FOLIA MEDICA CRACOVIENSIA
Vol. LXI, 3, 2021: 95–114
PL ISSN 0015-5616
DOI: 10.24425/fmc.2021.138954

Microvascular angina (Cardiac Syndrome X) from a historical overview, epidemiology, pathophysiology to treatment recommendations — a minireview

Jarosław Jarczewski[1], Aleksandra Jarczewska[1], Andrzej Boryczko[1], Adrian Poniatowski[1], Agata Furgała[1], Andrzej Surdacki[2], Krzysztof Gil[1]

[1]Department of Pathophysiology, Faculty of Medicine, Jagiellonian University Medical College, Kraków, Poland
[2]Second Department of Cardiology, Institute of Cardiology, Faculty of Medicine, Jagiellonian University Medical College, Kraków, Poland

Corresponding author: Agata Furgała, M.D., Ph.D.
Department of Pathophysiology, Jagiellonian University Medical College
ul. Czysta 18, 31-121 Kraków, Poland
Phone: +48 12 633 39 47; Fax: +48 12 632 90 56; E-mail: a.furgala@uj.edu.pl

Abstract: Microvascular angina (MVA) is a condition characterized by the presence of angina-like chest pain, a positive response to exercise stress tests, and no significant stenosis of coronary arteries in coronary angiography, with absence of any other specific cardiac diseases. The etiology of this syndrome is still not known and it is probably multifactorial. Coronary microvascular dysfunction is proposed as the main pathophysiological mechanism in the development of MVA. Altered somatic and visceral pain perception and autonomic imbalance, in addition to myocardial ischemia, has been observed in subjects with MVA, involving dynamic variations in the vasomotor tone of coronary microcirculation with consequent transient ischemic episodes. Other theories suggest that MVA may be a result of a chronic inflammatory state in the body that can negatively influence the endothelium or a local imbalance of factors regulating its function. This article presents the latest information about the epidemiology, diagnostics, etiopathogenesis, prognosis, and treatment of patients with MVA.

Key words: microvascular angina, cardiac syndrome X, angina pectoris with normal coronary arteries.

Submitted: 15-Jun-2021; **Accepted in the final form:** 30-Aug-2021; **Published:** 29-Sep-2021.

Introduction

Chest pain is one of the most common symptoms prompting patient referrals. In approximately 50% of these cases, the chest pain is of a cardiac origin [1]. However, sometimes cardiac angina cannot be linked to atherosclerotic coronary artery disease . Approximately 10% to 30% of patients who are referred for coronary angiography turn out to have negative coronary angiogram results [2]. In a significant study in the USA involving over 400 000 patients suspected of obstructive epicardial coronary disease, less than half of patients (37.6%) fulfilled criteria of obstructive coronary disease during invasive diagnostics (≥50% stenosis of the left main coronary artery or other major epicardial vessels). Unexpectedly, 59% of patients that undergo cardiac catheterization had either normal or non-obstructive (<50% stenosis) coronary artery disease (CAD) [3]. These groups of patients are diagnosed with primary microvascular angina (MVA), which generally is caused by specific coronary microvascular dysfunction. Microvascular angina is a condition characterized by the presence of angina-like chest pain, a positive response to exercise stress tests, and no significant stenosis of coronary arteries in coronary angiography with an absence of any other specific cardiac diseases [4]. It has been formerly defined as Cardiac syndrome X. However, from our current assumptions about its pathophysiology, the term microvascular angina seems to be more suitable, as it is believed to arise due to inadequate coronary microvascular vasodilation during times of increased cardiac workload, leading to insufficient oxygen delivery to the cardiomyocytes [3]. The term should not be confused with Metabolic syndrome X, which is a distinct medical condition and includes the concurrent diagnoses of hypertension, dyslipidemia, insulin resistance, and abdominal obesity [5]. On one hand, patients with angina or angina-like chest pain and no obstructive coronary artery disease have a good long-term prognosis, despite persistent pain for many years and decreased quality of life. The coronary morbidity and mortality are comparable to the general population. An increased risk for the incidence of coronary events occurs mainly in patients with additional risk factors [6, 7]. On the other hand, deteriorating and recurrent angina aside from physical distress may also lead to repeated hospital admissions, or even further coronary angiographies, which decrease the quality of life of these patients [8]. Presently, the greatest diagnostic challenge for the cardiologist is to find a reliable way to differentiate patients with microvascular angina from those with obstructive coronary artery disease, based on clinical characteristics and noninvasive evaluations. Dependable tools to correctly identify patients with MVA could reduce the number of unnecessary coronary angiography procedures, which are associated with risks to the patient, as well as lower healthcare costs [9].

Historical overview

F. Mason Sones performed the first cardiac catheterization and selective hand injection of contrast agent into the coronary artery on October 30, 1958, opening the era in cardiovascular medicine. He has made an invaluable contribution to the development of interventional cardiology and coronary artery bypass surgery [10]. Since the discovery of this new diagnostic method, it has been repeatedly observed that some patients with angina-like chest pain and positive stress tests who undergo coronary angiography to exclude coronary stenosis have no coronary obstruction. The term Cardiac syndrome X was first introduced for this clinical entity by Harvey Kemp in 1973, who proposed several hypotheses as to the underlying etiology, such as psychosomatic origin, misinterpretation of the arteriogram, defect of oxyhemoglobin dissociation, disease of myocardial small vessels, and coronary artery spasm [11]. In 1985, Richard O. Cannon and Stephen E. Epstein named the condition microvascular angina. Drawing conclusions from their research on coronary blood flow and myocardial metabolism, they become convinced that myocardial ischemia in this group of patients is caused by the inadequate vasodilator response of coronary microcirculation [12]. Subsequent guidelines of the European Society of Cardiology (ESC) categorize MVA and discuss its clinical presentation, diagnosis, and management. Based on the 2006 ESC guidelines, Cardiac syndrome X is defined as a variant of angina with normal coronary arteries, which in many aspects resembles chronic stable angina. Microvascular angina is classified as a condition in a subgroup of patients with Cardiac syndrome X demonstrating microvascular dysfunction [13]. In the 2013 ESC guidelines term, Cardiac syndrome X was replaced with "angina with normal coronary arteries". Experts point out the distinction between primary and secondary angina, which may occur in the setting of diseases such as hypertrophic cardiomyopathy or aortic stenosis. It was also mentioned that microvascular disease may coexist in patients with significant stenosis in the coronary arteries, and this situation can be suspected due to persistent symptoms or only minor improvement after successful revascularization [14]. The COVADIS group (Coronary Vasomotion Disorders International Study Group) has also proposed diagnostic criteria to define MVA [15]. According to the latest ESC guidelines from 2019, microvascular angina alongside vasospastic angina was included in the definition of "angina without obstructive disease in the epicardial coronary arteries". These guidelines underline the importance of a detailed assessment of the two main mechanisms of microvascular dysfunction: impaired microcirculatory conductance and arteriolar dysregulation. Detection of the affected pathway is essential in determining appropriate medical management [16].

Epidemiology

The incidence of MVA is estimated to be up to 30% in patients with stable angina and non-obstructive coronary arteries [17]. Chest pain coexisting with the absence of obstructive coronary artery disease (defined as ≥50% stenosis in ≥1 major coronary artery) is particularly common in women [18]. Among patients assessed with suspected ischemic symptoms, a diagnosis of normal coronary arteries is five times more common in women than in men [19]. Overall, 10% to 50% of women with acute coronary syndrome have a "normal" coronary angiography [2, 20]. About 19% of women with acute coronary syndrome, 30% of women with unstable angina, 9.1% of women with non-ST-segment elevation myocardial infarction, and 10% of women with ST-segment elevation myocardial infarction have normal coronary vessels or non-obstructive CAD, as confirmed by coronary angiography [21]. It is also important to note that women, particularly in postmenopausal age, are at an increased risk of developing MVA [22]. In addition, some MVA patients may suffer from psychological problems with increased pain perception [23].

