Syndrome of Coronary Artery Spasm of Normal Coronary Arteries. Clinical and Angiographic Features

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Abstract

To define the clinical and angiographic features of the syndrome of spasm of angiographically normal coronary arteries, 77 patients with spasm and fixed coronary stenosis equal to or greater than 50% (group A) were compared with 35 patients with spasm and normal or minimally diseased coronary arteries (group B).

Statistically significant differences between groups A and B were as follows: the incidence of rest angina (50.6% vs 85.7%; $p < 0.01$) and mixed angina (32.5% vs 5.7%; $p < 0.01$); the appearance of ST segment depression (53.3% vs 16%; $p < 0.01$) and no electrocardiographic changes during stress test (35.6% vs 76%; $p < 0.01$); and the tendency for arteriographically documented spasm to be focal (87.5% vs 71.4%; $p < 0.05$) and to affect only one vessel (76.6% vs 57.1%; $p < 0.05$). No differences were found between groups A and B in major coronary risk factors, history of previous myocardial infarction, electrocardiographic abnormalities at rest or during pain episodes, or arteries affected by spasm.

Thus, angina appearing exclusively at rest is the main clinical feature of spasm of normal coronary arteries. The electrocardiogram, whether at rest or during pain episodes, has no value for predicting the existence of underlying coronary lesions, whereas stress testing does. Spasm of normal arteries tends to be more diffuse than that superimposed on organic lesions and to affect more than one artery, suggesting different mechanisms in the genesis of both types of spasm.

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Introduction

Coronary artery spasm is a dynamic phenomenon that in certain cases leads to myocardial ischemia and constitutes an alternative to the classic concept of ischemia due to fixed atherosclerotic coronary obstructions.[1] Dynamic constriction and fixed coronary artery obstruction are separate and independent mechanisms, but often they act simultaneously, leading to myocardial ischemia.[2] It has been suggested that atherosclerotic lesions predispose to coronary spasm,[3] and there is also evidence to suggest that spasm could be one of the factors that favor the development of atherosclerotic plaques.[4]

From the point of view of anatomic localization, spasm can appear on a wide range of coronary lesions, varying from severe fixed preexisting lesions to angiographically normal coronary arteries.[5,6] With regard to this last situation, it has been postulated that the syndrome of coronary spasm superimposed on normal or nearly normal coronary arteries could be considered as a specific syndrome with its own clinical features.[7,8]

The present study deals with the clinical and angiographic findings that can differentiate the syndrome of spasm of normal coronary arteries from that superimposed on preexisting atherosclerotic lesions.

Methods

Patients

From 1325 selective coronary angiographic studies performed at our institution in two years, 112 patients were included in this study. The inclusion criteria were a history compatible with ischemic heart disease and the demonstration of ergonovine-induced or spontaneous (not catheter-induced) spasm during coronary arteriography. In most patients transient ischemic changes on the electrocardiogram during at least one spontaneous anginal attack could be documented as well.

The patients were classified into two groups. Group A included 77 patients with significant coronary artery lesions (fixed luminal narrowing in one or more coronary arteries equal to or more than 50%). Group B included 35 patients with normal or mildly diseased (less than 50% luminal narrowing) coronary arteries.

Clinical Manifestations

The presence of ischemic heart disease was documented by a history of angina pectoris and/or myocardial infarction. Angina pectoris was considered typical when a burning, squeezing, or pressing pain appeared in the midsubsternal area. Chest pain was considered atypical when it lacked these features. The classification into rest, exertional, or mixed angina was made according to the criteria of the Spanish Society of Cardiology.[9] Rest angina was defined by its appearance only at rest, with or without transient electrocardiographic alterations; exertional angina, as that elicited by exercise or other maneuvers that raise myocardial oxygen consumption; mixed angina was considered in those patients who had a recognizable threshold of exertion that they could never exceed without developing angina but who, in addition, had episodes of angina at rest or at levels of exertion that were usually quite well tolerated. A history of myocardial infarction was determined on the basis of prolonged substernal pain, rise in cardiac enzymes, and documented appearance of typical evolutionary ST-T changes or

preexisting Q waves on the electrocardiogram.

Study Protocol

Patients in whom it was not contraindicated performed a graded bicycle stress test. The exercise test terminated when the patient reported severe chest pain, when serious ventricular arrhythmias developed, or when the patient became exhausted. The test was considered negative when 85% or more than the maximal predicted heart rate was reached without significant ST segment changes. The criterion for a positive test was the documentation of ST segment depression of 0.1 mV or more in any lead.

Coronary angiography by the percutaneous femoral approach was performed within the first week after stress testing. In cases in which it was not contraindicated, ergonovine provocative testing for coronary spasm was performed according to the technique of Heupler et al.[10] Intracoronary nitroglycerin was injected at the first sign of an adverse effect or immediately after the demonstration of coronary spasm. The test was considered positive when a diffuse or focal narrowing of luminal diameter equal to or greater than 75% was documented in any coronary artery in comparison with the previous diameter of the same segment, with or without chest pain or electrocardiographic changes. The morphologic study of elicited coronary spasms was done according to the criteria of L'Abbate et al.[11]

Statistical Analysis

The chi-square test was used in order to determine individual p values, which were considered significant if equal to or less than 0.05.

