Structured Abstract

Objectives: We wished to determine whether high-intensity carotid plaques visualized by a non-contrast T1-weighted imaging (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 (MR) and measured IMT with ultrasonography. A carotid HIP was defined as a signal >200% that of the adjacent muscle. All patients were divided into two groups according to the presence or absence of HIP, i.e., HIP (n= 116) and non-HIP (n= 101) groups, and were followed for up to 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 [HR]: 3.10; 95% confidence interval [CI]: 1.79–5.01, $p<0.0001$) compared with IMT (HR: 1.79, 95% CI: 1.19–4.01, $p=0.021$) and other coronary risk factors.

Conclusions: Characterization of carotid plaques using MR imaging with MPRAGE provides more clinically relevant information for the risk assessment of CAD patients than IMT.

KEY WORDS: coronary artery disease, carotid artery, prognosis, magnetic resonance imaging

Abbreviations LIST

AMI = acute myocardial infarction

CAD = coronary artery disease

GFR = glomerular filtration rate

hs-CRP = high-sensitivity C-reactive protein

HIP = high-intensity plaque

HDL = high-density lipoprotein

IMT = intima-media thickness

LDL = low-density lipoprotein

MPRAGE = magnetization-prepared rapid acquisition with gradient echo

MR = Magnetic resonance

T1W = T1-weighted

UAP = unstable angina pectoris

Introduction

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.

Magnetic resonance (MR) can be used to noninvasively assess carotid plaque characteristics *in vivo*. High-intensity signals observed in carotid plaques using inversion recovery-based 3D 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 groups have used high-resolution multi-contrast MR imaging to examine the relationship between plaque composition and cerebrovascular events, and their data suggest that MR imaging can successfully identify vulnerable carotid plaques (11-14). However, no studies have evaluated the relationship between carotid artery plaque vulnerability detected by MR imaging 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 coronary artery disease (CAD).

Methods

Patients

Between 2002 and 2005, 665 consecutive patients who underwent MR imaging 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 (UAP), 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 one of the major coronary arteries. Six patients who underwent coronary artery bypass surgery and three 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 (The Ministry of Health, Labour and Welfare of Japan) and was approved by the ethics committees of the National Cardiovascular Center.

Magnetic Resonance Imaging

MR imaging was performed on a 1.5-T clinical system (Magnetom Sonata, Siemens, Erlangen) 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), 1500 ms) and water excitation technique to suppress fat signals. TR was defined as the interval between successive inversion pulses. Other imaging variables included: echo time (TE) 5.0 ms; flip angle 15 degrees; field-of-view 180×180 mm; matrix 256×204; slice thickness 1.25 mm; 56 partitions covering 70 mm around the carotid bifurcation; data acquisition time, 5 min. Multi-slab 3D time-of-flight (TOF) 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 degrees. The spatial resolution parameters were the same as with MPRAGE. Contrast MRA was performed after MPRAGE and 3D TOF MRA. Gadolinium diethylenetriamine penta-acetic acid (Gd-DTPA, Magnevist, Byer-Schering AG, Berlin, Germany) (0.1 mmol/kg body weight) was infused at a rate of 2.0–3.0 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 North American Symptomatic Carotid Endarterectomy Trial (NASCET) (15).

The methods used to evaluate MR images in this study have been described previously (8). Briefly, one experienced radiologist (N.Y) analyzed the carotid plaque signal intensity on MPRAGE relative to the adjacent muscle using a round region of interest (5–8 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 following admission but before MR imaging 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, 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 two 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.

Left ventricular function analysis

Left ventricular ejection fraction was measured by radioisotope image on single-photon-emission computed tomography before MR imaging in all patients.

Determination of serum C-reactive protein

High-sensitivity C-reactive protein (hs-CRP) was assayed by latex nephelometry in fasting serum samples (SRL, Tokyo, Japan).