Diagnosis criteria for MVA

To begin with, both the COVADIS group criteria [15] and 2019 ECS guidelines [16] suggest that the typical triad for MVA (presence of angina like chest pain, a positive response to exercise stress tests, and no significant stenosis of coronary arteries in angiography [4] is not sufficient to make a complete diagnosis of MVA (Table 1). The most recent guidelines emphasize that it is important to verify the presence of coronary microvascular dysfunction in particular patients with coronary syndromes to substantiate a diagnosis of MVA. Novel trials show the importance of a proper diagnosis in patients with angina-like chest pain and ischemia with no obstructive coronary arteries (INOCA) — such patients may suffer from vasospastic angina (variant angina) or non-cardiac chest pain instead of MVA [24]. In patients with INOCA all these diagnoses lead to different treatment strategies.

The first step to diagnose MVA is to confirm myocardial ischemia. Besides the classic symptoms, anginal chest pain in these patients is slightly different than in patients with CAD. The effect of short-acting nitrates has lesser impact on their symptoms [25], and pain sensation could be atypical — for example it could be elongated chest discomfort rather than pain [26]. Also the pain could appear not only during exercise, but also thereafter [7]. In addition, patients with microvascular dysfunction compared with patients with primary epicardial spasm also differ in pain characteristics, with symptoms occurring more frequently at rest, more often at night and in the early morning [27].

Table 1. Contemporary clinical criteria for diagnosis of MVA (from COVADIS group — Ong *et al.* [15]).

1. Symptoms of myocardial ischemia a. Effort and/or rest angina b. Angina equivalents (i.e. shortness of breath)
2. Absence of obstructive CAD (<50% diameter reduction or FFR >0.80) a. Coronary CTA b. Invasive coronary angiography
3. Objective evidence of myocardial ischemia a. Ischemic ECG changes during an episode of chest pain b. Stress-induced chest pain and/or ischemic ECG changes in the presence or absence of transient/reversible abnormal myocardial perfusion and/or wall motion abnormality
4. Evidence of impaired coronary microvascular function a. Impaired coronary flow reserve (cut-off values depending on methodology use between ≤2.0 and ≤2.5) b. Coronary microvascular spasm, defined as reproduction of symptoms, ischemic ECG shifts but no epicardial spasm during acetylcholine testing c. Abnormal coronary microvascular resistance indices (e.g. IMR >25) d. Coronary slow flow phenomenon, defined as TIMI frame count >25

Legend: CAD — coronary artery disease, CTA — computed tomographic angiography, ECG — electrocardiogram, FFR — fractional flow reserve, IMR — index of microcirculatory resistance, TIMI — thrombolysis in myocardial infarction. Definitive MVA is only diagnosed if all four criteria are present for a diagnosis of microvascular angina.
Suspected MVA is diagnosed if symptoms of ischemia are present (criteria-1) with no obstructive coronary artery disease (criteria-2) but only (a) objective evidence of myocardial ischemia (criteria-3), or (b) evidence of impaired coronary microvascular function (criteria-4) alone.

A diagnosis of MVA cannot be established based only on symptoms, and myocardial ischemia should be objectively excluded. Rest/stress electrocardiography or rest/stress echocardiography are often the first examinations of these patients during which patients with MVA will exhibit ST-segment changes and angina. Other non-invasive tests that could be performed are single photon emission computed tomography (SPECT), positron emission tomography (PET), or cardiac magnetic resonance (CMR). It is necessary to mention that in these patients there is a dissociation between clinical and testing signs of ischemia, probably because of the "patchy" distribution of ischemia resulting in coronary microvascular dysfunction, in contrast with full regional ischemia from CAD [28]. Non-invasive methods such as resting ECG may not demonstrate any ST- segment depression even during episodes of chest pain, exercise ECG may be unremarkable, and a negative treadmill stress test does not disqualify intermittent microvascular dysfunction [29]. Imaging with echocardiography is not sufficiently sensitive as microvascular dysfunction may not produce echocardiographically detectable dysfunction during stress testing even with the occurrence of angina, dyspnea, ECG changes [30]. This is the cause of false negative or

inconclusive test results in some patients. Only 30% of these patients could have transient perfusion defects in echocardiography, and a small percentage of them have wall motion abnormalities [31]. It has also been observed that during non-invasive tests patients with microvascular coronary spasm, besides effort angina, presented more frequently with ischemic ECG changes, exertional dyspnea, and intermittent rest angina [32].

Another required thing to diagnose MVA is ruling out obstructive or flow-limiting CAD as cause of patient's symptoms. Obstructive CAD is defined as stenosis causing >50% coronary artery diameter reduction assessed by conventional or computed tomography angiography (CTA), in which there is abnormal (<80%) fractional flow reserve (FFR). It is important to note that in intermediate stenoses (30–50%) with diffusely diseased epicardial arteries, it is necessary to measure FFR and evaluate if stenoses are hemodynamically relevant [33]. While FFR could be measured during classic coronary angiography, the non-invasive counterpart — CT-FFR — is a promising diagnostic modality, but it still needs more studies to prove itself as a good method in guiding cardiac practice [34].

In past years, these indicators would have been sufficient enough to diagnose MVA. Now it is also necessary to prove reduced coronary flow reserve or microvascular spasm leading to myocardial ischemia. In order to estimate CFR both invasive and non-invasive tests could be performed. In the group of non-invasive tests we can list PET [35, 36], cardiac magnetic resonance (CMR) [35], and even transthoracic Doppler echocardiography [37]. Large numbers of patients with symptomatic angina pectoris had coronary angiography, during which it is possible to evaluate CFR invasively. These methods include measuring coronary blood flow reserve using a combined pressure/thermodilution wire [38]. CFR values below or equal to 2.0 or 2.5, depending on the methodology, suggest coronary microvascular dysfunction. Besides measuring CFR, Doppler-derived hyperemic microvascular resistance and the thermodilution-derived index of microvascular resistance could be used to asses coronary microvascular disease (CMD) [39]. With respect to coronary microvascular spasm, the primary invasive test is intracoronary injection of acetylcholine [32]. During this test, a patient with CMD would experience an outbreak of symptoms or ischemic ECG shifts, but no epicardial spasm (which may suggest variant angina). Alongside the coronary microvascular spasm, it is also important to bear in mind the so-called "coronary slow flow phenomenon", in which increased distal coronary resistance causes the delayed flow of contrast during angiography. This entity could be diagnosed by the semi-quantitative thrombolysis in myocardial infarction (TIMI) frame count method, with >25 frame as confirmation of coronary slow flow [40, 41].

Other than the typical invasive and imaging methods of diagnosing MVA, nowadays we have novel biomarkers to use when coronary microvascular dysfunction is suspected. Odaka *et al.* noted that patients with this condition have significantly

higher plasma concentrations of serotonin. It is released from activated platelets and can cause vasoconstriction. As a result they highlighted that the level of this monoamine above 9.55 nmol/L can be a predictor for developing MVA [42]. Another promising biomarker can be serum concentrations of angiopoietin-2. This cytokine is produced by endothelial cells and functions as a growth factor enhancing angiogenesis through tyrosine kinase receptors. Rasmi *et al.* noticed significant increases of this angiogenic factor in MVA patients [43]. Last but not least is mid regional pro-adrenomedullin (MR-proADM) — a peptide fragment derived from the production of adrenomodulin that acts as a vasodilating hormone. Higher concentrations of MR-proADM can be another useful diagnostic tool in the MVA patient group [44].

