CONCLUSION

In conclusion, we showed that stents coated with an antisense ODN targeted to the PDGF A-chain effectively inhibited in-stent stenosis and preserved reendothelialization. These results indicate that stent-based delivery of antisense ODN targeted to the PDGF A-chain is a safe and feasible therapy for coronary arterial disease.

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Letter to the Editor

Generalized spasm of the right coronary artery after successful stent implantation provoked by intracoronary administration of ergonovine

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Abstract

Coronary spasm may be one of the reasons for the appearance of chest pain after successful percutaneous coronary interventions, and is potentially hazardous when myocardial ischemia occurs. Coronary spasm can be diagnosed by intracoronary administration of ergonovine as a selective spasm provocative test. We report here the case of a patient who had chest pain and ST segment elevation 10 days after successful right coronary artery stent implantation. Repeat angiography was performed, with results of no in-stent stenosis and no stenosis in other segments. Since coronary artery spasm was considered as a possible reason, a spasm provocative test was attempted. Following ergonovine administration (total dose, 50 μg) into the right coronary artery, severe spasm with 99% stenosis developed over the whole artery except the stented segment. Isosorbide dinitrate was injected immediately, and the provoked spasm was soon relieved. Intravascular ultrasound revealed no neointima at the stented segment and diffuse and mild low-echogenic concentric plaque at the distal as well as proximal segment of the stent. Most reports regarding coronary artery spasm provocative tests have focused on focal lesions before interventional therapy, or during interventional procedures. Although it is quite rare, potential coronary spasm should be considered when chest symptoms recur after percutaneous coronary interventions without angiographic representation.

Keywords: Coronary artery generalized spasm; Provocative test; Percutaneous coronary interventions; Intravascular ultrasound

1. Introduction

Coronary artery spasm is an important component in the clinical spectrum of coronary artery disease and is thought to represent the main pathogenetic mechanism of variant angina. There have been several studies on coronary artery spasm; however, most of them focused on focal spasm and lesions before interventional therapy [1–4]. Although coronary artery spasm after successful interventional therapy has rarely been reported, it may cause recurrent chest pain and ischemia even after coronary interventions. Coronary artery spasm can be diagnosed by provocative tests, using intravenous or intracoronary administration of ergonovine [1,5,6]. We report here a patient who developed generalized spasm of the right coronary artery after successful stent implantation, which was provoked by intracoronary administration of ergonovine.

2. Case report

A 57-year-old man presenting with severe chest pain, diagnosed as AMI at another clinic, was referred to our coronary care unit. He developed 2nd degree AV block and marked ST segment elevation in leads II, III, and aVF. Emergency coronary angiography revealed total occlusion of the proximal right coronary artery. Successful stent implantation was performed on the culprit lesion without residual stenosis. The patient was transferred to the general cardiovascular ward after the interventional therapy. However, 10 days later, he experienced recurrent chest pain at 9:30 pm

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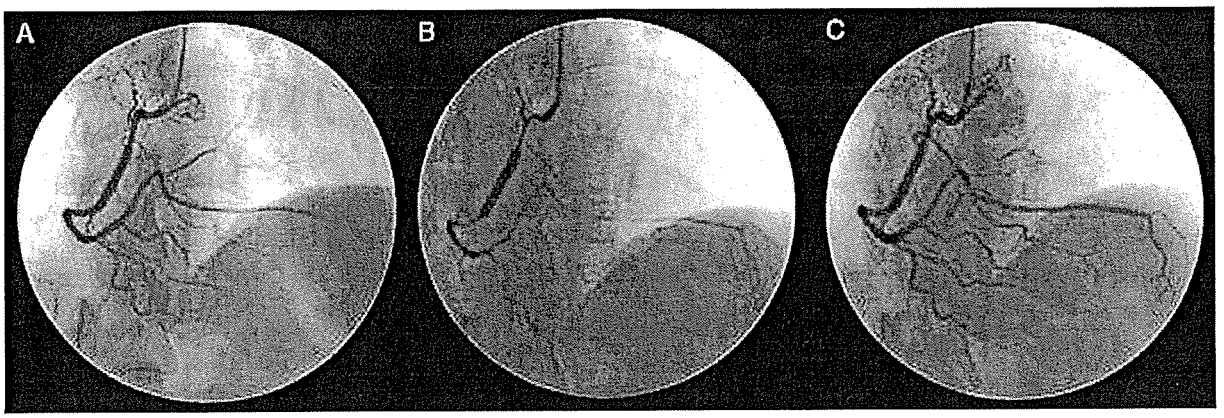

Fig. 1. A: Baseline coronary angiogram of the right coronary artery showing no in-stent restenosis and stenosis in other segments. B: Following intracoronary administration of ergonovine, diffuse spasm was provoked over the whole right coronary artery except the stented segment. C: After intracoronary administration of isosorbide dinitrate, the provoked spasm was relieved.

