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Cardiac Syndrome X: Clinical Characteristics and Left Ventricular Function

Long-Term Follow-Up Study

JUAN CARLOS KASKI, MD, FACC, GIUSEPPE M. C. ROSANO, MD, PETER COLLINS, MD, FACC,* PETROS NIHOYANNOPOULOS, MD, FACC,† ATTILIO MASERI, MD, FACC,† PHILIP A. POOLE-WILSON, MD, FRCP*

London, England, United Kingdom

Objectives. **Our aim was to study the clinical characteristics and evolution of symptoms and left ventricular function in a clinically homogeneous group of patients with syndrome X (angina pectoris, positive exercise test results and normal coronary arteriograms).**

Background. **The syndrome of angina with normal coronary arteriograms is heterogeneous and encompasses different pathogenetic entities. These characteristics may contribute to the existing controversy concerning the cause of syndrome X.**

Methods. **We studied 99 patients with syndrome X (78 women, 21 men; mean age ± SD 48.5 ± 8 years). All underwent clinical characterization, ambulatory electrocardiographic (ECG) monitoring and echocardiographic assessment of left ventricular function during a follow-up period of 7 ± 4 years.**

Results. **The syndrome was more common in women than in men. Of the women, 61.5% were postmenopausal before the onset of chest pain. All 99 patients had exertional angina, and 41 also had rest angina. The average duration of episodes of chest pain was >10 min in 53% of patients. Sublingual nitrate was effective for relief of pain in 42% of patients. Transient ST segment depression was observed during ambulatory ECG monitoring in 64 patients and myocardial perfusion abnormalities in 22. During the first stage of the exercise test, 32 patients had an increase >20 mm Hg in systolic blood pressure and showed an earlier onset of ST depression and shorter exercise time than did patients whose blood pressure increased ≤20%. During follow-up, no deaths or myocardial infarctions occurred, ventricular function was unchanged (shortening fraction 35.4 ± 4% vs. 35.6 ± 3%; heart failure developed in only one patient), systemic hypertension occurred in eight patients and conduction disturbances in four. Symptoms lessened in 11 patients, were variable or unchanged in 64 and worsened in 24.**

Conclusions. **Syndrome X, as defined in this study, occurs predominantly in postmenopausal women. Patients usually have chest pain typical for angina, but conventional antianginal treatment is not often successful. Myocardial perfusion abnormalities occur in a small proportion of patients. Long-term survival is not adversely affected, and deterioration of cardiac function rarely occurs.**

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The proportion of patients with anginal pain who are found to have normal coronary arteriographic findings is between 10% and 20%, depending on the characteristics of the patient group studied (1). The term "syndrome X," first used by Kemp (2) in 1973, is now frequently used as a diagnostic label for patients who have exertional angina, a positive response to exercise testing and angiographically normal coronary arteries (3).

The diagnosis of syndrome X requires exclusion of coronary and other cardiac and extracardiac causes of anginalike chest pain (3,4), and it is usually made after costly investigation in search of obstructive coronary artery disease. The documentation of normal coronary arteriograms, although welcomed by patient and physician, is not enough to solve the dilemma. The burden imposed on hospital resources by patients with angina and normal coronary arteries is considerable, as these patients continue to use hospital facilities, including emergency and coronary care beds, because of recurring, long-lasting chest pain. At present, despite many studies carried out over the past 2 decades, speculation prevails regarding the cause of their syndrome. The lack of both a consensus on criteria for the diagnosis of syndrome X and clinical gold standards to define myocardial ischemia is probably responsible for much of the existing controversy regarding the cause of chest pain in this syndrome (4,5).

To date, reports on the syndrome of angina and normal coronary arteries have included heterogeneous patient groups or focused on selected patient subgroups. Patients with chest pain, normal coronary arteriograms and "reduced" coronary blood flow reserve (with or without exercise-induced ST seg-

From St. George's Hospital Medical School, *The Royal Brompton National Heart and Lung Hospital and †Hammersmith Hospital, London, England, United Kingdom. This study was supported in part by the British Heart Foundation, London.

