



## Editorial

## Advances in understanding the mechanisms of angina pectoris in cardiac syndrome X

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**This editorial refers to 'Abnormal cortical pain processing in patients with cardiac syndrome X' by M. Valeriani *et al.*, doi:10.1093/eurheartj/ehi229**

Angina pectoris was initially described by Heberden in 1772 and is considered to be the hallmark of ischaemic heart disease. However, with the advent of selective coronary angiography, clinicians were confronted with a conundrum as some patients with 'unmistakable' angina had angiographically normal epicardial coronary arteries. This apparent disparity between the clinical symptoms and the angiographic findings appeared to be resolved when it was demonstrated that affected patients had electrocardiographic and metabolic evidence of ischaemia. Thus, it was hypothesized that the angina experienced by these patients was due to myocardial ischaemia secondary to coronary microvascular dysfunction. This new disorder was referred to as cardiac syndrome X and is typically characterized by exertional angina, electrocardiographic evidence of ischaemia on stress testing, angiographically smooth epicardial coronary arteries, and no other recognized cause for the chest pain. Multiple studies have subsequently demonstrated the presence of microvascular dysfunction in these patients.

Controversy arose when several well-controlled studies failed to identify metabolic evidence of ischaemia in these patients despite reproducing the chest pain. This led to divided opinion among the researchers, with views ranging from an 'ischaemic hypothesis', where technical limitations account for the inability to detect the ischaemia, to a 'non-ischaemic hypothesis' where alternative mechanisms are proposed to be responsible for the chest pain. Recent technical advances have assisted in demonstrating surrogate markers of ischaemia

in these patients, including subendocardial perfusion defects on magnetic resonance imaging,<sup>1</sup> production of oxidative stress markers during pacing-induced angina,<sup>2</sup> and a reduction of high-energy phosphates on nuclear magnetic spectroscopy.<sup>3</sup>

The 'non-ischaemic hypothesis' has been further advanced by the demonstration of altered pain perception in patients with syndrome X. Several studies investigating patients with this disorder have demonstrated an increased pain sensitivity to cardiac stimuli such as intracardiac catheter manipulation, radiographic contrast injection, intravenous adenosine administration, and atrial and ventricular pacing. Further studies suggested that the abnormal pain perception was a generalized phenomenon by demonstrating an increased pain sensitivity to a variety of peripheral stimuli including tourniquet application and electrical and thermal skin stimulation.<sup>4</sup>

The mechanism responsible for the increased pain sensitivity in syndrome X patients is likely to involve a defect in the nociceptive pathways responsible for angina pectoris. Our understanding of this pathway remains incomplete but the current perspective is summarized as follows. Noxious stimuli activate nociceptive receptors in sensory endings of thin myelinated (A $\delta$  fibres) and unmyelinated (C fibres) afferent nerve fibres. Several stimuli may be involved,<sup>5</sup> but adenosine has received considerable attention because intravenous administration to healthy volunteers produces angina-like chest pain without associated ischaemic ECG changes. This algogenic effect is mediated via A<sub>1</sub> receptors located on perivascular sympathetic nerves and is independent of adenosine's vasodilatory effect mediated via A<sub>2</sub> receptors.<sup>5</sup> The stimulated afferent cardiac pain fibres pre-dominantly ascend to the sympathetic ganglia (C7–T4) and synapse in the dorsal horn of the spinal cord along with other converging afferent nociceptive fibres. Subsequent nociceptive transmission

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is modulated by these converging impulses and by descending neural impulses. The spinothalamic tracts propagate the impulses to the posterior thalamus where further modulation of the signal occurs before cortical recognition of the pain in the somatosensory and cingulate cortex.

A number of studies have investigated various aspects of this nociceptive pathway in syndrome X patients. The exaggerated response to exogenous adenosine in syndrome X patients<sup>6</sup> could suggest an abnormality at the level of the adenosine receptor, and theophylline (a non-specific A<sub>1</sub>/A<sub>2</sub> antagonist) has been shown to increase the angina threshold in these patients. However, specific inhibition of the adenosine A<sub>1</sub> receptor by bamiphylline did not alter angina threshold, suggesting that this mechanism did not play a major role.