Results

Clinical Manifestations

Group A included 74 men and 3 women, average age fifty-two years (range thirty-three to seventy-six); group B included 32 men and 3 women, average age fifty years (range twenty-eight to sixty-three) (Table I). The incidence of athrosclerosis risk factors was similar, except for the lower incidence of overt diabetes mellitus in group B. In group A there was a significantly lower incidence of rest angina than in group B, while mixed angina was significantly more frequent in group A than in group B.

Electrocardiographic Findings

It was possible to obtain an electrocardiogram during pain in 50 patients in group A and 16 in group B (Table II). Anterolateral ischemia during pain was found significantly more often in group A patients than in those in group B. The incidence of arrhythmias was low in both groups.

Forty-five patients in group A and 25 in group B underwent stress testing. Abnormal stress test results were found significantly more often in group A than in group B.

Catheterization Findings

In all patients but 9 the spasm was ergonovine-induced. There were more single-vessel spasms in group A than in group B. In the patients in group B, spasms tended to affect more vessels than in group A patients (1.6 vs 1.35 spasms/patient). Furthermore, from the morphologic point of view, spasms were more often focal in group A than in group B patients.

In both groups, spasms on the right coronary artery appeared more often in its midportion than in proximal or distal ones (33% vs 9% and 6% respectively; $p < 0.01$); left anterior

TABLE I
Clinical manifestations

Trait	Group A (n=77) n	Group A (n=77) %	Group B (n=35) n	Group B (n=35) %	P
Male sex	74	96.1	32	91.4	ns
Risk factors					
Blood cholesterol ≥ 2.5 g/L	11	14.3	3	8.6	ns
Diabetes mellitus	7	9.1	0	0	*
Hypertension (≥ 150/100)	22	28.6	5	14.3	ns
Smoking (≥ 20 cig/day)	28	36.4	16	45.7	ns
Other vasospastic phenomena					
Migraine or vascular headache	10	13	8	22.9	ns
Raynaud's phenomenon	3	3.8	1	2.9	ns
Type of angina pectoris					
Rest angina	39	50.6	30	85.7	**
Exertional angina	9	11.7	1	2.9	ns
Mixed angina	25	32.5	2	5.7	**
Atypical chest pain	0	0	1	2.9	ns
No angina (previous MI)	2	2.6	0	0	ns
Previous MI	26	33.8	6	17.1	ns

*=p < 0.05; **=p < 0.01; MI=myocardial infarction; ns=not significant.

TABLE II
Electrocardiographic findings

Trait	Group A (n=77) n	Group A (n=77) %	Group B (n=35) n	Group B (n=35) %	P
Rest ECG					
Normal	32	41.6	21	60	ns
MI	26	33.7	5	14.2	ns
ECG during pain	50	64.9	16	45.7	ns
ST segment elevation	28	56†	12	75†	ns
ST segment depression	14	28†	2	12.5†	ns
No alterations	5	10†	1	6.3†	ns
T wave changes	3	6†	1	6.3†	ns
Arrhythmias during pain					
SVA	3	6	1	6.3	ns
PVC	6	12	2	12.5	ns
VT	1	2	2	12.5	ns
VF	1	2	—	—	ns
Location of ST segment changes during pain					
Precordial leads	30	66.7	5	33.3	*
Inferior leads	12	26.6	7	46.7	ns
Both	3	6.7	3	20.0	ns
Stress testing	45	58.4	25	71.4	ns
ST segment elevation	5	11.1†	2	8†	ns
ST segment depression	24	53.3†	4	16†	**
No alterations	16	35.6†	19	76†	**

†=Percentage calculated over the number of patients in which these data were collected; *=p < 0.05; **=p < 0.01; MI=myocardial infarction; ns=not significant; SVA=supraventricular arrhythmias; PVC=premature ventricular complexes; VT=ventricular tachycardia; VF=ventricular fibrillation.

descending spasms were more frequent in the proximal portion than in the distal one (29% vs 15%; $p < 0.01$).

TABLE III
Catheterization findings

Finding	Group A (n=77)		Group B (n=35)		P
	n	%	n	%	
Significant atherosclerotic lesions	77	100	0	0	—
Single-vessel	42	54.5	—	—	—
Two-vessel	23	29.8	—	—	—
Three-vessel	12	15.7	—	—	—
Coronary spasm					
Total number of spasms	104	—	56	—	—
Spasms/patient	1.35	—	1.6	—	—
Focal	91	87.5	40	71.4	*
Diffuse	13	12.5	16	28.6	ns
Vessels affected per patient					
One-vessel	59	76.6	20	57.1	*
Two-vessel	9	11.7	9	25.7	ns
Three-vessel	9	11.7	6	17.1	ns
Arteries affected by spasm					
LAD	38	36.5	16	28.6	ns
RCA	31	29.8	23	41.1	ns
OM	18	17.3	8	14.3	ns
Cx	9	8.7	8	14.3	ns
D	4	3.8	1	1.7	ns
PDA	4	3.8	0	0	ns

*=$p < 0.05$; Cx=circumflex artery; D=diagonal artery; LAD=left anterior descending; ns=not significant; OM=obtuse margin artery; PDA=posterior descending artery; RCA=right coronary artery.

