Late Stage Complicated Atheroma in Low-Grade Stenotic Carotid Disease: MR Imaging Depiction—Prevalence and Risk Factors[1]

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Purpose: To determine if complicated plaque can be found by using magnetic resonance (MR) imaging–depicted intraplaque hemorrhage (IPH), even among symptomatic patients with low-grade (≤50%) carotid stenosis.

Materials and Methods: The institutional ethics review board approved this retrospective study and waived requirements for written informed consent. Symptomatic patients with bilateral 0%–50% carotid stenosis referred for carotid MR imaging were considered. Risk factors (age, sex, hypertension, diabetes, hyperlipidemia, myocardial infarction, atrial fibrillation, smoking, coronary artery disease, and cerebrovascular disease), medications (antihypertensive drugs, diabetes drugs, statins, and aspirin), and the brain side causing symptoms were recorded. MR-depicted IPH prevalence in the carotid arteries ipsilateral and contralateral to the symptomatic side was compared by using the Fisher exact test. Multivariable regression was used to compare the MR-depicted IPH prevalence, while adjusting for risk factors and medications.

Results: A total of 217 patients (434 carotid arteries) were included. MR-depicted IPH was found in 13% (31 of 233) of carotid arteries ipsilateral and 7% (14 of 201) of arteries contralateral to symptoms ($P < .05$). Male sex ($P < .05$) and increasing age ($P < .05$) were associated with MR-depicted IPH after controlling for risk factors and medications.

Conclusion: Complicated carotid atheroma can be found among symptomatic patients with low-grade (≤50%) stenosis, and this is associated with male sex and increasing age. MR-depicted IPH may be useful to stratify risk for patients with low-grade carotid stenosis.

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Stroke is the second most common cause of mortality and a major cause of adult disability worldwide. Many stroke cases are attributed to carotid artery disease (1). Understanding the natural history of carotid disease is therefore vital to improving the prevention, treatment, and prediction of stroke.

The North American Symptomatic Carotid Endarterectomy Trial and the European Carotid Surgery Trial showed large, moderate, or no reduction in stroke risk after carotid endarterectomy among severe (70%–99%), moderate (50%–69%), and low-grade (0%–49%) carotid artery stenosis groups, respectively (2–4). Most studies have therefore focused on diagnosing carotid disease and predicting stroke risk in patients with severe and moderate stenosis. However, during the past decade, mounting evidence has shown that the inflammatory process of atherosclerosis and specific biologic characteristics of atheromas have clinical implications independent of stenosis severity (5). Various biologic markers have been implicated in plaque instability, including proinflammatory cytokines, macrophage recruitment, platelet adhesion, and intraplaque hemorrhage (IPH) (6). Of these, IPH is a major characteristic of complicated plaque, defined as type VI atheroma by the American Heart Association and at increased risk of rupture, which has emerged as a marker of plaque instability (7). Among patients with similar degrees of carotid stenosis severity, those with IPH are more likely than those without to experience adverse cardiovascular and cerebrovascular events (7).

The relative dearth of studies characterizing plaque in low-grade stenosis groups likely reflects limitations in existing techniques that attempt to characterize morphology in low-volume vessel wall disease. Histologic findings from endarterectomy are not available for low-grade stenosis, as they are for high-grade stenosis, because there is no indication for surgery in the former group. Noninvasive imaging markers of complicated atherosclerotic plaque that are sensitive enough to characterize plaque, especially for low-volume disease, are therefore required to study this low-grade stenotic group.

Plaque characteristics such as IPH may be more predictive of stroke than luminal stenosis (8,9). Magnetic resonance (MR) imaging–depicted IPH is a feature validated to detect complicated carotid plaque (10,11). The purpose of this study was to determine if complicated plaque can be found by using MR-depicted IPH, even among symptomatic patients with low-grade (≤50%) carotid stenosis.

Advances in Knowledge

- Patients with low-grade (≤50%) carotid stenosis may have complicated plaque defined by intraplaque hemorrhage (IPH) at MR imaging.
- Male sex is associated with the presence of IPH in low-grade (≤50%) carotid stenosis, independent of traditional cardiovascular risk factors and medication use.
- Increasing age is associated with the presence of IPH in low-grade (≤50%) carotid stenosis, independent of sex, traditional cardiovascular risk factors, and medication use.

