

Cardiac syndrome X: pathogenesis and management

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Abstract

The term Cardiac Syndrome X (CSX) describes patients presenting with typical exertional chest pain suggestive of myocardial ischemia, a positive exercise stress test result, and angiographically normal epicardial coronary arteries. CSX is more prevalent in women than in men, and the vast majority of women with CSX are peri or post-menopausal. Thus, oestrogen deficiency has been postulated to have a pathogenic role in CSX. Low oestrogen levels are associated with endothelial dysfunction and an impaired function of the natural endogenous opioid system, which results in increased pain perception. CSX patients have a reduced vasodilatory response of the coronary microcirculation that leads to myocardial ischemia in a proportion of patients. The present article reviews the possible pathogenic mechanisms responsible for CSX and briefly summarizes current therapeutic strategies.

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Introduction

The occurrence of typical chest pain and ST-segment changes suggestive of myocardial ischemia (*Figure 1*) in patients who otherwise have completely normal coronary arteriograms is known as “syndrome X”, as termed by Harvey Kemp in 1973 [1], or “cardiac syndrome X” (CSX), a name it acquired later in an attempt to differentiate this condition from the metabolic “syndrome X”, currently known as “metabolic syndrome”. CSX comprises a heterogeneous group of patients presenting with typical exertional chest pain, a positive exercise stress test, and angiographically normal epicardial coronary arteries, in whom non-cardiac causes of chest pain have been ruled out, along with coronary artery spasm (Prinzmetal’s variant angina), left ventricular hypertrophy, valvular heart disease, and cardiomyopathies. This article

briefly reviews the pathogenesis of CSX and summarizes current strategies for patient management.

It is estimated that approximately 30% of patients found to have normal coronary arteries on diagnostic angiography have features typical of CSX. The syndrome is more prevalent in women than in men, and the vast majority of women with CSX are peri- or postmenopausal. Postmenopausal women with CSX have abnormal endothelial function, which is improved by the administration of estrogen. Thus estrogen deficiency has been postulated to have a pathogenic role in CSX [2,3]. In addition, and of particular importance, low estrogen states are associated with an impaired function of the endogenous opioid system that controls pain perception. Low estrogen concentrations reduce or suppress the production or release of endorphins and enkephalins,

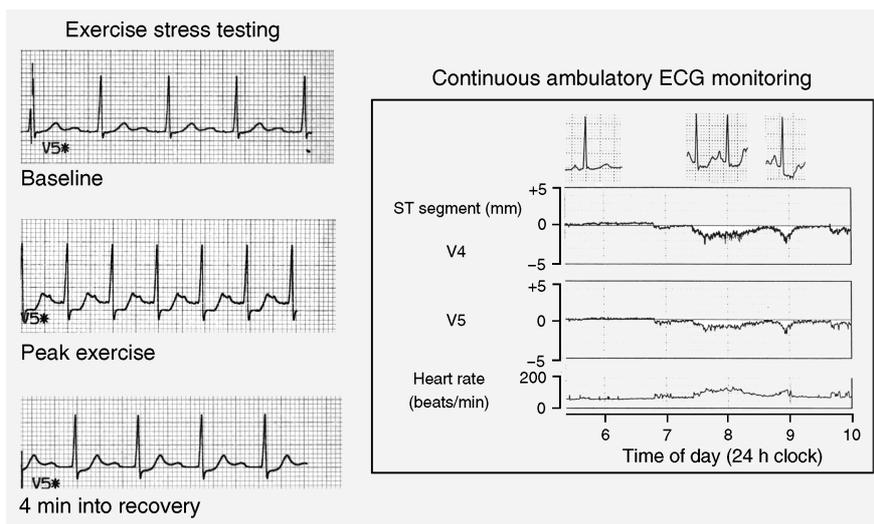


Figure 1. Typical electrocardiographic changes suggestive of myocardial ischemia in a patient with cardiac syndrome X. The tracings show (left) ST-segment depression during exercise stress testing, and (right) 24 h ambulatory monitoring in a patient with typical chest pain despite normal coronary arteriograms.

leading to increased pain perception [4,5], and this may provide a rational explanation for the occurrence of chest pain in women with CSX.

Pathogenesis

Interestingly, 35 years after the initial description of the syndrome, the debate continues as to the mechanisms responsible for CSX. Extracardiac causes, psychological abnormalities, myocardial ischemia, and abnormal pain perception are among the most commonly suggested pathogenic mechanisms.

