Clinical Studies

Abnormal Cardiac Pain Perception in Syndrome X

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Objectives. The purpose of this study was to determine whether a diminished cardiac pain threshold contributes to chest pain in patients with syndrome X.

Background. There have been some reports of altered pain perception in syndrome X.

Methods. Intracardiac catheter manipulation was performed in four groups of patients (syndrome X [group 1, 36 patients]; mitral valve disease and normal coronary arteries [group 2, 36 patients]; mitral valve disease and coronary artery disease [group 3, 36 patients]; and heart transplant recipients with normal coronary arteries [group 4, 36 patients]). Coronary flow velocity was measured in patients with syndrome X and in transplant recipients by use of an intracoronary Doppler catheter positioned in the left anterior descending coronary artery at intracardiac catheter manipulation. Coronary flow reserve in response to papaverine was also measured in patients with syndrome X and in transplant recipients.

Results. Intracardiac stimulation produced typical anginal chest pain in 34 group 1 (syndrome X) patients (94%). However, chest pain was produced only in five patients (14%) in group 2, seven patients (19%) in group 3 and no patients in group 4. There were no significant changes in coronary blood flow velocity associated with chest pain in group 1 patients. Coronary flow reserve in response to a hyperemic dose of intracoronary papaverine was significantly lower in the syndrome X group. There was no significant difference in the prevalence with which the stimulation tests produced chest pain in patients with syndrome X with an impaired coronary flow reserve or a positive radionuclide scan.

Conclusions. The results of our study suggest that abnormal cardiac pain perception is a fundamental abnormality in syndrome X.

In >10% of patients undergoing coronary angiography for assessment of chest pain, the coronary angiogram is normal (1–3). These patients are said to have “angina pectoris with a normal coronary angiogram,” and patients who also have a positive exercise test are said to have “syndrome X.” It is evident from a review of published reports that the mechanism of chest pain in patients with syndrome X is far from clear (4,5). Many have an abnormal coronary vasodilator reserve or esophageal dysmotility, or both (6–9). Nonetheless, a considerable number of patients with syndrome X do not have such abnormalities, and even those with such abnormalities often experience symptoms that appear to be disproportionate to the severity of the documented disease. Several causes have been suggested as the basis of chest pain in these patients, including various types of psychogenic syndromes (10–12). However, a satisfactory explanation has remained elusive.

The frequent finding in patients with syndrome X of severe, long-lasting chest pain, not associated with objective signs of myocardial ischemia, has led investigators to consider abnormal pain perception as an underlying contributing mechanism in some patients. Turiel et al. (13) showed that women with syndrome X had a reduced pain threshold for forearm ischemia and electrical skin stimulation. Shapiro et al. (14) observed that intraatrial boluses of normal saline solution and catheter pressure against the high right atrium in patients with syndrome X resulted in typical chest pain, whereas these manipulations failed to produce any symptoms in patients with coronary artery disease or mitral stenosis (14). Similar findings have also been reported by Cannon et al. (15). A lower threshold for adenosine-induced chest pain in patients with angina and a normal coronary angiogram has also been previously reported by Lagerqvist et al. (16). The present study was therefore performed to determine whether intracardiac manipulations in patients with syndrome X might affect coronary blood flow, thereby causing ischemia and chest pain, or whether a diminished cardiac pain threshold is a fundamental abnormality contributing to the chest pain in these patients.

Methods

We studied four groups of patients. In all groups the response to intracardiac instrumentation was studied. Coronary blood flow velocity and coronary flow reserve were also measured in patients with syndrome X and transplant recipients. Patients in the syndrome X group had undergone
cardiac catheterization before demonstrating normal coronary arteries and were being further investigated. Patients in all other groups were recruited from patients admitted to the unit for routine cardiac catheterization. Our heart transplant recipients are currently followed up by annual cardiac catheterization; the patients in this study were recruited from this group.

