Pathophysiological Dilemma of Syndrome X

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Many patients undergo coronary angiography each year because of chest pain syndromes believed to be indicative of coronary artery disease. A significant percentage of such patients, however, will be found to have normal-appearing coronary arteries. Several published series, including the National Institutes of Health (NIH)-sponsored Coronary Artery Surgery Study, have reported that from 10% to 30% of patients undergoing coronary angiography fall into this category.1-6

Historical Background

Soon after the advent of coronary angiography, it became clear that not all patients with clinical suspicion of coronary artery disease had evidence for obstructive atherosclerotic disease of the epicardial arteries. In 1967, Likoff et al7 reported 15 normotensive, nondiabetic women ranging in age from 30 to 53 years with normal coronary angiograms but with ECG abnormalities at rest (ST segment depression or T wave inversion) that were accentuated by exercise. Nine were reported as having typical angina pectoris (effort-provoked chest pressure relieved by rest or nitrates), with the remaining six having atypical features for angina pectoris (pain at rest, atypical location, or absence of relief after nitroglycerin). Despite the ECG changes during exercise, the hemodynamic response, as assessed by pulmonary artery pressures, cardiac output, and oxygen consumption, were reported as normal in the eight patients in whom these measurements were made (data not provided in the article). The authors of this article stated that “usual therapy of coronary artery disease was ineffective and unwarranted” in this setting.

That same year, Kemp et al8 reported studies performed in 50 patients (62% women) with angina pectoris (30% typical and 70% atypical) and normal coronary angiograms, commenting that as a group, “these patients may frequently have the most severe pain syndromes, often proving refractory to conventional forms of therapy.” Seventeen patients (34%) had either fasting hyperglycemia or abnormal glucose tolerance tests. Of the 41 patients who underwent metabolic study during isoproterenol stress, 11 (27%) demonstrated myocardial lactate production (coronary venous lactate concentration in excess of arterial lactate). Four of these 11 patients had ischemic-appearing ECGs during exercise stress. However, five additional patients with ischemic-appearing ECGs during exercise stress did not demonstrate myocardial lactate production during isoproterenol infusion.

These two studies, published almost 25 years ago, identified several aspects of this clinical problem that have been noted in subsequent investigations: a female predominance, chest pain commonly “atypical” for coronary artery disease with regard to provocation and location, chest pain that could be severe and disabling, metabolic and hemodynamic evidence for myocardial ischemia demonstrable, but only in a subset of patients, lack of a consistent relation of the stress ECG to confirmatory evidence of myocardial ischemia, and inconsistent responses to conventional anti-ischemic therapy.9-23 Although the common denominator of these investigations has been the study of patients with a chest pain syndrome in the presence of angiographically normal coronary arteries, the investigations have differed with regard to whether they focused only on patients with ischemic-appearing ECG responses to exercise; the characteristics of chest pain in the population studied; the inclusion or exclusion of patients with various conditions such as hypertension, left ventricular hypertrophy, or diabetes; the hemodynamic stress used in the study; and the methodology used to assess the effects of that stress. Further, sex- and age-matched healthy volunteers have not been studied for comparison because of the invasive design of most studies. Thus, in most cases, the true “normal” response to a hemodynamic or pharmacological stress is not known.

In a 1973 editorial, Kemp noted the heterogeneity of patients included in studies of patients with chest pain despite normal coronary angiograms, thereby increasing the difficulty of drawing general conclusions about this syndrome.24 The term “syndrome X” was used in this editorial to denote the uncertainty of chest pain etiology in these patients, a term subsequently used by other investigators but often with different criteria as to its definition.

Despite these differences, there has been virtually universal agreement that the long-term survival of patients with chest pain syndromes associated with normal coronary arteries is excellent (even if associated with an ischemic-appearing ECG response to exercise) and clearly more benign than that of patients with coronary artery disease.1-6,15,20,25-27 Despite this reassurance by cardiologists, however, most patients continue to have chest pain, receive treatment, and undergo repeat hospitalizations and cardiac catheterizations.1-5,25-27 This review will focus on those areas of cardiovascular investigation we believe to be most important with regard to this patient popula-

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tion as a whole: studies of coronary flow reserve, metabolic studies during stress, visceral sensitivity, and long-term changes in left ventricular function.

