Spasm of a Normal or Minimally Narrowed Coronary Artery in the Presence of Severe Fixed Stenoses of the Remaining Vessels: Clinical and Angiographic Observations

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SUMMARY Four patients with medically refractory unstable angina are presented. Each patient had ST-segment abnormalities during some episode of pain. Three patients had at least one episode of documented ST-segment elevation with their spontaneously occurring chest pain. One had recurrent ventricular tachycardia. Two patients had prior myocardial infarction. Angiography demonstrated localized left ventricular akinesis and a severe fixed stenosis in the coronary artery supplying the abnormal segment. There were severe, fixed lesions in two coronary arteries in two patients and in one vessel in two patients. After i.v. ergonovine maleate, coronary artery spasm was documented in a normal or minimally diseased coronary artery in each patient. In two patients, ergonovine-induced spasm not only occluded the vessel, but also markedly decreased retrograde filling of a vessel with severe, fixed narrowing. Each patient’s characteristic symptoms appeared with the ergonovine-induced spasm. Thus, ergonovine maleate can provoke spasm of a normal coronary artery, even in the presence of severe fixed stenoses of the remaining vessels. This observation may have an important role in the diagnosis and clinical management of patients with chest pain.

PATIENTS with stable angina occasionally experience symptomatic exacerbation. Their anginal pain occurs more frequently and can also appear at rest. This may represent worsening coronary artery disease, and if the angina is unresponsive to medical therapy, coronary angiography is considered. If severe, operable lesions are found, coronary bypass surgery is then considered.

We present four patients in whom this sequence occurred. However, most of their symptoms were apparently due to spasm of a normal or minimally diseased coronary artery. In our laboratory, coronary artery spasm was induced with ergonovine maleate using the following protocol: 0.05-mg doses are administered intravenously at 3-minute intervals until either chest pain or electrocardiographic abnormalities are noted or a total dose of 0.2 mg is given. Failure to identify the etiologic role of the coronary spasm would have led to inappropriate clinical decisions.

Case Reports

Case 1
A 59-year-old female had an inferior wall myocardial infarction in March 1977. Five months later she developed severe chest pain that required repeated hospitalizations. The pain was not always effort-related, and had a variable response to sublingual nitroglycerin. Cardiac catheterization revealed normal intracardiac pressures. The left ventricular angiogram showed an area of inferior wall akinesia and coronary angiography demonstrated total occlusion of the right coronary artery in its midportion. The remaining vessels were normal. Surgery was not recommended and her symptoms gradually diminished. She did well until her pain recurred in February 1979. It persisted despite increasing doses of propranolol, isosorbide dinitrate and nitroglycerin and frequently occurred at rest. The ECG revealed a normal sinus rhythm and an old inferior wall myocardial infarction. During some of the episodes of spontaneous pain, ST-segment depressions were noted in the anterior precordial leads. During one episode of spontaneous rest pain, transient ST-segment elevations were documented in leads V2–V6. Multiple episodes of ventricular arrhythmias were recorded during several other episodes of rest pain. A second catheterization was performed. The left ventricular end-diastolic pressure was slightly elevated. The left ventricular angiogram was unchanged. Coronary arteriography revealed a totally occluded right coronary artery that filled retrogradely through collaterals from the left. The left circumflex artery had become severely narrowed (75% reduction of luminal diameter). The left anterior descending coronary artery was normal (fig. 1A). Because of a history of rest pain, the possibility of coronary artery spasm was considered. Ergonovine maleate (total dose 0.2 mg) was given. Four minutes later the patient developed severe substernal pain. ST-segment elevations were noted on the ECG in the precordial leads. Another left coronary angiogram revealed severe spasm of the left anterior descending coronary artery (fig. 1B). The lesions in the left circumflex and right coronary arteries did not change. The right coronary artery was still seen to fill through collaterals from the left coronary artery. However, there was a marked decrease in opacification of the collaterals. Sublingual nitroglycerin relieved the chest pain and the spasm. ST-segment elevations returned to baseline.

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Received May 1, 1981; revision accepted June 24, 1981.
Circulation 65, No. 4, 1982.

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Case 2

A 65-year-old female was first admitted to the hospital in September 1977 with a chief complaint of crushing, substernal pain for several hours. Her ECG and chest film were normal. During her hospitalization, no evidence of acute myocardial infarction was noted. She was discharged and 3 days later she suddenly lost consciousness. She was resuscitated by her husband and during a second hospitalization, no infarction or arrhythmia was noted. However, just before discharge, she had severe chest pain with documented ST-segment elevations in leads II, II and aVF, followed by an episode of ventricular tachycardia and ventricular fibrillation requiring defibrillation. Sinus rhythm returned. New T-wave inversions were noted across the precordium.