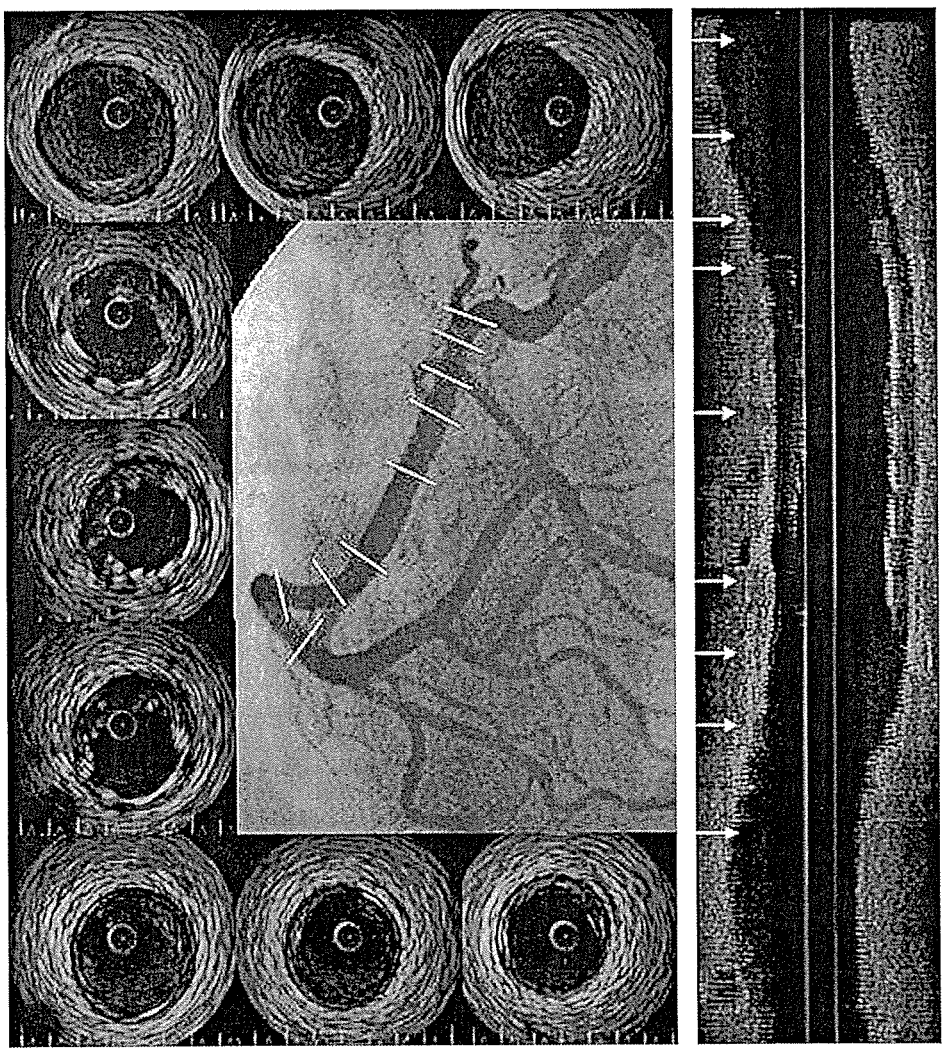

Fig. 2. Angiogram and IVUS images of the right coronary artery. Cross sectional images of the IVUS are shown on the left, and a longitudinal section image is shown on the right. In the stented segment, there is no neointima within the stent. In the distal as well as proximal segment of the stent, diffuse non-calcified mild concentric low-echogenic plaque can be seen on the IVUS images.

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and 4:30 am with ST segment elevation on Holter ECG. He underwent a repeat angiogram because of the recurrent angina with electrocardiographic changes. The angiogram did not demonstrate in-stent stenosis or other coronary stenosis (Fig. 1A). Coronary artery spasm was considered a strong possibility because of these symptoms and the electrocardiographic changes, and an ergonovine provocative test was therefore attempted after routine coronary angiography. An initial dose of 10 μg ergonovine maleate solution was injected into the right coronary artery and subsequent injections of 20 μg were repeated every 3 min, until evident spasm occurred or the total dose of ergonovine reached 50 μg [2]. Following administration of ergonovine with a total dose of 50 μg, the patient complained of chest pain and coronary angiography demonstrated severe spasm with 99% stenosis over the whole right coronary artery except the stented segment (Fig. 1B). Immediately after, 2.5 mg isosorbide dinitrate was injected into the right coronary artery; the spasm was relieved and the symptoms also disappeared (Fig. 1C). The left coronary artery did not develop spasm after the ergonovine provocative test on the right coronary artery. Intravascular ultrasound (IVUS) of the right coronary artery was performed with auto-pullback at 0.5 mm/s. In the stented segment, there was no neointima within the stent. At the distal as well as proximal segment of the stent, diffuse mild concentric low echogenic plaque without calcification was observed (Fig. 2). Based on these findings, nitrate and calcium antagonists were administered. There was no recurrence of symptoms during follow-up. An exercise tolerance test and myocardial perfusion scintigraphy did not reveal ischemia. Repeat coronary angiography at 6 months follow-up failed to demonstrate restenosis at the stented segment and stenosis at other segments of the right coronary artery and left coronary artery.

