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

Paolo G. Camici

MRC Clinical Sciences Centre and National Heart and Lung Institute, Imperial College, Hammersmith Campus, Du Cane Road, London W12 0NN, UK

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This editorial refers to 'Is subendocardial ischaemia present in patients with chest pain and normal coronary angiograms? A cardiovascular MR study' by I.A.C. Vermeltfoort et al., on page 1554

Over the past 30 years, the issue of chest pain in patients with a normal coronary angiogram has received much attention.1 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 reasons:

(i) The first is clinical. Does the patient have heart disease? Can the condition be effectively treated? Is the patient’s life expectancy shortened? (ii) The second one is relative to the pathophysiology of this condition. Is the chest pain in patients with syndrome X of ischaemic origin? And if the pain is due to myocardial ischaemia what are the mechanisms?

Clinically, in a significant proportion of patients with a history of chest pain, the coronary angiogram does not show significant narrowing of the vessel lumen. These patients usually have a poor response to conventional anti-ischaemic therapy, which may lead to the unnecessary performance of repeated coronary angiograms over the years because of recurrence of chest pain. With regard to their prognosis, a number of studies have consistently shown that these patients have a life expectancy similar to that of the general population,2 with the exception of those with conduction abnormalities such as left bundle branch block that may develop dilated cardiomyopathy during follow-up.3

From the pathophysiological point of view things are far from clear. The initial hypothesis that the chest pain is of ischaemic origin was based on the presence of ST-segment depression during spontaneous or stress-induced chest pain, as well as on the evidence of reversible stress-induced myocardial perfusion defects. Furthermore, some studies have provided evidence of reduced endothelium-dependent and independent coronary vasodilatation as well as metabolic evidence of myocardial ischaemia.4 Other studies, however, failed to find evidence of abnormal myocardial blood flow or coronary flow reserve (CFR) or metabolic or functional evidence of ischaemia during stress.4 It must be noted, however, that inclusion and exclusion criteria in the vast majority of these studies have not been especially strict. In particular, the category of ‘normal coronary angiogram’ has been a broad one, often including cases of coronary artery disease (CAD) ranging from minimal disease to coronary stenoses up to 50% of luminal diameter. A more homogeneous set of patients would be defined if the following exclusion criteria are employed: absence of left bundle branch block either on the resting or exercise electrocardiogram; absence of even minimal irregularities on the arteriogram; no evidence of diabetes mellitus, arterial hypertension, hyperlipidaemia, valve disease (including mitral valve prolapse), epicardial arterial spasm, and cardiomyopathy.

These exclusion criteria are essential because, more recently, it has become clear that abnormalities in the function and structure of the coronary microcirculation, which may be severe enough to contribute to myocardial ischaemia, occur in many of the above conditions.4 Most commonly, myocardial ischaemia is demonstrated in patients with CAD in whom CFR is reduced in parallel with the severity of coronary stenoses.5 However, a reduced CFR can also be demonstrated in patients with angiographically normal epicardial arteries and, in this circumstance, suggests coronary microvascular dysfunction (CMD). The latter has been demonstrated in patients who are at higher risk of developing CAD and is thought to represent the functional counterpart of traditional coronary risk factors. CMD can also occur in patients with primary (e.g. hypertrophic) or secondary (e.g. hypertensive) cardiomyopathies and is most commonly due to adverse remodelling of intramural arterioles [for a detailed review of CMD see Camici and Crea]. The term syndrome X (originally the Group x in the paper of Arbogast and Bourassa of 1973)6 was coined to stress the uncertainty over the pathophysiology of chest pain. Therefore, this term should not be used in patients, such as those with risk factors for CAD or cardiomyopathies, in whom myocardial ischaemia due to CMD is known to occur.

It is possible, however, that a subset of patients exists who have a reduced CFR and metabolic evidence of myocardial ischaemia in whom none of the known causes of CMD can be demonstrated. Maseri et al.7 have proposed that in...
these patients focal ischaemia in small myocardial regions scattered throughout the myocardium and caused by pre-arteriolar dysfunction might explain the paradox of angina and ST-segment depression. 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.

In an article published in 2002, Panting et al. have addressed this problem using cardiovascular magnetic resonance (CMR) imaging with the paramagnetic contrast agent gadolinium to assess myocardial perfusion in patients with cardiac syndrome X. In line with previous reports where CFR was measured, there was no significant difference in the value of the myocardial perfusion index (MPI) for transmural (i.e. full thickness) perfusion between controls and patients with syndrome X both at rest or following intravenous adenosine. However, while in the controls, the MPI increased significantly after adenosine in both the subepicardium and subendocardium, in the patients with syndrome X the MPI did not increase significantly in the subendocardium, but it did increase in the subepicardium. In addition, in their paper, Panting et al. showed pictures of subendocardial signal reduction on the first pass CMR images and 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 under-perfusion of the subendocardium.

One of the advantages of CMR is that perfusion measurements can be combined with the evaluation of global and regional left ventricular function. Unfortunately, Panting et al. failed to assess left ventricular function during stress and therefore they cannot prove whether the perfusion images obtained following adenosine are accompanied by the development of myocardial dysfunction (usually an early phenomenon in the cascade of events that follow myocardial ischaemia) and represent myocardial ischaemia rather than 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.

In this issue of the journal, Vermeltfoort et al. report the results of a study, that is very similar to that of Panting et al., where CMR was used to assess both visually and semi-quantitatively subendocardial and subepicardial perfusion, at rest and during intravenous adenosine in 20 patients with angina pectoris and normal coronary angiograms. Similarly to the study of Panting et al., Vermeltfoort et al. calculated the MPI using the normalized upslope of myocardial signal enhancement. An index for myocardial perfusion reserve (MPRI) was calculated by dividing the MPI values at maximal vasodilatation by the values at rest.

In contrast to the finding of Panting et al., in the study of Vermeltfoort et al., MPI increased significantly and, by a comparable amount, during adenosine infusion both in the subendocardium and the subepicardium. The transmural MPRI was $1.83 \pm 0.50$. In addition, they found that all patients showed initial subendocardial signal reductions on the first pass CMR images, which, however, disappeared after approximately five heart beats. As demonstrated by previous studies, these temporary signal losses are artifacts related to the first pass sequence and are different from the defects due to myocardial ischaemia which are characterized by a more sustained signal loss.

The results of the study of Vermeltfoort et al. are consistent with other studies where myocardial blood flow and flow reserve were measured in patients with cardiac syndrome X and age and sex matched controls using positron emission tomography (PET). In these PET studies, no difference in average transmural myocardial blood flow and flow reserve was found between patients and controls. Although the resolution of the PET scanner used in these studies did not allow selective measurement of subendocardial and subepicardial blood flow, a severe reduction in subendocardial flow, such as that suggested in the study of Panting et al. would have resulted in an appreciable reduction in average transmural flow and the CFR.

In conclusion, after more than 30 years and a wealth of different studies, the mystery that surrounds the mechanisms of chest pain in patients with cardiac syndrome X seems far from being resolved. Perhaps, at least in some of these patients, the origin of chest is not in the heart, but somewhere else as suggested by the work of Rosen et al.

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**References**