Cardiac syndrome X (CSX) continues to be a mystery for clinicians who see patients with symptoms suggestive of obstructive coronary disease but who in fact lack evidence of coronary obstruction. Mysterious, this syndrome also stands out by the fact that it appears to preferentially affect women. In this supplement issue of the Canadian Journal of Cardiology (CJC) focused on persistent cardiac pain, CSX rightly deserves discussion by Arthur et al., alongside other outstanding topics in cardiology, such as mechanisms of cardiac pain (Rosen), classification of nonrevascularizable patients (Jolicoeur et al.), refractory angina management (McGillon et al.), and the continued problem, impact, and management of stable angina (Parker). While Arthur et al. provide a comprehensive coverage of the current state of our knowledge of CSX, we, in this editorial, would like to emphasize some of the points raised regarding CSX in the hope of helping to demystify this syndrome and provide a useful roadmap for the future.

The American Heart Association has estimated that over 9 million people in the United States suffer from angina pectoris, which significantly impacts quality of life, ability to work, and costs to society. Within this group of people, a large number suffer a condition called CSX. The first description of patients with angina pectoris and normal coronary arteries appeared in 1967 and was followed by more reports. Arbogast and Bourassa described 10 patients with a definite electrocardiogram ischemic pattern during atrial pacing, typical or atypical angina pectoris, and normal or near normal coronary arteriograms, and labelled them as group X. In 1973, describing this patient group, Kemp first used the name syndrome X. Ingrained in its definition almost half a century ago, the mystery of this syndrome still continues to challenge our understanding of its mechanisms and hence few avenues for treatment have been proposed.

CSX is a condition that causes angina or angina-like chest pain with exertion. It is characterized by an ST-segment depression on treadmill exercise testing, but normal coronary arteriography, with no spontaneous or inducible epicardial coronary artery spasm on ergonovine or acetylcholine provocation and absence of cardiac or systemic diseases potentially associated with microvascular dysfunction (please see also the article by Arthur et al. in this supplement of the CJC). The disease can manifest as angina pectoris or acute coronary syndrome (ACS). Chest pain symptoms are similar in character and radiation to that of patients with confirmed obstructive disease and are often associated with ST-segment changes. CSX frequently leads patients to require emergency services.

The prevalence of CSX is usually calculated among those with angiographically nonobstructive coronary artery disease presenting with ACS. Normal or near-normal coronary arteries are a rather common finding among patients undergoing angiography, with estimates of prevalence of up to 30%. Compared with men, women are significantly overrepresented in this population. Overall, women, especially peri- or postmenopausal, are more likely than men to have nonobstructive disease. Estimates of prevalence of angiographically normal coronary arteries among women with stable angina or ACS range from 15% to 40%. For example, among 32,856 patients presenting for cardiac catheterization with symptoms suggestive of ischemic disease, such as ACS or stable angina, but angiographically normal coronary arteries, 7.1% were men vs 23.3% women. In the cohorts of patients with normal coronary arteries and ACS, not all but rather a substantial proportion of patients could be classified as having CSX. In conclusion, while differences in the epidemiology of ischemic heart disease in general between women and men remain largely unexplained, it is becoming widely accepted that CSX is more frequent in women than in men, hence suggesting a different pathology for women with ischemic symptoms.

Survival of CSX patients does not appear to be adversely affected, and deterioration of cardiac function rarely occurs. However, the disease significantly impairs the patient’s functioning and quality of life. Despite its good prognosis, CSX represents a major clinical challenge. First, diagnosis of CSX requires an extensive, and sometimes expensive, diagnostic work-up to exclude other cardiac and noncardiac causes of chest pain. Second, despite the typical chest pain for angina, conventional antianginal treatment is often not successful. Hence, treating physicians are often unclear as to the management of this cohort of patients. Consequently, there is neither a standard of care, nor a consensus as to how to treat CSX. Third, in the absence of effective treatment, CSX patients continue to seek help in the emergency services and pose a substan-
tial health care burden. There are observed sex differences in seeking health care due to ACS with normal coronary arteries that might have important social and economic implications. For example, compared with men, women with angiographically normal coronary arteries are approximately 4 times more likely to be readmitted to hospital for ACS and chest pain within 6 months. The estimated lifetime cost of healthcare utilization by a woman with chest pain and nonobstructive disease approaches USD1 million. Finally, while as a whole patient prognosis does not seem to be affected, some subgroups of patients with normal coronary arteries have a worse prognosis than others. For example, a significantly better survival is observed for patients with no angiographically-evident stenosis and negative dipyridamole echocardiography test, compared with those with a positive test. Hence, these groups should be identified in an effort to decrease mortality from ACS in patients with normal coronary arteries.

