

Review

Women, Cardiac Syndrome X, and Microvascular Heart Disease

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ABSTRACT

New data suggest that persistent chest pain, despite normal coronary angiography, is less benign than previously thought. It has long been recognized that cardiac syndrome X (CSX) is associated with significant suffering, disability, and health care costs, but the biggest shift in thinking comes in terms of long-term risk. It is now recognized that the prognosis is not benign and that a significant proportion of patients are at increased cardiovascular disease risk. Of major debate is the question of whether the mechanisms that explain this chest pain are cardiac vs noncardiac. The most current definition of CSX is the triad of angina, ischemia, and normal coronary arteries, which is associated with an increased cardiovascular risk. This paper provides a review of CSX, epidemiology of the problem, proposed explanatory mechanisms, and important next steps in research. Central to this review is the proposition that new insights into CSX will be fostered by both clinical and scientific collaboration between cardiovascular and pain scientists.

RÉSUMÉ

De récentes données suggèrent qu'une douleur thoracique, en dépit d'une coronarographie normale, est moins bénigne qu'on ne le croyait par le passé. Il a été longtemps reconnu que le syndrome X (SX) cardiaque était lié à une souffrance, une incapacité et des coûts de soins de santé importants, mais le plus grand changement dans la façon de penser a trait au risque à long terme. Il est maintenant reconnu que le pronostic n'est pas bénin et qu'une proportion significative de patients voit leur risque de maladie cardiovasculaire augmenté. La plus grande controverse est la question de savoir si les mécanismes qui expliquent cette douleur thoracique sont cardiaques ou non cardiaques. La définition la plus courante du SX cardiaque est la triade associant l'angine, l'ischémie et des artères coronaires normales, laquelle est liée à une augmentation du risque cardiovasculaire. Cet article passe en revue le SX cardiaque, l'épidémiologie du problème, les mécanismes explicatifs proposés et les prochaines étapes importantes de la recherche. Le point central de cette revue est la proposition de parrainage des nouvelles découvertes sur le SX cardiaque par la collaboration clinique et scientifique des chercheurs dans le domaine des maladies cardiovasculaires et de la douleur.

Every year, tens of thousands of Canadians are referred for diagnostic coronary angiography (CATH) due to symptomatology, particularly a complaint of chest pain, which is suggestive of coronary artery disease (CAD). Of those, up to 30% may be found to have normal or near normal epicardial coronary arteries.^{1,2} Sex differences have been observed in

regard to the data regarding normal CATH results. Women have been reported to have more nonobstructive CAD and better-preserved left ventricular function compared with men.^{3–6}

The discrepancy between degree of anatomical CAD and patients' symptoms has been a point of discussion since Warren's paper in the inaugural issue of the *New England Journal of Medicine* in 1812. In 1973, Arbogast and Bourassa⁷ described 10 patients with angina, stress-induced electrocardiogram ischemia and normal or near normal coronary angiograms whom they called group X. They compared their hemodynamic and myocardial function to those of 11 patients with significant

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CAD whom they called group C. In an editorial comment in the same issue of *American Journal of Cardiology*, Kemp referred to these patients as patients with syndrome X.⁸

Of major debate is the question of whether the mechanisms that explain this chest pain are cardiac vs noncardiac. Unfortunately, despite reassurance that there are no clinically important occlusions visible on the CATH, patients' continued symptoms result in frequent use of health care services, including visits to emergency departments, hospitalizations, and repeated diagnostic testing. Often patients are told that "the heart is fine," yet there are important sequelae in terms of quality of life, functional ability, and employment. Many people—frequently women—suffer from persistent and debilitating chest pain.

New data suggest that persistent chest pain despite normal CATH is less benign than previously thought. It is now recognized that the prognosis for patients with nonobstructive CAD is not benign and that a significant proportion of patients are at increased cardiovascular disease risk. The Women's Ischemia Syndrome Evaluation (WISE) study, funded by the National Institutes of Health, found that women with persistent chest pain had twice the rate of composite cardiovascular events, including nonfatal myocardial infarction, stroke, congestive heart failure, and cardiovascular deaths, compared with those without. Women with persistent chest pain also experienced a higher prevalence and severity of psychological symptoms. However, it is not clear whether the latter finding reflects a causal relationship or is a normal and expected reaction to severe, debilitating, and persistent pain. In addition, not all women with persistent chest pain are diagnosed with syndrome X.^{3,9,10}

Humphries et al.¹⁰ reported that women with persistent chest pain and normal CATH do worse than their male counterparts. The risk of recurrent cardiac events requiring hospitalization was significantly higher in women compared with men. This sex difference may reflect differences in healthcare-seeking behaviour, or possibly differences in the pathophysiology of the condition.

