Limited Role of Coronary Angioplasty and Stenting in Coronary Spastic Angina With Organic Stenosis

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**OBJECTIVES**
We investigated the efficacy of percutaneous coronary intervention (PCI) in patients with coronary spastic angina (CSA) and severe organic stenosis.

**BACKGROUND**
Coronary spasm occurs at the site of organic stenosis in most patients with CSA and severe stenosis, whereas multivessel spasm occurs frequently in those with normal coronary arteries. The incidence of multivessel spasm and the efficacy of PCI in patients with CSA and severe stenosis have not been fully elucidated.

**METHODS**
Forty-five patients with CSA and severe stenosis underwent spasm provocative testing with intracoronary acetylcholine before and 7 ± 3 months after PCI (20 patients had angioplasty and 25 patients had stenting), when all patients were free of restenosis.

**RESULTS**
Spasm was induced at the site of severe stenosis in 30 patients (66.7%) with and/or without spasm induced in another vessel. In the remaining 15 patients, spasm was induced at a different site in the stenotic vessel and/or in another vessel. Repeat provocative tests were performed in 43 of 45 patients. Although spasm was never induced at exactly the same site of the initial stenosis that had been dilated, spasm was induced at a different site in 28 (62.2%) of 45 patients on one or both provocations.

**CONCLUSIONS**
Spasm was frequently induced at a site different from the initial stenosis, even in the absence of restenosis after PCI. Calcium antagonists should be continued in most patients with CSA who show no restenosis after PCI. *(J Am Coll Cardiol 2002;39:1120–6) © 2002 by the American College of Cardiology Foundation*

The coronary anatomy in patients with coronary spastic angina (CSA) is variable, from angiographically normal coronary arteries to severe multivessel disease (1). However, when severe organic stenosis is present, spasm occurs at the site of organic stenosis in ~90% of cases (2). Therefore, elimination of severe stenosis by percutaneous coronary intervention (PCI) may be a useful treatment modality (3,4). Case reports have suggested that patients with medically refractory CSA and severe stenosis can be treated successfully with intracoronary stenting and calcium antagonist administration (4–6). However, multivessel coronary spasm occurs in many patients with CSA, especially in those with angiographically normal or nearly normal coronary arteries (7). The incidence of multivessel spasm in patients with CSA and severe organic stenosis remains to be determined.

We hypothesized that if coronary spasm occurs only at a site of severe organic stenosis, PCI may prevent spastic coronary occlusion. To determine whether coronary spasm occurs only at a site of severe organic stenosis or at different sites, we performed spasm provocative testing with intracoronary acetylcholine (ACh) before PCI in patients with CSA and a severe, obstructive lesion. We also performed repeat provocative testing at a time when there was no restenosis, to assess the inducibility of spasm in the absence of restenosis after PCI.

**METHODS**

**Patients.** For this study, the criteria for CSA were: 1) angina at rest, occurring predominantly from midnight to early morning; 2) pain relieved spontaneously or after the administration of sublingual nitroglycerin in <5 min; 3) ST-segment changes >0.1 mV, documented during pain and disappearing with relief of pain; 4) no subsequent evidence of myocardial infarction; or the provocation of these events with intracoronary ACh administration. Forty-five consecutive patients with CSA and severe organic stenosis (>70% lumen narrowing) who underwent PCI at Shibata Hospital between November 1995 and December 2000 comprised the study group of the present study (Table 1). All patients had rest angina, and 25 patients also had effort angina occurring mainly in the early morning. Thirty-nine (86.7%) of 45 patients were diagnosed as having variant angina, with documented ST-segment elevation associated with either spontaneous or provoked angina. Written, informed consent was acquired from each patient before the study, and ethical approval was obtained.

**Coronary arteriography (CAG) and intracoronary injection of ACh.** All vasodilator drugs, except nitroglycerin, were discontinued at least 48 h before CAG, which was performed using a percutaneous transfemoral approach. Control CAG images in the left and right anterior oblique projections were obtained. An electrode catheter was inserted into the right ventricular apex through the femoral vein and connected to a temporary pacemaker, with the pacing rate set at 40 to 50 beats/min.

