Acute Arterial Hypertension During Spontaneous Angina in Patients with Fixed Coronary Stenosis and Exertional Angina: An Associated Rather Than a Triggering Phenomenon

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SUMMARY **The role of systemic arterial hypertension as a possible trigger of myocardial ischemia during angina at rest was studied in 13 consecutive patients who also had a history of exertional angina. Significant (≥ 70%) stenosis of at least one major vessel was present in each of the 10 patients in whom coronary arteriography was carried out. After documentation of the electrocardiographic and arterial blood pressure changes during two or more episodes of resting angina, i.v. methoxamine was infused under continuous monitoring of the ECG, arterial blood pressure and pulmonary artery diastolic pressure. The heart rate was maintained either spontaneously or by atrial pacing to levels similar to those during angina at rest. Despite increases in arterial blood pressure and the double product (systolic blood pressure × heart rate) to levels higher than those during spontaneous angina in all patients, no chest pain or electrocardiographic changes occurred in nine patients. In the other four patients, however, angina supervened. Three of these four patients, but only one of the remaining nine, had a borderline or elevated pulmonary artery diastolic pressure at rest. We conclude that in a considerable number of patients with "nonvariant" resting angina, acute increases in arterial blood pressure during the spontaneous attacks are not likely to be the cause of myocardial ischemia. Nevertheless, in some of these patients, increases in resting pulmonary artery diastolic pressure may favor the development of ischemia during afterload augmentation.**

ANGINA AT REST commonly represents a culminating stage in patients with progressive exertional angina.[1-3] Contrary to variant angina,[4-6] where exertional symptoms are essentially absent,[7-10] the "nonvariant" form of resting angina is usually thought to relate to increases in myocardial oxygen needs when proportional increases in blood flow are prevented by fixed and critical coronary artery narrowings.[1, 3, 11, 12] These increased oxygen demands are believed to derive primarily from the sharp increases in arterial blood pressure that almost invariably accompany the spontaneous ischemic episodes.[1, 3, 10-20] The contention that these increases in blood pressure are the cause of resting ischemia has been questioned in studies where the onset of the arterial pressure rise and the onset of ischemic ECG changes have been shown to occur simultaneously.[13, 17, 19, 20] In this study, we investigated the role of the increases in blood pressure in the mechanism of nonvariant spontaneous angina by analyzing the clinical, electrocardiographic and hemodynamic effects of methoxamine-induced systemic hypertension.

Patients

The 13 consecutive patients in this study met the following criteria: history of typical exertional angina relieved either by rest or by nitroglycerin; history of typical angina at rest relieved spontaneously or by nitroglycerin and associated with acute and transient electrocardiographic changes; absence of valvular heart disease; absence of clinical signs of heart failure; presence of sinus rhythm and absence of bundle branch block, second- or third-degree atrioventricular block or frequent ectopic beats; and plasma creatine phosphokinase and glutamic oxaloacetic transaminase levels of less than twice the normal values. Patients with primarily nocturnal angina or effort angina only early in the morning were excluded.

There were 11 men and two women, ages 35–72 years (mean 55 years) (table 1). Eight patients had a history of systemic hypertension and four of them had electrocardiographic signs of left ventricular hypertrophy. Patients 2, 5 and 13 had evidence of an old inferior myocardial infarction. There were no deaths during the hospital course or during an average follow-up of 6 months.

Methods

During the methoxamine test, the pulmonary artery systolic and diastolic, pulmonary capillary wedge and right atrial pressures were measured using a #7F triple-lumen Swan-Ganz catheter introduced percutaneously into the subclavian or femoral vein. We measured blood pressure using a 2-inch, 18-gauge arterial line inserted percutaneously into the radial artery. A #6F USCI electrocatheter was placed percutaneously via the femoral vein into the right atrium for pacing. Both catheters, filled with a heparinized 5% dextrose solution, were connected to Hewlett-Packard 1280C pressure transducers and Hewlett-Packard pressure amplifiers. The pressures were recorded on a Hewlett-Packard 7754B strip-chart recorder. The zero reference was taken at the midchest level. The pressure values were taken by averaging measurements over two respiratory cycles. Cardiac output was

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TABLE 1. *Clinical and Angiographic Data*

Patient	Age (years)	Sex	History of hypertension	Episodes of angina	ECG changes with pain		Previous therapy	Coronary arteriogram (% stenosis)	Wall motion	Ejection fraction
					Type	Location				
1	49	M	No	4	ST↑ 12.0 mm*	I, aV_L V_1-V_6	Nifedipine 40 mg/day	LAD 75% Cfx 80%	Ap Dk Al Hk Dp Hk	0.50
2	65	F	Yes	3	T+	II, III aV_F	Propranolol 40 mg/day	—	—	—
3	66	M	No	15	ST↑ 1.0 mm	II, III aV_F	—	Cfx 85% RCA 100%	Ap Hk Dp Hk	0.55
4	60	M	Yes	4	ST↑ 7.0 mm	V_1-V_4	Nifedipine 40 mg/day	LAD 90%	Normal	0.70
5	56	M	Yes	3	ST↑ 1.0 mm	II, III aV_F	—	LM 75% LAD 85% RCA 75%	Ap Ak Al Hk Dp Hk	0.35
6	46	F	Yes	3	ST↑ 1.0 mm	V_1-V_3	Propranolol 80 mg/day	LAD 100%	Ap Ak Al Hk	0.40
7	46	M	No	4	ST↑ 6.0 mm	aV_L V_1-V_4	—	LAD 95%	Normal	0.65
8	59	M	No	6	ST↑ 5.0 mm	I, aV_L V_1-V_6	—	—	—	—
9	51	M	Yes	11	ST↓ 4.0 mm	I, II, aV_L V_2-V_6	Propranolol 240 mg/day Nifedipine 80 mg/day	LAD 95% Cfx 75% RCA 75%	Ap Hk Al Hk	0.60
10	60	M	Yes	7	ST↑ 2.0 mm	V_1-V_4	Propranolol 80 mg/day	LAD 95%	Normal	0.60
11	52	M	No	7	ST↑ 1.0 mm	III	Propranolol 40 mg/day	LAD 85% RCA 100%	Ap Ak Dp Hk	0.50
12	72	M	Yes	8	T+	V_1-V_4	Nifedipine 80 mg/day	—	—	—
13	35	M	Yes	5	ST↑ 1.0 mm	II, III aV_F	Propranolol 80 mg/day Nifedipine 80 mg/day	RCA 95%	Dp Ak Dl Ak	0.40

*Maximal ST-segment change.