Studies of Coronary Flow Reserve

In 1981, Opherk et al.\textsuperscript{16} reported limited increase in coronary blood flow (argon washout measurement) after dipyridamole (0.56 mg/kg) infused over 4 minutes in 21 normotensive nondiabetic patients (15 men and six women) with "typical stress-induced angina pectoris" and normal coronary angiograms (referred to as syndrome X), comparing their responses to 15 "controls" with "atypical chest pain" unresponsive to nitrates and with normal ECG responses to exercise (Figure 1). Of their 21 patients, two had resting left bundle branch blocks on ECG, two had left bundle branch block induced by exercise, and 12 had ischemic-appearing ECG changes during exercise. The remaining five patients terminated exercise because of chest pain without ECG changes. Eight patients and five controls also underwent rapid atrial pacing (heart rate, 150 beats per minute). Three of the eight patients demonstrated myocardial lactate production, compared with none of the controls. Left ventricular endocardial biopsies performed in 18 patients showed mitochondrial swelling in the majority, although controls and patients with coronary artery disease also reported in this article were not biopsied for comparison. No vascular abnormalities were noted in these endocardial specimens. This same group reported that left ventricular ejection fraction responses to exercise, measured by radionuclide angiography, were commonly abnormal in these patients, with five of 15 demonstrating a fall in left ventricular ejection fraction during bicycle exercise.\textsuperscript{28}

In 1983, Cannon et al.\textsuperscript{17} reported limitation in great cardiac vein flow (thermodilution measurement) response to rapid atrial pacing in patients who described their typical chest pain as being provoked by this stress. Patients were not selected for participation in this study on the basis of the characteristics of their pain or the results of noninvasive testing. To assess whether a dynamic component to this flow limitation was present (because patients commonly reported variation in their chest pain threshold), ergonovine (0.15 mg i.v.) was administered after the initial pacing stress, with repeat flow measurements during pacing stress at the same heart rate (150 beats per minute). Those patients who experienced their typical pain during pacing plus ergonovine increased great cardiac vein flow less from baseline than those remaining symptom-free and increased coronary vascular resistance compared with pacing before the administration of ergonovine (Figure 2). Because angiography during ergonovine-induced increased resistance demonstrated no significant change in epicardial coronary artery dimensions, it was concluded that the increase in coronary vascular resistance was caused by coronary microvascular constriction in response to ergonovine. In support of the concept that coronary flow delivery did not increase appropriately, it was found that myocardial oxygen extraction increased during pacing in those patients with a microvascular constrictor response to ergonovine, whereas it did not change in those patients without such a response.\textsuperscript{29,30}

Lactate consumption (arterial lactate concentration minus great cardiac vein lactate concentration multiplied by flow) during pacing was significantly lower in patients with a microvascular constrictor response to ergonovine than those without this response, although actual lactate production was demonstrable in only 10% of patients during pacing stress. In a subset of patients, dipyridamole administration (average dose, 0.67 mg/kg) resulted in a higher minimum coronary resistance (less vasodilatation) in those patients with compared with those without a microvascular constrictor response to ergonovine.\textsuperscript{29,30}

In 1985, Cannon and Epstein\textsuperscript{30} proposed the term "microvascular angina" for this patient population, in view of what appeared to be heightened sensitivity of the coronary microcirculation to vasoconstrictor stimuli associated with a limited microvascular vasodilator capacity. They proposed that dysfunction of small intramural prearteriolar coronary arteries might be the pathogenetic cause of this syndrome.\textsuperscript{31} The demonstration of coexisting abnormal forearm hyperemic responses to ischemia,\textsuperscript{32} esophageal motility abnormalities,\textsuperscript{33} and bronchoconstrictor responses to methacholine inhalation\textsuperscript{34} suggested that some patients with coronary microvascular dysfunction may have a generalized disorder of vascular and nonvascular smooth muscle function. This is further supported by the demonstration of coronary microvascular dysfunction in hypertensive patients (i.e., those with systemic vasoconstriction) who had chest pain, normal-appearing