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Acetylcholine chloride (Daichi Seiyaku, Tokyo, Japan) was dissolved in 0.9% saline, and incremental doses (50 and 100 \( \mu \)g) of ACh were injected into the left coronary artery over 20 s. The interval between each injection was >5 min. Left CAG was performed when either ST-segment changes or chest pain developed or 1.5 to 3 min after initiation of each injection. Acetylcholine in incremental doses of 20 and 50 \( \mu \)g was injected into the right coronary artery over 20 s, and right CAG was performed in the same way. If the induced coronary spasm did not resolve spontaneously within 5 min after the injection of ACh or if hemodynamic instability or intolerably severe symptoms occurred, isosorbide dinitrate (ISDN) (2.5 to 5 mg) was injected into the coronary artery. Arterial blood pressure and the 12-lead electrocardiogram (ECG) were continuously monitored during the study and recorded for 5 min after initiation of the intracoronary ACh injection. Coronary spasm was defined as total or subtotal occlusion (with delayed filling of the distal segment) associated with the onset of chest pain or ischemic ST-segment changes on the ECG, or both. At completion of the protocol, 2.5 to 5 mg of ISDN was injected into both coronary arteries, and CAG was performed in multiple projections.

The severity of coronary artery disease was assessed by the number of vessels with significant disease (>70% diameter stenosis after intracoronary ISDN administration). The significantly diseased segment was analyzed quantitatively, using an edge-detection system (Digital Cardiac Imaging, Phillips Medical System, Best, the Netherlands). A magnification factor based on the known size of the angiographic catheter was used for calibration.

Patients were medicated with calcium channel antagonists and antiplatelet agents immediately after completion of CAG.

**The PCI procedure.** Percutaneous coronary intervention was performed in the conventional manner through the femoral approach. Before the procedure, an intravenous bolus dose of 10,000 IU of heparin was injected, and 2.5 to 5 mg of ISDN was administered into the target coronary artery. Isosorbide dinitrate was also administered intravenously at a rate of 2.5 to 5.0 mg/h for ~24 h. If balloon angioplasty alone resulted in <30% residual stenosis by visual estimation, we judged this as an optimal result and finished the procedure. If optimal results were not obtained with balloon angioplasty alone, coronary stenting was performed to obtain adequate lumen diameter.

Quantitative CAG was performed before and immediately after PCI, and the minimal lumen diameter, reference diameter and percent diameter stenosis were determined. Acute occlusion (~24 h after PCI) and subacute occlusion (>24 h after PCI) were defined as total or subtotal occlusion of the target vessels.

All patients continued to receive adequate doses of calcium channel antagonists and antiplatelet drugs after PCI.

**Follow-up CAG and provocative testing.** Follow-up CAG and spasm provocative testing were performed approximately six months after PCI, similar to the way at the initial examination. If there was evidence of exercise-induced myocardial ischemia (demonstrated by ECG and/or myocardial scintigraphy) due to restenosis (defined as ≥50% diameter stenosis), repeat PCI was performed. Follow-up CAG and spasm provocative testing were performed again approximately six months after the repeat PCI. The last test, when restenosis was not present at the site of PCI, was used to assess the inducibility of coronary spasm after PCI.

**RESULTS**

Spasm provocation before PCI. Coronary spasm was induced at the site of severe organic stenosis in 30 (66.7%) of 45 patients (95% confidence interval [CI] 52.9% to
80.5% (Fig. 1A). Of these 30 patients, the induced spasm was limited to the site of the severe organic stenosis in 18 patients, but it was also induced in another vessel in 12 patients. Coronary spasm was not induced at the site of severe organic stenosis in 15 of 45 patients (Fig. 1B). Spasm occurred at a site different from the severe stenosis in the same vessel in 11 patients (proximal to the stenosis in 2 patients; distal in 9 patients) with (n = 6) or without (n = 5) spasm induced in another vessel, and spasm was limited to another vessel in 4 patients.

**Results of PCI.** Percutaneous coronary intervention was successful in all patients (Table 1). Twenty patients were treated with balloon angioplasty alone, and the remaining 25 patients were treated with intracoronary stenting. Coronary spasm did not occur during the procedure, and neither acute nor subacute occlusion was recognized in any patient. **Clinical follow-up.** All patients took calcium channel antagonists as prescribed. Anginal attacks, including both rest and effort angina, were completely suppressed in all but one patient during follow-up. This patient experienced recurrent
Follow-up CAG and spasm provocation. One patient with multivessel coronary artery spasm before PCI refused follow-up CAG, but had no scintigraphic evidence of myocardial ischemia six months after PCI. Another patient who had simultaneous left anterior descending and circumflex coronary artery spasm, as well as subsequent profound hypotension during spasm provocation before PCI, refused further provocative testing at follow-up. Five patients, including one patient with symptomatic recurrence, showed restenosis at the site of PCI and underwent a second PCI. One patient from this group had a second restenosis and underwent a third PCI.

