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Cardiac Syndrome X: Advances in Treatment for Chest Pain without Artery Stenosis

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Abstract:

The number of patients diagnosed with Cardiac Syndrome X continues to increase. This condition is marked by anginal pain despite the absence of abnormal findings on coronary angiography or coronary spasm. It is considered a form of ischemic heart disease, with its incidence being most common among women in the perimenopausal and postmenopausal stages. The aim of this article is to review therapeutic options for Cardiac Syndrome X. The most effective treatments commonly used include calcium channel blockers and beta-blockers,

including newer generation options that promote vasodilation in the endothelium. Angiotensin-converting enzyme (ACE) inhibitors are also frequently used to enhance therapeutic outcomes. Other medications used were nitrates, statins, ranolazine, imipramine, nicorandil, aminophylline, cilostazol, sildenafil, fasudil. Emerging theories suggest altered pain perception, potentially involving heightened neural sensitivity, may significantly contribute to the symptoms in CSX. Additionally, studies indicate that vitamin D supplementation, often beneficial for cardiovascular health, may alleviate symptoms in CSX. Non-pharmacological methods also have proven efficacy, such as Enhanced External Counterpulsation, spinal cord stimulation and transcutaneous electrical nerve stimulation. Lifestyle changes and (CBT) also play a crucial role in the comprehensive management of Cardiac Syndrome X (CSX), targeting factors that pharmacological treatments alone may not address.

Keywords: cardiac syndrome X, microvascular angina, ischemic heart disease, pharmacological therapy.

Introduction:

Cardiac Syndrome X or microvascular angina (MVA) is used interchangeably. Microvascular angina is often regarded as a form of ischemic heart disease, occurring more frequently among women in the perimenopausal and postmenopausal stages [1]. The epicardial coronary arteries do not show any significant stenosis on coronary angiography that could explain the reported symptoms.

The term 'Cardiac Syndrome X' was introduced by Harvey Kemp in 1973 [2], after he observed patients with suspected coronary artery disease exhibiting normal coronary angiography results [3]. Around 1988 Cannon and Epstein proposed the term microvascular angina (MVA) [4]. This term was used In ESC (European Society of Cardiology) 2013 guidelines where it was described as microcirculation vascular dysfunction. However, subsequent studies [5] revealed that not all patients diagnosed with cardiac syndrome X (CSX) experienced disturbances in coronary microcirculation. It is important to emphasize that the

chest pain associated with CSX has various pathophysiological causes, likely ranging from non-cardiac origins to coronary microvascular dysfunction (CMD) [6].

The diagnosis of the condition is made by exclusion, though some suggest specific criteria, such as stress-induced chest pain, the absence of spontaneous or induced spasms of the epicardial coronary arteries (using ergonovine or acetylcholine), ST-segment lowering during episodes of pain, normal epicardial coronary arteries on angiograph, and the lack of cardiac or systemic diseases associated with microvascular dysfunction, such as hypertrophic cardiomyopathy and diabetes [1] [8]. At the annual Coronary Vasomotion Disorders International Study Group (COVADIS) Summits in August 2014 and 2015, the following criteria were established for diagnosing microvascular angina: (1) symptoms indicating possible myocardial ischemia; (2) objective evidence of myocardial ischemia, identified using current diagnostic methods;(3) no presence of obstructive coronary artery disease (CAD), defined as <50% narrowing of coronary diameter and/or a fractional flow reserve (FFR) >0.80; (4) confirmation of reduced coronary blood flow reserve and/or inducible microvascular spasm [8].

Diagnostic Criteria for Cardiac Syndrome X (CSX)

Diagnostic Criteria	Details	Source/Methodology
Myocardial Ischemia Symptoms	Stress-induced chest pain	Patient history
Coronary Artery Status	No obstructive coronary artery disease (CAD)	Coronary angiography, FFR > 0.80
Evidence of Reduced Blood Flow	Reduced coronary flow reserve (CFR < 2.5)	Stress test, myocardial perfusion imaging
Exclusion of Other Diseases	Rule out diabetes, cardiomyopathy, etc.	Comprehensive clinical evaluation

In coronary artery disease, the Seattle Angina Questionnaire (SAQ) has become the most widely used tool for assessing disease-specific health status, helping to quantify patients with angina symptoms and the extent to which angina affects their functional abilities and quality of life [9].

The Seattle Angina Questionnaire-7

1. The following is a list of activities that people often do during the week. Although for some people with several medical problems it is difficult to determine what it is that limits them, please go over the activities listed below and indicate how much limitation you have had **due to chest pain, chest tightness or angina** **over the past 4 weeks**.

Place an X in one box on each line.

Activity	Extremely limited	Quite a bit limited	Moderately Limited	Slightly limited	Not at all limited	Limited for other reasons or did not do the activity
a. Walking indoors on level ground	☐	☐	☐	☐	☐	☐
b. Gardening, vacuuming or carrying groceries	☐	☐	☐	☐	☐	☐
c. Lifting or moving heavy objects (e.g. furniture, children)	☐	☐	☐	☐	☐	☐

2. Over the past 4 weeks, on average, how many times have you had **chest pain, chest tightness or angina**?

I have had **chest pain, chest tightness or angina…**

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

3. Over the past 4 weeks, on average, how many times have you had to take nitroglycerin (nitroglycerin tablets or spray) for your **chest pain, chest tightness or angina**?

I have taken nitroglycerin…

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

4. Over the past 4 weeks, how much has your **chest pain, chest tightness or angina** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not** limited my enjoyment of life at all
☐	☐	☐	☐	☐

5. If you had to spend the rest of your life with your **chest pain, chest tightness or angina** the way it is right now, how would you feel about this?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

Chan et al. [10]

Studies show that anxiety disorders were found in 64% of patients with CSX. Of these, 29% met the criteria for anxiety disorders with panic attacks, 21% had phobia-related anxiety disorders, and 14% were diagnosed with generalized anxiety disorder [11].

