Cardiac Syndrome X: Update

Shilpa Agrawal, BS[a], Puja K. Mehta, MD[b,*], C. Noel Bairey Merz, MD[b]

KEYWORDS

• Cardiac syndrome X • Angina • Ischemia • Microvascular endothelial dysfunction
• Myocardial hypersensitivity

KEY POINTS

- Up to 20% to 30% of patients presenting with chest discomfort characteristic of angina show no obstructive coronary artery disease (CAD), defined as 50% or more stenosis in at least 1 major coronary artery, on angiography.
- The lifetime cost of health care for a woman with chest pain and no obstructive CAD is estimated at approximately $1 million as a result of challenges in diagnosis and treatment.
- To diagnose cardiac syndrome X, noncardiac causes, large vessel coronary disorders, and coronary microvascular dysfunction with associated myocardial disease must be ruled out.
- The proposed theories for the underlying pathogenesis of cardiac syndrome X include coronary microvascular dysfunction and associated ischemia, abnormal cardiac pain sensitivity, or a combination of both.
- Treatment strategies include anti-ischemic medications, analgesic medications, nonpharmacologic procedures, and lifestyle modifications.

INTRODUCTION

Cardiovascular (CV) disease is the leading cause of death worldwide, and coronary artery disease (CAD) is the most common type of CV disease.[1] Yet, up to 20% to 30% of patients presenting with chest discomfort characteristic of angina show no signs of obstructive CAD, defined as 50% or more stenosis in at least 1 major coronary artery, on angiography.[2] These patients are often given noncardiac diagnoses such as gastrointestinal or psychiatric disorders.[3] However, evidence of electrocardiographic (ECG) and metabolic abnormalities during stress induced by right atrial pacing in a subset of these patients led to the designation of a new disorder by Harvey Kemp in 1973[4] named cardiac syndrome X (CSX).

CSX can be defined broadly as anginalike chest discomfort, with normal epicardial coronary

This article originally appeared in Cardiology Clinics, Volume 32, Issue 3, August 2014.
This work was supported by contracts from the National Heart, Lung, and Blood Institute, N01-HV-68161, N01-HV-68162, N01-HV-68163, N01-HV-68164, grants K23HL105787, U0164829, U01 HL649141, U01 HL649241, T32HL69751, R01 HL090957, 1R03AG032631 from the National Institute on Aging, GCRC grant MO1-RR00425 from the National Center for Research Resources and grants from the Gustavus and Louis Pfeiffer Research Foundation, Danville, NJ, The Women's Guild of Cedars-Sinai Medical Center, Los Angeles, CA, The Ladies Hospital Aid Society of Western Pennsylvania, Pittsburgh, PA, and QMED, Laurence Harbor, NJ, the Edythe L. Broad Women's Heart Research Fellowship, Cedars-Sinai Medical Center, Los Angeles, California, and the Barbra Streisand Women's Cardiovascular Research and Education Program, Cedars-Sinai Medical Center, Los Angeles, and the Linda Joy Pollin Women's Heart Health Program, Cedars-Sinai Medical Center, Los Angeles.
Disclosures: None of the authors has any relevant conflicts of interest to disclose.
[a] David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA 90095, USA; [b] Department of Medicine, Cedars-Sinai Medical Center, Barbra Streisand Women's Heart Center, Cedars-Sinai Heart Institute, 127 South San Vicente Boulevard, Los Angeles, CA 90048, USA
* Corresponding author. 127 South San Vicente Boulevard, Suite A3212, Los Angeles, CA 90048.
E-mail address: puja.mehta@cshs.org

Heart Failure Clin 12 (2016) 141–156
http://dx.doi.org/10.1016/j.hfc.2015.08.012
1551-7136/16/$ – see front matter

arteries on angiography. A proposed more strict definition of CSX entails the following criteria:

1. Exercise-induced, anginalike chest discomfort
2. ST segment depression during angina
3. Normal epicardial coronary arteries at angiography[2]
4. No spontaneous or inducible epicardial coronary artery spasm on egonovine or acetylcholine provocation
5. Absence of cardiac or systemic diseases associated with microvascular dysfunction, such as hypertrophic cardiomyopathy or diabetes[5]

