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Rationale and Design for a Study Using Intravascular Ultrasound to Evaluate Effects of Rosuvastatin on Coronary Artery Atheroma in Japanese Subjects

—— COSMOS Study (Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects) ——

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Background There have been few multicenter studies using intravascular ultrasound (IVUS) to assess the process of atherosclerosis in a Japanese population with hypercholesterolemia that is being treated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors for control of low-density lipoprotein-cholesterol.
Methods and Results An open-label multicenter study is planned to evaluate with IVUS whether treatment with rosuvastatin for 76 weeks results in regression of coronary artery atheroma volume in patients who have coronary heart disease (CHD) and hypercholesterolemia. Sample size is 200 subjects with CHD who are to undergo percutaneous coronary intervention. The planned duration is between October 2005 and October 2008.
Conclusions The COSMOS study will be the first multicenter cardiovascular study in a Japanese population and may provide new evidence on the effects of rosuvastatin on the progression of coronary atherosclerotic lesions. (*Circ J* 2007; **71**: 271–275)

Key Words: Atherosclerosis; Coronary disease; Intravascular ultrasound; Lipids; Rosuvastatin

Coronary heart disease (CHD) is the single largest cause of death of men and women in many countries. The Framingham Heart Study identified total cholesterol (TC) as a major contributor to CHD and strongly related to progression of the disease[1,2] The National Cholesterol Education Program Adult Treatment Panel II (NCEP ATP II) identified low-density lipoprotein (LDL)-cholesterol (C) as the primary target for cholesterol-lowering therapy to prevent CHD (NCEP ATP II 1993)[3] NCEP ATP III clinical updates include guidelines recommending intensive dietary and drug management of LDL-C in patients with CHD (ATP II) and more intensive LDL-lowering therapy for high-risk patients (ATP III) in order to achieve LDL-C levels <100 mg/dl [2.59 mmol/L] (NCEP ATP III 2001)[4] A high LDL-C level is recognized as an independent risk factor for CHD events and many guidelines therefore advocate LDL-C reduction. The Japan Lipid Intervention Trial (J-LIT), which is a national cohort study, showed that normalization of the lipid concentration reduced the risk of coronary events in 52,421 Japanese patients with hypercholesterolemia[5]

Statins are now the most widely used medication for the treatment of hypercholesterolemia because they partially inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is the rate-limiting step in cholesterol synthesis. HMG-CoA reductase inhibition consequently induces the compensatory upregulation of hepatic LDL receptors, which enhances the LDL-C uptake and results in a decrease in the plasma concentration of LDL-C. It has been well recognized that statins are associated not only with reduction of LDL-C levels but also with substantial reduction of the prevalence of coronary events. Clinical trials have confirmed that these agents reduce coronary events in subjects with and without coronary disease, reduce cardiovascular morbidity and mortality, and may even promote regression of atherosclerotic vascular lesions[6–10] The benefits of statin therapy on primary and secondary prevention in patients with a wide range of LDL-C levels is therefore well established. The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT)[11] and Treat to New Targets (TNT)[12] studies showed that intensive lipid-lowering therapy significantly reduces the risk of cardiovascular disease events compared with moderate lipid-lowering therapy (p=0.005 and p<0.001, respectively). These studies

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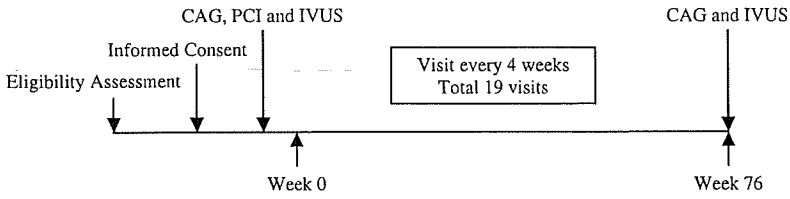

Fig 1. Flow chart showing the study timeline. CAG, coronary angiography; PCI, percutaneous coronary intervention; IVUS, intravascular ultrasound.

would suggest that very intensive lipid lowering is required to induce regression of atherosclerosis.

The ability of statins to reduce progression of coronary atherosclerosis or to induce its regression has been evaluated by coronary angiography in a number of studies: MARS[13] CCAIT[14] The Multicenter Anti-Atheroma study (MAAS Investigators 1994), and Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-I)[15] However, almost all the angiographic studies have revealed that the change in luminal parameters, such as the percent diameter stenosis and the minimal lumen diameter, was very subtle, although it was statistically significant. It was partially the vessel remodeling that masked the net change of plaque volume, and therefore, it has been recognized that direct plaque imaging might be more useful for assessing the effect of lipid-lowering drugs on the process of atherosclerosis.

Intravascular ultrasound (IVUS) is a modality that quantitatively represents atherosclerosis in vivo. IVUS enables accurate measurement of the lumen area, as well as atheroma size and distribution. The REVERSAL trial[16] (Reversal of Atherosclerosis with Aggressive Lipid Lowering) and ASTEROID trial[17] (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) have successfully investigated the effects of statins on atherosclerosis. Most particularly, ASTEROID is the first study to clearly show a reversal of the atherosclerotic disease process in major clinical studies. This was a 24-month single-arm, blinded endpoint, multinational study conducted in 9 countries: Australia, Belgium, Canada, France, Italy, Netherlands, Spain, the United Kingdom, and the United States of America. For the primary efficacy parameter of the percentage atheroma volume, the median was −0.79% (97.5% confidence interval (CI), −1.21% to −0.53%) ($p<0.001$ compared with baseline). This was accomplished with rosuvastatin 40 mg/day, and reduced LDL-C by 53.2% and increased high-density lipoprotein (HDL)-C by 14.7%. Rosuvastatin is the most effective of the new generation statins, and should enable more patients to achieve lipid goals with the starting dose![18]

In Japan, however, the beneficial effect of statin treatment on atherosclerotic lesions for 6 months after a coronary event was shown in the small, single-center, ESTABLISH Study![19] The subjects were randomized to atorvastatin (intensive lipid-lowering therapy) or control groups after percutaneous coronary intervention (PCI). LDL-C was significantly reduced by 41.7% in the atorvastatin group compared with an increase of 0.7% in the control group ($p<0.001$). Plaque volume was significantly reduced in the atorvastatin group (13.1±12.8% decrease) compared with the control group (8.7±14.9% increase; $p<0.0001$), even in patients with low baseline LDL-C (<125 mg/dl).

Based on a linear relationship identified between the decrease in LDL-C and the change in the luminal diameter of the coronary artery, it was suggested that at least 40% reduction in LDL-C is needed to arrest progression of the atherosclerotic process?[20] Birgelen et al[21] reported possible suppression of progression of plaque (area) at LDL-C levels of <75 mg/dl. The ASTEROID trial suggested that treatment to LDL-C levels below currently accepted guidelines, such as NCEP ATP III and the Third Joint Task Force European guidelines, when accompanied by significant HDL-C increase, could produce regression of atherosclerosis in coronary disease patients. Recently, a meta-analysis has demonstrated that the pleiotropic effects of statins do not seem to contribute an additional cardiovascular risk reduction benefit beyond that expected from the degree of LDL-C lowering?[22] Therefore, there might be a fundamental 1-to-1 relationship between LDL-C levels and CHD events. However, the most relevant parameter to provoke significant change of plaque volume, especially for the Japanese, is still unknown: an absolute level of LDL-C or the magnitude of change in LDL-C?

COSMOS Study

The COSMOS study will be the first multicenter study especially in a Japanese population to evaluate the effects of rosuvastatin on regression of coronary atherosclerosis. Comparisons will be made between the measurements of atherosclerosis at the beginning vs the end of drug treatment. This study is a single-arm study. As placebo controlled trials of statins in this population are no longer ethically acceptable, a comparator group receiving either placebo or a less active statin will not be included in the COSMOS study. Moreover, current US and EU guidelines also recommend achieving more intensive target levels in very high-risk, secondary-prevention patients?[23] IVUS was selected to evaluate coronary artery atheroma volume as the primary endpoint because of the high sensitivity of this imaging method compared to coronary angiography (CAG).

The COSMOS study will provide new evidence and therapeutic standards for the prevention of CHD in Japan by controlling LDL-C levels with rosuvastatin.

Study Design

This will be a 76-week, open-label, multicenter study to evaluate the effect of rosuvastatin on coronary artery atheroma volume as measured by IVUS in patients with CHD.

Eligible patients will begin treatment with rosuvastatin 2.5 mg once daily. The dosage will be increased by titration within the usual dose range with a treatment goal of lowering LDL-C below 80 mg/dl based on safety and the relationship between suppression of coronary artery plaque progression and LDL-C level in prior studies![11,15,16,19,21] If LDL-C levels are still 80 mg/dl or above after 4 weeks of treatment, the dosage may be increased up to a maximum of 20 mg/day. If the investigator finds it necessary to reduce the dosage because of an excessive decrease in LDL-C (<50 mg/dl) or occurrence of adverse events, the dosage may be reduced again to the starting dose of 2.5 mg once

daily.

A total of 19 scheduled visits are planned during the course of this study. Subjects will attend follow-up visits every 4 weeks over 76 weeks after starting the treatment with rosuvastatin. IVUS and CAG will be performed at baseline and Week 76.

Prior to any study-related activities, all subjects will sign an informed consent form. This study is approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of all of the participating centers (Fig 1). The planned duration is between October 2005 and October 2008.