Materials and Methods

Participants

The institutional research ethics review board approved this retrospective study and waived the requirement for written informed consent. Patients older than 50 years who were referred for MR-depicted IPH examination of their carotid arteries by a neurologist for neurologic symptoms suggestive of stroke or transient ischemic attack between February 1, 2003, and September 15, 2006, were considered for this study. Among those patients, only those with a Doppler ultrasonographic (US) image or a three-dimensional time-of-flight MR angiogram that showed carotid stenosis at 50% or less in both carotid arteries were included. Patients were excluded from the study if IPH MR images were unreadable or if complete information on age, sex, carotid stenosis, cardiovascular risk factors, or medications was unavailable.

Implications for Patient Care

- Complicated carotid atherosclerotic disease may be missed by relying on stenosis measurements alone.
- MR-depicted IPH can help identify complicated plaque despite low-grade carotid stenosis.

MR Protocol and Evaluation of MR-depicted IPH

Patients were imaged by using a 1.5-T MR imager (Twin Speed; GE Healthcare, Milwaukee, Wis) and an eight-channel neurovascular phased-array coil (USA Instruments, Aurora, Ohio). A three-dimensional T1-weighted fat-suppressed (Special [spectral inversion at lipids]; GE Healthcare) spoiled gradient-echo sequence (repetition time, 6.7 msec; echo time, 1.7 msec; flip angle, 15°; section thickness, 2 mm; 40 sections; field of view, 300 mm^2; matrix size, 320 × 320; interpolated effective pixel size, 0.94 × 0.94 × 1 mm; number of signals acquired, three) was used (Figs 1–3). Imaging time was 4 minutes 13 seconds. MR imaging of IPH depicts methemoglobin within IPH, which is a marker of complicated plaque. Although other MR images were often obtained as part of the patient's clinical work-up,

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Abbreviation:
IPH = intraplaque hemorrhage

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Potential conflicts of interest are listed at the end of this article.

Figure 1

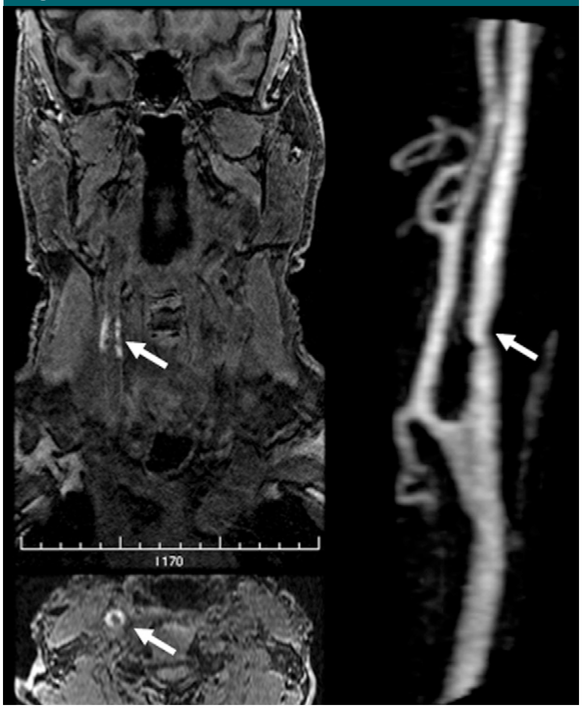

Figure 1: (Top left) Coronal and (bottom left) axial MR images depicting IPH in 71-year-old woman show high signal intensity in the right carotid artery (arrows). Right: MR angiogram of the right carotid artery in same patient shows minimal stenosis (arrow).

Figure 2

Figure 2: (Top left) Coronal and (bottom left) axial MR images depicting IPH in 73-year-old woman show high signal intensity in the left carotid artery (arrows). Right: MR angiogram of left carotid artery (arrow) in same patient.

these were not used for the purpose of this study.

MR-depicted IPH was defined as plaque signal intensity that exceeded the signal intensity of the adjacent skeletal muscle by 50%. This was subjectively assessed by three radiologists (A.R.M., more than 10 years of experience) who were blinded to all patient information. Patients with MR-depicted IPH signal intensity in one or both carotid arteries were considered to have a positive finding for MR-depicted IPH, whereas those without MR-depicted IPH signal hyperintensity in either carotid artery were considered to have a negative finding for MR-depicted IPH. A binary decision of positive finding for MR-depicted IPH or negative finding for MR-depicted IPH was made by consensus among a group of three radiologists.