Definitions

Women report more chest pain, despite lower rates of occlusion in the major coronary arteries.¹¹ Historically this phenomenon has been variously referred to as (1) chest pain despite normal coronary angiograms,¹² (2) cardiac syndrome X, or CSX, now its most common name,¹³⁻¹⁵ (3) persistent chest pain without obstructive CAD,^{9,16} (4) normal coronary angina syndrome,¹³ or (5) microvascular disease.¹⁷ Recently, Shaw et al.¹¹ and Cannon¹² introduced the term microvascular angina to describe women with nonobstructive CAD that results in symptoms suggestive of myocardial ischemia; they propose that the underlying explanation is microvascular dysfunction due to vascular inflammation and remodelling, as well as hormonal contributors that are specific to women.

Cardiac Syndrome X

The traditional or "classic" definition of cardiac syndrome X (CSX) is a triad consisting of 3 essential elements:

- (1) Effort-induced or persistent angina;
- (2) A positive exercise test for myocardial ischemia (ST-segment depression); and

- (3) Angiographically smooth coronaries arteries.¹⁵

Delcour et al. give 2 working definitions of CSX:

- (1) Ischemic changes on electrocardiogram in patients with angina and normal CATH; and
- (2) Typical angina without flow-limiting stenosis on CATH for which no noncardiac cause of chest pain can be identified.¹⁸

Clinically important coronary obstruction is typically viewed as stenosis of 1 or more major coronary arteries by more than 50%.¹⁶ Since the late 1950s, the prevailing paradigm has been that ischemic heart disease (IHD) is caused by atherosclerotic coronary obstruction severe enough to reduce blood flow through the coronary arteries and cause coronary insufficiency. This focus upon blood flow and obstructions in the main coronary arteries has had "profound, long-lasting influence on clinical practice, pharmacological development, and clinical research."¹⁹ This is particularly true in the case of CSX.

Patients with persistent chest pain who do not meet the criteria for defining CSX are often assumed to have noncardiac chest pain, a fact that has important implications for the treatment they receive or do not receive.¹⁶

In 2007, Lanza²⁰ proposed that the usual definition of CSX is inadequate for both clinical and research purposes because it is too broad. He argued that the current definition ("chest pain and normal coronary arteries") is applied to both people with CSX due to microvascular dysfunction as well as those with other problems. His recommendation, which is consistent with those of Shaw et al.¹¹ and Cannon¹² was to replace the current definition of CSX with a new one that is focused on a more homogeneous group: patients with stable effort angina which can be reasonably attributed to abnormalities in the coronary microvascular circulation (microvascular dysfunction).²⁰ According to Lanza, patients should be diagnosed with CSX if they have:

- Typical stable angina, exclusively or predominantly induced by effort—Lanza notes that there is frequently a prolonged (ie, more than 15-20 minutes) dull persistence of chest discomfort after effort ceases and a slow or incomplete response to short-acting nitrates;
- Findings consistent with myocardial ischemia or coronary microvascular dysfunction, including 1 or more of:
 - Diagnostic ST-segment depression during spontaneous or stress-induced typical chest pain;
 - Reversible perfusion defects on stress myocardial scintigraphy;
 - Documentation of stress-related coronary blood flow abnormalities by more advanced diagnostic techniques such as cardiac magnetic resonance imaging (MRI), positron emission tomography (PET), or Doppler ultrasound;
 - Metabolic evidence of transient myocardial ischemia, as shown by cardiac PET or MRI or invasive assessment;
- Normal or near normal coronary arteries on CATH (vascular wall irregularities or discrete very mild stenosis of < 20% in epicardial vessels); and
- Absence of any other specific cardiac disease (eg, variant angina, cardiomyopathy, valvular disease).²⁰

