Editorial Comment

Syndrome X
“What’s in a Name . . . ?”

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Classic angina pectoris (substernal discomfort induced by activity and relieved by rest) is generally predictive of myocardial ischemia secondary to obstructive coronary artery disease, particularly in men and those with risk factors for coronary artery disease. However, the predictive accuracy of this symptom complex is far from perfect—some patients with classic angina do not have angiographically demonstrable coronary artery disease. Alternatively, many patients with atypical features (e.g., nonsubsternal location of pain, variable provocative circumstances, absence of associated symptoms) are found to have angiographically significant coronary artery disease.

What about patients with angina pectoris (typical or atypical) but with normal-appearing coronary arteries by angiography? What differential diagnoses should the clinician consider? Assuming the angiograms are of high quality and have not been misinterpreted, at the very least, life-threatening considerations have been eliminated and the patient should be reassured. Despite this reassurance, however, many patients continue to complain of pain.¹

See p 1610

For more than 20 years, studies have been performed in these patients, reporting evidence for or against a cardiac cause for symptoms. The term “Syndrome X” was first used by Kemp² in an editorial accompanying a study by Arbogast and Bourassa,³ who performed pacing studies in patients with chest pain and normal coronary arteries and with ST segment depression during atrial pacing (no mention was made of exercise ST segment responses). Arbogast and Bourassa designated their patient cohort as group X. They concluded that myocardial ischemia was not provoked by rapid atrial pacing in this population. This term caught on but with different meanings in different studies. Many authors have sought to restrict the term Syndrome X to include only those patients with ischemic-appearing electrocardiographic responses to exercise.

Despite arguments for and against an ischemic cause of the chest pain, there is a convincing body of literature that some patients with anginalike pain and normal coronary angiograms have functionally abnormal coronary arteries with a reduction of vasodilatory responses to pharmacologic stimuli (dipyridamole) and stress (rapid atrial pacing, exercise) and a heightened vasoconstrictor sensitivity to ergonovine and cold pressor testing.⁴⁻¹² Because many of these studies have directly or indirectly demonstrated that myocardial ischemia probably occurs and that there is dysfunction of small coronary arteries, we have suggested that “microvascular angina” might be more suitable than Syndrome X for this syndrome. Our studies suggest that this cardiac vascular abnormality may coexist with other evidence of smooth muscle dysfunction in systemic arteries, the esophagus, and bronchi.¹³⁻¹⁵

However, even with these convincing demonstrations, several questions remain: Can strict clinical and hemodynamic criteria categorize a distinct syndrome? Can abnormal function of small coronary arteries cause myocardial ischemia? Is there a histologically identifiable abnormality of the coronary circulation? Or is the problem a functional one?

Several studies have reported an excellent prognosis for patients with angiographically normal coronary arteries, regardless of the etiology of the chest pain.¹⁶⁻¹⁸ However, assuming that several etiologies might cause anginalike (or atypical) chest pain in this population (e.g., abnormal esophageal function, acid reflux, musculoskeletal pain, panic attacks), what of patients with a possible abnormality of small coronary artery function limiting flow reserve? In this issue of Circulation, Opherk et al,¹⁹ the group that first described abnormal coronary flow responses to dipyridamole in patients with Syndrome X,⁴ report 4-year follow-up data in 40 of their patients. Beyond the definition of Syndrome X used by the authors (typical stress-induced anginal pain, normal coronary arteries, and unimpairred left ventricular performance at rest), matters become somewhat vague. Although the authors refer to previous demonstrations of abnormal lactate metabolism during stress in Syndrome X patients,⁴ we are
not provided the actual data for their current Syndrome X cohort. Twenty-five patients (group A) were categorized as having stress-induced ST-segment depression, although five of these patients had exercise limited by chest pain before the development of ST-segment depression because of “disabling anginal pain.” We have no information with reference to the onset of ST-segment depression (early in exercise or at high heart rates only), the configuration of ST-segment depression, or the duration of ST-segment depression after exercise. In all 12 group A patients who underwent radionuclide angiography, the exercise left ventricular ejection fraction was more than 55%. Thus, if exercise-induced ischemia was present, it must have been mild in severity.

A second group of 15 patients (group B) was characterized by conduction abnormalities on their ECG during exercise (either present at rest or rate dependent). One might question the inclusion of patients with conduction abnormalities during exercise—as ischemic ST-segment responses cannot be assessed, an abnormal ejection fraction response to exercise may be due to nonischemic dysynchrony of systolic function, and previous studies have suggested that these patients might have a latent cardiomyopathic process. However, the patients in these two groups were apparently similar in their clinical presentation, as were their end-diastolic pressures and volumes, ejection fraction during baseline left ventriculography, rest ejection fractions determined by radionuclide angiography in 19 patients, and coronary flow responses to dipyridamole. In addition, in those patients who underwent echocardiography, the left ventricular end-diastolic dimensions were similar between the two groups. During supine bicycle exercise in a subset of 27 patients, however, pulmonary artery mean pressure was higher in group B patients with conduction abnormalities during exercise (30±6 mm Hg) compared with that of group A patients (24±5 mm Hg).

At a mean follow-up of 4 years, all patients were alive, and symptom status was unchanged in most patients. Apparently, no patient had a spontaneous improvement or remission of symptoms. Five group B patients with rate-related bundle branch blocks on their initial exercise testing had persistent bundle branch blocks. Progression toward a dilated cardiomyopathy was noted in six group B patients as manifest by an increase in end-systolic and end-diastolic volumes and reduction in left ventricular ejection fraction. Further, pulmonary artery pressure during exercise increased to a greater degree (39±10 mm Hg) compared with their initial exercise pulmonary artery pressure (30±6 mm Hg) in the group B patients tested than did the exercise pulmonary artery pressures in the group A patients, which did not change over follow-up.

The patient population reported by Opherk et al is probably representative of patients described in other studies that have reported limited coronary flow responses to stress or pharmacologic provoca-

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systolic function is not as good and, thus, that they deserve closer follow-up for progression to a dilated cardiomyopathy. Whether the use of angiotensin converting enzyme inhibitors or other agents presently found useful in patients with dilated cardiomyopathies would be of benefit to these patients is not known at present.

Patients with normal noninvasive testing (nonischemic electrocardiographic response to exercise and normal ejection fraction response to exercise) may also have abnormal coronary flow response to stress or vasodilators.\(^\text{10,12}\) However, I believe an alternative etiology should be sought for chest pain (i.e., abnormal esophageal function or acid reflux by endoscopy, motility testing, and 24-hour pH monitoring). Although many patients with microvascular angina, regardless of whether they exhibit ischemia on exercise testing, respond to calcium channel blockers,\(^\text{22}\) not all do. This may be explained by the recent observation of inability of nifedipine to dilate coronary arteries of some patients.\(^\text{23}\) Other centers have found \(\beta\)-blockers to be of greater benefit,\(^\text{24}\) possibly by reducing myocardial oxygen demands. Emdin and coworkers\(^\text{25}\) have recently demonstrated improvement in effort duration, pressure-rate product achieved, and symptom response during bicycle exercise with abolition of ischemic-appearing ST-segment responses after aminophylline infusion.\(^\text{25}\) Whether the same benefit can be achieved with oral aminophylline preparations and, if so, whether the usual side effects and toxicity of this drug can be avoided remains to be demonstrated.

I hope future studies will provide insight as to the mechanism of abnormal vascular function in this syndrome as well as to its optimal identification and management.

References


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Syndrome X. "What's in a name...?".
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