Published in final edited form as:
Cardiol Clin. 2014 August ; 32(3): 463–478. doi:10.1016/j.ccl.2014.04.006.

Cardiac Syndrome X – Update 2014

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Summary

Cardiac Syndrome X (CSX), a condition characterized by angina-like chest discomfort, ST segment depression during exercise, and normal coronary epicardial arteries at angiography, has the highest prevalence in post-menopausal women. Historically CSX was considered to be a benign condition but recent reports have shown that individuals with CSX have a higher prevalence of adverse cardiovascular events compared to control subjects and a poor quality of life. Diagnosis of CSX is often difficult and expensive because the diagnosis is primarily one of exclusion. Furthermore, treatment of CSX is challenging because the underlying pathogenesis of the condition is not well understood. The two most popular theories of pathogenesis are coronary microvascular dysfunction, in which symptoms are thought to result from myocardial ischemia secondary to abnormal coronary microvasculature function, and abnormal cardiac pain sensitivity, in which symptoms are thought to be a result of myocardial hypersensitivity and exaggerated pain perception. Treatment options include traditional anti-ischemic medications such as nitrates, beta-blockers, and calcium channel antagonists. Furthermore, other anti-ischemic medications such as ranolazine, angiotensin-converting enzyme inhibitors, and statins can be used. Analgesic medications such as xanthine derivatives and tricyclic antidepressants have also shown efficacy. Non-pharmacological treatments include cognitive behavioral therapy, enhanced external counterpulsation, neurostimulation, stellate ganglionectomy, and lifestyle modifications. Studies have shown the efficacy of individual treatments but guidelines outlining the best course of therapy are lacking.

Keywords

Cardiac Syndrome X; Angina; Ischemia; Microvascular Endothelial Dysfunction; Myocardial Hypersensitivity

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Disclosures: There are no relevant conflicts of interest of any of the authors to disclose.

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 20-30% of patients presenting with chest discomfort characteristic of angina demonstrate no signs of obstructive CAD, defined as ≥50% stenosis in at least 1 major coronary artery, upon angiography.[2] These patients are often given noncardiac diagnoses such as gastrointestinal or psychiatric disorders.[3] However, evidence of electrocardiographic 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 named "Cardiac Syndrome X."[4]

Cardiac Syndrome X (CSX) can be defined broadly as angina-like chest discomfort with normal epicardial coronary arteries on angiography. A proposed more strict definition of CSX entails the following criteria:

1. Exercise-induced, angina-like 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 upon 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 angina-like chest pain and normal coronary arteries at angiography but fail to meet one of the above 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 electrocardiogram (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, 23.3% of women versus 7.1% of men were found to have normal coronaries following angiography.[7] Another study found that among 886 patients who were referred for chest pain and subsequently underwent angiography, a diagnosis of normal coronary arteries was more than five times more common in women than men (41% versus 8%).[8] Furthermore, women who were peri- or postmenopausal were found to have an increased risk of angina with no obstructive CAD.[5] A study of 99 CSX patients showed that the mean age of diagnosis was 48.5 years and that 61.5% of women were postmenopausal.[9]

Individuals with CSX have a higher likelihood of presenting with features of the metabolic syndrome (e.g. hypertension, dyslipidemia, and insulin resistance) than the general

population (30% versus 8%, respectively). Additionally, these patients have been shown to have a greater amount of endothelium-dependent and endothelium-independent impairment of cutaneous microvascular function in comparison to healthy controls.[10]

Prognosis

For many years, it was thought that CSX had a benign prognosis. One study followed 99 patients with CSX for an average of 7 years and showed no significant decline in ventricular function.[9] In another study of 1,491 patients with anginal symptoms and normal coronary arteries (no major epicardial artery with >25% stenosis), 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 ≥75% stenosis), myocardial infarction free survival rates were 97% at 5 years and 90% at 10 years.[11] Finally, a study of 7-year survival in patients with symptoms suggestive of CAD but exhibiting a normal or near-normal coronary arteriogram (< 50% stenosis in one or more epicardial arteries) revealed survival rates of 96% and 92% respectively in these two subpopulations.[12]

However, recent evidence has challenged the assumption that angina-like pain without obstructive CAD is a benign condition. In the Women's Ischemia Syndrome Evaluation (WISE) study, five-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 5,932 asymptomatic women. CV events included myocardial infarction, hospitalization for heart failure, stroke, cardiac mortality, and all-cause mortality.[13] Recent reports from Europe and Canada replicate this adverse prognosis.[14,15] Additionally, some subsets of patients tend to have poorer prognoses than others. In one study, 13 out 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 out of 20 symptomatic patients with normal coronary angiograms and no endothelial dysfunction showed resolution of chest pain 6-36 months post-angiography.[16] 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 work-up to rule out other potential causes of chest pain and can be relatively expensive. Treatment with conventional anti-anginal 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 work because of persistent symptoms. Prolonged and recurrent chest pain also necessitates repeated coronary arteriographies as well as regular outpatient visits. The lifetime cost of healthcare for a woman with nonobstructive chest pain is estimated at approximately $1 million.[5]