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Address for correspondence: Dr. Juan Carlos Kaski, Department of Cardiological Sciences, St. George's Hospital Medical School, London SW17 ORE, United Kingdom.

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ment depression), are considered to have "microvascular angina" (6). A sizable proportion of these patients also have systemic hypertension (7), and recently it has been suggested that patients with microvascular angina have insulin resistance (8,9). Other studies on angina and normal coronary arteries have included patients with "near normal" coronary arteries (10), coronary artery spasm (11) and left bundle branch block (12). The problem of "syndrome X" is further confused by the recent use (13) of the same term for a metabolic syndrome characterized by hyperinsulinemia, hypertriglyceridemia, hypertension and coronary artery disease.

In this study we describe the clinical features and evolution of left ventricular function in 99 patients with syndrome X who were studied from January 1972 to December 1991 and were followed up regularly over a period of 2 to 12.5 years at St. George's Hospital, the Royal Brompton National Heart & Lung Hospital and Hammersmith Hospital in London, England.

Methods

Patients. *Selection criteria.* From a series of 138 consecutive patients who were referred to our chest pain clinic for investigation of anginal pain, we studied 99 (78 women and 21 men; mean age ± SD 48.5 ± 8 years) who met stringent criteria for syndrome X: exercise-induced chest pain, positive response to exercise testing (≥1-mm ST segment depression) and normal coronary arteriograms in the absence of coronary artery spasm, left ventricular hypertrophy and systemic hypertension. Of the initial 138 patients, 3 refused participation in the study and 36 others were excluded for the following reasons: systemic hypertension in 11, left bundle branch block in 4, mitral valve prolapse in 4, diabetes mellitus (glucose plasma concentration >6 mmol/liter) in 3, negative exercise test results in 4, baseline ST segment depression >1 mm and flat or inverted T waves in leads V_2 to V_5 in 3, coronary irregularities at angiography in 5, and symptomatic hiatus hernia in 2. None of the 99 patients included in the study had Prinzmetal's variant angina pectoris (all had normal findings on hyperventilation or ergonovine tests, or both), valvular heart disease (including mitral valve prolapse) or overt cardiomyopathy. Left ventricular hypertrophy was ruled out by echocardiography in all patients. Although no patient was hypertensive (blood pressure >140/90 mm Hg) at study entry, systemic hypertension developed in eight patients during follow-up. Patients with baseline or exercise-induced left bundle branch block were not included in the study. All patients underwent investigations of esophageal function. Esophageal disturbances were assessed by manometry and pH measurements and were ruled out as the cause of chest pain in 84 patients. In the remaining 15 patients, the first in our series, radiologic and endoscopic examination (6 patients) or radiologic examination only (9 patients) showed no abnormalities.

Myocardial ischemia and blood flow reserve. Transient myocardial ischemia was systematically investigated in the 99 patients as part of their clinical characterization. Ninety-two patients underwent dipyridamole or exercise stress myocardial perfusion studies (thallium-201, sestamibi technetium-99 or rubidium-82 positron emission tomography), which showed reversible defects in 22 patients (24%) (Table 1), and 7 underwent exercise radionuclide ventriculography, which showed normal ventricular function in all. Thus, 22 (22%) of the 99 patients included in the study had findings compatible with stress-related transient myocardial ischemia, as assessed by radionuclide techniques. Coronary blood flow reserve, as assessed by dipyridamole positron emission tomography (15-oxygen water), was reduced in 16 (59%) of 27 patients (below the value of 2.5, as reported by Geltman et al. (14) using a similar technique), and in 13 (52%) of 25 patients, using Doppler flow velocity probes.

Table 1. Clinical, Electrocardiographic and Angiographic Characteristics of 99 Patients With Syndrome X

Female/male ratio	78/21
Age (yr)	48.5 ± 8
Coronary artery disease risk factors	
Family history	46
Cigarette smoking	29
Hypercholesterolemia (>5.4 mmol/liter)	29
Gynecologic status	
Hysterectomy	35
Age at hysterectomy (yr)	41 ± 6
Natural menopause	13
Baseline electrocardiogram	
Normal	81
Flat T waves	11
ST segment depression (≥0.05 mV)	7
Reversible myocardial perfusion defects	22

All data are expressed as number of patients or mean value ± SD.