3. Discussion

Chest pain after successful percutaneous coronary intervention constitutes a notable problem and may be potentially life threatening when myocardial ischemia occurs. Such pain suggests the presence of residual coronary stenosis, acute closure, coronary spasm or myocardial infarction. Management of each type of patient includes repeat coronary angiography and additional intervention. Coronary artery stenosis or acute closure can be clearly revealed by coronary angiography, whereas coronary spasm is difficult to demonstrate by routine angiography. Prolonged spasm is very dangerous, it might cause plaque rupture or/and prolonged coronary flow limitation and induce acute thrombus [3]. Coronary artery spasm can be diagnosed by the intracoronary administration of ergonovine as a selective provocative test [1,2,5,6].

Coronary artery spasm after stent implantation has rarely been reported. In the present case, although Holter ECG with chest pain revealed significant ischemic changes, coronary angiography did not show stenosis. Coronary artery spasm was considered to be the reason for the ischemic attack, and the ergonovine provocative test confirmed coronary artery spasm except in the stented segment. Previous researches have indicated that the frequency of coronary spasm is higher in Japanese than in Caucasians [1].

In a previous IVUS study, we found that coronary spasm is associated with the presence of moderate atherosclerosis without calcification [2]. In the present case, although there was no angiographic stenosis at the segment with spasm, IVUS demonstrated mild atherosclerotic plaque. This finding agrees with our previous IVUS results and other histological studies [2]. From our experience, non-calcified moderate eccentric plaque appears to be closely related to focal spasm, while generalized spasm as in the present case is associated with mild and diffuse concentric plaque. In the clinical setting, coronary spasm is most common in patients aged at around 50 years, and it decreases as age advances [7]. With older patients, coronary artery plaque calcification may reflect this situation. Some studies have shown that during the development of atherosclerosis, chemical mediators such as cytokines could be possible messengers for the induction of coronary spasm. Depressed production of nitric oxide appears to be another mechanism of spasm in the presence of atherosclerotic lesions [8]. Since non-calcified moderate atherosclerotic plaque seems to be closely related to the occurrence of coronary spasm, occult atherosclerotic lesions with documented vasospasm should be treated with nitrate and calcium antagonist. In about 5–30% patients, high doses of calcium antagonists and nitrates are not effective for the treatment of coronary spasm; adequate early stent implantation may prevent AMI [4,6]. Demonstration of non-calcified mild to moderate atherosclerotic plaque by IVUS may assist in determining the indications for treatment. Risk factors such as smoking and hypercholesterolemia should be strictly controlled when occult atherosclerosis is detected by IVUS [9]. Coronary spasm has been known to accelerate the progression of atherosclerosis, and preexisting atherosclerosis is one of the most important determinant factors of the long-term prognosis [4].

Although cases such as ours are rare, coronary artery spasm should be considered when chest symptoms recur after successful coronary interventions. Full-dose nitrate and calcium antagonists are necessary if the ergonovine provocative test is positive.

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GRAPHIC REPORT

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Multidetector computed tomography of a saphenous vein graft aneurysm

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Key words Multidetector computed tomography · Saphenous vein graft aneurysm

A 64-year-old man with a history of hypercholesterolemia, smoking, arteriosclerosis obliterans, and aortocoronary bypass grafting (CABG) presented with an enlarging right cardiophrenic angle mass found on routine chest X-ray (Fig. 1). At the time of his CABG 14 years earlier, the left internal mammary artery was used to graft the left anterior descending artery and the saphenous vein graft (SVG) was placed to the right coronary artery. He had a long-standing history of hypercholesterolemia. Multidetector computed tomography (MDCT) was performed using an Aquillion 16 (16-detector-row, Toshiba Medical, Tokyo, Japan). The scan protocol and image reconstruction method have been reported previously.[1–4] The reconstructed data were transferred to a computer workstation (M 900 quadra; AMIN, Tokyo, Japan) for processing of the surface volume rendering and multiplanar reformation images. The volume-rendering images (Fig. 2A,B) showed an aneurysm of the saphenous vein graft with a thick, low attenuation suggesting a thrombus. The native right coronary artery was totally occluded. The SVG–right coronary artery and left internal mammary artery–left descending artery grafts were patent. The multiplanar reformation image also showed a markedly dilated SVG (Fig. 2C). The short-axis image at the level of the maximum SVG dilatation (Fig. 2D) showed that the diameter of the SVG was 37 × 35 mm. The SVG aneurysm contained a thrombus and eccentric coronary artery lumen, and it compressed the right atrium. Conventional coronary angiography also demonstrated a tortuously dilated SVG graft but failed to show associated thrombus. With hesitation to carry out surgical treatment, the patient was maintained on oral anticoagulant therapy uneventfully.