Diagnosis

Clinical Features - History

In approximately 50% of CSX cases, patients present with a history of exercise-induced chest pain that is followed by 15-20 minutes of dull, persistent chest discomfort. Short-acting nitrates are often inadequate in relieving this pain.[18] Some patients also experience chest pain at rest in addition to the chest pain during exertion. Patients often describe the chest pain as retrosternal and radiating to the left arm. These episodes of chest pain occur frequently with one study illustrating that 31% of patients reported greater than 7 episodes per week and 30% of patients reported greater than 1 episode per day.[9]

Clinical Features – Electrocardiogram

By definition, patients with CSX have ST segment depression induced by exercise ECG testing. However, evidence from Holter monitoring show that patients also have transient ST depression during their daily activities. In one study where CSX patients underwent 48 hours of Holter monitoring, 63% of patients had transient ST segment depression. Transient ST depression is thought to occur in only 2% of healthy subjects. However, ST segment depression did not correlate with episodes of angina. In 50% of ST segment depression episodes, patients did not experience chest pain and in 75% of anginal episodes, patients did not have ST segment depression.[19]

Clinical Features – Coronary Angiography

Similar to the presence of ST depression, by definition, patients with CSX exhibit no obstructive CAD on angiography. The traditional definition of obstructive CAD is stenosis of 50% or more of the diameter of the left main coronary artery or stenosis of 70% or more of the diameter of a coronary vessel greater than 2 mm in diameter. However, most studies require no stenosis of 50% or more in any coronary vessel in order for a patient to be classified in CSX.[20]

Among patients with angina and normal coronary angiography, one study showed that approximately 75% of patients show ST segment depression during exercise treadmill testing. Among the 25% that do not show exercise-induced ST segment depression, 50% have detectable ST segment depression during their daily activities with Holter monitoring. A controversy in this field is whether patients with transient ST segment depression during Holter monitoring but not during exercise treadmill testing should be included in the definition of CSX.[21]

Differential Diagnosis

The diagnosis of CSX in patients with recurrent chest pain and absence of any angiographic lesion greater than 50% in any coronary vessel is primarily a diagnosis of exclusion (Figure 1).[22-26] Firstly, chest pain of non-cardiac origin (e.g. gastrointestinal, musculoskeletal, pulmonary, or psychiatric) must be ruled out. If the chest pain is of cardiac origin, imaging modalities such as echocardiogram can be used to rule out structural and inflammatory disorders, such as pericarditis. If a diagnosis of coronary dysfunction is likely, the distinction between large and small vessel dysfunction is important. The primary large

vessel coronary dysfunction, vasospastic angina, presents with angina at rest, reversible ischemic ECG changes (usually ST elevation rather than depression) and spontaneous/induced coronary spasm on angiography.[22,27] Various agents can be used for spasm provocation testing including ergonovine and acetylcholine, but standardized guidelines on when to test for spasm are lacking.[28] Catheter-induced coronary spasm can occur on routine angiography, especially during engagement of the right coronary artery. This is believed to occur due to mechanical irritation of the vessel, and factors such as the size of the catheter and catheter manipulation predispose to catheter-induced spasm. The clinical significance of asymptomatic catheter-induced spasm is unclear, but if a patient complains of chest pain during catheter-induced spasm, then a diagnosis of vasospastic angina can be made and treatment initiated. When catheter—induced spasm occurs, the arterial pressure wave-form can decrease and become ventricularized and/or dampened; in this setting, it is important to rule out significant ostial atherosclerosis. Intracoronary nitroglycerin or other epicardial vasodilators are routinely given in the setting of catheter-induced spasm.

With signs and symptoms of ischemia and no obstructive CAD, coronary microvascular dysfunction (CMD) should also be considered as an etiology for chest pain. CMD can be associated with several myocardial diseases listed in Figure 1. Whether this dysfunction is involved in the pathogenesis or is a consequence of these diseases is debatable, but the presence of myocardial diseases should be ruled out prior to making a diagnosis of CSX.[26] Lastly, CSX must be distinguished from two other CMD disorders not associated with myocardial disease: microvascular angina and coronary slow flow phenomenon. In microvascular angina, CMD is present as indicated by impaired coronary vasodilator capacity. However, unlike in individuals with CSX, these patients do not show evidence of stress-induced ischemia. These patients primarily experience angina with rest rather than exertion and do not show ST depression during exercise ECG testing.[22] Coronary slow flow phenomenon, sometimes referred to as Syndrome Y, is characterized by delayed distal vessel contrast flow on angiography. In contrast to CSX, clinical features include a higher prevalence in males and rest or mixed-pattern angina rather than angina on exertion.[29]

Pathogenesis Overview

The pathogenesis of CSX remains unclear, but several theories have been proposed. The two major hypotheses are 1) CMD, in which symptoms are thought to result from myocardial ischemia secondary to abnormal coronary microvasculature function, and 2) abnormal cardiac pain sensitivity, in which symptoms are thought to be a result of altered pain perception of myocardial hypersensitivity. These processes could be acting synergistically, or different subpopulations of CSX patients may have different underlying etiologies.[6]