Myocardial ischemia

The presence of unobstructed coronary arteries, the poor response to the administration of nitrates in 50% of patients and the negative stress echocardiograms in the majority of patients have cast doubts as to the role of myocardial ischemia as a potential cause of CSX [6–8]. However, in patients fulfilling strict selection criteria – typical chest discomfort, ischemic electrocardiographic changes, transient myocardial perfusion abnormalities – myocardial ischemia remains a plausible mechanism. The question also remains as to the mechanisms leading to myocardial ischemia in these patients. Functional coronary microvascular abnormalities leading to a reduced coronary blood flow reserve, often associated with endothelial dysfunction, are likely to be the cause of myocardial ischemia (“microvascular angina”) in patients with CSX.

Indeed, myocardial ischemia has been demonstrated in patients with CSX, using phosphorus-31 nuclear magnetic resonance spectroscopy. Buchthal

et al [9] measured high-energy phosphates in the myocardium of women with CSX, before and after stress testing, and found abnormal results compatible with myocardial ischemia in approximately 20% of the patients. Moreover, in an invasive study assessing lipid hydroperoxides and conjugated dienes (two sensitive, independent markers of ischemia-reperfusion oxidative stress) in patients with CSX, before and after pacing-induced tachycardia, Buffon et al [10] found a large cardiac release of these lipid peroxidation products after pacing, consistent with an ischemic origin of CSX. Concordantly, Panting et al [11], using cardiovascular magnetic resonance imaging, demonstrated subendocardial hypoperfusion during the intravenous administration of adenosine in patients with CSX.

Structural and functional coronary microcirculation abnormalities

Whether functional or structural abnormalities in the coronary microvessels are responsible for the findings described above is still under discussion. Structural abnormalities of the coronary microcirculation have been suggested to cause myocardial ischemia in patients with CSX. Endomyocardial biopsy specimens have shown evidence of fibromuscular thickening of vessels less than 100 μm in diameter [12], and both a relative lack of coronary capillaries and narrowing of the capillary lumen as a result of swollen endothelium, have been demonstrated in patients with CSX [13]. Furthermore, morphologic measurements revealed a significant increase in media thickness : lumen diameter ratio in arteries obtained from patients with CSX [14]. Antonios et al [15] reported a significant reduction in skin capillary density in patients

with CSX compared with that in age- and sex-matched controls. These findings appear to indicate that CSX may represent a generalized microcirculatory abnormality, rather than a problem confined just to the coronary microcirculation, but this requires further investigation in ad-hoc studies.

Functional abnormalities of the coronary microvessels have been demonstrated by many investigators over the past three decades [6]. More recently, Masci et al [16] assessed the relation between systemic endothelial dysfunction (abnormal brachial artery flow-mediated dilatation) and myocardial perfusion abnormalities in 41 patients diagnosed with CSX. Patients who had myocardial perfusion defects had significantly lower flow-mediated dilatation values than patients with normal cardiac perfusions scans, indicating a correlation between endothelial dysfunction and abnormalities of myocardial blood flow in CSX. An impaired coronary microvascular vasodilator capacity in patients with CSX was reported by Opherk et al in the 1980s [17]. They showed that patients with CSX had a markedly impaired coronary vasodilator capacity in response to the administration of dipyridamole, a potent vasodilator of coronary arterioles, suggesting that functional abnormalities of the coronary microcirculation could, at least in part, contribute to the pathophysiology of the syndrome by critically impairing myocardial perfusion. Of interest, Kaski et al [18] found that, compared with healthy controls, patients with CSX have greater circulating concentrations of endothelin-1*, a potent constrictor of the coronary microvessels that is produced by the endothelium. Studies from the same group showed a correlation between endothelin concentrations and abnormal coronary microvascular responses in patients with CSX [19]. It is therefore likely that endothelial dysfunction resulting in both increased production of endothelin and reduced bioavailability of nitric oxide is responsible for the abnormal microvascular responses that lead to angina in patients with CSX. Impairment of endothelium-mediated vasodilatation has been demonstrated in patients with this syndrome, and was prevented by the administration of L-arginine (a substrate for nitric oxide production) [20]. Several investigators have also reported the occurrence of endothelial dysfunction, as assessed by different means, affecting both the epicardial coronary arteries and the coronary microvessels in patients with CSX.