Abbreviations: LAD = left anterior descending coronary artery; Cfx = left circumflex coronary artery; RCA = right coronary artery; LM = left main trunk; Ap = apical segment; Al = anterolateral segment; Dp = diaphragmatic segment; Pl = posterolateral segment; Dk = dyskinetic; Hk = hypokinetic; Ak = akinetic; ST↑ = ST-segment elevation; ST↓ = ST-segment depression; T+ = positive T wave.

measured in triplicate by the thermodilution method using an Edwards Laboratory 9510 cardiac output computer.

The derived hemodynamics were calculated from the measured variables as follows: cardiac index = cardiac output/body surface area (l/min/m²); stroke index = stroke volume/body surface area (ml/beat/m²); systemic vascular resistance = 80 (mean blood pressure − right atrial pressure)/cardiac output (dyn-sec-cm^{-5}). The double product (systolic blood pressure × heart rate) was used to estimate myocardial oxygen demands.

Protocol

On admission to the coronary care unit, all patients were placed on complete bed rest. One lead of the ECG was monitored continuously and displayed on an oscilloscope. The blood pressure was measured by cuff every 2–4 hours and also during and after chest pain. A 12-lead ECG was taken every 24 hours and during and after chest pain. Total plasma creatine phosphokinase and glutamic oxaloacetic transaminase were measured every 8 hours during the first 48 hours.

The methoxamine test was performed within 24 hours after one of the episodes of spontaneous angina whenever two or more episodes had already been documented in the coronary care unit. The test included the insertion of arterial and pulmonary artery catheters and an electrocatheter. After measurements of control values, an i.v. infusion of methoxamine was started at a rate of 2 mg/min. The administration of the drug was aimed to raise the systolic blood pressure to levels at least 10 mm Hg higher than the highest value measured during the previous spontaneous attacks, for a minimum of 5 minutes. The heart rate was maintained either spontaneously or by atrial pacing at rates similar to those during resting angina.

Continuous pressure and ECG recordings were obtained during the methoxamine administration. At the point of maximal increase in blood pressure and after measurement of cardiac output, the methoxamine in-

fusion was discontinued and shortly thereafter sublingual nitroglycerin was given to accelerate the return of blood pressure to control levels. A 12-lead ECG was taken during the control measurements, at the peak of the blood pressure elevation, and when blood pressure had returned to control values. Coronary arteriography and left ventriculography were performed in 10 patients within the next 30 days.

After admission, all patients received 5 mg of sublingual isosorbide dinitrate every 4 hours. Other medications used are listed in table 1. In most patients, all drugs except sublingual nitroglycerin were discontinued at least 12 hours before the methoxamine test.

Each patient gave informed consent before entering the study.

Results

Clinical Data

We analyzed an average of six episodes of resting angina per patient (table 1). All anginal episodes were short and readily relieved either spontaneously or by sublingual nitroglycerin. All patients experienced resting angina during waking hours and eight patients also had angina at night.

Electrocardiographic Changes

During pain, there was acute ST-segment elevation $\geq$ 1 mm in one or more leads in 10 patients and generalized ST-segment depression $\geq$ 1 mm in one patient. In the other two patients, the only ischemic changes during angina were positive T waves. In these two patients the T waves were flat before pain occurred. Reciprocal changes were usually seen in several leads during ST-segment elevation, and the degree of the ST-segment shifts frequently varied in the same patient throughout the different episodes of pain. The direct or primary ischemic changes were localized in the anteroseptal areas (leads V_1 to V_4) in six patients, in the anterolateral area (leads I, aV_L and V_1 to V_6) in two patients and in the inferior area (leads II, III and aV_F) in four patients. In patient 9, the ECG changes (ST-segment depression) were generalized. This patient had the most severe coronary arteriographic findings. Sinus rhythm was present in each patient during spontaneous angina.

Hemodynamics

Blood pressure was normal at rest in all patients. In four patients, systolic blood pressure occasionally increased to 160 mm Hg or more, and in two of them, diastolic pressure increased concurrently to 95 mm Hg or more. During resting angina, systolic and diastolic pressures always increased (table 2). The extent of these increases varied in individual patients and tended to become smaller during propranolol treatment. There were no appreciable changes in heart rate during pain in the majority of patients. Only in patients 7 and 11 did heart rate increase by more than 10 beats/min.

The double product increased during angina in every patient. The resting pulmonary artery diastolic pressure was normal in nine patients and moderately increased in the remaining four. Values for pulmonary artery diastolic pressure and pulmonary capillary wedge pressure were comparable in each patient.

Coronary Arteriography

All patients had a stenosis greater than 70% in at least one major vessel (table 1). The left anterior descending coronary artery was involved in eight patients, the right coronary artery in four and the left circumflex coronary artery in three. Eight patients had poor or nonexistent collateral vessels. No coronary spasms occurred during the angiographic study.