Patients. Group 1. Group 1 included 36 patients with syndrome X (mean ± SEM age 49 ± 10 years; 24 [67%] women). All patients had typical anginal chest pain, a positive exercise test and normal coronary arteries and a normal left ventricle on angiography. The exercise test was performed using the standard Bruce protocol. The test was considered to be positive when there was a horizontal or downsloping ST segment depression ≥1 mm for 80 ms after the J point. Only those patients who had these changes in the anterior chest leads were included in the study. Twenty (8 men, 12 women) of the 36 patients had reversible regional perfusion abnormalities during exercise as assessed by technetium-99m hexamibi scans. Eighteen (8 men, 10 women) of the 20 patients had an anterior reversible perfusion defect, and two patients (both women) had a reversible inferior perfusion defect. The coronary angiograms were reviewed by two independent observers to confirm that the coronary arteries were completely normal. If patients had even minor irregularities, or if there was no consensus, they were excluded from the study. All patients underwent echocardiographic assessment and M-mode and cross-sectional assessment of the left ventricular posterior wall and septal thickness. Patients with valve disease or left ventricular hypertrophy were excluded from the study, as were patients with diabetes mellitus or hypertension. All patients had continued to have chest pain despite reassurance after their cardiac catheter.

Group 2. Thirty-six patients with mitral valve disease and significant coronary artery disease on angiography comprised group 2 (mean age 68 ± 9 years; 23 [64%] women). Twenty-six patients (72%) had reported chest pain typical of angina before their cardiac catheter, and 18 of these had a positive exercise test. Ten patients did not give a history of chest pain. Significant coronary artery disease was defined as >50% lumen diameter narrowing of at least one major coronary artery. Patients with diabetes mellitus or hypertension were excluded.

Group 3. Thirty-six patients with mitral valve disease and completely normal coronary arteries on angiography formed group 3 (mean age 47 ± 7 years; 24 [67%] women). None of these patients had a history of chest pain. Patients with diabetes mellitus or hypertension were excluded.

Group 4. Group 4 included 36 heart transplant recipients (mean age 47 ± 11 years; 6 [17%] women). Mean duration posttransplantation was 15.3 ± 0.43 months. None of these patients reported chest pain, and all had a negative exercise test. There was no evidence of sinus arrhythmia on the rest ECG. All had completely normal coronary arteries on angiography. Patients with left ventricular hypertrophy, diabetes mellitus or hypertension were excluded.

Cardiac stimulation study protocol. All cardiac medications were stopped at least 48 h before cardiac catheterization. Patients were premedicated with diazepam (10 mg orally). A standard femoral approach using the Judkins technique was used for cardiac catheterization, and the catheters were introduced through short vascular sheaths. The patients were instructed to report any chest pain during catheterization and, if chest pain was felt, to decide whether this was typical of their usual chest pain (groups 1 and 2).

In group 1 (syndrome X) and group 4 (transplant), a 3.6F 20-MHz intracoronary Doppler-tipped catheter (Schneider U.K.) was also positioned in the proximal left anterior descending coronary artery over a 0.014-in. (0.035 cm) guide wire to measure coronary flow velocity. Heparin sodium (10,000 U) was administered before the study. The intracoronary Doppler was connected to a standard Millar velocimeter (MDV-20, Millar Instruments), and phasic and mean coronary blood flow velocity signals were recorded on a Mingograf recorder (Siemens-Elema). The Millar velocimeter was range gated and calibrated so that 1 kHz = 3.75 cm/s.

A surface ECG was also recorded. A Gensini right heart catheter was advanced into the right atrium in all patients through a femoral vein sheath. The catheter was then rotated rapidly and moved backward and forward in the right atrium. As the catheter was being manipulated within the vascular sheath the patients were not aware of the movements at the distal (operator) end. Patients were not warned before the start of the catheter manipulations. The catheter was then advanced into the right ventricle, and the movements were repeated. Only chest pain in the absence of any ectopic beats was considered a positive result. Efforts were made to ensure that the Gensini catheter appeared to contact the wall of the cardiac chamber with every movement and that the intensity of the catheter movements was similar in all groups and not unduly vigorous in the syndrome X group. The maneuver was stopped if the patient reported chest pain; otherwise, stimulation was carried out for a duration of 60 s.

It was also noted whether the administration of 5 ml of contrast medium in the left and right coronary arteries and movement of catheters in the aortic root produced any chest pain.

