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Syndrome X and Microvascular Coronary Dysfunction

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Introduction

Chest pain evaluation remains a challenge in medical practice comprising 7% to 24% of the primary care population visits(Kroenke, Arrington et al. 1990). For women presenting for evaluation of suspected ischemic symptoms, a diagnosis of normal coronary arteries is five times more common compared to men(Sullivan, Holdright et al. 1994). The challenge to diagnose coronary artery disease (CAD) in women is amplified with the presence of more atypical symptom burden, functional disability and often a greater degree of comorbidity and clustering of cardiac risk factors in women when compared to men(Shaw, Bairey Merz et al. 2006). Prior studies demonstrate that the presence of obstructive (CAD) can be predicted with less certainty in women than men(Sullivan, Holdright et al. 1994), and that women are less likely than age-matched men to have obstructive CAD(Mieres, Shaw et al. 2005).

Women with cardiac chest pain indicated by signs and symptoms of myocardial ischemia in the absence of obstructive CAD are often labelled as cardiac syndrome X (CSX)(Kemp 1973). A subset of patients with CSX may have symptoms of ischemia due to microvascular dysfunction. Angina due to microvascular coronary dysfunction (MCD)(Cannon and Epstein 1988) is an etiologic mechanism in women with vascular dysfunction. The conditions of CSX and its subentity MCD are increasingly investigated but yet full elucidation of their pathogenesis remains lacking. This has resulted in a lack of consensus regarding diagnosis, treatment, and a considerable drain in health resources(Shaw, Merz et al. 2006). Understanding the pathogenesis and contributing factors underlying chest pain and normal coronaries at angiography is of vital importance for appropriate management of CSX.

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Epidemiology

CSX (symptoms and signs of myocardial ischemia in the absence of CAD), although occurs in men and women with certain predisposition, however, is classically acknowledged as a female predominant disorder and nearly 70% of patients diagnosed as having CSX are women (Kaski, Rosano et al. 1995). In a large patient cohort suspected to have myocardial ischemia and referred for clinically indicated coronary angiography, 41% of them versus only 8% of the men studied showed non-significant epicardial CAD(Sullivan, Holdright et al. 1994). Similar findings were reported in the large CASS registry where nearly 25,000 patients were characterized after undergoing angiography, further pointing towards the female predominance of having chest pain with normal coronary arteries(Davis, Chaitman et al. 1995)**.** Other causes of non obstructive CAD which can present as chest pain include coronary spasms, coronary bridging, slow flow phenomenon and Takostubos or Apical Ballooning Syndrome which are more defined and seem to be their own phenomenon however there is evidence to show they also involve dysregulation of the microvasculature, neurohormonal and vasodilatory pathways similar to those found in CSX (Beltrame, Limaye et al. 2002; Herrmann, Higano et al. 2004; Kawano and Ogawa 2005; Gianni, Dentali et al. 2006). Women with CSX are usually in their perimenopausal or menopausal stage of life with their onset of symptoms between 40 and 50 years(Cannon 2009).

