Editorial Comment

Syndrome X: Still an Appropriate Name*

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The present study. The puzzling observation by Camici et al. (1) in this issue of the Journal suggest that syndrome X continues to deserve its name. The authors studied the cardiac performance, myocardial metabolism and coronary hemodynamics of 12 patients with angina, an abnormal exercise test, a normal coronary angiogram and no evidence of epicardial coronary artery spasm at rest or during pacing. Patients were carefully characterized and therefore seem to represent a homogeneous group that could be considered to represent one extreme end of the spectrum of syndrome X.

All of these patients developed angina and ischemic ST segment depression during pacing, as well as a lesser increase of blood flow in the great cardiac vein compared with that of normal control subjects. However, they also exhibited a pattern of extraction of metabolic substrates and changes in cardiac function during pacing that have not been reported previously and that have, as yet, no clear explanation.

1. At rest and compared with the normal control subjects, the patients with syndrome X had a greater myocardial extraction of glucose (1.3 vs. 2.8) and glycerol (3.8 vs. 17) and a significantly lower extraction of pyruvate (40 vs. 16: p < 0.01). They had an average 3% rate of extraction of alanine compared with a 3% rate of release of alanine in control subjects.

2. Pacing caused angina and diagnostic ischemic ST depression in all the syndrome X patients but in none of the control subjects. Blood flow in the great cardiac vein was slightly lower in the patients than in control subjects but oxygen extraction was similar in both groups. Left ventricular function, assessed by ventricular angiography, was normal at peak pacing, whereas ejection fraction was increased significantly over that at rest (p < 0.05) and end-diastolic pressure (measured by a fluid-filled catheter) was lower than that of control subjects. Lactate extraction was similar to that of control subjects but the metabolic handling of other substrates was significantly different in the patients. Carbohydrate oxidation was lower in patients with syndrome X, which was in keeping with the failure of the respiratory quotient to increase in these patients (0.70) compared with values in control subjects (0.89). Finally, during maximal pacing the estimated myocardial energy expenditure was significantly lower in the syndrome X patients (42.5 vs. 61.7, p < 0.01) despite a significant increase in ejection fraction compared with the basal value (p < 0.05), which should suggest a greater efficiency of left ventricular pump function.

Comments. Calculated arteriovenous differences are subject to inaccuracies when these differences are small compared with the error associated with the measurement of arterial and venous concentrations of substrates. These errors are combined with errors in flow measurement when uptake is calculated. For individual measurements such inherent errors may lead to some puzzling findings. A classic example of this is provided by the analysis of the individual values for myocardial oxygen uptake in Table 1 of the report by Opferk et al. (2): after administration of dipyridamole, calculated myocardial oxygen uptake more than doubled in some patients whose heart rate and blood pressure remained constant, whereas it decreased in other patients whose heart rate and blood pressure nearly doubled. In the study of Camici et al. (1), the similar trend observed for lactate, pyruvate and alanine in multiple paired samples, together with the consistency of a decreased glucose uptake and increased free fatty acids uptake with the behavior of the respiratory quotient, may lend some credibility to the data. The absence of ventricular function abnormalities during peak pacing contrasts with some reports (3). The absence of lactate production during pacing-induced angina contrasts with previous reports that describe, at least in some patients, myocardial lactate production or decreased extraction (4) and increased myocardial oxygen extraction (5). Because patients included in previous studies by other groups might not have been carefully characterized and because syndrome X is likely to be very heterogeneous, these discrepancies might be related to the differences in patient groups.

However, Camici et al. (1) not only found no objective signs of ischemia in their patients with angina and normal coronary arteries, but also provide data that suggest that the pattern of myocardial substrate utilization in these patients is opposite to that observed during myocardial ischemia and appears to be associated with an increased mechanical efficiency of the ventricular pump function. The authors interpret the metabolic changes observed in those patients with syndrome X as being due to an increased fatty acid oxidation that inhibits pyruvate entry into the Krebs cycle (consistent with the lower carbohydrate oxidation and respiratory quotient during peak pacing). However, such different metabolic handling of substrates does not explain the anginal pain, the "ischemic" ST segment depression or the reduced coronary vasodilator response that apparently is the most consistent feature of this syndrome (6).

A prearteriolar constriction was postulated (7.8) to ac-
count for the reduced vasodilator response and anginal pain observed after administration of dipyridamole in patients with syndrome X. A compensatory production of adenosine could explain the development of angina in the presence of a patchy distribution of ischemia and even in its absence (8). Unfortunately, we have no information on the effects of dipyridamole in the 12 patients studied in this report; thus, the relation between vasomotor and metabolic abnormalities remains undefined.

Implications. As a reviewer of manuscripts, I am more inclined to accept controversial data from established investigators (even though at times I have to admit humbly that I do not understand them) than data that behave very obediently and consistently, as everyone expects. Controversial reports from groups with experience in the field may open up new avenues for research. The possibility that a metabolic abnormality exists deserves to be considered even if it seems to lead to conclusions that contrast with prevailing opinions and even if, at this stage, it fails to explain all the clinical findings. Controversial reports should also serve as a stimulus for future studies on carefully characterized and homogeneous groups of patients. Further studies should attempt to 1) confirm whether a metabolic abnormality is present in syndrome X despite the presence of an improved mechanical efficiency of the left ventricle, 2) identify its cause, and 3) explore the causes of reduced vasodilator reserve, anginal pain, ischemic ECG changes and the signs of ischemia often reported by other investigators in apparently similar patients. In such studies a careful and comprehensive characterization of patients is essential because those patients who are now labeled as having syndrome X may not be a homogeneous group and their chest pain and "ischemic" ST segment changes may have different causes.

Time, an open mind and careful studies will eventually allow the term syndrome X to be replaced by other terms indicating the various alterations.

References