Coronary flow reserve studies. These studies were performed in the patients with syndrome X (group 1) and transplant recipients (group 4). After the stimulation protocol the baseline mean rest and phasic coronary blood flow velocities were again recorded. After an initial 2-mg intracoronary test dose of papaverine hydrochloride through the guide catheter, further injections of up to 14 mg of papaverine (2 mg/ml in 0.9% saline solution) were given in 2-mg increments until maximal flow was achieved. The hyperemic response was recorded in the form of maximal mean and phasic blood flow velocities. Coronary flow reserve was defined as the ratio of peak hyperemic coronary flow velocity to rest coronary flow velocity. An impaired coronary flow reserve was defined as <3.0.
Ethical approval. The study was approved by the Huntingdon Health Authority Ethical Committee as part of a coronary flow study. Informed written consent was obtained from all patients before the study.

Statistical analysis. Results between groups for the symptoms of chest pain were compared using the Fisher exact test and chi-square test when appropriate. Data are given as mean values ± SEM. Coronary flow velocity measurements before and after intracardiac stimulation in groups 1 and 4 were compared using the paired t test. Coronary flow reserve in the syndrome X and transplant groups were compared using a two-factor analysis of variance, and p < 0.05 was considered significant.

Results

Right atrial stimulation (Table 1). Thirty patients (83%) in group 1 (syndrome X) reported typical chest pain during right atrial stimulation. However, there were no ECG changes associated with the pain. There was no significant difference in coronary flow velocity measured before and after the period of stimulation (8.8 ± 0.6 vs. 8.7 ± 0.6 cm/s). Only five patients (14%) in group 2 and seven patients (19%) in group 3 reported chest pain on right atrial stimulation. All five patients in group 2 (coronary artery disease) recognized the pain as typical of their usual pain. The seven patients in group 3 reported their chest pain as a sensation they had not experienced before. None of the patients in group 4 experienced chest pain, and there was no significant difference in coronary flow velocity measured before and after the period of stimulation (8.0 ± 0.5 vs. 8.1 ± 0.5 cm/s).

Movement of the catheter in the superior and inferior vena cavae and coronary sinus did not produce chest pain in any patient.

Aortic root manipulation. Movement of the catheter in the aortic root produced chest pain in 13 (36%) of the 36 patients in group 1 (Table 1). None of the patients in the other groups reported any pain.

Intracoronary contrast medium injection. Injection of contrast medium into the left coronary artery produced pain in 18 (50%) of the 36 patients in group 1 (Table 1). Four patients (11%) in group 3 also experienced chest pain. None of the patients in groups 2 and 4 reported any chest pain.

In all of these stimulation maneuvers the patients reported their chest pain voluntarily, and no new episodes of chest pain were reported in response to the investigators' questions.

Coronary flow reserve measurements (Table 2). Coronary flow reserve was significantly lower in the syndrome X group vs. the transplant group (Table 2). There was no significant difference in coronary flow velocity measured before and after the period of stimulation (8.6 ± 0.5 vs. 9.0 ± 0.6 cm/s), and again there were no changes on the ECG. Only three patients (8%) in group 2 and four (11%) in group 3 reported any chest pain on right ventricular stimulation. None of the patients in group 4 experienced any chest pain, and there was no significant difference in coronary flow velocity measured before and after the period of stimulation (8.1 ± 0.5 vs. 8.1 ± 0.5 cm/s).

Movement of the catheter in the superior and inferior vena cavae and coronary sinus did not produce chest pain in any patient.

Table 1. Symptoms of Chest Pain

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Atrial Stimulation</th>
<th>RV Stimulation</th>
<th>Aortic Root Stimulation</th>
<th>LMCA Injection</th>
<th>RCA Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n = 36)</td>
<td>30*</td>
<td>34*</td>
<td>13*</td>
<td>18*</td>
<td>9*</td>
</tr>
<tr>
<td>2 (n = 36)</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3 (n = 36)</td>
<td>7</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>4 (n = 36)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Significantly different from groups 2 to 4 (p < 0.01). †Significantly different from group 4 (p < 0.01). Data presented are number of patients. LMCA = left main coronary artery; RCA = right coronary artery; RV = right ventricular.