Methoxamine Test

The interval between the initiation of the test and the immediately preceding episode of spontaneous angina ranged from 3–24 hours (mean 14 hours). No anginal pain or ECG changes were elicited in nine patients during the methoxamine infusion, despite the marked increases in blood pressure (fig. 1) and double product, which were maintained for a minimum of 5 minutes (table 2, fig. 2). In two of the remaining four patients (nos. 6 and 12), the increases in blood pressure were associated with angina and electrocardiographic changes similar to those during the spontaneous episodes of pain. The other two patients (nos. 5 and 11) also developed angina during the increase in blood pressure, but the accompanying ECG changes differed from those during the spontaneous episodes; instead of ST-segment elevation and positive T waves in leads II, III and aV_F and ST-segment depression in leads V_4 to V_6 recorded during spontaneous pain, there was only ST-segment depression in leads V_4 to V_6 (fig. 3). Three of these four patients who experienced angina during the methoxamine test and only one of the remaining nine had a resting pulmonary artery diastolic pressure of 12 mm Hg or more. Patient 3, who did not present angina with the drug-induced hypertension, later developed pain and ischemic ECG changes when, in addition to the elevated blood pressure, the heart rate was increased by atrial pacing, by 20 beats/min over that during spontaneous angina (fig. 4). The ECG changes in this instance were again limited to ST-segment depression in leads V_5 to V_6, and the ST-segment elevation in the inferior leads noted during the spontaneous attacks was absent.

The increases in blood pressure by methoxamine were associated with important increases in pulmonary artery diastolic pressure in each patient. These changes were more pronounced during the occurrence of angina (table 2, figs. 5 and 6). The stroke index declined at the peak of blood pressure elevation in most patients. Patients 3, 11 and 12 had spontaneous angina during right-heart catheterization just before the beginning of the methoxamine infusion, and patient 1 developed atrial flutter at a heart rate of 140

TABLE 2. *Hemodynamic Data During Spontaneous Angina and During Infusion of Methoxamine*

Patient	SBP/DBP (mm Hg)	HR (beats/min)	SBP × HR × 10^{-2}	CI (l/min/m²)	SI (ml/beat/m²)	RAP (mm Hg)	PASP/ PADP (mm Hg)	SVR (dyn/sec/cm^{-5})
1 C1	130/90	65	84.5	—	—	—	—	—
A	145/95	74	107.3	—	—	—	—	—
C2	106/60	74	78.4	2.87	38.7	4	17/8	1027
Mtx	190/100	80	152.0	2.88	35.9	5	25/18	1802
2 C1	150/90	75	112.5	—	—	—	—	—
A	180/110	67	120.6	—	—	—	—	—
C2	130/70	64	83.2	1.55	24.2	4	24/11	2520
Mtx	230/120	70	161.0	1.48	21.2	4	28/15	4690
3 C1	115/90	75	86.2	—	—	—	—	—
A	160/120	72	115.2	—	—	—	—	—
C2	160/80	75	120.0	2.53	33.4	1	18/8	1900
Mtx	215/100	68	146.2	—	—	—	34/11	—
4 C1	125/90	84	105.0	—	—	—	—	—
A	170/110	84	142.8	—	—	—	—	—
C2	175/85	70	122.5	3.22	45.9	3	18/5	1644
Mtx	235/130	75	176.2	2.16	28.8	5	30/14	3243
5 C1	100/70	67	67.0	—	—	—	—	—
A	160/100	70	112.0	—	—	—	—	—
C2	120/65	75	90.0	1.89	25.2	5	26/12	1868
Mtx-A	180/100	75	135.0	1.62	21.6	8	48/26	3317
6 C1	125/75	56	70.0	—	—	—	—	—
A	215/130	75	161.2	—	—	—	—	—
C2	165/80	60	99.0	2.43	40.5	2	18/6	2034
Mtx-A	260/135	75	195.0	2.64	35.1	6	38/23	3054
7 C1	100/70	57	57.0	—	—	—	—	—
A	140/100	68	95.2	—	—	—	—	—
C2	130/65	73	94.9	3.81	52.2	2	22/8	925
Mtx	210/110	65	136.5	2.44	37.5	5	45/24	2310
8 C1	150/95	96	144.0	—	—	—	—	—
A	170/110	90	153.0	—	—	—	—	—
C2	140/95	100	140.0	2.67	26.7	2	18/10	1870
Mtx	190/120	94	178.6	2.37	25.2	3	25/16	2732
9 C1	110/80	62	68.2	—	—	—	—	—
A	150/110	60	90.0	—	—	—	—	—
C2	105/55	60	63.0	—	—	3	20/6	—
Mtx	165/90	56	92.4	—	—	4	28/9	—
10 C1	120/80	58	69.6	—	—	—	—	—
A	160/90	58	92.8	—	—	—	—	—
C2	160/80	72	115.2	1.94	26.9	4	24/10	2321
Mtx	220/100	53	116.6	1.58	29.9	5	36/16	3697
11 C1	140/75	75	105.0	—	—	—	—	—
A	190/120	95	180.5	—	—	—	—	—
C2	170/80	77	130.9	2.79	36.2	5	27/17	1409
Mtx-A	200/112	96	192.0	2.00	20.8	7	55/37	2546
12 C1	150/80	70	105.0	—	—	—	—	—
A	190/105	78	148.2	—	—	—	—	—
C2	140/65	75	105.0	3.36	44.8	8	30/18	1027
Mtx-A	195/95	86	167.7	3.71	43.1	10	55/34	1339
13 C1	140/100	90	126.0	—	—	—	—	—
A	170/110	98	166.6	—	—	—	—	—
C2	150/100	90	135.0	1.75	19.4	5	25/14	2719
Mtx	225/145	95	213.7	1.86	19.6	8	46/31	3744

Abbreviations: SBP = systolic arterial pressure; DBP = diastolic arterial pressure; HR = heart rate; CI = cardiac index; SI = stroke volume index; RAP = right atrial pressure; PASP = pulmonary artery systolic pressure; PADP = pulmonary artery diastolic pressure; SVR = systemic vascular resistance; C1 = measurements taken within 60 minutes before the spontaneous episode of angina with the highest increase in arterial pressure; A = measurements taken during the spontaneous episode of angina with the highest increase in arterial pressure; C2 = measurements taken before infusion of methoxamine; Mtx = measurements taken at the peak of arterial pressure elevation by methoxamine without angina; Mtx-A = with angina.

beats/min during positioning of the electrocatheter; the atrial flutter lasted 20 minutes and was not followed by pain or ECG changes. No complications were observed during the administration of methoxamine. In 10 patients, spontaneous angina recurred within the first 48 hours after the methoxamine test.