Pathophysiology

Coronary microvascular dysfunction is proposed as the main pathophysiological mechanism in the development of MVA, which has led many clinicians and researchers to call this condition microvascular angina [45, 46]. It is now acknowledged that MVA most likely encompasses a wide pathophysiological spectrum (Fig. 1). The etiology of this syndrome is still not known and it is probably multifactorial. In addition to myocardial ischemia, altered somatic and visceral pain perception and high adrenergic drive with subsequent increase of alpha-adrenergic receptor expression may play a role in the development of angina-like chest pain. The autonomic nerves modulate tonic

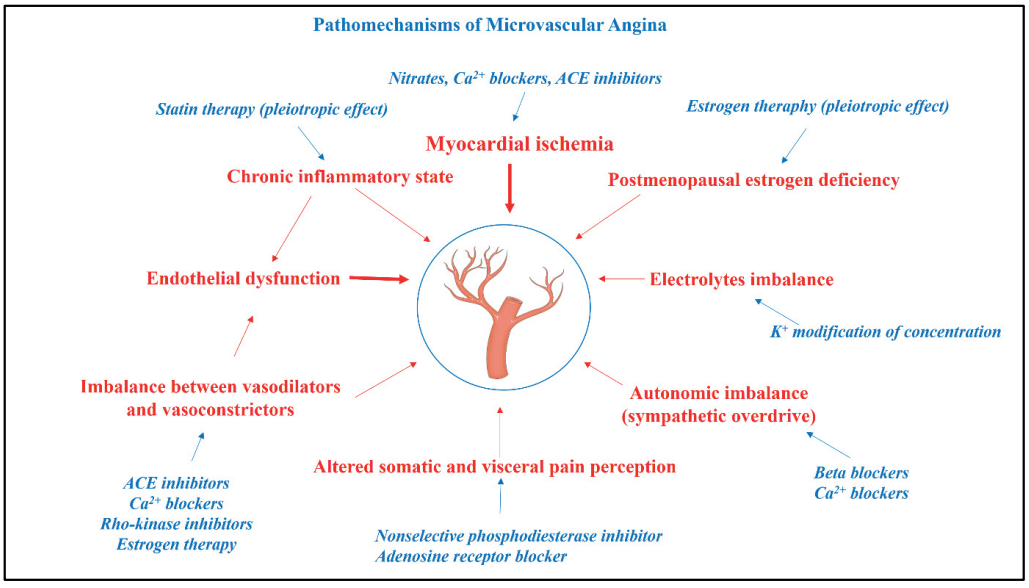

Fig. 1. Pathomechanisms of microvascular angina.

activity of the vascular smooth muscles. Abnormalities of autonomic control may result in reduction of coronary and visceral blood flow [46]. Other theories suggest that it may be a result of a chronic inflammatory state in the body that can negatively influence the endothelium or a local misbalance of factors regulating its function.

Angina-like chest pain of noncardiac origin continues to present major diagnostic and therapeutic difficulties. Investigations over the past two decades have not found a specific cause for MVA [45]. Patients with angina-like chest pain usually have a long history of drug use that have spasmolytic action not only on the smooth muscle cells of the blood vessels but also on those of the esophagus, with decreased lower esophageal sphincter tone and impaired esophageal clearing [47, 48]. These data suggest also the involvement of the smooth muscle of the gastrointestinal tract in MVA patients, and the hypothesis of general vasoconstriction of the body's smooth muscles seems reasonable. However, Brunelli *et al.* [49] demonstrated that cerebrovascular vasodilator reserve is well preserved in MVA patients, which contradicts the hypothesis of MVA being a diffuse smooth muscle disorder.

Another issue connected with development of MVA is endothelial dysfunction. Zehier *et al.* proved that endothelial malfunction not responding to vasodilators, can cause myocardial ischemia, especially when combined with exercise [50]. In MVA, this can be expressed in an imbalance of vasoactive factors, such as intercellular adhesion molecule 1 [51], increased concentrations of endotelin-1, and overactive superoxide dismutase (SOD) causing higher amounts of reactive oxygen species. All of these contractile factors mentioned above are not compensated by endogenous NO and other vasodilators. This lowered amount of vasodilators was demonstrated in the abnormal result of the acetylcholine test [32]. The theory of endothelial causes of MVA was refuted in studies showing lowered response in peripheral vessels to endothelin administration in patients with MVA [52]. However, noninvasive assessment of pulse wave velocity — as reflection of vessel compliance — indicated similar disturbances in the reactivity of arteries in MVA patients and CAD patients [53]. Moreover, the ailing endothelium mobilizes the bone marrow to produce increased amounts of endothelial progenitor cells. Unfortunately, their function is impaired regardless of increased concentration, resulting in incorrect proliferative function [54].

The proper function of the endothelium can be easily disrupted by a systemic inflammatory state [55]. It has been observed that MVA patients present elevated concentrations of CRP [56, 57] or even hs-CRP [58] suggesting that the pathophysiology of this disease may be connected with an inflammatory state. Recio-Mayoral *et al.* after investigating patients with systemic lupus erythematosus or rheumatoid arthritis suggested that coronary microvascular dysfunction and reduced coronary flow reserve may be connected with prolonged chronic systemic inflammation [59]. Disturbances in the immune system and its cells can explain the impairment of endothelial function. Activation of NK-cells and high amounts of proinflammatory

cytokines promote vasoconstriction and induce production of ROS. Oxidative stress is also caused by lymphocyte recruitment [60, 61]. Autoimmune diseases are not the only ones that can cause chronic inflammation leading to endothelial dysfunction. Chronic Helicobacter pylori infection was found in MVA patients more often than in the control group. Various determinants can explain this issue. Firstly, CAD risk factors were significantly more frequent in the MVA group, especially hyperlipidemia and hypertension. Additionally, the dysregulation of immune responses caused by this bacteria can lead to endothelial dysfunction [20, 62].

The chronic inflammatory hypothesis was confirmed by increased amounts of inflammatory cytokines like IL-6 [57, 63], IL-10 [57], as well as the amount of white blood cells [63, 64] and monocytes in this condition. Activation of platelets results in higher expression of its soluble CD40 ligand, resulting in further cytokine release but also causing pro-atherogenic effects. Further, Aslan *et al.* demonstrated increased serum concentrations of soluble suppression of tumorigenicity 2 (sST2) receptor for IL-33. Activation of this receptor results in cardiac fibrosis and endothelial dysfunction in MVA patients. Levels of this cytokine can be lowered by statin therapy [65]. To support inflammation as an etiology in the of pathophysiology of MVA, patients present lower levels of serum dihydroxyeicosatrienoic acid — the main example of the group of epoxyeicosatrienoic acids, which are endothelial metabolites with anti-inflammatory and vasodilation properties. Its production occurs in cytochrome P450 (CYP) 2C19, and in CSX patients the amount of poor metabolizers of this cytochrome was significantly higher, resulting in unopposed vasoconstriction of small vessels [66, 67]. Another disturbance of anti-inflammatory mechanisms in MVA patients is depletion of Vitamin D [68]. Interestingly, Horvath *et al.* demonstrated that MVA patients have an increased terminal pathway activation complex due to mobilization of the lecithin pathway of the complement system. This was confirmed by highlighting increased amounts of ficolin-2 and ficolin-3 not only while comparing MVA patients with healthy volunteers but also with coronary heart disease patients [69, 70]. Additionally the imbalance of pro- and anti-inflammatory factors is even intensified by lowered amounts of high density lipoprotein cholesterol [64], an inhibitor of vascular inflammation. In light of this finding, therapy increasing HDL blood levels needs to be assessed. This therapy may have a pleiotropic effect — some researchers suggest that microvascular disturbances may be due to "hidden" atherosclerosis — not visible in regular angiography but only in intravascular ultrasonography. It can cause micro-embolization or narrowing of vessel lumen causing troubles with blood flow [71]. Although the inflammatory theory is very convenient, there is insufficient data of the positive effect of anti-inflammatory drugs on the pathogenesis of MVA.