The role of inflammation

Inflammation has been investigated as a possible cause for endothelial dysfunction, and both symptoms and ECG changes, in CSX. Increased concentration of circulating C-reactive protein (CRP) – an acute-phase reactant and a marker of chronic inflammation and

vascular disease – correlates with vascular abnormalities in patients with CSX, as reported by several authors [21–23]. Teragawa and colleagues [21] showed that the increase in coronary blood flow in response to the administration of acetylcholine – a marker of endothelial function – was attenuated in patients with chest pain and normal coronary arteries who had increased CRP concentrations, compared with patients in whom CRP concentrations were normal. Moreover, Arroyo-Espliguero et al [22] showed that, compared with control individuals, patients with CSX have greater serum concentrations of CRP, increased common carotid artery intima-media thickness, and increased carotid artery stiffness, suggesting a direct relationship between inflammation and vascular abnormalities.

Cosin-Sales et al [23] investigated the relationship among CRP, symptoms, exercise stress test responses, and ST-segment changes during daily life in 137 consecutive patients (mean age 57 years; 33 men) with typical chest pain and normal coronary angiograms. All underwent exercise stress testing, 24 h ambulatory ECG monitoring, and CRP measurements at study entry. CRP concentrations were greater in patients with frequent and prolonged episodes of chest pain and in those with ST-segment depression on exercise testing and Holter monitoring, compared with patients with shorter episodes of chest pain, negative exercise stress testing, and no ST-segment shifts on Holter monitoring. They found a correlation between CRP concentration and number of ischemic episodes during Holter monitoring and with the magnitude of ST-segment depression on exercise testing. CRP was the only independent variable capable of predicting positive findings on Holter monitoring and exercise testing.

Reduced bioavailability of nitric oxide as a result of endothelial dysfunction and enhanced expression of endothelin-1, promoted by inflammatory mechanisms, may be implicated in the impairment of systemic endothelial vasoreactivity leading to microvascular angina in CSX [23].

Abnormal pain perception in cardiac syndrome X

Altered pain perception is likely to be responsible for the occurrence of chest pain in at least a proportion of patients with CSX, as suggested by several clinical observations and recently discussed in a clinical article by Kaski [24]. Shapiro and colleagues [25] demonstrated that patients with CSX developed chest pain during intra-atrial injection of saline – a stimulus which is otherwise painless in other clinical conditions. In a study carried out by Lanza et al [26], global or regional abnormalities, or both, in cardiac meta-iodobenzylguanidine (MIBG) scintigraphy were

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observed in a high proportion of patients with CSX, suggesting the presence of an abnormal function of efferent cardiac sympathetic nerve endings and supporting a cardiac origin for chest pain in these patients. Spinal cord stimulation, which is believed to act through enhancement of pain-gate control in the dorsal horn, has been reported to improve anginal symptoms in patients with CSX [27]. As mentioned previously, abnormal responses by the endogenous opioid system have also been implicated in the abnormal pain perception observed in women with CSX [28]. The combined effects of endothelial dysfunction, leading to minor reductions in myocardial blood flow, and increased pain perception may explain the prolonged episodes of typical chest pain observed in subgroups of patients with CSX in whom myocardial ischemia cannot be detected.

Patient management

Despite recurrent chest pain and prolonged episodes of ST-segment depression both on exertion and at rest, prognosis is good in patients with CSX [7,24]. Exceptions to this are patients with left bundle branch block, who may develop dilated cardiomyopathy during long-term follow-up, and patients in whom angina results from the presence of serious conditions affect-

ing the coronary microvessels, such as amyloidosis and myeloma [24]. Quality of life is often poor in patients with CSX, because of the presence of recurrent and prolonged chest pain. Treatment usually requires a combination of pharmacologic agents and lifestyle changes (Figure 2) [24]. Successful management usually depends on identifying the prevailing pathogenic mechanism in a given individual, and the therapeutic intervention should be tailored to the needs of the individual patient. Advice on lifestyle changes and aggressive risk factor management are of major importance in almost all patients with CSX [24]. Sublingual nitrates are often effective in patients with documented myocardial ischemia – that is, those with abnormal myocardial perfusion scans.

Analgesic strategies

Treatment with drugs that increase the patient's pain threshold is usually effective in CSX. Both imipramine [29], an antidepressant affecting pain perception, and aminophylline [30,31], an adenosine receptor antagonist, improve chest pain symptoms in patients with CSX. Transcutaneous electrical nerve stimulation and spinal cord stimulation appear to be valuable options for pain control, but larger studies are necessary to define the true role of these treatments in CSX.