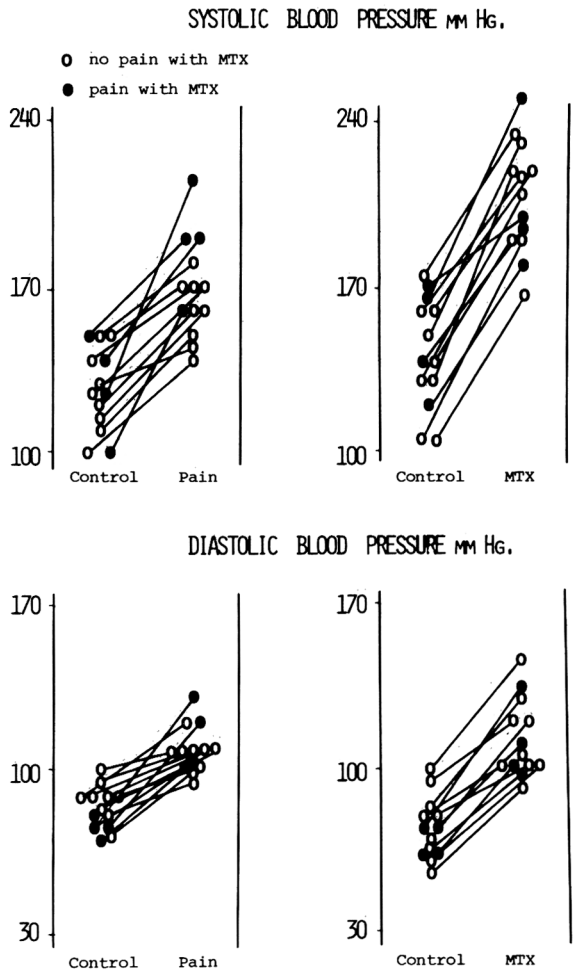

FIGURE 1. *Changes in systolic and diastolic blood pressure during spontaneous angina (left panels) and during the methoxamine (MTX) test (right panels). The higher increases in blood pressure during the drug administration than during spontaneous angina are apparent.*

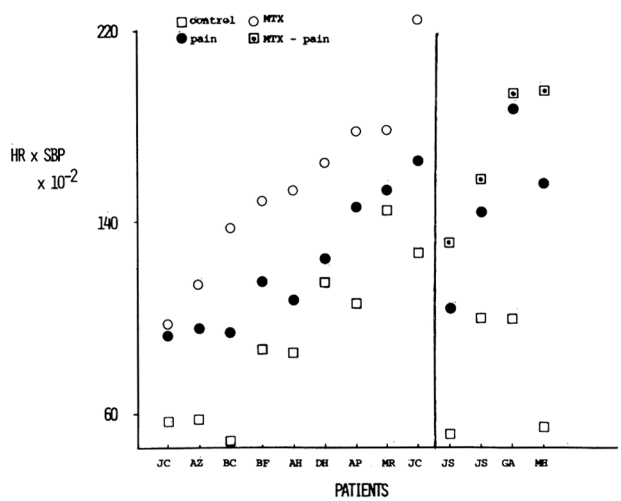

FIGURE 2. *Individual values for the double product (systolic blood pressure × heart rate [SBP × HR]) at rest (control), during spontaneous angina (pain) and at the peak of the blood pressure elevation with methoxamine (MTX). Patients were ordered according to the level of double product attained during the methoxamine test. Patients represented by symbols to the left of the vertical line did not have angina during the test; those to the right did have angina with methoxamine.*

Discussion

The occurrence of angina at rest in patients with an unequivocal history of exertional angina is usually associated with severe coronary artery disease[3, 4, 20-22] and acute ECG changes manifested as ST-segment depression or peaked positive or negative T waves.[1, 3] Elevation of the ST segment during pain has also been encountered in these circumstances,[1, 19, 20, 23, 24] although it is far more frequent in patients who present clinical features of variant angina, such as nocturnal pain with a circadian rhythm and lack of significant effort angina.[6-10, 25]

The incidence of ST-segment elevation during pain in our patients with nonvariant resting angina was higher than that reported by others.[1, 3] Most studies on this subject, however, fail to provide specific information regarding the type of ECG changes during resting angina,[13, 14, 16, 18] or limit their ECG recordings to one or two leads,[1, 3] possibly hampering the recognition of a substantial number of cases of ST-segment elevation because the reciprocal ECG changes (ST-segment depression) often involve a larger number of leads. Thus, recording a 12-lead

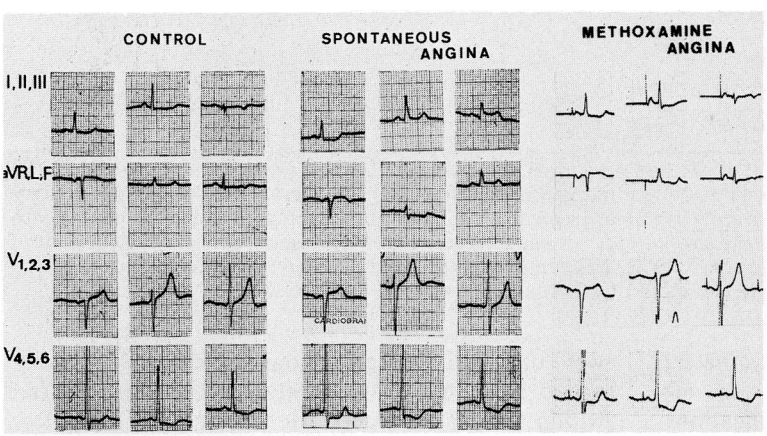

FIGURE 3. *ECGs taken at rest (left), during an episode of spontaneous angina (center) and during the methoxamine-induced angina (right). Note the presence of ST-segment elevation in the inferior leads during spontaneous angina and its absence during the methoxamine-induced angina.*