Prevalence of MVA is higher in women than in men, especially considering those of peri- or postmenopausal age. That finding suggests that it may be connected with estrogen deficiency. It is well known that estrogen concentration is one of the

modulators of proper endothelial function. It works pleiotropically — not only increasing the concentration of endogenous NO, but also decreasing the concentration of endothelin-1, which can be beneficial especially where its amount is basally increased [72, 73]. Often patients suffering from MVA have comorbid insulin resistance, hyperlipidemia and dyslipidemia, hypertension, and addiction to smoking, such risk factors being very similar to those of coronary arterial disease [74]. All these factors negatively influence coronary flow reserve (CFR). The decrease in CFR was first noted in patients with symptoms suggesting MVA [75]. Nowadays, investigators using Doppler Echocardiography, MRI [35], PET [50] are confirming this finding. Besides non-invasive assessment, some researchers use invasive tools as well, such as the index of microcirculatory resistance (IMR) or fractional flow reserve (FFR), with similar results [38]. The list of probable etiological factors is growing: endothelial dysfunction, chronic inflammation or components of metabolic syndrome. According to this data, treatment using ACE inhibitors seems to be reasonable.

An autonomic imbalance has been observed in subjects with MVA, involving the dynamic variations in the vasomotor tone of coronary microcirculation and with consequent transient ischemic episodes [23, 76–80]. Crea *et al.* made a suggestion that a drop in coronary reserve is caused most likely by increased sympathetic activity [81]. Excessive activation may lead to the contraction of smooth muscles mainly in coronary prearterioles, causing impaired blood flow and decrease of coronary reserve. This theory supports numerous clinical observations, such as elevated mean heart rate and rate-pressure product [82], increased contractility of the left ventricle, shortened diastolic time during physical effort and prolongation of the QT interval [83]. Further, except for increased sympathetic activation, some researchers suggest that in this condition we can assess parasympathetic withdrawal using non-invasive autonomic nervous system tests [84].

The dominance of the adrenergic system in MVA patients is also indicated by scintigraphic studies which showed uptake disturbances of the used marker, an analogue of adrenaline, competitive to endogenous catecholamines in the autonomic nerve endings of the heart muscle [85]. A similar conclusion is supported by disturbances in the neural control system of the heart action estimated by spectral analysis of the RR segments and metabolic studies [38, 79–86]. According to Erikssen *et al.*, symptoms of adrenergic activation in MVA patients may partially result from tissue hypersensitivity to the unstable level of endogenous catecholamines [87]. Such hypersensitivity of the adrenergic receptors is probably not limited to the heart and respiratory disturbances, but reflect the stimulating effect of the receptors in the bronchial tree and pulmonary vascular bed in these patients. Other examples of adrenergic overactivity are decreases in the vasodilative reserve of the forearm, esophageal dysmotility, or functional anomalies of skeletal muscles. During physical exertion,

the drop in intramuscular pH and phosphocreatinine concentrations is too fast and has a prolonged return back to normal levels [88].

There is another important theory of the pathomechanism of MVA, namely electrolyte imbalance. Botker *et al.* found that concentrations of potassium increase during physical exercise compared to controls, which would account for signs of MVA, e.g. chest pain, since potassium could act as one of the mediators of cardiac pain [89]. During echocardiography of MVA patients we can expect enlargement of epicardial adipose tissue (EAT). It is part of the visceral fat with a primary metabolic function for the heart — delivery of fatty acids directly to the coronary lumen. Unfortunately, its growth can have an adverse effect and have proinflammatory, prothrombotic, and vasoactive effects directly on local small vessels. Apparent enlargement of EAT is associated with metabolic syndrome [90–91].

Treatment recommendations

The first attempts to treat microvascular angina were symptomatic because of the unknown etiology of the disease [29]. Generally, in treatment, it is very important to distinguish whether there is spasm of microcirculation arterioles after acetylcholine. In the case of microvascular contraction, the ESC 2019 guidelines recommend beta blockers (BB), angiotensin converting enzyme inhibitors — ACEI or angiotensin receptor blockers — ARB, and statins, while in the absence of contraction, calcium channel blockers — CCB (as in Prinzmetal angina, even two CCBs together from different groups). It is always very important to control risk factors, ASA can be given, and imipramine can be considered in resistance; nitrates rather temporarily, because they work poorly in contrast to classic angina [16].

Traditional anti-ischemic drugs were recommended as a good choice. Although they started to be used as symptom relieving drugs. Taking into consideration in the pathophysiology of MVA important role of the activation of the autonomic nervous system, it seems their use may target etiological factor. Beta blockers have been used successfully for many years, and they are especially effective in patients with increased sympathetic tone. Their effect on lowering the number of anginal episodes and their beneficial effect on diastolic function guarantee beta blockers an essential place in the treatment of MVA [92–94].

The results of Ca-blocker therapy (like verapamil or diltiazem) are uncertain — some studies proved their beneficial effect as anti-ischemic drugs or in lowering the number of anginal attacks [95–96], others did not [92]. The primary target for these drugs is vasodilation to improve coronary blood flow. Ca-blockers are recommended for some groups of patients with microvascular angina, especially when β-blockers are contraindicated or inefficient [97]. It can be beneficial to combine them with ACE

inhibitors — not only to dilate the affected vessels but also to lower the amount of vasoconstrictors.

With respect to nitrates, the results of the research on the use of short-acting nitrates are inconsistent. Some studies confirm that using short-acting nitrates could relieve chest pain syndromes [78]. Others, however, outlined that their effect is minimal [26]. Russo *et al.* suggest that nitrates are effective in alleviating symptoms and in improving the exercise stress test in patients with stable CAD but not helpful in patients with microvascular dysfunction [26].

Many studies over the years have proven the effectiveness of ACE-inhibitors in the treatment of microvascular angina. It is well known that increased sympathetic tone has a major influence on the renin-angiotensin-aldosterone system. Usage of ACE inhibitors not only stops excessive activation of this system but it decreases exercise-induced ischemia by regulating microvascular arterial tone. Lower levels of angiotensin II promote vasodilation as this agent is one of the strongest known vasoconstrictors [98–100].

Statins are another important group of drugs used in microvascular angina therapy. Their pleiotropic effects on endothelial function improvement and reduction of vascular inflammation play an important role in the alleviation of symptoms in MVA patients. Lowering levels of endothelin and increasing levels of plasma HDL facilitate both endothelium-dependent and independent vasodilation Moreover, the beneficial aspects of statin therapy are visible in normolipidemic patient as well. Placebo-controlled studies showed improvement in patients' condition, increasing not only their quality of life but also improving their stress tests results [96, 101, 102].