![Figure 1: Bar graphs give mean±SD values of total coronary blood flow (CBF) and coronary resistance (CR) before and after administration of dipyridamole (0.5 mg/kg) in controls and patients with angina pectoris and normal arteriograms. Reprinted with permission.\textsuperscript{16}]](http://circ.ahajournals.org/doi/10.1161/01.CIR.85.3.884)
coronary angiograms, and no left ventricular hypertrophy by echocardiography. 35

Almost 200 patients studied at the NIH for chest pain syndromes and normal coronary angiograms have undergone exercise stress testing and, in most cases, rest and exercise radionuclide angiography. 36,37 Of these, 144 (72%) were women, and the average age was 49 years. One third were hypertensive or gave a history of hypertension, but no patient had left ventricular hypertrophy by echocardiography, as this was an exclusion criterion for study. The 136 patients with a coronary microvascular constrictor response to ergonovine (microvascular angina) were divided into three groups based on their ECG response to exercise, and their radionuclide left ventricular ejection fraction responses were compared with those of the 56 patients without a vasoconstrictor response to ergonovine, all but three of whom had a normal ECG response to exercise (Figure 3). Conservative criteria for abnormal left ventricular ejection response (no change or a fall in left ventricular ejection fraction from rest to peak exercise and/or a new wall motion abnormality induced by exercise) were used to avoid misinterpretation of sex- and age-related effects on the left ventricular ejection fraction response to exercise. Of the 95 microvascular angina patients with a normal-appearing ECG response to exercise, 33 (35%) had an abnormal left ventricular ejection fraction response and/or development of a wall motion abnormality to exercise. The prevalence of abnormal left ventricular ejection fraction response to exercise for patients with an ischemic-appearing ECG response was 53% (16 of 30), and for patients with bundle branch block, it was 64% (seven of 11). All three microvascular angina groups had a higher prevalence of abnormal left ventricular functional responses to exercise than patients with no microvascular abnormality. The coronary flow responses to ergonovine during pacing and to pharmacological vasodilatation with dipyridamole of the three microvascular angina exercise groups were compared. The microvascular constrictor responses to ergonovine were no different among the three groups, although the administration of dipyridamole caused significantly less vasodilatation in those microvascular patients with ischemic-appearing ECG or bundle branch block responses to exercise. 38

Other Invasive Studies of Flow Reserve in Patients
With Normal Coronary Angiograms

Virtanen 39 measured coronary sinus flow (thermodilution measurement) responses to pacing stress (ap-

FIGURE 2. Plots show great cardiac vein (GCV) flow (top) and coronary resistance (mean blood pressure/GCV flow) (bottom) in the basal state, during pacing at a heart rate of 150 beats per minute, and during repeat pacing at the same heart rate after administration of ergonovine (0.15 mg i.v.). , 87 patients who experienced chest pain during pacing after administration of ergonovine; ●, 26 patients who experienced no chest pain during the entire pacing study. Data are indicated as mean ± 1 SD. Reprinted with permission. 30