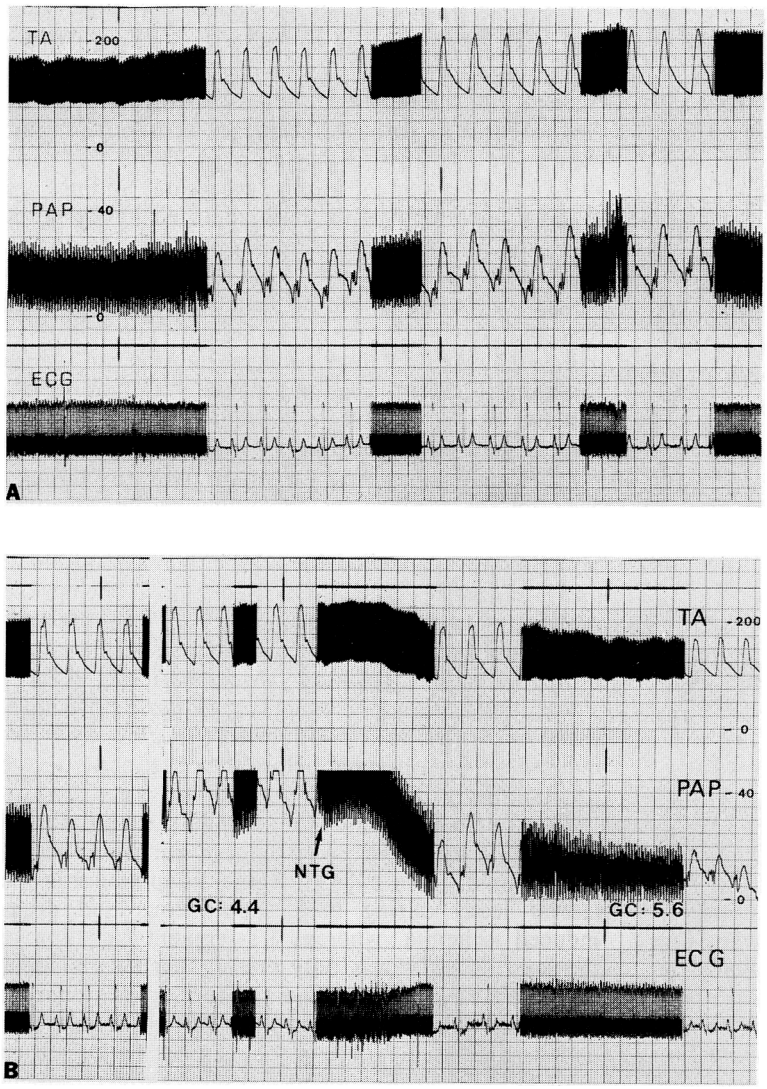

FIGURE 4. *Continuous recording of blood pressure, pulmonary artery pressure (PAP) and one lead of the ECG during the administration of methoxamine in patient 3. (A) The progressive increase in both pressures in the absence of pain. (B) The tracings obtained a few minutes later, when angina supervened after an increase in the heart rate by pacing. Because atrial pacing was immediately stopped upon onset of angina, pacing spikes do not appear in the figure, which only shows changes at the peak of pain. The ischemic ECG changes were only apparent in a simultaneous recording of a 12-lead ECG. Cardiac output was lower during angina than after its relief by nitroglycerin (NTG).*

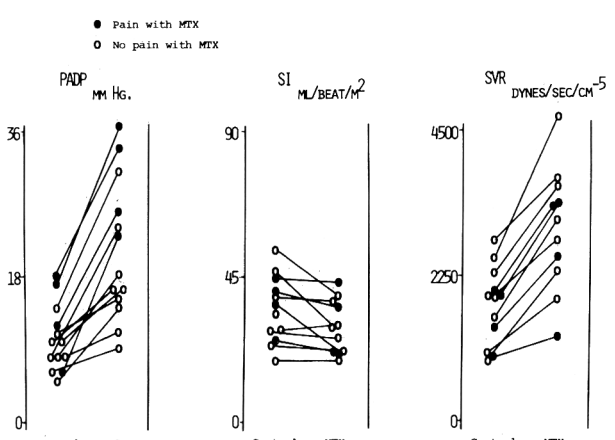

FIGURE 5. *Changes in pulmonary artery diastolic pressure (PADP), stroke index (SI) and systemic vascular resistances (SVR) during the methoxamine (MTX) test. The control PADP was 12 mm Hg or more in three of the four patients who developed angina but in only one of the nine patients who did not develop angina during the test. SVR increased during methoxamine infusion in each patient.*

ECG during pain would probably reveal a higher incidence of ST-segment elevation among these patients.