Other medications, such as ranolazine [103, 104], ivabradine [105], nicorandil [106] could be potentially used in MVA. Their main mechanism of action in MVA is increasing anti-anginal effects. Nicorandil can be beneficial in increasing CFR. The results of studies on the use of trimetazidine in MVA show divergent effects [107]. All of these drugs are regarded as 2 and 3 stage therapy for patients with refractory MVA [81]. Estrogen therapy [72, 108] may be considered in women with MVA due to its pleiotropic effect as it improves the blood lipid profile, decreases insulin resistance, and more importantly, enhances responses to vasodilators such as NO. Additionally, estrogen therapy can reduce the amount of endothelin-1, one of the main vasoconstrictors in MVA. Therapy which improves endothelial function may be particularly beneficial during exercise or stress, when sympathetic action disturbs the imbalance between vasodilators and vasoconstrictors. The treatment effect was visible in some patients who used aminophylline, which acts as a nonselective phosphodiesterase inhibitor and adenosine receptor blocker. Adenosine antagonizing doses improve exercise tolerance in patients with MVA by decreasing pain perception through antagonism of the effect of adenosine [109–111].

Rho-kinase inhibitors are being investigated as new drugs for MVA, because of induced endothelial as well as non-endothelial dependent vasodilation. Rho-kinase inhibits myosin phosphatase activity triggering calcium-independent smooth muscle contraction. A specific rho-kinase inhibitor, Fasudil, reduces myocardial ischemia especially in patients with coronary microvascular spasm [112–113].

Besides pharmacological treatment, non-pharmacological treatment is also used in patients with MVA. A spinal cord stimulation implant in the thoracic spine is a neurostimulator which has already been used with success in relieving pain in refractory angina. It can be beneficial in MVA patients with an exaggerated sensation of pain. Targeting the malfunction of autonomic nervous system as one of the important pathological factors of the disease relieves the perception of cardiac pain in patients as well as limits sympathetic influence on microvascular circulation [114]. PET examination showed redistribution of blood flow in microvascular circulation and increased perfusion of ischemic parts. The positive effect was visible additionally in improving quality of life and decreasing the amount of hospital admissions [115–116].

Enhanced external counter pulsation (EECP) is another method used successfully in treating refractory angina. It is performed using with three sets of pneumatic cuffs attached to each of the patient's legs at the calf and lower and upper thigh contracting sequentially during diastole. EECP leads to improved coronary blood flow, reduces pro-inflammatory cytokine levels, increases NO release and the resultant vasodilation. Similarly to spinal cord stimulation, the positive effects of the therapy are mainly related to the improvement of quality of life in MVA patients [57, 64, 117].

Conclusion

In conclusion, in the diagnosis of MVA are used both invasive and non-invasive diagnostic tools. The prognosis of MVA patients without traditional cardiac risk factors has been reported to be good. The therapy of MVA is effective in relieving symptoms in a large proportion of patients affected by this condition. Although further research is required in areas such as non-invasive assessment of coronary microcirculation, pain perception abnormalities and pharmacological treatments aim to target specific pathomechanisms.

Authors' contributions

A.F., A.S. and K.G. contributed to the review conception. Papers collection and selection were performed by J.J., A.J. and A.B. The first draft of the manuscript was written by J.J. and A.J. and all authors commented and corrected on subsequent versions of the manuscript. A.P. English linguistic proofreading.

All authors read and approved the final version of the manuscript.

Conflict of interest

None declared.

References

1. *Lenfant C.*: Chest pain of cardiac and noncardiac origin. Metabolism. 2010; 59 (Suppl. 1): S41–46. doi: 10.1016/j.metabol.2010.07.014
2. *Hochman J.S., Tamis J.E., Thompson T.D., et al.*: Sex, clinical presentation, and outcome in patients with acute coronary syndromes. N Engl J Med. 1999; 341 (4): 226–232. doi: 10.1056/NEJM199907223410402
3. *Lanza G.A., De Vita A., Kaski J.C.*: "Primary" microvascular angina: Clinical characteristics, pathogenesis and management. Interv Cardiol Rev. 2018; 13 (3): 108–111. doi: 10.15420/icr.2018.15.2
4. *Lanza G.A.*: Cardiac syndrome X: A critical overview and future perspectives. Heart. 2007; 93 (2): 159–166. doi: 10.1136/hrt.2005.067330
5. *Cheng T.O.*: Cardiac syndrome X versus metabolic syndrome X. Int J Cardiol. 2007; 119 (2): 137–138. doi: 10.1016/j.ijcard.2006.06.062
6. *Lichtlen P.R., Bargheer K., Wenzlaff P.*: Long-term prognosis of patients with anginalike chest pain and normal coronary angiographic findings. J Am Coll Cardiol. 1995; 25 (5): 1013–1018. doi: 10.1016/0735-1097 (94)00519-V
7. *Lamendola P., Lanza G.A., Spinelli A., et al.*: Long-term prognosis of patients with cardiac syndrome X. Int J Cardiol. 2010; 140 (2): 197–199. doi: 10.1016/j.ijcard.2008.11.026
8. *Di Monaco A., Lanza G.A., Bruno I., et al.*: Usefulness of impairment of cardiac adrenergic nerve function to predict outcome in patients with cardiac syndrome X. Am J Cardiol. 2010; 106 (12): 1813–1818. doi: 10.1016/j.amjcard.2010.07.052
9. *Singh M., Singh S., Arora R., Khosla S.*: Cardiac syndrome X: Current concepts. Int J Cardiol. 2010; 142 (2): 113–119. doi: 10.1016/j.ijcard.2009.11.021
10. *Ryan T.J.*: *The Coronary Angiogram and Its Seminal Contributions to Cardiovascular Medicine over Five Decades*. Circulation. 2002; 106 (6). doi: 10.1161/01.CIR.0000024109.12658.D4
11. *Kemp H.G., Vokonas P.S., Cohn P.F., Gorlin R.*: The anginal syndrome associated with normal coronary arteriograms. Report of a six year experience. Am J Med. 1973; 54 (6): 735–742. doi: 10.1016/0002-9343 (73)90060-0
12. *Cannon R.O., Epstein S.E.*: "Microvascular angina" as a cause of chest pain with angiographically normal coronary arteries. Am J Cardiol. 1988; 61 (15): 1338–1343. doi: 10.1016/0002-9149 (88) 91180-0
13. *Fox K., Alonso Garcia M.A., Ardissino D., et al.*: Guidelines on the management of stable angina pectoris: Executive summary — The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J. 2006; 27 (11): 1341–1381. doi: 10.1093/eurheartj/ehl001
14. *Montalescot G., Sechtem U., Achenbach S., et al.*: 2013 ESC guidelines on the management of stable coronary artery disease. Eur Heart J. 2013; 34 (38): 2949–3003. doi: 10.1093/eurheartj/eht296
15. *Ong P., Camici P.G., Beltrame J.F., et al.*: International standardization of diagnostic criteria for microvascular angina. Int J Cardiol. 2018; 250: 16–20. doi: 10.1016/j.ijcard.2017.08.068
16. *Knuuti J., Wijns W., Achenbach S., et al.*: 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020; 41 (3): 407–477. doi: 10.1093/eurheartj/ehz425
17. *Diver D.J., Bier J.D., Ferreira P.E., et al.*: Clinical and arteriographic characterization of patients with unstable angina without critical coronary arterial narrowing (from the TIMI-IIIA trial). Am J Cardiol. 1994; 74 (6): 531–537. doi: 10.1016/0002-9149 (94)90739-0

