Editorials
Is the chest pain in cardiac syndrome X due to subendocardial ischaemia?

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Over the past 30 years the issue of chest pain in patients with a normal coronary angiogram has received much attention[1,2]. The interest in this condition, which has also been termed (cardiac) *syndrome X* when the pain is accompanied by ST segment depression during exercise electrocardiography, has two main causes: a) the first is clinical. Does the patient have heart disease? Can the condition be effectively treated? Is the patient's life expectancy shortened? b) the second one is that many of us thought that a better understanding of the pathophysiology of this condition would have improved our knowledge of the coronary circulation and of its control.

Clinically, we have learned that in up to 20% of patients with anginal chest pain, the coronary angiogram, usually obtained because of "positive" findings at one or more noninvasive tests, does not show significant narrowing of the vessel lumen[3]. Furthermore, patients with syndrome X usually have a poor response to conventional antiischemic therapy, which may lead to the unnecessary performance of repeated coronary angiography over the years because of recurrence of chest pain[4]. With regard to prognosis, a number of studies have consistently shown that these patients have a life expectancy similar to that of the general population, with the exception of those with conduction abnormalities such as left bundle branch block. The latter patients may develop dilated cardiomyopathy during follow-up[5-7].

The initial assumption regarding the pathophysiology of cardiac syndrome X was that the pain was due to myocardial ischaemia[8-11]. A number of factors pointed to this: the quality of the chest pain, the fact that it was often induced by exertion and the ischaemic-like changes on the exercise electrocardiogram.

Most commonly, myocardial ischaemia is demonstrated in patients with coronary artery disease (CAD) in whom the coronary vasodilator reserve (CVR, the ratio of myocardial blood flow during near maximal vasodilatation to the resting flow) is reduced in parallel with the severity of coronary stenoses[12]. However, a reduced CVR can also be demonstrated in patients with angiographically normal epicardial arteries and, in this circumstance, suggests dysfunction of the coronary microvasculature[13]. For instance, a reduced CVR has been demonstrated in patients with hypertrophic cardiomyopathy and in those with left ventricular hypertrophy secondary to systemic hypertension despite a normal coronary angiogram[14]. In both cases massive hypertrophy of smooth muscle in the media of the intramural coronary arteries was demonstrated with a resultant increase in the wall/lumen ratio; this microvascular remodelling is thought to be the main factor responsible for the reduced CVR in these patients.

Similarly, microvascular dysfunction has been proposed as a mechanism of ischaemia in cardiac syndrome X. In the '80s Cannon and Epstein[15] demonstrated that the administration of ergonovine induced a fall in myocardial blood flow during atrial pacing in patients with normal epicardial arteries who experienced chest pain compared with those who did not experience pain, with no associated change in the epicardial vessel calibre. In view of this background, the term "microvascular angina" was coined and it was suggested that er-

gonovine probably induced vasoconstriction of the "small intramural pre-arteriolar vessels" in the patients who had chest pain. Since then, the CVR in syndrome X has been the object of many studies which overall, however, have failed to provide definitive evidence in favour or against the ischaemic hypothesis[16-19]. These inconsistencies can be explained, at least in part, by a number of reasons including inappropriate selection of the study population, inherent limitations of the techniques used to measure the CVR and the lack of appropriate normal controls[2]. One argument used by the supporters of the ischaemic origin of pain in syndrome X, is that ischaemia could be confined to small areas of the heart particularly in the subendocardium. Most of the techniques used so far for the measurement of myocardial blood flow and CVR are not provided with a spatial resolution sufficient to enable the true measurement of the subendocardial and subepicardial blood flow in man.