Clinical and electrocardiographic (ECG) characteristics in all patients entered in the study are summarized in Table 1.

Clinical characterization. All patients underwent systematic characterization of their chest pain and coronary artery disease risk factors, exercise response, continuous ambulatory ECG monitoring and left ventricular function at rest. During follow-up, which ranged from 2 to 12.5 years (mean 7 ± 4 years), patients were seen at regular intervals (at least two annual visits).

Chest pain. A standardized angina questionnaire was completed by every patient. Temporal onset, location and radiation of chest pain, number of anginal episodes/week, average duration of episodes, triggers of chest pain, association of chest pain with exertion, presence of chest pain at rest, associated symptoms and the response to sublingual nitrates were investigated (Table 2).

Exercise testing. All patients underwent exercise testing using the modified Bruce protocol. Exercise tests were performed while patients were taking no antianginal medications. Nitrates and calcium antagonists were withdrawn ≥2 days and beta-adrenergic blocking agents ≥6 days before the study. Exercise test end points were progressive angina, ST segment depression ≥3 mm, systolic blood pressure ≥250 mm Hg and

Table 2. Characteristics of Chest Pain in 99 Patients With Syndrome X

Chest Pain Episodes	No.
Onset	
Gradual	75
Rapid	24
Average duration	
<5 min	21
5–10 min	25
>10–15 min	20
>15 min	33
Localization	
Retrosternal	84
Epigastric	4
Left shoulder	11
Radiation	
Left arm	35
Jaw or neck	7
Back	6
Arms and neck/back	19
None	32
Average no./week	
1–3	32
3–7	36
>7	31
Relation to	
Exertion	99
+ emotion	9
+ rest	41
Predominantly rest pain	14

Table 3. Events During Follow-Up in 99 Patients With Syndrome X

Events	No.
Cardiac death	0
Myocardial infarction	0
Chest pain	
Markedly decreased	11
Variable	29
Unchanged	35
Worse	24
Hospital admissions	29
For suspected myocardial infarction	5
For suspected unstable angina	24
Systemic hypertension	8
Conduction abnormalities	4
Left bundle branch block	2
Complete heart block	1
Intraventricular conduction disturbances	1
Impaired left ventricular function	1

fatigue. Twelve-lead ECGs were recorded and blood pressure was taken at rest, at 1-min intervals during exercise and for ≥6 min after exercise. The level of ST segment depression, 60 ms after the J point, was calculated by a computer-assisted system (CASE Marquette 12, Marquette Electronics) in all 12 leads. The ECG lead showing the greatest ST segment depression was selected for analysis. Baseline heart rate and heart rate–systolic blood pressure product were measured. Peak ST segment depression, exercise time, heart rate and rate-pressure product at 1 mm of ST segment depression and at peak exercise were measured. The onset of angina during exercise was noted. A positive ECG response was defined as horizontal or downsloping ST segment depression >1 mm at 60 to 80 ms after the J point occurring in at least 16 consecutive beats. A small proportion of patients had minor baseline ECG changes, as described earlier, but these did not preclude the interpretation of ST segment changes during exercise.

Ambulatory ECG monitoring. Ambulatory ECG monitoring was performed with the use of Oxford Medilog frequency-modulated recorders (Oxford Medical Systems) in the first 19 patients of the series and Marquette 8500 2-channel amplitude-modulated tape recorders in the remaining patients. Recordings were analyzed with an Oxford Medical System Medilog 2 Analyser and with a Marquette Laser Holter System 8500, respectively. In each subject, two leads corresponding to a modified inferior lead (or lead V_3 in five patients) and lead V_5 were selected. The lead showing the greatest ST segment depression during exercise was always used for assessment. The heart rate was measured on an analog recording of the heart rate versus time obtained from the playback system (trend recording). The number and duration of ischemic episodes (defined as horizontal or downsloping ST segment depression ≥1 mm from baseline, occurring 0.060 s after the J point and lasting at least 60 s) were assessed. The relation of ST depression to heart rate changes and the presence or absence of angina was investigated.