Epidemiology

Up to 30% of women sent for CATH may have normal arteries.⁹ A Canadian study reported rates within these broad parameters: 23% of women and 7% of men.¹⁰ Based on data from the **G**lobal **U**talization of **S**treptokinase and **T**issue-**P**lasminogen **A**ctivator for **O**cccluded **C**oronary **A**rteries (GUSTO) and **T**hrombolysis in **M**yocardial **I**nfarction (TIMI) trials, Bugiardini et al. stated that normal arteries occur in 10%-25% of women presenting with acute coronary syndrome and ST-segment elevation acute myocardial infarction compared with 6%-10% of men.²¹ In the Canadian study, it was calculated that women undergoing angiography were 3 times more likely to be categorized as angiographically normal compared with men. A commonly-cited statistic is that 70% of patients with CSX are postmenopausal women.²²

While it is commonly accepted that approximately 42% of women with cardiac chest pain in the absence of obstructive CAD have coronary microvascular dysfunction²³ a slightly higher estimate is that as many as 58% of patients with non-obstructive CAD have microvascular dysfunction due to endothelial dysfunction.¹⁶ Common CAD risk factors such as smoking or dyslipidemia do not appear to be useful in predicting CSX or microvascular disease. The metabolic syndrome, on the other hand, was associated with a doubling of the 4-year relative risk of cardiac events for women in the WISE study compared with those without metabolic syndrome. Thus, metabolic syndrome may be associated with increased prevalence of subclinical disease.²⁴

Studies have suggested that CSX patients have significant psychological morbidity.¹⁰ It is not clear whether these problems have a causal relationship with CSX, are coincidental comorbidities, or are actually the result of living with a condition that is painful, debilitating, and poorly understood.

To summarize, between 10% and 30% of people who undergo CATH due to complaints of chest pain may have no identifiable CAD. Of those, about half may have microvascular heart disease. In Ontario alone, there were 55,409 diagnostic CATHs during the fiscal year 2005-2006, of which 18.2% were repeat tests within the same fiscal year.²⁵ Given a base of approximately 45,300 (approximately 82% of 55,409) and a prevalence of between 10% and 30%, it is likely that between 4,530 and 13,590 patients per year will have angiographically normal coronary arteries. Of these, approximately half (ie, between 2265 and 6795) may have cardiac microvascular dysfunction. Furthermore, if 70% of those with microvascular dysfunction are women, the incidence of CSX in Ontario women may be within the range of 1586 to 4756 per year. Extrapolated to Canada as a whole, the potential number of patients with this complex and costly problem (in both human and financial terms) is of significant importance to cardiac care.

Etiology

A number of causal mechanisms have been proposed for CSX. They include:²²

- Coronary endothelial cell dysfunction in the microcirculation (microvascular disease);
- Diffuse atherosclerosis (ie, an even layer of fatty deposits that line the small coronary vessels and restrict blood flow but is difficult to see by angiography; in some cases, diffuse atherosclerosis may lead to remodelling of the arte-

rial wall, in which the wall thickens and expands outward without intruding into the lumen of the blood vessel);²¹

- Hematologic issues such as large platelets that obstruct the small blood vessels or higher red blood cell aggregation or increased tendency to cluster together (aggregability), all of which can lead to a cascade of events that alter the functioning of the endothelium;²⁶
- Underlying or systemic inflammation;
- Diffuse conduit vessel vasoconstriction;
- Myocardial ischemia (reduced blood flow) due to 1 or more of a number of factors (endothelial cell dysfunction, diffuse atherosclerosis, abnormal vasoconstriction, or increased coronary blood flow resistance);
- Estrogen deficiency (primarily based on the observation that postmenopausal women are at greater risk of CSX); and
- Abnormal pain perception through increased pain sensitivity.

Microvascular Dysfunction

Even when noncardiac explanations are ruled out, understanding the causes of CSX and of cardiac microvascular disease remain a puzzle, despite nearly 3 decades of research.¹⁵ There may be a number of causal mechanisms and to understand them requires some awareness of the factors influencing coronary blood flow. The first key point is that between 40% and 50% of the resistance to blood flow in the main coronary arteries is determined by the small coronary blood vessels (microvascular system).¹² Thus, the ability of the small vessels to dilate and contract can have a profound effect on blood flow in the large coronary arteries and their ability to respond to demands for increased blood flow (eg, during effort).

Currently, the three leading explanations for microvascular dysfunction are:¹⁴

- Endothelial dysfunction: abnormal release of, or response to, vasodilators (such as nitric oxide) or vasoconstrictors;
- Inflammation leading to endothelial dysfunction: it has been found that levels of C-reactive protein are high in CSX patients. However, it is possible that inflammation is associated with other risk factors and is not the cause of the endothelial dysfunction;
- Microcirculation abnormalities: a reduction in coronary blood flow reserve, an increase in arterial resistance, or both.

