation associated with hemorrhagic microvessels in human atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2003;23:440–446.
12. Chu B, Kampschulte A, Ferguson MS, Kerwin WS, Yarnykh VL, O'Brien KD, Polissar NL, Hatsukami TS, Yuan C. Hemorrhage in the atherosclerotic carotid plaque: a high-resolution MRI study. *Stroke*. 2004;35:1079–1084.
13. Murphy RE, Moody AR, Morgan PS, Martel AL, Delay GS, Allder S, MacSweeney ST, Tennant WG, Gladman J, Lowe J, Hunt BJ. Prevalence of complicated carotid atheroma as detected by magnetic resonance direct thrombus imaging in patients with suspected carotid artery stenosis and previous acute cerebral ischemia. *Circulation*. 2003;107:3053–3058.
14. Yuan C, Mitsumori LM, Ferguson MS, Polissar NL, Echelard D, Ortiz G, Small R, Davies JW, Kerwin WS, Hatsukami TS. In vivo accuracy of multispectral magnetic resonance imaging for identifying lipid-rich necrotic cores and intraplaque hemorrhage in advanced human carotid plaques. *Circulation*. 2001;104:2051–2056.
15. Hishikawa T, Iihara K, Yamada N, Ishibashi-Ueda H, Miyamoto S. Assessment of necrotic core with intraplaque hemorrhage in atherosclerotic carotid artery plaque by MR imaging with 3D gradient-echo sequence in patients with high-grade stenosis. Clinical article. *J Neurosurg*. 2010;113:890–896.
16. Ota H, Yarnykh VL, Ferguson MS, Underhill HR, Demarco JK, Zhu DC, Oikawa M, Dong L, Zhao X, Collar A, Hatsukami TS, Yuan C. Carotid intraplaque hemorrhage imaging at 3.0-T MR imaging: comparison of the diagnostic performance of three T1-weighted sequences. *Radiology*. 2010;254:551–563.
17. Takaya N, Yuan C, Chu B, Saam T, Underhill H, Cai J, Tran N, Polissar NL, Isaac C, Ferguson MS, Garden GA, Cramer SC, Maravilla KR, Hashimoto B, Hatsukami TS. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI—initial results. *Stroke*. 2006;37:818–823.
18. Yamada N, Higashi M, Otsubo R, Sakuma T, Oyama N, Tanaka R, Iihara K, Naritomi H, Minematsu K, Naito H. Association between signal hyperintensity on T1-weighted MR imaging of carotid plaques and ipsilateral ischemic events. *AJNR Am J Neuroradiol*. 2007;28:287–292.
19. Clinical alert: benefit of carotid endarterectomy for patients with high-grade stenosis of the internal carotid artery. National Institute of Neurological Disorders and Stroke Stroke and Trauma Division. North American Symptomatic Carotid Endarterectomy Trial (NASCET) investigators. *Stroke*. 1991;22:816–817.
20. Lansberg MG, Thijs VN, O'Brien MW, Ali JO, de Crespigny AJ, Tong DC, Moseley ME, Albers GW. Evolution of apparent diffusion coefficient, diffusion-weighted, and T2-weighted signal intensity of acute stroke. *AJNR Am J Neuroradiol*. 2001;22:637–644.
21. Warach S, Gaa J, Siewert B, Wielopolski P, Edelman RR. Acute human stroke studied by whole brain echo planar diffusion-weighted magnetic resonance imaging. *Ann Neurol*. 1995;37:231–241.
22. Chou MC, Tzeng WS, Chung HW, Wang CY, Liu HS, Juan CJ, Lo CP, Hsueh CJ, Chen CY. T2-enhanced tensor diffusion trace-weighted image in the detection of hyper-acute cerebral infarction: comparison with isotropic diffusion-weighted image. *Eur J Radiol*. 2010;74:e89–e94.
23. Sadoshima S, Fukushima T, Tanaka K. Cerebral artery thrombosis and intramural hemorrhage. *Stroke*. 1979;10:411–414.
24. Spagnoli LG, Mauriello A, Sangiorgi G, Fratoni S, Bonanno E, Schwartz RS, Piepgras DG, Pistolesse R, Ippoliti A, Holmes DR Jr. Extracranial thrombotically active carotid plaque as a risk factor for ischemic stroke. *JAMA*. 2004;292:1845–1852.
25. Altaf N, MacSweeney ST, Gladman J, Auer DP. Carotid intraplaque hemorrhage predicts recurrent symptoms in patients with high-grade carotid stenosis. *Stroke*. 2007;38:1633–1635.
26. Zhu DC, Ferguson MS, DeMarco JK. An optimized 3D inversion recovery prepared fast spoiled gradient recalled sequence for carotid plaque hemorrhage imaging at 3.0 T. *Magn Reson Imaging*. 2008;26:1360–1366.
27. Bitar R, Moody AR, Leung G, Symons S, Crisp S, Butany J, Rowsell C, Kiss A, Nelson A, Moggisano R. In vivo 3D high-spatial-resolution MR imaging of intraplaque hemorrhage. *Radiology*. 2008;249:259–267.
28. Saam T, Cai J, Ma L, Cai YQ, Ferguson MS, Polissar NL, Hatsukami TS, Yuan C. Comparison of symptomatic and asymptomatic atherosclerotic carotid plaque features with in vivo MR imaging. *Radiology*. 2006;240:464–472.
29. Singh N, Moody AR, Gladstone DJ, Leung G, Ravikumar R, Zhan J, Moggisano R. Moderate carotid artery stenosis: MR imaging-depicted intraplaque hemorrhage predicts risk of cerebrovascular ischemic events in asymptomatic men. *Radiology*. 2009;252:502–508.
30. Ouhlous M, Flach HZ, de Weert TT, Hendriks JM, van Sambeek MR, Dippel DW, Pattynama PM, van der Lugt A. Carotid plaque composition and cerebral infarction: MR imaging study. *AJNR Am J Neuroradiol*. 2005;26:1044–1049.
31. Bornstedt A, Burgmaier M, Hombach V, Marx N, Rasche V. Dual stack black blood carotid artery CMR at 3T: application to wall thickness visualization. *J Cardiovasc Magn Reson*. 2009;11:45.

CLINICAL PERSPECTIVE

Carotid intraplaque hemorrhage has been associated with symptomatic stroke and can be accurately detected with magnetization-prepared rapid acquisition with gradient-echo (MPRAGE). However, an association between carotid hemorrhage, as detected by MPRAGE signal, and territorial ischemic events, as detected by diffusion restriction in the acute setting, has not been shown. Our aim was to determine the association of carotid MPRAGE signal with acute territorial ischemic events using carotid MPRAGE and brain diffusion tensor imaging in patients with suspected acute stroke within 24 hours. In patients undergoing acute stroke workup, MPRAGE-positive carotid plaque was associated with acute territorial ischemic events detected by brain diffusion tensor imaging. This association was present across all categories of carotid stenosis. These data add further support to the understanding of the pathophysiology of carotid embolic stroke and the notion of MPRAGE-positive plaques as a marker of vulnerability with increased risk of embolic events. Routine use of the MPRAGE sequence may lead to improved risk assessment for stroke in patients with carotid disease, which may greatly improve diagnosis of cerebral embolic sources. Clinical trials to determine the optimal treatment for patients with vulnerable carotid plaque are warranted.

Carotid Magnetization-Prepared Rapid Acquisition With Gradient-Echo Signal Is Associated With Acute Territorial Cerebral Ischemic Events Detected by Diffusion-Weighted MRI

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