Coronary artery spasm provocation with intracoronary ACh was performed in 43 patients at 7 ± 3 months after the first provocative test, at a time when all patients were free of restenosis. Although coronary spasm was never induced at exactly the same site of the initial stenosis that had been dilated (Fig. 1), spasm was induced at a site different from the initial stenosis in the dilated vessel in 30 patients with (n = 23) or without (n = 7) spasm induced in another vessel, and it was induced only in another vessel in 3 patients. Coronary spasm was not induced in any vessel in 10 patients (22.2%; 95% CI 10.1% to 34.3%).

Figure 1A shows the results of follow-up provocative testing in 30 patients with spasm superimposed on the severe organic stenosis before PCI. Coronary spasm was induced at a site different from the initial stenosis in the dilated vessel in 18 (60%) of 30 patients (95% CI 42.5% to 77.5%) with spasm superimposed on the severe organic stenosis before PCI. Of the 18 patients with spasm initially limited to severe organic stenosis without another vessel spasm, spasm was not induced in any vessel in 9 patients and was induced at a site different from the initial stenosis in the dilated vessel in the remaining 9 patients. Of the 12 patients with spasm induced both at the site of severe organic stenosis and in another vessel before PCI, spasm was induced at a site different from the initial stenosis in the dilated vessel in 9 patients. Figure 1B shows the results of follow-up provocative testing in 15 patients without spasm superimposed on the severe organic stenosis before PCI. Spasm was induced at a site different from the initial stenosis in all patients of this group.

Coronary spasm was not induced in any vessel in 5 of 20 patients treated with balloon angioplasty alone (Fig. 2A) or in 5 of 25 patients treated with coronary artery stenting (Fig. 2B). Although a mild coronary vasoconstrictor response was recognized, coronary spasm was never induced at the site of the initial stenosis that had been dilated by balloon angioplasty alone. Coronary vasoconstriction was completely suppressed, and coronary spasm was never induced at the site of the initial stenosis that had been dilated by coronary artery stenting. However, coronary spasm was induced at the edge of the implanted stent in 7 (28%) of 25 patients (95% CI 10.4% to 45.6%) (Fig. 3). Spasm was induced at the distal edge in four patients and at the distal and the proximal edges in three patients.

Multivessel spasm occurred on one or both spasm provocative tests in 28 (62.2%) of 45 patients (95% CI 48.0% to 76.4%) with CSA and severe stenosis.

DISCUSSION

Although coronary spasm is most commonly induced at the site of severe organic stenosis before PCI and never induced at the dilated site on the follow-up test, when there is no restenosis after PCI, coronary spasm is induced at a site different from the initial stenosis in the dilated vessel and/or in another vessel in most patients at follow-up. Multivessel spasm occurs frequently, even in patients with CSA and severe stenosis.

Spasm provocation with intracoronary ACh in patients with CSA and significant stenosis. MacAlpin (2) reported that coronary spasm occurs at a site of preexisting organic stenosis in almost 90% of patients with CSA. Other reports have also shown that most coronary spasms are superimposed on fixed, severe atherosclerotic narrowing (8,9). These studies used intravenous ergonovine to provoke coronary spasm (8,9). Once the spasm was induced in one coronary artery, the test was terminated, because nitroglycerin was administered to relieve the coronary spasm (10,11). Thus, the response of the other coronary artery to higher doses of ergonovine could not be examined. In patients with CSA and severe organic stenosis, coronary spasm was induced at the site of severe stenosis, using a relatively low dose of ergonovine (3). Therefore, multivessel coronary spasm was rarely recognized during provocative testing, using ergonovine maleate in patients with CSA and severe, obstructive lesions.

Intracoronary injections of ACh have been used for provocation of coronary spasm (7,12,13). The sensitivity and reliability of ACh are as high as those of ergonovine (13). The action of ACh is remarkably short, and the spasm usually resolves spontaneously within 2 to 3 min in most patients, without administration of nitroglycerin. Thus, it is possible to examine the effect of ACh on the contralateral artery (7,13). By this method, multivessel coronary artery spasm can be recognized in many patients with CSA, especially in those with angiographically normal or nearly normal coronary arteries (7). However, no systematic studies have reported the incidence of multivessel coronary spasm in patients with CSA and severe organic stenosis. We found that spasm was most commonly induced at the site of severe organic stenosis, but more than half of the patients had multivessel coronary spasm, even in the presence of severe organic stenosis. Multivessel coronary spasm is not a rare phenomenon; it can occur or be induced in many patients with CSA who have coexistent severe coronary stenosis.
Provocation of coronary spasm after coronary angioplasty or stenting. The results of PCI for patients with CSA and severe organic stenosis have been shown to be less satisfactory than those for patients with fixed organic stenosis (3,8,14). Patients in whom calcium channel antagonists were discontinued soon after PCI have an exceedingly high rate of restenosis, and continued spasm is associated with restenosis (3,8). Furthermore, patients with restenosis have
coronary spasm superimposed on restenosis (8,9). Bertrand et al. (8) have shown that coronary spasm can be induced at the restenosis site in 81.5% of patients with CSA.