Echocardiography. A two-dimensional echocardiographic study was performed in all 99 patients at study entry and in 93 patients at the last follow-up visit (the echocardiographic study was not repeated at follow-up in 6 patients who were poor echocardiographic subjects). Cardiac images were recorded on a 0.75-in. (1.9-cm) video tape recorder for subsequent review. Left ventricular end-diastolic and end-systolic dimensions and wall thickness (mm) were obtained from a parasternal long-axis projection, and the percent fractional shortening contraction of the left ventricle (%) was subsequently calculated. All measurements were performed by using the echocardiographic equipment software. In every patient we assessed both global and regional left ventricular function. Assessment was performed without knowledge of patient identity or clinical features.

Follow-up (Table 3). The mean follow-up time was 7 ± 4 years (range 2 to 12.5). Patients were followed up regularly at 6-month intervals during outpatient visits to ascertain health status. At each visit, physical examination, blood pressure reading and rest baseline ECG were repeated. Exercise testing was carried out annually, and echocardiographic assessment of left ventricular function was performed at least twice during follow-up. Chest pain, drug compliance, quality of life and performance at work were assessed by means of standardized questionnaires. Hospital admission for suspected cardiac conditions was noted and hospital reports were obtained where appropriate. Patient compliance was excellent.

Statistical analysis. Data are expressed as mean value ± 1 SD. Two-tailed Student *t* test and chi-square tests were used to calculate differences in continuous and discrete variables among groups, respectively. A p value < 0.05 was considered significant.

Results

Clinical features. Table 1 shows the baseline clinical and ECG characteristics and risk factors for coronary artery disease of the 99 patients. Eleven patients (11%) had flat T waves and seven (7%) had minor ST segment depression (≥0.05 mV) in the baseline ECG. No patient, by selection, had left bundle branch block.

There was a female predominance (79% vs. 21%), and 45% of the women (35 of 78) had undergone hysterectomy at an average of 8 years before the onset of chest pain. Forty-eight women (61.5%) were postmenopausal (13 as a consequence of natural menopause and 35 after hysterectomy). No patient was receiving hormone replacement therapy at the onset of chest pain. Fourteen patients who had "vascular instability" symptomatic of estrogen deficiency were receiving hormone replacement therapy. None of the other postmenopausal patients were systematically treated with estrogens during the study.

Chest pain. The characteristics of chest pain in all 99 patients are presented in Table 2. The symptomatic period spanned 2 to 17 years. The chest pain usually had a gradual onset, was mainly retrosternal and radiated to the left arm. Episodes of chest pain were frequently prolonged (>10 min in 53% of patients and >15 min in 33%) and occasionally lasted >30 min (in 48 patients). In all patients the chest pain was related to effort, but 41% of the patients also had chest pain at rest. Rest pain was the predominant symptom in 14 patients. Episodes of chest pain occurred frequently: Thirty-one patients (31%) reported >7 episodes/week and 30 (30%) had >1 episode/day.

Exercise testing (Table 4). All exercise test results were positive (with angina in 79% of patients). Two groups of patients were identified on the basis of the systolic blood pressure response to exercise testing: Group 1 (67 patients [67%] who showed an increase ≤20 mm Hg during the first stage of the exercise protocol), and Group 2 (32 patients [32%] who had an increase >20 mm Hg). Blood pressure at rest was similar in the two patient groups, but systolic blood pressure at 1 mm of ST segment depression and at peak exercise was significantly higher in patients in Group 2. In the latter patients, exercise time was significantly shorter, and the magnitude of the ST segment depression significantly greater, than that of patients in Group 1.

Ambulatory ECG monitoring. Transient ST segment depression ≥1 mm (mean 1.7 ± 0.3 mm) was observed in 64 patients. A total of 211 episodes, with a mean duration of 16.8 ± 21 min, were recorded; 49% of these were associated with chest pain. The onset of ST segment depression was preceded by an increased heart rate (>100 beats/min) in 78% of episodes. One hundred twenty-four episodes of chest pain that were not associated with ST segment depression were recorded in 80 patients. Ventricular arrhythmias were observed in five patients (bigeminy in two patients, multifocal ventricular premature beats in one patient and short runs of ventricular tachycardia in two patients). These arrhythmias were not associated with episodes of ST segment depression.