Epidemiologic studies have shown that predictive indicators for CSX outcome and events are based on intermediate-term follow-up studies that included women either exclusively(Bugiardini, Manfrini et al. 2004; Johnson, Shaw et al. 2006; Shaw, Merz et al. 2006), as a majority(Kaski, Rosano et al. 1995; Suwaidi, Hamasaki et al. 2000), or as a minority(Lichtlen, Bargheer et al. 1995). Intermediate-term survival was not adversely affected(Kaski, Rosano et al. 1995; Schroeder, Adams et al. 2004) and the coronary morbidity and mortality in CSX patients were similar to the overall population(Lichtlen, Bargheer et al. 1995). An increased risk for the development of coronary event is found mainly in patients with elevated risk factors (Lichtlen, Bargheer et al. 1995). In a recent series, a reported five-year death or myocardial infarction (MI) rate was 4 %(Shaw, Merz et al. 2006). Deterioration of cardiac function rarely occurred in one of the series(Kaski, Rosano et al. 1995). However, some of the data in this regard are based on heterogeneous enrollment and small numbers of patients with CSX, as well as non-uniform assessment of patients for factors like epicardial coronary spasm, endothelial dysfunction, and intravascular ultrasound (IVUS) characterization of coronary lesions, the issues which may argue their limitations(Bairey Merz, Shaw et al. 2006). Recent IVUS findings in 30 patients with classically defined CSX have shown normal coronary arteries in 12 patients, atheromatous disease (mean area stenosis 38%) in 10 and marked intimal thickening in 8 patients. In response to exercise, those with abnormal coronary arteries showed vasoconstrictive response while others with normal coronary arteries displayed vasodilatory response(Wiedermann, Schwartz et al. 1995), findings that also raise the question of occult coronary disease in some patients with CSX (Chaudhary and Kaski 2011). Subsequently, CSX was not viewed as entirely benign condition through several other studies(Diver, Bier et al. 1994; Johnson, Shaw et al. 2006; Shaw, Bugiardini et al. 2009) especially those incorporating in their methods endothelial function assessment and cohort longitudinal follow up(Takusagawa, Komori et al. 1999; Schachinger, Britten et al. 2000; Suwaidi, Hamasaki et al. 2000; von Mering, Arant et al. 2004; Pepine, Anderson et al. 2010). In addition, considering the symptom burden and quality of life in CSX patients, all these factors may profoundly change the concept of risk stratification and management strategy in those patients(Kaski, Rosano et al. 1995; Bairey Merz, Shaw et al. 2006; Shaw, Merz et al. 2006).

Symptom-driven care for women is costly in the absence of obstructive CAD(Shaw, Merz et al. 2006). For women with no obstructive CAD the average lifetime costs for ischemic heart disease (IHD) is $ 767,288, approaching the magnitude to the lifetime cost on average of >$ 1 million dollars for women with obstructive CAD. Based on these data, the societal economic burden for CAD care for women with angina could exceed $162 billion dollars annually in the US, with an estimated half of this expenditure on women with no obstructive CAD(Shaw, Merz et al. 2006).

Pathogenesis

The etiology of CSX appears as non-homogenous and despite the considerable effort of research over the last 4 decades(Cannon 2009), there is no universally accepted understanding of the etiopathophysiology of chest pain with evidence of ischemia and non-obstructive CAD(Bairey Merz, Eteiba et al. 2007; Cannon 2009). Suggested mechanisms (Kaski 2004; Bairey Merz, Eteiba et al. 2007; Cannon 2009) of CSX include microvascular dysfunction, altered regulation of coronary microcirculation through autonomic dysregulatory mechanisms, generalized vascular disorder and abnormal subendocardial perfusion. Other suggested contributing factors include inflammation, hyperinsulinemia, enhanced sodium-hydrogen exchange, hormonal deficiency, abnormal pain perception and lastly inherent pathogenetic pathways.

Pathophysiology of Microvascular Coronary Dysfunction

MCD is a major etiologic mechanism underlying chest pain evoked by ischemia in patients with CSX. It refers to abnormalities in the vasomotor or metabolic regulators of the small coronary arterioles (<500um). However, structural abnormalities of vessel wall of microcirculation (for example smooth muscle cell hypertrophy) have been described by some (Opherk, Zebe et al. 1981), but not all studies(Richardson, Livesley et al. 1974). Although small coronary arterioles are not visualized during coronary angiography, they are the major determinants of coronary vascular resistance(Camici and Crea 2007). Experimental studies and clinical observations emphasize the role of sex in influencing the microvascular mechanisms that may reflect upon microvascular pathophysiology(Vaccarino, Badimon et al. 2011). Recent data support a role of female-specific ischemic heart disease pathophysiology that includes dysfunction of the coronary microvasculature. Evidence from autopsy data suggests that women may have a higher frequency of coronary plaque erosion and microembolization(Burke, Kolodgie et al.), which could result in greater microvascular dysfunction. Results from research work using retinal photography also implicates sex-specific dysfunction of the microvasculature. Retinal arterial narrowing, a measure of microvascular disease, is related to cardiovascular disease risk and mortality in women but *not* in men (Wong, Hubbard et al. 2002). Specifically, for women, every standard deviation decrease in retinal arteriole-to-venule ratio was associated with a 37% increase in coronary heart disease death and myocardial infarction (MI) that was independent of the presence of hypertension or diabetes(Burke, Farb et al. 1998).