Patient Population

All patients have to meet all of the inclusion criteria: aged 20–75 years undergoing CAG or PCI; serum cholesterol level either (a) untreated patients: LDL-C ≥140 mg/dl [calculated with Friedewald equation (triglyceride (TG) <400 mg/dl) or directly measured] or TC ≥220 mg/dl, or (b) patients already treated with lipid-lowering agents: LDL-C ≥100 mg/dl [calculated with Friedewald equation (TG <400 mg/dl) or directly measured] or TC ≥180 mg/dl; the patient must have at least 1 significant stenosis of 75% or more and be a candidate for PCI, and in addition to the candidate lesion for PCI, there must be at least 1 lesion ≤50% stenosis that can be imaged by IVUS.

Exclusion criteria are: (1) acute myocardial infarction within 72 h of the onset of the study, (2) heart failure of New York Heart Association class III or IV, (3) secondary hyperlipidemia, (4) administration of cyclosporine, (5) hemodialysis, (6) lesions requiring intervention, (7) left main coronary artery disease of >50% stenosis, (8) uncontrolled hypertension (diastolic blood pressure ≥110 mmHg or systolic blood pressure ≥200 mmHg for all measurements during the screening period), (9) uncontrolled diabetes (hemoglobin A1c ≥9.5%), (10) active liver disease or liver dysfunction with ≥2.5×ULN (upper limit of the normal) of either alanine aminotransferase, aspartase aminotransferase or alkaline phosphatase, or ≥3.0 mg/dl of total bilirubin, (11) creatinine clearance <30 ml/min or serum creatinine >2.0 mg/dl, (12) serum creatine kinase >3×ULN, (13) short plaque lesions with a length less than 6 mm.

IVUS Examination

IVUS will be used to examine lumen area, atheroma size and distribution at baseline and after 76 weeks of treatment. Investigators will be required to use the same imaging system with the same type of IVUS catheter for both the baseline and follow-up examinations: Clearview®, Galaxy™ ultrasound system or Galaxy2™ ultrasound system with the Atlantis™ SR Pro 2 40 MHz imaging catheter (Boston Scientific, Natick, MA, USA). The images will be optimized under visual inspection by manipulating the system settings. The gain settings will be determined with the intention of maximizing image morphology without excessive dropout, not saturating adventitial intensity, and minimizing noise. The automated pullback device will be set with a speed of 0.5 mm/s. IVUS images will be recorded on super-VHS (S-VHS) videotapes or Digital Video Disk plus Re-Writable (DVD+RW) disk. The images will be logged and analyzed blind by 2 experienced technicians in the core lab.

IVUS Analysis

Plaque volume will be assessed by volumetric analysis with the echoPlaque2 system (Indec Systems Inc). Baseline and follow-up IVUS images will be reviewed side-by-side on a display, and the target segment selected. The target segment to be monitored will be determined in a non-PCI site (>5 mm proximal or distal to the PCI site) with a reproducible index such as side branches, calcifications, or stent edges.

Endpoints

The primary endpoint is the percent change in the plaque atheroma volume (target lesion length measured will be a minimum of 6 mm) from baseline to Week 76.

The secondary endpoints are actual volume changes and percentage changes in plaque area, in the vascular cross-sectional lumen area and total vascular area from baseline to Week 76 at the same preselected coronary artery cross-section.

Percent changes from baseline to specified measurement time points in TC, LDL-C, very LDL-C (VLDL-C), HDL-C, non-HDL-C (TC-HDL-C), TG and remnant like particle (RLP-C), apoprotein (Apo)A-I, ApoA-II, ApoB, lipoprotein (a) (Lp(a)), small dense LDL, HDL-2 and HDL-3 will also be calculated.

Changes in high sensitivity C-reactive protein from baseline to specified measurement time points will be calculated. RLP-C will be measured by the immunity adsorption method and ApoA-I, ApoA-II and ApoB by turbidimetric immunoassay. Lp(a) will be measured by latex-enhanced turbidimetric immunoassay and small dense LDL, HDL-2 and HDL-3 by the ultracentrifugation method. All laboratory measurements will be performed at a central clinical laboratory (SRL, Inc, Tokyo, Japan).

Safety

Safety will be observed throughout the study. Adverse events, subjective symptoms/objective findings, body weight, resting 12-lead ECG, chest X-ray, general blood tests (hematology, renal and liver functions, glucose metabolism), urinalysis, and vital signs (blood pressure, pulse) will be observed.

Sample Size

In the protocol, the assumptions used for power calculations require a sample size of 126 patients to provide 80% power (assuming a SD of 24.9%) to detect a 6.3% difference in the primary endpoint with 2.5% type I error rate for a 1-sided test. It was therefore determined that the enrollment of 200 patients per treatment would provide an adequate number of patients.

Analysis Population

The primary analysis population for efficacy will comprise subjects who comply with the protocol and have IVUS data that can be evaluated at both baseline and Week 76. This analysis population is defined as a per-protocol set. A full analysis set, defined separately, will be used as the secondary analysis population.

Efficacy Analysis

The primary endpoint and secondary endpoints defined as percentage changes or changes from baseline will be summarized by mean, standard deviation, minimum, median and maximum, and then 95% CIs will be calculated. The null hypothesis that percentage change or change from baseline is equal to 0 is tested by 1-sample t-test.

Safety Analysis

For safety evaluation, the numbers and prevalence of adverse events (including abnormal changes in physical values and clinical laboratory values) and the prevalence of adverse drug reactions (adverse events to which causality of rosuvastatin cannot be ruled out) will be calculated. Adverse events and adverse drug reactions will be summarized by type, severity, causality and duration of event.

Study Organization

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Conclusion

The COSMOS study will be the first multicenter study performed in a Japanese population using IVUS to evaluate the effects of rosuvastatin on regression of coronary atherosclerosis. We hope to show that intensive LDL-C lowering by rosuvastatin reduces coronary artery atheroma volume from baseline in diseased coronary segments.

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Appendix 1

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What is the Optimal Management for Preventing Saphenous Vein Graft Diseases?

— Early Results of Intravascular Angioscopic Assessment —

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Background The predominant mechanism of early failure of saphenous vein grafts (SVG) after coronary bypass remains unclear, so angioscopy was used to identify the morphological changes.

Methods and Results Of the 31 SVGs assessed 15 had both yellow plaque and thrombi, whereas in the remaining 16 SVGs the intima was clear white. The serum low-density lipoprotein cholesterol level was significantly higher in the diseased SVG group. Eight patients of the normal SVG group were prescribed ticlopidine, compared with only 1 from the diseased SVG group (p=0.015).

Conclusions This is the first direct demonstration of yellow plaque and/or thrombosis in SVGs by intravascular angioscopy. In addition to the importance of prescribing statins, it might be vital to also add ticlopidine to aspirin therapy. (*Circ J* 2007; **71**: 286–287)

Key Words: Anticoagulant therapy; Intra-coronary angioscopy; Saphenous vein graft

Despite advances in the relevant technologies and techniques, nearly 25% of saphenous vein grafts (SVGs) occlude within 1 year of surgery, and 50% of SVGs fail within 10 years. However, the ready availability of SVGs still accounts for its use in over 70% of coronary artery bypass grafting (CABG). Although the time course of the development and nature of SVG disease in patients after CABG has recently been defined, as a consequence of the increasing use of intravascular ultrasound (IVUS)[1] the predominant mechanism of early graft failure after CABG remains debatable. The aim of this study was to identify the morphological changes in SVG using intra-coronary angioscopy and to determine the optimal management strategies for the maintenance of post-CABG SVG patency.

Thirty-one SVGs from 31 patients undergoing post CABG coronary angiography were assessed by intravascular angioscopy. Except for 6 patients who had recurrent angina, there were no instances of coronary events. The average angioscopic study interval after surgery was 61 months, ranging from 1 to 300 months. None of the SVGs showed intimal thickening or deterioration on histological examination at the time of the surgery. The average age was 66.3±8.2 years, ranging from 57 to 80 years. We evaluated the presence of yellow plaque and/or thrombosis in the SVGs and evaluated the characteristics of the patients who had diseased SVGs in comparison with those of the patients with normal SVGs. The statistical analysis was conducted by the Student's t-test and Fisher's exact test. P values of less than 0.05 were considered to be statistically significant.

Both yellow plaque and thrombi were detected in 15 grafts (48.4%) (Fig 1), although angiographic SVG stenosis was identified in only 5 of these. Twelve of the 15 SVGs were anastomosed to right coronary arteries and the other 3 grafts were anastomosed to circumflex territories. All target coronary artery stenoses were greater than 75%. In the re-

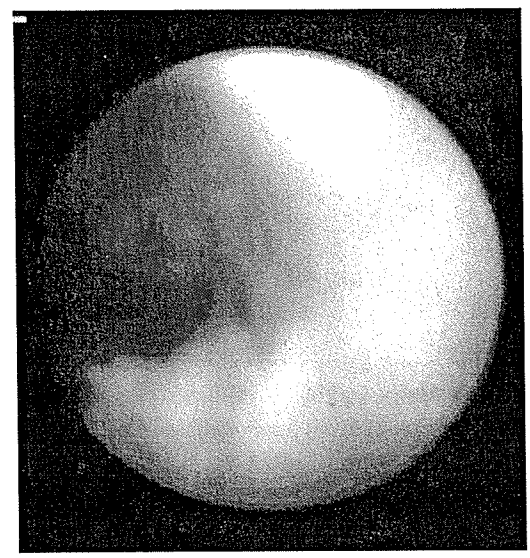

Fig 1. Atherosclerotic yellow plaque and thrombosis in a saphenous vein graft.