Statistical Analysis

Analyses were performed by using statistical software (SPSS, version 13.0; SPSS, Chicago, Ill), and *P* values less than .05 were considered to indicate statistically significant differences.

Neurologic symptoms were attributed to the left, the right, or both sides of the brain. The age and sex of the patient, the presence or absence of cardiovascular risk factors (history of hypertension, diabetes, hyperlipidemia, myocardial infarction, atrial fibrillation, smoking, coronary artery disease, and cerebrovascular disease or transient ischemic attacks), and the use of medications (hypertension drugs, diabetes drugs, statins, and aspirin) were noted. The average age and the percentage of men in the study group were calculated. Differences in risk factors and medications between the sexes were calculated by using multivariable logistic regression.

A Fisher exact test was used to compare the prevalence of MR-depicted IPH in carotid arteries ipsilateral and contralateral to the symptomatic side. A Clopper-Pearson test was used to determine the 95% confidence interval for the prevalence of MR-depicted IPH in at least one caroid artery for a patient in this group. Multivariable logistic regression was used to compare the prevalence of MR-depicted IPH on a per-patient basis while adjusting for age, sex, cardiovascular risk factors, and medications.

Results

Five hundred twenty-four patients were screened. Of these, 51 (9.7%) of 524 were excluded because these patients did not have IPH MR images or the images were unreadable, 95 (20%) of 473 patients were excluded because Doppler US or time-of-flight MR images were not available, 63 (17%) of 378 were excluded because one or more carotid arteries had greater than 50% stenosis, and 98 (31%) of 315 were excluded because complete information on neurologic symptoms, risk factors, and medications were unavailable.

A total of 217 patients (with a total of 434 carotid arteries) met the inclusion

Figure 3

Figure 3: (Top left) Coronal and (bottom left) axial MR images depicting IPH in 83-year-old man show high signal intensity in the right carotid artery (arrows). Right: MR angiogram of right carotid artery (arrow) in same patient.

Figure 4

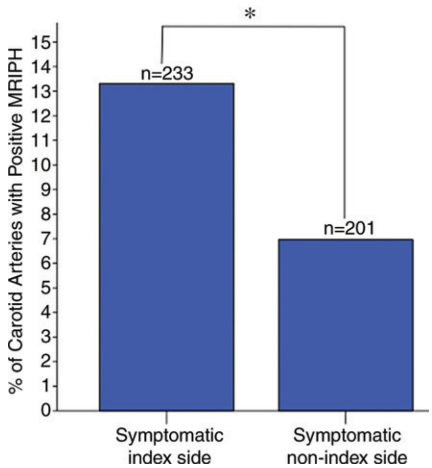

Figure 4: Graph shows prevalence of MR-depicted IPH in index arteries (ipsilateral to neurologic symptoms) compared with nonindex arteries (contralateral to neurologic symptoms) by using Fisher exact test. * = Significant difference ($P < .05$).

Table 1

Differences in Cardiovascular Risk Factors and Medications between Men and Women

Characteristic	Frequency in Patients: Men (n = 109)	Women (n = 108)	P Value*
Age (y)†	69.3 ± 10.3	70.1 ± 11.3	.761
History			
Hypertension	70 (64)	66 (61)	.510
Diabetes	27 (25)	13 (12)	.181
Hyperlipidemia	61 (56)	50 (46)	.440
Myocardial infarction	15 (14)	5 (5)	.065
Atrial fibrillation	11 (10)	13 (12)	.973
Smoking	35 (32)	20 (19)	.031‡
Coronary artery disease	27 (25)	19 (18)	.606
Cerebrovascular disease or transient ischemic attack	38 (35)	34 (31)	.148
Medication			
Hypertension	69 (63)	70 (65)	.283
Diabetes	28 (26)	10 (9)	.043‡
Statins	55 (50)	49 (45)	.464
Aspirin	58 (53)	48 (44)	.307

Note.—Unless otherwise indicated, data are numbers of patients, with percentages in parentheses.

* P values were determined by using multivariable logistic regression.

† Data are means ± standard deviations.

‡ $P < .05$ (significant difference).

criteria. Of these, 50% (109 of 217) were men. The mean age was 69.7 years (age range, 50–92 years). By using multivariable logistic regression, it was determined that men were more likely than women to smoke ($P < .05$). They were also more likely to be taking diabetic medications ($P < .05$). All other characteristics measured were not significantly different between sexes (Table 1).