Treatment options:

Older studies indicate that atenolol (100 mg/day) markedly reduces the frequency of anginal episodes [12] and has been found to greatly decrease symptoms, exercise tolerance, and diastolic function in CSX patients when compared to placebo [13]. Atenolol, a cardioselective β-1 adrenergic blocker, specifically targets β-1 adrenergic receptors in the heart and vascular smooth muscle. By binding selectively to these receptors, it prevents the positive inotropic and chronotropic effects triggered by endogenous catecholamines like isoproterenol, norepinephrine, and epinephrine. This inhibition of sympathetic stimulation leads to a

reduction in heart rate, blood pressure, and myocardial contractility [14]. Similarly, propranolol has been shown to substantially decrease the average number of ischemic episodes over a 24-hour period in comparison to placebo [15]. Propranolol is a nonselective beta-adrenergic receptor blocker and is also categorized as a class II antiarrhythmic agent. Its mechanism of action involves competitively inhibiting both beta-1 and beta-2 adrenergic receptors in the heart. Beta-2 receptor activation typically raises cyclic AMP levels, which then activates protein kinase A, promoting smooth muscle relaxation in various tissues and blood vessels. However, when beta-2 receptors are inhibited, this causes a mild degree of vasoconstriction [16]. Beta-blockers such as propranolol, nebivolol, and carvedilol have been documented to exhibit a 75% efficacy in patients with cardiac syndrome X (CSX), demonstrating improvements in both exercise tolerance and symptomatic relief. The newer third-generation beta-blockers, particularly nebivolol and carvedilol, not only achieve their therapeutic effects through traditional mechanisms but also enhance endothelial vasodilatory activity, suggesting that they may possess superior efficacy compared to conventional beta-blockers [17]. The newer study revealed that following a single dose of carvedilol, 10 out of 15 CSX patients experienced no anginal pain during peak exercise, while 5 out of 15 patients showed ST shifts of less than 1 mm. These results were statistically significant compared to placebo ($p<0.01$) [18]. Carvedilol is a nonselective adrenergic antagonist, classified as a non-selective beta-blocker that also possesses alpha-1 adrenergic receptor antagonist properties. This medication functions as a nonselective cardiac beta blocker with peripheral vasodilatory effects, enhancing blood circulation throughout the body. Thanks to its unique mechanism of action, carvedilol helps sustain cardiac output by reducing afterload through cardiac beta blockade. Additionally, it has a milder impact on heart rate compared to purely selective beta-blockers [19]. In general, beta-blockers could be considered the primary treatment option for patients with CSX [20].

Calcium channel antagonists, such as Amlodipine (10 mg/day), have been supported by studies as an effective treatment class for CSX [12]. Amlodipine blocks voltage-dependent L-type calcium channels, thereby inhibiting the initial influx of calcium ions. The resultant decrease in intracellular calcium levels leads to diminished contractility of vascular smooth muscle, enhanced relaxation of smooth muscle, and consequent vasodilation. Furthermore, amlodipine is linked to improved vascular endothelial function in individuals with hypertension. By promoting smooth muscle relaxation and vasodilation, amlodipine

effectively lowers blood pressure [21]. Verapamil and nifedipine have demonstrated efficacy in reducing the frequency of anginal episodes and extending exercise duration when compared to placebo. Conversely, the administration of intravenous diltiazem did not enhance coronary flow reserve in patients experiencing angina, despite having normal coronary arteries and diminished coronary flow reserve [22] [23].

The next drug evaluated in studies was isosorbide-5-mononitrate (ISMN) in a retard formulation, 50 mg/ day [12]. Isosorbide is a nitrate that exerts its pharmacological effects by releasing nitric oxide (NO), a factor derived from the endothelium that promotes relaxation. NO is naturally produced in the endothelium to facilitate the dilation of blood vessels. Isosorbide undergoes bioactivation in the endoplasmic reticulum via cytochrome P450 enzymes, leading to the release of NO, which subsequently activates soluble guanylyl cyclase in vascular smooth muscle. This activation elevates intracellular levels of cGMP and related protein kinases, including cGMP-dependent protein kinases (cGK-I). The increase in cGMP activates myosin light chain phosphatase (MLCP), resulting in the dephosphorylation of the myosin light chain. Additionally, cGMP-cGK-I inhibits the release of calcium from inositol-1,4,5-trisphosphate (IP3)-dependent pathways, thereby reducing intracellular calcium levels. [24] [25]. Furthermore in an observational study involving 99 patients with CSX, chest pain episodes were alleviated in 42% of the participants through the use of either sublingual nitrates or a combination of oral nitrates and calcium antagonists [18]. It should be noted that while nitrates have a short-term effect and significantly enhance stress test outcomes in individuals with coronary artery disease (CAD), they do not produce comparable results in patients with microvascular angina (MVA). Due to their limited vasodilatory effect on the smaller coronary vessels, these treatments demonstrated only modest efficacy. [26] Despite that nitrates have long been considered the cornerstone of therapy for CSX, serving as the principal treatment strategy throughout medical history [27].

Another treatment option is Ranolazine. Ranolazine acts by inhibiting the late inward sodium channel, which can interrupt this cycle by decreasing intracellular calcium buildup and the associated rise in ventricular wall tension. This leads to several beneficial outcomes: the decrease in wall tension during diastole is anticipated to reduce the consumption of oxygen and ATP required for contractile work, which in turn lowers oxygen demand. Additionally, reduced wall tension can help relieve vascular compression. Since vascular compression leads to the closure of small blood vessels and a decrease in blood flow, reducing this compression

may enhance myocardial nutritive blood flow and increase oxygen delivery to the myocardium during diastole [28]. In symptomatic patients with a coronary flow reserve (CFR) below 2.5 but no obstructive coronary artery disease (CAD), treatment with ranolazine led to enhanced myocardial perfusion [29]. This drug ability to modulate neuronal voltage-gated sodium channels contributes to the management of potential neuropathic pain in patients with cardiac syndrome X (CSX). According to the Seattle Angina Questionnaire, ranolazine is recognized as a valuable treatment for women experiencing anginal symptoms without any indications of coronary artery obstruction [30].

Research in the literature supports the use of ivabradine, which blocks the IF current (also known as the pacemaker or funny current) in the sinus node, thereby selectively lowering the heart rate. This mechanism results in decreased cardiac oxygen demand and enhances coronary blood flow by extending diastolic duration [31]. Although the positive effects in patients with stable obstructive coronary artery disease (CAD) have been documented, no prior studies have evaluated the impact of ivabradine in individuals with microvascular angina (MVA). Comparative analysis between the ivabradine and ranolazine groups indicated that ranolazine produced superior outcomes [32].