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maining 16 SVGs the intima was clear white (Fig 2). There were no significant differences between the patients of the diseased SVG group and the normal SVG group in terms of age, sex, body mass index, coronary risk factors, target coronary artery for SVG, postoperative ejection fraction, or follow-up interval. Although there were no significant differences in terms of the serum levels of total cholesterol, high-density lipoprotein-cholesterol, or triglyceride between the groups, the serum low-density lipoprotein (LDL)-cholesterol level was significantly higher in the diseased SVG group (138.7±68.9 mg/dl) than in the normal SVG group (97.0±34.5 mg/dl, p=0.049). All the patients in both groups were taking 100 mg of aspirin and 10 mg of pravastatin daily. Two patients (12.5%) from the normal SVG group and 5 (33.3%) from the diseased SVG group were also receiving warfarin (no significant difference in the proportion between the 2 groups). Eight patients from the normal SVG group were prescribed ticlopidine for reasons such as minor stroke or post-coronary intervention, whereas only 1 patient (6.7%) from the diseased SVG group was taking ticlopidine (p=0.015).

This is the first direct demonstration of yellow plaque and/or thrombosis in SVGs by intravascular angioscopy. In this series, although the yellow plaque and/or thrombosis were found in 15 SVGs, angiographic stenosis was identified in only 5 cases, which suggests that angiography may not be a suitable method for identifying unstable lesions in SVGs. IVUS can also detect SVG diseases, such as eccentric plaques[1] but it is relatively insensitive for identifying thrombi, which are often confused with echolucent plaques. Angioscopy is an excellent tool for identifying thrombi and is even more sensitive than angiography or IVUS for this purpose[2] Angioscopy is therefore suitable for studying the efficacy of strategies to prevent SVG disease.

It is evident from the present angioscopic study that the major features of SVG diseases are the presence of atherosclerotic plaque and unstable thrombi. SVG atherosclerosis especially predisposes to thrombosis because of the high content of lipids and tissue factors, chronic flow disturbances, and associated impairment of vasodilatation. SVG atheromas are more diffuse and vulnerable to rupture, and the major consequences of plaque rupture in SVGs seem to be rapid platelet aggregation and certain thrombotic occlusion[3] Therefore, antiplatelet agents and cholesterol-lowering therapy are theoretically attractive options for the prevention of such consequences.

A post-CABG trial has shown that aggressive lowering of LDL is effective in reducing the progression of atherosclerosis in SVGs; low-dose warfarin, on the other hand, had no effect[4] In the present study, the serum LDL level was significantly higher in the patients with diseased SVGs. Furthermore, ticlopidine also showed an additional effect of reducing the likelihood of developing SVG thrombosis. Conditions that create nonlaminar or sluggish flow within the SVG may be expected to influence the development of SVG thrombosis. Several investigators have reported that the addition of ticlopidine to aspirin therapy significantly

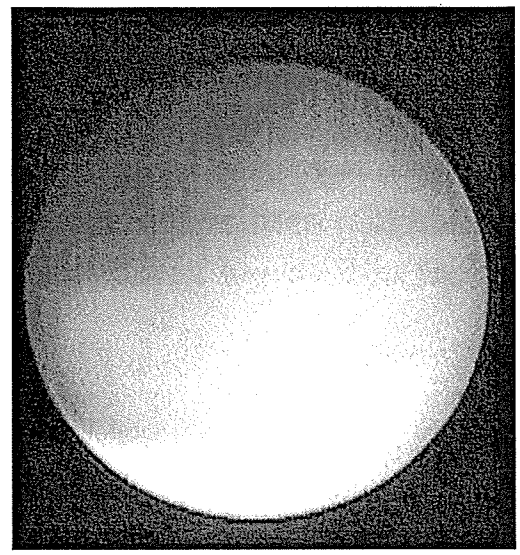

Fig 2. Normal white intima in a saphenous vein graft.

inhibited high-shear-stress-induced platelet aggregation[5] The present study results appear to suggest that in addition to the extremely important measure of lowering the serum LDL level for reducing the incidence of SVG disease, it might be invaluable to also add ticlopidine to aspirin therapy in these patients.

The number of cases in the present study was, however, small, and it is necessary to conduct a prospective randomized trial.

In conclusion, we present angioscopic findings of SVG diseases post CABG, which suggest that in addition to the extreme importance of prescribing statins for the prevention of SVG diseases, it might be vital to also add ticlopidine to aspirin therapy in these cases.

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CASE REPORT

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Postinfarction cardiac rupture despite immediate reperfusion therapy in a patient with severe aortic valve stenosis

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Abstract A 74-year-old woman with severe aortic valve stenosis (AS) was admitted to our hospital because of dyspnea on exertion. On day 2, she developed acute anterior wall myocardial infarction (MI) with ST elevation. Tissue plasminogen activator (tPA) was administered 10 min after the onset of chest pain, and emergency percutaneous coronary intervention was performed to induce coronary reperfusion after another 50 min. Five hours after MI onset, however, she suddenly went into electromechanical dissociation and died from cardiac rupture. This is the first case report of postinfarct cardiac rupture with severe AS occurring in spite of instituting immediate reperfusion therapy. High intraventricular pressure may be a critical risk factor for cardiac rupture in patients with AS complicated with acute MI. Further studies are required to clarify the risk and benefit of tPA administration before percutaneous coronary intervention and the necessity of the emergency correction of AS to prevent cardiac rupture.

Key words Cardiac rupture · Acute myocardial infarction · Aortic valve stenosis · Reperfusion therapy

Introduction

Cardiac rupture occurs in 1.5%–8% of patients with acute myocardial infarction (MI) and is involved in 5%–24% of in-hospital deaths due to MI.[1] The risk factors for cardiac rupture are a first transmural MI, anterior wall MI, advanced age, female gender, the absence of collaterals, a history of hypertension, and recurrent chest pain.[1–5] Here we report on a patient with severe aortic valve stenosis (AS) who developed acute MI complicated with blow-out type cardiac rupture.

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Case report

A 74-year-old woman with hypertension and diabetes was admitted complaining of increasing dyspnea on exertion. Her blood pressure was 116/85 mmHg on admission and there was no jugular venous distention or peripheral edema present. However, an S4 and a grade III systolic ejection murmur at the right second rib interspace near the right border of the sternum were audible. Electrocardiography showed a normal sinus rhythm at a rate of 82 beats/min with strain T waves in leads I, aV_L, and V_{4-6} (Fig. 1a), and a chest X-ray showed prominence of the left ventricle, with a cardiothoracic ratio of 57% and mild congestion in the upper lobes. Echocardiography also revealed severe AS, left ventricular hypertrophy, and global hypokinesia, with a fractional shortening of 21%. The estimated pressure gradient across the left ventricular outflow was 177 mmHg and the aortic valve area was 0.3 cm^2. The patient was treated with 20 mg of intravenous furosemide and soon became free from dyspnea.

On day 2, she suffered sudden chest pain while at rest. Electrocardiography and emergency echocardiography indicated anterior wall MI (Fig. 1b). Tissue plasminogen activator (tPA; monteplase, 1 600 000 units) was administered 10 min after the onset of chest pain, intravenous nitroglycerin and heparin were given, and emergency coronary angiography was started. It was subsequently determined that the proximal left anterior descending coronary artery was occluded. Percutaneous coronary intervention (PCI) was thus performed and a metallic stent (Bx Velocity Stent with Hepacoat, 3.0 × 23 mm, Cordis, Miami, FL, USA) was inserted after predilation was carried out using a same-size balloon catheter (Maverick^2 Monorail Balloon Catheter, Boston Scientific, Natick, MA, USA). Coronary flow to the left anterior descending artery was re-established 1 h after the onset of chest pain (Fig. 2), although a distal embolic

occlusion was found at the distal end of the left anterior descending artery at the end of the PCI.

The patient's systolic blood pressure was kept strictly below 120 mm Hg during and following the PCI via the infusion of intravenous nitroglycerin. Her total creatine kinase (CK), CK-MB, and CK-MB% 4 h from the onset were 4999 U/l, 238 U/l, and 4.8%, respectively. Five hours after the onset, she suddenly lost consciousness. Electrocardiography showed electromechanical dissociation, and echocardiography showed pericardial effusion with cardiac tamponade (Fig. 3). Cardiac rupture was suggested, and she underwent emergency sternotomy and open cardiac massage, while at the same time emergency percutaneous cardiopulmonary support was initiated. Despite immediate resuscitation, the patient died.

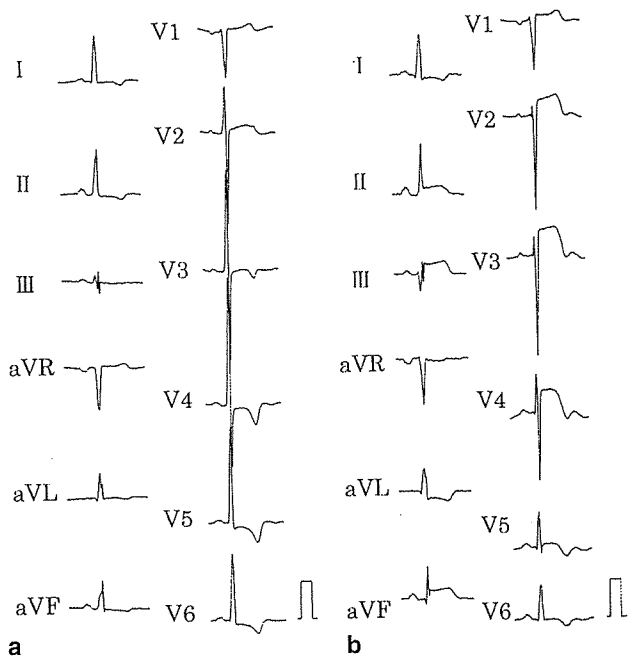

Fig. 1. Electrocardiograms of the patient. **a** The electrocardiogram on admission showed strain T waves in leads I, aV_L, and V_{4-6}. **b** ST segment elevation was observed in leads II, III, aV_F, and V_{1-5} at the onset of chest pain

Discussion

Although the patient underwent reperfusion therapy immediately after the onset of MI, she could not be rescued from catastrophic cardiac rupture, which occurred 5 h after the onset of chest pain. Blow-out rupture is characterized by the rapid development of hemodynamic collapse associated with sinus bradycardia and slow atrioventricular junctional rhythm (i.e., electromechanical dissociation), and is usually fatal. It was also difficult to keep her alive although she was subjected to full resuscitation immediately after the appearance of hemodynamic collapse.