FIGURE 3. Bar graph shows the prevalence of abnormal left ventricular responses to graded supine bicycle exercise (defined as no change or a fall in ejection fraction [EF] from rest to exercise and/or development of a wall motion abnormality [WMA]) for 56 patients with no flow abnormality identified by pacing studies after ergonovine and 136 patients with microvascular constrictor response to pacing stress after ergonovine administration. Microvascular angina patients are separated by their ECG responses to exercise: normal (Normal exercise treadmill test [ETT]), ischemic-appearing (ST ), or bundle branch block (BBB). Reprinted with permission. 37
proximately 130 beats per minute) and to dipyridamole (0.5 mg/kg), comparing nine patients with "typical effort angina" and ischemic-appearing ECGs during exercise with 14 patients without ischemic-appearing ECG responses. The coronary flow responses to pacing stress and dipyridamole were similar between the groups, as were peak myocardial lactate and oxygen consumption during pacing. Legrand et al. reported exercise radionuclide angiography and 201TI scintigraphy results and coronary flow reserve (digital subtraction measurement) before and after intracoronary contrast media in 18 men with chest pain (10 with atypical features for angina pectoris), 11 of whom were hypertensive (no echocardiographic data reported). The seven patients with abnormal exercise radionuclide studies had lower regional coronary flow responses to intracoronary contrast media than the 11 with normal radionuclide test results. Greenberg et al. reported that 10 of 27 patients with chest pain poorly responsive to anti-ischemic medications (16 with a history of hypertension but no echocardiographic data reported, 13 with atypical features for "classic angina pectoris," and three with non-insulin-dependent diabetes) demonstrated myocardial lactate production during rapid atrial pacing. The group with pacing-induced lactate production had significantly less increase in coronary sinus venous flow (thermol dilution measurement) in response to pacing stress than patients without lactate production. Bortone et al. reported coronary flow reserve studies after dipyridamole and epicardial coronary vasomotion during exercise in 11 men and two women with chest pain (described as "typical angina pectoris" in 10). All patients were normotensive. ST segment depression was noted during bicycle exercise in nine of the 13 patients. During supine bicycle exercise, coronary angiography was performed at rest, at 2 minutes into exercise, at peak exercise, and postexercise after sublingual nitroglycerin. Six patients demonstrated vasoconstriction of the distal epicardial arteries during exercise compared with vasodilatation of all epicardial segments in the remaining seven patients. Coronary sinus flow (thermol dilution measurement) response to dipyridamole (0.56 mg/kg) was lower in the patients with exercise-induced distal coronary artery constriction than in those with exercise-induced epicardial coronary artery vasodilatation.

**Coronary Flow Reserve by Positron Emission Tomography**

Positron emission tomography (PET) with either 15O-labeled water or 13N-labeled ammonia makes noninvasive quantification of regional myocardial perfusion reserve possible in humans. Geltman et al. studied 17 patients (13 males) with chest pain and normal or near-normal (reductions in coronary diameter, <50%) coronary angiograms using 15O-labeled water. There were no differences in myocardial perfusion after dipyridamole (0.56 mg/kg) infusion between patients and 16 healthy control subjects (3.68±2.02 versus 4.62±1.58 ml/min/kg, p=NS). When the response to dipyridamole among patients was analyzed with respect to "normal" responses (peak-to-rest myocardial perfusion ratio, >2.5), however, eight of 17 patients exhibited myocardial perfusion ratio of less than 2.5, compared with two of 16 control subjects. The same authors reported that myocardial perfusion was homogeneous in normal subjects and patients at rest and after dipyridamole.

Camici et al. measured regional myocardial perfusion with 11N-labeled ammonia in 22 normotensive patients (19 females) with chest pain, ischemic-appearing ECG responses to exercise, and normal coronary angiograms and in 15 control subjects. In agreement with the data of Geltman et al., regional myocardial perfusion was found to be homogeneous both at rest and after the administration of dipyridamole (0.56 mg/kg). Myocardial perfusion at rest was 0.99±0.22 and 1.06±0.29 ml/min/g (p=NS) in normal subjects and patients, respectively. After dipyridamole, however, myocardial perfusion increased significantly more in control subjects than in patients (2.92±1.03 versus 2.13±0.91 ml/min/g, p<0.05). Galassi et al. studied 13 patients and seven normal subjects using 15O-labeled water. The eight patients who had chest pain and ST segment depression after dipyridamole infusion (0.6 mg/kg) had significantly higher resting perfusion (1.43±0.30 ml/min/g) than patients without chest pain and ST changes (0.97±0.20 ml/min/g) and normal subjects (0.88±0.13 ml/min/g). After dipyridamole, myocardial perfusion increased less in patients (independently of the symptomatic and ECG responses to dipyridamole) than in normal subjects (2.98±0.85 and 2.95±0.96 ml/min/g in the two patient groups versus 3.45±0.82 ml/min/g in normal subjects, p<0.05). In addition, myocardial perfusion after dipyridamole was found to be more heterogeneous in patients than in normal subjects.