The next group of medications are statins, they amplify the vasodilatory effects of the endothelium and could prove beneficial for patients with cardiac syndrome X. Statins are selective, competitive blockers of hydroxymethylglutaryl-CoA (HMG-CoA) reductase, the enzyme that converts HMG-CoA into mevalonate in the cholesterol synthesis pathway. By lowering cholesterol production in the liver, statins boost the expression of LDL receptors, which in turn promotes the uptake of LDL cholesterol from the bloodstream into the liver. This therapy reduces the liver's production of apo B100-containing lipoproteins, resulting in decreased levels of both cholesterol and triglycerides. Additionally, HMG-CoA reductase inhibitors exhibit a variety of pleiotropic effects, such as anti-inflammatory, antioxidant, antiproliferative, and immunomodulatory actions. They also contribute to the stability of plaques and help inhibit platelet aggregation [33]. Statin treatment improved exercise-induced ischemia and flow-mediated dilation (FMD), likely due to enhanced endothelial function. [34]. A meta-analysis study demonstrated that statin treatment led to a significant enhancement in endothelial function, with a standardized mean difference (SMD) of 0.66, 95% CI 0.46-0.85, $p < 0.001$ [35]. There also was a significant increase in brachial artery flow-mediated dilation, with a relative rise of 52% ($p < 0.0001$). Additionally, the duration until greater than 1-mm

ST-segment depression occurred during stress testing was extended by the conclusion of the study ($p < 0.0001$) [36]. Combination therapy using fluvastatin and diltiazem is more effective for improving endothelial function and exercise tolerance compared to treatment with either drug alone in patients with cardiac syndrome X [36]. The advantages of this dual approach may be attributed to increased levels of nitric oxide and decreased levels of endothelin-1 [37].

ACE inhibitors have also demonstrated considerable advantages. They work by inhibiting the breakdown of bradykinin in the endothelium, resulting in enhanced vasodilatory effects [38]. ACE inhibitors are competitive antagonists of angiotensin converting enzyme, blocking the transformation of angiotensin I into angiotensin II. Angiotensin II is a powerful vasoconstrictor, therefore, its inhibition can lead to a reduction in blood pressure by promoting vasodilation and decreasing aldosterone secretion [39]. Consequently, they are believed to be advantageous for managing CSX patients. ACE inhibitors have demonstrated improvements in exercise tolerance, endothelial function, coronary flow rates, and reductions in angina among these individuals. Research indicates that both cilazapril and enalapril enhance overall exercise duration, extend the time until 1 mm of ST segment depression occurs, and reduce the severity of ST segment depression when compared to placebo [18] [40]. Quinapril (80 mg/Day) was found to decrease the frequency of anginal episodes and enhance coronary flow rate. Patients who exhibited the lowest baseline coronary flow rate experienced the greatest benefits from quinapril [41].

Another drug that underwent testing was Nicorandil, which has the ability to generate nitric oxide (NO) with the help of enzymes, leading to the relaxation of vascular smooth muscle. It effectively dilates coronary arteries and capillaries, and it stimulates ATP-sensitive potassium channels by activating guanylate cyclase. This action reduces calcium influx, increases potassium outflow, lowers intracellular calcium levels, and promotes cell hyperpolarization, improving vascular endothelial function. Nicorandil significantly dilates microvessels with diameters of 100-200 μm, enhancing blood flow and thus helping to treat microvascular angina [42]. Nicorandil also lowers peripheral resistance, decreases both the pre-load and post-load on the heart, and reduces myocardial oxygen demand. Additionally, it enhances collateral circulation and improves blood supply to the subendocardial region [43]. During research nicorandil significantly lowered the index of microvascular resistance (IMR) compared to the control medications (WMD: -7.63; 95% CI: -11.82 to -3.44; P = 0.0004) [44].

Research also suggests the use of Trimetazidine, an anti-ischemic medication commonly employed to manage coronary artery disease. It functions by inhibiting the mitochondrial enzyme long-chain 3-ketoacyl coenzyme A thiolase, which enhances mitochondrial metabolism by decreasing myocardial fatty acid uptake and oxidation, while simultaneously promoting glucose oxidation. Unlike traditional medications, trimetazidine does not affect coronary blood flow, contractility, blood pressure, or heart rate. It also lacks significant inotropic or vasodilatory effects, both at rest and during physical activity [45] [46]. In a study evaluating the effects of trimetazidine on clinical symptoms and exercise tolerance in 34 patients with cardiac syndrome X, an exercise test was performed before treatment and after 1 and 6 months of therapy (20 mg three times daily). While the drug had no significant impact on heart rate or blood pressure, exercise duration was significantly extended after 1 month (652.9 +/- 206.2 vs. 563.4 +/- 190.4 s, P = 0.0047) and 6 months (650.3 +/- 207.8 s, P = 0.0094). Trimetazidine also reduced anginal symptoms during exercise [47].

Considering the role of altered pain perception in patients with Cardiac Syndrome X (CSX), analgesic pharmacotherapy may provide significant benefits. Medications like xanthine derivatives, which block adenosine receptors, and aminophylline could be beneficial options [54]. Aminophylline's precise mechanism remains partially unclear, but it functions by releasing theophylline, which is responsible for its bronchodilatory effects. Theophylline works by non-selectively inhibiting type III and IV phosphodiesterase enzymes, increasing levels of cAMP and cGMP. This leads to the relaxation of smooth muscle in the lungs and pulmonary vessels, diuresis, and stimulation of the central nervous and cardiovascular systems. However, the bronchodilatory effects are not fully achieved at typical therapeutic doses, and inhibiting type IV enzymes reduces the release of inflammatory mediators, but only at higher concentrations. Theophylline also blocks adenosine receptors (A1, A2, and to a lesser extent, A3), preventing bronchoconstriction by suppressing the release of histamine and leukotrienes. Additionally, it improves diaphragm function by promoting calcium uptake, which enhances muscle contraction. [48] In a double-blind crossover trial and a single-blind, placebo-controlled study, patients with cardiac syndrome X (CSX) who received oral aminophylline for three weeks reported a significant reduction in the frequency of chest pain episodes while on the medication compared to their experience with the placebo. Additionally, after three weeks of aminophylline treatment, patients experienced an increased threshold for exercise-induced chest pain. However, there were no significant changes in the frequency of

ST depression measured by Holter monitoring or in peak exercise ST depression with the medication [49] [50].

It remains uncertain whether the positive effects of SSRIs lead to a reduction in atherogenesis or fewer cardiovascular events in patients with coronary heart disease (CHD) who also experience depression [51]. While studies show that SSRIs can improve endothelial function, reduce inflammatory markers, and potentially influence other mechanisms connecting depression with CHD, recent evidence suggests that SSRIs do not significantly alter the long-term prognosis for patients with both CHD and depression [52].