Table 2. Coronary Flow Reserve in Patients With Syndrome X and in Transplant Recipients

<table>
<thead>
<tr>
<th>At Rest</th>
<th>Posthyperemic Papaverine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (beats/min)</td>
</tr>
<tr>
<td>Transplant recipients</td>
<td>88 ± 1.3</td>
</tr>
<tr>
<td>Pts with syndrome X</td>
<td>70 ± 1.2</td>
</tr>
</tbody>
</table>

*Significantly lower than in transplant recipients (p < 0.05). Data presented are mean values ± SEM. CBFV = coronary blood flow velocity; CFR = coronary flow reserve; HR = heart rate; Pts = patients; SBP = systolic blood pressure.
There was no significant difference in heart rate or mean arterial pressure after injection of the hyperemic dose of papaverine. Using the definition of an abnormal flow reserve <3.0, 20 patients (56%) had an impaired flow reserve. Twenty-nine patients (81%) in the syndrome X group had a flow reserve <3.5. In contrast, only one transplant recipient had a flow reserve <3.5. None of the patients reported any chest pain on injection of intracoronary papaverine.

Chest pain and coronary flow reserve. A total of 34 patients with syndrome X experienced chest pain on either intracardiac stimulation or coronary artery contrast medium injection. Twenty of the 36 patients with syndrome X had an impaired coronary flow reserve, 18 of whom had a positive stimulation test. All 16 patients with a normal flow reserve had a positive stimulation test. Therefore, the prevalence of a positive stimulation test was similar in patients with an impaired flow reserve and in patients with a normal flow reserve (p = NS).

Exercise radionuclide tests, chest pain and flow reserve. All 20 patients who had a positive radionuclide perfusion test experienced chest pain on intracardiac stimulation. Fourteen of the remaining 16 patients with a normal perfusion test experienced chest pain on intracardiac stimulation. Eleven of the 20 patients with a positive perfusion scan had an impaired coronary flow reserve, as opposed to 9 of 16 with a normal scan.

Discussion

Previous studies. It has been observed that during unrestricted daily life, patients with syndrome X have transient ischemic ST segment depression (17). Both silent and painful episodes of diagnostic ST segment changes occur with the same circadian distribution and a similar magnitude and duration in those ECG leads that had shown ischemia during exercise testing (17). However, although the average magnitude of the ischemic ST segment depression is smaller than that in patients with chronic stable angina, patients with syndrome X have a significantly greater proportion of painful episodes than in an average group of patients with stable or variant angina (18-20). These findings, together with the observation that many patients with syndrome X do not have convincing evidence of myocardial ischemia, have led several groups to consider abnormal pain perception as a fundamental abnormality in this patient population.

Turiel et al. (13) reported that 12 women with "typical angina," a normal coronary angiogram and an ischemic-like ECG response to exercise had a lower pain threshold and tolerance for forearm ischemia and electrical skin stimulation than women with coronary artery disease (13). The differences in pain threshold and tolerance values were similar in magnitude to those reported by Droste and Roskamm (21) in their study of patients with coronary artery disease and symptomatic and asymptomatic myocardial ischemia.

Shapiro et al. (14) provoked chest pain by high right atrial catheter manipulation and intrathoracic boluses of normal saline solution in 10 of 11 patients studied with chest pain and angiographically normal coronary arteries. However, 4 of the 11 patients had a negative exercise test. Neither test provoked pain in seven patients with coronary artery disease or in nine patients with mitral valve disease. Cannon et al. (15) reported similar findings in 36 patients with chest pain and a normal coronary angiogram. However, they included patients with atypical chest pain, and only 4 patients (11%) had a positive exercise test. In their study typical pain was provoked by catheter manipulations or electrical pacing of the right ventricular apex of the heart at a rate 5 beats/min faster than basal and then an incremental increase of the pacing stimulus intensity to 10 mA (15). Furthermore, in >50% of patients studied, their typical pain was provoked by injection of contrast medium into the left coronary artery. These pain responses were rarely seen in patients with coronary artery disease and were not seen in patients with valvular heart disease. The prevalence with which these intracardiac manipulations reproduced typical chest pain was virtually identical in patients with impaired coronary flow reserve (microvascular angina) and in those without any coronary flow abnormality. However, in contrast to the study by Turiel et al. (13), Cannon et al. (15) found that abnormal cardiac sensitivity in patients with chest pain and normal coronary arteries does not appear to be linked with heightened sensitivity to cutaneous stimuli. Indeed, their patients with chest pain and normal coronary arteries had a higher cutaneous pain threshold to thermal pain than did patients with hypertrophic cardiomyopathy or coronary artery disease.