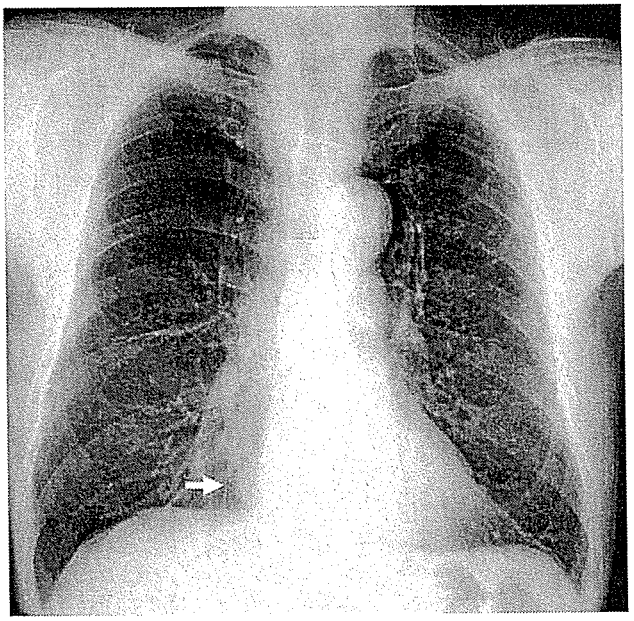

Fig. 1. Chest X-ray reveals a right cardiophrenic angle mass (*arrow*)

Saphenous vein graft aneurysm after CABG is a rare condition. There are approximately 70 cases reported in the literature. The mechanism of SVG aneurysm formation is uncertain, but it is frequently associated with atherosclerosis and hyperlipidemia.[5,6] Patients with SVG aneurysm are usually asymptomatic,[7] but are in a potentially fatal situation, since SVG aneurysms may develop myocardial ischemia due to occlusion and periodic emboli,[8] and rupture.[9] In asymptomatic patients, an abnormal mass detected on

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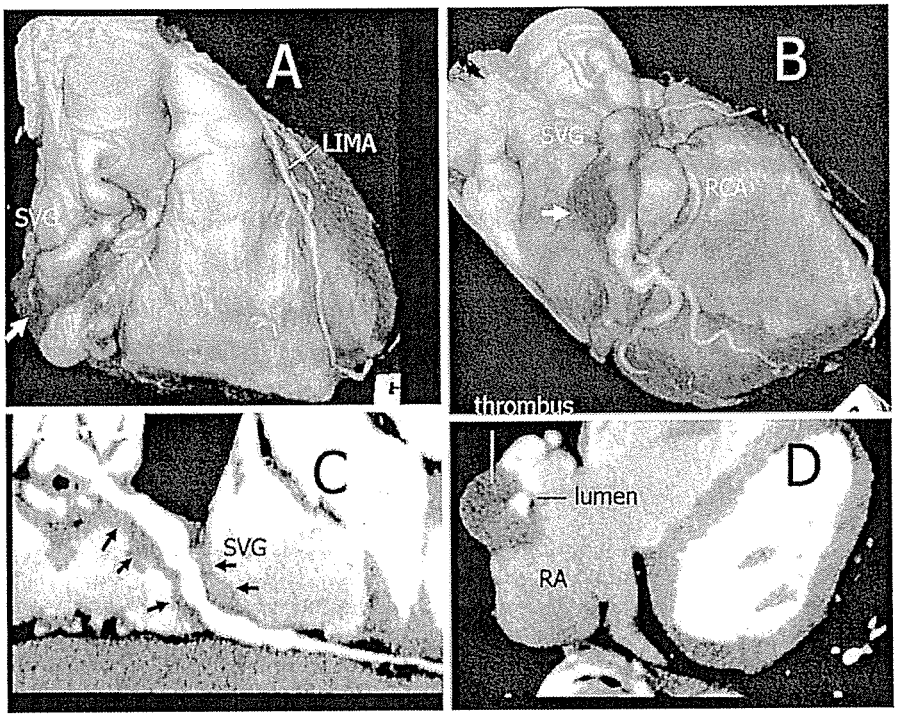

Fig. 2. **A** Right anterior oblique view of the volume-rendering image showing a tortuously dilated saphenous vein graft (*SVG*) with a low-attenuation mass suggesting a thrombus (*arrow*). The left internal mammary artery (*LIMA*) – left anterior descending artery (*LAD*) graft is patent. **B** Bottom view of the volume-rendering image shows a dilated SVG (*arrow*) and the patent SVG – right coronary artery (*RCA*). **C** Curved multiplanar reformation image illustrates a diffuse thrombus (*arrows*) along the RCA. **D** Axial image shows that the SVG aneurysm contains laminated thrombus and eccentric, contrast-filled lumen. *RA*, right atrium

chest X-ray usually leads to a further workup and correct diagnosis.[7] Echocardiography is capable of detecting large SVG aneurysms, but visualization of the whole SVG is not possible. With its high spatial resolution, MDCT can become the first choice of diagnostic modality because it permits the accurate measurement of the size of the aneurysm and the detection of thrombus. The long-term prognosis and treatment for asymptomatic patients with SVG aneurysms are uncertain since a large-scale clinical trial is unavailable because of the low incidence. However, in a small series of patients ($n = 11$), Dieter et al.[10] have reported no survival advantage with an early aggressive interventional approach. In conclusion, MDCT has the potential to be the standard diagnostic tool for the evaluation of SVG aneurysm after CABG.

