Coronary Vasodilator Reserve, Pain Perception, and Sex in Patients With Syndrome X

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Background It remains unclear whether myocardial ischemia due to coronary microvascular dysfunction is the cause of chest pain in syndrome X (chest pain, ischemic-like stress ECG despite angiographically normal coronary arteries). To assess the function of the coronary microcirculation and its relation to pain perception, we measured myocardial blood flow (MBF) and coronary vasodilator reserve (CVR) in 29 patients with syndrome X and 20 matched normal control subjects.

Methods and Results MBF at rest and after intravenous dipyridamole (0.56 mg · kg⁻¹ over 4 minutes) was measured using positron emission tomography with H₂¹⁸O. CVR was calculated as MBF_dipyridamole/MBF_rest. ECG changes and chest pain after dipyridamole in syndrome X were compared with those in 35 patients with coronary artery disease (CAD). Resting and postdipyridamole MBFs were homogeneous throughout the left ventricle in syndrome X patients and control subjects. MBF was 1.05 (0.25), mean (SD) versus 1.00 (0.22) mL · min⁻¹ · g⁻¹ (P=NS) at rest and 2.73 (0.81) versus 3.00 (1.00) mL · min⁻¹ · g⁻¹ (P=NS) after dipyridamole in patients and control subjects, respectively. CVRs were 2.66 (0.76) and 3.06 (1.08) (P=NS) and after correction of resting MBF for rate-pressure product were 2.35 (0.83) and 2.34 (0.90) (P=NS) in patients and control subjects, respectively. Female syndrome X patients had higher resting MBF than males, at 1.18 (0.20) versus 0.88 (0.19) mL · min⁻¹ · g⁻¹ (P<.001). Chest pain after dipyridamole occurred in syndrome X as frequently as in CAD (21/29 versus 22/35, P=NS).

Conclusions When patients with syndrome X are compared with control subjects, no differences are found in MBF either at rest or after dipyridamole, despite syndrome X patients experiencing chest pain after dipyridamole to the same extent as patients with CAD. These findings, together with the absence of any relation among MBF, chest pain, and ECG changes under stress, cast further doubt on ischemia as the basis of the chest pain, at least in the majority of syndrome X patients. (Circulation. 1994;90:50-60.)

Key Words • angina • angiography • vasodilators • positron emission tomography • sympathetic nervous system

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severity of chest pain in patients with syndrome X after dipyridamole and at cardiac catheterization were compared with those in a matched group of patients with coronary artery disease.

## Methods

### Study Population

**Syndrome X Patients**

Twenty-nine patients (12 men, 17 women; mean age, 54 [8, SD] years), recruited over 2 years, were studied. All were normotensive, nondiabetic, and had a history of typical angina pectoris (according to the London School of Hygiene questionnaire) either on exertion only or at rest as well as on exertion. Three patients experienced pain at rest only. Apart from two patients having partial right bundle branch block and three having nonspecific ST-T wave abnormalities, the resting ECGs were otherwise normal. All patients developed >0.1 mV rectilinear or downsloping ST segment depression on the exercise ECG. No patients developed left bundle branch block on exercise. Subsequent cardiac catheterization revealed angiographically normal coronary arteries, without even minimal luminal irregularities in all subjects. Epicardial arterial spasm was excluded by testing either with intravenous ergonovine (n=13) or by hyperventilation (n=16). Left ventricular function, assessed by ventriculography, was normal in all cases. Echocardiography excluded valve disease (including mitral valve prolapse) and left ventricular hypertrophy. No patients had any intercurrent systemic illness; in particular, there was no clinical evidence of thyroid disease. Baseline characteristics of the patient group are shown in Table 1.

### Normal Control Subjects

Twenty healthy matched volunteers were recruited from hospital staff (12 men, 8 women; mean age, 51 [15] years; $P=NS$ versus patients). These volunteers gave no history of cardiac or pulmonary disease and had no risk factors for coronary artery disease; all had normal resting and stress ECG and normal effort tolerance.

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**Table 1. Patients’ Baseline Data**

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<th>Pt</th>
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<th>DBP, mm Hg</th>
<th>ECG (Rest)</th>
<th>ETT</th>
<th>Dip Pain</th>
<th>Dip ECG+</th>
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Pt indicates patient; HR, heart rate; bpm, beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; ETT, exercise treadmill test; Dip, dipyridamole; ECG+, ischemic-like ECG changes after Dip; RBBB, right bundle branch block; Nonspec ST, nonspecific ST segment changes; Y, yes; N, no; and +, >0.1 mV rectilinear or downsloping ST depression.
Study Protocol

Patients and normal control subjects were investigated by means of PET for the quantification of MBF at rest and after intravenous dipyridamole infusion.