Discussion

Variant angina is not the only manifestation of vasospastic myocardial ischemia. At present we know that coronary spasm is a physiopathologic phenomenon with a wide spectrum of clinical presentations.[12] From an anatomic point of view, we can consider two types of spasm, that which is superimposed on significant underlying organic lesions and that which affects normal or minimally diseased coronary arteries.

This last variety, spasm of normal or nearly normal coronary arteries, has been recognized as a syndrome with its own clinical characteristics.[7,8] The difficulties in establishing its diagnosis and its possibility of producing sudden death or myocardial infarction are important and urgent reasons to define its clinical features in order to make an early diagnosis.[13]

General Characteristics

The frequency of this syndrome has not been precisely established. Our 35 cases from 1325 coronary angiography studies give an incidence of 2.6%. Higgins et al[14] reported a 0.3% incidence, whereas in a later paper by Bertrand et al[1] a 5% incidence was found. This increase is probably due to the routine use of provocative maneuvers during coronary angiography, because spasm rarely appears spontaneously during this procedure.[8]

There were no significant differences in age between patients with normal or diseased coronary arteries, and in both groups male sex was very predominant. This finding is in

accordance with several European studies,[12,15] but it seems that American authors find a higher percentage of coronary vasospasm in female patients.[16]

Heavy smoking was a prominent risk factor in patients in both groups, especially in those with normal coronary arteries. Even though the relationship between vasospasm and smoking has not yet been clearly stated,[17] a high incidence of heavy smokers among patients with spasm and normal coronary arteries has been reported by several authors.[15,18,19]

Clinical Manifestations

Rest angina was significantly more frequent in patients with normal coronary arteries than in those with diseased ones (85.7% vs 50.6%; $p < 0.01$), while in the former the incidence of exertional angina was low. On the other hand, patients with diseased arteries showed a higher incidence of mixed angina than those with normal coronary arteries did (32.5% vs 5.7%; $p < 0.01$). Thus, mixed angina strongly suggests the presence of severe underlying coronary lesions. This spectrum of manifestations of coronary vasospasm differs slightly from the findings of Heupler[8] and Sato et al,[19] while it is very similar to that obtained by Bertrand et al from a population similar to ours.[15]

Some authors have suggested that spasm of normal coronary arteries is a benign event, showing a low incidence of myocardial infarction and presenting short anginal episodes.[7] In our series, no significant differences were found between groups of patients in the incidence of myocardial infarction or in the severity and duration of anginal episodes.

Electrocardiographic Features

The resting electrocardiogram was usually normal in the two groups of patients, and no significant differences were found between the groups in the incidence of abnormal resting electrocardiograms.

During the pain episodes, ST segment elevation was the commonest electrocardiographic alteration, being significantly more often located in anterior leads in patients with spasm of diseased arteries, as has been reported previously.[20]

Abnormal results from stress tests were found in 64% of the patients with spasm of diseased arteries and only in 24% of those with spasm or normal coronary arteries. As could be expected, ST segment depression during exercise was significantly more frequent in patients with diseased arteries than in those with normal coronary arteries (53% vs 16%; $p < 0.01$). Furthermore, 4 of the 6 patients of the group with normal arteries who had abnormal stress test results showed ST segment depression. This finding, from our point of view, is one of the main limitations of stress testing in this particular group of patients. First, because stress testing results are normal in the great majority of these patients; and second because the specific alterations (ST segment elevation) are quite uncommon. Nevertheless an abnormal stress test result in a patient with spasm suggests that underlying lesions are present, but it does not reliably differentiate those with and without severe coronary obstructions.

Stress testing results reported in patients with coronary spasm are very heterogeneous. Some authors have found a high percentage of abnormal results and use the exercise test as a first-choice provocation maneuver.[21] The experience of, at least, an equally large group of authors is quite the opposite.[13] It appears to be well established that abnormal stress test results in patients with vasospasm are related to the degree of activity of the spastic disorder and not to the severity or location of coronary atherosclerotic lesions.[22]

Coronary Angiographic Features

In the patients with significant obstructive coronary lesions, spasm tended to be focal, ie, restricted to the underlying atherosclerotic plaque. Spasm of normal coronary arteries, on the other hand, showed a greater tendency to be diffuse, involving the entire length of the artery. Another distinctive feature of spasm of normal arteries, in our experience and that of others,[23] is its tendency to affect more than one vessel. In our group of patients with diseased arteries, spasm involved a single vessel in 76% of the cases, while in the group of those with normal arteries, a single vessel was affected in only 57% of the cases.

These anatomic differences between the groups would permit the postulation of different pathogenetic mechanisms for each type of spasm. So, the fact that spasm of diseased arteries tends to be focal and limited to the diseased portion of the artery probably indicates that local factors play a greater role than in those without coronary obstructions.

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