Despite decades of history, the disease mechanisms remain a mystery. It is believed that CSX might represent a heterogeneous syndrome, which is suggested to encompass pathogenic mechanisms such as increased sensitivity to pain, estrogen deficiency, heightened sympathetic activity, parasympathetic dysfunction, and inflammation. Widely studied, but still controversial, is the role of ischemia in the pathogenesis and symptomatology of the syndrome. Active mechanisms that transiently reduce coronary blood flow might indeed underlie the pathogenesis of CSX and explain occurrence of angina at rest and with minimal exertion. Hence, the term “microvascular angina” has also been applied to describe the syndrome. Myocardial ischemia was proposed to be a mechanism responsible for chest pain in at least 20% of patients with CSX, while others propose that ischemia is generally not the basis of the chest pain in these patients. Associations of CSX with changes in carotid-femoral pulse, pulse wave velocity, ascending aorta pulse, and fractional pulse pressures attest to the decrease in the ability of arteries to distend. Interestingly, endothelium-dependent, but not endothelium-independent, vasodilation appears to be impaired in CSX patients. Hence, endothelial dysfunction recently came to the forefront of theories of CSX pathogenesis. Indeed, elevated endothelin activity, blunted nitric oxide (NO), and endothelin responsiveness to intravenously-infused insulin in patients with angina and normal coronary arteriograms provide a pathophysiologic basis for the demonstration of endothelial dysfunction in such patients. Several studies suggest that the NO-dependent vasodilation mechanism appears to be suboptimal and defective in patients with CSX. Thus, therapies directed to correct endothelial dysfunction and enhance NO-pathways hold promise.

CSX is not a benign illness in terms of long-term morbidity. Effective therapies for CSX are not in place, partly due to the lack of understanding of the pathophysiology of the condition and partly due to the lack of sufficiently powered randomized controlled trials. In the absence of standardized and evidence-based treatment guidelines, there is a general confusion among clinicians as to how to treat these patients. While conventional antianginal treatments are rather ineffective, common treatment practices most likely include administration of these conventional antianginal medications, although this issue requires further scrutiny. A few clinical studies were conducted with various antianginal agents, but the results of these studies can barely serve as a foundation for definitive conclusions, partly due to the small sample sizes and concern regarding validity, reliability, and generalizability. Among antianginal medications, β-blockers, but not calcium channel blockers or nitrates, appear to have some benefits in CSX. Atenolol has been shown to improve symptoms, exercise performance, and diastolic function in CSX. Another β-blocker, nebivolol, which also works on improving endothelial function and NO release, might have utility in treating CSX. Angiotensin-converting enzyme inhibition was suggested to lessen exercise-induced ischemia in patients with CSX and microvascular angina, probably by a direct modulation of coronary microvascular tone. On the other hand, a drug working on a similar pathway, the angiotensin II receptor, type I, antagonist irbesartan, produced no significant subjective or objective improvements in patients with CSX. Other classes of medications, such as α1-adrenergic blockers and the α2-agonist clonidine, were not found to be efficacious in CSX. Some studies suggest that physical training, aminophylline, imipramine, spinal cord stimulation, and estrogen therapy in postmenopausal women might be beneficial in treating CSX. Given the discussed role of the NO pathway and endothelial dysfunction in the pathogenesis of CSX, drugs that affect endothelial function appear to be promising candidates for CSX therapy. Drugs such as the anti-p-kinase inhibitor, fasudil, and NO precursor L-arginine, are found to be effective in microvascular angina and could represent an effective strategy for CSX treatment, as could phosphodiesterase inhibitors, such as sildenafil, tadalafil, and bosentan. However, most of these studies were either negative or not large enough to provide useful therapeutic avenues.

CSX continues to pose a mystery, affect a significant number of patients, especially women, and pose serious burden to health services. We still do not have evidence-based guidelines for treating CSX. Hundreds of pages of research into this condition suggest that the cohort of patients with angina and angiographically normal or near-normal coronary arteries is heterogeneous and that CSX might be a label that oversimplifies diverse ranges of conditions that entertain different pathogenic pathways and require different treatments. Classification of CSX is key to our knowledge. Hence, critical to future research is to synchronize the understanding and to standardize the definition of CSX across clinicians and researchers and to define and use a standardized algorithm for diagnosing CSX (potentially using angiography, intravascular ultrasound, acetylcholine testing, and others). Stratification of CSX into subgroups based on the obstruction of coronary arteries (normal vs near-normal), endothelial function, and coronary vasodilator reserve might be important to tease out potential differences in pathogenesis and eventual therapies. Similarly, CSX preference for women might require directing our resources to more meticulous studying of this disease in female populations. Practical steps in addressing these issues might start with national and international surveys of cardiologists, and international forums on CSX. The mystery of CSX most likely resides in the details and the way we classify and diagnose this elusive condition, which appears to preferentially affect women.
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