Coronary Microvascular Dysfunction

Normal Coronary Microvascular Function

The coronary arterial system is composed of three types of vessels. The most proximal vessels are the large epicardial coronary arteries ranging in diameter size from 500 μm to 2-5 mm. The function of these vessels is to store blood from the heart as flow changes. The prearterioles are distal to the epicardial coronary arteries, and these prearterioles are 100 to

500 μm in diameter. Their function is to maintain pressure with changes in blood flow. Finally, the most distal vessels are the intramural arterioles, which have a diameter of less than 100 μm. Their function is to match blood supply to tissue oxygen demand.[16] The coronary microcirculation is composed of the coronary arteries that are too small to be visualized by angiography (<500 μm) but are important in regulating blood flow to match oxygen demand, growth, inflammation, coagulation, and permeability.[30]

Normally, when the heart tissue increases its oxygen consumption in response to increased work, for example, the intramural arterioles dilate in response to the release of metabolites from the myocardium. This dilation results in a decrease in pressure, triggering a dilation of the prearterioles and epicardial coronary arteries, increasing blood flow, and therefore, matching the increased oxygen demand of the tissue.[16]

Assessment of Coronary Microvascular Function

Since the vessels involved in the microcirculation are too small to be visualized by angiography, coronary blood flow measurements at baseline compared with maximal hyperemic stimuli are used to evaluate the function of the microcirculatory vessels. Hyperemic stimuli can be endothelium-independent or endothelium-dependent and therefore, dysfunction of both types of stimuli must be assessed. Adenosine is used as the gold standard to invoke an endothelium-independent hyperemic response in vessels less than 150 μm by stimulating the adenosine A2 receptors on smooth muscle cells. Acetylcholine is commonly used to assess endothelial-dependent dilation of the microvasculature.[30] A newer, less-invasive diagnostic method is the use of cardiac magnetic resonance imaging to assess myocardial perfusion reserve index (MPRI) in response to adenosine. A recent study showed that women with previously confirmed CMD had lower MPRI values globally and in subendocardial and subepicardial regions in comparison to controls.[31]

Impaired Coronary Microvascular Function

It is thought that patients with CSX have impaired relaxation and/or increased sensitivity to vasoconstriction in the intramural arterioles and prearterioles. This results in impaired myocardial blood supply and episodes of ischemia causing chest pain.[2] According to the traditional definition of CMD, coronary volumetric blood flow increases by less than 2.5 times baseline blood flow with maximal hyperemic stimuli.[30]

Studies in favor of the CMD theory underlying the pathogenesis of CSX have shown that CSX patients have impaired vasodilation in response to endothelium-dependent and endothelium-independent hyperemic stimuli, greater ischemic metabolite production after pacing-induced tachycardia, decreased phosphocreatine:ATP ratio post-exercise, more heterogenous blood flow, and greater thallium scan defects compared to healthy controls (Table 1).[32-40] Studies opposing the ischemic genesis hypothesis for CSX have shown that patients with CSX lack cardiac wall motion abnormalities during both hyperemic stimuli-mediated vasodilation and right atrial pacing, lack production of ischemic metabolites during right atrial pacing, and do not show significant change in myocardial blood flow with hyperemic stimuli when compared to control subjects (Table 2).[41-46]

Maseri et al. proposed a hypothesis that explains these seemingly contradictory studies. He described a population of CSX patients with a large number of abnormally constricted prearteriolar vessels who demonstrate reduced coronary flow reserve and myocardial ischemia. He also described another population of patients with a limited and patchy distribution of abnormally constricted prearteriolar vessels. These vessels may stimulate the local release of adenosine, which, if intense and prolonged, could cause anginal pain. This pain could occur in the absence of signs of ischemia and reduction in total coronary flow reserve because of compensation by non-constricted vessels.[47] Furthermore, a patchy distribution of myocardial ischemia may be adequate to produce ST depression on ECG but may not result in detectable contractile dysfunction due to the presence of normal surrounding tissue and may not result in detection of ischemic metabolites due to dilution with blood flow from normal tissue.[48]

Other possible reasons for the contradictory studies include methodological limitations and patient selection factors. None of the invasive or noninvasive techniques used in the assessment of coronary blood flow can accurately measure absolute flow. Furthermore, because the definition of CSX remains debatable, different studies have recruited patients with different inclusion criteria, making comparison between studies difficult.[2]

Risk Factors

Risk factors for CMD, and hence, potentially CSX, have not yet been fully elucidated. Traditional risk factors for atherosclerosis account for less than 20% of the variability seen in coronary reactivity to hyperemic stimuli.[49] Other potential risk factors include nitric oxide metabolism disorders, dysregulation of inflammatory cytokines, estrogen, or adrenergic pathways, and disruption in the expression and production of local vasoactive substances.[50]