Some reports emphasizes the efficacy of vitamin D in the treatment of the Microvascular Angina. This study indicates that administering high doses of vitamin D (300,000 IU via intramuscular injection every two weeks for a duration of two months) to patients with cardiac syndrome X and concurrent vitamin D deficiency significantly alleviates ischemic symptoms through direct effects on the cardiovascular system [53].

Imipramine has been shown to reduce the frequency of chest pain by approximately 50%. The analgesic effects of tricyclic antidepressants (TCAs) are linked to their ability to inhibit the reuptake of serotonin and noradrenaline, making them potentially beneficial for patients with Cardiac Syndrome X (CSX). The American College of Cardiology recommends imipramine for CSX patients who do not respond to beta-blockers, calcium channel blockers, or nitrates. However, the use of imipramine in managing CSX has been controversial due to concerns about its side effects [54]. Imipramine's anticholinergic effects can lead to unwanted side effects, including blurred vision, constipation, rapid heartbeat, confusion, dry mouth, difficulty urinating, delirium, and an increased risk of narrow-angle glaucoma [55].

With the addition of cilostazol to standard medications, angina intensity scores showed a relative reduction of 78.9%, and the frequency of angina decreased by 73.5% ($P < 0.001$). [56] Cilostazol is a phosphodiesterase III (PDE3) inhibitor that works by blocking the activity of PDE3 enzymes, which are primarily located in cardiac and vascular smooth muscle tissues. These enzymes typically break down cyclic nucleotides cAMP and cGMP, which regulate muscle contractility in the heart and blood vessels. By inhibiting PDE3, cilostazol prevents the degradation of cAMP, leading to higher cAMP levels in platelets and blood vessels. This increase in cAMP activates protein kinase A (PKA), which plays a key role in inhibiting platelet aggregation. Additionally, elevated PKA levels in smooth muscle cells promote

vasodilation by inactivating myosin light-chain kinase, reducing muscle contraction and improving blood flow [57].

Sildenafil, a PDE5 inhibitor, has been shown to produce immediate increases in coronary flow reserve (CFR), particularly in women diagnosed with microvascular angina (MVA) who have a CFR of less than 2.5. This effect suggests sildenafil may improve coronary microvascular function and enhance blood flow [58]. Sildenafil's molecular structure closely resembles that of cyclic guanosine monophosphate (cGMP), allowing it to act as a competitive inhibitor of PDE5, the enzyme responsible for breaking down vasodilatory cGMP. By binding to the catalytic site of PDE5, sildenafil prevents cGMP degradation, leading to its accumulation. This rise in cGMP activates cGMP-dependent protein kinase, which phosphorylates various targets within the smooth muscle cell. These actions reduce intracellular calcium, increase potassium efflux, and inactivate myosin light-chain kinase, collectively promoting smooth muscle relaxation and enhancing blood flow [59].

Research indicates that Fasudil effectively prevents acetylcholine (ACh)-induced coronary artery spasms and subsequent myocardial ischemia in patients with vasospastic angina. This suggests that Fasudil, as a Rho-kinase inhibitor, could serve as a promising therapeutic option for managing ischemic coronary syndromes triggered by coronary artery spasms [60]. Inhibiting Rho-kinase affects the small GTP-binding protein Rho, which promotes myosin light chain phosphorylation by suppressing the myosin phosphatase myosin-binding subunit. This process results in excessive contraction of vascular smooth muscle [61].

Non-pharmacological options consist of Cognitive Behavioral Therapy (CBT), the efficacy of which was demonstrated after eight weeks of treatment in a cohort of women experiencing retrosternal pain with normal coronary angiography results [62]. As a result, anxiety levels decreased, depressive symptoms were alleviated, and exercise tolerance improved [63]. Cognitive Behavioral Therapy (CBT) should be included in managing cardiac syndrome X (CSX), particularly for patients who continue to experience pain even after trying medication-based treatments.

Enhanced External Counterpulsation (EECP) is a non-invasive treatment option for patients with refractory angina pectoris. Its mechanism of action resembles that of an intra-aortic balloon pump (IABP), delivering a strong pressure pulse through external blood pressure

cuffs during the diastolic phase [64]. Enhanced External Counterpulsation (EECP) was administered to 30 patients suffering from refractory angina caused by cardiac syndrome X, resulting in an initial improvement in CCS angina class (from 3.57 to 1.43; $p<0.001$) and a reduction in regional ischemia across all treated patients. After an average follow-up of 11.9 months, 87% of patients maintained reduced angina [65].

Neural pathways have been suggested for certain patients. Neural electrical stimulation focuses on reducing the heightened pain sensitivity seen in CSX, particularly in individuals who do not respond to medication. Techniques such as spinal cord stimulation and transcutaneous electrical nerve stimulation (TENS) are used [66]. These therapies are believed to enhance parasympathetic activity, which helps to improve endothelial dysfunction and decrease pain sensitivity. Additionally, spinal cord stimulation has been reported to increase coronary blood flow [67]. In the study, patients experienced a mean pain reduction of 57%, along with a 30% increase in exercise capacity, and walking distance improved from 0.73 (0.83) to 1.62 (1.62) ($p=0.018$). According to the Seattle Angina Questionnaire, the 'disease perception' domain rose from 38.89 (16.61) to 49.31 (21.83) ($p=0.004$), the 'physical limitation' domain increased from 29.89 (15.10) to 40.97 (22.63) ($p=0.001$), and 'anginal frequency' improved from 41.67 (24.08) to 55.00 (23.03) ($p=0.005$). Additionally, nitroglycerin use decreased significantly from 7.85 (8.49) to 1.98 (2.19) ($p=0.001$) [68]. These findings indicate that spinal cord stimulation (SCS) can significantly decrease anginal symptoms and enhance exercise tolerance in many patients with refractory angina and normal coronary arteries, suggesting it should be regarded as a valuable treatment option for this patient population [69].

Lifestyle changes, such as regular exercise, smoking cessation, and adopting a Mediterranean diet, along with Cognitive Behavioral herapy (CBT), address aspects of CSX that pharmacological treatments alone may not fully manage [70]. These modifications have been shown to improve endothelial function, which is key in lowering the risk of adverse cardiovascular events and managing Cardiac Syndrome X (CSX) [71] [72] [73].

Conclusion:

Once considered benign, Cardiac Syndrome X (CSX) is now recognized as a condition marked by significant morbidity, including angina-like chest pain, normal coronary arteries,

and ST segment depression on ECG. However, recent research has revealed that it is associated with considerable morbidity and an elevated risk of cardiovascular events. The diagnosis of CSX is both complex and costly, as it requires ruling out other potential causes of symptoms, often involving extensive testing to confirm the absence of coronary artery blockages [74].

