Angiographic Demonstration of Spontaneous Diffuse Three Vessel Coronary Artery Spasm

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The spontaneous occurrence of diffuse three vessel coronary artery spasm was documented during routine coronary angiography in three patients with a history of variant angina. Quantitative angiographic analysis of 18 arterial segments demonstrated that the mean luminal diameter of 1.47 mm during spasm increased to 2.47 mm after the administration of nitroglycerin (p < 0.0001). The underlying coronary arteries were normal or near normal.

Although multivessel spasm has previously been considered to be uncommon and its spontaneous occurrence during angiography only rarely documented, these cases suggest that it may be more common than previously recognized. In addition to important diagnostic considerations, this phenomenon may have important implications regarding the pathophysiologic role of endothelium in coronary artery spasm.

Case Reports

Case 1

A 66 year old woman had been treated at the Mayo Clinic for 5 years for presumed variant angina. During this time she had undergone two coronary angiograms after recurrent episodes of chest pain. At the first angiogram, mild catheter tip-induced spasm of the proximal right coronary artery had been noted and ergonovine provocation was not attempted because of recurrent asystole after each coronary injection of contrast medium. An exercise stress test had been stopped at 3 min because of fatigue and chest pain without associated ST segment changes on the electrocardiogram (ECG). Findings on a second angiogram, performed years later, were normal; however, it is noteworthy that she was premedicated with both nitroglycerin and nifedipine. A clinical diagnosis of variant angina was made and she was maintained on treatment with a combination of isosorbide dinitrate, nifedipine and aspirin. Additional investigations included upper gastrointestinal endoscopy, which revealed mild duodenitis, and esophageal manometry and abdominal ultrasound examination, which yielded normal findings.

Angiographic findings. Chest pain, always relieved with nitroglycerin, continued intermittently for another 2 years until she was admitted on this occasion with severe prolonged chest pain that continued overnight in the coronary care unit. No ECG changes were noted during the pain. The following morning, having received no coronary vasodilators for at least 12 h, she was transferred directly to the catheterization laboratory where coronary angiography was performed during chest pain. Severe diffuse narrowing was noted of the entire coronary artery tree (Fig. 1A and B).
Figure 1. Case 1. Coronary angiogram during chest pain, demonstrating spontaneous diffuse vasoconstriction of the right coronary artery (A) and left coronary artery (B). After injection of intracoronary nitroglycerin, both the right (C) and left (D) coronary arteries appear normal. Each angiographic frame of the right coronary artery is shown from a left anterior oblique projection; the left coronary artery is shown from a cranial left anterior oblique projection.

Intracoronary nitroglycerin injected into the right and then left coronary arteries resulted in rapid relief of pain. Repeat coronary angiography revealed the arteries to be completely normal (Fig. 1C and D). The left ventricular end-diastolic pressure was then measured to be 24 mm Hg, after which a ventriculogram was performed revealing mild hypokinesia of the apical segment. The patient was later discharged on a regimen of verapamil, diltiazem and isosorbide dinitrate; 2 months after a further similar presentation to this hospital, she continues to experience mild symptoms of similar chest pain.

Case 2

A 54 year old man was referred to the Mayo Clinic for assessment of chest pain after presenting 7 months earlier to his local hospital with a 3 h episode of severe chest pain. An initial ECG revealed small Q waves in the inferior leads and incomplete right bundle branch block; precordial T wave inversion developed the following day although the serum creatine kinase level remained normal. Results of an exercise ECG and two-dimensional echocardiogram were apparently normal and treatment with diltiazem was begun.

The patient continued to experience similar chest pains
that had no relation to exertion, meals or posture and he was referred to this hospital. He had stopped smoking 8 years earlier. Results of physical examination and routine laboratory testing were normal. The ECG showed persistent small inferior Q waves with an incomplete right bundle branch block configuration.