PET Measurement of Myocardial Blood Flow

The PET scans were performed18,19 using an ECAT 931-08/12 multislice positron scanner (CTI/Siemens). The scanner comprises eight rings of bismuth germanate detectors, allowing 15 cross-sectional images of the heart to be viewed simultaneously in a 10.5-cm axial field of view. Emission scans were reconstructed with a Hanning filter with cutoff at the Nyquist frequency. The transaxial resolution achieved was 8.4 (0.7) mm, full width at half maximum, for the emission data at the center of the field of view. Simultaneous myocardial and blood tracer concentrations could thus be recorded.

Scanning Procedure

All subjects abstained from caffeine-containing drinks for 24 hours before the scan. Patients refrained from taking any medication for 24 hours before the scan; in the case of any patient on β-blockade, these were weaned at least a week before the scan. Subjects were positioned in the scanner, and a 5-minute rectilinear transmission scan was recorded to facilitate positioning of the left ventricle within the window of view of the scanner. The transmission scan was performed by exposure of a circular ring source of 68Ge. Subsequently a 20-minute transmission scan was performed to correct all emission scans for tissue attenuation. To maintain a fixed position of the subject with respect to the camera, a cross-shaped ink mark on the subject's chest was kept constant under a cross-shaped low-power laser light. After the transmission scan, radioactive gases were delivered at a constant rate via a light face mask (MC oxygen mask, Henleys Medical). A blood pool scan was performed by inhalation of 15O-labeled carbon monoxide (C15O), delivered via the face mask at a rate of 500 mL min⁻¹ with 3 MBq mL⁻¹ activity for 4 minutes. The inhaled C15O rapidly forms [15O]carboxyhemoglobin. A single-frame, 6-minute scan was started 1 minute after the end of inhalation of the C15O. Venous blood samples were taken before and after the C15O inhalation, and activity was recorded using a sodium iodide well counter for cross calibration with the scanner. After a 10-minute period (corresponding to approximately 5 half-life periods of 15O) to allow for decay, 15O-labeled carbon dioxide (C15O2) was administered for 3.5 minutes with 4 MBq mL⁻¹ activity at a rate of 300 mL min⁻¹. The C15O2 is immediately converted into H15O by carbonic anhydrase in the lung.20 A 25-frame scan was recorded, commencing 30 seconds before C15O2 delivery and continuing for a total of 7 minutes. A buildup scan over 3.5 minutes and a washout scan over 3 minutes are thus produced (frame durations were 1×30 seconds, 6×5 seconds, 6×10 seconds, 6×20 seconds, and 6×30 seconds).

After allowing an additional 10 minutes for decay, a second flow measurement was carried out after infusion of dipyridamole (0.56 mg kg⁻¹ IV), given over 4 minutes. Ninety seconds after the end of the infusion, the C15O2 was repeated as above. Blood pressure and heart rate were recorded automatically by Dinamap (Critikon Inc) at 1-minute intervals during dipyridamole infusion and monitored continuously throughout the procedure, and the 12-lead ECG was recorded every 2 minutes by a three-channel Mingograph electrocardiograph (Siemens). ECG changes in the form of rectilinear or downsloping ST segment depression >0.1 mV (80 milliseconds after the J point) after the dipyridamole infusion were defined as ECG+.

PET Data Analysis

The sinograms obtained were corrected for attenuation and reconstructed on a Microvax II computer (Digital Equipment Corporation) using dedicated array processors and standard reconstruction algorithms. Images were transferred to a SUN 3/60 workstation for further analysis with ANALYZE (Mayo Foundation)21 and PRO-MATLAB (The Mathworks Inc) software packages.

The blood volume image was produced from the C15O data by dividing the raw image by the product of the average venous blood radioactivity and the density of blood (1.06 g mL⁻¹). Regions of interest were drawn within the left atrium on three consecutive image planes and projected onto the dynamic H215O images to generate time-activity curves for these regions, the average being used as an arterial input function. An extravascular volume image was constructed by subtraction of the blood volume image from the normalized transmission image. The normalization was achieved by first rescaling the transmission image such that the mean pixel count in a region of interest situated in the left ventricle was 1.06 (the density of blood). A conversion from milliliters to grams of tissue was then made by dividing by the density of tissue (1.04 g mL⁻¹). After this, the blood volume images were subtracted from the integrated time frames of the washout phase of the H215O scans. The extravascular volume and extravascular H215O images were used for the delineation of four myocardial regions of interest (septal, anterior, lateral, and inferoposterior) over five to eight short axis planes of the left ventricle. The regions of interest were superimposed onto the kinetic time frames recorded during the C15O inhalation and washout; this produced a plane-averaged time-activity curve for each region. These curves, together with the arterial input function, were fitted to a single compartment tracer kinetic model to give values for regional MBF (in milliliters per minute per gram), as previously reported.19 In addition, whole heart MBF was determined by defining additional regions of interest, each drawn to encompass the whole of the left ventricle within each image plane. These whole heart regions were superimposed onto the kinetic time frames, as described above for the subregions, to provide a single whole left ventricle time-activity curve before the calculation of MBF. Thus, whole heart and regional values of MBF were obtained. Resting MBF was also corrected for the resting rate-pressure product (RPP), according to the following formula: Corrected MBFrest = MBFrest/RPPrest × 10⁶. In addition, the coefficient of variation was also derived for MBF at rest and after dipyridamole as an index of homogeneity of flow distribution. The coefficient of variation was calculated per subject as the standard deviation