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GRAPHIC REPORT

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Diagnosis of anomalous origin of the right coronary artery using multislice computed tomography: evaluation of possible causes of myocardial ischemia

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Abstract Anomalous origin of the right coronary artery (RCA) is a rare condition, but may cause myocardial ischemia and sudden death. Multislice computed tomography, which allows three-dimensional visualization of the coronary artery with high spatial resolution, may be the most promising imaging modality for diagnosing this anomaly. We describe a patient with anomalous origin of the RCA arising from the left sinus of Valsalva. Volume rendering, and axial and curved multiplanar images showed stenosis in the proximal portion of the RCA that coursed between the aorta and the pulmonary artery, and an acute angled take-off of the RCA from the aorta. Three-dimensional virtual angioscopic images showed a hypoplastic RCA orifice and luminal narrowing in the proximal portion of the RCA. Multislice computed tomography was thought to be useful for detecting anomalous origin of the RCA and for evaluating possible causes of myocardial ischemia.

Key words Multislice computed tomography · Anomalous origin of coronary artery · Virtual angioscopy

Introduction

Anomalous origin of the right coronary artery (RCA) from the left sinus of Valsalva is a rare congenital anomaly with an incidence ranging from 0.03% to 0.71%.[1–4] Nonfatal or fatal acute myocardial infarction[5] and sudden death[6] occur in such patients, most notably in young athletes.[7,8] We describe a patient in whom multislice computed tomography (MSCT) was useful for identifying anomalous origin of the RCA. Three-dimensional virtual coronary angioscopy showed a hypoplastic RCA orifice and narrowing of the proximal portion of the RCA, which coursed between the aorta and the pulmonary artery. These findings suggest possible causes of exercise-induced myocardial ischemia.

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Case report

A 71-year-old woman underwent MSCT coronary angiography because of oppression of the chest on effort. She had no previous history suggesting myocardial ischemia or coronary risk factors, such as hypercholesterolemia, diabetes mellitus, hypertension, or smoking. Exercise myocardial perfusion single-photon emission computed tomography (SPECT) using a rest ^{201}thallium/stress ^{99m}Tc-tetrofosmin dual-isotope, separate acquisition protocol revealed a reversible perfusion defect on the inferior myocardial segments. Multislice computed tomographic coronary angiography was performed using a Somatom Volume Zoom (4-detector-row; Siemens, Nuremberg, Germany) with a collimation of 1.0 mm; table feed, 1.5 mm/rotation; 140 kV; 320 mA; and gantry rotation time, 500 ms. Our scan protocol and image reconstruction method have been reported previously.[9–11] Metoprolol (40 mg) was given 90 min prior to the scan in order to reduce the heart rate to perform the single-phase algorithm. Following determination of the contrast transit time from the cubital vein to the ascending aorta by injection of 15 ml of nonionic contrast medium (Iomeron 350 100-ml syringe; Eisai, Tokyo, Japan), the remaining contrast medium (85 ml) was injected at a speed of 2.8 ml/s. Image reconstruction was made with a reconstruction window (250 ms) positioned immediately before the atrial contraction period, which could be recognized by the peak of the P wave on the monitor ECG. The reconstructed data were transferred to a computer workstation (3D Vir-