Altered Regulation of Coronary Microcirculation

Autonomic Imbalance

Autonomic imbalance has been suggested as a mechanism for altered microvascular tone. Abnormal cardiac adrenergic nerve function was detected in 75% of patients with CSX(Lanza, Giordano et al. 1997). It is hypothesized that norepinephrine spillover and enhanced adrenergic drive may lead to increased microvascular tone and sensitize small coronary arteries to vasoconstrictor stimuli(Lanza, Giordano et al. 1997). Recent data show that women have a delayed norepinephrine re-uptake at the synapse level, further suggesting

a role of sex-specific difference in the pathophysiology of cardiac symptoms(Schroeder, Adams et al. 2004). This autonomic imbalance may result in reduction of coronary flow reserve and heterogeneity of myocardial perfusion uptake (Lanza, Giordano et al. 1997). Conversely, Gulli et al reported that parasympathetic rather than sympathetic tone was impaired in about two thirds of their series of patients with CSX as compared to no impairment in the normal controls(Gulli, Cemin et al. 2001). Interestingly, studies have identified autonomic dysregulation in relation to vasospasm with patients with variant type angina, further pointing towards a role of both sympathetic and parasympathetic imbalances as a cause of chest pain(Takusagawa, Komori et al. 1999; Inazumi, Shimizu et al. 2000). Identification of autonomic impairment and its type is potentially important for devising appropriate targeted therapeutic strategies aimed at increasing vagal tone including aerobic exercise and transdermal scopolamine(La Rovere, Mortara et al. 1994), or blocking adrenergic function(Lanza, Giordano et al. 1997) .

Nitric Oxide-Endothelin Imbalance

Another proposed disrupted regulatory mechanism of microvascular circulation is an imbalance between the endothelial-derived nitric oxide (NO) (vasodilator) and Endothelin-1 (ET-1) (vasoconstrictor). Reduced bioavailability of endogenous NO and increased plasma levels of ET-1 may be responsible for abnormal vasoreactivity in patients with CSX. ET-1 was significantly higher and its baseline level showed abnormal coronary vascular response in patients with CSX(Cox, Botker et al. 1999). An abnormal response to ET-1 was also observed in CSX patients even though its plasma concentration was not elevated(Newby, Flint et al. 1998). Genetic abnormality underlying the altered endothelial production of NO in patients with CSX has been recently suggested(Sinici, Atalar et al. 2010). Findings from a patient-controlled genetic study of polymorphism of endothelial Nitic Oxide Synthase gene (eNOS is the enzyme responsible for the synthesis of NO), displayed higher frequency of Intron 4aa genotype in controls compared to patients with CSX suggesting its protective effect (Sinici, Atalar et al. 2010)

Coronary Endothelial Dysfunction

Coronary endothelial dysfunction is suggested to be at least one of the possible several mechanisms contributing to MVA(Suwaidi, Hamasaki et al. 2000; Bugiardini and Bairey Merz 2005; Pepine, Kerensky et al. 2006). In one study, a normal endothelial-dependent function was defined as an increase of more than 50% of coronary blood flow in response to acetylcholine administration(Suwaidi, Hamasaki et al. 2000). In large arteries, endothelial dysfunction is considered among the earliest changes associated with atherosclerosis before structural changes to the vessels are appreciated(Schachinger, Britten et al. 2000) and appears to predict the development of obstructive CAD(Bugiardini, Manfrini et al. 2004). The suggested underlying mechanisms for endothelial dysfunction are based upon the observations that endothelial vasodilator dysfunction correlates with failure of coronary blood flow to increase during dipyridamole (Opherk, Zebe et al. 1981; Cannon and Epstein 1988) or acetylcholine(Egashira, Inou et al. 1993) infusion, pacing(Quyyumi, Cannon et al. 1992), or cold exposure(Zeiher, Krause et al. 1995). Recent evidence suggests that altered circulating endothelial progenitor cells, normally involved in the biological repair of vascular injury, constitutes an underlying contributing factor to endothelial dysfunction encountered in many patients with CSX (Huang, Chen et al. 2007).

