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

Reply

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