Follow-up study

After MR imaging data were obtained, the 217 patients with stable CAD were followed at our hospital for a period for 12 to 72 months or until the occurrence of one of the

following clinical coronary events: cardiac death, non-fatal acute myocardial infarction (AMI), unstable angina pectoris (UAP), or unplanned hospitalization for recurrent angina. PCI-related restenosis was not considered a coronary event. UAP was defined as ischemic discomfort presenting without elevation of maximal value of MB fraction of creatine kinase (CK-MB) exceeding twice the upper limit of normal control level in our institute, and ischemic discomfort that was Canadian Cardiology Society class 3 or 4. Unplanned hospitalization for recurrent angina was defined as unplanned coronary revascularization (i.e., percutaneous coronary intervention, or coronary artery bypass graft surgery) due to stable effort angina. Chart review was conducted by independent attending cardiologists to determine if subject hospitalizations and/or deaths qualified as primary endpoints of the study. These cardiologists were blinded to the patients' HIP status. In addition, a radiologist (N.Y) who categorized HIP status was also blinded to clinical events of study patients. All stable CAD patients received standard medical therapy outlined in Table 1.

Statistical analysis

Continuous baseline variables with normal distribution were expressed as means ± SD and compared by unpaired *t*-test. The Mann-Whitney *U* test was used to evaluate differences in IMT, hs-CRP, and carotid artery stenosis. Categorical baseline variables were compared by Fisher exact test or chi-square analysis where appropriate. Survival analysis was carried out using the Kaplan–Meier method (log-rank test), according to the presence or absence of HIP. The data were analyzed initially using a univariate model to determine the risk factors that had a significant association with future coronary events. Multivariate Cox regression analysis was then applied using only the covariates that significantly predicted coronary events in the univariate analysis. All analyses were conducted using SPSS (SPSS Japan Inc., Tokyo, Japan).

Results

Baseline clinical characteristics

The baseline clinical characteristics of the study patients are shown in Table 1. The median, 1st quartile, and 3rd quartile range of carotid plaque signal intensity relative to the adjacent muscle was 3.10, 2.67, 3.63, respectively in the HIP group and 1.51, 1.39, 1.70, respectively in the non-HIP group. The HIP group had significantly higher levels of hs-CRP and LDL cholesterol, higher rates of multi-vessel CAD and previous MI,

lower levels of HDL cholesterol, and increased IMT_{max} values. There was no significant difference in the degree of carotid artery stenosis between the two groups, and there were no differences in the administered medications between the two groups.

Magnetic resonance imaging of the carotid artery and prognostic value of HIP in stable CAD patients

One hundred-sixteen of the 217 patients were categorized to the HIP group. Figure 1 shows representative MR images of patients in the HIP (Fig. 1A, B) and non-HIP groups (Fig. 1D, E). Patients were followed for a mean of 38.3 months. There were 31 coronary events in the HIP group during the follow-up period, but there were only five such events in the non-HIP group (n = 101) ($p < 0.001$) (Table 2). When these data were subjected to Kaplan–Meier analysis, the presence of HIP was significantly associated with an increased probability of coronary events in patients with stable CAD ($p < 0.001$ by log-rank test) (Fig. 2). Univariate analysis of coronary risk factors, carotid ultrasound data, and MR imaging analysis showed that IMT_{max}, HIP, multi-vessel CAD, hs-CRP, and previous MI were all significant predictors of clinical coronary events ($p < 0.05$) (Table 3). When these factors were further analyzed by a multivariate Cox regression analysis, the presence of HIP was found to be the most significant independent predictor of future coronary complications in patients with stable CAD (HR: 3.15, 95% CI: 1.93-5.58, $p < 0.0001$) compared with the continuous value of IMT (HR: 1.62, 95% CI: 0.97–2.44, $p = 0.055$), hs-CRP, previous MI, and multi-vessel CAD. To further compare the presence of HIP to IMT, as shown in Table 4, we used a cutoff value of >2.78 mm (i.e. the third quartile of IMT in the present study) to define elevated IMT and performed an alternative multivariate Cox regression analysis. When this cutoff value was used, IMT was significantly associated with cardiac events (HR: 1.79, 95% CI: 1.19–4.01, $p = 0.021$), but the presence of carotid HIP (HR: 3.10, 95% CI: 1.79–5.01, $p < 0.0001$) remained the strongest indicator of future coronary events.