The patient had several risk factors for postinfarct cardiac rupture such as a history of hypertension, female gender, first transmural MI, anterior wall MI, and advanced age, and these factors may have contributed to the catastrophic event. In addition to these traditional risks, she had severe AS. Several case reports have shown that postinfarct cardiac rupture occurs in patients with coexisting severe AS.[6,7] In the presence of AS, the left ventricular wall is

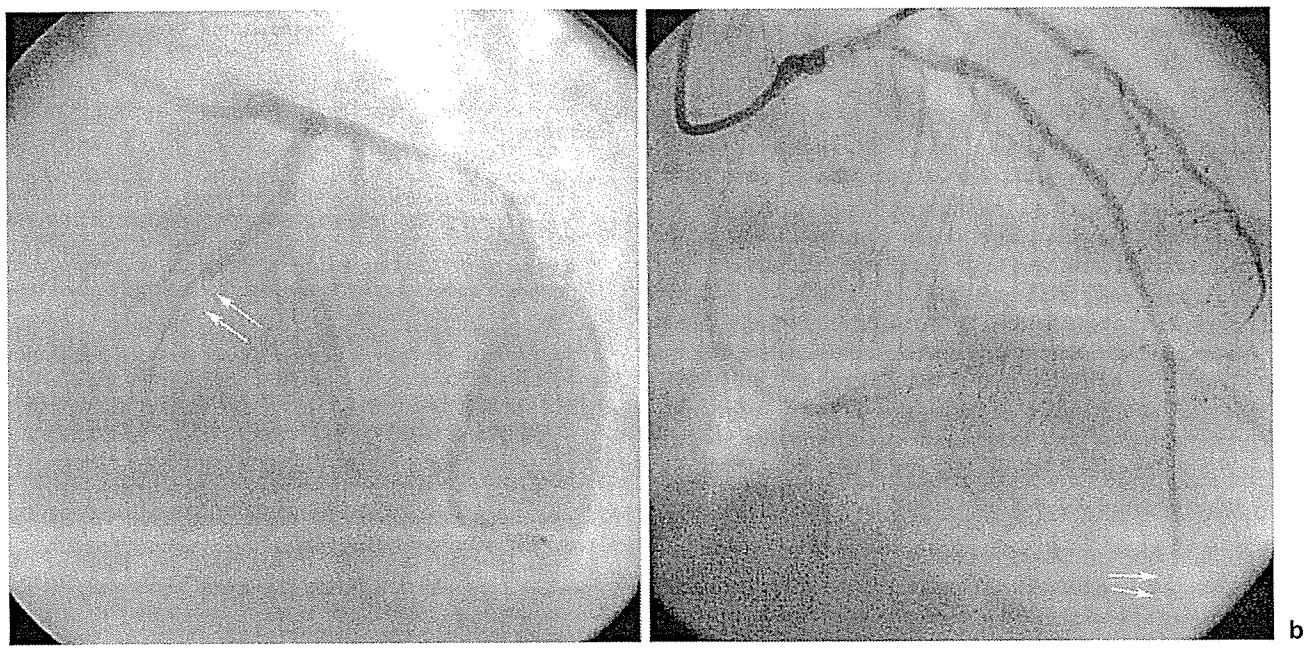

Fig. 2. **a** Coronary angiography showing an occlusion of the proximal left anterior descending coronary artery (*arrows*). **b** Coronary reperfusion was achieved in the left anterior descending artery, although a distal embolic occlusion was present (*arrows*)

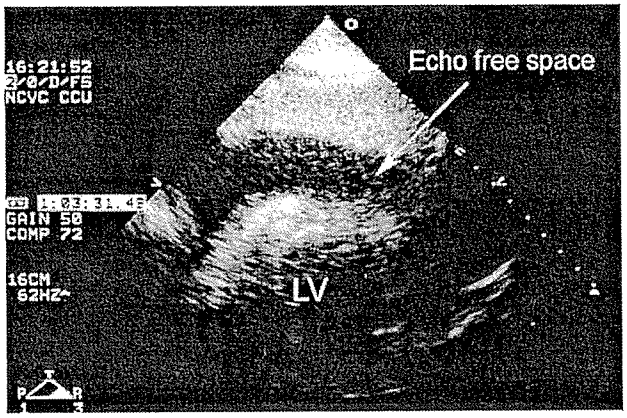

Fig. 3. Echocardiography showing pericardial effusion with findings of cardiac tamponade, indicating cardiac rupture (*arrows*). *LV*, left ventricle

subjected to an increased systolic pressure load. Furthermore, if the infarct size is small, the overall contractile strength of the left ventricle is preserved, thereby generating a high intracavitary pressure in the presence of a vulnerable infracted myocardium. High pressure in the left ventricle subsequently exhausts the infracted muscle and leads to cardiac rupture even though the peripheral blood pressure is normal. In the present case, the estimated gradient across the valve was beyond 170 mmHg. In this situation, arterial blood pressure reduction induced by vasodilatory drugs was of no help for the compromised infarcted myocardium that had been exposed to high pressures. Cardiac rupture was inevitable even though the peripheral blood pressure had been kept strictly as low as possible during and after reperfusion therapy. Therefore, the presence of severe AS is a critical risk factor that accelerates cardiac rupture, in addition to conventional risk factors.

Generally, early recanalization reduces mortality in patients with acute MI. The PACT Trial showed that the combination therapy of short-acting reduced-dose thrombolysis and immediate planned rescue angioplasty facilitates greater LV function preservation with no significant differences in adverse events compared with primary PCI.[8] Therefore, early PCI facilitated by reduced-dose thrombolytic therapy is a beneficial and favorable strategy. On the other hand, the administration of thrombolytic drugs may increase the incidence of early cardiac rupture. In GISSI-1, the increased number of deaths during the first 6 h among patients treated with intravenous streptokinase was largely attributed to heart failure and electromechanical dissociation, and the latter was potentially a manifestation of cardiac rupture.[9] An excess of cardiac rupture events within the first 48 h was also reported in ISIS-2.[10]

Two peaks exist for the incidence of cardiac rupture after the onset of acute MI, where an early peak occurs within the first 72 h and a late peak occurs after 5–14 days.[1,11,12] Different mechanisms may be responsible for these peaks. In patients with early-phase rupture, there is hardly any thinning of the infarcted area, whereas late-phase rupture generally develops in already expanded infarcted tissue. Thrombolytic therapy may enhance the degree of early-phase rupture, although it decreases the degree of late-phase rupture and the overall death rate. The LATE study showed that, among patients treated within 12 h, the proportion of rupture deaths in the tPA group was higher than in the placebo group.[13] A large registry of these events in the United States also showed that death from cardiac rupture occurs earlier in patients treated with thrombolytic therapy, with a clustering of events within 24 h of drug administration.[14] Reperfusion may contribute to significant intramyocardial hemorrhage, which dissects through the infarcted myocardium, thus contributing to early cardiac rupture. In contrast, several studies recently found that primary direct angioplasty reduces the risk of rupture compared with thrombolysis for acute MI.[15,16] The present case had many risk factors of cardiac rupture, and the administration of tPA before PCI might have further accelerated the development of rupture no matter how early it could have been administered.

Case reports exist on patients who experienced post-MI cardiac rupture in the presence of severe AS, and who were rescued by surgical treatment.[7,17–19] However, they all had a subacute type (i.e., oozing) of cardiac rupture. No case of abrupt, catastrophic (i.e., blow-out) rupture has ever been rescued. This is the first report showing that post-MI cardiac rupture with severe AS can occur in spite of the use of immediate reperfusion therapy. Medical treatment involving immediate thrombolytic therapy followed by PCI and strict blood pressure control may have limitations in patients with severe AS. However, it remains unclear whether primary PCI alone is adequate or should be followed by the emergency correction of severe AS by aortic valve replacement or aortic valvloplasty. Further studies are thus necessary to determine an optimal treatment strategy.

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ORIGINAL RESEARCH

Association between Signal Hyperintensity on T1-Weighted MR Imaging of Carotid Plaques and Ipsilateral Ischemic Events

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BACKGROUND AND PURPOSE: To investigate associations between cerebral ischemic events and signal hyperintensity in T1-weighted MR imaging (T1WI) of carotid plaque according to stenosis severity and to estimate persistence of T1WI signal hyperintensity.

METHODS: A total of 222 patients (392 atherosclerotic carotid arteries) underwent plaque imaging using 3D inversion-recovery-based T1WI (magnetization-prepared rapid acquisition with gradient-echo [MPRAGE]). Carotid plaque with intensity on MPRAGE of >200% that of adjacent muscle was categorized as "high signal intensity" and correlated with ipsilateral ischemic events within the previous 6 months. A total of 58 arteries (35 patients) underwent repeat MR imaging a total of 70 times at a median interval of 279 days (range, 10–1037 days).