Relation to Coronary Flow Reserve

Reduced coronary flow reserve (CFR) appears to be a common underlying factor noted in many of the studies exploring the pathogenesis of patients with chest pain and normal coronary angiograms(Cannon and Epstein 1988; Zeiher, Drexler et al. 1991; Egashira, Inou

et al. 1993; Cannon 2009; Pepine, Anderson et al. 2010). Zeiher et al. examined patients with chest pain and normal or minimally affected coronary arteries, using Single Photon Emission Tomography (SPECT) imaging, and demonstrated that impaired endothelial-dependent regulation of coronary blood flow in the resistance arterioles was associated with stress-induced myocardial ischemia(Zeiher, Krause et al. 1995). However, it was not clear whether this was due to an abnormal production or destruction of endothelium-derived relaxing factors like NO, an abnormality of endothelial cell membrane receptors, or a non-specifically reduced sensitivity of vascular smooth muscle cell to relax (Zeiher, Krause et al. 1995). A reduced CFR in response to intracoronary adenosine injection was also reported in 47% of women with chest pain and normal or minimal coronary artery irregularities, suggesting an endothelial-independent mechanism of microvascular dysfunction (Reis, Holubkov et al. 2001).

Noninvasive diagnosis of impaired CFR using Positron Emission Tomography (PET) imaging, suggests a heterogeneous distribution of the microvascular defects which is not confined to a single coronary artery distribution, the method which is commonly used during invasive CFR assessment(Marroquin, Holubkov et al. 2003). These abnormalities in smooth muscle relaxation as well as reduction in CFR in patients with no flow limiting stenosis on coronary angiography supports the hypothesis that signs and symptoms were microvascular in origin(Kaski 2004; Bugiardini and Bairey Merz 2005; Bairey Merz, Shaw et al. 2006; Pepine, Kerensky et al. 2006).

Relation to Myocardial Ischemia

Documenting the presence of myocellular ischemia as etiological for chest pain in individuals with normal coronary angiograms remains the focus of many current studies (Cannon and Epstein 1988; Zeiher, Krause et al. 1995; Buchthal, den Hollander et al. 2000; Panting, Gatehouse et al. 2002; Marroquin, Holubkov et al. 2003). Testing of CSX is not well defined, however non-invasive imaging has been used to determine whether ischemia is present or not and also to risk stratify patients with CSX and MVA.(Mieres, Shaw et al. 2005; Shaw, Bairey Merz et al. 2006). The use of SPECT imaging revealed myocardial perfusion defects in response to exercise in some patients with CSX (Zeiher, Krause et al. 1995). An abnormal response of coronary resistance vasculature to acetylcholine during diagnostic coronary angiography is also suggested to identify patients likely to have myocardial perfusion defects in response to stress(Zeiher, Krause et al. 1995). Using PET in women with chest pain and no coronary obstruction by angiogram, the adenosine-induced changes in myocardial perfusion reflected a heterogeneous pattern of microvascular dysfunction (Marroquin, Holubkov et al. 2003). In a cohort of women with chest pain and no obstructive CAD studied by cardiac magnetic resonance imaging (MR), one fifth of them showed an abnormal decrease in myocardial high-energy phosphate (a metabolic marker of ischemia) during light handgrip exercise. The magnitude of the decrease was equal to or greater than that observed in patients with at least 70% epicardial stenosis of the left anterior descending artery. (Panting, Gatehouse et al. 2002)

Endothelial dysfunction in the absence of obstructive CAD may not consistently cause myocardial ischemia that can be detected non-invasively(Suwaidi, Hamasaki et al. 2000; Bugiardini and Bairey Merz 2005). This can be explained by the fact that the commonly applied nuclear-based techniques for ischemia depend upon regional differences in perfusion and/or function that identified by normalizing radiotracer uptake across the myocardium. This will obfuscate detection of diffuse microvascular abnormalities. Further analyses demonstrated that even in apparently normal scans, the majority of patients with CSX showed reduced thallium-201 uptake and washout in comparison to their controls (Rosano, Peters et al. 1995). Given the fact that traditional nuclear imaging techniques rely on