![Graph](image-url)
per mean of the whole heart MBF values, expressed as a percentage.

**Assessment of Chest Pain**

The subjective sensation of chest pain was assessed in two situations: (1) syndrome X patients' and normal control subjects' self-rating of the presence and maximal severity of chest pain provoked by the intravenous injection of dipyridamole was recorded by means of an arbitrary scale from 0/10 (no chest pain) to 10/10 (unbearable chest pain), and (2) the experience of chest pain by syndrome X patients at cardiac catheterization either during intracardiac manipulation of the catheter or after injection of dye into the coronary arteries was recorded. Pain at catheterization was noted as Catheter+. The results were compared with equivalent data for 20 consecutive patients who underwent cardiac catheterization and in whom angiographically obvious coronary artery disease (at least one coronary arterial stenosis >50%) was found. All the coronary artery disease patients had reported typical angina pectoris and had a positive exercise ECG; none were diabetic or had valve disease.

Ethical approval was obtained from the Research Ethics Committee, Royal Postgraduate Medical School and Hammersmith Hospital. Radiation exposure was licensed by the UK Administration of Radioactive Substances Advisory Committee.

**Statistical Analysis**

All data are expressed as mean (SD). Two-tailed unpaired t tests were used to compare the data on age, heart rate, blood pressure, and RPP and to compare the coefficients of variation for intrasubject regional MBF between the patient and control groups. The data for regional MBF for patients and control subjects were examined using a one-way ANOVA and Scheffe's test to localize the source of any differences. The comparison of MBF between groups and between the sexes was performed using the Mann-Whitney U test. The latter was also used for comparison of CVR results in the following pairs: Catheter+ and Catheter− (all patients and then male versus female syndrome X patients); ECG+ and ECG− (all patients and then male versus female syndrome X patients). The Spearman correlation was used to examine the relation between CVR and pain score after dipyridamole. The distribution of MBF for syndrome X patients and normal control

### Table 2: Hemodynamic and Pain Data in Patients and Control Subjects

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<tr>
<th></th>
<th>Syndrome X</th>
<th>Control Subjects</th>
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<td>Age, y</td>
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<td>Mean arterial pressure, mm Hg</td>
<td>73.1 (8.9)</td>
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<td>Rate-pressure product, mm Hg · bpm</td>
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<td>93.3 (8.5)</td>
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<td>Dipyridamole</td>
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<td>Heart rate, bpm</td>
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<td>84.4 (12.1)</td>
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<td>Diastolic blood pressure, mm Hg</td>
<td>71.4 (11.3)</td>
<td>72.2 (11.2)</td>
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<td>Mean arterial pressure, mm Hg</td>
<td>91.6 (14.3)</td>
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<td>Rate-pressure product, mm Hg · bpm</td>
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<td>10880 (2631)</td>
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<td>MBF (Dip), gL·min⁻¹·g⁻¹</td>
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<td>COV (Dip), %</td>
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<td>ECG+ (syndrome X vs control subjects)</td>
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bpm indicates beats per minute; MBF, myocardial blood flow; Dip, dipyridamole; COV, coefficient of variation of regional MBF; Catheter+, chest pain during cardiac catheterization; CAD, coronary artery disease; Pain+, chest pain during Dip infusion; Pain score, score on an arbitrary scale (0-10) of severity of chest pain during Dip infusion; and ECG+, ischemic-like ECG changes after Dip. Values are mean (SD) where indicated.
subjects both at rest and after dipyridamole was subjected to a normality test (STAIWORKS 1.2) and the Kolmogorov-Smirnov test used to compare MBF at rest and after dipyridamole between the patient and normal control groups. Comparisons in the categories Pain+/Pain _, ECG+/ECG _, and Catheter+/Catheter _ were made using a \( \chi^2 \) test with Yates’ continuity correction. A value of \( P<.05 \) was considered statistically significant.