Han et al.²⁷ examined patients with obstructive CAD by conducting simultaneous intravascular ultrasound and assessment of coronary reactivity. They found that men had more atheroma burden while women had more disease of the microcirculation. The degree to which these findings can be extended to women with nonobstructive CAD is uncertain, but they may shed light on the reason for a higher prevalence of chest pain in women with normal CATH results.

Endothelial Dysfunction

A key factor in regulating the "tone" of blood vessels is the endothelium. Impairment of vasodilation has been described in type 1 and 2 diabetes, CAD, congestive heart failure, and chronic renal disease. It has also been demonstrated in people

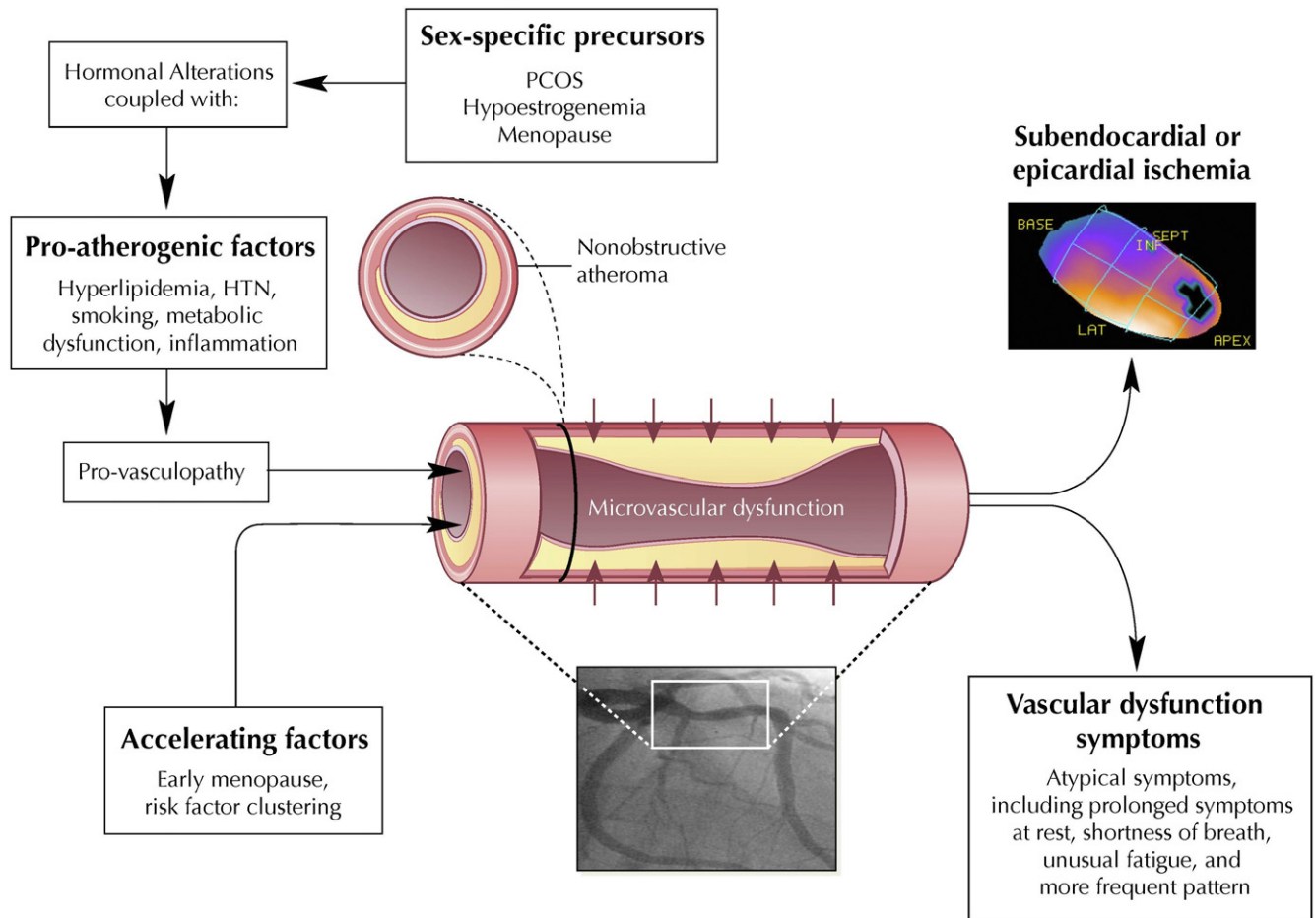


Figure 1. Model of microvascular angina in women. HTN, hypertension; PCOS, polycystic ovary syndrome. Reproduced with permission from Shaw et al.¹¹ Copyright © 2009 American College of Cardiology Foundation.