Enhanced Pain Sensitivity

Origin of the enhanced pain sensitivity theory

The pain sensitivity theory was first proposed by Shapiro et al when they observed that patients with CSX experienced chest pain during cardiac catheterization. This chest pain was similar to the recurrent episodes that were experienced prior to catheterization and was stimulated when the venous catheter was moved within the proximal 3-5 cm of the superior vena cava and the entire right atrium. Furthermore, injection of saline into the right atrium also provoked the pain. In contrast, none of the patients with CAD or mitral valve disease experienced pain during movement of the catheter. Shapiro et al proposed that the mechanism underlying chest pain in CSX may be hyperawareness of changes in right atrial pressure and volume during exertion.[51] Additional studies with larger patient populations confirmed these observations and found that CSX patients also had a low tolerance to pain induced by adenosine.[52,53]

Psychologic and behavioral factors

Several groups have proposed that patients with CSX have an exaggerated response to pain. Studies have revealed that certain behavioral characteristics such as hypochondriasis,

anxiety, and panic disorders are common in CSX patients. Wielgosz et al. found that among 217 patients, a high hypochondriasis score (assessed by the Minnesota Multiphasic Personality Inventory) was the strongest determinant of continued pain in patients with no coronary artery stenosis.[54] In women experiencing chest pain, a history of anxiety disorders is associated with a lower probability of CAD on angiography.[55] Panic disorder is thought to affect 1-2% of the U.S. population but approximately 1/3 of patients with unexplained chest pain and angiographically normal coronary arteries.[56]

It remains unclear whether increased pain sensitivity or increased pain perception plays a role in this theory. A study was conducted by Pasceri et al. where CSX patients and control subjects underwent false and true pacing. The investigators found that patients with CSX had both increased cardiac pain sensitivity and higher likelihood of reporting pain with the expectation of pain but absence of stimulus (false pacing).[57]

Pathogenesis Summary

CMD and enhanced pain sensitivity may be independent etiologies manifesting in different subsets of patients with CSX. Alternatively, Crea and Lanza have proposed a combined theory where repeated episodes of transient ischemia may functionally alter cardiac afferent nerve endings to a hypersensitive state. Novel techniques and additional studies are necessary to further elucidate the pathogenesis of CSX.[6]

Treatment Overview

Management of patients with CSX remains a significant challenge due to the limited effectiveness of conventional anti-anginal therapies. The difficulties in management may be due to our incomplete understanding of the pathophysiology underlying CSX and hence the inability to target the underlying pathophysiology.[58] Current therapies include anti-ischemic and analgesic pharmacological treatments, non-pharmacological procedures, and lifestyle modifications (TABLE 3).

Anti-ischemic Pharmacological Treatments

Nitrates

The therapeutic effect of nitrates results from the release of nitric oxide (NO) from nitrite, the activation of guanylyl cyclase, and the relaxation of blood vessels.[59] Although the effectiveness of nitrates in CSX has not been evaluated in large randomized clinical trials, observational studies have shown that nitrates have limited efficacy in alleviating chest pain. In an observational study of 99 CSX patients, both sublingual nitrates as well as oral nitrates with calcium antagonists relieved episodes of chest pain in 42% of patients.[9] Furthermore, Russo et al. demonstrated that while patients with CAD had significantly improved exercise stress test results with the administration of short-acting nitrates, patients with microvascular angina did not. These findings supported the hypothesis that the dilator effect of nitrates on small coronary vessels is poor.[60] Despite their unpredictable effectiveness, nitrates have historically been the mainstay of CSX therapy.[61]

Beta-Adrenergic Receptor Blockers

Beta-adrenergic receptor blockers (beta-blockers) work as an anti-anginal therapy by blocking catecholamine-induced increases in heart rate, blood pressure, and myocardial contractility, thereby reducing myocardial oxygen consumption.[62] They have been shown to improve anginal symptoms, functional capacity, and exercise testing in up to 75% of patients with CSX.[63] Propranolol has been shown to significantly reduce the average number of ischemic episodes per 24 hours compared to placebo and atenolol has been shown to significantly improve symptoms, exercise performance, and diastolic function in CSX patients when compared to placebo.[64,65]

In comparison to traditional beta-blockers, the third generation beta-blockers nebivolol and carvedilol have additional endothelium-dependent vasodilating properties and may be more effective than traditional beta-blockers.[66] In CSX patients, nebivolol has been shown to significantly increase circulating endothelial function parameters, such as plasma asymmetric dimethylarginine (ADMA), L-arginine, and NO levels, and improve exercise stress test parameters, such as exercise duration to 1-mm ST depression and total exercise duration, compared to metoprolol.[67] Kaski et al. showed that after administration of a single dose of carvedilol, 10 out of 15 CSX patients did not have angina at peak exercise and 5 out of 15 patients had ST shifts of less than 1 mm ($p<0.01$ compared to placebo).[68] Overall, beta-blockers may represent the first line of treatment for CSX patients.[64]