Results

PET Study

Hemodynamics

There were statistically significant differences in heart rate and RPP at rest and after dipyridamole between syndrome X patients and control subjects (Fig 1). There were no differences for the other hemodynamic parameters (Table 2).

Myocardial Blood Flow

Homogeneity of Myocardial Blood Flow Distribution. The mean coefficient of variation for MBF was comparable in patients and control subjects both at rest (18.5% [9.6] versus 18.1% [11.1], \( P=NS \)) and after dipyridamole (20.6% [12.0] versus 19.4% [12.0], \( P=NS \)).

Absolute Myocardial Blood Flow. As shown in Table 2 and Fig 2, there were no differences in global resting MBF or postdipyridamole MBF between syndrome X patients and normal control subjects. MBF in the anterior, lateral, inferior, and septal regions, at rest and after dipyridamole, was comparable both within and between the patient and control groups (Table 3 and Fig 3). There was no difference from normality in the distribution of values of MBF for both patients and control subjects both at rest (patients: normality statistic, 0.12 and significance, 0.27; control subjects, 0.21 and 0.18, respectively) and after dipyridamole (patients: normality statistic, 0.11 and significance, 0.28; control subjects, 0.11 and 0.31, respectively). Using the Kolmogorov-Smirnov test to compare the distribution of MBF between the patient and normal control groups at rest and after dipyridamole, no significant differences were found either for resting MBF (Kolmogorov-Smirnov statistic, 0.26 and significance, 0.19) or for MBF after dipyridamole (Kolmogorov-Smirnov statistic, 0.24 and significance, 0.20), suggesting that the distribution is comparable.

Coronary Vasodilator Reserve. The CVR for patients was 2.66 (0.76) versus 3.06 (1.08) for normal control subjects (\( P=NS \)). After correction for resting RPP, the resulting values were 2.35 (0.83) and 2.34 (0.90) (\( P=NS \)) for patients and normal control subjects, respectively (Fig 4).

ECG Changes

Nine of 29 patients with syndrome X developed ischemic-like changes on the ECG after dipyridamole infusion compared with none in the normal control group (\( P<.05 \)). There were no differences in the CVR between syndrome X patients who were ECG+ and those who were ECG _. The CVR for the ECG+ patients was 2.91 (0.75) and that for the ECG _ patients was 2.54 (0.76) (\( P=NS \)). Also, no relation could be demonstrated between resting or postdipyridamole heart rate and the development of ECG +,

Pain Perception

Dipyridamole-Induced Chest Pain

Twenty-one of 29 patients with syndrome X developed chest pain due to dipyridamole, but none of the normal control subjects did (\( P<.0001 \)). The mean pain score for patients was 3.7 (3.0). There was no significant relation between heart rate (resting or postdipyridamole), CVR, and chest pain, either overall or between the sexes. No relation could be demonstrated between pain score and the development of positive ECG changes due to dipyridamole. The syndrome X patients were also compared with a consecutive series of 35 patients (8 women, 27 men; mean age, 56 [9] years; \( P=NS \) versus syndrome X patients) with angiographically significant coronary artery disease (ie, at least one vessel with \( >50\% \) diameter stenosis) who received the same dose of dipyridamole (0.56 mg · kg \(^{-1} \)) in the course of a pharmacological stress echocardiogram. The syndrome X and coronary artery disease patients did not differ significantly with respect to the presence of chest pain (21/29 and 22/35, respectively; \( \chi^2 \) with Yates’ continuity correction of 1.97, \( P=.16 \)) nor with respect to the severity of pain experienced (pain scores, 3.8 [3.0] and 2.5 [2.6], respectively; \( P=NS \)).

Pain During Cardiac Catheterization

Thirteen of 29 patients with syndrome X reported chest pain similar to their usual angina during cardiac catheterization. Among an age- and sex-matched group of patients with symptomatic and angiographically proven coronary artery disease, only one of 25 reported chest pain during cardiac catheterization (\( P<.01 \), syndrome X versus coronary artery disease patients).

Relations Among Heart Rate, Rate-Pressure Product, Coronary Vasodilator Reserve, ECG Changes, and Pain Perception

Patients were stratified according to the following subsets: (1) ECG+ and ECG _, depending on whether ischemic-like ECG changes developed in response to the infusion of dipyridamole; (2) Pain+ and Pain _,
reflecting the development of chest pain after dipyridamole infusion; and (3) Catheter+ and Catheter−, according to the perception of chest pain during cardiac catheterization.