Hemodynamically, variant angina is characterized by a decrease in cardiac output and an increase in left ventricular filling pressure, without a noticeable change in blood pressure or sometimes with a decrease.[4, 6-8, 17, 26, 27] In contrast, in most patients with nonvariant resting angina, increases in blood pressure are systematically present during pain, even though cardiac output is decreased and left ventricular filling pressure is increased.[1, 3, 12, 13, 20] It is widely accepted that no increases in myocardial oxygen needs occur before the onset of ischemia in variant angina.[4-6, 8-10, 19, 26, 27] However, the significance of the acute arterial hypertension during nonvariant resting angina is controversial. Some investigators claim that such blood pressure changes are the triggering factor of myocardial ischemia,[1, 3, 11, 12] whereas others contend that ischemia occurs before or in conjunction with the increases in blood pressure.[15, 17, 19, 20] Continuous intraarterial blood pressure recordings have disclosed

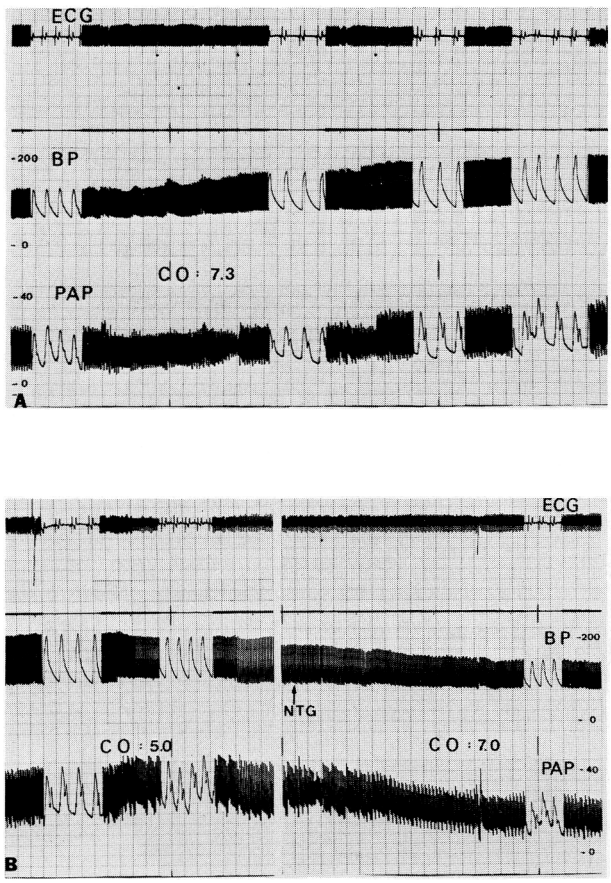

FIGURE 6. *Continuous recording of blood pressure, pulmonary artery pressure (PAP) and one lead of the ECG during methoxamine infusion in patient 7. (A) The increase in both pressures in the absence of pain. (B) The peak of the pressure increase and the concomitant reduction in cardiac output (CO, l/min). Return of both pressures and an increase in CO followed cessation of the methoxamine infusion and the administration of sublingual nitroglycerin (NTG).*

that the onset of the ischemic ECG changes and the onset of blood pressure changes in nonvariant resting angina are virtually simultaneous.[13, 17, 20] Therefore, it is nearly impossible to ascertain the precise relationship between these two phenomena. As the spontaneous ischemia progresses, an initial peak of hypertension is reached before the pain sets in, and a second and higher peak is often observed as the pain becomes more severe.[13, 17, 20] The very modest increases in blood pressure at the beginning of myocardial ischemia, however, and the lack of concurrent increases in heart rate suggest that arterial hypertension is an unlikely cause of such ischemia. This is particularly so if one considers that the real onset of ischemia, as demonstrated by the initiation of biochemical and mechanical derangements after experimental occlusion, may already precede the onset of the ECG changes.[28, 29]

Our results in nine patients who developed hypertension during spontaneous angina, but in whom we failed to produce ischemia by raising the blood pressure with methoxamine to levels higher than those measured during the spontaneous pain, bear out the concept that the increases in blood pressure, and thus the increases in myocardial oxygen demands, do not seem to be operative in the causal mechanism of nonvariant resting angina. In this regard, our findings are in close agreement with those reported by Bernd et al.,[30] who, in similar patients, showed that the double product (systolic pressure × heart rate) necessary to produce ischemia by atrial pacing was much higher than that during spontaneous angina. The failure of pharmacologically induced hypertension to cause myocardial ischemia in our patients cannot be attributed to a coincidental improvement in their clinical condition, because the study was performed within the 24 hours after one of the pain episodes and because recurrence of resting angina on the same day or on ensuing days was documented in 10 patients. Some authors have considered the increases in blood pressure during myocardial ischemia as being the product of a reflex mechanism.[17, 20, 30] Several experimental works have substantiated the occurrence of sympathetically mediated vasoconstrictor reflexes stemming from the ischemic myocardium.[31-34] In man, sharp increases in blood pressure during exercise-induced angina observed before the onset of pain have been similarly interpreted.[35]

The four patients in whom angina occurred during the methoxamine infusion deserve particular attention. Two of them had ST-segment depression in the lateral leads during both spontaneous and drug-induced ischemia, whereas ST-segment elevation in the inferior leads was only present during the spontaneous attacks. These findings support the concept that in patients with fixed coronary artery lesions, subendocardial ischemia can be caused by increased myocardial oxygen demand and, alternatively, subendocardial or transmural ischemia can occur by a spontaneous reduction of the coronary blood flow. These observations are not at variance with those of investigators who have documented ST-segment elevation during spontaneous angina and ST-segment depression during exercise-induced angina in the same patients.[6, 8] Patient 3, who did not have angina during methoxamine infusion, developed ST-segment depression and chest pain when the heart rate was increased by 20 beats/min over that during the spontaneous episodes. It is likely, therefore, that the spontaneous angina in these patients could have been caused by a decrease in coronary flow. Two patients had ST-segment elevation during both spontaneous and methoxamine-induced angina. In these two patients, the increases in blood pressure might have accounted for the appearance of ischemia, at least during the methoxamine test. Three of these four patients had a borderline or elevated left ventricular filling pressure at rest, whereas all but one of the remaining nine had normal filling pressures, which suggests that they had a decreased ventricular compliance, mild left ventricular failure or both,[36] which could have favored the development of ischemia as the

afterload was being increased by methoxamine. Epstein et al.[37] showed that in patients with left ventricular failure, the benefits of increasing blood pressure by angiotensin in the supply/demand ratio were readily reversed. Also in line with our findings, Khaja et al.[38] reported a reduction of the anginal threshold when the left ventricular filling pressure was increased by increasing the preload during atrial pacing.