**Angiographic findings.** Coronary angiography revealed a mildly dilated left ventricle with mild hypokinesia of the anterolateral, apical and apical septal segments. Selective coronary angiography was performed without prior nitrate administration and revealed diffuse narrowing of the entire right coronary artery, mid to distal left anterior descending artery and first and second obtuse marginal arteries. Angiographic injections were repeated after sublingual nifedipine and nitroglycerin administration and revealed normal coronary arteries. No ST segment changes were noted during the procedure. A diagnosis of spontaneous coronary artery spasm was made, and the patient was discharged on treatment with isosorbide dinitrate.

**Case 3**

A 50 year old man was referred to this institution because of probable coronary artery spasm. Eight months before this current admission, he had complained of episodes of exertional chest and arm pain that were relieved by nitroglycerin. Coronary angiography at another hospital revealed an 80% stenosis of the proximal left anterior descending artery, a 50% stenosis of the proximal left circumflex artery, a 60% stenosis of the first obtuse marginal artery and a 40% stenosis of the right coronary artery; all stenoses were focal, smooth and tubular. The patient completed 8 min of an exercise test (Bruce protocol) with no chest pain, but had I mm ST segment depression on a postexercise ECG. Concomitant thallium scintigrams revealed normal findings. Because treatment with atenolol, nifedipine and aspirin failed to control his symptoms, coronary angioplasty of the left anterior descending artery stenosis was planned. However, repeat angiography revealed only a 30% stenosis of this artery and no attempt at dilation was made. Despite continued medical treatment he continued to experience exertional and nocturnal chest pain and was referred to our hospital.

On presentation, the patient was noted to have a history of treated hypertension for 5 years. In addition to being overweight, he had a history of cigarette smoking; his father had died of coronary artery disease. Mild elevation of serum cholesterol (279 mg/dl) was detected on laboratory testing.

**Angiographic findings.** Coronary angiography was repeated without prior use of nitroglycerin although chest pain was present before angiography and became more severe during the procedure. The left ventricular pressure was 190/16-31 mm Hg. Ventriculography revealed moderate left ventricular hypertrophy and dilation, with mild to moderate hypokinesia of the anterolateral, apical septal and postero-
lateral segments and dyskinesia of the apical segment. Coronary angiography revealed severe diffuse spasm of all the coronary arteries. Both the spasm and the pain were relieved with sublingual nifedipine and nitroglycerin although residual 30% to 40% stenoses in the proximal left anterior descending, left circumflex and right coronary arteries were noted. No ST segment abnormalities were seen during the procedure. The patient was discharged with a diagnosis of spontaneous coronary artery spasm with advice to stop smoking and reduce weight. Atenolol administration was discontinued and isosorbide dinitrate and diltiazem were prescribed.

**Quantitative Coronary Angiographic Analysis**

All three coronary angiograms were subjected to quantitative analysis using a method described previously (3). Five to seven arterial segments were selected from each patient's angiogram, and luminal diameter and cross-sectional area were measured in each segment. A total of 18 segments were analyzed and, for each segment, paired analysis was made between the vasoconstricted and vasodilated states (after nitroglycerin) (Fig. 2). Statistical significance was determined by paired t tests (alpha = 0.05). To minimize errors in the comparison between these two states, the angiographer (A.L.) had attempted to use identical projection angles for each angiographic comparison.

The results of this analysis demonstrate that the mean luminal diameter increased significantly from 1.47 mm during vasospasm to 2.43 mm after nitroglycerin administration (p < 0.0001). Similarly, the mean luminal area increased from 1.91 to 4.90 mm² (p < 0.0001).

**Discussion**

To our knowledge, angiographic evidence of spontaneous and diffuse three vessel coronary spasm occurring simulta-
necessarily has been reported only once (1). In this early study by Maseri et al. (1) of 30 patients with coronary artery spasm, it appears that one patient with significant two vessel disease had diffuse spasm involving all three arteries, although it is not clear how severe the spasm was in the left coronary artery. We believe that our three patients represent the only other documented cases of spontaneous, diffuse spasm occurring simultaneously in all three coronary arteries.