Table 4. Exercise Test Variables in 99 Patients With Syndrome X

	All Patients (n = 99)	Patients With SBP Increase <20 mm Hg (n = 67)	Patients With SBP Increase >20 mm Hg (n = 32)
Rest (before exercise)			
Heart rate (beats/min)	84 ± 15	84 ± 16	83 ± 14
Blood pressure (mm Hg)	126 ± 7	125 ± 18	127 ± 16
1-mm ST depression			
Heart rate (beats/min)	132 ± 23	133 ± 24	130 ± 22
Blood pressure (mm Hg)	152 ± 25	142 ± 19	176 ± 21*
Time (s)	324 ± 246	379 ± 219	296 ± 170†
Peak exercise			
Heart rate (beats/min)	151 ± 21	152 ± 22	147 ± 19
Blood pressure (mm Hg)	163 ± 26	154 ± 22	184 ± 24*
Time (s)	502 ± 197	569 ± 224	460 ± 159*

*$p < 0.01$. †$p < 0.05$ versus patients with systolic blood pressure (SBP) increase <20 mm Hg. All data are expressed as mean value ± SD.

Left ventricular function (Table 5). No patient had structural or functional valve disease, and all had normal global and regional left ventricular wall motion at baseline examination.

No patient, by selection, had echocardiographic evidence of left ventricular hypertrophy. Left ventricular mass index was 86 ± 3 g/m^2 in the 78 women and 101 ± 8 g/m^2 in the 21 men. Mean left ventricular ejection fraction was 68 ± 8% (range 53% to 85%). A left ventricular ejection fraction >75% was observed in nine patients (9%).

Patient characterization costs. The cost of initial diagnostic investigations using conventional techniques including coronary arteriography ranged from £2,200 ($3,520) to £3,830 ($6,128), depending on whether clinical presentation was with chronic exertional chest pain or with rest angina that suggested the possibility of unstable angina or non-Q wave myocardial infarction. The burden on the health service was not negligible during follow-up, as 29 patients required a repeat hospital admission for suspected myocardial infarction or unstable angina and 6 patients underwent repeat coronary arteriogra-

Table 5. Left Ventricular Function As Assessed by Echocardiography in 99 Patients With Syndrome X at Study Entry and at Follow-Up*

	Baseline (n = 99)	Follow-Up (n = 93)
LVEDD (mm)	49.6 ± 2.7	49.4 ± 3.0
LVESD (mm)	32.0 ± 2.0	31.7 ± 2.2
Shortening fraction (%)	35.4 ± 4.0	35.6 ± 3.0

*Mean follow-up interval ± SD = 7 ± 4 years. All data are expressed as mean value ± SD. LVEDD (LVESD) = left ventricular end-diastolic (end-systolic) dimension.

phy. Regular outpatient visits were also necessary because of persistent symptoms in the majority of patients.

Follow-up. *Chest pain and major coronary events.* The majority of our patients continued to have chest pain, but none died or had an acute myocardial infarction during follow-up. Despite the overall good prognosis, 29 patients were admitted to the hospital, including the coronary care unit, at some stage of follow-up. Twenty-four patients were admitted with the diagnosis of unstable angina (usually rest angina and ST segment or T wave changes), and five were admitted for suspected non-Q wave acute myocardial infarction. Conduction disturbances developed in four patients: two had left bundle branch block, one had intraventricular conduction disturbances, and one had complete heart block that required implantation of a permanent pacemaker.

Exercise response. The mean exercise duration and peak ST segment depression were similar at baseline and last follow-up visit (526 s vs. 512 s, and 1.9 mm vs. 1.8 mm, respectively). Systemic hypertension developed in 8 patients; six (75%) of these were in the group that showed a greater blood pressure increase during stage I of the exercise protocol.

Left ventricular function. Average echocardiographic rest left ventricular volumes and left ventricular shortening fraction, as well as global and regional left ventricular function, remained unchanged during follow-up (Table 5). In only 2 (2%) of the 93 patients who underwent repeat echocardiographic measurements was global ejection fraction significantly reduced from the baseline value (from 53% to 21% and from 61% to 54%, respectively). Symptomatic left ventricular failure and intraventricular conduction disturbances also developed in the first of these two patients, and left bundle branch block developed in the other during follow-up. Baseline and follow-up echocardiographic measurements are presented in Table 5.

