Patients with cardiac syndrome X (CSX)—typical chest pain and electrocardiographic changes suggestive of myocardial ischemia despite normal coronary arteriograms—represent a diagnostic and therapeutic riddle. CSX is not associated with an increased mortality or an increased risk of cardiovascular events, but it often severely impairs quality of life and represents a substantial cost burden to the healthcare system. This syndrome of chest pain with normal coronary arteries encompasses a variety of pathogenic subgroups and is predominantly seen in postmenopausal women. Lack of understanding of the syndrome by the cardiovascular physician not infrequently results in discounting the clinical problem. Treatment remains elusive, but management strategies can improve the patient’s quality of life and reduce the financial burden imposed on health services.

Case Report: A 55-year-old white female pharmacist underwent diagnostic coronary arteriography for the assessment of typical exertional chest pain, which had started 18 months previously and had gradually become more frequent and severe despite treatment with oral and sublingual nitrates and atenolol (50 mg daily). Central chest pain and dyspnea occurred at rest and with emotional stress and responded rather poorly to sublingual nitrate administration. ECG exercise stress test was positive (Figure 1), and transient perfusion defects were found on thallium-201 dipyridamole testing (Figure 2). She had long-lasting excruciating chest pain after dipyridamole infusion. Risk factors included a family history of coronary artery disease, a low-density lipoprotein-cholesterol level of 4.2 mmol/L, a high-density lipoprotein-cholesterol level 0.9 mmol/L, menopausal status, a previous history of smoking, body-mass index of 28 kg/m², and raised high-sensitivity C-reactive protein levels (3.8 mg/L). Coronary arteries and left ventricular function were completely normal. Coronary intravascular ultrasound showed no significant subangiographic disease. After reassurance by her cardiologist, all cardiac medications were discontinued. Symptoms continued to deteriorate over the ensuing months, however, to the point that she was unable to work and required help with her supermarket shopping and household tasks. She was referred to our CSX clinic for treatment.

Esophageal manometry and pH measurements showed 4 asymptomatic episodes of gastroesophageal reflux without associated ECG changes. Specialist psychological assessment revealed no abnormalities. Coronary artery spasm and musculoskeletal conditions were ruled out as the cause of her symptoms. Transient ST-segment depression and chest pain detected during ambulatory monitoring were usually associated with tachycardia (Figure 3). It was noted that 20% of the episodes of ST-segment depression occurred with a heart rate <80 bpm. Brachial artery flow-mediated dilatation was reduced to 1.3%, indicating systemic endothelial dysfunction. Dobutamine stress-echocardiogram showed no regional wall motion abnormalities despite the occurrence of ST-segment depression and chest pain. Treatment was initiated with diltiazem 360 mg daily, simvastatin 40 mg daily, imipramine 50 mg daily, and sublingual nitrates. An exercise program was devised for this patient, and she received advice regarding diet and lifestyle changes. The patient decided against estrogen replacement therapy.

Clinical Results: Symptoms improved significantly over an 8-month period and the patient was able to return to work. Improvements were observed in body mass index (23 kg/m²), high-density lipoprotein-cho-
lesterol level (1.3 mmol/L), low-
density lipoprotein-cholesterol level
(2.8 mmol/L), and flow-mediated di-
latation (4.2%). Exercise test was
borderline positive, with up-sloping
ST-segment depression but without
chest pain (peak heart rate 158 bpm,
peak blood pressure 180/88 mm Hg;
stage 4 Bruce protocol).

**Background**

Although patients with typical exer-
tional chest pain and positive exercise
tests usually have obstructive coronary
artery disease, particularly when risk
factors are present, approximately 20%
of these patients have normal coronary
angiograms.1,2 Even this stringent angiographic criterion
has limitations, as coronary arteriography
provides no information regarding early
atherosclerotic events within the arterial
wall.