RESULTS: Ipsilateral ischemic events were more frequent in patients with MPRAGE high signals than in patients with low signals in the 0%–29%, 30%–69%, and 70%–99% stenosis groups: Relative risk (95% confidence interval) was 2.50 (0.96–6.51), 7.55 (1.84–31.04), and 1.98 (1.01–3.90), respectively. In the 70 cases of repeat MR imaging, 29 of 30 cases with high signals on the preceding MR imaging maintained high signals. Of the 58 arteries that underwent repeat MR imaging, 4 of 22 carotid arteries with high signals developed ipsilateral subsequent ischemic events within 1 year, whereas none with low signals developed subsequent events.

CONCLUSIONS: Carotid plaque signal hyperintensity on T1WI is strongly associated with previous ipsilateral ischemic events, persisting over a period of months, and may indicate risk of subsequent events. Larger clinical trials are warranted to clarify associations between signal hyperintensity and risk of subsequent cerebral ischemic events.

Atherosclerotic carotid plaque represents a major cause of cerebral ischemia.[1] Superiority of carotid endarterectomy to medical treatment has been confirmed for symptomatic carotid artery with severe stenosis (70%–99%) by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST), but ≥7 operations were performed to avoid 1 stroke.[2,3] At the same time, symptomatic patients with 50%–69% stenosis have been shown to benefit from moderate reduction of stroke risk by surgery, whereas patients with <50% stenosis do not benefit from surgery.[2,3] However, cerebral ischemic episodes are not restricted to severe stenosis of the carotid artery,[2-4] and a substantial fraction of ischemic strokes in the territory of the carotid artery are unrelated to carotid stenosis.[1] Methods of noninvasively identifying "at risk" plaques are thus required.

Many studies have focused on MR imaging to characterize carotid plaques by using various imaging sequences. However, standardized sequence parameters and evaluation criteria to identify "at risk" plaques in MR imaging have not yet been established. Signal hyperintensity of carotid plaque in inversion recovery-based 3D T1-weighted imaging (alternatively known as magnetization-prepared rapid acquisition with gradient echo [MPRAGE])[5] was associated with recent ischemic events,[6,7] and was related to complicated plaques (type VI as proposed by the American Heart Association).[8,9]

We have performed carotid plaque imaging using MPRAGE since December 2001 for patients with suspected or confirmed carotid artery stenosis. The present study investigated associations between ischemic events and MPRAGE signal hyperintensity according to severity of stenosis in the carotid artery, and estimated persistence of MPRAGE signal hyperintensity as a potential risk factor for ischemic events.

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Methods

Population

Since December 2001, MR imaging of the carotid artery has been performed for patients with suspected or confirmed atherosclerosis of the carotid artery after provision of oral informed consent on admission to the Departments of Neurology or Neurosurgery of our hospital. We reviewed the medical records of 222 consecutive patients who underwent MR imaging between December 2001 and June 2004. This study was performed in accordance with the ethics guidelines of our hospital. Of the 444 carotid arteries, 45 occluded arteries (at origin of the internal carotid artery, $n = 39$; common carotid artery, $n = 1$; top of the internal carotid artery or horizontal portion of the middle cerebral artery, $n = 5$) and 7 surgically treated carotid arteries (endarterectomy, $n = 5$; stent grafting, $n = 2$) were excluded from the study. A total of 392 carotid arteries from 222 patients were thus enrolled in this study.

Patient characteristics were recorded retrospectively by reviewing medical records. Ischemic events ipsilateral to the carotid artery within the previous 6 months were recorded, including cerebral infarction, transient ischemic attack, and retinal ischemia (amaurosis fugax and retinal artery occlusion). Emboligenic cardiac diseases (including persistent and paroxysmal atrial fibrillation, mitral valve stenosis, implantation of pros-

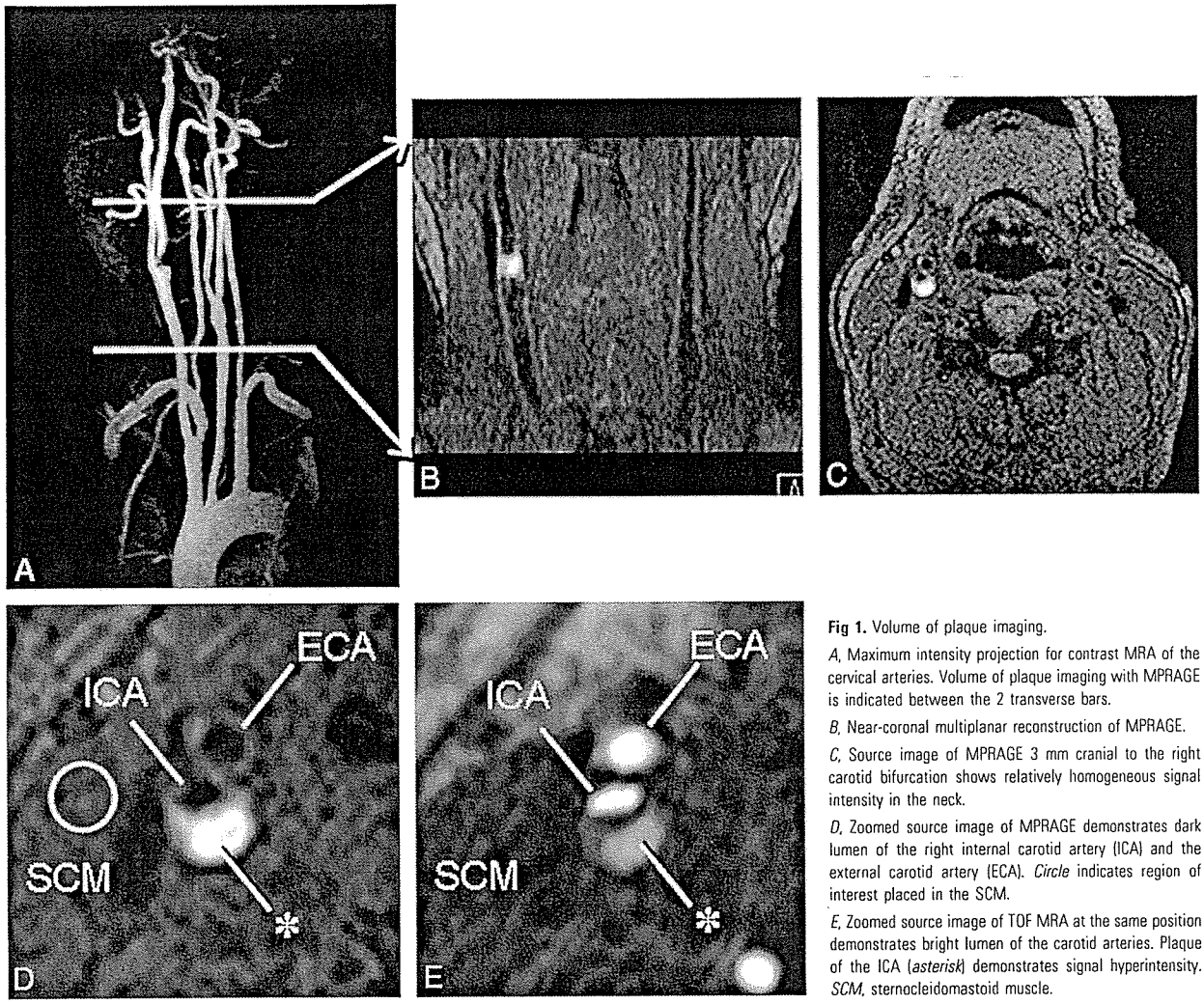

Fig 1. Volume of plaque imaging.

A, Maximum intensity projection for contrast MRA of the cervical arteries. Volume of plaque imaging with MPRAGE is indicated between the 2 transverse bars.

B, Near-coronal multiplanar reconstruction of MPRAGE.

C, Source image of MPRAGE 3 mm cranial to the right carotid bifurcation shows relatively homogeneous signal intensity in the neck.

D, Zoomed source image of MPRAGE demonstrates dark lumen of the right internal carotid artery (ICA) and the external carotid artery (ECA). *Circle* indicates region of interest placed in the SCM.

E, Zoomed source image of TOF MRA at the same position demonstrates bright lumen of the carotid arteries. Plaque of the ICA (*asterisk*) demonstrates signal hyperintensity. *SCM*, sternocleidomastoid muscle.

thetic heart valves, dilated cardiomyopathy, endocarditis, and acute myocardial infarction within the previous 6 months) were also recorded. Recorded risk factors of atherosclerosis included hypertension, diabetes mellitus, hyperlipidemia, and cigarette smoking.

MR Imaging

MR imaging was performed using a Magnetom Sonata 1.5T system (Siemens, Erlangen, Germany) with standard neck array and spine array coils (Fig 1). Plaque imaging was performed using MPRAGE in transaxial section with null blood condition (effective inversion time, 660 ms; TR, 1500 ms) and the water excitation technique to suppress fat signals. TR was defined as the interval between successive inversion pulses. Other imaging variables were: TE, 5.0 ms; FOV, 180 × 180 mm; matrix, 256 × 204; section thickness, 1.25 mm; 56 partitions; covering 70 mm around the carotid bifurcation; data acquisition time, 5 minutes. Multislab 3D time-of-flight (TOF) MR angiography (MRA) was also performed to facilitate delineation of lumen shape and plaque morphology (TE, 4.4 ms; TR, 35 ms; same spatial resolution as MPRAGE). Contrast MRA was performed after MPRAGE and 3D TOF MRA using rapid infusion of 0.1 mmol/kg body-weight gadolinium-diethylene-triaminepentaacetic acid (Gd-DTPA) at a rate of 2.0–3.0 mL/s after a test bolus of 1 mL Gd-DTPA for timing evaluation at the same rate. Typical imaging variables comprised: TR, 3.2 ms; TE, 1.3 ms; section thickness, 1.0 mm; 64 partitions; FOV, 360 × 200 mm; matrix, 512 × 208; data acquisition time, 14 seconds; near coronal section.