Present study. Our study suggests that patients with syndrome X may have a state of heightened intracardiac sensitivity. This is the largest reported study of strictly characterized patients with syndrome X and is the first to measure coronary blood flow in response to intracardiac stimulation. The results show that patients with syndrome X are significantly more likely to experience their usual chest pain on intracardiac and aortic stimulation and coronary artery contrast medium injection. However, in the patients with syndrome X who experienced their usual chest pain on intracardiac stimulation, there was no reduction in rest coronary blood flow velocity to suggest myocardial ischemia. Only those patients with exercise test changes in the anterior leads were included in the study because we measured coronary blood flow velocity in the left anterior descending coronary artery. It is reasonable to assume that one may expect changes in coronary blood flow in the left anterior descending coronary artery if myocardial ischemia was responsible for the chest pain produced by intracardiac stimulation in patients with syndrome X. The observations of our study lead further support to the theory that abnormal pain perception is a fundamental abnormality in these patients, which may explain why microvascular dysfunction, which appears to cause little myocardial ischemia, may be associated with severe pain in patients with syndrome X. Patients with a denervated heart after cardiac transplant...
tion did not experience chest pain with intracardiac stimulation or intracoronary injection of contrast medium.

In this study we investigated patients with chest pain and a normal coronary angiogram who had a positive exercise test. We did not study any patient who had chest pain and a normal coronary angiogram but a negative exercise test. In previous studies patients were not selected on the basis of the ECG response to exercise, but the patient group still had an exaggerated pain response compared with their respective control groups. It may be that an exaggerated pain sensitivity is a phenomenon that is common to patients with chest pain and a normal coronary angiogram regardless of the results of noninvasive testing.

Coronary contrast medium injection. The effect of right coronary artery contrast medium injection has not been reported previously. In our study 25% of the patients with syndrome X reported their usual chest pain on right coronary artery contrast medium injection, although these patients did not have any ECG changes in the inferior leads on exercise testing to suggest myocardial ischemia. Only one of the patients who experienced chest pain showed an inferior perfusion defect on the radionuclide perfusion scan. This again suggests a mechanism for chest pain other than myocardial ischemia alone. Also, only half of the patients who experienced chest pain with left coronary injection had chest pain with right coronary injection. This may be due to regional differences in the underlying abnormality.

Similar to the observations of Cannon et al. (15), the prevalence with which the stimulation tests provoked typical chest pain in our study was not significantly different in patients with an impaired coronary flow reserve and in those with a normal coronary flow reserve. The prevalence was also not significantly different in patients with an abnormal perfusion scan and in those with a normal perfusion scan. The prevalence of impaired flow reserve was similar in patients with a normal and abnormal perfusion scan.