Coronary vascular resistance was higher in these four patients than in the remaining patients (perhaps caused by a greater emotional reaction to catheterization), which may explain their different response to methoxamine. Two of four patients and only one of the other nine had presented spontaneous angina during the procedure.

Large coronary arteries have a proved capacity to constrict in response to stimulation of the α receptors.[39, 40] Given the progressive recognition of the presence of coronary spasm in the different coronary syndromes,[4-6, 10, 19, 27, 41-43] it would not be unreasonable to consider that a similar mechanism could also account for spontaneous angina associated with hypertension. We conclude, therefore, that the inability of pharmacologically induced arterial hypertension to produce myocardial ischemia in the majority of our patients suggests that increases in blood pressure during nonvariant resting angina are more likely to represent an associated rather than a triggering phenomenon, and that mechanisms other than increased myocardial oxygen demand seem to play a more decisive role in the genesis of this type of spontaneous angina.

References

1. Roughgarden JH: Circulatory changes associated with spontaneous angina pectoris. Am J Med **41:** 947, 1966
2. Gazes PC, Mobley EM Jr, Faris HM Jr, Duncan RC, Humphries GB: Preinfarctional (unstable) angina — a prospective study — ten year follow-up. Circulation **48:** 331, 1973
3. Cannom DS, Harrison DC, Schroeder JS: Hemodynamic observations in patients with unstable angina pectoris. Am J Cardiol **33:** 17, 1974
4. Oliva PB, Potts DE, Pluss RG: Coronary arterial spasm in Prinzmetal angina. N Engl J Med **288:** 745, 1973
5. Dhurandar RW, Watt DL, Silver MD, Trimple AS, Adelman AG: Prinzmetal's variant form of angina with arteriographic evidence of coronary arterial spasm. Am J Cardiol **30:** 902, 1972
6. Maseri A, Mimmo R, Chierchia S, Marchesi C, Pesola A, L'Abbate A: Coronary artery spasm as a cause of acute myocardial ischemia in man. Chest **68:** 625, 1975
7. Prinzmetal M, Kennamer R, Merliss R, Wada T, Bor N: Angina pectoris. I. A variant form of angina pectoris. Am J Med **27:** 375, 1959
8. MacAlpin RN, Kattus AA, Alvaro AB: Angina pectoris at rest with preservation of exercise capacity. Prinzmetal's variant angina. Circulation **47:** 946, 1973
9. Gensini GG: Coronary artery spasm and angina pectoris. Chest **68:** 709, 1975
10. Yasue H, Touyama M, Shimamoto M, Kato H, Tanaka S, Akiyama F: Role of the autonomic nervous system in the pathogenesis of Prinzmetal's variant form of angina. Circulation **50:** 534, 1974
11. Robinson BF: Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris. Circulation **35:** 1073, 1967
12. Littler WA, Honour AJ, Sleight P, Stott FD: Direct arterial pressure and electrocardiogram in unrestricted patients with angina pectoris. Circulation **48:** 125, 1973
13. Scheidt S, Wolk M, Killip T: Unstable angina pectoris. Natural history, hemodynamics, uncertainties of treatment and the ethics of clinical study. Am J Med **60:** 409, 1976
14. Friesinger GC, Conti CR, Pitt B: Observations on left ventricular pressure during angina pectoris. Circulation **35** (suppl II): II-115, 1967
15. Gorlin R: Pathophysiology of cardiac pain. Circulation **32:** 138, 1965
16. Amsterdam EA, Manchester KH, Kemp HC, Gorlin R: Spontaneous angina pectoris: hemodynamic and metabolic changes. Clin Res **17:** 255, 1969
17. Guazzi M, Polese A, Fiorentini C, Magrini F, Olivari MT, Bartorelli C: Comparison between angina with ST-segment depression and angina with ST-segment elevation. Br Heart J **37:** 401, 1975
18. Lecerof H: Central haemodynamics during spontaneous angina pectoris. Br Heart J **36:** 1087, 1974
19. Maseri A, Severi S, De Nes M, L'Abbate A, Chierchia S, Marzilli M, Ballestra A, Parodi O, Biagini A, Distante A: "Variant angina": one aspect of a continuous spectrum of vasospastic myocardial ischemia. Am J Cardiol **42:** 1019, 1978
20. Figueras J, Singh BN, Ganz W, Charuzi Y, Swan HJC: Mechanisms of rest and nocturnal angina: observations during continuous hemodynamic and electrocardiographic monitoring. Circulation **59:** 955, 1979
21. Cohen LS, Elliot WC, Klein MD, Gorlin R: Coronary heart disease. Clinical, cinearteriographic and metabolic correlations. Am J Cardiol **17:** 153, 1966
22. Conti CR, Brawley RK, Griffith LS, Pitt B, Humphries JO, Gott VL, Ross RS: Unstable angina pectoris: morbidity and mortality in 57 consecutive patients evaluated angiographically. Am J Cardiol **32:** 75, 1973
23. Fortuin NG, Friesinger GC: Exercise-induced ST-segment elevation. Am J Med **49:** 459, 1970
24. Plotnick GD, Conti CR: Transient ST-segment elevation in unstable angina. Clinical and hemodynamic significance. Circulation **51:** 1015, 1975
25. Higgins CB, Wexler L, Silverman JF, Schroeder JS: Clinical and angiographic features of Prinzmetal's variant angina: documentation of etiologic factors. Am J Cardiol **37:** 831, 1976
26. Guazzi M, Polese A, Fiorentini C, Magrini F, Bartorelli C: Left ventricular performance and related hemodynamic changes in Prinzmetal's variant angina pectoris. Br Heart J **33:** 84, 1971
27. Curry CR Jr, Pepine CJ, Sabom MB, Conti CR: Similarities of ergonovine-induced and spontaneous attacks of variant angina. Circulation **59:** 307, 1979
28. Scheuer J, Brachfield N: Coronary insufficiency: relations between hemodynamic, electrical, and biochemical parameters. Circ Res **18:** 178, 1966
29. Weiner JM, Apstein CS, Arthur JH, Pirzada FA, Hood WB Jr: Persistence of myocardial injury following brief periods of coronary occlusion. Cardiovasc Res **10:** 678, 1976
30. Bernd TB, Fitzgerald J, Harrison DC, Schroeder JG: Hemodynamic changes at the onset of spontaneous versus pacing-induced angina. Am J Cardiol **39:** 784, 1977
31. Hanley HG, Gostin JC, Skinner NS Jr: Differential reflex adjustments in cutaneous and muscle vascular beds during experimental coronary artery occlusion. Am J Cardiol **27:** 513, 1971
32. Eckstein RW, Rowen HE, Shintani F, Shimoura K: Identification of canine left coronary artery branch in which serotonin initiate reflex pressor response. (abstr) Fed Proc **28:** 710, 1969
33. Malliani A, Peterson DF, Bishop VS, Brown AM: Spinal sympathetic cardiac reflexes. Circ Res **30:** 158, 1972
34. Staszewska-Barczak J: The reflex stimulation of catecholamine secretion during the acute stage of myocardial infarction in the dog. Clin Sci **41:** 419, 1971
35. Kattus AA, Alvaro AB, Colson A: Effectiveness of isosorbide dinitrate and nitroglycerin in relieving angina pectoris during uninterrupted exercise. Chest **67:** 640, 1975
36. Mann T, Goldberg S, Mudge GH Jr, Grossman W: Factors contributing to altered left ventricular diastolic properties during angina pectoris. Circulation **59:** 14, 1979
37. Epstein SE: Protection of ischemic myocardium by nitro-