Nine patients were ECG+ and 20 ECG−. The CVR for the ECG+ group was 2.91 (0.75), and that for the ECG− subset was 2.54 (0.76) (P=.NS). Twenty-one patients were Pain+, and 8 patients were in the Pain− subset. The CVR of the Pain+ group was 2.57 (0.76) versus 2.72 (0.75) for the Pain− subset (P=NS). Separation of the patients according to the perception of chest pain during cardiac catheterization revealed 13 patients to be Catheter+ and 16 to be Catheter−. The CVR of the Catheter+ patients was 2.66 (0.75) versus 2.65 (0.79) for the Catheter− group (P=NS).

To test for associations among (1) the perception of chest pain during cardiac catheterization, (2) the experience of chest pain due to dipyridamole infusion, and (3) ischemic-like ECG changes after dipyridamole, these subsets were compared by means of the x² test. Comparing the Catheter+ and Catheter− subsets and the Pain+ and Pain− subsets, x² with Yates’ continuity correction was 0.036 (P=.96). A comparison of the Catheter+ and Catheter− subsets and the ECG+ and ECG− subsets produced a value of x² with Yates’ continuity correction of 1.40 (P=.24). Comparing the ECG+ and ECG− subsets and the Pain+ and Pain− subsets, a x² with Yates’ continuity correction of 0.53 (P=NS) was obtained.

A comparison of the heart rates at rest and after dipyridamole between the ECG+ and ECG− subsets, the Pain+ and Pain− subsets, and the Catheter+ and Catheter− subsets revealed no significant differences. Similarly, there were no significant differences for resting RPP between the ECG+ and ECG− subsets, the Pain+ and Pain− subsets, and the Catheter+ and Catheter− subsets. Thus, there are no discernible relations among CVR, ECG changes after dipyridamole, chest pain after dipyridamole, and pain perception at cardiac catheterization.

**Sex Differences in Syndrome X Patients**

No differences were found between female and male patients for general hemodynamic parameters. These data and the results below for MBF and pain perception are summarized in Table 4.

**Myocardial Blood Flow**

Resting MBF for female syndrome X patients was 1.18 (0.20) mL·min⁻¹·g⁻¹ versus 0.88 (0.19) mL·min⁻¹·g⁻¹ for male patients (P<.01). After correction for RPP, resting MBF for female syndrome X patients was 1.35 (0.32) versus 1.02 (0.25) arbitrary units for male patients (P<.01). After dipyridamole, the MBF results were comparable: 2.90 (0.67) mL·min⁻¹·g⁻¹ for female patients versus 2.50 (0.96) mL·min⁻¹·g⁻¹ for male patients (P=NS) (Fig 5).

**Coronary Vasodilator Reserve**

The CVR for female syndrome X patients was 2.55 (0.74) versus 2.81 (0.80) for male patients (P=NS). After correction of the resting MBF for RPP, these values were 2.27 (0.78) and 2.45 (0.92), respectively (P=NS).

![Myocardial blood flow](image1)

**Fig 3.** Bar graph shows regional myocardial blood flow at rest and after dipyridamole (Dip) in syndrome X patients (hatched columns) and normal control subjects (open columns). Columns represent mean (SEM).

![Coronary Vasodilator Reserve](image2)

**Fig 4.** Scatterplot shows coronary vasodilator reserve uncorrected for resting rate-pressure product (RPP) (left) and corrected for resting RPP (right). MBF indicates myocardial blood flow.
TABLE 4. Hemodynamic and Pain Data of Syndrome X Patients According to Sex

<table>
<thead>
<tr>
<th></th>
<th>Syndrome X (F)</th>
<th>Syndrome X (M)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>17</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>56.0 (6.6)</td>
<td>51.6 (10.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70.4 (9.1)</td>
<td>67.0 (11.3)</td>
<td>NS</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>125.3 (15.2)</td>
<td>131.7 (20.6)</td>
<td>NS</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>71.5 (8.4)</td>
<td>75.4 (9.4)</td>
<td>NS</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>90.0 (10.6)</td>
<td>95.6 (14.9)</td>
<td>NS</td>
</tr>
<tr>
<td>RPP, mm Hg · bpm</td>
<td>8861 (1841)</td>
<td>8868 (2136)</td>
<td>NS</td>
</tr>
<tr>
<td>MBF (rest), mL/min</td>
<td>1.18 (0.20)</td>
<td>0.88 (0.19)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MBF (rest)/RPP</td>
<td>1.35 (0.32)</td>
<td>1.02 (0.25)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>MBF (Dip), mL/min</td>
<td>2.90 (0.67)</td>
<td>2.50 (0.96)</td>
<td>NS</td>
</tr>
<tr>
<td>CVR</td>
<td>2.55 (0.74)</td>
<td>2.81 (0.80)</td>
<td>NS</td>
</tr>
<tr>
<td>CVR (corr)</td>
<td>2.27 (0.78)</td>
<td>2.45 (0.92)</td>
<td>NS</td>
</tr>
<tr>
<td>Pain+</td>
<td>14</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Pain score</td>
<td>4.8 (3.2)</td>
<td>2.6 (2.4)</td>
<td>.06</td>
</tr>
<tr>
<td>ECG+</td>
<td>8</td>
<td>1</td>
<td>.07</td>
</tr>
<tr>
<td>Catheter+</td>
<td>10</td>
<td>3</td>
<td>NS</td>
</tr>
</tbody>
</table>