In addition, we have demonstrated for the first time the response to nitroglycerin by means of quantitative angiography with a significant increase in luminal diameter and cross-sectional area. It is noteworthy that two patients had angiographically normal coronary arteries and the third had only minor luminal irregularities. Although Feldman et al. (4) described four patients with diffuse three vessel spasm, no distinction was made between spasm occurring spontaneously or after ergonovine administration. Diffuse three vessel spasm after ergonovine is also extremely rare and potentially fatal (5).

Coronary artery spasm during angiography. During coronary angiography, spasm may be provoked by ergonovine (6) or, less commonly, may occur spontaneously (2-9). In a large series from France (2), 24% of 165 patients with coronary artery spasm had spontaneous spasm that was focal and exclusive of catheter-induced spasm. Catheter-induced spasm, particularly of the right coronary artery (10), is well recognized and should not be considered spontaneous in origin.

Multivessel coronary spasm can be diagnosed indirectly with a combination of clinical and angiographic evidence (11-13), but angiographic evidence of spontaneous and simultaneous two or three vessel spasm has been distinctly uncommon with only three reported cases in English language journals (14-16), although a few cases have been described in European studies (2). However, in these cases, with the exception of one with diffuse spasm of a dominant left coronary artery (15), spasm was focal rather than the diffuse spasm seen in our patients.

The low incidence of spontaneous coronary spasm seen during coronary angiography may be partly explained by several factors. Potential spasm may be masked in some patients by administration of nitroglycerin or by the vasodilative effect of contrast medium administered after a ventriculogram before selective coronary angiography. The common nocturnal occurrence of variant angina and the reluctance of physicians, until recently, to perform angiography on patients during acute chest pain may also contribute to this low incidence. The lower prevalence of multivesSEL spasm would further contribute to its rarity during angiography.

The importance of administration of nitroglycerin to reverse any spasm, particularly intracoronary administration in cases of severe spasm, is emphasized. An important implication of our results is that ergonovine administration to patients with unrecognized multivessel spasm could be extremely hazardous with the risk of electromechanical dissociation and death (5,15). In a recent study (17) of selective intracoronary injection of acetylcholine in patients with variant angina, multivessel spasm was found in 76%, particularly those with normal or near normal coronary arteries, and it was suggested that intracoronary injection of acetylcholine may be a safer method than intravenous administration of ergonovine to document multivessel spasm.

Electrocardiographic abnormalities. The paucity of ECG changes in our patients deserves some comment. One possible explanation was the lack of 12 lead monitoring during angiography because it is usual in our laboratory to monitor only three leads. However, in Case 1, no ST segment changes were documented during a number of hospital admissions despite the opportunity to record 12 lead ECGs during pain. Although ST elevation is a very specific indicator of coronary spasm, it may be relatively insensitive (4,18). The absence of ECG changes in patients with diffuse multivessel spasm has been noted before and it was postulated that global ischemia may prevent the development of an electrical gradient between different myocardial regions (4).

Pathophysiologic implications. Current concepts of the mechanisms for coronary artery spasm have focused on a complex interplay among neurohumoral factors, platelet aggregation with release of vasoactive substances and endothelial injury at the site of spasm (19). Whereas it is not clear why these patients experienced diffuse rather than focal spasm, it seems apparent that the stimulus for spasm in these patients caused vasoconstriction along the entire coronary artery tree.

It seems unlikely that disrupted endothelium played a key role in these cases because one would have to speculate that the entire coronary tree had diffuse endothelial injury despite angiographically normal or near normal coronary arteries. However, this study did not attempt to elucidate the mechanisms of the spontaneous spasm, and the role of endotheli um in spasm remains to be defined.

Conclusions. Diffuse three vessel coronary artery spasm can develop spontaneously in patients with variant angina and may be unaccompanied by ECG changes. The close temporal association of these three cases suggests that this finding may be more common than previously suspected. The importance of studying these patients without prior medication with vasoactive drugs or prior ventriculography is emphasized as is the intracoronary administration of nitroglycerin to relieve severe coronary spasm.

References
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