Patients with systemic hypertension,
left ventricular hypertrophy, and dia-
betes mellitus are excluded from CSX,
as it is assumed that the cause for their
angina is known. Consideration
whether or not such exclusions are
justifiable is beyond the scope of this
manuscript. Patients with coronary ar-
tery spasm and those with objectively
documented extracardiac causes for
the pain (such as chest wall syndrome,
psychological disturbances, and esoph-
ageal spasm) are also excluded.1

Despite intense investigation over
the past 30 years regarding the patho-
gensis of CSX, many fundamental
questions remain unanswered. Among
these, the following feature promi-
nently: (1) Is the chest pain cardiac in
origin?; (2) Is it caused by myocardial
ischemia?; (3) Are other mechanisms
involved?; and (4) What are the re-
pective roles of microvascular dys-
function and reduced pain threshold?

**Pathogenesis**

**Coronary Microvascular
Dysfunction (Microvascular
Angina)**

Microvascular angina (reduced coro-
nary microvascular dilatory responses
and increased coronary resistance)3
has been consistently found in CSX
patients and suggested as a cause for
regional myocardial blood flow abnor-
malities and heterogeneous myocardial
perfusion. Endothelial dysfunction,
with reduced bioavailability of endog-
ous NO and increased plasma levels
of endothelin-1 (ET-1), may explain
the abnormal behavior of the coronary
microvasculature in CSX.4-6 Transient
myocardial perfusion defects have
been reported in areas supplied by
arteries showing endothelial dysfunction and increased levels of ET-1 correlated with impaired coronary microvascular dilator responses in patients with chest pain and normal coronary arteries. Moreover, a lower NO/ET-1 ratio has been found in CSX patients compared with control subjects. From the initial description of CSX, it has been speculated that myocardial ischemia could be its pathogenic mechanism. However, this mechanism has proven elusive, as ischemia is objectively documented in only a minority (approximately 25%) of patients. Evidence of myocardial ischemia in these patients derives from myocardial perfusion studies, from investigations using metabolic markers such as myocardial lactate and isoprostane production, and from coronary sinus blood oxygen and pH changes. Studies using myocardial-perfusion MRI and 31-Phosphorus nuclear magnetic resonance have provided fresh evidence for myocardial ischemia in CSX patients. Because many authors question the role of myocardial ischemia in CSX based on its good prognosis, the poor response to nitrates in many cases, the normal results of stress echocardiography, and the absence of objective markers of ischemia in many CSX patients, non-ischemic mechanisms have been proposed to explain the occurrence of CSX, including autonomic nervous system dysfunction and increased pain perception. Negative findings regarding ischemia, however, may be due to dilution of study groups by subjects with non-cardiac chest pain and to poor sensitivity of diagnostic techniques.

Abnormal Pain Perception
Increased pain perception is common in patients with CSX, but the reason remains elusive. Potassium and adenosine release, as well as abnormalities in the central modulation of pain perception, have been suggested to play a role. Greater and more extensive cortical activation, particularly of the right insula, suggesting abnormal handling of afferent stimuli by the central nervous system is seen in CSX patients as compared with controls. CSX patients may thus have an ineffective thalamic gate that would allow inadequate cortical activation by afferent stimuli from the heart, resulting in increased pain perception. Although endothelial dysfunction in CSX appears to be multifactorial and linked to risk factors such as smoking, obesity, hypercholesterolemia, and inflammation, high plasma C-reactive protein levels, a marker of inflammation, have been shown to correlate with disease activity and endothelial dysfunction. CSX patients with multiple risk factors often have subangiographic coronary atheroma that may further impair endothelial function. Insulin resistance has also been suggested to have a major pathogenic role.

Given the high prevalence (approximately 70% in most series) of postmenopausal women in the CSX population, estrogen deficiency has been suggested as a pathogenic agent acting via endothelium-dependent and endothelium-independent mechanisms. Impaired endothelial function in postmenopausal CSX patients is improved by the administration of 17β-estradiol. Myocardial Ischemia
From the initial description of CSX, it has been speculated that myocardial ischemia was a major pathogenic role in CSX patients with multiple risk factors. Moreover, a lower NO/ET-1 ratio has been found in CSX patients compared with control subjects.
nomic nervous system imbalance with increased adrenergic activity and impaired parasympathetic tone could explain both increased pain sensitivity and endothelial dysfunction. Possible interactions between pain threshold and microvascular dysfunction in CSX are presented in Figure 4.