Discussion

We wished to identify a technique to allow for the better stratification of patients at risk of coronary events, and we hypothesized that the nature of atherosclerotic plaques throughout the vasculature could be associated with coronary plaque instability. As such, we used MPRAGE to examine the intensity of atherosclerotic plaques in the carotid arteries and followed patients with both high and low intensity plaques for the subsequent development of coronary events. Our data suggest that the presence of HIP

visualized by MPRAGE is a significant and independent predictor of future coronary events in patients with stable CAD. Furthermore, the presence of HIP was a stronger predictor of coronary events than increased carotid artery IMT. Thus, characterization of carotid plaques by MR imaging is clinically informative for risk stratification of patients with CAD.

Plaque instability and rupture were previously thought to be isolated events at a specific site within the vasculature, but recent observations suggest that plaque destabilization is a characteristic of some patients that occurs at multiple sites throughout systemic vascular beds (17,18). Thus, the presence of vulnerable carotid plaques may reflect a systemic problem with plaques within the coronary vasculature equally at risk to rupture and associated infarction. B-mode ultrasound of the carotid arteries can identify plaques and measure IMT, and both have been used as surrogate markers for cardiovascular disease. Although IMT and the presence of carotid plaques are highly related (19), the overall plaque area was a stronger predictor of future coronary events than IMT (20). Additionally, carotid plaque characteristics, e.g. echolucency, predicted coronary plaque complexity and the development of coronary complications in patients with CAD (2,21). While current data indicate that other radiologic measures may be better than IMT for coronary risk stratification, we elected to use IMT in this study because IMT is a more established technique, more widely available, and better validated in large populations (22).

In the present study, we used the MR imaging modality MPRAGE to characterize carotid plaques in patients with stable CAD. MPRAGE is a T1-weighted technique that highlights intraplaque components with short T1 signal with high signal intensity. It is thought that the lipid-rich necrotic cores of vulnerable plaques give rise to the observed short T1 signal (14,23-25). Alternatively, this may arise from intraplaque hemorrhage and thrombus formation (9,14,26,27). The presence of high-intensity signals suggestive of complicated plaques was associated with subsequent ischemic cerebrovascular events, and this was recognized as an indicator of vulnerable carotid plaques (8,9). However, our current data greatly expand the significance of carotid HIP by showing that carotid HIP is a significant and independent predictor of future coronary events in patients with stable CAD. In fact, the presence of carotid HIP is a stronger indicator of future coronary events than increased IMT.

Recent advances in technology have allowed for the development of techniques that allow for the direct examination of coronary artery plaque composition, e.g. intravascular ultrasound and angioscopy. However, these techniques are invasive

and are not practical for use in routine screening for the management and risk assessment of patients with CAD. Therefore, non-invasive imaging modalities capable of identifying patients harboring unstable coronary lesions are needed. Thus, the MR imaging-based evaluation of carotid plaques described here provides clinically important information on the vulnerability of coronary atherosclerotic plaques to rupture and correlates with future clinical outcome.

Inflammation plays important roles in atherogenesis and plaque rupture (15,28-31). A common inflammatory pathway linking carotid and coronary artery plaque activation has been proposed based on the observed high C-reactive protein levels seen in patients with CAD and echolucent carotid plaques (32). In this study, the plasma levels of hs-CRP were significantly higher in the patients with HIP compared to the non-HIP group, and increased levels of hs-CRP were independently associated with the presence of HIP. Increased hs-CRP levels are an independent predictor of cardiovascular disease (33), and our results suggest that the presence of both MPRAGE-detected HIP and elevated hs-CRP levels may indicate the presence of both vulnerable and inflammatory activated plaques.

Study limitations

This study was limited by the relatively small number of patients examined, and a few patients experienced a primary endpoint during the study. Hlatky, et al. reported that a greater number of outcome events are needed to provide adequate statistical power to fully evaluate whether a novel risk marker contributes additional prognostic information to an established set of risk factors in a multivariable model rather than simply indicating whether the new marker is a prognostic tool by itself (34). Therefore, while our data show that the presence of HIP is a risk factor for coronary events, the relative importance of HIP compared to other cardiac risk factors should be evaluated and confirmed in a larger prospective study. We enrolled patients with stable CAD with >50% stenosis, and most acute coronary events occur with low-grade or mild coronary stenosis. Additionally, we did not use a multi-contrast approach including three basic contrast weightings (T1W, proton density, T2W). Use of these multi-contrast approaches in conjunction with TOF MRA has been shown to provide information regarding the thickness of the fibrous cap, the lipid-rich necrotic core, and intraplaque hemorrhage (12,35-37). The combination of MPRAGE with proton density and T2W techniques could further enhance imaging based predictions of coronary plaque vulnerability.