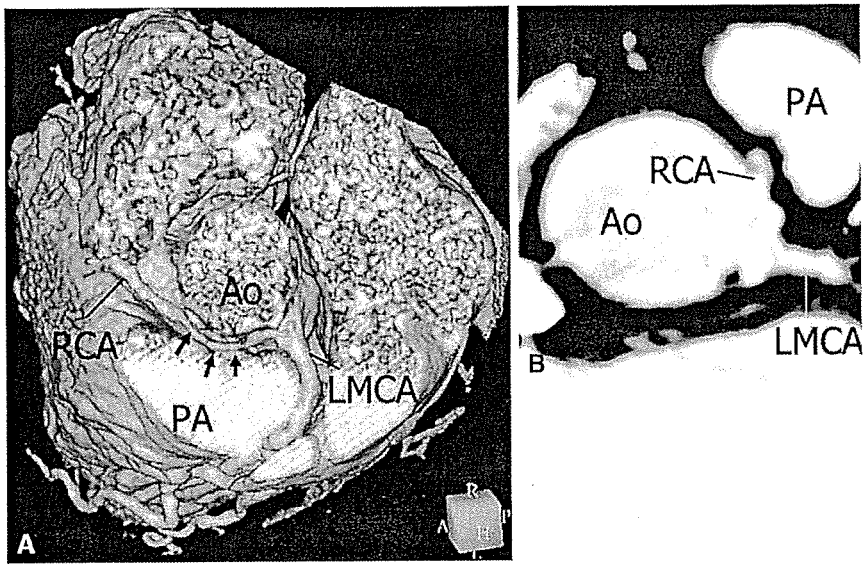

Fig. 1. **A** Volume-rendering image showing the anomalous origin of the right coronary artery (*RCA*), which arises from the left sinus of Valsalva, separately from the left main coronary artery (*LMCA*). **B** The proximal portion of the RCA is narrowed and courses between the aorta (*Ao*) and the pulmonary artery (*PA*)

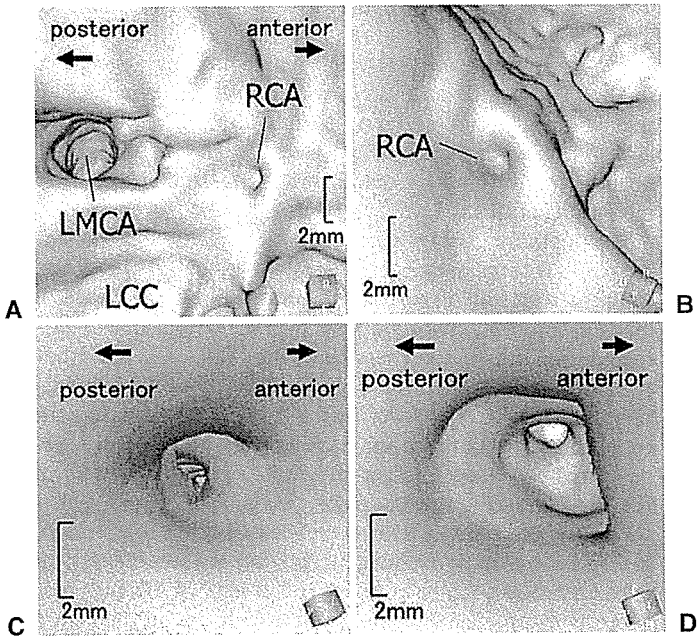

Fig. 2. **A** Three-dimensional virtual angioscopic image of the left sinus of Valsalva showing a small orifice of the right coronary artery (*RCA*) as compared to the orifice of the left main coronary artery (*LMCA*). *LCC*, left coronary cusp. **B** Magnified view of the RCA orifice. **C** The view into the distal side of the RCA showing the slit-like appearance of the RCA lumen. **D** The view from the portion distal to the stenotic lumen

tuoso; Siemens) to process surface volume-rendering, and curved multiplanar reformation images. The three-dimensional (3D) virtual coronary angioscopic images were created by another 3D workstation (Real Intage; KGT, Tokyo, Japan).

The volume-rendering image (Fig. 1A) showed that the RCA arose from the left sinus of Valsalva with an acute angle, and coursed anteriorly between the aortic root and the pulmonary artery to enter the right atrioventricular groove. The proximal portion of the RCA was significantly narrowed as compared to the distal portion. The axial image (Fig. 1B) showed an acute angled take-off of the RCA from the left sinus of Valsalva, separate from the left main coronary artery. Three-dimensional virtual angioscopic images (Fig. 2) demonstrated that both the left main coronary artery and the RCA arose separately from the left sinus of Valsalva (Fig. 2A). The orifice of the RCA was hypoplastic (Fig. 2B). The proximal portion (8–15 mm from the orifice) of the RCA was stenotic (Fig. 2C). Beyond this portion, the luminal size became normal (Fig. 2D).

The patient refused conventional coronary angiography and medical treatment with β-blocker was initiated. She became free from chest pain and the second myocardial perfusion SPECT under medication revealed a negative test result.

Discussion

Anomalous origin of the RCA is a rare condition, but it has clinical importance because nonfatal or fatal myocardial infarction and sudden death occur in up to 30% of the patients.[12] In the majority of patients, the RCA courses between the aortic root and the pulmonary artery[4] as documented in our patient. The causes of myocardial ischemia remain unclear, but the acute-angle take-off and kinking of the RCA as it arises from the aorta, the flap-like closure of the abnormal coronary orifice, compression of the RCA between the aorta and the pulmonary artery, and spasm of the anomalous RCA have been thought to be possible mechanisms.[6–8] In our patient, MSCT demonstrated a small RCA orifice, the acute angle take-off of the RCA from the aorta, and stenosis of the proximal RCA segment as it coursed between the aorta and the pulmonary artery. Three-dimensional virtual angioscopic images showed a small RCA orifice and narrowing of the proximal RCA segment which corresponded to the portion between the aorta and the pulmonary artery. The accuracy of 3D virtual angioscopy in detecting significant stenosis determined by intravascular ultrasound has been described previously.[13] Although these findings suggest possible causes of exercise-induced myocardial ischemia, our data could not clarify the exact mechanism of myocardial ischemia because MSCT images were obtained only in end-diastole, but not in systole during which compression of the RCA by the great vessels might have occurred. In addition, the flap-like texture of the RCA orifice might have been overlooked because the spatial resolution of MSCT was limited. Conventional coronary angiography, which is still a domain in the diagnosis of coronary artery anomalies, was not performed in our patient. However, identification of coronary artery anomalies is frequently difficult with conventional coronary angiography because of the lack of 3D information which relates the course of the RCA to the great vessels.[14] Magnetic resonance imaging is an alternative, noninvasive imaging modality that is capable of detecting coronary anomalies.[15,16] Future development of MSCT hardware should provide higher spatial resolution and allow motion analysis during the whole cardiac cycle, and would be more informative for the evaluation of the mechanisms by which myocardial ischemia is provoked in patients with anomalous origin of the RCA.