F indicates female; M, male; bpm, beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; RPP, rate-pressure product; MBF, myocardial blood flow; Dip, dipyridamole; CVR, coronary vasodilator reserve; corr, corrected for resting RPP; Pain+, chest pain developed during Dip infusion; Pain score, score on an arbitrary scale (0-10) of severity of chest pain during Dip infusion; ECG+, ischemic-like ECG changes after Dip; and Catheter+, chest pain during cardiac catheterization. Values are mean (SD) where indicated.

Chest Pain Perception and ECG Changes

The chest pain reported after dipyridamole by female syndrome X patients was scored nonsignificantly more severe: 4.8 (3.2) for women versus 2.6 (2.4) for men (P=.06). Ten of 17 females and 3 of 12 males reported chest pain during cardiac catheterization (P=NS), and 8 of 9 patients who developed positive ECG changes during dipyridamole infusion were female (P=.07).

Discussion

This study is one of very few to compare directly a tightly defined group of syndrome X patients with matched normal control subjects. Overall, the results show that global and regional MBF and CVR in response to dipyridamole are comparable in syndrome X patients and normal control subjects. In the patient group, baseline MBF was significantly higher in women than in men. However, a trend toward a higher MBF after dipyridamole in women with syndrome X produced results for CVR that were comparable between the sexes. Chest pain after dipyridamole was as prevalent and about as severe in syndrome X patients as in patients with coronary artery disease, despite the absence of a demonstrable relation between pain, ECG changes, and CVR in the syndrome X group. In contrast, chest pain at cardiac catheterization was very rare in coronary artery disease patients but common in syndrome X patients. Chest pain both after dipyridamole administration and during cardiac catheterization tended to be more frequently and more severely felt by female patients with syndrome X.

Hemodynamic Parameters

The hemodynamic results show higher heart rate and RPP both at rest and after dipyridamole in syndrome X patients.
patients compared with normal control subjects, although the blood pressure results for both groups were within normal limits. These results are of interest in their own right in view of the increasing body of data, such as left ventricular hypercontractility and exercise-induced impairment of diastolic time, that suggest enhanced sympathetic activity. In addition, metabolic studies in syndrome X patients during atrial pacing have demonstrated net production of pyruvate with normal lactate extraction and reduced carbohydrate oxidation with a greater uptake and oxidation of lipids, in contrast to normal subjects. This metabolic pattern is compatible with inhibition of pyruvate oxidation by concomitantly increased lipid oxidation secondary to enhanced sympathetic drive. Finally, dysregulation of the neural control of the heart has been recently demonstrated in syndrome X patients by means of power spectral analysis of the ambulatory ECG, and the QT, has been observed to be prolonged.

**Myocardial Blood Flow**

Clinically, the main problem in patients with syndrome X is that of understanding whether their chest pain is a consequence of myocardial ischemia. It has been proposed that in some of these patients myocardial ischemia is due to dysfunction of the coronary microcirculation. This prompted the coining of the term "microvascular angina." The coronary microcirculation is not visible on angiography or by any other current in vivo technique. The only way in which to assess the coronary microcirculation in vivo is to test its function. In practice, this entails measuring MBF at baseline and during maximal vasodilatation to test its capacity to increase perfusion (vasodilator reserve). Initially, the evidence for a blunted coronary vasodilator reserve in syndrome X was derived from invasive studies in which blood flow was measured only in patients who had presented with a history of chest pain, with or without ischemic-like changes in the stress ECG.