The size of HIP as well as dichotomous criteria for HIP might contribute to risk assessment for cardiac events. We recently showed that carotid plaques with subsequent ischemic cerebrovascular events did not depend on volumes of HIP on T1W image (8). In contrast to this finding, Takaya, et al. reported that larger mean intra plaque hemorrhage size was associated with the development of subsequent ischemic cerebrovascular events (38). Thus, there were conflicting results over this issue. In this study, while measurement of HIP size could be one approach to determine the optimal indices of plaque evaluation by MRI, we wished to determine the additional value that the presence of HIP contributes to risk assessment for cardiac events.

The risks of nephrogenic systemic fibrosis (NSF) were less clearly understood during the study period in 2002–2005, and we did not exclude patients with a glomerular filtration rate (GFR) < 45 mL/min/1.73 m^2. The overall mean GFR of the study population was 78±19 mL/min/1.73 m^2, and only six (2.7%) of the 217 patients had a GFR less than 45 mL/min/1.73 m^2. None of these patients developed NSF after administration of gadolinium.

Additionally, although we excluded nine patients who suffered cardiac events in the first year of follow-up, the inclusion of these patients in the analyses did not affect the study results (data not shown). Finally, the number of clinical events in the study group was small, and follow-up was limited to three years. A more substantial, longer-term study with more patients is needed to clarify the short- and long-term prognostic roles of MRI as well as the role of MRI screening in high-risk asymptomatic patients.

Conclusions

The presence of HIP detected by MPRAGE in the carotid arteries predicts the development of future coronary complications in patients with stable CAD. Non-invasive evaluation of carotid plaques using MR imaging with MPRAGE is clinically informative in the risk stratification of CAD patients.

References

1. Crouse JR, 3rd, Craven TE, Hagaman AP, et al. Association of coronary disease with segment-specific intimal-medial thickening of the extracranial carotid artery. Circulation 1995;92:1141-7.
2. Honda O, Sugiyama S, Kugiyama K, et al. Echolucent carotid plaques predict future coronary events in patients with coronary artery disease. J Am Coll Cardiol 2004;43:1177-84.
3. Nichols WW, Pepine CJ, O'Rourke MF. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke. N Engl J Med 1999;340:1762-3.
4. Mugler JP, 3rd, Brookeman JR. Three-dimensional magnetization-prepared rapid gradient-echo imaging (3D MP RAGE). Magn Reson Med 1990;15:152-7.
5. Moody AR. Magnetic resonance direct thrombus imaging. J Thromb Haemost 2003;1:1403-9.
6. Murphy RE, Moody AR, Morgan PS, et al. 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;107:3053-8.
7. Moody AR, Allder S, Lennox G, et al. Direct magnetic resonance imaging of carotid artery thrombus in acute stroke. Lancet 1999;353:122-3.
8. Yamada N, Higashi M, Otsubo R, et al. Association between signal hyperintensity on T1-weighted MR imaging of carotid plaques and ipsilateral ischemic events. AJNR Am J Neuroradiol 2007;28:287-92.
9. Moody AR, Murphy RE, Morgan PS, et al. Characterization of complicated carotid plaque with magnetic resonance direct thrombus imaging in patients with cerebral ischemia. Circulation 2003;107:3047-52.
10. Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation 1995;92:1355-74.
11. Mitsumori LM, Hatsukami TS, Ferguson MS, et al. In vivo accuracy of multisequence MR imaging for identifying unstable fibrous caps in advanced human carotid plaques. J Magn Reson Imaging 2003;17:410-20.
12. Saam T, Ferguson MS, Yarnykh VL, et al. Quantitative evaluation of carotid

plaque composition by in vivo MRI. Arterioscler Thromb Vasc Biol 2005;25:234-9.