To summarize the coronary flow studies in patients with chest pain and normal epicardial coronary arteries, it seems clear that a large proportion of patients have limited flow responses to pacing stress and to pharmacological vasodilatation. These abnormalities have been demonstrated by several different methodologies, a fact that further strengthens the conclusion that an abnormal vasodilator reserve does in fact exist. It seems equally clear, however, that other patients with chest pain and normal coronary arteries do not have any evidence of an abnormality of coronary flow or flow reserve. Therefore, these results suggest that syndrome X, even if defined by the ECG response to exercise, probably consists of more than one distinct pathophysiological entity.

The cause of abnormal vasodilator reserve in patients who manifest microvascular dysfunction is unknown. Some investigators have proposed heightened sympathetic tone, although Galassi et al. did not find selective α-adrenergic blockade to be of ECG or symptom benefit. Others implicate abnormal microvascular endothelial function and the vascular effects of hyperinsulinemia. That the limit to vasodilatation is not fixed is suggested by studies of Cannon et al. and Montorsi et al., which showed that abnormalities in coronary microvascular function can be reversed in part by drugs capable of inhibiting the entry of calcium into cells.

**Metabolic Studies During Stress**

Myocardial lactate extraction and consumption have been assessed in patients with chest pain and normal
coronary angiograms in an attempt to demonstrate myocardial ischemia during stress. Invasive metabolic studies performed in healthy young volunteers and in patients with chest pain syndromes, normal coronary angiograms, and no evidence for inducible myocardial ischemia by exercise stress testing, however, have not only provided insight as to normal myocardial metabolic function at rest and during stress but also elucidated the pitfalls of using simple myocardial lactate differences as evidence for myocardial ischemia. In Gertz et al’s study of myocardial metabolic responses to prolonged coronary sinus pacing in normal volunteers, lactate extraction decreased from baseline in most individuals. Indeed, seven of 16 subjects had myocardial lactate extraction less than 10% at rest or during pacing. These findings are probably the consequence of a linear relation between arterial levels of lactate and myocardial extraction of this substrate and an inverse relation between the arterial levels of free fatty acids and myocardial lactate extraction. Further, a reduction in lactate extraction during stress or pharmacological vasodilatation can be demonstrated to be due to the physiological reduction of substrate extraction that is associated with increasing coronary flow rates in excess of myocardial energy requirements. Thus, low values of myocardial lactate extraction are not reliable indicators of myocardial ischemia. Further, when arterial and myocardial venous lactate concentrations are low and approach the sensitivity of most lactate assays, small technical errors may produce erroneous changes in the computation of the myocardial extraction fraction and even falsely indicate myocardial lactate production.

Performing studies of myocardial substrate uptake and release and calculating metabolic energetics at rest and during rapid atrial pacing, Camici et al found no evidence of myocardial lactate production in 11 women with “typical angina pectoris” and normal coronary angiograms who had chest pain and ischemic-appearing ECG changes during exercise stress; no patient had diabetes mellitus, arterial hypertension, or any resting ECG or echocardiographic abnormality. Compared with a group of 10 control subjects (six men and four women) with chest pain syndromes and normal ECG responses to exercise, however, some metabolic differences were noted (Figure 4). In particular, glycerol was extracted more efficiently and pyruvate less efficiently in patients than in control subjects at rest. In addition, significant myocardial extraction of alanine occurred in patients, whereas alanine release was found in control subjects. The metabolic changes observed in the patients during atrial pacing were not consistent with myocardial ischemia, despite the occurrence of typical chest pain and ST depression in all patients. In the six control subjects who underwent pacing, carbohydrate oxidation increased significantly during maximal pacing, whereas it was negligible in patients despite considerable myocardial uptake of carbohydrate equivalents (Figure 5). Conversely, patients showed greater uptake and oxidation of lipid fuel than controls. Net myocardial pyruvate release was observed in patients during pacing and recovery, whereas in controls pyruvate was consistently extracted during all the study steps (Figure 4). The different metabolic pattern observed in these patients might be explained, at least in part, by increased