detection of abnormalities that are compared to a normalized myocardium, diffuse CAD will appear as normal (Bugiardini and Bairey Merz 2005; Shaw, Bairey Merz et al. 2006). Recently, stress MR is capable of defining epicardial as well as subendocardial hypoperfusion following administration of IV adenosine in women with signs and symptoms of ischemia but no obstructive CAD(Panting, Gatehouse et al. 2002). Adenosine may also induce global and regional left ventricular diastolic dysfunction as demonstrated by both radionuclide imaging and stress echocardiography in patients with MVA. In the same study, the long axis diastolic dysfunction detected by tissue-Doppler study of the mitral annular was also suggestive of subendocardial of ischemia(Vinereanu, Fraser et al. 2002).

Relation to Other Mechanisms of Chest Pain

Whereas chest pain associated with MCD is presumed to be due to myocardial ischemia the etiology of chest pain in CSX that is unrelated to myocardial ischemia remains unclear(Kaski 2004; Bairey Merz, Shaw et al. 2006). Abnormal cardiac sensitivity(Cannon, Quyyumi et al. 1990), abnormal pain perception (Rosen, Paulesu et al. 2002) or pain threshold (Turiel, Galassi et al. 1987) were observed in some patients with CSX. An altered vascular tone due to heightened sensitivity to vasoconstrictor stimuli may result in pre-arteriolar vasoconstriction. This can be followed by significant post-arteriolar vasodilatation. The abnormal local release of adenosine, the “metabolic messenger” for pain initiation, or abnormal function of adenosine receptors was an alternate suggestion(Maseri, Crea et al. 1991), but this does not exclude the possibility of ischemia or coronary steal. Abnormal pain perception in some patients with CSX was hypothesized and based upon observation of peculiar cerebral activity detected by cerebral SPECT imaging that was simultaneous with provoked chest pain and ECG-like ischemic changes by dobutamine infusion in a number of studied patients with CSX (Rosen, Paulesu et al. 2002). Rosen et al. suggested that changes in myocardial stretch during increased cardiac work may generate increased afferent nerve firing. In a normal healthy individual, a continuous stream of afferent stimuli reaches the brain, but the signals do not reach consciousness therefore, they do not perceive pain. During myocardial ischemia, the intensity of afferent signaling from the heart is enhanced, possibly due to the presence of an altered thalamus as a regulating gate, resulting in increased cortical activation and pain. The authors argued that CSX might be a cortical pain syndrome with a “top down” process rather than a “bottom up” triggered type of pain by ischemia(Rosen, Paulesu et al. 2002). But again this proposed mechanism does not rule out the presence of coexisting ischemia.

Other Related Conditions and Possible Contributing Factors

Insulin Resistance or Hyperinsulinemia

Some evidence has suggested that CSX might be related to insulin resistance or hyperinsulinemia(Reaven 1993) whereas interventions aiming at improving insulin sensitivity have been shown to improve endothelial function and decrease myocardial ischemia in patients with CSX (Jadhav, Ferrell et al. 2006). However, *other* specific studies demonstrate that CSX per se is not associated with hyperinsulinemia or insulin resistance when other confounding factors are excluded(Cavallo Perin, Pacini et al. 2000).

Sodium –Hydrogen Exchange

Sodium-hydrogen exchange in red cells has been found enhanced 3-fold in patients with CSX when compared to those with atherosclerosis or healthy subjects suggesting its potential role as a marker of coronary vascular dysfunction(Koren, Koldanov et al. 1997).

Hyperglycemia

Studying the role of chronic hyperglycemia in the pathogenesis of endothelial dysfunction reveals a significantly reduced both endothelial-dependent as well as endothelial-independent coronary vasodilator function in a high-risk group of women(Di Carli, Janisse et al. 2003).

Inflammation

*H*igh levels of C-reactive protein, as a marker of low grade chronic inflammation, were associated with increased frequency of ischemic episodes, detected by ambulatory ECG, regardless of whether chest pain was present or not(Cosin-Sales, Pizzi et al. 2003). It is well known that inflammatory processes are activated in the presence of oxidative stress. Some investigators described a high level of thioredoxine (known to be induced and released from cells by oxidative stress) in patients during coronary spasm.(Miwa, Fujita et al. 2005)

Vascular and Non- Vascular Smooth Muscle Abnormalities

The hypothesis that MVA represents a more generalized abnormality of vascular and non vascular smooth muscle function is supported by studies on forearm arterial function(Turiel, Galassi et al. 1987; Pepine, Kerensky et al. 2006) and airway hyperresponsiveness frequently demonstrated in patients with MCD(Cannon, Peden et al. 1990).