glycerin: experimental and clinical results. Circulation **53** (suppl I): I-191, 1976
38. Khaja F, Sanghvi V, Mark A, Parker JO: Effect of volume expansion on the anginal threshold. Circulation **43:** 824, 1971
39. Zuberbuhler RC, Bohr DF: Responses of coronary smooth muscle to catecholamines. Circ Res **16:** 431, 1965
40. Feigl EO: Sympathetic control of coronary circulation. Circ Res **20:** 262, 1967
41. Oliva PB, Breckinridge JC: Arteriographic evidence of coronary arterial spasm in acute myocardial infarction. Circulation **56:** 366, 1977
42. Curry RC, Pepine CJ, Sabom MB, Feldman RL, Christie LG, Conti CR: Effects of ergonovine in patients with and without coronary artery disease. Circulation **56:** 803, 1977
43. Yasue H, Omote S, Takizawa A, Nagao M, Miwa K, Tanaka S: Circadian variation of exercise capacity in patients with Prinzmetal's variant angina: role of exercise-induced coronary arterial spasm. Circulation **59:** 938, 1979

Coronary Artery Spasm During Exercise: Treatment with Verapamil

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SUMMARY Six patients who had documented coronary spasm and no coronary artery with organic obstruction > 50% developed angina and ST-segment elevation on exercise testing. Oral verapamil, 160–480 mg/day, prevented exercise-induced ischemia in all patients and increased maximal work capacity from 611 ± 250 kpm to 808 ± 160 kpm ($p < 0.02$). In two patients, a relationship between the prevention of exercise-provoked ischemia and the plasma concentration of verapamil was demonstrated, and in one of these, the relationship had a diurnal pattern. Patients with variant angina may develop coronary spasm on effort and often respond to verapamil.

EXERCISE-INDUCED ANGINA is usually caused by an imbalance between increased myocardial oxygen demand and blood supply to the myocardium because of fixed atheromatous coronary artery obstruction. Rarely, exertional angina may result from a transient decrease in coronary blood flow due to an increase in coronary vasomotor tone, producing spasm.[1-4] Verapamil is effective in preventing spontaneous attacks of angina at rest in patients with coronary artery spasm.[5] In this report we present six patients with chest pain on exercise thought to be produced by coronary artery spasm. Verapamil prevented both chest pain and ST-segment elevation on effort. Two patients demonstrated a dose-response relationship.

Materials and Methods

Patient Selection

Six patients with chest pain and ST-segment elevation on exercise, but without significant organic coronary obstruction (> 50% luminal diameter reduction) at coronary arteriography, were selected for study. All patients had been referred for diagnostic cardiac catheterization because of recurrent chest pain present for an average of 23 months (range 2–108 months). Five men and one woman were studied, mean age 56 years (range 49–64 years). All had experienced chest pain on exertion, but the predominant symptom was angina at rest. Five had recurrent nocturnal chest pain that awoke them from sleep. At presentation, five of the patients were taking β-blocking drugs, which had not reduced the frequency or severity of symptoms. The resting ECG was normal in five and showed left ventricular hypertrophy with ST-T-wave changes in one. No patient had a history of myocardial infarction.

Coronary Arteriography and Ergonovine Testing

Selective coronary arteriography was performed using either the Judkins or Sones technique. Left and right anterior oblique and angulated views were routinely obtained and the films were reviewed independently by two experienced angiographers. No patient showed obstruction of more than 50% in any coronary artery, but all showed 20–50% obstruction in one or more arteries. Coronary artery spasm was confirmed by ergonovine provocation in all patients, using incremental doses from 0.05 mg to 0.3 mg, as previously described.[6] In two patients, ergonovine was given during angiography and spasm was visualized by repeat coronary injection.[6] The four other patients were given ergonovine after angiography and the resulting ischemia was inferred by transient ST-seg-

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