with metabolic syndrome and dyslipidemia, and may be associated with obesity, hyperhomocysteinemia, smoking, and a sedentary lifestyle—even in the absence of overt cardiovascular disease. Endothelial dysfunction may precede the development of symptomatic disease.²⁸

As sex hormones affect vascular constriction and dilation, it has been suggested that women may be at increased risk of microvascular disease because of a history of fluctuating hormone levels (puberty, pregnancy, and menopause).²⁹ Although hormones may help to delay the development of atherosclerosis in the major arteries in women, this protection may not extend to the microvascular system. The degree to which hormonal factors contribute to the sex ratio of CSX is unknown; knowledge regarding sex differences in coronary heart disease is still far from complete.¹¹

The hypothetical model of microvascular angina in women proposed by Shaw et al.¹¹ unites CAD risk factors, microvascular dysfunction, and endothelial dysfunction in a framework designed to illustrate a current representation of the pathophysiology involved. It should be noted that Shaw et al. do not use the term CSX, instead preferring to use ischemic IHD and microvascular angina. The IHD terminology is of particular relevance to this report as will be explained in the section on CSX as a chronic pain problem (Fig. 1).¹¹

Diagnosis

In most cases, making the diagnosis of CSX requires excluding cardiac and noncardiac conditions that could be alternative explanations for chest pain. Individuals with diagnosed diabetes, coronary artery spasm, left ventricular hypertrophy, and cardiomyopathy are not usually considered to have CSX.¹⁴ Other conditions thought to exclude a diagnosis of CSX include:

- Coronary bridging, a congenital anomaly in which a segment of a large coronary artery is tunneled in the myocardium and compression of the artery occurs during systole. Chest pain associated with bridging is evidenced by ischemia in the area of the left anterior descending coronary artery;
- Chest wall syndrome, in which the pain is caused by musculoskeletal disorders such as costochondritis or Tietze's syndrome, arthritis, or muscle damage;
- Pulmonary embolism;
- Gastroesophageal conditions such as esophageal spasm or reflux disease;
- Pleurisy;
- Psychological disturbances such as panic disorders, depression, or anxiety disorders, according to *Diagnostic*

and *Statistical Manual of Mental Disorders, 4th Edition* criteria; and

- Abnormal visceral pain sensitivity.

Recent thorough reviews of CSX and microvascular angina^{11,12,20} suggest that the diagnosis of CSX should be limited to those with evidence of microvascular dysfunction. An objective diagnosis of microvascular dysfunction is not easy as small coronary vessels cannot be studied directly through noninvasive means.²⁰ Current methods which include MRI, PET, and single-photon emission computed tomography are complex and often not superior to simpler methods of exercise stress testing. Measurement of coronary flow reserve is invasive, influenced by drugs, and limited to the territory of a single vessel. Computed tomography scan may help to exclude obstructive CAD, but does not explore the coronary microcirculation. Lanza²⁰ states that the definitive test for CSX-associated microvascular dysfunction may be multislice spiral computed tomography CATH, which has a high negative predictive value for significant CAD (more than 95%) and would avoid the small but definite risk associated with CATH. Recently, Matsuzawa et al.³⁰ investigated the ability of digital reactive hyperemia peripheral arterial tonometry (RH-PAT) in predicting both obstructive CAD and nonobstructive CAD in women. They found that reactive hyperemia peripheral arterial tonometry can predict patients with IHD, especially nonobstructive CAD, before angiography. These findings have important possible implications for women with CSX.

Making the diagnosis using these methods is not available in most clinical settings and carries a number of methodologic and practical issues. For example, microvascular dysfunction may affect the coronary circulation in a diffuse or heterogeneous manner, so there may be poor concordance between different arteries. As a result, the traditional invasive procedure of measuring coronary flow reserve in a single coronary artery (eg, in the left anterior descending) may not provide an accurate assessment of microvascular functioning. The development, testing, and standardization of novel coronary imaging techniques may be needed to advance our understanding.