18. *Reis S.E., Holubkov R., Smith A.J.C., et al.*: Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: Results from the NHLBI WISE study. Am Heart J. 2001; 141 (5): 735–741. doi: 10.1067/mhj.2001.114198
19. *Noel Bairey Merz C., Eteiba W., Pepine C.J., Johnson B.D., Shaw L.J., Kelsey S.F.*: Cardiac syndrome X: Relation to microvascular angina and other conditions. Curr Cardiovasc Risk Rep. 2007; 1 (2): 167–175. doi: 10.1007/s12170-007-0027-3
20. *Bugiardini R., Merz C.N.B.*: Angina with "normal" coronary arteries: A changing philosophy. J Am Med Assoc. 2005; 293 (4): 477–484. doi: 10.1001/jama.293.4.477
21. *Krumholz H.M., Douglas P.S., Lauer M.S., Pasternak R.C.*: Selection of patients for coronary angiography and coronary revascularization early after myocardial infarction: Is there evidence for a gender bias? Ann Intern Med. 1992; 116 (10): 785–790. doi: 10.7326/0003-4819-116-10-785
22. *Kaski J.C.*: Overview of gender aspects of cardiac syndrome X. Cardiovasc Res. 2002; 53 (3): 620–626. doi: 10.1016/s0008-6363 (01)00460-6
23. *Pasceri V., Lanza G.A., Buffon A., Montenero A.S., Crea F., Maseri A.*: Role of abnormal pain sensitivity and behavioral factors in determining chest pain in syndrome X. J Am Coll Cardiol. 1998; 31 (1): 62–66. doi: 10.1016/s0735-1097 (97)00421-x
24. *Ford T.J., Stanley B., Good R., et al.*: Stratified Medical Therapy Using Invasive Coronary Function Testing in Angina: The CorMicA Trial. J Am Coll Cardiol. 2018; 72 (23): 2841–2855. doi: 10.1016/j.jacc.2018.09.006
25. *Kanatsuka H., Eastham C.L., Marcus M.L., Lamping K.G.*: Effects of nitroglycerin on the coronary microcirculation in normal and ischemic myocardium. J Cardiovasc Pharmacol. 1992; 19 (5): 755–763.
26. *Russo G., Di Franco A., Lamendola P., et al.*: Lack of effect of nitrates on exercise stress test results in patients with microvascular angina. Cardiovasc Drugs Ther. 2013; 27 (3): 229–234. doi: 10.1007/s10557-013-6439-z
27. *Ohba K., Sugiyama S., Sumida H., et al.*: Microvascular coronary artery spasm presents distinctive clinical features with endothelial dysfunction as nonobstructive coronary artery disease. J Am Heart Assoc. 2012; 1 (5): e002485. doi: 10.1161/JAHA.112.002485
28. *Maseri A., Crea F., Kaski J.C., Crake T.*: Mechanisms of angina pectoris in syndrome X. J Am Coll Cardiol. 1991; 17 (2): 499–506. doi: 10.1016/S0735-1097 (10)80122-6
29. *Lanza G.A., Crea F.*: Primary coronary microvascular dysfunction: Clinical presentation, pathophysiology, and management. Circulation. 2010; 121 (21): 2317–2325. doi: 10.1161/CIRCULATIONAHA.109.900191
30. *Nihoyannopoulos P., Kaski J.C., Crake T., Maseri A.*: Absence of myocardial dysfunction during stress in patients with syndrome X. J Am Coll Cardiol. 1991; 18 (6): 1463–1470. doi: 10.1016/0735-1097 (91)90676-z
31. *Panza J.A., Laurienzo J.M., Curiel R. V, et al.*: Investigation of the mechanism of chest pain in patients with angiographically normal coronary arteries using transesophageal dobutamine stress echocardiography. J Am Coll Cardiol. 1997; 29 (2): 293–301. doi: 10.1016/s0735-1097 (96)00481-0
32. *Ong P., Athanasiadis A., Borgulya G., Mahrholdt H., Kaski J.C., Sechtem U.*: High prevalence of a pathological response to acetylcholine testing in patients with stable angina pectoris and unobstructed coronary arteries: The ACOVA study (abnormal coronary vasomotion in patients with stable angina and unobstructed coronary arteries. J Am Coll Cardiol. 2012; 59 (7): 655–662. doi: 10.1016/j.jacc.2011.11.015
33. *White C.W., Wright C.B., Doty D.B., et al.*: Does Visual Interpretation of the Coronary Arteriogram Predict the Physiologic Importance of a Coronary Stenosis? N Engl J Med. 1984; 310 (13): 819–824. doi: 10.1056/NEJM198403293101304
34. *Hulten E., Di Carli M.F.*: FFR CT : Solid PLATFORM or Thin Ice? J Am Coll Cardiol. 2015; 66 (21): 2324–2328. doi: 10.1016/j.jacc.2015.09.065
35. *Thomson L.E.J., Wei J., Agarwal M., et al.*: Cardiac magnetic resonance myocardial perfusion reserve index is reduced in women with coronary microvascular dysfunction: A national heart, lung, and

blood institute-sponsored study from the women's ischemia syndrome evaluation. Circ Cardiovasc Imaging. 2015; 8 (4). doi: 10.1161/CIRCIMAGING.114.002481

