The complex link between brain and heart in cardiac syndrome X

G A Lanza, F Crea

There are new insights into the neural mechanisms responsible for enhanced cardiac pain perception in syndrome X

In cardiac syndrome X, the presence of ischaemic-like ST segment changes during chest pain, in the absence of epicardial coronary stenoses, suggests that myocardial ischaemia caused by coronary microvascular dysfunction is responsible for angina. This view is supported by the documentation of abnormalities in myocardial perfusion on radionuclide studies¹ and abnormal coronary blood flow response to vasoactive stimuli. Furthermore, several abnormalities able to cause microvascular dysfunction have been reported, including increased adrenergic function,⁴ increased stress induced coronary sinus release of endothelin-1,⁵ and increased activity of sodium–hydrogen countertransport.⁶ Yet several studies failed to show myocardial lactate production and left ventricular dysfunction⁷–¹⁴ during angina and ST segment depression, thus casting some doubts on the ischaemic origin of chest pain and ECG changes.⁵

In 1988, Shapiro and colleagues reported the observation that syndrome X patients refer chest pain during intra-atrial saline injection, suggesting that an abnormally increased perception of pain during usually painless cardiac stimuli could be the mechanism responsible for chest pain in cardiac syndrome X. Several studies consistently confirmed this finding,⁷–¹⁰ lending further support to the hypothesis that a reduced cardiac pain threshold might be the predominant cause of the syndrome. These observations generated some new questions:

1. Is enhanced perception of painful stimuli confined to the heart or is rather generalised?
2. Where does the abnormality responsible for enhanced pain perception reside in the nervous system?
3. What is the cause of this neural abnormality?

CONFICTING RESULTS

As far as the first point is concerned, studies gave conflicting results,⁷–¹⁰ but the only study which used a controlled, blind protocol failed to find evidence of generalised enhanced pain perception.⁹

Accordingly, using a randomised, double blind, “sham” controlled design, we found that enhanced cardiac pain perception is indeed present in syndrome X patients and is mainly confined to ventricular myocardium.⁶

In an interesting study published in a recent issue of Heart, Rosen and colleagues⁶ provide new insights into the neural mechanisms responsible for enhanced cardiac pain perception in syndrome X. They performed dynamic H₁⁸O positron emission tomography to map regional cerebral blood flow (rCBF) in eight syndrome X patients (six females) and in eight sex and age matched healthy controls. rCBF was evaluated at rest and during echocardiographic dobutamine stress test; the results were also compared with those obtained in a group of historical patients with stable angina and coronary artery disease (CAD) (n = 9, two females). No control subject developed chest pain or ECG changes during dobutamine infusion. In contrast, all syndrome X patients developed typical anginal pain and ST segment depression, in the absence of detectable left ventricular wall motion abnormalities. rCBF distribution showed significant differences between syndrome X patients and controls, mainly consisting of an increased flow/activity in the right anterior insula, at the level of the frontal operculum junction in the former group. Of note, this latter finding also distinguished syndrome X from CAD patients. Thus, the authors propose that syndrome X may be a “cortical pain syndrome”, resulting in a “top down” process which facilitates the transmission to the cortex of pain stimuli which are usually blocked at the subcortical level.

This working hypothesis is certainly interesting, but it does not seem to be fully supported by the results of the study nor by recent reports on cardiac abnormalities in syndrome X. Firstly, as also recognised by the authors, the peculiar increase of right insula activity detected during chest pain in syndrome X patients does not necessarily have to be ascribed to an abnormal cortical influence, but it might be caused by afferent impulses originating from the heart, abnormal signal transmission and/or modulation at subcortical level(s), or by a variable combination of these abnormalities. Secondly, the comparison of rCBF between syndrome X and CAD patients during dobutamine induced chest pain presents limitations, as the latter were predominantly males, were studied with a different technique, and developed stress induced left ventricular dysfunction, all of which may have influenced the pattern of rCBF. Finally, rCBF measurements provide indirect information about changes in neural function and might miss functional changes of small neural areas.
that previously demonstrated by Rosen and colleagues in anginal CAD patients.  

 Authors’ affiliations  
 G A Lanza, F Crea, Istituto di Cardiologia, Università Cattolica del Sacro Cuore, Roma, Italy  

REFERENCES  
Images in Cardiology

Microvascular obstruction and missed infarction

A 68 year old retired physician with no previous cardiac history presented with a four hour history of central crushing chest pain. His pulse was 90 beats/min, blood pressure 170/90 mm Hg, with no evidence of heart failure. His ECG demonstrated right bundle branch block, and the troponin T was raised at 0.4 µg/ml (normal < 0.1 µg/ml). Over the next 24 hours he had further chest pain. Cardiac x ray angiography demonstrated normal left ventricular function and minor non-flow limiting disease of the mid left anterior descending (LAD) and right coronary (RCA) arteries.

Cardiovascular magnetic resonance (CMR) was performed. The blood flow of the left side septum was akinetic on cine imaging. After gadolinium-DTPA, in the early phase (< 5 minutes) there was extensive microvascular obstruction (arrow) in the territory of the first septal branch of the LAD. During the late phase (> 10 minutes), these areas still persist but with surrounding hyperenhancement (arrows). Gadolinium-DTPA is a small molecule that diffuses into the extracellular fluid making the tissue appear bright on CMR. It does not cross intact cell membranes. Because of myocardial death, myocardial infarction tissue has an increased volume of extracellular fluid making the tissue appear bright on CMR. It does not cross intact cell membranes. Because of myocyte death, extracellular fluid is seen on CMR because of capillary collapse and microvascular obstruction, and this is best seen in the early phase. If microvascular obstruction is extensive there will be no flow down the subtending coronary artery, even if the artery is re-opened—the no-reflow phenomenon. Microvascular obstruction is associated with a worse prognosis. The transmural extent of infarction predicts subsequent functional recovery and the potential for recovery after revascularisation.

In the light of the CMR findings, the x ray angiography was reviewed. The first septal did not opacify and a stump off the LAD was noted. This case illustrates how CMR can make the diagnosis of coronary disease where angiography proved difficult to interpret because of ostial occlusion of a side branch vessel. The diagnosis was acute myocardial infarction because of occlusion of the first septal artery with microvascular obstruction.