CSX as a Chronic Central Pain Problem

Rosen and Camici³¹ have raised vital questions in relation to the problem of CSX, such as: "Does the patient have heart disease? Can the condition be effectively treated? Is the patient's life expectancy shortened? Is the chest pain in patients with syndrome X of ischemic origin? And, if the pain is due to myocardial ischemia, what are the mechanisms?" (p. 131).

Underpinning these questions is a reconceptualization of pain, from the erroneous notion of a localized pain centre in the brain to that of a network of brain regions that interact in complex ways. Pain is not only registered in higher centres, but is modulated; modulation may range from complete blockage of the conscious perception of pain to feelings of severe pain with little or no peripheral stimulus. Mood, cognitions, context, and complex structural and neurochemical inhibitory and excitatory factors contribute to pain modulation and the nervous system is able to habituate (either adaptively or maladaptively) to repeated stimuli.³¹ Interestingly, Valeriani et al.³² have demonstrated that patients with CAD appear to habituate to peripheral noxious stimuli whereas those with CSX do not. Thus, an

important consideration in understanding the etiology of CSX is the possibility of abnormal visceral pain perception.

More intriguing is the work of Eriksson et al.,³³ who studied the effect of epinephrine infusion (using 3 different protocols) in 8 patients with CSX and found that, in most cases, patient's typical chest pain was reproduced in the absence of ST-segment changes and no evidence of left ventricular wall motion abnormality. As cited in Rosen and Camici,³¹ Eriksson et al.³³ concluded that CSX might be "a sympathetic maintained pain of neurogenic origin due to dysregulation in the complex cardiac nervous system" (p. 133). The summation of findings from research by Eriksson et al.,³³ Camici et al.,^{34,35} Rosano et al.,³⁶ and Rosen et al.³⁷ weakens the case for CSX being the sole result of myocardial ischemia.

In 2002, Rosen et al.³⁸ subjected 3 groups of patients (CAD, normal controls, and CSX) to dobutamine stress while monitoring regional responses in the brain using PET. Symptomatically, each group responded as follows: the CAD patients developed chest pain with documented ischemia, the controls experienced a powerful heart beat but no pain, and the CSX patients reported chest pain that lasted several minutes after discontinuation of the dobutamine but with no evidence of ischemia or left ventricular dysfunction. Rosen et al. propose that the chest pain arising from CSX involves modulation of cardiac afferent signals in the cerebral cortex. The afferent signals in response to dobutamine were inappropriately encoded, generating the conscious perception of pain, despite the absence of tissue injury. There may be numerous contributors to this abnormal pain processing. Please see the article by Rosen in this supplement for a full explanation of pain mechanisms related to CSX and other persistent cardiac pain phenomena.³⁹

Treatment

Given the accumulating evidence that patients with CSX are likely to be at increased cardiovascular risk, a cornerstone of treatment should be addressing prevention via modification of risk factors associated with CAD. A comprehensive prevention program includes recommendations related to diet, exercise, and behavioural and psychosocial issues, ideally using a chronic disease management approach.^{40,41} Pharmacologic treatments that have been suggested for CSX include:²²

- Statins (which may help to improve endothelial function);
- Angiotensin-converting enzyme (ACE) inhibitors (may also improve endothelial function);
- A combination of statins and ACE inhibitors;
- Anti-ischemic medications such as nitroglycerin;
- β -Blockers;
- Calcium channel blockers;
- Imipramine, a tricyclic antidepressant that also has analgesic effects; and
- Estrogen replacement.

A review by Bugiardini and Merz²¹ notes that there is some evidence supporting the use of β -blockers and imipramine for the treatment of specific patients with abnormal cardiac pain perception, but none for calcium channel blockers and only anecdotal evidence for the use of nitrates. Although the combination of statins and ACE inhibitors appears promising, more research is needed. Less common treatments have included a xanthine oxidase inhibitor typically used for gout,

nicorandil (a potassium channel activator), a sodium/hydrogen exchanger inhibitor, L-arginine (a precursor of nitric oxide), the diabetes medication metformin, spinal cord stimulation, exercise training, and psychological interventions such as cognitive behavioural and group therapy.^{11,13,29,42} Exercise training may address physical deconditioning secondary to struggling with an uncertain disease and effort-induced angina and/or have a beneficial effect on conventional CAD risk factors.⁴³

Pain relief with current therapies is seldom sustained over time, and patients are commonly prescribed a large number of drugs.¹² The most common therapy for angina—nitroglycerin—appears to be effective in controlling symptoms in only 40% to 50% of patients with CSX. These data however, are based on observational studies and should be interpreted with caution.¹⁵

Estrogen is known to have a beneficial effect on endothelial function, plasma lipid levels, and vasodilation, but as recent studies have shown, this may not translate into cardiac benefits.²⁹ Given current concerns about the short- and long-term effects of hormone replacement therapy,⁴⁴ evidence of benefit would be required before estrogen could be recommended as a routine treatment for CSX.