13. Trivedi RA, J UK-I, Graves MJ, et al. Multi-sequence in vivo MRI can quantify fibrous cap and lipid core components in human carotid atherosclerotic plaques. Eur J Vasc Endovasc Surg 2004;28:207-13.
14. Yuan C, Mitsumori LM, Ferguson MS, et al. In vivo accuracy of multispectral magnetic resonance imaging for identifying lipid-rich necrotic cores and intraplaque hemorrhage in advanced human carotid plaques. Circulation 2001;104:2051-6.
15. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1998;339:1415-25.
16. Bitar R, Moody AR, Leung G, et al. In vivo identification of complicated upper thoracic aorta and arch vessel plaque by MR direct thrombus imaging in patients investigated for cerebrovascular disease. AJR Am J Roentgenol 2006;187:228-234.
17. Goldstein JA, Demetriou D, Grines CL, et al. Multiple complex coronary plaques in patients with acute myocardial infarction. N Engl J Med 2000;343:915-22.
18. Rothwell PM, Villagra R, Gibson R, et al. Evidence of a chronic systemic cause of instability of atherosclerotic plaques. Lancet 2000;355:19-24.
19. Bots ML, Hofman A, De Jong PT, et al. Common carotid intima-media thickness as an indicator of atherosclerosis at other sites of the carotid artery. The Rotterdam Study. Ann Epidemiol 1996;6:147-53.
20. Johnsen SH, Mathiesen EB, Joakimsen O, et al. Carotid atherosclerosis is a stronger predictor of myocardial infarction in women than in men: a 6-year follow-up study of 6226 persons: the Tromso Study. Stroke 2007;38:2873-80.
21. Saito D, Shiraki T, Oka T, et al. Morphologic correlation between atherosclerotic lesions of the carotid and coronary arteries in patients with angina pectoris. Jpn Circ J 1999;63:522-6.
22. Folsom AR, Kronmal RA, Detrano RC, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med 2008;168:1333-9.
23. Rogers WJ, Prichard JW, Hu YL, et al. Characterization of signal properties in atherosclerotic plaque components by intravascular MRI. Arterioscler Thromb

Vasc Biol 2000;20:1824-30.

24. Toussaint JF, Southern JF, Fuster V, et al. T2-weighted contrast for NMR characterization of human atherosclerosis. Arterioscler Thromb Vasc Biol 1995;15:1533-42.
25. Yuan C, Kerwin WS, Ferguson MS, et al. Contrast-enhanced high resolution MRI for atherosclerotic carotid artery tissue characterization. J Magn Reson Imaging 2002;15:62-7.
26. Cappendijk VC, Cleutjens KB, Heeneman S, et al. In vivo detection of hemorrhage in human atherosclerotic plaques with magnetic resonance imaging. J Magn Reson Imaging 2004;20:105-10.
27. Cappendijk VC, Cleutjens KB, Kessels AG, et al. Assessment of human atherosclerotic carotid plaque components with multisequence MR imaging: initial experience. Radiology 2005;234:487-92.
28. Falk E, Shah PK, Fuster V. Coronary plaque disruption. Circulation 1995;92:657-71.
29. Fuster V, Badimon L, Badimon JJ, et al. The pathogenesis of coronary artery disease and the acute coronary syndromes (1). N Engl J Med 1992;326:242-50.
30. Libby P. Molecular bases of the acute coronary syndromes. Circulation 1995;91:2844-50.
31. Ridker PM, Rifai N, Rose L, et al. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002;347:1557-65.
32. Lombardo A, Biasucci LM, Lanza GA, et al. Inflammation as a possible link between coronary and carotid plaque instability. Circulation 2004;109:3158-63.
33. Best LG, Zhang Y, Lee ET, et al. C-reactive protein as a predictor of cardiovascular risk in a population with a high prevalence of diabetes: the Strong Heart Study. Circulation 2005;112:1289-95.
34. Hlatky MA, Greenland P, Arnett DK, et al. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. Circulation 2009;119:2408-2416.
35. Cai JM, Hatsukami TS, Ferguson MS, et al. Classification of human carotid atherosclerotic lesions with in vivo multicontrast magnetic resonance imaging. Circulation 2002;106:1368-73.
36. Hatsukami TS, Ross R, Polissar NL, et al. Visualization of fibrous cap thickness and rupture in human atherosclerotic carotid plaque in vivo with high-resolution magnetic resonance imaging. Circulation 2000;102:959-64.