One of the key challenges in managing CSX lies in the incomplete understanding of its underlying pathogenesis. The exact mechanisms that lead to this syndrome remain unclear, making treatment more difficult. This uncertainty contributes to variability in how the condition is addressed, with no clear guidelines on the optimal treatment strategy. A range of pharmacological and non-pharmacological therapies, including medications, lifestyle changes, and even advanced procedures like spinal cord stimulation, have demonstrated some level of effectiveness in alleviating symptoms. However, these treatments are often tailored to individual patients based on trial and error, as a standardized approach for managing CSX has yet to be established. This lack of consensus adds to the challenge, leaving both patients and clinicians with limited guidance on how to best manage the condition over the long term [1].

Disclosure

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References:

[1] Agrawal S, Mehta PK, Bairey Merz CN. Cardiac Syndrome X: update 2014. Cardiol Clin. 2014 Aug;32(3):463-78. doi: 10.1016/j.ccl.2014.04.006. Epub 2014 Jun 2. PMID: 25091971; PMCID: PMC4122947.

[2] Kemp HG Jr. Left ventricular function in patients with the anginal syndrome and normal coronary arteriograms. Am J Cardiol. 1973 Sep 7;32(3):375-6. doi: 10.1016/s0002-9149(73)80150-x. PMID: 4725594.

[3]Kemp HG, Kronmal RA, Vlietstra RE, Frye RL. Seven year survival of patients with normal or near normal coronary arteriograms: a CASS registry study. J Am Coll Cardiol. 1986 Mar;7(3):479-83. doi: 10.1016/s0735-1097(86)80456-9. PMID: 3512658.

[4] Cannon RO 3rd, Epstein SE. "Microvascular angina" as a cause of chest pain with angiographically normal coronary arteries. Am J Cardiol. 1988 Jun 1;61(15):1338-43. doi: 10.1016/0002-9149(88)91180-0. PMID: 3287885.

[5] Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabaté M, Senior R, Taggart DP, van der Wall EE, Vrints CJ; ESC Committee for Practice Guidelines; Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S; Document Reviewers; Knuuti J, Valgimigli M, Bueno H, Claeys MJ, Donner-Banzhoff N, Erol C, Frank H, Funck-Brentano C, Gaemperli O, Gonzalez-Juanatey JR, Hamilos M, Hasdai D, Husted S, James SK, Kervinen K, Kolh P, Kristensen SD, Lancellotti P, Maggioni AP, Piepoli MF, Pries AR, Romeo F, Rydén L, Simoons ML, Sirnes PA, Steg PG, Timmis A, Wijns W, Windecker S, Yildirir A, Zamorano JL. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013 Oct;34(38):2949-3003. doi: 10.1093/eurheartj/eht296. Epub 2013 Aug 30. Erratum in: Eur Heart J. 2014 Sep 1;35(33):2260-1. PMID: 23996286.

[6]Karamitsos TD, Arnold JR, Pegg TJ, Francis JM, Birks J, Jerosch-Herold M, Neubauer S, Selvanayagam JB. Patients with syndrome X have normal transmural myocardial perfusion

and oxygenation: a 3-T cardiovascular magnetic resonance imaging study. Circ Cardiovasc Imaging. 2012 Mar;5(2):194-200. doi: 10.1161/CIRCIMAGING.111.969667. Epub 2012 Feb 8. Erratum in: Circ Cardiovasc Imaging. 2012 Jul;5(4):e56. PMID: 22322441.

[7]Melikian N, De Bruyne B, Fearon WF, MacCarthy PA. The pathophysiology and clinical course of the normal coronary angina syndrome (cardiac syndrome X). Prog Cardiovasc Dis. 2008 Jan-Feb;50(4):294-310. doi: 10.1016/j.pcad.2007.01.003. PMID: 18156008.

[8]Ong P, Camici PG, Beltrame JF, Crea F, Shimokawa H, Sechtem U, Kaski JC, Bairey Merz CN; Coronary Vasomotion Disorders International Study Group (COVADIS). International standardization of diagnostic criteria for microvascular angina. Int J Cardiol. 2018 Jan 1;250:16-20. doi: 10.1016/j.ijcard.2017.08.068. Epub 2017 Sep 8. PMID: 29031990.

[9]Thomas M, Jones PG, Arnold SV, Spertus JA. Interpretation of the Seattle Angina Questionnaire as an Outcome Measure in Clinical Trials and Clinical Care: A Review. JAMA Cardiol. 2021 May 1;6(5):593-599. doi: 10.1001/jamacardio.2020.7478. PMID: 33566062; PMCID: PMC8651216.

[10]Chan PS, Jones PG, Arnold SA, Spertus JA. Development and validation of a short version of the Seattle angina questionnaire. Circ Cardiovasc Qual Outcomes. 2014 Sep;7(5):640-7. doi: 10.1161/CIRCOUTCOMES.114.000967. Epub 2014 Sep 2. PMID: 25185249; PMCID: PMC4282595.

[11]Piegza M, Wierzba D, Piegza J. Cardiac syndrome X - the present knowledge. Psychiatr Pol. 2021 Apr 30;55(2):363-375. English, Polish. doi: 10.12740/PP/OnlineFirst/113196. Epub 2021 Apr 30. PMID: 34365485.

[12] Lanza GA, Colonna G, Pasceri V, Maseri A. Atenolol versus amlodipine versus isosorbide-5-mononitrate on anginal symptoms in syndrome X. Am J Cardiol. 1999 Oct 1;84(7):854-6, A8. doi: 10.1016/s0002-9149(99)00450-6. PMID: 10513787.

[13] Bugiardini R, Borghi A, Biagetti L, Puddu P. Comparison of verapamil versus propranolol therapy in syndrome X. Am J Cardiol. 1989 Feb 1;63(5):286-90. doi: 10.1016/0002-9149(89)90332-9. PMID: 2643845.

[14]Helfand M, Peterson K, Christensen V, Dana T, Thakurta S. Drug Class Review: Beta Adrenergic Blockers: Final Report Update 4 [Internet]. Portland (OR): Oregon Health & Science University; 2009 Jul. PMID: 21089245.

[15] Leonardo F, Fragasso G, Rossetti E, Dabrowski P, Pagnotta P, Rosano GM, Chierchia SL. Comparison of trimetazidine with atenolol in patients with syndrome X: effects on

diastolic function and exercise tolerance. Cardiologia. 1999 Dec;44(12):1065-9. PMID: 10687257.