**Figure 4.** Pyruvate (top panel) and alanine (bottom panel) myocardial extraction in normal subjects and patients with “syndrome X” during the different study phases. In control subjects, pyruvate is extracted and alanine is produced by the heart. In contrast, in patients, pyruvate extraction, lower than in normal subjects at baseline, is turned into production during atrial pacing and recovery, whereas alanine is extracted throughout the study. B, baseline; P1 to Pmax, pacing steps; R1 to R5, recovery steps. Data are mean±SEM values. Reprinted with permission.
fat oxidation, which in turn may derive from increased sympathetic nervous system activity. Indeed, patients had significantly higher systolic blood pressure in the catheterization laboratory than controls, despite the two groups having equivalent and normal blood pressures on the ward. Increased fat oxidation generates signals (increased citrate, acetyl-coenzyme A-to-coenzyme A ratio, and ATP) that inhibit two rate-limiting nonequilibrium reactions in glucose metabolism, the phosphofructokinase and the pyruvate dehydrogenase steps. Under these circumstances, both glycolysis and pyruvate oxidation are restrained.

Recently, insulin resistance has been reported in a small series of patients with chest pain and normal coronary angiograms. It is possible that myocardial handling of glucose and lactate is also abnormal in some patients because of higher circulating levels of gluconeogenic substrates (lactate and alanine), as has been shown in non-insulin-dependent diabetes mellitus. The demonstration of myocardial lactate output in patients with abnormal insulin and glucose responses to a carbohydrate load may therefore not necessarily be a metabolic marker of ischemia.

In summary, metabolic studies have shown that a decrease in myocardial lactate extraction depends in part on substrate availability and may be a normal response to pacing stress. The majority of published studies have shown actual lactate production during pacing or isoproterenol stress to be uncommon in this patient population and often to be unassociated with the same hemodynamic responses as noted in patients with coronary artery disease. Mild subendocardial myocardial ischemia, however, may be missed by transmural sampling of coronary venous blood. Also, the absence of metabolic evidence of ischemia during pacing stress does not necessarily obviate the possibility of ischemia during exercise stress.

**Pain Perception in Patients With Chest Pain Syndromes**

The recognition that many patients with chest pain and angiographically normal coronary arteries do not have convincing evidence of myocardial ischemia, in addition to the atypical features of pain (severe intensity, prolonged duration, variable response to anti-ischemic medications), has led several groups to consider abnormal pain perception as a fundamental abnormality in this patient population. Turiel et al reported that 12 women with "typical angina," normal coronary angiograms, and ischemic-appearing ECG responses to exercise had a lower pain threshold and tolerance for forearm ischemia and electrical skin stimulation than did 10 women with coronary artery disease. Shapiro et al found that in 10 of 11 patients with chest pain and normal coronary angiograms, their typical chest pain was provoked by catheter pressure against the high right atrium and by intra-atrial boluses of normal saline, manipulations unappreciated by patients with coronary artery disease or mitral stenosis. Cannon et al reported similar findings in patients with chest pain and normal coronary angiograms; the patients' typical pain was provoked by catheter probing or electrical pacing of the right ventricular apex of the heart at a rate 5 beats per minute faster than basal and then incremental increase of the pacing stimulus intensity to 10 mA. Further, in more than 50% of patients studied, their typical pain was provoked by injection of contrast
media into the left coronary artery and was particularly intense during sustained inspiration for performance of the angiogram. Of interest, the pain provoked during this testing was often severe and commonly lasted several minutes. These pain responses were rarely seen in patients with coronary artery disease and were not seen in patients with valvular heart disease (Figure 6). The prevalence with which these intracardiac manipulations reproduced the patients’ typical chest pain was virtually identical in patients with microvascular angina and in patients without any coronary flow abnormality and bore no relation to the ECG response to exercise stress or to whether or not the chest pain was “typical” for angina pectoris.