Treatment. Antianginal medication. Assessment of antianginal therapy was beyond the scope of this study and drug efficacy was not systematically investigated. However, clinical characterization of medical therapies used during follow-up was carried out. Therapy with a single agent appeared to be of symptomatic benefit in 29 patients (29%). Calcium antagonists, usually verapamil (240 mg/day) or diltiazem (180 to 360 mg/day), lessened both exertional and rest angina in 21 (31%) of 68 patients. Beta-adrenergic blocking agents (usually atenolol 50 to 100 mg/day) were effective for relief of symptoms in 8 (19%) of 42 patients in whom the agent was tried. In 13 (45%) of the 29 patients, lessening of symptoms was long lasting (≥8 months). Oral nitrates (isosorbide dinitrate or mononitrate) were useful in combination with calcium antagonists in 28 (42%) of 66 patients and with beta-blockers in 10 (30%) of 33 patients. Sublingual isosorbide dinitrate or nitroglycerin promptly relieved episodes of chest pain in 42 (42%) patients of the 99 patients, but these agents were less effective in 26 patients (26%) or not effective in 31 patients (31%). In 67 (67%) of the 99 patients, diverse combinations of antianginal agents were required for treatment of chest pain. In these patients, symptomatic improvement in response to the diverse antianginal drug combinations and dosages was often short-lived (mean 3 ± 3 months).

Hormone replacement therapy for menopausal women with syndrome X. Only 14 women received estrogen replacement therapy for control of menopausal symptoms. We did not attempt to formally characterize the response to hormone replacement therapy in patients with syndrome X until 1991. Preliminary results of these studies (15,16) have recently been reported.

Life-style. Eleven patients were asymptomatic or felt significantly improved at last follow-up visit, whereas 35 patients reported no change in symptoms from baseline. In 29 patients, symptomatic periods (frequently during the cold winter months) of variable duration alternated with periods of few or no symptoms. Twenty-four patients were significantly limited in daily activities, and eight of these abandoned work because of refractory chest pain. "Spontaneous" remission of chest pain (≥6 months) was observed in six patients (6%) who received no antianginal treatment.

Discussion

The patients described in this study fulfilled stringent criteria for syndrome X and represent the largest clinically homogeneous series of patients with this syndrome reported on to date. We required the presence of a positive response to exercise testing for the diagnosis of syndrome X in an attempt to reduce clinical heterogeneity and to try to identify patients whose chest pain was likely to have a cardiac origin. However, even if defined by "ischemic" ECG changes during exercise, syndrome X may still encompass diverse pathophysiologic entities. The absence of ST segment depression during exercise does not rule out "microvascular angina," as described by Cannon et al. (7), but even in that group's series (17), an ischemic response of the left ventricular ejection fraction to exercise was more common in patients with transient ST segment depression than in patients without ST segment shifts. Cannon et al. (17) also observed that coronary flow reserve was significantly lower in patients with microvascular angina who had an ischemic ST segment response to dipyridamole than in those who did not have ST segment changes. These observations are in agreement with findings by Camici et al. (18), who observed that 12 of 14 patients with reduced coronary flow reserve, compared with 16 of 29 with normal flow reserve, had ischemic ST segment depression during exercise testing.

Clinical features. Our results confirm previous observations (19,20) of a female prevalence among patients with syndrome X and suggest that estrogen deficiency may play a pathogenetic role in women with this syndrome, as discussed elsewhere (21). Indeed, of the 78 women in our study, 48 were postmenopausal. The finding of a female prevalence in syndrome X is not universal; Pasternak (22) and Kemp (23) and their coworkers did not find such a high prevalence of women in their series. It may be that patients included in their large studies did not fulfill the strict criteria for syndrome X that we applied to the patients in our prospective study. Their patients

had normal or "near-normal" coronary arteries, and some had systemic hypertension or negative exercise test results. In our study, although we included a large number of consecutive patients, some bias could have been introduced by the proportion of patients who were referred to our chest pain clinic by cardiologists aware of our interest in syndrome X. However, these factors do not explain why there appears to be an increased prevalence of the syndrome in women.