[16]Shahrokhi M, Gupta V. Propranolol. 2023 May 1. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 32491733.

[17]Helfand M, Peterson K, Christensen V, Dana T, Thakurta S. Drug Class Review: Beta Adrenergic Blockers: Final Report Update 4 [Internet]. Portland (OR): Oregon Health & Science University; 2009 Jul. PMID: 21089245.

[18] Kaski JC, Rosano GM, Collins P, Nihoyannopoulos P, Maseri A, Poole-Wilson PA. Cardiac syndrome X: clinical characteristics and left ventricular function. Long-term follow-up study. J Am Coll Cardiol. 1995 Mar 15;25(4):807-14. doi: 10.1016/0735-1097(94)00507-M. PMID: 7884081.

[19] Singh S, Preuss CV. Carvedilol. 2024 Jan 10. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 30521289.

[20] Ferrari R, Pavasini R, Camici PG, Crea F, Danchin N, Pinto F, Manolis A, Marzilli M, Rosano GMC, Lopez-Sendon J, Fox K. Anti-anginal drugs-beliefs and evidence: systematic review covering 50 years of medical treatment. Eur Heart J. 2019 Jan 7;40(2):190-194. doi: 10.1093/eurheartj/ehy504. Erratum in: Eur Heart J. 2020 Dec 21;41(48):4588. doi: 10.1093/eurheartj/ehaa561. PMID: 30165445.

[21]Bulsara KG, Patel P, Cassagnol M. Amlodipine. 2024 Apr 21. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 30137793.

[22] Cannon RO 3rd, Watson RM, Rosing DR, Epstein SE. Efficacy of calcium channel blocker therapy for angina pectoris resulting from small-vessel coronary artery disease and abnormal vasodilator reserve. Am J Cardiol. 1985 Aug 1;56(4):242-6. doi: 10.1016/0002-9149(85)90842-2. PMID: 4025160.

[23] Sütsch G, Oechslin E, Mayer I, Hess OM. Effect of diltiazem on coronary flow reserve in patients with microvascular angina. Int J Cardiol. 1995 Nov 24;52(2):135-43. doi: 10.1016/0167-5273(95)02458-9. PMID: 8749873.

[24] Balasubramanian S, Chowdhury YS. Isosorbide. 2023 May 16. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 32491771.

[25] Etter EF, Eto M, Wardle RL, Brautigan DL, Murphy RA. Activation of myosin light chain phosphatase in intact arterial smooth muscle during nitric oxide-induced relaxation. J Biol Chem. 2001 Sep 14;276(37):34681-5. doi: 10.1074/jbc.M104737200. Epub 2001 Jul 18. PMID: 11461918.

[26] Russo G, Di Franco A, Lamendola P, Tarzia P, Nerla R, Stazi A, Villano A, Sestito A, Lanza GA, Crea F. Lack of effect of nitrates on exercise stress test results in patients with microvascular angina. Cardiovasc Drugs Ther. 2013 Jun;27(3):229-34. doi: 10.1007/s10557-013-6439-z. PMID: 23338814.

[27] Larsen W, Mandleco B. Chest pain with angiographic clear coronary arteries: A provider's approach to cardiac syndrome X. J Am Acad Nurse Pract. 2009 Jul;21(7):371-6. doi: 10.1111/j.1745-7599.2009.00425.x. PMID: 19594655.

[28] Luiz Belardinelli, John C. Shryock, Heather Fraser, The mechanism of ranolazine action to reduce ischemia-induced diastolic dysfunction, European Heart Journal Supplements, Volume 8, Issue suppl_A, February 2006, Pages A10–A13, https://doi.org/10.1093/eurheartj/sui091.

[29] Rambarat CA, Elgendy IY, Handberg EM, Bairey Merz CN, Wei J, Minissian MB, Nelson MD, Thomson LEJ, Berman DS, Shaw LJ, Cook-Wiens G, Pepine CJ. Late sodium channel blockade improves angina and myocardial perfusion in patients with severe coronary microvascular dysfunction: Women's Ischemia Syndrome Evaluation-Coronary Vascular Dysfunction ancillary study. Int J Cardiol. 2019 Feb 1;276:8-13. doi: 10.1016/j.ijcard.2018.09.081. Epub 2018 Sep 26. PMID: 30293664; PMCID: PMC6324974.

[30] Mehta PK, Goykhman P, Thomson LE, Shufelt C, Wei J, Yang Y, Gill E, Minissian M, Shaw LJ, Slomka PJ, Slivka M, Berman DS, Bairey Merz CN. Ranolazine improves angina in women with evidence of myocardial ischemia but no obstructive coronary artery disease. JACC Cardiovasc Imaging. 2011 May;4(5):514-22. doi: 10.1016/j.jcmg.2011.03.007. PMID: 21565740; PMCID: PMC6364688.

[31] Reed M, Kerndt CC, Gopal S, Pellegrini MV, Nicolas D. Ranolazine. 2024 Feb 28. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 29939605.

[32] Villano A, Di Franco A, Nerla R, Sestito A, Tarzia P, Lamendola P, Di Monaco A, Sarullo FM, Lanza GA, Crea F. Effects of ivabradine and ranolazine in patients with microvascular angina pectoris. Am J Cardiol. 2013 Jul 1;112(1):8-13. doi: 10.1016/j.amjcard.2013.02.045. Epub 2013 Apr 1. PMID: 23558043.

[33] Sizar O, Khare S, Patel P, Talati R. Statin Medications. 2024 Feb 29. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 28613690.

[34] Kayikcioglu M, Payzin S, Yavuzgil O, Kultursay H, Can LH, Soydan I. Benefits of statin treatment in cardiac syndrome-X1. Eur Heart J. 2003 Nov;24(22):1999-2005. doi: 10.1016/s0195-668x(03)00478-0. PMID: 14613735.

[35] Reriani MK, Dunlay SM, Gupta B, West CP, Rihal CS, Lerman LO, Lerman A. Effects of statins on coronary and peripheral endothelial function in humans: a systematic review and meta-analysis of randomized controlled trials. Eur J Cardiovasc Prev Rehabil. 2011 Oct;18(5):704-16. doi: 10.1177/1741826711398430. Epub 2011 Mar 4. PMID: 21450596.