37. Toussaint JF, LaMuraglia GM, Southern JF, et al. Magnetic resonance images lipid, fibrous, calcified, hemorrhagic, and thrombotic components of human atherosclerosis in vivo. Circulation 1996;94:932-8.

38. Takaya N, Yuan C, Chu B, et al. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI--initial results. Stroke 2006;37:818-23

Figure legends.

Figure 1: Representative plaque images of atherosclerotic carotid arteries.

A, B, and C show a patient with HIP. MPRAGE (A) displays hyper-intensity signals in the thick plaque of the right internal carotid artery (arrowheads). TOF-MRA (B) displays no significant luminal stenosis of the internal carotid arteries bilaterally. Contrast MRA of the right carotid artery (C) showing no significant stenosis.

D, E, and F show a patient lacking HIP. MPRAGE (D) displays iso-intensity signals in the plaques of the internal carotid artery bilaterally. The plaque of the left internal carotid artery is thick (arrowheads). TOF-MRA (E) displays no significant luminal stenosis of the internal carotid arteries bilaterally (arrows). Contrast MRA of the left carotid artery (F) showing no significant stenosis.

Figure 2: Kaplan–Meier curves comparing the probability of a coronary event occurring during the follow-up period of 72 months in 217 patients with stable coronary artery disease, grouped according to the presence or absence of high-intensity plaques (HIP). The **solid blue line** indicates patients with HIP (n = 116), and the **dotted blue line** indicates confidence intervals. The **solid red line** indicates patients without HIP (n = 101), and the **dotted red line** indicates confidence intervals.

Figure 1: Representative plaque images of atherosclerotic carotid arteries

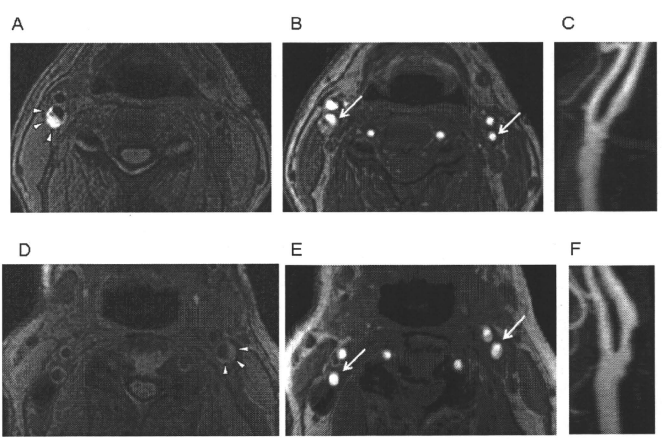
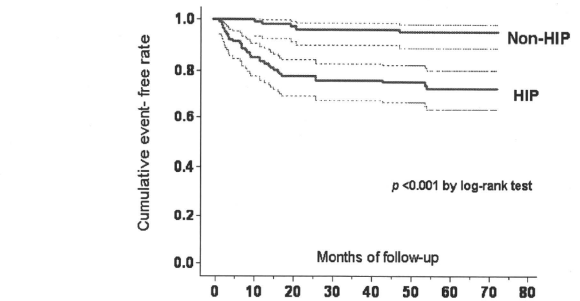


Figure 2: Kaplan-Meier curves comparing the probability of a coronary event



Number of patients at risk								
HIP	116	99	88	86	26
Non-HIP	101	101	97	95	40

Table 1. Comparison of Baseline Clinical Characteristics

	HIP (n=116)	Non-HIP (n=101)	p Values
Age (yrs)	69 ± 8	68 ± 9	0.39
Male gender	99 (85%)	89(82%)	0.41
Diabetes mellitus	35 (30%)	32 (32%)	0.81
Hypertension	79 (68%)	61(60%)	0.24
Smoking	30 (26%)	30 (30%)	0.52
BMI (kg/m^2)	24.2 ± 2.5	23.8 ± 3.7	0.35
Total cholesterol (mg/dL)	198 ± 37	199 ± 40	0.84
HDL cholesterol (mg/dL)	43 ± 11	48 ± 16	0.007
LDL cholesterol (mg/dL)	136 ± 31	125 ± 29	0.008
hs-CRP (mg/dL)*	2.1 (1.0, 3.6)	1.35 (0.5, 2.3)	0.001
IMT (mm)	2.47 ± 1.0	1.67 ± 1.0	<0.001
Carotid artery stenosis (%)*	22.5 (15.0, 46.1)	20.5 (9.0, 4.9)	0.97
Medications			
Aspirin	110 (95%)	98 (97%)	0.41
Beta-blocker	67(58%)	62 (61%)	0.59
Statin	71 (61%)	64 (63%)	0.74
ACEI or ARB	50 (43%)	47 (47%)	0.61
Multi-vessel CAD	55 (55%)	31 (31%)	0.01
LV dysfunction (EF < 40%) (%)	8 (7%)	6 (6%)	0.77
Previous MI	42 (36%)	21 (21%)	0.01