There was no other evidence to suggest infarction. Ten days later, she had a sudden episode of sinus bradycardia with a nodal escape rhythm. She subsequently underwent cardiac catheterization. Right- and left-sided pressures were normal. The left ventricular angiogram showed a mildly hypokinetic left ventricle with a dyssynchronous area at the apex. Coronary angiography revealed a 60% narrowing of the diameter of the left anterior descending coronary artery. The left circumflex and right coronary arteries were normal. Because of her rest pain and recurrent ventricular arrhythmias, coronary artery spasm was considered. Ergonovine maleate (total dose 0.2 mg) was administered. Two minutes later, the patient complained of chest pain similar to that occurring just before her arrhythmias. The ECG revealed ST-segment elevations in leads II, III, and aVF, and ventricular tachycardia occurred. Arteriography revealed that the right coronary artery had become totally occluded. The distal vessel was not seen. The left anterior descending and left circumflex coronary arteries were unchanged. Sublingual nitroglycerin relieved the pain and the coronary spasm. Despite medical treatment, the patient continued to have crushing chest pain and many episodes of ventricular tachycardia requiring resuscitation. She underwent coronary bypass surgery in November 1977. Surgery included saphenous vein bypass grafting to the distal, normal right coronary artery as well as to the left anterior descending coronary artery. She did well after surgery and became completely asymptomatic.

In March 1978, she had another cardiac catheterization. Intracardiac pressures and cardiac index were again normal. The left ventricular angiogram was unchanged. Selective injection of the graft to the right coronary artery revealed a patent graft filling the right coronary artery. The native right coronary artery appeared free of disease. The graft to the left anterior descending coronary artery was also patent with good distal flow. Injection of the native right coronary artery was normal with some retrograde filling of the graft noted. Injection of the native left anterior descending coronary artery now showed 90% narrowing of the diameter of the proximal portion of the vessel.

After ergonovine maleate (total dose 0.2 mg), the patient experienced mild pressure in her throat. No electrocardiographic changes or arrhythmias were noted. Injection of the graft to the right coronary artery showed a patent graft; however, severe narrowing in the right coronary artery was noted in its first third and distally, just beyond the site of anastomosis. However, this time the entire vessel was opacified. Nitroglycerin was then given and the spasm relieved. Two years later, the patient continues to be asymptomatic.

Case 3

A 59-year-old female was well until January 1980, when she had an acute anterior wall myocardial infarction. One month later, she developed recurrent episodes of chest pain which radiated down both arms. The pain occurred at rest and was relieved with nitroglycerin. She was treated with nitroglycerin ointment, isosorbide dinitrate and propranolol without relief.

Her physical examination revealed a 1/6 systolic
murmur at the apex. The chest film was normal. The ECG revealed an anterior wall myocardial infarction.

Cardiac catheterization was performed. The right- and left-sided intracardiac pressures were normal. The cardiac index was minimally decreased. The left ventricular angiogram revealed a small apical aneurysm.

Selective coronary arteriography demonstrated that the left anterior descending coronary artery was totally occluded just distal to the origin of the first septal perforating artery. The distal vessel filled through collaterals from the right coronary artery (fig. 2A). The right coronary artery was mildly irregular. The left circumflex coronary artery was normal. Since the patient's angina occurred predominantly at rest, the possibility of coronary artery spasm was considered.

Ergonovine maleate (total dose 0.2 mg) was given. Two minutes later, the patient complained of her typical, severe chest pain. The ECG revealed marked ST-segment elevation in leads II, III, and aVF. Selective injection of the right coronary artery showed almost total occlusion due to spasm at two separate points in its middle third. Collaterals to the left coronary artery were no longer seen (fig. 2B). The left coronary artery itself was unchanged. Sublingual nitroglycerin relieved the spasm, the patient's pain subsided and her ECG returned to baseline. She was subsequently treated with nifedipine with marked improvement.