We performed a spasm provocative test at a time when follow-up angiography showed no evidence of restenosis, to determine whether dilation of severe stenosis and no subsequent restenosis prevent spastic occlusion of the dilated vessel. The results revealed that not only were the vasoconstrictor response and spasm mechanically suppressed at the site of the initial stenosis that had been dilated by intracoronary stenting, but also that coronary spasm was suppressed at the site of the initial stenosis that had been dilated by balloon angioplasty alone. However, only 10 (22.2%) of 45 patients had no evidence of coronary spasm at follow-up provocation, even in the absence of restenosis. Spasm was induced at the different site in the dilated vessel in 70% of patients and in another vessel in 60% of patients.

Of the 30 patients with spasm superimposed on the severe organic stenosis before PCI, 18 patients (60%) showed spasm induced at a site distal to the dilated lesion. The possibility of multifocal spasm in the same vessel, which could not be recognized when the spasm occurred at a proximal stenosis, should be considered even when the spasm was limited to severe organic stenosis before PCI. Interestingly, spasm occurred at the edge of the implanted stent in 28% of patients treated with intracoronary stenting. A diffuse disorder in coronary artery vasomotility is recognized in Japanese patients with CSA (15,16). Coronary stents may trigger the vasospasticity of the vessel at the edge of the stent when a diffuse disorder of coronary artery vasomotility is present.

Heterogeneity of coronary artery spasm. Coronary spastic angina with coexistent organic stenosis probably includes two apparently distinct types. One type is a "localized" vasomotility disorder, including typical Prinzmetal’s variant angina, which results from a temporary occlusion of a large diseased artery due to normal increases in vascular wall tone (as suggested by Prinzmetal) or due to abnormally increased vasospasticity in the severely stenotic lesion (17–20). This type of CSA may be common in American and European
patients, most of whom have severe organic stenosis, in contrast to most Japanese patients, who have nearly normal coronary arteries (1,2,7,17–19). Bertrand et al. (9) showed that coronary spasm was induced in only 16 (26.6%) of 60 patients who were free of restenosis after PCI. Corcos et al. (3) also demonstrated that coronary spasm was not induced in most patients with CSA, in the absence of restenosis after PCI. These results differ from the present findings that spasm was not inducible in only 22.2% of patients who were free of restenosis after PCI. Most of the patients included in these studies appear to have typical Prinzmetal’s variant angina, with spasm occurring only at the site of severe stenosis. Therefore, PCI would probably be more effective in treating CSA with severe organic stenosis in American and European patients, as compared with Japanese patients.

The other type is coronary spasm in which a diffuse, not localized, disorder in vasomotility is involved, even in the presence of organic severe stenosis. This type is commonly found in Japanese patients with CSA and normal or nearly normal coronary arteries (15,16), and most of these patients show multivessel spasm (7). Our study revealed that most coronary spasms were not the “localized” type, even in the presence of severe atherosclerotic coronary stenosis in Japanese patients. This type of CSA is never cured by elimination of the coexistent severe organic stenosis using PCI.

**Study limitations.** Spasm provocation with intracoronary ACh was highly sensitive, but failed to induce coronary spasm in some patients with very low disease activity (13). In the present study, spasm induced in nondilated vessels before PCI became negative at follow-up in four patients. These findings may be due to markedly reduced disease activity, because coronary spasm was completely suppressed by calcium channel antagonists during the follow-up period after PCI. A time-related decrease in inducibility of spasm has been recognized, even after the interruption of calcium channel antagonists (21). Therefore, spasm not induced at follow-up does not necessarily indicate a cure of CSA. The provocation rate of coronary spasm would have been underestimated at the time of follow-up.

**Clinical implications.** Coronary spasm was never induced at exactly the same site of the initial severe stenosis that had been dilated in the absence of subsequent restenosis, but it did occur at a different site in the dilated vessel and/or in another vessel after elimination of the organic stenosis in most patients. Calcium channel antagonists should be continued in most patients who underwent PCI for the treatment of CSA with severe stenosis, even in the absence of subsequent restenosis. Discontinuation of calcium channel antagonists should be limited to patients who have localized spasm superimposed on severe organic stenosis before PCI, with no subsequent restenosis after PCI and no inducible spasm at follow-up.

**REFERENCES**