Follow-Up MR Imaging

Of the 222 patients, 28 patients underwent one repeat MR imaging and 7 patients underwent 2 repeat MRIs for follow-up of carotid atherosclerosis up to June 2005, depending on clinical demands. Among the 28 patients with one repeat MR imaging, 4 carotid arteries were excluded because of occlusion and 6 arteries were excluded as a result of surgical treatment before initial MR imaging ($n = 1$) and between initial and repeat MR imaging ($n = 5$). Among the 7 patients with 2 repeat MRIs, 2 arteries were excluded because of occlusion. MPRAGE signals from plaques were thus compared a total of 70 times in 58 arteries from 35 patients. For arteries that underwent 2 repeat MRIs, first repeat MR imaging was compared with initial MR imaging, and the second repeat MR imaging was compared with the first repeat MR imaging.

Evaluation of MR Imaging

Carotid stenosis was measured using contrast MRA according to the methods defined by the NASCET[10] and categorized into 3 groups: mild or no stenosis (0%–29%), moderate stenosis (30%–69%), and severe stenosis (70%–99%). One observer evaluated signal intensity of plaques on MPRAGE relative to signal intensity in adjacent muscle

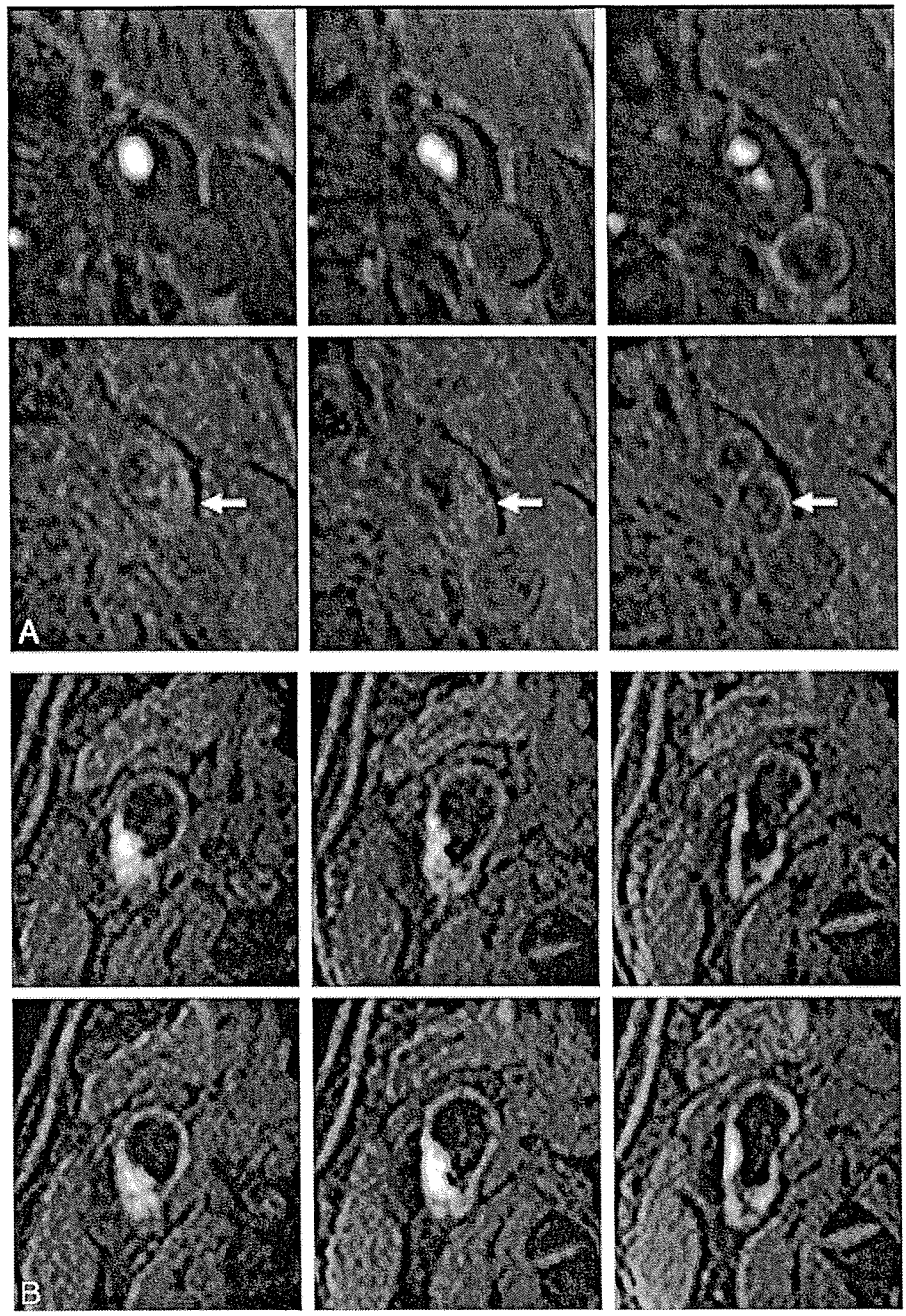

Fig 2. Examples of classic carotid plaques.

A, An example of low signal intensity plaque. Top and bottom rows show 3 corresponding sections with 2.5-mm intervals of TOF MRA and MPRAGE, respectively. A 76-year-old man has left carotid artery stenosis and no history of ipsilateral ischemic events. The carotid plaque (*arrows*) displays no signal hyperintensity relative to the adjacent muscle.

B, An example of high signal intensity plaque. Top and bottom rows show 3 corresponding sections with 2.5-mm intervals in initial and follow-up MR imaging. A 58-year-old man experienced cerebral infarction in the territory of the right middle cerebral artery 12 days before initial MR imaging, which reveals a right carotid plaque with heterogeneous MPRAGE signal hyperintensity (top row). At 4 months after initial MR imaging, the patient again developed cerebral infarction in the right middle cerebral artery territory. Follow-up MR imaging at 5 months after initial MR imaging (bottom row) shows mild increase of MPRAGE high signal intensity region.

(typically the sternocleidomastoid muscle) as measured by placing a round region of interest 5–8 mm in diameter on a standard console of the clinical MR system (Fig 1*D*). If the plaque displayed signal intensity >200% of muscle intensity at any place or section in the plaque, that plaque was categorized as "high signal intensity." Otherwise, the plaque was categorized as "low signal intensity" (Fig 2).

For carotid plaque with high signal intensity, volume of the region with signal intensity >200% of the muscle intensity was calculated using Dr. View/PRO version 5.2 software (Asahi Kasei Information Systems, Tokyo, Japan) on a stand-alone workstation.

Statistical Analysis

Two-tailed *t* tests or Mann-Whitney tests were used for comparison of means, 2-sided Fisher exact tests for comparison of proportions, paired *t* tests for comparison of paired variables, and χ^2 tests for linear trends of ischemic events according to stenosis severity. Associations

Table 1: Baseline characteristics of carotid arteries according to symptoms

	Symptomatic (n = 74)	Asymptomatic (n = 318)	P
Age (years)	69.9 ± 8.3*	70.0 ± 7.6	.8872
Female sex	14.9 (11/74)	17.3 (55/318)	.7309
AF and prosthetic heart valve	5.4 (4/74)	6.9 (22/318)	.7982
Hypertension	79.7 (59/74)	83.3 (265/318)	.4957
Diabetes mellitus	39.2 (29/74)	39.9 (127/318)	1.0000
Hyperlipidemia	62.2 (46/74)	56.0 (178/318)	.3630
Cigarette smoking	29.7 (22/74)	23.3 (74/318)	.2930

Note:—AF indicates atrial fibrillation. Values for age represent mean ± SD; other values represent percentage of carotid arteries, with raw numbers provided in parentheses.

between MPRAGE signal intensity and ipsilateral ischemic events were analyzed by considering each artery independently. All analyses were performed using Prism version 4.0 software for Windows (GraphPad Software, San Diego, Calif).

To calculate interobserver variability in categorization of carotid plaque as high or low signal intensity, a second observer categorized carotid plaque signals for the first 100 arteries after completing consensus reading of the last 10 carotid plaques as training between first and second observers. For calculation of intraobserver variability, the first observer repeated categorization of plaque signals for the first 100 arteries at >1 month after first observation. All interpretations of MR imaging were performed in a blinded manner. Interobserver and intraobserver agreement was calculated using κ statistics.

Results

Association between Signal Hyperintensity and Previous Ischemic Events

A total of 74 carotid arteries were associated with ipsilateral ischemic events within the previous 6 months (cerebral infarctions, $n = 45$; transient ischemic attack, $n = 20$; retinal ischemia, $n = 9$). Patients displaying carotid arteries with and without ipsilateral ischemic events exhibited no significant differences in age, sex, hypertension, diabetes mellitus, hyperlipidemia, or cigarette smoking status. A total of 24 carotid arteries were present in patients with atrial fibrillation, whereas 2 carotid arteries were from a single patient with a prosthetic aortic valve (Table 1). No patients were diagnosed with mitral stenosis, dilated cardiomyopathy, endocarditis, or acute myocardial infarction.

