Therapeutic Approach to Microvascular Angina (Syndrome X)

I read with interest the study by Kaski et al. (1) on the use of enalapril in syndrome X. The therapeutic approach to this condition continues to focus on vasodilator agents despite previous reports of limited efficacy (2). Metabolic studies (3) have provided evidence of systemic insulin resistance in patients with syndrome X. Myocardial metabolism in animal models of insulin resistance is characterized by increased cellular oxidation of fatty acids and markedly impaired oxidative glucose metabolism (4). This pattern of myocardial energy metabolism has also been demonstrated in patients with syndrome X (5) and suggests an alternative therapeutic approach to the condition. Inhibition of fatty acid oxidation with carnitine palmitoyl transferase inhibitors normalizes myocardial carbohydrate and fatty acid metabolism in animal models of insulin resistance (4). Furthermore, carnitine palmitoyl transferase inhibitors are nontoxic in vivo and have undergone trials as hypoglycemic agents in humans (6).

Carnitine palmitoyl transferase inhibitors will be beneficial in syndrome X if the clinical manifestations of the condition result from the abnormal myocardial metabolism associated with insulin resistance. Certainly, exertional muscle pain is a recognized feature of metabolic myopathies. In addition, the occurrence of apparent ischemic electrocardiographic changes is well documented in intramyocardial metabolic disturbances (7). The generalized abnormalities of vascular smooth muscle function characteristic of syndrome X have been demonstrated in both insulin-resistant and insulin-deficient states in humans (8). Both of these conditions are associated with increased cellular oxidation of fatty acids and impaired oxidative glucose metabolism. Experimental studies (9) indicate that normal cellular glucose oxidation may be important for endothelium-dependent vascular smooth muscle relaxation. Hence, it is at least conceivable that the clinical manifestations of syndrome X result from the deranged energy metabolism associated with insulin resistance and could, therefore, be altered by carnitine palmitoyl transferase inhibitors. On the basis of the available evidence a trial of metabolic therapy in syndrome X appears to be justified.

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References


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LETTERS TO THE EDITOR

I am grateful to Seery for his interesting comments. I share Seery’s concern that the therapeutic approach to the so-called cardiac syndrome X has focused mainly on antianginal agents, whether vasodilators or otherwise. However, there are reasons for this. An ischemic origin for syndrome X has been postulated in view of the anginal character of the chest pain, ST segment depression on exercise testing and findings of “objective” evidence for myocardial ischemia and reduced coronary blood flow reserve in some patients (1). Studies by Cannon et al. (2) further confirmed that patients with angina and normal coronary arteriographic findings had transient myocardial ischemia, as assessed by transmyocardial lactate measurements and radionuclide ventriculography. In the absence of epicardial narrowings, prearteriolar microvascular dysfunction was postulated as the mechanism responsible for ischemia in this condition (“microvascular angina”) (2). Recently, both microvascular endothelial dysfunction and ischemia were documented by Egashira et al. (3) in patients with syndrome X. However, despite evidence of myocardial ischemia in some patients, controversy exists as to the true nature of syndrome X. Indeed, abnormal coronary blood flow reserve and microvascular ischemia can be objectively demonstrated in only a minority of patients with angina and normal coronary arteries (4). Other hypotheses have therefore been postulated; among these are abnormal pain perception, increased sympathetic activity and metabolic abnormalities. Studies have now focused on these mechanisms, and it has been shown (5) that imipramine, a drug that has been used successfully in the management of chronic pain syndromes, improved the symptoms of patients with chest pain and normal coronary arteriographic results. We recently observed (6) that patients with syndrome X have impaired autonomic function on the basis of reduced heart rate variability. Relevant to this observation, and to the effects of enalapril in patients with syndrome X (7), is the fact that angiotensin II facilitates sympathetic nerve influences in the heart. Treatment with angiotensin-converting enzyme inhibitors is known to attenuate sympathetically mediated coronary vasoconstriction (7), and this could explain the beneficial effects of enalapril in our patients with syndrome X and microvascular angina. Increased sympathetic drive is certainly an attractive pathogenetic hypothesis in the setting of angina with normal findings on the coronary arteriogram. Interaction between the central and sympathetic nervous systems may influence pain perception (4), and increased sympathetic drive is present in patients with insulin resistance, recently described in association with syndrome X (8).