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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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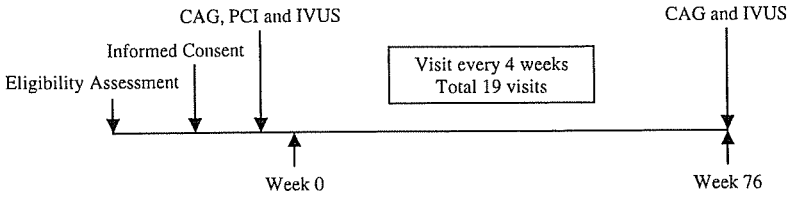

Fig 1. Flow chart showing the study timeline. CAG, coronary angiography; PCI, percutaneous coronary intervention; IVUS, intravascular ultrasound.

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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Steering Committee Tetsu Yamaguchi, Cardiovascular Center, Toranomon Hospital, Tokyo, Japan; Hiroyuki Daida, Department of Cardiology, Juntendo University School of Medicine, Tokyo, Japan.

Core Laboratory Satoshi Saito, Department of Advanced Medicine, Nihon University School of Medicine, Tokyo, Japan.

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-

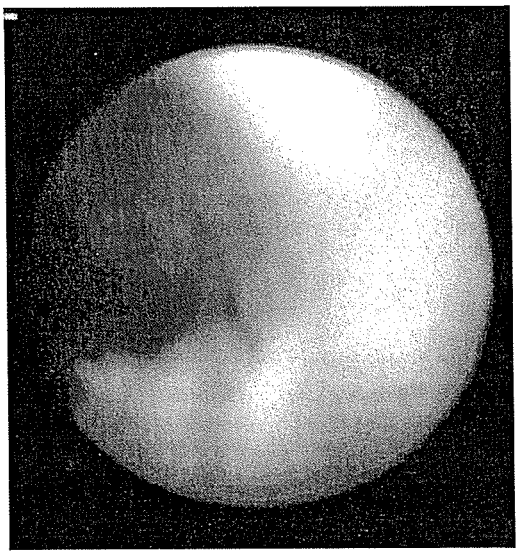

Fig 1. Atherosclerotic yellow plaque and thrombosis in a saphenous vein graft.

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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

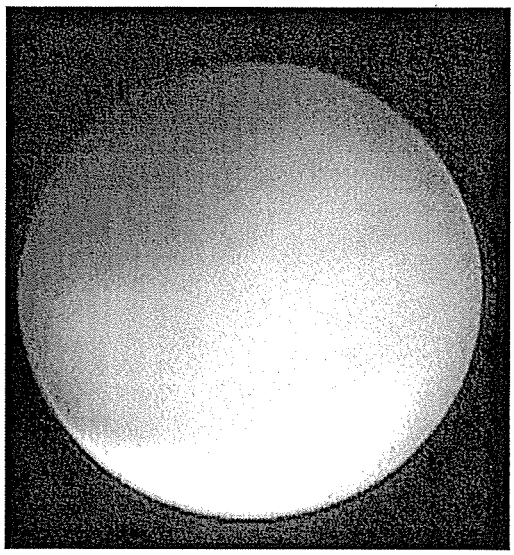

Fig 2. Normal white intima in a saphenous vein graft.

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.