36. *Gould K.L., Johnson N.P., Bateman T.M., et al.*: Anatomic versus physiologic assessment of coronary artery disease: Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. J Am Coll Cardiol. 2013; 62 (18): 1639–1653. doi: 10.1016/j.jacc.2013.07.076
37. *Galiuto L., Sestito A., Barchetta S., et al.*: Noninvasive Evaluation of Flow Reserve in the Left Anterior Descending Coronary Artery in Patients With Cardiac Syndrome X. Am J Cardiol. 2007; 99 (10): 1378–1383. doi: 10.1016/j.amjcard.2006.12.070
38. *Lee B.K., Lim H.S., Fearon W.F., et al.*: Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease. Circulation. 2015; 131 (12): 1054–1060. doi: 10.1161/CIRCULATIONAHA.114.012636
39. *Ng M.K.C., Yeung A.C., Fearon W.F.*: Invasive assessment of the coronary microcirculation: Superior reproducibility and less hemodynamic dependence of index of microcirculatory resistance compared with coronary flow reserve. Circulation. 2006; 113 (17): 2054–2061. doi: 10.1161/CIRCULATIONAHA.105.603522
40. *Beltrame J.F.*: Defining the coronary slow flow phenomenon. Circ J. 2012; 76 (4): 818–820. doi: 10.1253/circj.CJ-12-0205
41. *Gibson C.M., Cannon C.P., Daley W.L., et al.*: TIMI frame count: A quantitative method of assessing coronary artery flow. Circulation. 1996; 93 (5): 879–888. doi: 10.1161/01.CIR.93.5.879
42. *Odaka Y., Takahashi J., Tsuburaya R., et al.*: Plasma concentration of serotonin is a novel biomarker for coronarymicrovascular dysfunction in patients with suspected angina and unobstructive coronary arteries. Eur Heart J. 2017; 38 (7): 489–496. doi: 10.1093/eurheartj/ehw448
43. *Rasmi Y., Roshani-Asl E., KhademAnsari M., SeyedMohammadza M., Rostamzadeh A.*: Angiopoietin-2 as a biomarker for patients with Cardiac Syndrome X. J Am Coll Cardiol. 2016; 68 (16): C24. doi: 10.1016/j.jacc.2016.07.092
44. *Uğurlu M., Karahan Z., Sezer F., et al.*: OP-024 A Novel Biomarker in Syndrome X Disease: Mr-Proadrenomedullin. Am J Cardiol. 2016; 117: S9. doi: 10.1016/j.amjcard.2016.04.070
45. *Cannon R.O. 3rd, Camici P.G., Epstein S.E.*: Pathophysiological Dilemma of Syndrome X. Circulation. 1992; 85 (3): 883–892.
46. *Rosano G.M., Ponikowski P., Adamopoulos S., et al.*: Abnormal autonomic control of the cardiovascular system in syndrome X. Am J Cardiol. 1994; 73 (16): 1174–1179. doi: 10.1016/0002-9149 (94)90177-5
47. *Börjesson M., Albertsson P., Dellborg M., et al.*: Esophageal dysfunction in syndrome X. Am J Cardiol. 1998; 82 (10): 1187–1191. doi: 10.1016/s0002-9149 (98)00598-0
48. *Kao C.H., Hsieh J.F., Tsai C.S., Ho Y.J., Lee J.K.*: Evidence of abnormal esophageal motility in syndrome X by radionuclide esophageal transit test. Digestion. 2000; 62 (1): 26–30. doi: 10.1159/000007774
49. *Brunelli C., Nobili F., Spallarossa P., et al.*: Cerebral blood flow reserve in patients with syndrome X. Coron Artery Dis. 1996; 7 (8): 587–590. doi: 10.1097/00019501-199608000-00005
50. *Zeiher A.M., Krause T., Schächinger V., Minners J., Moser E.*: Impaired endothelium-dependent vasodilation of coronary resistance vessels is associated with exercise-induced myocardial ischemia. Circulation. 1995; 91 (9): 2345–2352. doi: 10.1161/01.cir.91.9.2345
51. *Lin C.-P., Lin W.-T., Leu H.-B., Wu T.-C., Chen J.-W.*: Differential mononuclear cell activity and endothelial inflammation in coronary artery disease and cardiac syndrome X. Int J Cardiol. 2003; 89 (1): 53–62. doi: 10.1016/s0167-5273 (02)00428-x
52. *Newby D.E., Flint L.L., Fox K.A.A., Boon N.A., Webb D.J.*: Reduced responsiveness to endothelin-1 in peripheral resistance vessels of patients with syndrome X. J Am Coll Cardiol. 1998; 31 (7): 1585–1590. doi: 10.1016/S0735-1097 (98)00143-0

53. *Kidawa M., Krzeminska-Pakula M., Peruga J.Z., Kasprzak J.D.*: Arterial dysfunction in syndrome X: Results of arterial reactivity and pulse wave propagation tests. Heart. 2003; 89 (4): 422–426. doi: 10.1136/heart.89.4.422
54. *Shmilovich H., Deutsch V., Roth A., Miller H., Keren G., George J.*: Circulating endothelial progenitor cells in patients with cardiac syndrome X. Heart. 2007; 93 (9): 1071–1076. doi: 10.1136/hrt.2005.077909
55. *Trott D.W., Fadel P.J.*: Inflammation as a mediator of arterial ageing. Exp Physiol. 2019; 104 (10): 1455–1471. doi: 10.1113/EP087499
56. *Dollard J., Kearney P., Clarke G., Moloney G., Cryan J.F., Dinan T.G.*: A prospective study of C-reactive protein as a state marker in Cardiac Syndrome X. Brain Behav Immun. 2015; 43: 27–32. doi: 10.1016/j.bbi.2014.07.011
57. *Demir B., Önal B., Özyazgan S., et al.*: Does Inflammation Have a Role in the Pathogenesis of Cardiac Syndrome X? A Genetic-Based Clinical Study With Assessment of Multiple Cytokine Levels. Angiology. 2015; 67 (4): 355–363. doi: 10.1177/0003319715590057
58. *Recio-Mayoral A., Rimoldi O.E., Camici P.G., Kaski J.C.*: Inflammation and microvascular dysfunction in cardiac syndrome X patients without conventional risk factors for coronary artery disease. JACC Cardiovasc Imaging. 2013; 6 (6): 660–667. doi: 10.1016/j.jcmg.2012.12.011
59. *Recio-Mayoral A., Mason J.C., Kaski J.C., Rubens M.B., Harari O.A., Camici P.G.*: Chronic inflammation and coronary microvascular dysfunction in patients without risk factors for coronary artery disease. Eur Heart J. 2009; 30 (15): 1837–1843. doi: 10.1093/eurheartj/ehp205
60. *Konst R.E., Guzik T.J., Kaski J.C., Maas A.H.E.M., Elias-Smale S.E.*: The pathogenic role of coronary microvascular dysfunction in the setting of other cardiac or systemic conditions. Cardiovasc Res. 2020; 116 (4): 817–828. doi: 10.1093/cvr/cvaa009
61. *Ahmed A., Hollan I., Curran S.A., et al.*: Brief Report: Proatherogenic Cytokine Microenvironment in the Aortic Adventitia of Patients with Rheumatoid Arthritis. Arthritis Rheumatol. 2016; 68 (6): 1361–1366. doi: 10.1002/art.39574
62. *Karbalaei M., Sahebkar A., Keikha M.*: Helicobacter pylori infection and susceptibility to cardiac syndrome X: A systematic review and meta-analysis. World J Meta-Analysis. 2021; 9 (2): 208–219. doi: 10.13105/wjma.v9.i2.208
63. *Li J.J., Zhu C.G., Nan J.L., et al.*: Elevated circulating inflammatory markers in female patients with cardiac syndrome X. Cytokine. 2007; 40 (3): 172–176. doi: 10.1016/j.cyto.2007.09.005
64. *Tenekecioglu E., Yilmaz M., Demir S., et al.*: HDL-cholesterol is associated with systemic inflammation in cardiac syndrome X. Minerva Med. 2015; 106 (3): 133–141.
65. *Aslan G., Polat V., Bozcali E., Opan S., Çetin N., Ural D.*: Evaluation of serum sST2 and sCD40L values in patients with microvascular angina. Microvasc Res. 2019; 122: 85–93. doi: 10.1016/j.mvr.2018.11.009
66. *Akasaka T., Sueta D., Arima Y., et al.*: CYP2C19 variants and epoxyeicosatrienoic acids in patients with microvascular angina. IJC Hear Vasc. 2017; 15: 15–20. doi: 10.1016/j.ijcha.2017.03.001
67. *Akasaka T., Sueta D., Arima Y., et al.*: Association of CYP2C19 variants and epoxyeicosatrienoic acids on patients with microvascular angina. Am J Physiol — Hear Circ Physiol. 2016; 311 (6): H1409–H1415. doi: 10.1152/ajpheart.00473.2016
68. *Güler G.B., Güler E., Hatipoğlu S., et al.*: Assessment of 25-OH vitamin D levels and abnormal blood pressure response in female patients with cardiac syndrome X. Anatol J Cardiol. 2016; 16 (12): 961–966. doi: 10.14744/AnatolJCardiol.2016.6862
69. *Horváth Z., Csuka D., Vargova K., et al.*: Elevated C1rC1sC1inh levels independently predict atherosclerotic coronary heart disease. Mol Immunol. 2013; 54 (1): 8–13. doi: 10.1016/j.molimm.2012.10.033
70. *Horváth Z., Csuka D., Vargova K., et al.*: Association of Low Ficolin-Lectin Pathway Parameters with Cardiac Syndrome X. Scand J Immunol. 2016; 84 (3): 174–181. doi: 10.1111/sji.12454