Two hundred thirty-three (54%) of 434 carotid arteries were associated with unilateral neurologic symptoms, and 201 (46%) of 434 were not. MR-depicted IPH was found in 31 (13%) of 233 carotid arteries ipsilateral to the symptomatic cerebral hemisphere, compared with 14 (7%) of 201 contralateral carotid arteries ($P < .05$, Fisher exact test) (Fig 4). Seven patients had bilateral MR-depicted IPH, and a total of 38 (17.4%) of 217 (95% confidence interval with Clopper-Pearson test: 12.7%, 23.1%) patients had MR-depicted IPH in at least one artery.

Men were more likely to have MR-depicted IPH in one or both carotid arteries than women, even after controlling for age, cardiovascular risk factors, and relevant medication use ($P < .05$) (Fig 5a). Increasing age was also

Figure 5

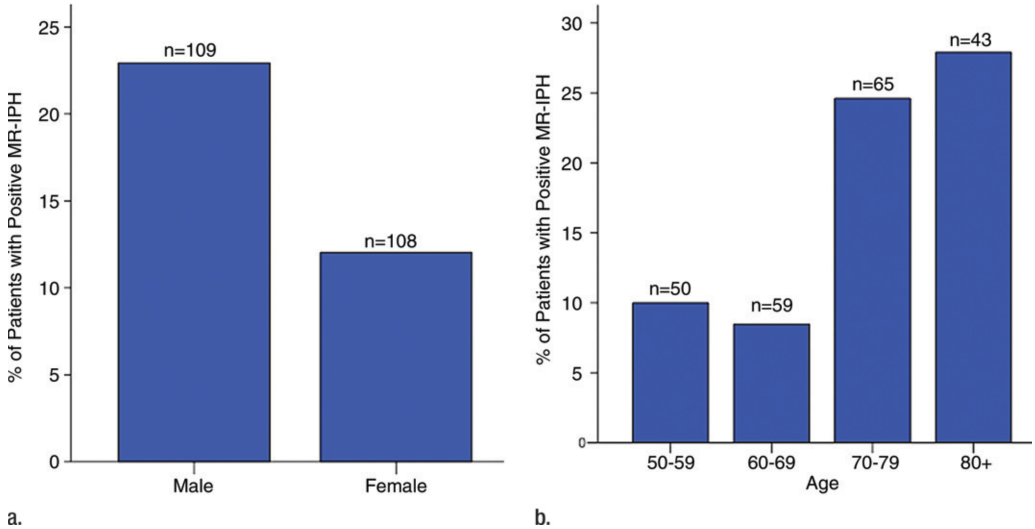

Figure 5: Graphs show prevalence of unilateral or bilateral MR-depicted IPH in **(a)** men versus women and **(b)** different age groups.

associated with MR IPH signal intensity ($P < .05$) (Table 2) (Fig 5b).

Discussion

The present study confirmed that IPH can be found even among patients with low-grade carotid stenosis and is associated with ipsilateral symptoms. This finding refutes the underlying assumption that stenosis and plaque morphology are necessarily linked, although worsening plaque morphology is associated with increasing stenosis (12). Although this group reflects patients with complicated type VI plaque, they would typically be labeled as having early stage disease on the basis of stenosis, and histologic study of carotid arteries of this stenosis is uncommon because carotid endarterectomy specimens are rarely obtained. These findings suggest that complicated carotid disease will therefore be missed by relying on stenosis measurement alone.

This study also looked at the effect of risk factors in the low-grade stenosis group and found that male sex and age were associated with IPH. This was consistent with previous studies that have suggested that women tend to have a more stable plaque phenotype than men and that the aging process increases endothelial dysfunction and inflammatory oxidative stress (13–21). This study did not find a significant correlation between IPH and other risk factors; whether this is because the correlation was not sufficiently robust or whether IPH is not related to these factors as some studies have suggested (22) is unclear.

Few studies in the literature have examined patients with low-grade carotid stenosis by using either wall imaging or histologic techniques. There have been several studies that have found carotid atheroma and plaque vascularization among patients with low-grade stenosis (12,23–26), some of which have suggested that IPH in these groups may be associated with plaque growth (25) and cerebrovascular events (12). The study of plaque morphology in low-grade stenotic carotid disease provides a means of studying the early natural history of vessel wall disease without the additional influence of high-grade stenosis. Recent evidence has shown that the presence of carotid IPH in carotid endarterectomy specimens is associated with an individual's systemic vascular risk (27). While no evidence exists regarding the effect of carotid IPH in low carotid stenosis on systemic vascular outcome, this raises the possibility of identifying the vulnerable patient at an early stage of systemic disease.

