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High-Intensity Signals in Carotid Plaques on T1-Weighted Magnetic Resonance Imaging Predict Coronary Events in Patients With Coronary Artery Disease

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Objectives The purpose of this study was to determine whether high-intensity carotid plaques visualized by a noncontrast T1-weighted imaging technique, magnetization-prepared rapid acquisition with gradient echo (MPRAGE), predict future coronary events in patients with clinically stable coronary artery disease (CAD).

Background Coronary plaque vulnerability to rupture can be assessed by examining for the presence of atherosclerosis and measuring intima media thickness (IMT) in surrogate vessels such as the carotid arteries. We previously showed that MPRAGE successfully identifies vulnerable carotid plaques as high-intensity signals. It remains unclear, however, if the presence of carotid high-intensity plaques (HIP) is associated with an increased risk of coronary events.

Methods We examined the signal intensity of carotid plaques in 217 patients with clinically stable CAD using MPRAGE with magnetic resonance imaging and measured IMT with ultrasonography. A carotid HIP was defined as a signal >200% that of the adjacent muscle. All patients were divided into 2 groups according to the presence or absence of HIP, namely, the HIP group (n = 116) and the non-HIP group (n = 101), and were followed up for as long as 72 months.

Results The presence of HIP was significantly associated with cardiac events compared to the non-HIP group (log-rank $p < 0.0001$). Furthermore, multivariate Cox regression analysis identified the presence of HIP as the strongest independent predictor of cardiac events (hazard ratio: 3.15; 95% confidence interval: 1.93 to 5.58, $p < 0.0001$) compared with IMT (hazard ratio: 1.62, 95% confidence interval: 0.97 to 2.44, $p = 0.055$) and other coronary risk factors.

Conclusions Characterization of carotid plaques using magnetic resonance imaging with MPRAGE provides more clinically relevant information for the risk assessment of CAD patients than IMT. (J Am Coll Cardiol 2011;58:416–22)

Rupture of vulnerable atherosclerotic plaques in the coronary vessels leads to acute coronary syndromes. Collectively, recent studies suggest that, rather than simply being a local vascular incident, plaque instability is a systemic problem present in multiple vascular beds throughout the body. Thus, it may be possible to assess the vulnerability of coronary artery plaques to rupture and the development of acute coronary syndromes by evaluating the stability and composition of plaques in other vessels (1–3). However, this has not been clearly established, and prospectively identifying a high-risk coronary artery disease (CAD) population vulnerable to plaque rupture remains difficult.

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Magnetic resonance imaging (MRI) can be used to noninvasively assess carotid plaque characteristics in vivo. High-intensity signals observed in carotid plaques using inversion recovery-based 3-dimensional T1-weighted imaging—alternatively known as magnetization-prepared rapid acquisition with gradient echo (MPRAGE) (4) or magnetic resonance direct thrombus imaging (MRDTI) (5,6)—are associated with recent ischemic cerebrovascular events (6–8) and are related to complex plaques (type VI as proposed by the American Heart Association) (9,10). Several

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groups have used high-resolution multicontrast MRI to examine the relationship between plaque composition and cerebrovascular events, and their data suggest that MRI can successfully identify vulnerable carotid plaques (11–14). However, no studies have evaluated the relationship between carotid artery plaque vulnerability detected by MRI and subsequent coronary events. In the present study, we hypothesized that the presence of carotid high-intensity plaques (HIP) visualized by MPRAGE predicted future coronary events in patients with clinically stable CAD.

Methods

Patients. Between 2002 and 2005, 665 consecutive patients who underwent MRI with suspected or confirmed atherosclerosis of the carotid artery at our institute were considered for enrollment. The exclusion criteria for the study were acute myocardial infarction (AMI), unstable angina pectoris, severe valvular heart disease, end-stage renal failure, cardiomyopathy, and infectious, chronic inflammatory, and autoimmune diseases. Among the 665 possible patients, 226 had a history of CAD described in their medical records at our hospital. Stable CAD was defined as the absence of episodes of angina at rest on admission in patients with angiographically documented stenosis >50% in at least 1 of the major coronary arteries. Six patients who underwent coronary artery bypass surgery and 3 patients who were hospitalized for heart failure in the first 12 months of the study were excluded. Thus, a total of 217 patients with clinically stable CAD were ultimately enrolled in this study. This study conformed to the 2005 version of the Ethical Guidelines for Clinical Study (Ministry of Health, Labour and Welfare of Japan), and was approved by the ethics committees of the National Cardiovascular Center.