Prognosis

Prognosis of CSX is determined by its components including chest pain, endothelial dysfunction defined by reduced coronary blood flow (CBF) to acetylcholine and myocardial ischemia. In a large cohort of women with chest pain and no obstructive CAD by angiography, persistent chest pain defined as chest pain (typical or atypical), that lasts over a year during follow-up, occurred in 45% of patients and was associated with significantly more than twice the cardiovascular events, including MIs, strokes, congestive heart failure and cardiovascular death compared to women without persistent chest pain(Johnson, Shaw et al. 2006). Subsequent functional disability secondary to chest pain was reported in half of women with non-obstructive CAD, repeated angiography rate was 13.2%, and the repeated hospitalization after one-year follow-up was 1.8-fold higher than those with 1-vessle disease(Shaw, Merz et al. 2006). Endothelial dysfunction also predicted the later development of obstructive CAD (Bugiardini, Manfrini et al. 2004). In a recent report(Pepine, Anderson et al. 2010) from Women's Ischemia Syndrome Evaluation (WISE) study, 189 women were followed-up for a mean period of 5.4 years after having their basal coronary flow reserve (CFR) measured using intracoronary adenosine. In their study, lower CFR was associated with adverse CV outcome whether women had or had no significant coronary obstruction. Also, CFR significantly improved the prediction of adverse CV outcome over angiographic severity and other risk factors. Prior results from the same study have shown that in women suspected to have myocardial ischemia, abnormal response to intracoronary acetylcholine was an independent predictor of adverse CV events including hospitalization for worsening angina, MI, congestive heart failure, stroke, revascularization and death(von Mering, Arant et al. 2004). The inter-relation between the vessel wall structure versus its function has been suggested as critical in the prognosis of atherosclerotic disease, whereas endothelial dysfunction seems to modulate the impact of a given atheroma burden(Mancini 2004). Thus, the worst expected prognosis occurs when severe grades of endothelial dysfunction are concomitant with high degrees of atheroma burden (Mancini 2004). Follow-up results of 157 patients with mild coronary atherosclerosis associated with microvascular endothelial dysfunction revealed that cardiac events occurred only in those with severe degree of endothelial dysfunction while no adverse events were detected in individuals with normal or mild dysfunction(Suwaidi, Hamasaki et al. 2000).

As previously reported(Kaski, Rosano et al. 1995), the expected cost of initial conventional diagnostic investigations including coronary angiography approximately ranged from $3500-6000. Recently, Shaw et al reported an expected consumption of nearly $750 000 of cardiovascular health care resources related to the burden of ongoing symptoms and medications (4.8% is directed to anti-ischemic therapy) throughout the lifespan of women with chest pain but normal angiogram(Shaw, Merz et al. 2006). Hence, the authors' reasoning that such women be reclassified as being at intermediate risk, compared to those with obstructive CAD, appears to be justified(Bairey Merz, Shaw et al. 2006).

Treatment

In general, the ACC/AHA guidelines for the management of ST- segment elevation and non- ST-segment elevation as well as chronic artery disease are "silent" or "neutral" on treatment by sex(Newby, Douglas et al. 2011). Although the AHA is recently maintaining a set of prevention guidelines specifically for women(Mosca, Banka et al. 2007), there are no existing guidelines for the management of MCD. Added to that is the paucity of evidence-based treatment in this population. Table 1 outlines the currently recommended guidelines for the management of CSX patients(Braunwald, Antman et al. 2002).