I agree with Seery that carnitine palmitoyl transferase inhibitors could be beneficial in patients with syndrome X for the reasons expressed in his letter. However, it would be erroneous to assume, as Seery appears to do, that cardiac syndrome X is caused by abnormal cardiac metabolism due to insulin resistance, and, therefore, that interventions aimed at improving this metabolic abnormality will be...
universally beneficial for patients with this syndrome. We ought to remember that the term "syndrome X" is a descriptive term only, and a poor one indeed. Syndrome X is a heterogeneous entity, and different patient subgroups have now been identified. In some patients, symptoms may be caused by myocardial ischemia or microvascular endothelial dysfunction, or both; in others by increased pain perception, estrogen deficiency, psychologic disturbances or a combination of these. Patients with insulin resistance may represent another pathogenic subgroup. However, the proportion of patients with syndrome X in whom insulin resistance is responsible for the clinical manifestations is not yet known.

A trial of metabolic therapy, as suggested by Seery, may be justifiable in syndrome X. However, this approach is likely to succeed in only those patients whose symptoms are caused by the metabolic disorder but not in every patient with angina and normal coronary arteriographic findings. Too often since the initial description of syndrome X have investigators mistakenly attempted to identify a single etiologic mechanism for this heterogeneous condition. Let us not fall into this trap yet again.

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References

Assessment of Cardiovascular Autonomic Function

I read the report by Zarich et al. (1) with immense interest. However, I am concerned about the methodology used in testing the autonomic function of their patients. The cutoff points for an "abnormal" test result for the Valsalva maneuver and the systolic blood pressure response to standing were taken as 1.25 and 20 mm Hg, respectively. In fact, these should be 1.0 for the Valsalva maneuver and 30 mm Hg for a decrease in systolic blood pressure. Zarich et al. did not take into consideration the heart rate response to standing, which tests the parasympathetic autonomic nervous system. The involvement of the parasympathetic autonomic nervous system is inferred by Zarich et al. to be more involved in diabetic autonomic neuropathy, causing the circadian pattern of myocardial ischemia. Again, the autonomic score is given as 0, 1 or 2, depending on whether a test result is normal, borderline or abnormal. A "battery" of at least five autonomic tests should be performed rather than the four used by Zarich et al. because no single test is sensitive enough to detect and classify types of autonomic dysfunction. Despite the battery of five autonomic tests, ~6% of patients with autonomic insufficiency are unclassifiable and are grouped as "atypical" (2,3). I note that the Valsalva maneuver was performed only once, whereas a mean of three successive maneuvers is recommended (4). Such tests would stratify patients differently, and the differences in circadian patterns of ambulatory myocardial ischemia between groups I and II in the Zarich et al. study might therefore not hold true.

The frequency of silent myocardial ischemia in patients with autonomic insufficiency may be explained by a higher pain sensitivity threshold and ischemia tolerance in diabetic patients with autonomic neuropathy (5,6). In experimental animals, a "denervation supersensitivity," causing enhanced sensitivity to the action of the sympathetic nervous system may occur (7). Pericardial prostaglandins released in the pericardial fluid, modulating the sympathetic effects of the heart, is an interesting hypothesis (7). Myocardial ischemia as the cause rather than the effect of neuropathy, including autonomic neuropathy, particularly in early myocardial ischemia, is an exciting new concept and requires further confirmation (8,9).

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References

Reply

Siddiqi asserts that there is one battery of cardiovascular tests of the autonomic nervous system with universally accepted cutoffs between normal and abnormal test results. In reality, there are a number of different tests assessing cardiovascular autonomic function and no single established battery (1-3). Any test used to assess cardiovascular autonomic function should have acceptable sensitivity, specificity and reproducibility. Some investigators (2-4) have reported, for example, that the heart rate response to standing, a test advocated by Siddiqi, does not fulfill these criteria. The four tests that we used in our study to measure autonomic function satisfy the sensitivity, specificity and...


classified as the context in which the information is presented.