[36] Fábián E, Varga A, Picano E, Vajo Z, Rónaszéki A, Csanády M. Effect of simvastatin on endothelial function in cardiac syndrome X patients. Am J Cardiol. 2004 Sep 1;94(5):652-5. doi: 10.1016/j.amjcard.2004.05.035. PMID: 15342302.

[37] Zhang X, Li Q, Zhao J, Li X, Sun X, Yang H, Wu Z, Yang J. Effects of combination of statin and calcium channel blocker in patients with cardiac syndrome X. Coron Artery Dis. 2014 Jan;25(1):40-4. doi: 10.1097/MCA.0000000000000054. PMID: 24256699.

[38] Löffler AI, Bourque JM. Coronary Microvascular Dysfunction, Microvascular Angina, and Management. Curr Cardiol Rep. 2016 Jan;18(1):1. doi: 10.1007/s11886-015-0682-9. PMID: 26694723; PMCID: PMC4835180.

[39] Goyal A, Cusick AS, Thielemier B. ACE Inhibitors. 2023 Jun 26. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 28613646.

[40] Nalbantgil I, Onder R, Altintig A, Nalbantgil S, Kiliçcioglu B, Boydak B, Yilmaz H. Therapeutic benefits of cilazapril in patients with syndrome X. Cardiology. 1998;89(2):130-3. doi: 10.1159/000006768. PMID: 9524014.

[41] Pauly DF, Johnson BD, Anderson RD, Handberg EM, Smith KM, Cooper-DeHoff RM, Sopko G, Sharaf BM, Kelsey SF, Merz CN, Pepine CJ. In women with symptoms of cardiac ischemia, nonobstructive coronary arteries, and microvascular dysfunction, angiotensin-converting enzyme inhibition is associated with improved microvascular function: A double-blind randomized study from the National Heart, Lung and Blood Institute Women's Ischemia Syndrome Evaluation (WISE). Am Heart J. 2011 Oct;162(4):678-84. doi: 10.1016/j.ahj.2011.07.011. Epub 2011 Sep 6. PMID: 21982660; PMCID: PMC3191889.

[42] Zhang Y, Wang X, Liu R, Li Q, Tian W, Lei H, Shi C. The effectiveness and safety of nicorandil in the treatment of patients with microvascular angina: A protocol for systematic review and meta-analysis. Medicine (Baltimore). 2021 Jan 15;100(2):e23888. doi: 10.1097/MD.0000000000023888. PMID: 33466132; PMCID: PMC7808505.

[43] Huang Q, Wang WT, Wang SS, Pei A, Sui XQ. Cardiovascular magnetic resonance image analysis and mechanism study for the changes after treatments for primary microvascular angina pectoris. Medicine (Baltimore). 2021 May 28;100(21):e26038. doi: 10.1097/MD.0000000000026038. PMID: 34032727; PMCID: PMC8154500.

[44] Zhu H, Xu X, Fang X, Zheng J, Zhao Q, Chen T, Huang J. Effects of the Antianginal Drugs Ranolazine, Nicorandil, and Ivabradine on Coronary Microvascular Function in Patients With Nonobstructive Coronary Artery Disease: A Meta-analysis of Randomized Controlled Trials. Clin Ther. 2019 Oct;41(10):2137-2152.e12. doi: 10.1016/j.clinthera.2019.08.008. Epub 2019 Sep 21. PMID: 31548105.

[45] Dézsi CA. Trimetazidine in Practice: Review of the Clinical and Experimental Evidence. Am J Ther. 2016 May-Jun;23(3):e871-9. doi: 10.1097/MJT.0000000000000180. PMID: 25756467; PMCID: PMC4856171.

[46] Iskesen I, Saribulbul O, Cerrahoglu M, Var A, Nazli Y, Sirin H. Trimetazidine reduces oxidative stress in cardiac surgery. Circ J. 2006 Sep;70(9):1169-73. doi: 10.1253/circj.70.1169. PMID: 16936431.

[47] Rogacka D, Guzik P, Wykretowicz A, Rzeźniczak J, Dziarmaga M, Wysocki H. Effects of trimetazidine on clinical symptoms and tolerance of exercise of patients with syndrome X: a preliminary study. Coron Artery Dis. 2000 Mar;11(2):171-7. doi: 10.1097/00019501-200003000-00012. PMID: 10758819.

[48] Zafar Gondal A, Zulfiqar H. Aminophylline. 2023 Jul 31. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 31424759.

[49] Emdin M, Picano E, Lattanzi F, L'Abbate A. Improved exercise capacity with acute aminophylline administration in patients with syndrome X. J Am Coll Cardiol. 1989 Nov 15;14(6):1450-3. doi: 10.1016/0735-1097(89)90380-x. PMID: 2809002.

[50] Yoshio H, Shimizu M, Kita Y, Ino H, Kaku B, Taki J, Takeda R. Effects of short-term aminophylline administration on cardiac functional reserve in patients with syndrome X. J Am Coll Cardiol. 1995 Jun;25(7):1547-51. doi: 10.1016/0735-1097(95)00097-n. PMID: 7759705.

[51] Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, Czajkowski SM, DeBusk R, Hosking J, Jaffe A, Kaufmann PG, Mitchell P, Norman J, Powell LH, Raczynski JM, Schneiderman N; Enhancing Recovery in Coronary Heart Disease Patients Investigators (ENRICHD). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart

Disease Patients (ENRICHD) Randomized Trial. JAMA. 2003 Jun 18;289(23):3106-16. doi: 10.1001/jama.289.23.3106. PMID: 12813116.

[52] Pizzi C, Mancini S, Angeloni L, Fontana F, Manzoli L, Costa GM. Effects of selective serotonin reuptake inhibitor therapy on endothelial function and inflammatory markers in patients with coronary heart disease. Clin Pharmacol Ther. 2009 Nov;86(5):527-32. doi: 10.1038/clpt.2009.121. Epub 2009 Jul 29. Erratum in: Clin Pharmacol Ther. 2009 Dec;86(6):683. doi: 10.1038/clpt.2009.180. PMID: 19641491

[53] Andishmand A, Ansari Z, Soltani MH, Mirshamsi H, Raafat S. Vitamin D replacement therapy in patients with cardiac syndrome X. Perfusion. 2015 Jan;30(1):60-3. doi: 10.1177/0267659114526629. Epub 2014 Apr 10. PMID: 24722851.

[54] Mahtani AU, Padda IS, Johal GS. Cardiac Syndrome X. 2023 Jun 3. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 35201710.

[55] Fayez R, Gupta V. Imipramine. 2023 May 22. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 32491588.