A sizable proportion of our patients had a family history of coronary disease and elevated plasma cholesterol levels. This finding could be explained by the fact that, in our system, physicians frequently perform cardiac catheterization in "high risk" patients with angina, particularly in younger patients who also have coronary artery disease risk factors.

Chest pain and myocardial ischemia. In our patients, chest pain was mainly exertional and practically indistinguishable in character, location and radiation from that in patients with obstructive coronary artery disease. However, as observed by other investigators (7), angina in the majority of patients had atypical features, including the presence of rest pain, a prolonged duration of attacks and a poor response to sublingual nitrates.

In the present study, both effort-induced chest pain and rest angina were associated with ST segment depression suggestive of myocardial ischemia. Although ST segment depression is not an entirely specific sign of myocardial ischemia, this finding cannot be summarily dismissed as an index of ischemia. Transient myocardial ischemia may indeed be the cause of chest pain in syndrome X. However, the atypical features of the pain in some patients, the lack of myocardial dysfunction in our study and that of others (24) and the essentially good prognosis (1,10,20,22) have cast doubts as to the ischemic nature of syndrome X (4,5,25). In the present study, we obtained objective documentation of transient myocardial perfusion abnormalities in a substantial proportion of patients. However, whether such abnormalities in these patients truly indicate myocardial ischemia requires confirmation. The presence of ischemia in syndrome X is controversial, but net lactate production (26–29), a decrease in coronary sinus oxygen saturation (30), transient abnormalities of myocardial perfusion (11,31) and left ventricular function (32) have been found in patients with syndrome X or microvascular angina, or both. Data by Opherk et al. (33) suggest that syndrome X in some patients may represent a "cardiomyopathic" process that results from repeated ischemic myocardial injury associated with coronary microvascular dysfunction. Although myocardial ischemia may be the underlying mechanism in at least some patients with syndrome X, the tools commonly used to detect myocardial ischemia in clinical practice may not be sensitive enough to detect the rather less severe or "patchy" (34) ischemia of syndrome X.

It is also conceivable that mechanisms other than myocardial ischemia may cause syndrome X, as suggested by the paucity of objective signs of ischemia despite severe and prolonged chest pain in many patients with syndrome X. It has been speculated (35) that chest pain in syndrome X is the result of an abnormal pain perception. Turiel et al. (35), Shapiro et al. (36) and Cannon et al. (37) observed an increased sensitivity to pain in response to diverse stimuli in patients with angina and normal coronary arteriograms. Although pain perception may be abnormally heightened in patients with syndrome X, this is unlikely to be the only explanation for the syndrome. Local release of adenosine (34), a mediator of cardiac pain, and an abnormal function of adenosine receptors (38) have been suggested as an alternative explanation for chest pain in the absence of myocardial ischemia in syndrome X. Further supporting a nonischemic origin for syndrome X, Camici et al. (39) recently identified a small group of patients with normal coronary arteriograms and positive exercise test results who had myocardial metabolic abnormalities during atrial pacing. These abnormalities were not consistent with myocardial ischemia despite the occurrence of typical chest pain and ST segment depression.

Hemodynamic and ECG response during exercise testing. On average, patients with syndrome X and coronary artery disease have a similar time course of ST segment depression during exercise testing (40). Recently, however, it has been observed (41) that some patients with syndrome X have an exaggerated response of the rate-pressure product during exercise, which may be the result of an increased sympathetic drive. This hypothesis is further suggested by the findings of Galassi et al. (42), who observed that patients with syndrome X had a higher heart rate at rest throughout the 24 h (as assessed by ambulatory ECG monitoring) than did normal persons or patients with coronary artery disease. In our study, systolic blood pressure increased by >20 mm Hg during the first stage of the exercise protocol in one third of patients. Increased sympathetic activity may be one explanation for this observation. These patients subsequently showed a higher incidence of systemic hypertension during follow-up. An association between borderline or established hypertension and syndrome X may exist. One third of patients reported by Cannon et al. (7) were hypertensive or reported a history of hypertension, although they did not have left ventricular hypertrophy. It has been shown (11,43,44) that systemic hypertension, even without left ventricular hypertrophy, can be associated with reduced coronary vasodilator reserve.