Exercise test and coronary flow reserve. A number of definitions of syndrome X have been used in the past, with differing criteria. The definition that we used (typical chest pain, a positive exercise test and a completely normal coronary angiogram) is now widely used. Others, however, require the presence of objectively documented myocardial ischemia. Cannon and Epstein (22) coined the term "microvascular angina" to indicate the presence of an abnormal vasodilator capacity of the coronary microcirculation. This finding is the sine qua non of the syndrome of microvascular angina, whereas exercise-induced ST segment depression is not relevant to the diagnosis. An abnormality of the microcirculation may also explain the occurrence of perfusion deficits on exercise radionuclide studies in these patients, even though the epicardial coronary arteries were completely normal on angiography. Using this definition, in one study only 10% of 115 patients with documented microvascular angina had ischemic ST segment changes with exercise testing (23). It was suggested that this low sensitivity of the ECG for detecting myocardial ischemia is probably caused by the mildness of ischemia in such patients and possibly by the existence of a diffuse pattern of ischemia obviating the development of a net electric vector. In a separate study, however, Camici et al. (24) found that the exercise ECG was abnormal in 86% of 14 patients with an impaired flow reserve, but it was also positive in 16 (55%) of the 29 patients with a normal flow reserve. Therefore, in the study by Camici et al., in contrast to that by Epstein et al., the exercise ECG had a good sensitivity (86%) in identifying patients with an impaired coronary flow reserve, but it has a low specificity (45%). This illustrates the difficulty in conducting an investigation of syndrome X. Patients who do not have a positive exercise test may indeed have an abnormal flow reserve, as shown by Epstein et al. (23). Only 20 (56%) of the 36 patients with syndrome X had an impaired coronary flow reserve in our study. Therefore, the presence of ischemic ECG changes on the exercise test seems to be a variable marker in identifying patients with an impaired coronary flow reserve and has a low specificity. This also suggests that factors other than myocardial ischemia may play a role in determining the symptoms and ECG changes in these patients. This is supported by the work of Camici et al., (25) who have shown no metabolic evidence of myocardial ischemia during rapid atrial pacing in patients selected because they had syndrome X. In addition, in our study there was no correlation between coronary flow reserve measurements and reversible perfusion abnormalities during radionuclide testing. Patients with a positive perfusion scan had no greater likelihood of having impaired coronary flow reserve in response to papaverine infusion than patients with a normal scan. This questions the significance of the ECG response to exercise, the measurement of coronary flow reserve and the results of thallium perfusion imaging in this patient population.

Coronary flow response to papaverine. Until recently, it was thought that an impaired coronary flow reserve was the one finding that could be demonstrated in a substantial proportion of patients with syndrome X, and its presence was used as the strongest argument in favor of the ischemic nature of this syndrome (5). However, there have been recent reports of a normal vasodilator response to intracoronary papaverine in patients with syndrome X (26,27). In both of these studies coronary flow response to intracoronary papaverine was measured with an intracoronary Doppler catheter, and the results have suggested that coronary flow reserve is normal in patients with syndrome X. However, the number of patients in these studies was small, and there was no proper control group. In both studies the control group comprised patients with chest pain, a normal coronary angiogram and a negative exercise test. In many previous studies of patients with chest pain and normal coronary arteries, such patients have been classified as having "syndrome X." The ideal control group would have been healthy volunteers, but such a study is not possible because of ethical considerations.

A normal heart with normal coronary arteries is capable
of increasing coronary flow by approximately fourfold to fivefold (28). Previous animal models have demonstrated that intracoronary papaverine is capable of inducing maximal hyperemia, resulting in a fourfold to sixfold increase in coronary blood flow after intracoronary administration (29–31). Several studies in humans have shown that the coronary flow reserve values obtained in response to papaverine, using the same technique as our study, averaged $4.7 \pm 0.2$ (32–35). The response of heart transplant recipients to intracoronary papaverine has been reported previously (33). The coronary flow results in the transplant group in our study are in keeping with the normal coronary flow reserve values reported previously (32,33). Many patients with syndrome X in our study had a flow reserve <3.0 (20 patients, 56%). In comparison, only one transplant recipient (4%) had a flow reserve <3.5. It would not be unreasonable to conclude that the findings of our study demonstrate impaired coronary flow reserve in response to papaverine in syndrome X because the flow reserve is reduced well below the 95% confidence intervals previously defined for normal subjects as well as control measurements in heart transplant recipients.

The mechanism of action of papaverine is not dependent on the endothelium or on adenosine production. The reduced flow response to papaverine in the syndrome X group seems to exclude the possibility that impaired flow responses could be related to an abnormal endothelium-dependent function or adenosine responsiveness. The results of our study suggest that the abnormalities in flow reserve in syndrome X are related to either a structural abnormality in the microcirculation or a functional abnormality in smooth muscle relaxation that affects both adenosine- and papaverine-mediated vasodilation. However, the presence of an impaired endothelial-dependent vasodilation in patients with syndrome X has also been reported previously (36). It is clear from our study that there are a number of patients with syndrome X who have a normal flow response to papaverine, and it may be that some of them have an impaired endothelial-dependent vasodilation.