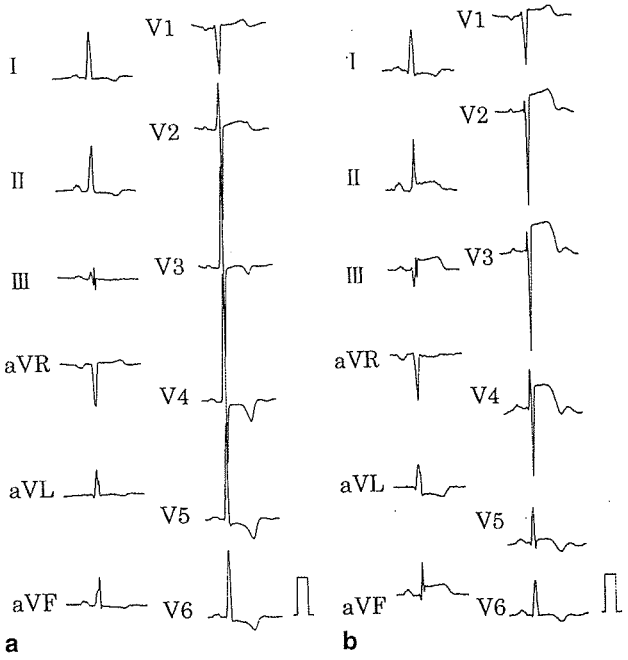

Fig. 1. Electrocardiograms of the patient. **a** The electrocardiogram on admission showed strain T waves in leads I, aV_L, and V_{4-6}. **b** ST segment elevation was observed in leads II, III, aV_F, and V_{1-5} at the onset of chest pain

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

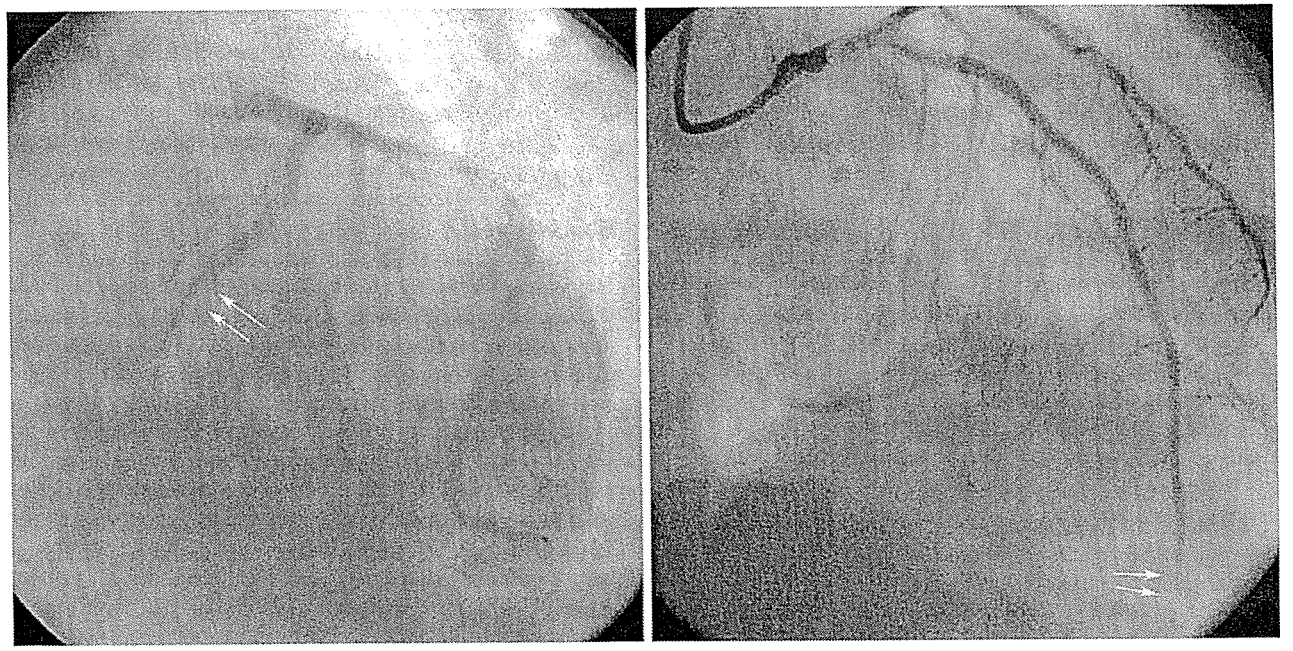

Fig. 2. **a** Coronary angiography showing an occlusion of the proximal left anterior descending coronary artery (*arrows*). **b** Coronary reperfusion was achieved in the left anterior descending artery, although a distal embolic occlusion was present (*arrows*)

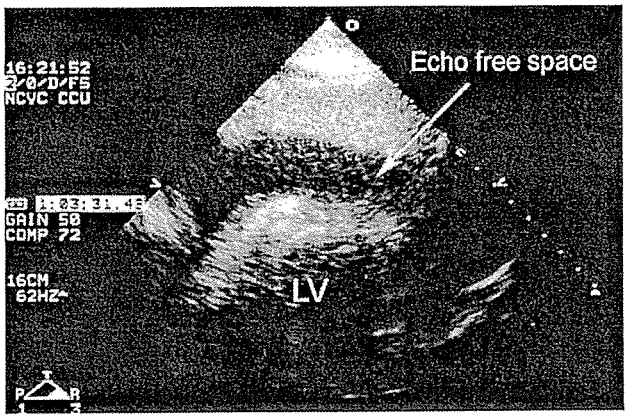

Fig. 3. Echocardiography showing pericardial effusion with findings of cardiac tamponade, indicating cardiac rupture (*arrows*). *LV*, left ventricle

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 mm Hg. 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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