The goals of the therapeutic options, whether pharmacologic or non-pharmacologic, available for the treatment of MCD may comprise treatment of ischemia, amelioration of oxidative stress, reducing the burden of symptoms, maintaining quality of life, maximizing cost effectiveness and using valid research results to the benefit of diagnosis and treatment of patients with MVA. Table 2 summarizes the randomized clinical trials regarding treatment of MVA (Bairey Merz, Eteiba et al. 2007)

Summary

In conclusion, CSX and MCD and their potential links with atherosclerosis and obstructive CAD are challenging medical conditions that predominantly concern however, are not limited to women. New data provide improve understanding of coronary vascular dysfunction and resultant myocardial ischemia that Characterize MCD among patients with cardiac syndrome X. MCD has an adverse prognosis and health care cost expenditure comparable to obstructive CAD. The high prevalence of this condition, particularly in women, adverse prognosis and substantial health care costs, coupled with a lack of evidence regarding treatment strategies, places MCD as a research priority area.

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Table 1

Summary of recommendations for management of Syndrome X from the ACC/AHA Guidelines(Braunwald, Antman et al. 2002)

Recommendations
Class I
1. Reassurance and medical therapy with nitrates, beta-blockers, and calcium antagonists alone or in combination. (Level of Evidence: B)
2. Risk factor reduction. (Level of Evidence: C)
Class II b
1. Intracoronary ultrasound to rule out missed obstructive lesions. (Level of Evidence: B)
2. If no ECGs are available during chest pain and coronary spasm cannot be ruled out, coronary arteriography and provocative testing with methylergonovin, acetylcholine, or methacholine. (Level of Evidence: C)
3. HRT in postmenopausal women unless there is a contraindication. (Level of Evidence: C)
4. Imipramine for continued pain despite Class I measures. (Level of Evidence: C)
Class III
Medical therapy with nitrates, beta-blockers, and calcium antagonists for patients with non-cardiac chest pain. (Level of Evidence: C)

ACC= American College of Cardiology; AHA= American Heart Association; ECG=electrocardiogram; HRT= hormone replacement therapy.

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Table 2

Randomized Trials for CSX/Microvascular Angina Treatment

Medication	Dose	N	Type of Study	Treatment Period	Outcomes	Author (year)
Calcium Antagonists						
Verapamil	40mg qid	17	R, DB, PC	4W	Ang+, ExT+	(Cannon, Watson et al. 1985)
Nefedipine	10-30mg qid	9	R, DB, PC	4W	Ang+, ExT+	(Cannon, Watson et al. 1985)
Lidoflazine	360mg/day	22	R, DB, PC	7W	Ang+, ExT+, CBF+, Unsafe	(Cannon, Brush et al. 1990)
Diltiazem (intravenous)	10mg	16	Patient-Controlled	During functional angiography	CBF-	(Sutsch, Oechslin et al. 1995)
Nitrate-Potassium, Channel Opener						
Nicorandil	5mg tid	13	R, DB, PC	2W	Ex-Isc+, Alt HRV−	(Chen, Lee et al. 1997)
L-Arginine						
L-Arginine (infusion)	50mg/min	8	Patient-Controlled	During functional angiography	CBF+	(Egashira, Hirooka et al. 1996)
L-Arginine supplementation	3gm tid	26	R, DB, PC	6M	Ang+, CBF+, PEt+	(Lerman, Burnett et al. 1998)
Statins and ACE Inhibitors						
Pravastatin	40mg/day	38*	R, SB, P, CO	3M	ExT+, Ex−Isc+, FMD+	(Kayikcioglu, Payzin et al. 2003)
Rimapril+ Atorvastatin	10mg/day 40mg/day	45*	R, SB, PC	6M	Ang+, ExT+, FMD+	(Pizzi, Manfrini et al. 2004)
Enalapril	10mg/day	20	R, DB,PC	8W	ExT+, CFR+, NOm+	(Chen, Hsu et al. 2002)

N=Number of patients; W=week; M=month; R=Randomized; DB=Double Blind; PC=Placebo Controlled; SB=Single Blind; CO= Cross Over; + = improvement; − = no improvement; Ang=Angina; ExT=Exercise tolerance; Ex-Isc=exercise-induced ischemia; CBF=coronary blood flow; Alt HRV=altered heart rate variability; PEt=plasma endothelin; *= patients with CSX but have noninvasive determined endothelial function evaluation; FMD= flow-mediate dilatation (brachial); CFR=coronary flow reserve; NOm=nitric oxide metabolism.

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