Calcium Channel Antagonists

Calcium channel antagonists block L-type calcium channels thereby reducing intracellular calcium concentrations. This results in negative chronotropic and inotropic effects as well as a decrease in peripheral vascular resistance.[69] The efficacy of calcium channel antagonists for treating CSX remains unclear. Verapamil and nifedipine have been shown to decrease the frequency of anginal episodes and prolong exercise duration in comparison to placebo.[70] However, administration of intravenous diltiazem did not increase coronary flow reserve in patients with angina, normal coronary arteries, and reduced coronary flow reserve.[71] Furthermore, beta-blockers have been shown to be more effective than calcium channel antagonists. Propranolol was shown to be more effective than verapamil and atenolol was more effective than amlodipine in reducing frequency of anginal episodes.[72]

Ranolazine

The functional molecular mechanisms of ranolazine, a newer anti-anginal medication, have been debated, but the current consensus is that ranolazine inhibits the late inward sodium channel thereby preventing high intracellular sodium concentrations from disrupting myocardial function.[69] Chaitman et al. have demonstrated in patients with chronic severe angina that ranolazine used as monotherapy increases exercise performance, and when combined with standard doses or atenolol, amlodipine, or diltiazem, provides additional anti-anginal relief.[73,74] Furthermore, ranolazine has been shown to modulate neuronal voltage-gated sodium channels involved in neuropathic pain, and therefore, may be especially beneficial as an anti-anginal therapy for CSX patients.[75] Mehta et al. showed that in women with angina, evidence of ischemia, and no obstructive CAD, 4-week treatment

with ranolazine improves physical functioning, angina stability, and quality of life as measured by Seattle Angina Questionnaire scores.[76]

Angiotensin Converting Enzyme Inhibitors

Angiotensin converting enzyme inhibitors (ACE-I) have two main mechanisms of action. First, they decrease production of angiotensin II, which has vasoconstrictive properties, and therefore are used in blood pressure management. Secondly, they decrease degradation of endothelial bradykinin, which stimulates the production of NO and other vasodilators and is anti-apoptotic. .[77] Therefore, they are hypothesized to be beneficial for treating CSX patients. ACE-I have been shown to improve exercise tolerance, improve endothelial function, improve coronary flow rates, and decrease angina in CSX patients. Studies have shown that both cilazapril and enalapril increase total exercise duration, prolong time to 1 mm of ST segment depression, and decrease magnitude of ST segment depression compared to placebo.[78,79] Chen et al. showed that enalapril improved endothelial function by reducing von Willebrand factor and ADMA levels while increasing NO and L-arginine to ADMA ratio levels.[80] Finally, Pauly et al. showed that quinapril improved anginal episode frequency as well as increased coronary flow rate. The women that presented with the lowest baseline coronary flow rate benefited the most from quinapril.[81]

Statins

Similar to ACE-I, statins have two main mechanisms of action. They are used primarily to lower cholesterol because of their ability to inhibit HMG-CoA reductase. However they also improve endothelium-dependent vasomotion and hence may be beneficial in CSX patients.[82] Studies have shown that CSX patients receiving pravastatin or simvastatin show significant improvement in both exercise-induced ischemia as well as in brachial artery flow mediated dilatation within 4 months.[83,84] Statins combined with calcium channel blockers have also proven beneficial. Zhang et al. showed that patients who were treated with fluvastatin and diltiazem for 90 days showed improved coronary flow reserve and prolonged time to 1 mm ST segment depression as well as a significant increase in NO levels and a reduction in endothelin-1 when compared to patients treated with either medication alone.[85]

Analgesic Pharmacological Treatments

Xanthine Derivatives

As mentioned previously, enhanced pain sensitivity has been proposed as one of the pathophysiological mechanisms underlying the pain experienced by CSX patients. Therefore it has been proposed that xanthine derivatives, which are adenosine receptor blockers, can modulate the anginal pain in CSX.[86] In a double blind crossover study, patients with CSX who were given oral aminophylline for 3 weeks reported fewer episodes of chest pain when they were taking the medication than when they were taking placebo pills. Furthermore, after 3 weeks of aminophylline, patients had a higher exercise induced chest pain threshold. However, frequency of ST depression measured by Holter monitoring and peak exercise ST depression did not change with the medication.[86] Improved exercise capacity with aminophylline has also been documented in other studies.[87,88] Despite their demonstrated efficacy when taken over a span of several weeks, Lanza et al. showed that xanthine

derivatives may not have any acute benefit. They showed that one intravenous infusion of bamiphylline had little effect on anginal pain during exercise testing in patients with CSX.[89]

Tricyclic Antidepressants

In addition to their antidepressive effects, tricyclic antidepressants exhibit analgesic activity due to their balanced reuptake inhibition of the neurotransmitters serotonin and noradrenaline.[90] In a study of patients with chest pain and normal angiograms, patients experienced a 52% decrease in episodes of chest pain during the imipramine-treatment phase. Additionally, patients experienced significant improvement in sensitivity to cardiac pain during right ventricular electrical stimulation or intracoronary infusion of adenosine compared to baseline.[91] Cox et al. also showed that imipramine treatment decreased anginal frequency. However, they also reported the failure of imipramine to improve quality of life likely due to the side effects of treatment including dry mouth, dizziness, nausea, and constipation.[92]

Non-pharmacological Treatment

Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) consists of opportunities for patients to discuss their experiences of pain and its management, receive counseling and education about cardiac disease and angina, learn stress management and relaxation techniques, regain exposure to activities avoided because of pain, and engage in light physical exercise.[93,94] In women with chest pain despite normal angiography, eight weeks of CBT can help reduce patients' anxiety, depression, and disability as well as increase exercise tolerance.[94] Furthermore, CBT can reduce yearly hospital admissions among patients with CSX likely because educating patients and demystifying angina put patients at greater ease. One study showed that 8 weeks of CBT decreased total hospital admissions from 2.40 to 1.78 per patient per year and decreased total hospital bed day occupancy from 15.48 to 10.34 days per patient per year.[93] CBT should be considered in the management of CSX, especially when patients have continued pain despite pharmacological treatment.