Enhanced external counterpulsation (EECP) involves wrapping cuffs around the patient's legs and using compressed air to apply sequential pressure from the lower legs to the lower and upper thighs in early diastole to propel blood back to the heart. In addition to increasing blood flow to the heart, it is theorized that EECP may help to improve endothelial function and promote collateral blood flow. A comprehensive review of EECP is contained in the Guidelines for the Management of Refractory Angina (see McGillion et al., in this supplement⁴⁵) and may be considered for improvements in aspects of health-related quality of life and severity of angina symptoms; however these recommendations are 'weak' and the evidence is rated as 'low quality.'

The largest single problem in treating CSX is that most clinical studies to date have had small sample sizes. There is a need for larger and more methodologically rigorous trials with sufficient power to demonstrate efficacy. Using the search term "cardiac syndrome" and "syndrome X" did not retrieve any clinical practice guidelines from either the National Guideline Clearinghouse (www.guideline.gov) or the Canadian Medical Association Clinical Practice Guidelines Infobase (www.cma.ca).

Implications

Improved diagnosis and treatment of CSX and microvascular angina would benefit all patients who are currently struggling with this often debilitating disorder. As discussed, the persistent pain associated with CSX can significantly reduce the quality of life of those afflicted. Moreover, we now know that many of these patients are at significant increased risk of cardiovascular disease in the future.

Currently, there is no reliable estimate of the prevalence or incidence of CSX in Canada. As a result, it is impossible to estimate the potential healthcare costs that could be avoided. Persistent chest pain in the absence of obstructive CAD has been associated with increased use of health services. In general, women are more likely to seek and use health care services than

men.^{46,47} Paradoxically, it has been recommended that women with angiographically normal coronary arteries be considered for additional medical evaluations.⁴⁸ This recommendation is supported by the fact that even after adjustment for psychological factors, women with nonobstructive CAD in the WISE study had approximately double the rate of major cardiovascular events as women without persistent chest pain or CAD.⁹ Thus, increased use of health services is likely to persist in this patient population until new knowledge enhances our ability to diagnose and treat CSX. If prevention and management were improved, it is possible that unnecessary healthcare costs (eg, repeat angiograms and hospitalizations) could be reduced. At minimum, one would expect increased efficiencies and effectiveness in the use of health resources.

There is a need for both clinical and basic science research relevant to CSX and microvascular disease. Basic research is needed on the normal and abnormal functioning of the coronary microvasculature and the endothelium. Research in this area is already under way,³⁰ although it tends to be identified with disease entities other than CSX, such as diabetic heart disease or CAD. In addition to basic research on the underlying disease process, there is a need for applied and clinical research to support disease prevention, diagnosis, and management. Large scale randomized controlled trials are necessary. Presently, 2 studies were identified in the International Standard Randomized Controlled Trial Number Register: (1) The Impact of Support Group Membership on Social Support, Psychological Morbidity and Quality of Life in Patients with Cardiac Syndrome X (ISRCTN42487707); and (2) Metformin in Women with Cardiac Syndrome X: A Randomized, Double Blind, Placebo Controlled Trial (ISRCTN28863939). To summarize, research is needed to:

- Establish the epidemiology of CSX/microvascular angina in Canada (eg, currently, there is no evidence as to whether prevalence or incidence varies by ethnicity or socioeconomic status);
- Enable better identification of those at risk (eg, identification of risk factors and screening protocols);
- Make possible better diagnostic modalities (eg, noninvasive means of studying microvascular function);
- Advance our understanding of the disease process and prognosis;
- Support the development of better treatment modalities and evidence-based diagnosis and treatment algorithms; and
- Explore psychological, neurophysiological, and pharmacological interventions for the treatment of CSX; ideally, these avenues should be viewed as conceptually integrated, though the research in each area may be pursued separately.

Research teams that combine scientists with cardiology and pain expertise are perhaps best positioned to make significant progress for this perplexing problem.

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