Spinal cord stimulation has been shown to be of benefit in alleviating severe angina associated with syndrome X.<sup>7</sup> The mechanism proposed for this therapy is stimulation of inhibitory neurons within the dorsal columns of the spine, thereby modulating afferent cardiac nociceptive transmission. However, the benefit of spinal cord stimulation is more complex because this therapy also appears to have anti-ischaemic properties, possibly modulated via alterations in cardiac autonomic function.

In recent years, attention has been directed to altered supraspinal responses in patients with syndrome X. Continuing their innovative studies on delineating the central neural pathways mediating angina, Rosen *et al.*<sup>8</sup> demonstrated a selective increase in regional cerebral blood flow into the right anterior insular cortex in syndrome X but not in control patients following dobutamine stress testing. They proposed that syndrome X patients have an 'ineffective thalamic gate' allowing unregulated transmission of nociceptive stimuli to the cortex, which are usually inhibited in healthy subjects or patients with coronary artery disease. Hence, the focus had shifted from the 'heart to the head' with data also suggesting a generalized disturbance in pain perception among patients with syndrome X.

The publication of Valeriani *et al.*<sup>9</sup> represents a further important advancement in understanding the anginal mechanism in syndrome X. This innovative study utilized a validated technique of assessing the cerebral cortical electrical potentials evoked following administration of cutaneous laser pulses (laser evoked potentials, LEPs). The laser pulses were applied at 2.5 times greater than the perceivable energy threshold to the chest wall and right hand of patients with syndrome X, refractory angina, and healthy controls. Each study region received three sequences (administered 5 min apart) of 30 stimuli. In addition to monitoring LEPs, subjects were asked to record the intensity of their pain on a visual analogue scale (VAS). Unlike many of the previous studies examining pain perception in syndrome X patients, this study employed a double-blind methodology and ensured appropriate matching of baseline angina frequency with the coronary artery disease patient group. Furthermore, although only cutaneous stimuli were utilized, the chest wall stimulation corresponded to the referred pain sites in the angina patient groups and thus could potentially

be transmitted via the nociceptive pathways responsible for angina pectoris. However, stimulation of the right hand (i.e. non-anginal distribution) produced similar results suggesting the stimulus was non-specific.

The first fundamental finding of the study is that pain threshold to cutaneous laser pulses did not differ among the three study groups, contradicting the previous concept (derived from unblinded/single-blind studies) that syndrome X is associated with a generalized increase in pain sensitivity. Although this investigation clearly shows no difference in threshold to cutaneous stimuli applied to the chest and hand, differences in pain sensitivity to cardiac stimuli cannot be excluded. Indeed, in the double-blind study undertaken at the same institution, patients with syndrome X were shown to have a higher sensitivity to threshold cardiac pacing than healthy controls.<sup>10</sup>

The second major finding of the current study is the absence of habituation to repetitive nociceptive stimuli in the syndrome X patients. The LEPs generated from neurons in the cingulate cortex (N2/P2 responses) showed a reduced response to successive sequences of laser stimuli applied to the chest wall in healthy control and coronary artery disease patients. Correspondingly, there was a reduction in the perceived pain intensity on the VAS to the consecutive stimuli sequences. In contrast, the syndrome X patients showed the same LEP and VAS responses to the first and last stimulus sequences. Thus, the prolonged episodes of angina frequently observed in patients with syndrome X may be due to the lack of habituation in this disorder.

Considering the current evidence relating to mechanisms of angina pectoris in patients with syndrome X, a 'contemporary hypothesis' would implicate both microvascular dysfunction and altered nociceptive perception. The latter appears to involve an increased cardiac but not cutaneous pain sensitivity with altered central nociceptive processing contributing to the abnormal perception. Perhaps, future studies will explore the inter-relationship between this nociceptive pathway and other higher cerebral centres. Such studies may provide insight into the puzzling 'post-angina fatigue' experienced by some patients with syndrome X, where they describe extreme exhaustion requiring bed rest during resolution of an anginal episode.

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