Possible underlying mechanism of abnormal cardiac pain perception. Although no motor end-plates have been found in the myocardium, it is densely innervated, and during morphogenesis there is an obligate relation between the growth of neurons and myocytes. In the adult heart, afferent nerves carry information from the local environment. This is effectuated by mechanoreceptors and chemoreceptors on a beat-to-beat basis (37). Chemoreceptors monitor the metabolic state of the tissue. This tonic nervous activity is modulated within the cardiac nervous system in relation to the external environment. Cardiac function is adapted locally with respect to vasomotion, inotropism, compliance and metabolic potential (38). There is a complex interplay between excitatory and inhibitory processes, effects of summation and sensitization and the transmitters and neuropeptides of the cardiac nervous system.

The mechanisms responsible for the chest pain experienced by patients with syndrome X may be mediated by a release of mediators at the level of the autoregulatory vessels that may stimulate pain receptors even in the absence of myocardial ischemia. Adenosine has been proposed to be one such mediator and is considered to be the link between the energy state of the myocyte and vasoregulation (4). In patients with syndrome X an abnormal coronary flow reserve may lead to a release of adenosine to compensate for the increased coronary resistance, thereby leading to arteriolar vasodilation (4). Adenosine may stimulate pain receptors regardless of whether the subsequent arteriolar vasodilation is adequate to prevent the ischemia. An increased sensitivity to endogenously produced adenosine may also be an important mechanism of chest pain production, as suggested by Lagerqvist et al. (16). In patients with syndrome X without microvascular dysfunction, trigger mechanisms other than ischemia, such as ectopic beats and changes in heart rate, may be important in the release of these mediators.

However, there may be alternative explanations for the apparently heightened cardiac sensitivity in patients with syndrome X. It is possible that an increased release of factors that trigger pain (e.g., potassium, kallikreins) may be responsible. Hence, trigger factors, such as ectopic beats or minor reductions in myocardial blood flow, may result in an excessive release of such factors, causing pain that may continue even in the absence of ischemia. This may explain the atypical features of chest pain noted in many patients. Chest pain may also result from mechanical distortion of cardiac sensory receptors by catheter manipulation. It may be that there exists a state of heightened sensitivity of such receptors in patients with syndrome X. It is recognized that mechanoreceptors and chemoreceptors exist in the heart that are either specific, with a high threshold, or nonspecific, with a low threshold (38). Of importance, however, is the observation that additional chemical stimuli may modulate or facilitate (sensitize) the action of both mechanoreceptors and chemoreceptors (38). It may be that altered pain perception in syndrome X is a result of the interplay between a number of different mechanisms.

Conclusions. It is now generally believed that syndrome X almost certainly encompasses several pathophysiologic disease entities. Coronary flow reserve studies have demonstrated an impaired flow response to pacing stress and to pharmacologic vasodilation. The fact that these abnormalities have been demonstrated by several different methodologies further strengthens the conclusion that an abnormal flow reserve does exist. However, it is also clear that other patients with chest pain and normal coronary arteries do not have any evidence of an abnormal coronary flow reserve, suggesting that syndrome X, even if defined by the ECG response to exercise, probably consists of more than one distinct pathophysiologic entity. Therefore, it would be unreasonable to ascribe the angina in all patients with syndrome X to an impaired flow reserve. This suggest that other factors must also be important. A significant reduction in coronary blood flow on esophageal acid stimulation (39), a significant reduction in coronary blood flow on hyperventilation with and without epicardial coronary constriction
(40,41), a heightened sympathetic tone (42), insulin resistance (43,44) and an abnormal microvascular endothelial dysfunction (35) have all been reported in syndrome X and highlight the heterogeneous nature of this syndrome. This study demonstrated that intracardiac stimulation can produce typical anginal chest pain in many syndrome X patients. This study has also shown for the first time, by measuring coronary blood flow velocity, that the chest pain occurs in the absence of any changes in coronary blood flow. Because the typical anginal chest pain occurred in the absence of any correlation with abnormalities of flow reserve or radionuclide perfusion scans, this suggests that abnormal cardiac pain perception may be an important factor in the pathophysiology of syndrome X.

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