Enhanced External Counterpulsation

Enhanced external counterpulsation consists of treatment sessions in which cuffs are wrapped around a patient's legs and inflated and deflated in sequence with the cardiac cycle. During early diastole, the cuff is inflated sequentially from the lower legs to the upper thighs thereby propelling blood to the heart. During end-diastole, the cuff is deflated reducing vascular resistance. This technique is thought to provide anginal relief through several mechanisms:

1. Increased transmyocardial pressure gradients during the treatment sessions may open collaterals in the heart.
2. When the coronary and peripheral arterial beds are exposed to increased blood flow and shear forces, the endothelium increases production of NO and prostacyclin.
3. Increased blood flow may regulate paracrine substances involved in vascular remodeling and reactivity.[95]

Kronhaus and Lawson have shown that enhanced external counterpulsation is beneficial in patients with CSX. In their study they showed that enhanced external counterpulsation treatment in 30 patients with CSX resulted in an improvement in angina and regional ischemia. After 12 months, 87% of these patients maintained their improvement in angina.[96]

Neurostimulation

Neural modulation can be performed either through transcutaneous electrical nerve stimulation (TENS) or spinal cord stimulation. It has been proposed that an autonomic imbalance with increased sympathetic activity and decreased parasympathetic activity may be causing both endothelial dysfunction and increased pain sensitivity in CSX patients.[97,98] Neurostimulation is thought to enhance parasympathetic activity and reduce spinothalamic tract cell activity thereby potentially being an effective therapy for CSX patients.[99]

De Vries et al. performed a study in which patients who presented with anginal pain, normal coronary arteries, and benefit from a 2-week trial of transcutaneous electrical nerve stimulation were treated with continued transcutaneous electrical nerve stimulation for 5 years. If patients developed side effects, they had the option of switching to spinal cord stimulation. After 5 years of neurostimulation, patients reported a 57% reduction in pain and a 30% improvement in exercise capacity.[99] Furthermore, Lanza et al. reported that patients with angina and normal coronary arteries who underwent spinal cord stimulation showed an improvement in the Seattle Angina Questionairre, reduction in angina severity and duration, and improvement in ischemic burden as measured by Holter monitoring.[100]

Stellate Ganglionectomy

Sympathetic blockade is a technique used to block sympathetic fibers. One type of sympathetic blockade is the stellate (cervicothoracic) blockade. This blockade involves the stellate ganglion, which is formed from the fusion between the lower cervical and first thoracic ganglia, and provides part of the sympathetic innervation to the head, neck, arm, and heart. The heart lacks sensory nerves and therefore the sympathetic nervous system transmits the sensation of angina to the brain. Blocking the stellate ganglion, and hence sympathetic transmission, is thought to provide relief from angina.[101] Blockade is usually performed with an anesthetic and is transient. To achieve long-term blockade, a ganglionectomy can be performed.[102] Case reports of successful treatment with stellate ganglionectomy have been reported in conditions with augmentation of sympathetic activity including congenital long QT syndrome, ventricular tachycardia storm, and palmar hyperhidrosis.[103-105] Furthermore, it has been shown as a safe and effective procedure for pain conditions including chronic refractory angina.[101] Stellate ganglionectomy could be a viable option for CSX patients but further research is necessary.

Lifestyle Modifications

The only lifestyle modification that has been evaluated in CSX patients is exercise. Eriksson et al. showed that exercise training for 8 weeks resulted in an increased exercise capacity with later onset of anginal pain. Exercise training also increased endothelium-dependent blood flow. However, training did not improve cardiac hypersensitivity to low-dose

adenosine infusion.[106] Another study showed that the tolerated exertion during six minutes of walking and the health-related qualify of life measured by both the Stress and Crisis Inventory and the Sickness Impact Profile improved when CSX patients underwent 8 weeks of physical training.[107]

Along with these results, the INTERHEART study, a global case-control study involving 27,098 participants from 52 countries, showed that not only does physical activity decrease the risk of a future MI but that physical activity is more protective in women than in men.[108] Physical activity can be performed by patients on their own or as part of a Cardiac Rehabilitation program. Cardiac Rehabilitation programs are group- or home-based cardiovascular exercise programs that focus on improving aerobic conditioning, functional capacity, muscular strength, endurance, and flexibility.[109] Asbury et al. showed that women with CSX who underwent an 8-week Cardiac Rehabilitation program showed improved exercise tolerance, quality of life, symptom severity, and psychological morbidity not found among control CSX women.[109]

