INFLAMMATION AND CARDIAC SYNDROME X - 2010

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Since its first description by Kemp et al. [1], the term "Cardiac X Syndrome" (CSX) has been used generically to encompass patients with chest pain and normal angiography in whom the pain is thought to be cardiac in nature [2]. CSX is often defined by the following characteristics: (a) exertional angina, (b) typical ST segment depression on exercise stress testing, and (c) angiographically normal epicardial coronary arteries [3]. The chronic anginal pattern experienced by these patients produces significant disability, although it is seldom associated with coronary events [2]. Work from our group in London in the past two decades

has focused on the pathogenesis and pathophysiology of CSX. This article briefly summarises some of our work in the field.

PATHOPHYSIOLOGY

The pathophysiology CSX is not homogeneous (Figure 1). Although chest pain associated with this disorder was initially ascribed to *myocardial ischemia*, as demonstrated by Arbogast and Bourassa [4], it became apparent shortly after the Kemp editorial article [1] that myocardial ischemia was not a universal finding in these patients. Whether this was due to the limited tools available for the detection of ischemia or to the heterogeneous nature of the condition continues to be an issue for debate. CSX has been also defined as "microvascular angina" (MVA) [5], as it has been shown to be associated with coronary abnormalities predominantly affecting the coronary microcirculation. Increased basal coronary vascular resistance and/or blunted vasodilator response of the endothelium were subsequently supported by several clinical studies [6-9]. However, other studies have failed to identify an evidence for ischemia despite the typical chest pain symptoms [10-12]. This led to speculating that other mechanisms –and not myocardial ischaemia- were responsible for the chest pain in this condition [13]. Among these, *altered pain perception* [14], *autonomic nervous system dysfunction* with increased sympathetic tone [15], o*estrogen deficiency* [16], *psychological abnormalities* [17] and *oesophageal dysmotility* [18,19] were some of the mechanisms proposed.

Microvascular endothelial dysfunction has been shown to be responsible for at least some of the abnormalities detected in the coronary circulation of CSX patients [20]. The role of *inflammation* as a pathogenic mechanism of CSX has been proposed given its strong link with endothelial dysfunction in CSX, and has been the focus of our research in recent years.

INFLAMMATION AND ENDOTHELIAL DYSFUNCTION

Reduced nitric oxide bioavailability due to endothelial dysfunction and enhanced endothelin-1 (ET-1) expression, promoted by raised C-reactive protein (CRP) levels may be implicated in the impairment of systemic endothelial vasoreactivity leading to MVA and

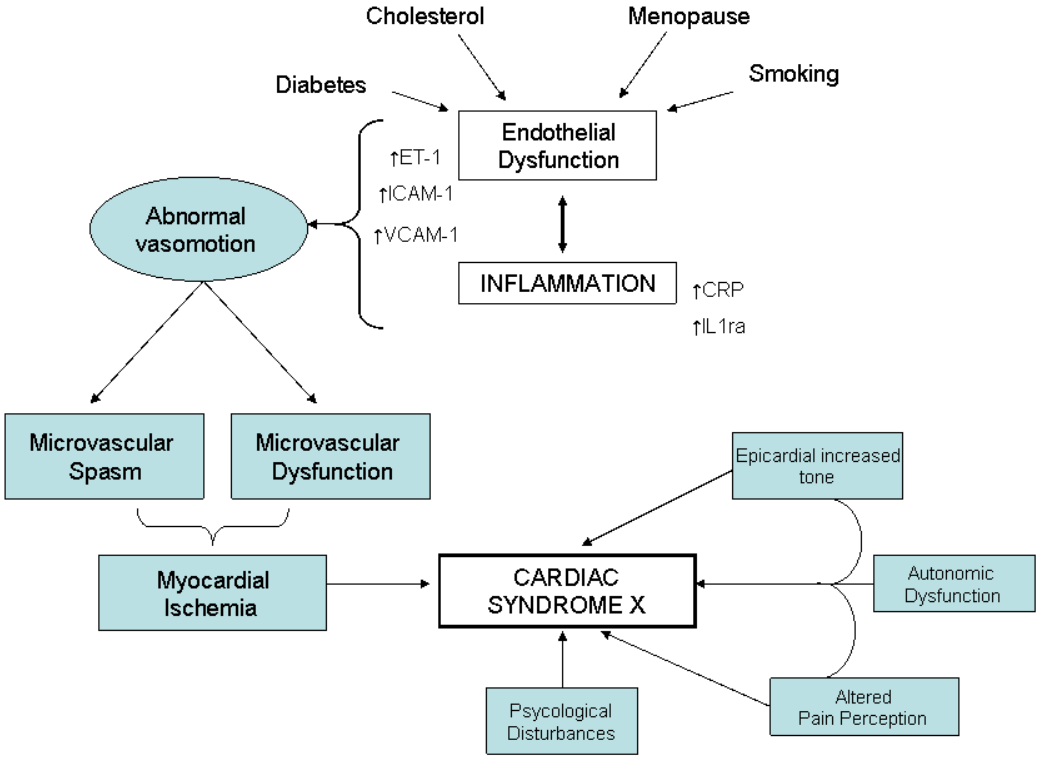
impaired coronary flow reserve in CSX. The contribution of inflammatory mechanisms to endothelial activation and dysfunction in CSX was first suggested by Tousoulis et al. [21], who found higher blood levels of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) in individuals with CSX than in healthy controls. Moreover, Cosin Sales et al. [22] showed increased levels of CRP and evidence of more active disease in these patients, as indicated by more severe angina, more frequent episodes of ST-segment depression during Holter monitoring, and earlier and more evident ischemic ST-segment changes during an exercise stress test. Furthermore, studies by Arroyo-Espliguero et. al. [23] endorsed the pathogenic link between inflammation and endothelial dysfunction, providing evidence that systemic inflammation could affect coronary and peripheral conduit arteries and lead to generalized vascular dysfunction and early atherosclerotic changes in CSX. In addition, more recent studies from our group have shown that chronic inflammation, as seen in rheumatoid arthritis and systemic lupus erythematosus can lead to microvascular dysfunction even in the absence of conventional risk factors for coronary artery disease [24]. These data taken together reinforce the notion that microvascular dysfunction in CSX can be triggered and maintained by inflammatory mechanisms.

EVOLVING TREATMENTS AND FUTURE DIRECTIONS

It has been shown that coronary risk factors, such as arterial hypertension, hypercholesterolemia, and diabetes are associated with an impairment of endothelial function in CSX patients. Of interest, their amelioration can reverse, at least in part, endothelial dysfunction. At this point, it seems reasonable to focus on therapeutic options that can effectively address these issues, ie. Reduce inflammation and oxidative stress. *Lifestyle changes* directed towards improving cardiovascular risk factors are effective and should therefore be firmly encouraged. *Statins* have been shown to reduce CRP levels and improve signs of myocardial ischemia in different clinical settings including CSX. Indeed statins and *ACE inhibitors (ACEI)* have been shown to improve exercise-induced ischemic ST segment depression and endothelial dysfunction in CSX patients [22]. Moreover, these agents have

been shown to have beneficial effects in reducing intima-media thickness (effects not necessarily directly related to their actions on lipids) [25]. Given the findings described above in relation to inflammation in CSX, more research is needed to discover the causes and molecular mechanisms responsible for the link between inflammation and CSX, as a better understanding of the pathogenesis of CSX can lead to more effective therapies.

FIGURE 1 Pathophysiology of CSX



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