Psychiatric Morbidity
CSX patients have high rates of psychiatric morbidity; approximately 30% have a treatable psychiatric disorder and another 30% have psychological problems, factors that probably contribute to the continuing symptoms characteristic of the condition. Psychiatric morbidity varies in different series depending on the referral sources of these patients and may, particularly in anxiety disorders, be secondary to inappropriate reassurance about often disabling cardiovascular symptoms, uncertainty as to the nature of the condition, and failure of conventional treatments to improve quality of life.

Prognosis and Management
With the exception of patients who present with left bundle branch block and subjects with microvascular angina secondary to serious systemic diseases (such as amyloidosis or myeloma), prognosis is good regarding survival and left ventricular function in patients with CSX. Quality of life, however, is poor in a large proportion of CSX patients.

Treatment is a challenging and often frustrating exercise for both patients and physicians. Kaski and Valenzuela Garcia have reviewed treatment options available for CSX, and American Heart Association/American College of Cardiology treatment guidelines are available for management of CSX in the context of the acute coronary syndrome. Successful management usually depends on identifying the prevailing pathogenic mechanism and tailoring the intervention to the individual patient. Advice on lifestyle changes and risk factor management—in particular aggressive lipid lowering therapy with statins—should be considered vital components of any therapeutic strategy. A multidisciplinary approach is required in most cases. Figure 5 depicts an algorithm used in our institution for the management of CSX patients. Briefly, antagonists such as calcium antagonists and β-adrenergic blockers are useful in patients with documented myocardial ischemia or abnormal myocardial perfusion. Sublingual nitrates are effective in 50% of CSX patients. Little evidence is available in relation to the efficacy of nicorandil, α-adrenergic blockers, trimetazidine, and angiotensin-converting enzyme inhibitors in this setting.

Analgesic Intervention
Analgesic intervention with imipramine, an antidepressant with analgesic properties, and with aminophylline, an antagonist of adenosine receptors, has been shown to improve symptoms in patients with chest pain and normal coronary arteriograms. Transcutaneous electrical nerve stimulation and spinal cord stimulation can offer good pain control. As with other interventions in CSX, studies in larger numbers of patients are lacking.

Hormone Therapy
Hormone therapy improves chest pain and endothelial function in women with CSX. Estrogens antagonize the effects of ET-1 and dilate the coronary vasculature. Controlled clinical trials have suggested, however, that the risk of developing cardiovascular disease and breast cancer increases in women taking hormone therapy (HT). Thus, although HT has potential cardiovascular benefits, it can also cause harm. The US Preventative Services Task Force has suggested that routine postmenopausal HT should not be advised for the prevention of chronic conditions, and women should take an active part in decisions regarding HT. These recommendations apply also to CSX patients. However, HT may be useful in specific cases where a direct relationship exists between estrogen deficiency and CSX symptoms.

Psychological Intervention
Psychological intervention may be beneficial for a substantial number of patients, whether or not organic factors are involved. Studies support the role of a structured cognitive behavioral approach to the management of CSX patients with non-ischemic chest pain, and this treatment is more likely to be effective if it is begun early after diagnosis.

Physical Training
As a result of physical deconditioning and low pain threshold, CSX patients have an impaired exercise capacity. Physical training improves pain threshold and endothelial function and...
delays the onset of exertional pain in patients with typical chest pain and normal coronary arteries. 25

Summary and Final Considerations

Controversy surrounds the pathogenesis and management of CSX patients. Although the majority of these patients has non-ischemic mechanisms and increased pain sensitivity, only a minority has documented myocardial ischemia. Identification of the prevailing mechanism is important for rational management. A multidisciplinary approach and a genuine, sympathetic appreciation by the physician of the devastating effect of CSX on the patient’s quality of life usually have a positive therapeutic impact.

References

Pathophysiology and Management of Patients With Chest Pain and Normal Coronary Arteriograms (Cardiac Syndrome X)
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