Data are presented as the mean ± SD or number (%) of patients. *Median, first quartile, and third quartile. ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; CAD; coronary artery disease; hs-CRP = high sensitivity C-reactive protein; HIP = high-intensity plaques; EF = ejection fraction; HDL; high-density lipoprotein; IMT = maximum intima-media thickness; LDL = low-density lipoprotein; LV = left ventricular; MI = myocardial infarction.

Table 2. Summary of coronary events during the follow-up period in patients with coronary artery disease

	HIP (n=116)	Non-HIP (n=101)	p Values
Composite end-points	31	5	< 0.001
Cardiac death	4	0	0.125
Non-fatal acute MI	4	1	0.375
Unstable angina	16	2	0.002
Hospitalization for recurrent angina	7	2	0.180

Abbreviations as in Table 1.

Table 3. Univariate analysis of risk factors for a coronary event in patients with coronary artery disease

	Hazard ratio	95% CI	p Values
Age (yrs)	1.02	0.98–1.05	0.60
Male gender	1.71	0.72–3.32	0.29
Diabetes mellitus	1.68	0.88–4.41	0.15
Hypertension	0.89	0.47–1.61	0.71
Smoking	1.51	0.68–2.99	0.28
BMI (kg/m^2)	0.98	0.79–1.01	0.18
Total cholesterol (mg/dL)	0.86	0.71–1.00	0.17
HDL cholesterol (mg/dL)	0.95	0.98–1.05	0.21
LDL cholesterol (mg/dL)	1.12	0.98–1.05	0.35
hs-CRP (mg/dL)	1.41	1.02–1.51	0.03
IMT(mm)	1.55	1.12–1.89	0.004
Multi-vessel CAD	2.18	1.21–6.12	0.001
LV dysfunction (EF < 40%)	1.70	0.81–2.33	0.11
Previous MI	1.95	1.19–5.35	0.001
Presence of HIP	1.76	1.21–3.32	<0.001

CI = confidence interval; other abbreviations as in Table 1.

Table 4. Multivariate Cox regression analysis of risk factors for a coronary event

	β	SE	Hazard Ratio	p Value	95% CI
Presence of HIP	1.130	0.291	3.10	< 0.0001	1.79–5.01
IMT (mm) (> 2.78 mm)	0.581	0.201	1.79	0.021	1.19–4.01
hs-CRP (> 3.0 mg/dL)	0.334	0.179	1.40	0.099	0.94–2.02
Previous MI	0.168	0.20	1.18	0.401	0.56–1.22
Multi-vessel CAD	0.268	0.206	1.31	0.194	0.51–1.15

Abbreviations as in Table 1.

Journal of Nuclear Medicine, published on April 15, 2011 as doi:10.2967/jnumed.110.084848

Experimental Pig Model of Old Myocardial Infarction with Long Survival Leading to Chronic Left Ventricular Dysfunction and Remodeling as Evaluated by PET

Noboru Teramoto[1], Kazuhiro Koshino[1], Ikuo Yokoyama[2,3], Shigeru Miyagawa[4], Tsutomu Zeniya[1], Yoshiyuki Hirano[1], Hajime Fukuda[1], Junichiro Enmi[1], Yoshiki Sawa[4], Juhani Knuuti[5], and Hidehiro Iida[1]

[1]Department of Investigative Radiology, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan; [2]School of Medicine and Faculty of Medicine, The University of Tokyo, Tokyo, Japan; [3]Department of Cardiovascular Medicine, Sanno Hospital, International University of Health and Welfare, Tokyo, Japan; [4]Department of Cardiac Surgery, Osaka University, School of Medicine, Osaka, Japan; and [5]Turku PET Centre, University of Turku, Turku, Finland