Other lifestyle modifications that can be encouraged include weight loss, smoking cessation, and a Mediterranean diet. Both weight loss and smoking cessation have been shown to improve endothelial function and therefore may be beneficial in women with CSX.[110,111] The current American diet consists of highly processed, calorie-dense, and nutrient depleted foods which trigger oxidative stress causing inflammation and damage to the endothelium. The Mediterranean diet, which is rich in minimally processed, high-fiber, plant-based foods such as vegetables and fruits, whole grains, legumes, and nuts reduces oxidative stress, inflammation, and damage to the endothelium.[112]

Treatment Conclusion

In patients with CSX, a combination therapeutic approach including anti-ischemic and analgesic pharmacological treatment and lifestyle modifications is often necessary. Non pharmacological therapies can be added as necessary. Studies have shown the effectiveness of individual therapies but further work is needed in evaluating the best combination of treatments and guidelines are necessary for the order in which treatments should be administered.

Conclusion

CSX, the condition of angina, normal coronary arteries, and ST segment depression on ECG, was once characterized as benign. However, it is now recognized as a condition that carries significant morbidity and increases the risk for cardiovascular events. Diagnosis of the syndrome is challenging and expensive. The pathogenesis is not fully understood which makes treatment difficult. Many pharmacological and non-pharmacological treatments have shown to be at least partially effective but guidelines are lacking on the best course of treatment.

Acknowledgments

This work was supported by contracts from the National Heart, Lung and Blood Institute, nos. N01-HV-68161, N01-HV-68162, N01-HV-68163, N01-HV-68164, grants K23HL105787, U0164829, U01 HL649141, U01 HL649241, T32HL69751, 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, Inc., 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 .

Appendix

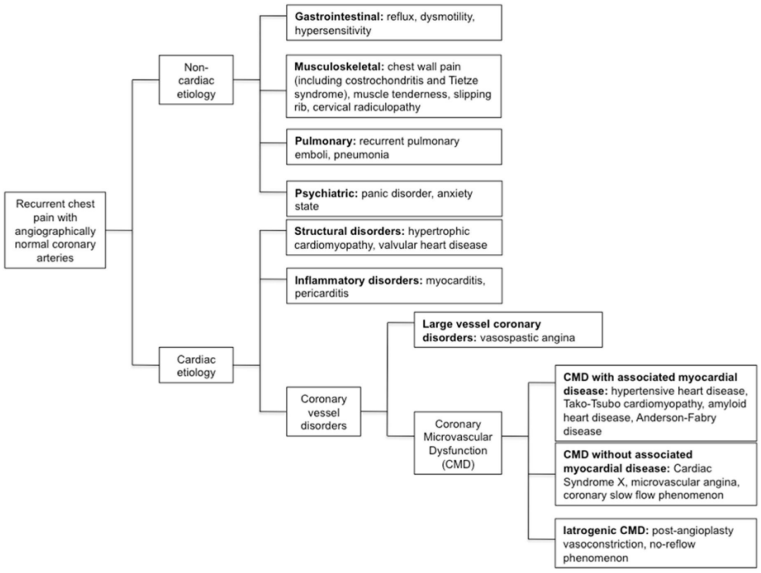

Figure 1.

Differential Diagnosis of Recurrent Chest Pain with Angiographically Normal Coronary Arteries. Adapted from Refs [22-26].

Table 3

Overview of Treatment Strategies for Cardiac Syndrome X.

Anti-ischemic Pharmacological Treatments
Nitrates
Beta-blockers
Calcium Channel Antagonists
Ranolazine
Angiotensin Converting Enzyme Inhibitors
Statins
Analgesic Pharmacological Treatments
Xanthine Derivatives
Tricyclic Antidepressants

- Non-pharmacologic Treatments
  - Cognitive Behavioral Therapy
  - Enhanced External Counterpulsation
  - Neurostimulation
    - Transcutaneous Electrical Stimulation
    - Spinal Cord Stimulation
  - Stellate Ganglionectomy
- Lifestyle Modifications
  - Exercise
  - Weight Loss
  - Smoking Cessation
  - Dietary Changes (Mediterranean Diet)

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Key Points

- Up to 20-30% of patients presenting with chest discomfort characteristic of angina demonstrate no obstructive CAD, defined as ≥50% stenosis in at least 1 major coronary artery, upon angiography.

- The lifetime cost of healthcare for a woman with chest pain and no obstructive CAD is estimated at approximately $1 million due to challenges in diagnosis and treatment.

- To diagnose Cardiac Syndrome X one must rule out non-cardiac etiologies, large vessel coronary disorders, and coronary microvascular dysfunction with associated myocardial disease.

- 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, non pharmacological procedures, and lifestyle modifications.