That an autonomic imbalance that results in a predominance of sympathetic activity is present in syndrome X has been confirmed by recent studies from our group (45) using heart rate variability analysis. This observation is in agreement with recent findings by Montorsi et al. (46) in patients with angina, normal coronary arteriograms and abnormal baseline ECGs. Moreover, the observation by Tousoulis et al. (47) of left ventricular hypercontractility in patients with syndrome X also favors the hypothesis that increased sympathetic tone may play a pathogenic role in syndrome X. However, the alpha-adrenergic blocker prazosin does not appear to be effective for treatment of this syndrome (48).

Left ventricular function at follow-up. As also suggested by other studies (1,10,49,50), syndrome X is associated with a benign prognosis, particularly in relation to cardiac mortality,

the development of serious coronary events and heart failure. Indeed, none of our patients died or had a myocardial infarction during long-term follow-up, and dilated cardiomyopathy and heart failure developed in only one patient. These results differ from findings by Opherk et al. (33), who observed a decline in left ventricular ejection fraction during follow-up in 13 of 27 patients with syndrome X. Different inclusion criteria and patient selection may explain these differences. The patients described by Opherk et al. (33) were predominantly male and a large proportion had left bundle branch block at baseline or during exercise at study entry. In patients with chest pain and normal coronary arteriograms, progressive deterioration of left ventricular function thus appear to occur more frequently in those who present with left bundle branch block or develop intermittent left bundle branch block during exercise or pacing (33,51). We did not include patients with left bundle branch block, and it developed in only two patients during follow-up. These findings may explain why heart failure was such a rare event in our study. However, it is important that left bundle branch block developed in one of the two patients who had a reduced ejection fraction at follow-up and that an intraventricular conduction disturbance developed in the other.

Although not systematically investigated with objective means, single-drug antianginal treatment was effective in controlling symptoms in a relatively small proportion of patients in the study. In the majority of patients, frequent dosage adjustments and different combinations of antianginal agents were required. Sublingual nitroglycerin was ineffective in relieving chest pain in >50% of patients. These findings are in agreement with observations by Kemp et al. (23). The majority of our patients remained symptomatic throughout the follow-up period, and some were disabled because of persistent chest pain. A long-lasting decrease in anginal symptoms was noticed in only a small proportion of patients. Thus, although patients with syndrome X as defined in this study have a good prognosis in terms of survival, preservation of left ventricular function and major coronary events, most are seriously limited by chest pain.

Patient characterization costs. The financial burden imposed by this condition to the health service, insurance companies or the patient is not negligible. Costs are particularly high in patients who have prolonged chest pain at rest that does not respond promptly to sublingual nitrates. Because their symptoms can mimic unstable angina or non-Q wave myocardial infarction, these patients often require admission to the coronary care unit and costly investigations. In our study, for example, costs for diagnostic investigation of patients who presented with prolonged angina at rest usually exceeded £3,500 ($5,600). Costs for the initial assessment of patients with chronic exertional angina exceeded £2,200 ($3,520). Patient evaluation costs in the United States are likely to average $7,000 (Lonny Reisman, MD, personal communication, March 1994).

Conclusions. Syndrome X occurs more commonly in postmenopausal women than in men or other women. Chest pain is often typical of angina pectoris, but may be prolonged and poorly responsive to conventional antianginal therapy. Myocardial ischemia, as detected by conventional means other than the ECG, appears to account for the chest pain in a relatively small proportion of patients. In some patients, borderline hypertension may be a contributory mechanism, and the blood pressure response during exercise may help to identify these patients. Although long-term survival is not adversely affected in patients with syndrome X, life style is often impaired by prolonged and recurrent chest pain. Deterioration of left ventricular function rarely occurs in patients with syndrome X as defined in this study. Investigation and treatment of patients with this syndrome are usually costly, and therapy with conventional antianginal agents is rarely successful.

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