Whether the heightened intracardiac sensitivity of these patients represents one extreme of the normal bell curve distribution of visceral sensory function or is indicative of a true abnormality in visceral sensory function is unknown. Nonetheless, this finding may explain why microvascular dysfunction, which appears to provoke mild or no evident myocardial ischemia, is associated with such severe pain. These patients may represent the opposite end of the noxious spectrum from that subgroup of patients with coronary artery disease who have “silent ischemia”; that is, they experience no ischemic pain even when myocardial ischemia is severe. Similar observations of exaggerated visceral sensitivity have been made within the esophagus and may explain why high esophageal pressures and acid reflux, generally unrecognized by healthy subjects, cause such severe pain in this patient population.

The mechanisms responsible for the chest pain experienced by patients with microvascular dysfunction may be similar to those believed responsible in part for the pain of patients with coronary artery disease. Thus, increased coronary resistance, caused either by coronary artery disease or by microvascular constriction, may lead to release of adenosine at the level of autoregulatory vessels, compensating for the elevated resistance that occurs in more proximal coronary arteries and thereby leading to arteriolar vasodilation. Adenosine may stimulate pain receptors regardless of whether or not the subsequent arteriolar vasodilation is adequate to prevent the ischemia that might occur secondary to the increased resistance caused by more proximal coronary arteries. In patients with chest pain and normal epicardial coronary arteries but without microvascular dysfunction, triggering mechanisms other than ischemia may be operative (such as ectopic beats; changes in heart rate, rhythm, or contractility; or changes in loading conditions).

**Long-term Ventricular Function**

Although virtually all studies have indicated a benign prognosis with regard to mortality in patients with chest pain and normal coronary angiograms, recent studies suggest that a subgroup may experience deterioration in left ventricular function over time. Cannon et al and Treasure et al reported coronary microvascular dysfunction in patients with dilated cardiomyopathy, raising the possibility of a pathogenetic link in some patients between microvascular dysfunction and dilated cardiomyopathy, as observed in the Syrian hamster model of dilated cardiomyopathy. Opherk et al reported that of 40 patients with syndrome X (defined as “typical stress-induced anginal pain,” normal coronary arteries, and unimpaired left ventricular function at rest), patients with left bundle branch block on resting or exercise ECGs commonly demonstrated deterioration in rest (62±5% to 55±5%, p<0.05) and exercise (59±6% to 49±5%, p<0.01) left ventricular ejection fraction and exercise pulmonary artery pressure (30±6 to 39±10 mm Hg, p<0.005) over an average follow-up of 4 years. All five patients with left bundle branch block restudied with rapid atrial pacing showed myocardial lactate production at the time of their follow-up examination. Apparently, no patients without conduction abnormality on ECG were restudied in this manner. Further, no mention was made with regard to evidence for myocardial ischemia during the patients’ initial evaluation or to any association with long-term deterioration in left ventricular function.

Relevant to these findings, Cannon et al in a preliminary report, studied the 4½-year follow-up of 61 patients with microvascular angina; 15 (25%) demonstrated significant deterioration in resting left ventricular function (decline in ejection fraction %>10 and/or new wall motion abnormality). In contrast with Opherk’s study, decline in left ventricular function was not restricted to patients with left bundle branch block patterns on the initial or follow-up ECG. Further, a decline in function was actually seen more commonly in patients without ischemic-appearing ECG responses to exercise stress (11 of 39 patients, three of whom had no evidence of inducible ischemia on radionuclide angiography) than in patients with ischemic-appearing ST segment depression during exercise (0 of 15 patients, p=0.024). Left ventricular endocardial biopsies in a subset showed patchy fibrosis interspersed with myocellular hypertrophy, even in normotensive subjects. In no case was there evidence of inflammation or amyloid deposition.