Table 1

Evidence supporting Coronary Microvascular Dysfunction (CMD) in Cardiac Syndrome X

Authors and Year	Assessment Method	Key Findings
Lanza GA, Buffon A, Sestito A, et al. (2008).[37]	Dobutamine, Adenosine mediated dilatation	- At peak dobutamine stress test, reversible perfusion defects found in 56% of CSX patients but in none of the control subjects (p=0.004) - Coronary flow rate to adenosine lower in CSX patients than in control subjects (p=0.0004)[37]
Panting JR, Gatehouse PD, Yang GZ, et al (2002).[39]	Adenosine mediated dilatation	- While myocardial perfusion index in response to adenosine increased in both the subepicardium and subendocardium in normal controls, it did not change significantly in the subendocardium for CSX patients (p=0.11). - Adenosine provoked chest pain in 95% of CSX syndrome patients but only 40% of normal controls (p<0.001).[39]
Buffon A, Rigattieri S, Santini SA, et al (2000).[34]	Metabolite Production	- Lipid hydroperoxides and conjugated dienes, two markers of ischemia-reperfusion oxidative stress, increased in the great cardiac vein in CSX patients (p<0.01) but did not change in normal controls after pacing-induced tachycardia.[34]
Buchthal SD, den Hollander JA, Merz CN, et al (2000).[33]	Phosphocreatine: ATP ratio post-exercise	- 7/35 women with CSX had decreases in the phosphocreatine:ATP ratio during isometric handgrip exercise that were more than 2 SD below the mean value in controls providing evidence of an abnormal metabolic response to exercise consistent with myocardial ischemia.[33]
Bottcher M, Botker HE, Sonne H, et al (1999).[32]	Dipyridamole mediated dilatation	- Hyperemic response to intravenous dipyridamole less in CSX group compared with normal controls (p<0.05)[32]
Chauhan A, Mullins PA, Taylor G, et al (1997).[35]	Papaverine, Acetylcholine mediated dilatation	- Mean increase in coronary blood flow to endothelium-independent vasodilator papaverine and endothelium-depending vasodilator acetylcholine was less in CSX subjects than normal controls (p<0.001)[35]
Meeder JG, Blanksma PK, Crijns HJ, et al (1995).[38]	Heterogeneity of perfusion using positron emission tomography	- Mean perfusion and its coefficient of variation, as a measure of perfusion heterogeneity, were higher in patients with CSX compared to normal controls indicating patchy distribution of hyperactive small coronary vessels with compensatory release of adenosine.[38]
Galassi AR, Crea F, Araujo LI, et al (1993).[36]	Dipyridamole mediated dilatation	- Baseline and post-intravenous dipyridamole myocardial blood flow more heterogeneous in CSX patients than in healthy controls (p<0.01)[36]
Tweddel AC, Martin W, Hutton I (1992).[40]	Thallium scan	- 98/100 patients with angina and normal coronary arteriograms had thallium scan defects that suggest microvascular angina[40]

Data from Refs 32-40.

Table 2

Evidence against Microvascular Coronary Dysfunction (CMD) in Cardiac Syndrome X

Authors and Year	Assessment Method	Key Findings
Panza JA, Laurienzo JM, Curiel RV, et al. (1997).[44]	Dobutamine mediated dilatation	- Like normal controls, CSX patients showed a quantitatively normal myocardial contractile response without development of wall motion abnormalities in response to dobutamine.[44]
Rosano GM, Kaski JC, Arie S, et al. (1996).[45]	Blood pH and lactate levels during right atrial pacing	- Patients with coronary artery disease showed a greater fall of coronary sinus pH, oxygen saturation, and lactate extraction ratio compared to CSX patients ($p<0.01$, $p<0.05$, and $p<0.01$ respectively).[45]
Rosen SD, Uren NG, Kaski JC, et al. (1994).[46]	Dipyridamole mediated dilatation	- Myocardial blood flow in CSX patients and control subjects at rest was 1.05 and 1.00 respectively and after dipyridamole administration was 2.73 and 3.00 respectively (p=NS).[46]
Camici PG, Gistri R, Lorenzoni R, et al. (1992).[41]	Dipyridamole mediated dilatation	- Among patients with chest pain and angiographically normal coronary arteries, 1/3 had reduced coronary vasodilatory reserve post-dipyridamole administration. 12/14 patients with reduced reserve had exercise ST segment depression but 16/29 patients with normal reserve also had ST depression suggesting the role of factors other than reduced coronary reserve and ischemia in the genesis of ST depression.[41]
Camici PG, Marraccini P, Lorenzoni R, et al. (1991).[42]	Analysis of metabolites during rapid atrial pacing	- No net lactate release in patients with CSX during atrial pacing - CSX patients carried out the same external work with a smaller increase in blood flow, oxygen consumption, and energy expenditure than normal controls - During atrial pacing, CSX patients continued to rely on fatty acid substrates for oxidative metabolism.[42]
Nihoyannopoulos P, Kaski JC, Crake T, et al. (1991).[43]	Stress two-dimensional echocardiogram during right atrial pacing	- In patients with CSX, no regional wall motion abnormalities seen on two-dimensional imaging of any myocardial segment. - Percent systolic wall thickening increased over values at rest in each myocardial segment during right atrial pacing.[43]

Data from Refs 41-46.