Magnetic resonance imaging. The MRI was performed on a 1.5-T clinical system (Magnetom Sonata, Siemens, Erlangen, Germany) with standard neck and spine array coils. Plaque imaging was performed using MPRAGE in transaxial sections using a null blood condition (effective inversion time 660 ms; repetition time [TR] 1,500 ms) and water excitation technique to suppress fat signals. The TR was defined as the interval between successive inversion pulses. Other imaging variables included echo time (TE) 5.0 ms; flip angle 15°; field of view 180 × 180 mm; matrix 256 × 204; slice thickness 1.25 mm; 56 partitions covering 70 mm around the carotid bifurcation; and data acquisition time 5 min. Multislab 3-dimensional time-of-flight magnetic resonance angiography (MRA) was also performed to determine lumen shape and plaque morphology with the following parameters: TE 4.4 ms; TR 35 ms; flip angle 15°. The spatial resolution parameters were the same as with MPRAGE. Contrast MRA was performed after MPRAGE and 3-dimensional time-of-flight MRA. Gadolinium diethylenetriamine penta-acetic acid (Gd-DTPA, Magnevist, Bayer-Schering AG, Berlin, Germany), 0.1 mmol/kg body weight, was infused at a rate of 2.0 to 3.0 ml/s after a test bolus of 1 ml Gd-DTPA. Contrast MRA imaging parameters included TR 3.2 ms; TE 1.3 ms; slice thickness 1.0 mm; 64 partitions; field-of-view 360 × 200 mm; matrix 512 × 208; data acquisition time 14 s; near-coronal section. Carotid stenosis was measured using contrast MRA according to the methods defined by the NASCET (North American Symptomatic Carotid Endarterectomy Trial) (15).

Abbreviations and Acronyms

AMI = acute myocardial infarction
CAD = coronary artery disease
CI = confidence interval
HIP = high-intensity plaque
HR = hazard ratio
hsCRP = high-sensitivity C-reactive protein
IMT = intima media thickness
MPRAGE = magnetization-prepared rapid acquisition with gradient echo
MRA = magnetic resonance angiography
MRI = magnetic resonance imaging
TE = echo time
TR = repetition time

The methods used to evaluate MR images in this study have been described previously (8). Briefly, an experienced radiologist (N.Y.) analyzed the carotid plaque signal intensity on MPRAGE relative to the adjacent muscle using a round region of interest (5 to 8 mm in diameter). Figure 1 shows representative cases with atherosclerotic plaques within the carotid arteries. Criteria for the assessment of hyperintense carotid plaques have been previously reported (8,16), and patients with plaques in either the right or left carotid artery in which any region of the plaque exhibited a signal intensity >200% of the adjacent muscle were placed in the "HIP group" (Fig. 1A). Otherwise, patients were placed in the "non-HIP group" (Fig. 1D). The κ values for interobserver and intraobserver agreement for the categorization of carotid plaques as HIP or non-HIP were 0.73 and 0.79, respectively (8).

Ultrasound evaluation. A carotid ultrasound examination was performed in the ultrasound laboratory using a 7.5-MHz, linear-array transducer (SSA-270A, Toshiba, Tokyo, Japan) shortly after admission but before MRI in all patients. Two operators performed all carotid scans, and they were unaware of the clinical characteristics of the patients. The common carotid arteries were imaged bilaterally in the anterior oblique, lateral, and posterior oblique planes to identify atherosclerotic lesions. On a longitudinal image of each common carotid artery, intima media thickness (IMT) was defined as the distance from the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface. The maximal IMT (IMT_{max}) was defined as the thickest region of the far walls of either the left or right common carotid artery. All measurements were performed in a centralized laboratory by 2 trained physicians who were unaware of the subjects' clinical data. The interreader variability defined by Spearman correlation coefficients on maximum wall thickness of the common carotid artery was 0.90.