Deterioration in left ventricular function could be a consequence of microvascular dysfunction and resulting ischemia or of a metabolic disorder. Of possible relevance
to this question is the observation that the progressive decline in left ventricular function occurred even in patients taking vasodilating anti-ischemic medications in both the Heidelberg\(^9\) and NIH patients.\(^7\) There are, of course, no data relating to the possibility that anti-ischemic medications, although not preventing the development of left ventricular dysfunction, decreased its frequency. Resolution of this question awaits further studies.

**Management of Patients With Chest Pain and Normal Coronary Angiograms**

Complex measurements of myocardial metabolism during stress and invasive determination of coronary flow reserve during stress or in response to a pharmacological vasodilator provide the most comprehensive and revealing evaluation of patients presenting with chest pain and normal coronary arteries. We appreciate, however, that such procedures are impractical for routine clinical assessment of patients because of time and resource limitations. Evidence for ischemia, however, can be supported by noninvasive testing, such as abnormal regional and/or global left ventricular ejection fraction responses to exercise by radionuclide angiography (the stress ECG alone is highly insensitive and sufficiently nonspecific to make a definitive diagnosis of ischemia in this patient population uncertain).

Trials of anti-ischemic therapy are warranted in patients with evidence of inducible myocardial ischemia. In patients with normal coronary angiograms and normal noninvasive testing, although microvascular dysfunction may be demonstrable in some, it seems likely that inducible myocardial ischemia is minimal at most. These patients will probably not respond to anti-ischemic medications, but because with existing tests we cannot definitively exclude ischemia, an empirical trial may be helpful. Chest pain provoked during intracoronary catheter manipulation and intracoronary dye injection may identify patients in whom a chronic visceral pain syndrome is likely or who are very sensitive to mild ischemia. Further studies will be needed to determine whether pain sensitivity within the esophagus or heart identifies a group of patients who will be helped by drugs that affect visceral neural function or central nervous system autonomic regulatory centers. Further studies may show that assessment of glucose intolerance and insulin resistance and the response to specific treatment (e.g., diet and weight loss) may be important in this patient population with regard to symptoms, coronary hemodynamics, and left ventricular function. Normal activity and exercise should be encouraged, and the use of narcotics and repeat hospitalizations and catheterizations after episodes of chest pain should be avoided.

**Conclusions**

 Syndrome X, a term coined almost 20 years ago, has since been used to define the not uncommon patient presenting with chest pain and normal epicardial coronary arteries. Unfortunately, these past 2 decades of investigation have not revealed a specific cause of this syndrome. If anything, as more information has been obtained, the syndrome has become more confusing: some patients appear to have an abnormal myocardial flow reserve and some do not; some patients appear to have ischemia and some do not; most alarmingly, some patients develop a deterioration in left ventricular function over time, regardless of the presence or absence of evidence of ischemia. Such observations have served to further confound attempts to identify a unique pathophysiological mechanism responsible for their clinical presentation and long-term course.

These considerations lead us to believe that syndrome X almost certainly encompasses several pathophysiological disease entities, perhaps including a group of diseases associated with coronary microvascular dysfunction (causing ischemia in a subset of patients), one or more previously unidentified cardiomyopathy processes, and a disorder of visceral nociception that causes these patients to seek medical attention. The diffuse disorder of vascular and nonvascular smooth muscle tone demonstrated in some patients further suggests that we may eventually uncover a primary disorder of smooth muscle or factors that regulate smooth muscle, be they endothelial, neural, or hormonal. Finally, the recent evidence that some patients with syndrome X exhibit insulin resistance raises other interesting etiologic possibilities. Thus, although much uncertainty exists, there are now enough clues about syndrome X to be optimistic that the decade of the 1990s will see marked progress in our understanding of this fascinating entity.

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