Microvascular dysfunction in cardiac syndrome X: the role of inflammation

Between 10% and 30% of patients who undergo diagnostic coronary angiography because of typical symptoms of angina pectoris are found to have "normal" or "near normal" epicardial coronary arteries. Of these patients, those who have predominantly effort-induced chest pain and ST-segment depression or transient myocardial perfusion abnormalities, or both, suggestive of myocardial ischemia during spontaneous or provoked angina are considered to have cardiac syndrome X (CSX). Patients with coronary artery spasm, left ventricular hypertrophy, diabetes mellitus and cardiomyopathy are usually not considered to have the syndrome.

Although CSX is not associated with an increased risk of death, it often severely impairs quality of life and represents a substantial cost burden to the health care system.[1]

CSX is a heterogeneous condition that encompasses several possible causal mechanisms. Cardiac and noncardiac mechanisms have been proposed, among which endothelial dysfunction of the coronary microcirculation features prominently.

The amount by which coronary flow increases in response to maximal arteriolar dilatation represents what is known as "coronary blood flow reserve" and reflects mainly the vasodilator capacity of the coronary microcirculation. A reduction in this reserve or an increase in coronary artery resistance, or both, may alter the balance between coronary blood flow supply and myocardial metabolic demand. Myocardial ischemia resulting from coronary microcirculation abnormalities ("microvascular angina") has been suggested to be a plausible pathogenic mechanism in CSX. The causes of microvascular dysfunction in CSX have not been fully elucidated as yet and are likely to be multiple.

Endothelial dysfunction, with an imbalance between vasodilator forces such as nitric oxide and vasoconstrictor forces such as endothelin-1, may explain, at least in part, the abnormal behaviour of the coronary microvasculature seen in CSX patients. Endothelial dysfunction in patients with microvascular angina appears to be a generalized process involving both coronary and peripheral conduit arteries. Brachial artery dilatation in response to increased blood flow is mainly caused by endothelial release of nitric oxide (endothelial-dependent flow-mediated dilatation [FMD]), and ultrasound assessment of such dilatation represents a surrogate index of coronary endothelial function. As recently reported by our group, abnormal brachial artery FMD responses showed a correlation with transient myocardial perfusion defects in CSX patients, as assessed by radionuclide tests.[2] This finding supports the pathogenic role of endothelial dysfunction and myocardial ischemia in CSX patients with microvascular angina.

Recent findings have suggested that inflammation may play a pathogenic role in endothelial dysfunction in CSX. C-reactive protein (CRP), a marker of chronic inflammation and a predictor of vascular events, has been associated with impaired endothelial function in patients who have coronary artery disease (CAD) but also with coronary microvascular endothelial dysfunction in patients who have CSX. Emerging data also suggest that CRP is not merely an inflammatory marker but also a potential cause of endothelial activation in CSX, since it has been associated with enhanced levels of cellular adhesion molecules, increased endothelin-1 expression and reduced bioavailability of nitric oxide. CRP levels have been reported to be elevated in patients with CSX[3] and to correlate with electrocardiogram markers of myocardial ischemia and clinical disease activity.[4] However, endothelial dysfunction has also been linked to CAD risk factors, such as smoking, dyslipidemia, estrogen deficiency, obesity and insulin resistance, all of which are frequently present in CSX patients. Therefore, whether elevated CRP levels in CSX patients truly reflect an inflammatory-mediated pathogenesis of the condition or the burden imposed by CAD risk factors is a crucial issue that requires investigation (unpublished studies from our group suggest that the former is likely to be the case). As also observed in patients with CAD, elevated CRP levels in CSX patients have been shown to be independent of age, sex, obesity and cholesterol levels, which suggests that inflammation may enhance the effect of certain conventional risk factors on promoting endothelial dysfunction and atherogenesis.[3] Subangiographic atheroma have been detected in CSX patients with the use of coronary intravascular ultrasonography, a finding that emphasizes the limitations of coronary angiography — the "gold standard" to define normal coro-

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nary vessels in CSX — to detect early signs of atherosclerosis. Inflammation and endothelial dysfunction may also be implicated in promoting intima–media thickening, a noninvasive surrogate marker of early atheroma formation. We have recently shown that CRP concentrations correlate with the intima–media thickness of the common carotid artery in CSX patients, which confirms the presence of an impaired arterial wall structure and some degree of atherosclerotic burden in these patients, despite normal findings on coronary angiography. The reason why angiographic evidence of CAD progression is rare in patients with true CSX remains speculative. Protective mechanisms perhaps operate in these patients and deserve further investigation.

The potential importance of inflammation in the pathogenesis of CSX is highlighted by the beneficial effects observed with the use of statins and angiotensin-converting-enzyme (ACE) inhibitors, alone or together, in patients with CSX.[5] Statins have been shown to reduce CRP levels in different clinical settings, and the return to normal of CRP levels over time has been associated with a significant improvement in endothelium-dependent flow responses in CAD patients. In patients with CSX, statins and ACE inhibitors improve exercise-induced ischemic ST-segment depression and endothelial function. Moreover, ACE inhibitors and statins have been associated with improvements in intima–media thickness not directly related to lipid profile. Thiazolidinediones — oral insulin sensitizers that are peroxisome proliferator-activated receptor-gamma agonists — may also be useful in these patients, because these agents have anti-inflammatory effects, improve endothelial function and reduce carotid artery intima–media thickness even in patients without diabetes mellitus.

Research into the role of inflammation as a pathogenic mechanism of CSX has opened new avenues that may help to identify more rational strategies for managing this difficult and heterogeneous syndrome. Inflammatory markers and noninvasive measurements of arterial wall structure and function may be useful in identifying CSX patients at risk of recurrent and severe anginal symptoms, and even those in whom the prognosis may not be as good as in others and who may benefit from aggressive interventions on endothelial dysfunction. Whether the return to normal of CRP levels with drug therapy results in improved clinical symptoms and quality of life in CSX patients requires further assessment in prospective studies.

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