Table 2

Multivariable Logistic Regression for Positive Findings of MR-depicted IPH in One or Both Carotid Arteries according to Risk Factors

Characteristic	*P* Value*
Age	.015†
Sex	.035†
History	
Hypertension	.317
Diabetes	.739
Hyperlipidemia	.815
Myocardial infarction	.493
Atrial fibrillation	.630
Smoking	.218
Coronary artery disease	.395
Cerebrovascular disease or transient ischemic attack	.907
Medication	
Hypertension	.126
Diabetes	.830
Statins	.427
Aspirin	.220

* *P* values were determined by using multivariable logistic regression.

† *P* values < .05.

Other imaging techniques currently used to quantify and characterize plaque include Doppler US, high-spatial-resolution multicontrast MR imaging, computed tomography (CT), fluorine 18 fluorodeoxyglucose positron emission tomography (PET), and B-mode US. Doppler US is an excellent tool for detecting luminal stenosis, but it is limited in characterizing plaque morphology, making it of little use in characterizing nonstenotic plaque (28). High-spatial-resolution multicontrast MR imaging, CT, and fluorine 18 fluorodeoxyglucose PET can help characterize plaque components but are limited by long acquisition times, radiation exposure, and low resolution, respectively (28–31). B-mode US can help measure intima-media thickness but primarily reflects changes due to age and hypertension rather than atherosclerotic disease processes and has limited reproducibility and interreader variability (32–35). Therefore, MR-depicted IPH remains one of the simplest imaging techniques shown to depict complicated plaque and to predict stroke outcomes.

The study population was relatively large and homogeneous because all 434 carotid arteries were from symptomatic patients with low-grade stenosis referred from the neurology department. The population included only clinical patients and therefore reflected the group in which diagnosis and screening of carotid disease may be most beneficial in the future. While this population may be more applicable to clinical practice, the neurologic events in these patients were unconfirmed, which may lead to an underestimation of the true prevalence of IPH in a confirmed symptomatic group. Another limitation of this study was that the MR-depicted IPH technique has not specifically been validated for patients with 0%–50% stenosis. However, previous studies have shown that this technique has low subjectivity (interobserver agreement, $\kappa = 0.75$ when comparing two independent readers; intraobserver agreement, $\kappa = 0.9$) and is a good surrogate of advanced disease (predictive of cerebrovascular events) in patients with moderate and severe stenosis (10). The protocol used is quick (<5 minutes) and has been used clinically to detect complicated plaque at our center for more than 5 years. We expect that this technique will be as specific, although possibly less sensitive in the low-grade stenosis population, which may cause underestimation of the prevalence of MR-depicted IPH in this group because of decreased disease volume. Another limitation of this study was that the Fisher exact test assumes that carotid arteries from the same patient are independent. However, this is not unreasonable given that emboli from each carotid artery are unlikely to enter the contralateral circulation. This assumption has been made in similar studies (8,10). The only exception to this would be blood crossing to the contralateral brain by retrograde flow in the circle of Willis, which is actually less likely in our patient population than in previous studies given that the patients all have carotid arteries with stenosis of 50% or less and have few to no hemodynamic effects related to their carotid disease. This study was also limited by the use of a retrospective rather than a prospective study design.

Future studies to evaluate patient outcomes in this population (similar to previous studies correlating IPH to outcomes in the high-grade stenosis group), to determine the cause of sex- and age-related differences in IPH, and to correlate MR-depicted IPH with laboratory findings and other imaging studies may be beneficial. This technique may be useful in following the development of IPH to further elucidate the natural history of plaque progression and the role of IPH. Because this technique is simple to implement, it may prove to be useful clinically in screening and observing patients at high risk of cerebrovascular events even if they have low-grade stenosis. However, to detect very small volumes of IPH, development of higher resolution techniques with increased sensitivity for the T1 shortening effects of methemoglobin may be required. If adverse outcomes are associated with the presence of high-risk complicated carotid disease in patients with low-grade stenosis, this may stimulate treatment trials in an attempt to prevent further progression of disease with adverse cerebrovascular outcomes.

MR-depicted IPH can detect complicated carotid atheroma even among symptomatic patients with low-grade (≤50%) carotid stenosis, and this is associated with male sex and increasing age.

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