Recently, Panting et al.[20] have addressed this problem using cardiovascular magnetic resonance imaging with the paramagnetic contrast agent gadolinium to assess myocardial perfusion in patients with cardiac syndrome X. In line with previous reports in which CVR was measured[19], there was no significant difference in the value of the myocardial perfusion index for transmural (i.e. full thickness) perfusion between controls and patients with syndrome X both at rest or following intravenous adenosine. However, whilst in the controls the myocardial perfusion index increased significantly after adenosine in both the subepicardium and subendocardium, in the patients with syndrome X the myocardial perfusion index did not increase significantly in the subendocardium, but it did increase in the subepicardium. They speculated that chest pain in these patients might be explained by ischaemia secondary to diminished (or absent) vasodilatation of the coronary microvasculature following infusion of adenosine, leading to relative underperfusion of the subendocardium.

Previous studies in animals have demonstrated that the rate of contrast wash-in is linearly related to perfusion with good agreement with the microsphere measurement of myocardial blood flow. However, this depends on a uniform and rapid injection of contrast into a catheter positioned in the superior vena cava to minimise the effect of extracellular leakage and of changes in flow that would otherwise introduce inaccuracies to the value of the perfusion parameter. In addition, it assumes linearity of the signal intensity with gadolinium, which does not hold true near the peak values of the signal intensity in the blood pool. Furthermore, the estimate of a perfusion index does not provide information about the absolute values of coronary flow reserve[21,22].

One of the advantages of cardiac magnetic resonance is that perfusion measurements can be combined with the evaluation of global and regional left ventricular functions[23]. Unfortunately, Panting et al.[20] failed to assess the concomitant left ventricular function and therefore they could not prove whether the perfusion images obtained following adenosine were accompanied by the development of myocardial dysfunction (usually an early phenomenon in the cascade of events that follow myocardial ischaemia) and whether they represented myocardial ischaemia rather than a heterogeneity in transmural perfusion. In this respect several previous studies with stress echocardiography consistently demonstrated that, despite the provocation of chest pain, patients with syndrome X had no impairment in contractility[24,25].

In summary, the study of Panting et al.[20], although provocative, does not provide definite evidence on whether the chest pain in syndrome X is due to myocardial ischaemia. To confound the whole issue even further, previous studies have shown that the typical chest pain reported by patients with normal coronary angiograms can be evoked by mechanical and/or electrical stimulation of the right atrial and ventricular myocardium, which clearly do not cause myocardial ischaemia[26].

We have previously studied angina pectoris as a model of visceral pain, by employing functional brain imaging with positron emission tomography and oxygen-15 labeled water, measuring the regional cerebral blood flow as an index of the regional synaptic activity during pharmacologically-induced myocardial ischaemia. Using this approach, we were able to "map" the neural systems involved in the perception of anginal pain in patients with CAD[27]. Subsequently, the technique was applied to investigate the difference between CAD patients with painful or silent myocardial ischaemia[28]. Since the distinguishing feature between these two populations was the cortical activation rather than any demonstrable differences either in the heart or lower in the neuraxis, we concluded that an abnormal central nervous system handling of afferent signals might determine the perception of cardiac pain for comparable levels of afferent inputs. A corollary of this was our hypothesis that an abnormal central nervous system handling of afferent signals might *per se* produce a syndrome characterized by cardiac chest pain.

Therefore, in a recent study[29] we aimed to ascertain whether cardiac syndrome X patients have a distinct pattern of cortical activation during chest pain by measuring the regional cerebral blood flow at rest and during dobutamine-induced chest pain in a group of patients with syndrome X and in an equal number of matched normal volunteers. The results were also compared with data from patients with known CAD. Syndrome X patients and normal controls had comparable regional cerebral blood flow responses to dobutamine stress, with activations in the hypothalamus, thalami, right frontal cortex and the anterior temporal poles, associated with the sensation of a fast or powerful heartbeat. However, in the syndrome X patients, but not in the controls, the dobutamine stress also generated severe chest pain. This was associated with an increased

activity in the right anterior insula at the junction with the frontal operculum. Conversely, there was greater activity in the left insula and right cingulate cortex in controls. A comparison with our earlier published data from patients with angina due to CAD also showed greater right anterior insular activity in the syndrome X patients during high dose dobutamine infusion. Therefore, we believe that right insula activation has a significant role in the perception of chest pain in syndrome X (the insula is known to receive cardiopulmonary inputs).

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