More recently, the advent of PET has made it possible to measure absolute MBF noninvasively in humans. In one previous study a comparison of MBF was made between 17 patients with angina and angiographically normal coronary arteries (but including coronary artery disease with <50% reductions in luminal diameter) and 16 normal control subjects (who were, however, significantly younger than the patients), using PET and $H_2^{15}$O. This study revealed no difference in MBF between patients and control subjects either at rest (1.38 [0.46] versus 1.25 [0.28] mL·min$^{-1}$·g$^{-1}$) or after dipyridamole 0.56 mg·kg$^{-1}$ (3.68 [2.02] versus 4.62 [1.58] mL·min$^{-1}$·g$^{-1}$). The absolute values of MBF in the syndrome X group of the current study are comparable to the values just quoted. Similarly, the wide dispersion of MBF results in patients in the current study, at rest and after dipyridamole, is equivalent to that in the earlier $H_2^{15}$O PET study, as is the homogeneity of MBF distribution.

A study of 25 patients with intracoronary Doppler probe for velocity measurement very recently found a CVR value of 3.5 (0.8) for syndrome X patients given the same dose of dipyridamole as in the present study. The values for individual patients were similarly dispersed to the present study and previous studies.

Normal control data were not presented because the study was invasive.

A further point of relevance is that when considering the normal subjects in the current study, the wide dispersion of MBF results at rest and after dipyridamole and the homogeneity of MBF distribution is equivalent to that of two recent PET studies of MBF in normal subjects. It is important to note that in a substantial number of control subjects, MBF values after dipyridamole are as low as in some of the syndrome X patients.

It is of interest that, in our study, the results for the patient and normal control groups were even closer after correction of resting MBF for myocardial demand. Using the RPP to correct for variations in resting myocardial oxygen demand, a more accurate and reproducible measure of MBF is achieved. Unfortunately, previous studies of MBF in syndrome X have not been adjusted in this way, making comparison with other data impossible.

The finding that both MBF and its coefficient of variation (at rest and after dipyridamole) are comparable between syndrome X patients and normal subjects is in contrast to a number of studies using single-photon emitters, which have suggested abnormalities of regional flow distribution. The reasons for these discrepancies, which we believe to be due principally to factors linked with patient selection and/or the methodologies used, have been discussed in detail elsewhere.

**Is the Distribution of Myocardial Blood Flow Values in Syndrome X Unimodal?**

In an earlier report from our group, MBF and CVR were measured by means of PET and $^{13}$NH$_3$ in a group of 45 syndrome X patients with a history of chest pain and a normal coronary arteriogram, with or without ischemic-like changes in the stress ECG. No normal control data were presented. Analysis of that data indicated that MBF values after dipyridamole were widely dispersed (in a manner comparable to the present study). Subsequent analysis of the frequency of distribution suggested that a subgroup of patients could be identified with a lower CVR, although it was noted that there was no correspondence between the flow data and ECG changes on exercise. It was hypothesized that there was increased adrenergic activity in these patients, and, on this basis, it was suggested that limitation of the MBF response to dipyridamole observed in some syndrome X patients might be due to $\alpha$-mediated coronary vasoconstriction. A preliminary open study was therefore performed to measure the effect of the $\alpha$ antagonist doxazosin in a group of patients with syndrome X with CVR at the lower end of the range. Doxazosin was indeed shown to increase MBF after dipyridamole. However, in 7 of 10 patients dipyridamole-induced chest pain persisted despite a significant improvement of CVR, a finding consistent with the present study. It should be emphasized that in the doxazosin study there was no control group. It is quite possible that doxazosin may increase MBF after dipyridamole in normal control subjects whose CVR values are at the lower end of the range.

Turning again to the patients and control subjects of the present study, it should be noted that despite superficial appearances to the contrary, the normality test
showed that distribution of MBF values for both patients and control subjects did not differ significantly from normal at rest or after dipyridamole; also, using the Kolmogorov-Smirnov test, no significant differences were found in the distribution of MBF between the patient and control groups at rest and after dipyridamole.

Relations Among Heart Rate, Rate-Pressure Product, Coronary Vasodilator Reserve, Pain Perception, and ECG Changes

Consistent with previous studies, no relations were demonstrated among heart rate or RPP and CVR, chest pain, sex, or ECG changes after dipyridamole. Although these cannot be completely excluded due to the limited power of the study, the failure to demonstrate any strong relations must cast some doubt on their existence. This is consistent with earlier work that has shown that although the exercise stress test is sensitive in the identification of patients whose CVR is at the lower end of the normal range, its specificity is low.

The ECG findings could be explained in terms of an abnormality of potassium flux across the cardiomyocyte membrane producing a leak of potassium into the extracellular space, a biochemical lesion that could also account for the chest pain of syndrome X. It is also well recognized that enhanced sympathetic activity per se can produce ischemic-like ECG changes with stress.

We have shown that in syndrome X patients the prevalence and severity of chest pain after dipyridamole is equal to that in patients with coronary artery disease. This is despite the fact that in syndrome X, MBF at rest and after dipyridamole is within the normal range. However, the actual trigger that causes the pain pathway to be activated in syndrome X patients remains to be elucidated.