[56] Yoo SY, Song SG, Lee JH, Shin ES, Kim JS, Park YH, Kim J, Chun KJ, Kim JH. Efficacy of cilostazol on uncontrolled coronary vasospastic angina: a pilot study. Cardiovasc Ther. 2013 Jun;31(3):179-85. doi: 10.1111/j.1755-5922.2012.00312.x. PMID: 22953758; PMCID: PMC3654168.

[57] Balinski AM, Preuss CV. Cilostazol. 2023 Mar 27. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 31335083.

[58] Denardo SJ, Wen X, Handberg EM, Bairey Merz CN, Sopko GS, Cooper-Dehoff RM, Pepine CJ. Effect of phosphodiesterase type 5 inhibition on microvascular coronary dysfunction in women: a Women's Ischemia Syndrome Evaluation (WISE) ancillary study. Clin Cardiol. 2011 Aug;34(8):483-7. doi: 10.1002/clc.20935. Epub 2011 Jul 21. PMID: 21780138; PMCID: PMC3151010.

[59] Smith BP, Babos M. Sildenafil. 2023 Feb 14. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 32644404.

[60] Shimokawa H, Sunamura S, Satoh K. RhoA/Rho-Kinase in the Cardiovascular System. Circ Res. 2016 Jan 22;118(2):352-66. doi: 10.1161/CIRCRESAHA.115.306532. PMID: 26838319.

[61] Masumoto A, Mohri M, Shimokawa H, Urakami L, Usui M, Takeshita A. Suppression of coronary artery spasm by the Rho-kinase inhibitor fasudil in patients with vasospastic angina. Circulation. 2002 Apr 2;105(13):1545-7. doi: 10.1161/hc1002.105938. PMID: 11927519.

[62] Potts SG, Lewin R, Fox KA, Johnstone EC. Group psychological treatment for chest pain with normal coronary arteries. QJM. 1999 Feb;92(2):81-6. doi: 10.1093/qjmed/92.2.81. PMID: 10209659.

[63] Moore RK, Groves DG, Bridson JD, Grayson AD, Wong H, Leach A, Lewin RJ, Chester MR. A brief cognitive-behavioral intervention reduces hospital admissions in refractory angina patients. J Pain Symptom Manage. 2007 Mar;33(3):310-6. doi: 10.1016/j.jpainsymman.2006.10.009. PMID: 17349500.

[64]Jan R, Khan A, Zahid S, Sami A, Owais SM, Khan F, Asjad SJ, Jan MH, Awan ZA. The Effect of Enhanced External Counterpulsation (EECP) on Quality of life in Patient with Coronary Artery Disease not Amenable to PCI or CABG. Cureus. 2020 May 6;12(5):e7987. doi: 10.7759/cureus.7987. PMID: 32523843; PMCID: PMC7273423.

[65] Kronhaus KD, Lawson WE. Enhanced External Counterpulsation is an effective treatment for Syndrome X. Int J Cardiol. 2009 Jun 26;135(2):256-7. doi: 10.1016/j.ijcard.2008.03.022. Epub 2008 Jun 30. PMID: 18590931.

[66] Sun L, Peng C, Joosten E, Cheung CW, Tan F, Jiang W, Shen X. Spinal Cord Stimulation and Treatment of Peripheral or Central Neuropathic Pain: Mechanisms and Clinical Application. Neural Plast. 2021 Oct 21;2021:5607898. doi: 10.1155/2021/5607898. PMID: 34721569; PMCID: PMC8553441.

[67] Sestito A, Lanza GA, Le Pera D, De Armas L, Sgueglia GA, Infusino F, Miliucci R, Tonali PA, Crea F, Valeriani M. Spinal cord stimulation normalizes abnormal cortical pain processing in patients with cardiac syndrome X. Pain. 2008 Sep 30;139(1):82-89. doi: 10.1016/j.pain.2008.03.015. Epub 2008 Apr 28. PMID: 18440702.

[68] de Vries J, Dejongste MJ, Durenkamp A, Zijlstra F, Staal MJ. The sustained benefits of long-term neurostimulation in patients with refractory chest pain and normal coronary arteries. Eur J Pain. 2007 Apr;11(3):360-5. doi: 10.1016/j.ejpain.2006.04.002. Epub 2006 Jun 9. PMID: 16762572. Vitamin D replacement therapy in patients with cardiac syndrome X.

[69] Lanza GA, Sestito A, Sandric S, Cioni B, Tamburrini G, Barollo A, Crea F, De Seta F, Meglio M, Bellocci F, Maseri A. Spinal cord stimulation in patients with refractory anginal pain and normal coronary arteries. Ital Heart J. 2001 Jan;2(1):25-30. PMID: 11214698.

[70] Mangiacapra F, Viscusi MM, Verolino G, Paolucci L, Nusca A, Melfi R, Ussia GP, Grigioni F. Invasive Assessment of Coronary Microvascular Function. J Clin Med. 2021 Dec 31;11(1):228. doi: 10.3390/jcm11010228. PMID: 35011968; PMCID: PMC8745537.

[71] Eriksson BE, Tyni-Lennè R, Svedenhag J, Hallin R, Jensen-Urstad K, Jensen-Urstad M, Bergman K, Selvén C. Physical training in Syndrome X: physical training counteracts deconditioning and pain in Syndrome X. J Am Coll Cardiol. 2000 Nov 1;36(5):1619-25. doi: 10.1016/s0735-1097(00)00931-1. PMID: 11079667.

[72] Tyni-Lenne R, Stryjan S, Eriksson B, Berglund M, Sylven C. Beneficial therapeutic effects of physical training and relaxation therapy in women with coronary syndrome X. Physiother Res Int. 2002;7(1):35-43. doi: 10.1002/pri.239. PMID: 11992983.

[73] Raitakari OT, Adams MR, McCredie RJ, Griffiths KA, Celermajer DS. Arterial endothelial dysfunction related to passive smoking is potentially reversible in healthy young adults. Ann Intern Med. 1999 Apr 6;130(7):578-81. doi: 10.7326/0003-4819-130-7-199904060-00017. PMID: 10189327.

[74]Huang Q, Wang WT, Wang SS, Pei A, Sui XQ. Cardiovascular magnetic resonance image analysis and mechanism study for the changes after treatments for primary microvascular angina pectoris. Medicine (Baltimore). 2021 May 28;100(21):e26038. doi: 10.1097/MD.0000000000026038. PMID: 34032727; PMCID: PMC8154500.