Case 4

This 37-year-old male first noted the onset of left arm pain associated with left axillary discomfort in 1978. These symptoms occurred both at rest and with strenuous activity and lasted from 5-15 minutes. In 1979, the patient was begun on long-acting nitrates and noted a decrease in the frequency of these episodes. A thallium stress test at that time revealed decreased radionuclide uptake in the anteroseptal region with exercise. In mid-1979, the patient noted an increase in the frequency of these attacks, five or six episodes per day, despite treatment with propranolol in increasing doses and long-acting nitrates. He was referred for cardiac catheterization. In the hospital, ST-segment elevations were documented in leads II, III and aVF during spontaneous rest pain. His medical history was remarkable for ulcerative colitis, rheumatoid arthritis and peptic ulcer disease. His cardiac risk factors included smoking, elevated triglycerides and mild hypertension.

The physical exam revealed a short, obese male with no other abnormal findings. The chest film and ECG were within normal limits. Cardiac catheterization revealed mildly elevated left and right ventricular end-diastolic pressures. The cardiac index was normal. The left ventricular angiogram demonstrated a severely hypokinetic anterolateral wall, a mildly hypokinetic inferior wall and a small area of apical dyskinesia. Coronary arteriography showed that the left anterior descending coronary artery was totally obstructed in its proximal portion. The distal two-thirds of the vessel were visualized via intercoronary collaterals from the left circumflex coronary artery. This portion of the left anterior descending coronary artery was of thin caliber but without any obstruction. The left circumflex coronary artery gave rise to a moderate-size first obtuse marginal branch, a small second obtuse marginal branch and a large third obtuse marginal branch. The second obtuse marginal branch was mildly diseased at its origin; the third obtuse marginal branch was severely obstructed in its proximal portion (80% reduction of luminal diameter). The right coronary artery was the dominant vessel. Aside from mild proximal irregularity, it was free of obstruction (fig. 3A). Several septal collaterals arose from it, but the left anterior descending coronary artery was not visualized.

In view of the history of frequent and cyclical rest pain, variant angina was considered as a possible cause of the pain. Ergonovine maleate (total dose 0.2 mg) was given. The patient developed chest pain and
arm discomfort approximately 3 minutes after the last dose of ergonovine maleate. The pain was identical to that of his previous episodes. Two millimeters of ST-segment elevation were noted in the inferior leads on ECG. A repeat left coronary angiogram showed severe spasm in the third obtuse marginal branch of the left circumflex coronary artery. A repeat right coronary angiogram revealed that the proximal right coronary artery was now severely narrowed. Intracoronary nitroglycerin was given in both the left and right coronary arteries (300 μg were injected into the left coronary artery and 200 μg into the right coronary artery). His pain persisted. Repeat arteriography showed that the right coronary artery had become totally obstructed in its proximal portion (fig. 3B). An additional 200 μg of nitroglycerin was injected into the right coronary and 1/150 grain of sublingual nitroglycerin was also given. The pain subsided, and restudy of the right coronary artery demonstrated relief of the proximal total occlusion. However, some spasm persisted. Another angiogram of the left coronary artery revealed that it had returned to its preergonovine appearance. The ST-segment abnormalities on the ECG returned to baseline. Several hours after the procedure, the patient again developed severe chest pain. The ECG demonstrated ST-segment elevation in the inferior leads. Morphine sulfate, sublingual nitroglycerin and sublingual isosorbide dinitrate were given. Both the pain and the electrocardiographic changes resolved. The patient was then placed on i.v. nitroglycerin with no further pain. Later that day, oral nifedipine was added. The next day, serum myocardial enzymes were elevated and serial electrocardiographic tracings confirmed an inferior wall myocardial infarction.

**Discussion**

Prinzmetal et al,1 first described the syndrome of variant angina more than 20 years ago. They attributed the chest pain and the electrocardiographic findings of ST-segment elevation to temporary, total occlusion of a large, diseased coronary artery. They suggested that an increase in the tone of the smooth muscle of the already narrowed vessel wall was the cause. They did not discount the fact that other vessels were diseased, but felt that they did not play a significant role in producing the clinical picture. In the next decade, cases of variant angina with normal coronary arteries were reported, calling for further study of this clinical syndrome.2–5

Ergonovine maleate was found to produce coronary artery spasm and has since been used as a provocative test to induce spasm.6–8 The clinical parameters of spasm, chest pain and ST-segment elevation, have been reproduced with the administration of ergonovine, and the presence of concomitant spasm has been angiographically confirmed.9,10 Patients have been shown to have spasm of normal coronary vessels with varying degrees of fixed obstruction.3,11–14 Spasm of a normal or minimally diseased vessel occurring together with severe fixed obstructions of the remaining one or two vessels, however, is less well documented. In this report we present four such cases.