There are several groups of patients who have anginalike chest pain and normal coronary arteries at angiography but fail to meet one of these criteria. Examples of these patients include those with angina predominantly at rest, those with diabetes or hypertension, or those with lack of ST depression on ECG during angina. It remains unclear whether the pathogenesis of angina in these patients is the same as in patients who fall under the strict definition of CSX. Throughout the scientific literature, the broad and strict definitions of CSX are used variably, reflecting the mystery that has historically surrounded the syndrome.[6]

EPIDEMIOLOGY

What is known is that CSX is relatively more prevalent in women. In a study of 32,856 patients presenting for their first cardiac catheterization with suspected ischemic heart disease,[7] 23.3% of women versus 7.1% of men were found to have normal coronaries after angiography. Another study[8] found that among 886 patients who were referred for chest pain and subsequently underwent angiography, a diagnosis of normal coronary arteries was more than 5 times more common in women than men (41% vs 8%). Furthermore, women who were perimenopausal or postmenopausal were found to have an increased risk of angina with no obstructive CAD.[5] A study of 99 patients with CSX[9] showed that the mean age of diagnosis was 48.5 years and that 61.5% of women were postmenopausal.

Individuals with CSX have a higher likelihood of presenting with features of the metabolic syndrome (eg, hypertension, dyslipidemia, and insulin resistance) than the general population (30% vs 8%, respectively). In addition, these patients have been shown to have a greater amount of endothelium-dependent and endothelium-independent impairment of cutaneous microvascular function compared with healthy controls.[10]

PROGNOSIS

For many years, it was believed that CSX had a benign prognosis. One study[9] followed 99 patients with CSX for an average of 7 years and showed no significant decline in ventricular function. In another study of 1491 patients with anginal symptoms and normal coronary arteries (no major epicardial artery with >25% stenosis),[11] myocardial infarction–free survival rates were 99% at 5 years and 98% at 10 years. In 486 patients with angina and no obstructive CAD (no major epicardial artery with $\geq$75% stenosis), myocardial infarction–free survival rates were 97% at 5 years and 90% at 10 years. A study[12] of 7-year survival in patients with symptoms suggestive of CAD but showing a normal or near-normal coronary arteriogram (<50% stenosis in $\geq$1 epicardial arteries) showed survival rates of 96% and 92%, respectively, in these 2 subpopulations.

However, recent evidence has challenged the assumption that anginalike pain without obstructive CAD is a benign condition. In the WISE (Women's Ischemia Syndrome Evaluation) study,[13] 5-year annualized event rates for CV events were 16.0% in 222 symptomatic women with nonobstructive CAD (stenosis in any coronary artery of 1%–49%), 7.9% in 318 symptomatic women with normal coronary arteries (0% stenosis in all coronary arteries), and 2.4% in 5932 asymptomatic women. CV events included myocardial infarction, hospitalization for heart failure, stroke, cardiac mortality, and all-cause mortality. Recent reports from Europe and Canada[14,15] replicate this adverse prognosis. In addition, some subsets of patients tend to have poorer prognoses than others. In 1 study,[16] 13 of 22 symptomatic patients with normal coronary angiograms and endothelial dysfunction assessed through acetylcholine-mediated dilatation developed CAD when followed for greater than 10 years. In contrast, 20 of 20 symptomatic patients with normal coronary angiograms and no endothelial dysfunction showed resolution of chest pain 6 to 36 months after angiography. Impaired coronary vasomotor response to acetylcholine has also been independently linked to earlier CV events regardless of CAD severity.[17]

Furthermore, CSX remains a major diagnostic and therapeutic challenge causing significant deterioration in a patient's functioning and quality of life. Diagnosis of CSX requires an extensive workup to rule out other potential causes of chest pain and can be expensive. Treatment with conventional antianginal medications is often not successful, which results in patients being limited in their daily activities, seeking emergency care for their chest pain, and needing to take time off or abandon their