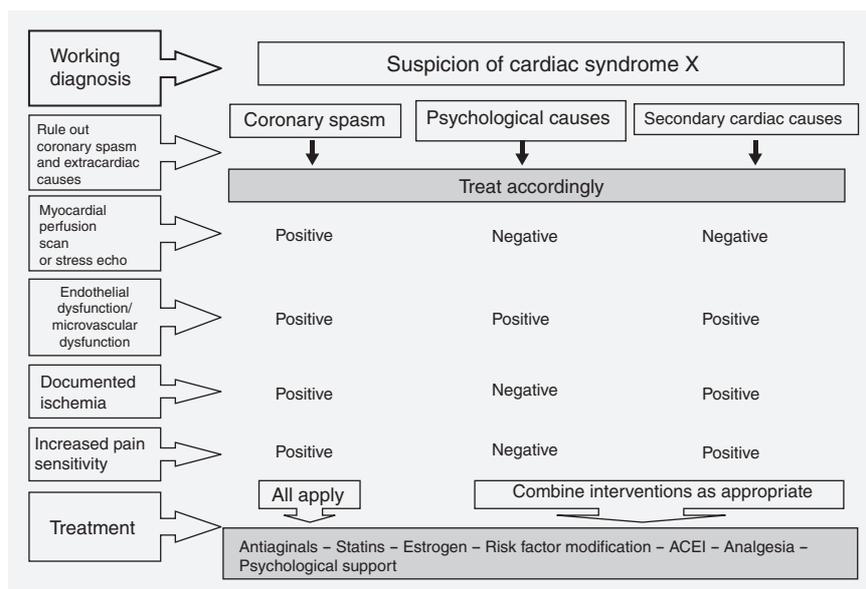


Figure 2. Flow chart showing suggested diagnostic and therapeutic steps in patients with cardiac syndrome X (CSX). Non-cardiac causes of chest pain and coronary artery spasm have to be ruled out. Patients with suspected CSX should undergo objective assessment of myocardial ischemia and endothelial dysfunction, as these conditions determine the therapeutic strategy. Of importance, treatment needs to be tailored to the patient's needs, and largely depends on the prevailing mechanisms responsible for chest pain and the electrocardiographic changes in a given individual. Nitrates, calcium-channel blockers, angiotensin-converting enzyme inhibitors (ACEI), and β -blockers are useful in patients with documented myocardial ischemia and those with microvascular dysfunction. Statins have been shown to improve endothelial function and exercise-induced myocardial ischemia in patients with CSX. Analgesic interventions are useful in individuals with a decreased pain threshold, and estrogen replacement therapy may be effective in postmenopausal women with CSX and endothelial dysfunction. Psychological intervention is effective in several subgroups of patients with CSX, and patients should be assessed accordingly.

Estrogen therapy

Hormone therapy has been shown to improve chest pain and endothelial function in women with CSX [2]. Estrogen treatment antagonizes the effects of endothelin-1 and dilates the coronary vessels, in addition to modulating pain perception at a central level [2,3,5]. It has been recommended that hormone replacement therapy should not be given for the prevention of chronic conditions [32], and these recommendations apply also to CSX. Short-term estrogen treatment, however, may be useful in specific patients with CSX in whom a direct relationship has been established between estrogen deficiency and symptoms [24].

Cognitive behavioral intervention

Various psychological treatments have been shown to be beneficial in patients with CSX [33]. Cognitive behavioral therapy has been used successfully in the management of patients with CSX with non ischemic chest pain [34].

Exercise

Physical exercise improves pain threshold and endothelial function and delays the onset of exertional pain in patients with typical chest pain and normal coronary arteriograms [35].

Antianginal agents

Commonly used antianginal agents include sublingual nitrates for the relief or prevention of angina, calcium-channel blockers and – in certain patients – β -blockers and nicorandil. Angiotensin-converting enzyme inhibitors and statins have been reported to improve exercise-induced angina in patients with CSX [24,36,37].

Conclusions

Cardiac syndrome X encompasses heterogeneous patient subgroups in whom the common denominator is typical chest pain and ECG changes despite angiographically normal coronary arteries. Controversy still surrounds the pathogenesis of CSX, which is likely to differ in different subgroups of patients. Increased sensitivity to pain and myocardial ischemia as a result of microvascular dysfunction (“microvascular angina”) [38] are two of the most likely pathogenic mechanisms, albeit ischemia is documented in a small proportion of patients. Identification of pathogenic mechanisms is important if rational management is to be provided. A multidisciplinary approach – involving cardiologists, general physicians, pain units, and psychologists,

together with phone “hot” lines or internet “clinics” – is usually effective, and reduces unnecessary hospital admissions and expensive investigations. Lifestyle changes are of paramount importance to improve endothelial function. Pharmacologic interventions should be directed towards the relief of angina and myocardial ischemia. Prognosis is generally good in patients with CSX.

*See glossary for definition of these terms. ■

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