Maseri et al,12 have reported evidence to support the coexistence of disease in just the pattern we have demonstrated in these four cases. They had 13 patients with ischemic changes characterized by ST-segment depression on the ECG observed during a stress test but in leads different from those showing ST-segment elevation at rest. This strongly suggested that the ischemic regions at rest and during exercise might not be the same.12

Haywood et al. described the presence of angina
secondary to myocardial ischemia occurring in different regions of the myocardium and resulting from different pathogenic mechanisms in the same patient.18

MacAlpin18 reported that 10% of patients with single-vessel organic disease had spasm in another vessel which had little or no organic disease and suggested that it may be incorrect to assume without further proof that spasm is occurring solely in the diseased vessel. However, he did not note, in his series of nine patients with spasm, the presence of spasm in normal coronary vessels when the remaining coronary arteries had fixed obstructions. He also questioned whether other authors' reports of "normal coronaries" were indeed correct.

We have provided angiographic evidence that spasm of normal or minimally diseased coronary vessels may be the cause of recurrent symptoms despite severe, fixed lesions in the other vessels and previous infarction in the distribution of the diseased vessels. With this in mind, strong consideration should be given to systematically trying to demonstrate such spasm in each patient despite finding fixed stenoses. The presence of these stenoses, while offering one explanation for angina, might draw attention from an alternative explanation, such as that noted in our patients.

The implications of this finding are likewise important when considering the indications for and results of coronary bypass surgery. Perhaps persistent angina after coronary bypass surgery represents spasm of a vessel that was normal or mildly narrowed. The possibility that coronary spasm may be responsible for some or all of a patient's symptoms could be overlooked when severe, fixed obstructions are noted at catheterization.17

Coronary artery bypass surgery for spasm of normal coronary arteries has usually not produced good results. Our patient number 3 was studied and bypassed in 1977. She had proved refractory to all medical therapy and was having recurrent, life-threatening arrhythmias. Our fortuitous result is not a recommendation for bypass surgery in these patients. A trial of calcium antagonists is warranted.

In two of our patients, spasm of the nonobstructed coronary artery appeared to jeopardize collateral circulation to a coronary vessel with a severe fixed obstruction. In case 3, there was no opacification of the collaterals. This finding could offer an alternative explanation for some of our patients' symptoms. Perhaps when a normal coronary artery that is supplying collaterals to a vessel with fixed obstructions suddenly goes into spasm, it acutely decreases flow to the vessels with fixed obstruction. Thus, spasm of a normal vessel may cause ischemia in the distribution of a coronary vessel with a fixed obstruction.

Some criticism might be directed at our documentation of spasm with ergonovine. Higgins et al.19 questioned how well provoking spasm with ergonovine approximates the spontaneous entity. Maseri et al.12 reported two cases in whom complete vessel occlusion was observed during a spontaneous attack, but only diffuse luminal reduction was noted when ergonovine was used. In a third patient, the reverse occurred. These differences may relate to the intensity of the vasospastic stimulus or perhaps to the actual timing of angiographic injection. However, in our patients, the symptoms induced by ergonovine closely matched those that occurred spontaneously.

Ergonovine maleate administration is not without potential severe complications, as suggested by our case 4. Buxton et al.18 reported five such cases with three subsequent deaths. Heupler proposed several guide lines to limit the risk of complication.19

All four cases serve to illustrate the coexistence of spasm and fixed lesions in patients with worsening symptoms and in two cases with prior infarction. However, unlike most previous reports, the spasm was distinctly limited to normal or minimally diseased coronary vessels. The clinical picture may often be confusing or the presence of fixed obstructions misleading. One might be tempted to attribute a patient's symptoms solely to the fixed lesions unless further study with ergonovine is undertaken. The failure to identify the role of coronary spasm in these patients would then result in potentially ineffective medical therapy and perhaps inappropriate coronary bypass surgery.20 It seems quite reasonable, then, to consider an ergonovine maleate protocol during cardiac catheterization when fixed coronary artery obstructions are observed, but do not explain the clinical picture or the electrocardiographic abnormalities.

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Spasm of a normal or minimally narrowed coronary artery in the presence of severe fixed stenoses of the remaining vessels: clinical and angiographic observations.

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Circulation. 1982;65:825-830
doi: 10.1161/01.CIR.65.4.825

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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