A pig model of reduced left ventricular (LV) function and remodeling or chronic heart failure with long survival after myocardial infarction (MI) has not been established. The aim of this study was to evaluate the pathophysiologic status of a pig model of old MI using a series of PET studies. **Methods:** Twenty-seven male farm pigs were divided into 2 groups: 7 animals in the control group and 20 animals that underwent a proximal coronary artery (CA) occlusion using an ameroid constrictor after distal CA ligation. A series of PET examinations was performed to assess LV volumes, LV functions, myocardial perfusion response to adenosine, and viability as water-perfusable tissue index. **Results:** The distal CA ligation inhibited arrhythmia during and after the operation, and a transmural anteroseptal MI, with an infarction area of 27% ± 5% of the whole left ventricle, was generated with a survival rate of 75% at 4 mo. Wall motion evaluated by ^{18}F-FDG PET was diffusely reduced, including the noninfarcted wall. Global LV ejection fraction as assessed by gated C^{15}O PET was reduced (39% ± 16%) in the group undergoing occlusion, compared with the control group (66% ± 16%, $P < 0.05$). LV end-systolic (31.4 ± 9.2 cm^3) and end-diastolic (52.7 ± 10.2 cm^3) volumes were increased, compared with controls (15.2 ± 9.4 cm^3, $P < 0.01$, and 41.7 ± 11.5 cm^3, $P < 0.05$, respectively). Histology showed hypertrophy and development of microscopic fibrosis in noninfarcted myocardium. PET demonstrated the reduced myocardial perfusion response to adenosine and also reduced water-perfusable tissue index in remote segments. **Conclusion:** The pig model of old MI generated by the chronic proximal CA obstruction after distal ligation was characterized by LV dysfunction and remodeling, with a high survival rate.

Key Words: experimental model; PET; myocardial flow reserve; remodeling; regeneration therapy

J Nucl Med 2011; 52:761–768
DOI: 10.2967/jnumed.110.084848

Chronic heart failure (CHF) is an increasing health concern (*1*). Myocardial infarction (MI) is the cause of CHF in two thirds of the patients, and the morbidity and mortality remain high (*2,3*). The potential therapies, such as new class of pharmacologic agents and cell therapy (*4*), need to be tested in proper animal models to demonstrate the effects and outcome before initiating clinical trials. Dogs have been extensively used in heart research. Because the coronary arterial systems in dogs can develop collaterals quickly when myocardial ischemia occurs, it has been difficult to produce a large MI that typically introduces CHF with general characteristics of left ventricular (LV) remodeling (*5*).

Pigs have been considered better suited than dogs for pathophysiologic research of ischemic heart diseases, because the coronary system of pigs is more similar to that of humans (*6*). Tolerance of ischemia and denervation after ischemia in pigs is also similar to that in humans (*6*). Because of the delayed development of collaterals after occlusion, ligation of a peripheral part of the coronary arterial system generates a small MI (*7*). However, an experimental model of large MI introducing global LV dysfunction is difficult to develop, because sudden cardiac death (SCD) due to fatal arrhythmias and an intolerance of ischemia frequently occurs in pigs (*8*). The models of small MI made by the ligation of a peripheral part of the coronary arterial system demonstrate reasonably good survival rates but only for a small infarction. The model of small MI using a coronary ameroid constrictor (model MRI-2.50-TI; Research Instruments SW) has also demonstrated moderate SCD rates (*6,8–13–15*), but the animals develop primarily chronic ischemia or hibernating myocardium, without a significant amount of scar tissue. Thus, the limitations of current models are that the infarcted region is small and that the hearts are not developing a clinical picture of CHF with global LV dysfunction, LV dilatation, and remodeling.

On the other hand, Shen et al. (*16*) developed an experimental pig model of MI and heart failure. Sequential

Received Oct. 30, 2010; revision accepted Dec. 9, 2010.
For correspondence or reprints contact: Hidehiro Iida, Department of Investigative Radiology, National Cardiovascular Center Research Institute, 5-7-1 Fujishiro-dai, Suita City, Osaka, Japan 565-8565.
E-mail: iida@ri.ncvc.go.jp