Differences Between Male and Female Syndrome X Patients

Although a significant difference was demonstrated between the sexes for resting MBF, the nonsignificant trend toward a higher postdipyridamole MBF resulted in very similar values for CVR.

To our knowledge, this is the first comparison of female and male perception of chest pain in syndrome X, and we did not demonstrate unequivocally that the threshold in female patients was lower than in male patients. Studies of peripheral somatic painful stimuli have never demonstrated unequivocally that women have a lower pain threshold than men. Previously Turiel et al reported a lower threshold to peripheral painful somatic stimuli in women with syndrome X than in women with coronary artery disease. Also, in a previous report by Cannon et al the vast majority of patients with a chest pain syndrome and normal coronary arteries were female, and there was no stratification of the results according to sex. In another study by Shapiro et al there is no indication as to the sex of the seven syndrome X patients.

Despite most published series of syndrome X patients reporting an excess of female representation, earlier assumptions that women have a greater tendency to report pain for either cultural or psychological reasons look increasingly invalid. Our own study (S.D. Rosen, A.P. Corlando, P.G. Camici, unpublished data, 1994) using the symptom rating test, demonstrated no difference between men and women with syndrome X with respect to depression, anxiety, inadequacy, or lack of assertiveness. Overall, however, the patient group did display a significant tendency to somatization.

It might be argued that a reduced pain threshold is incompatible with increased sympathetic activity (eg, the reduced or absent perception of injuries during high-stress situations such as battle). One could hypothesize that in this group of patients, sympathetic arousal makes them more alert to afferent visceral signals. This could account for the increased tendency to somatization that we found in the syndrome X group.

Limitations of the Study

Patient Definition

A recurrent weakness inherent in much of the literature on syndrome X is that of patient definition. In this study patients were selected according to strict criteria to achieve as clinically homogeneous a patient group as possible.

Resolution of Scanning Technique

It is categorically impossible to rule out the existence of small regions of ischemia within the myocardium below the level of resolution of the scanning technique (approximately 8.4 mm). Such regions could, theoretically, provide an adequate trigger for the reported chest pain in circumstances of reduced visceral pain threshold, possibly operating via adenosine release or altered potassium flux. If so, however, it is assumed that such small regions are too insignificant to affect regional wall motion or to allow measurable release of lactate under stress. Furthermore, given the known excellent prognosis in syndrome X, it is likely that such small regions exert no long-term deleterious effects on ventricular function.

Adequacy of Pharmacological Stress

Dipyridamole may not always induce maximal MBF, and a number of patients may be less responsive to it. However, its efficacy as a pharmacological stressor in coronary artery disease and its reproducibility and use in so many parallel syndrome X studies permitted a more direct comparison of the different techniques. Nonetheless, as noted above, the relatively small number of ECG+ patients after dipyridamole may be due to inadequacy of the drug itself or of the dose used in our study (0.56 mg·kg⁻¹), although as a pharmacological stressor it is comparable to adenosine, and a comparative study of the effects of adenosine, dipyridamole, and papaverine on CVR in patients with syndrome X found normal values for these patients whichever vasodilator was used. In addition, it should be noted that the finding of a normal vasodilator response to the non–endothelium-dependent vasodilator dipyridamole is not in conflict with recent reports that endothelium-dependent vasodilatation might be impaired in these patients.

Subjectivity of Pain Assessment

Subjective methods of pain assessment can be criticized as being inherently weak, although by assessing the subjects’ sensations of chest pain either during or as
close as possible to the episode, the effects of retrospective reflection were minimized. Pain is a subjective experience; the only physiological variables measurable at the time were heart rate and blood pressure responses, and certainly with dipyridamole-induced chest pain, changes in these variables are not directly due to the presence of pain. For future studies, it is possible that measurement of phasic skin conductance response might approximate to an objective indication of painful reactivity.

Conclusions

The reported findings in syndrome X of normal MBF and distribution at rest and after pharmacological stress cast further doubt on ischemia as the basis of the reported chest pain, at least in the majority of patients. This position is strengthened by the absence of any relation among MBF, chest pain, and ECG changes under stress. Abnormal perception of chest pain can be readily demonstrated. Since it is known that activation and interactions of the central and sympathetic nervous systems can influence pain perception, sympathetic activation remains a unifying hypothesis with much to commend it, bearing in mind the increasing body of evidence that demonstrates sympathetic nervous system activation in syndrome X. The tendency toward greater sensitivity to chest pain and toward ischemic-like stress ECG changes in female syndrome X patients compared with male patients may explain the excessive representation of female patients in published studies of syndrome X.

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