MPRAGE high signal intensity was assigned to 170 of 392 carotid plaques (Fig 2). The κ values for interobserver and intraobserver agreement were 0.729 and 0.792, respectively (good agreement). After excluding carotid arteries from patients with atrial fibrillation or prosthetic heart valves, a total of 370 carotid arteries were included in evaluation of association with previous ischemic events. Relative risks (95% confidence interval) of carotid arteries with MPRAGE high signals compared with carotid arteries with MPRAGE low signals for 0%–29%, 30%–69%, 70%–99% stenosis groups were 2.50 (0.96–6.51), 7.55 (1.84–31.04), and 1.98 (1.01–3.90), respectively (Table 2). In addition, risk of high signal intensity carotid arteries with 0%–29% and 30%–69% stenoses resembled risk of low signal intensity carotid arteries with 70%–99% stenosis: relative risks (95% confidence intervals [CI]) were 0.87 (0.34–2.24) and 1.34 (0.65–2.78), respectively. Frequency of ischemic events in MPRAGE high signal intensity plaques increased with stenosis severity (P = .0133). Median interval between MR imaging and previous ischemic events for MPRAGE high and low signal intensity groups was 20 days (range, 0–180 days) and 51 days (range, 6–179 days), respectively. Mann-Whitney tests revealed no significant differences between the 2 intervals (P = .0854).

In MRPAGE high signal intensity plaques, volume of the high signal intensity region was larger in symptomatic plaques than in asymptomatic plaques. Mean (± SD) volume for 0%–29%, 30%–69%, and 70%–99% stenosis groups in symptomatic plaques was 249 ± 301, 186 ± 327, and 166 ± 331 mm^3, respectively—larger than in asymptomatic plaques at 48 ± 72, 123 ± 169, and 115 ± 200 mm^3, respectively. Mann-Whitney tests revealed a significant difference for 0%–29% stenosis (P = .0247) but not for 30%–69% (P = .5102) or 70%–99% stenosis (P = .3177).

Follow-Up MR Imaging

A total of 70 comparisons in 58 arteries were performed between successive MRIs at a median interval of 279 days (range, 10–1037 days). Initial status of high or low signal intensity was maintained on repeat MR imaging for most comparisons; only 4 of 40 low signal intensity carotid arteries changed to high signal intensity, and only 1 of 30 high signal intensity carotid arteries changed to low signal intensity (Table 3). Volume of the region with signal intensity >200% of muscle intensity tended to be similar between successive MRIs (P = .690) (Fig 3). Mean stenosis did not change significantly in the 70 comparisons, at 44.2 ± 30.0% for the preceding MR imaging and 45.0 ± 30.2% for follow-up MR imaging (P = .487).

For investigation of subsequent events, 6 arteries from patients with atrial fibrillation and 2 arteries with ipsilateral middle cerebral artery occlusion at the horizontal portion were excluded from the 58 arteries. Among the remaining 50 carotid arteries, 4 of 22 carotid arteries with high signals displayed subsequent events, compared with 0 of 28 arteries with low signals (P = .0473) (Table 4). Repeat MR imaging of the 4 carotid arteries with subsequent events was performed at 9, 16, 16, and 27 days after subsequent events. Volume of the 4 arteries did not reveal any specific features compared with the other arteries (Fig 3).

Discussion

More ischemic events occurred in patients with high signals on MPRAGE than in those who showed low signals in each of the subgroups of patients with mild, moderate, and severe stenosis. Volume of high signal intensity was significantly larger in symptomatic plaque than in asymptomatic plaque for patients with mild stenosis. We also demonstrated in a subgroup that underwent multiple MR imaging that hyperintensity was maintained over a period of months, and MPRAGE high signals may offer an indicator of risk for subsequent events.

MPRAGE is a T1WI and displays intraplaque components that have short T1 as high signal intensity. Mechanisms of the short T1, however, are complex. Many previous studies have shown that lipid-rich necrotic cores display signal hyperintensity on T1WI.[11-14] Other studies have shown that intraplaque hemorrhage or thrombus exhibit high signal intensity on T1WI.[9,14-16] Although methemoglobin is considered to be a cause of high signal intensity, the duration of methemoglobin in carotid plaques remains unclear. Lipid signals are very weak in advanced plaques.[11] Signal hyperintensity in this study was not attributable to lipids, as fat-suppression technique was

Table 2: Risk of ipsilateral ischemia according to MPRAGE signal intensity and stenosis after excluding patients with atrial fibrillation and prosthetic heart valves

	0%–29% (n = 152)			30%–69% (n = 114)			70%–99% (n = 100)			Total (n = 366)		
Stenosis	S	A	F (%)	S	A	F (%)	S	A	F (%)	S	A	F (%)
MPRAGE												
High signal intensity	6	26	18.8	18	44	29.0	27	36	42.9	51	106	32.5
Low signal intensity	9	111	7.5	2	50	3.8	8	29	21.6	19	190	9.1
P		0.0889			0.0004			0.0498			<0.0001	
Relative risk (95% CI)		2.500 (0.9603–6.508)			7.548 (1.836–31.041)			1.982 (1.008–3.900)			3.573 (2.201–5.801)	

Note:—MPRAGE indicates magnetization-prepared rapid acquisition with gradient echo; S, symptomatic within previous 6 months; A, asymptomatic within previous 6 months; F, frequency of carotid arteries in patients with ipsilateral symptom; CI, confidence interval. P values were calculated using the Fisher exact test between MPRAGE high and low groups for symptoms (S) in each stenosis group. Relative risk of ischemic events was calculated for MPRAGE high carotid arteries compared with low carotid arteries in each stenosis group.

Table 3: Number of carotid arteries displaying MPRAGE high and low signal intensity according to interval between repeat and the preceding MRI, and signal intensity change on repeat MRI

	Number on Preceding MRI		Number Associated with Signal Intensity Change on Repeat MRI	
Interval	High	Low	High to Low	Low to High
<90 days	5	9	1	0
90–179 days	8	7	0	1
180–364 days	9	8	0	0
≥ 365 days	8	16	0	3
Total	30	40	1	4

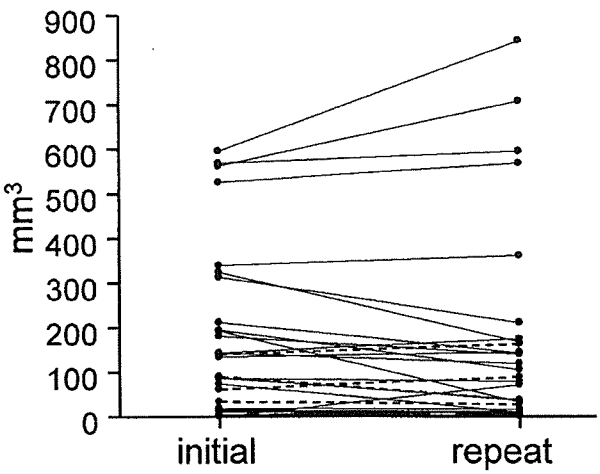

Fig 3. Comparison of high signal intensity volume between successive MR imaging. Comparison was done 34 times between 2 successive MR imagings with high signal intensity in both or either of the 2 MR images. Median interval was 279 days (range, 10–1037 days). High signal intensity volume (mean ± SD) was 149 ± 182 mm^3 at the initial MR imaging and 144 ± 217 mm^3 at the repeat MR imaging. Paired t test displayed no significant change (P = .690). Broken lines indicate 4 carotid arteries associated with subsequent events within 1 year after initial MR imaging.

used. Protein-rich viscous tissue can form another cause of signal hyperintensity.[17-19] The actual cause of T1WI signal hyperintensity should thus be investigated further.

In the follow-up study, signal hyperintensity was repeatedly observed (Table 3), and high signal intensity volume did not change significantly. Repeat MR imaging of 4 carotid arteries with subsequent events that was performed 9–27 days after these events exhibited no specific change in volume compared with the other arteries (Fig 3). These results may be attributable to continuous or recurrent intraplaque hemorrhage. However, we cannot conclude that signal hyperintensity is due to recent hemorrhage in this study. Erythrocyte membranes and iron have been shown to be present within the necrotic cores of human atherosclerotic coronary plaques even in the absence of recent hemorrhage, and intraplaque hemorrhage is related to progression and instability of such lesions.[20] If this is the case in carotid plaque, as in coronary plaque, the necrotic core of a carotid plaque can be at least partially formed by intraplaque hemorrhage, and thus no clear border would exist between intraplaque hemorrhage and necrotic core.

Size and location of high signals may be important for vulnerability. In the coronary artery, "at risk" plaques can be morphologically characterized by a large lipid-rich core and thin fibrous cap.[8,21] In the case of the carotid artery, however, numerous authors have stressed the importance of intraplaque hemorrhage.[22,23] Conversely, other authors have reported no significant differences in frequency of hemorrhage between symptomatic and asymptomatic patients.[24-26] The real causes of carotid plaque vulnerability thus remain controversial. Volume of the high signal intensity region was significantly larger in symptomatic carotid plaque than in asymptomatic plaque for the 0%–29% stenosis category, but not for the 30%–69% or 70%–99% categories. Carotid plaques with subsequent events did not display extremely large volumes for high signal intensity regions (Fig 3). Assessment of fibrous cap thickness and integrity is also important when evaluating plaque vulnerability and has been achieved using T2-weighted imaging and TOF MRA.[11,27,28] Some authors have reported higher percentages of symptomatic patients for ruptured caps (70%) compared with thick caps (9%) using multicontrast MR imaging.[29] Plaque ulceration may be related to stroke risk.[30,31] Better prediction of vulnerability may be achieved by combining MPRAGE with these techniques.

This study was performed using a commercially available clinical machine and standard neck- and spine-array coils without additional hardware. Image acquisition time was short (5 minutes for MPRAGE). MPRAGE with fat suppression and null blood condition suppresses background signals and highlights signal hyperintense tissues with short T1, so image interpretation is relatively simple.[7,9,32] Although motion artifacts were present to various degrees, predominantly attributable to respiration and swallowing, these were insufficient to result in the exclusion of any patients from the present study. 3D data acquisition is essential for visualizing the entirety of irregularly shaped plaques.

This study examined suspected and confirmed atherosclerotic carotid stenosis that may be related to cerebral ischemia depending upon clinical demands. Some biases in the study population

Table 4: Subsequent ipsilateral events according to stenosis severity and MPRAGE signals: results of 1 year follow-up after initial MRI

Stenosis	Number at Initial MRI	Subsequent Events		
		Ischemic Events	Surgical Treatment	Censored
Number of low signal intensity carotid arteries				
0%–29% Stenosis	9	0	0	1
30%–69% Stenosis	13	0	0	0
70%–99% Stenosis	6	0	3	0
Total	28	0	3	1
Number of high signal intensity carotid arteries				
0%–29% Stenosis	6	0	0	0
30%–69% Stenosis	7	1	1	0
70%–99% Stenosis	9	3	5	0
Total	22	4	6	0

Note:—MPRAGE indicates magnetization-prepared rapid acquisition with gradient echo. Ischemic events include ischemic stroke and transient ischemic attack. Surgical treatment includes carotid endarterectomy and endovascular stenting.

may thus be present. Reasons for MR imaging of the carotid artery varied, including screening of cervical artery stenosis, suspicion of complicated plaque on ultrasonography, inconclusive ultrasonography results due to calcification and high position of stenosis, refusal of conventional angiography by patients, and preoperative evaluation of carotid artery stenosis. Potential embolic sources, such as complicated plaque in the aortic arch and persistent foramen ovale, were not surveyed.

Conclusion

We conclude that carotid plaque hyperintensity on MPRAGE, a heavy 3D T1WI technique, is associated with previous cerebral ischemic events. MPRAGE hyperintense signals persist over a period of months, and may represent a potential indicator of risk for subsequent cerebral ischemia. Longitudinal studies with large subject populations are required to clarify whether MPRAGE hyperintense signals indicate risk of subsequent cerebral ischemic events.

Acknowledgments

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Case Reports

Revascularization of Malignant Coronary Instent Restenosis Resulting From Takayasu's Arteritis Using Sirolimus-Eluting Stents

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SUMMARY

A 37 year-old female who had suffered from arteritis for 20 years underwent a Bentall operation. Since severe stenosis was observed in her left main coronary artery (LMCA) the following year, a minimally invasive direct coronary artery bypass (MIDCAB) operation was performed. Unfortunately, she again complained of angina about 6 months after the second surgery and coronary angiography (CAG) revealed that her left internal thoracic artery graft was totally occluded. Although a 4.0 × 15 mm S670 stent was placed in her LMCA, the LMCA restenosed every 3 months and she underwent reintervention 8 times. We placed 2 sirolimus-eluting stents for treating the LMCA using the culottes stenting technique. CAG 6 months after the index procedure showed no stenosis at her LMCA. Sirolimus-eluting stents were effective for treating stenosis resulting from arteritis as well as that caused by atherosclerosis. (Int Heart J 2006; 47: 795-801)

Key words: Arteritis, Restenosis, Sirolimus, Stent

SIROLIMUS has an antiproliferative effect against vascular smooth muscle cells, and many investigators have already reported that sirolimus-eluting stent (SES) placement is more effective for treating atherosclerotic coronary artery narrowing than conventional bare metal stent placement. However, there have been very few reports on whether SES placement is effective against coronary artery stenosis caused by arteritis.

We report herein the case of a young female patient suffering from arteritis in whom malignant instent restenosis was treated successfully with an SES. This is a rare case showing the efficacy of SES for treating LMCA stenosis caused by arteritis.

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CASE REPORT

A 37 year-old female was referred to our institution by another hospital in order to treat her transluminally. She had suffered from Takayasu's arteritis for 20 years, and received an aortic valve replacement (AVR) using a bioprosthetic valve when she was 27 years old. In the following year, complete atrioventricular block appeared, and she underwent permanent pacemaker implantation. Since an aortic root aneurysm appeared when she was 34 years old, a Bentall operation and reAVR were performed. That is, her aortic valve was exchanged to a mechanical prosthetic valve and her LMCA was reconstructed using the Piehler technique.[1] Another year later, she complained of chest pain and coronary angiography (CAG) revealed that her native LMCA was severely stenosed. Her left internal thoracic artery (LITA) was grafted onto her left anterior descending coronary artery (LAD) with a minimally invasive direct coronary artery bypass (MID-CAB) operation. She again complained of angina about 6 months after the MID-CAB operation and CAG revealed that her LITA graft was totally occluded (Figure 1). A 4.0 × 15 mm S670 stent (Medtronic AVE) was placed onto the

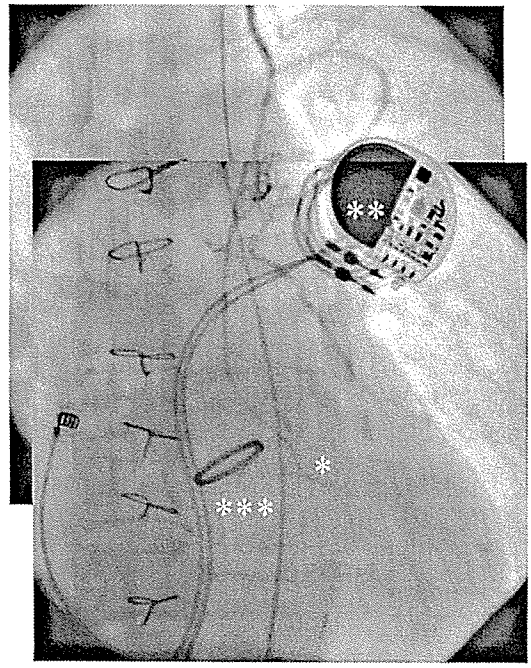

Figure 1. Angiography of left internal thoracic artery.
* : Anastomosis of left internal thoracic artery graft was occluded.
** : Implanted permanent pacemaker
*** : Replaced prosthetic aortic valve

stenosed LMCA and it was adequately postdilated using a 6.0 × 20 mm Maverick-XL balloon catheter (SciMed, Boston Scientific). After this stenting, however, her stented LMCA restenosed about every 3 months, and conventional or cutting balloon angioplasty was performed to compress the intrastent neointima to the exterior of the stent struts on all such occasions. She underwent a total of 8 transcatheter target lesion revascularizations.

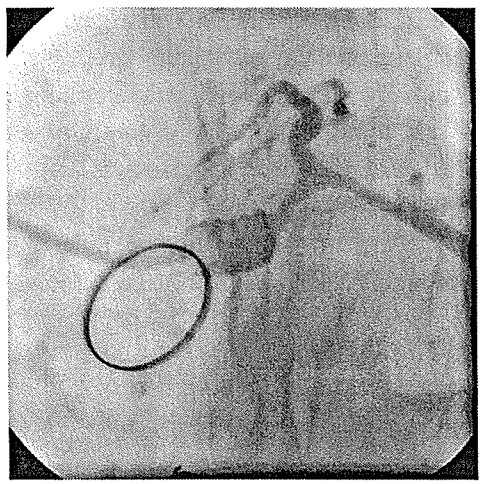

Figure 2. Preprocedural spider view of left coronary angiography: left main coronary artery (LMCA) was severely stenosed.

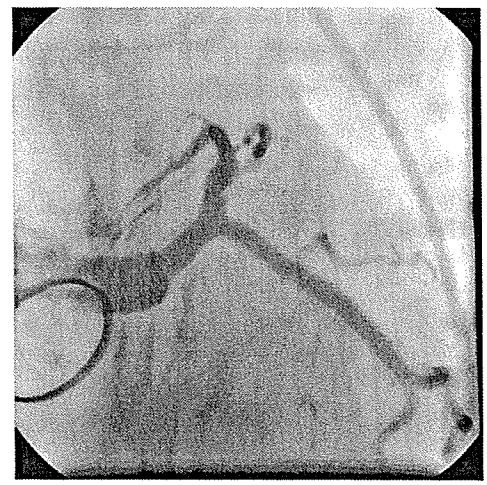

Figure 3. Postprocedural spider view of left coronary angiography: LMCA bifurcation lesion was dilated with the culottes stenting technique using 2 Cypher stents.

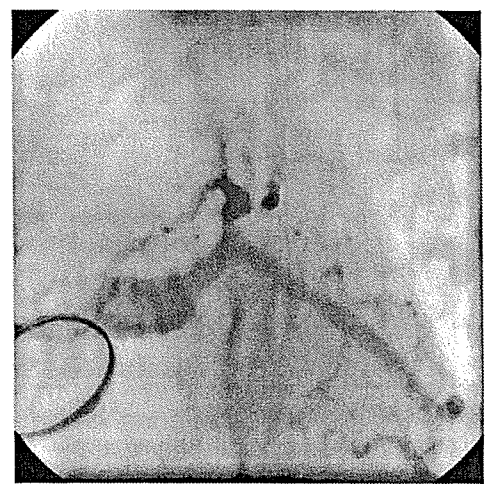

Figure 4. Chronic phase angiography of left coronary artery: No restenosis was observed.