71. *Cenko E., Amaduzzi P.L., Bugiardini R.*: Microvascular angina as a cause of ischemia: An update. In: Gender Differences in the Pathogenesis and Management of Heart Disease. Springer International Publishing; 2018: 135–163. doi: 10.1007/978-3-319-71135-5_9
72. *Kaski J.C.*: Cardiac syndrome X in women: The role of oestrogen deficiency. Heart. 2006; 92 (Suppl. 3): 5–9. doi: 10.1136/hrt.2005.070318
73. *Gilligan D.M., Badar D.M., Panza J.A., Quyyumi A.A., Cannon R.O.*: Acute vascular effects of estrogen in postmenopausal women. Circulation. 1994; 90 (2): 786–791. doi: 10.1161/01.CIR.90.2.786
74. *Lim T.K., Choy A.J., Khan F., Belch J.J., Struthers A.D., Lang C.C.*: Therapeutic development in cardiac syndrome X: A Need to target the underlying pathophysiology: REVIEW. Cardiovasc Ther. 2009; 27 (1): 49–58. doi: 10.1111/j.1755-5922.2008.00070.x
75. *Opherk D., Mall G., Zebe H., et al.*: Reduction of coronary reserve: a mechanism for angina pectoris in patients with arterial hypertension and normal coronary arteries. Circulation. 1984; 69 (1): 1–7. doi: 10.1161/01.CIR.69.1.1
76. *Meeder J.G., Blanksma P.K., Crijns H.J.G.M., et al.*: Mechanisms of angina pectoris in syndrome X assessed by myocardial perfusion dynamics and heart rate variability. Eur Heart J. 1995; 16 (11): 1571–1577. doi: 10.1093/oxfordjournals.eurheartj.a060780
77. *Saghari M., Assadi M., Eftekhari M., et al.*: Frequency and severity of myocardial perfusion abnormalities using Tc-99m MIBI SPECT in cardiac syndrome X. BMC Nucl Med. 2006; 6: 1–8. doi: 10.1186/1471-2385-6-1
78. *Kaski J.C., Rosano G.M.C., Collins P., Nihoyannopoulos P., Maseri A., Poole-Wilson P.A.*: Cardiac syndrome X: Clinical characteristics and left ventricular function. Long-term follow-up study. J Am Coll Cardiol. 1995; 25 (4): 807–814. doi: 10.1016/0735-1097 (94)00507-M
79. *Furgała A., Kolasińska-Kloch W., Kloch M., Laskiewicz J., Thor P.J.*: Heart rate variability in cardiological syndrome X patients | Zmienność rytmu serca u chorych z kardiologicznym zespołem X. Folia Cardiol. 2003; 10 (4).
80. *Adamopoulos S., Rosano G.M., Ponikowski P., et al.*: Impaired baroreflex sensitivity and sympathovagal balance in syndrome X. Am J Cardiol. 1998; 82 (7): 862–868. doi: 10.1016/s0002-9149 (98)00493-7
81. *Crea F., Camici P.G., Merz C.N.B.*: Coronary microvascular dysfunction: An update. Eur Heart J. 2014; 35 (17): 1101–1111. doi: 10.1093/eurheartj/eht513
82. *Chen J.W., Hsu N.W., Ting C.T., Lin S.J., Chang M.S.*: Differential coronary hemodynamics and left ventricular contractility in patients with syndrome X. Int J Cardiol. 2000; 75 (1): 49–57. doi: 10.1016/s0167-5273 (00)00285-0
83. *Mammana C., Salomone O.A., Kautzner J., Schwartzman R.A., Kaski J.C.*: Heart rate-independent prolongation of QTc interval in women with syndrome X. Clin Cardiol. 1997; 20 (4): 357–360. doi: 10.1002/clc.4960200411
84. *Gulli G., Cemin R., Pancera P., Menegatti G., Vassanelli C., Cevese A.*: Evidence of parasympathetic impairment in some patients with cardiac syndrome X. Cardiovasc Res. 2001; 52 (2): 208–216. doi: 10.1016/S0008-6363 (01)00369-8
85. *Antonio L.G., Alessandro G., Christian P., et al.*: Abnormal Cardiac Adrenergic Nerve Function in Patients With Syndrome X Detected By [123I]Metaiodobenzylguanidine Myocardial Scintigraphy. Circulation. 1997; 96 (3): 821–826. doi: 10.1161/01.CIR.96.3.821
86. *Lee W.L., Chen J.-W.W., Kong C.W., et al.*: Changes in Cardiac Autonomic Activities in Patients with Syndrome X: A Study of Spectral Analysis of Heart Rate Variability. Angiology. 1996; 47 (10): 929–939. doi: 10.1177/000331979604701001
87. *Eriksson B., Jansson E., Kaijser L., Sylvan C.*: Exercise performance, autonomic control and skeletal muscle function in syndrome X. Circulation. 1997; 96 (8S).
88. *Rosano G.M., Kaski J.C., Arie S., et al.*: Failure to demonstrate myocardial ischaemia in patients with angina and normal coronary arteries. Evaluation by continuous coronary sinus pH monitoring and

lactate metabolism. Eur Heart J. 1996; 17 (8): 1175–1180. doi: 10.1093/oxfordjournals.eurheartj.a015034
89. *Bøtker H.E., Sonne H.S., Frøbert O., Andreasen F.*: Enhanced exercise-induced hyperkalemia in patients with syndrome X. J Am Coll Cardiol. 1999; 33 (4): 1056–1061. doi: 10.1016/S0735-1097(98)00683-4
90. *Villasante Fricke A.C., Iacobellis G.*: Epicardial Adipose Tissue: Clinical Biomarker of Cardio-Metabolic Risk. Int J Mol Sci. 2019; 20 (23). doi: 10.3390/ijms20235989
91. *Kalçik M., Yesin M., Güner A., et al.*: Echocardiographic measurement of epicardial adipose tissue thickness in patients with microvascular angina. Interv Med Appl Sci. 2019; 11 (2): 106–111. doi: 10.1556/1646.11.2019.12
92. *Lanza G.A., Colonna G., Pasceri V., Maseri A.*: Atenolol versus amlodipine versus isosorbide-5-mononitrate on anginal symptoms in syndrome X. Am J Cardiol. 1999; 84 (7): 854–856. doi: 10.1016/S0002-9149 (99)00450-6
93. *Leonardo F., Fragasso G., Rossetti E., et al.*: Comparison of trimetazidine with atenolol in patients with syndrome X: effects on diastolic function and exercise tolerance. Cardiologia. 1999; 44 (12): 1065–1069.
94. *Erdamar H., Sen N., Tavil Y., et al.*: The effect of nebivolol treatment on oxidative stress and antioxidant status in patients with cardiac syndrome-X. Coron Artery Dis. 2009; 20 (3): 238–244. doi: 10.1097/MCA.0b013e32830936bb
95. *Ozçelik F., Altun A., Ozbay G.*: Antianginal and anti-ischemic effects of nisoldipine and ramipril in patients with syndrome X. Clin Cardiol. 1999; 22 (5): 361–365. doi: 10.1002/clc.4960220513
96. *Zhang X., Li Q., Zhao J., et al.*: Effects of combination of statin and calcium channel blocker in patients with cardiac syndrome X. Coron Artery Dis. 2014; 25 (1): 40–44. doi: 10.1097/MCA.0000000000000054
97. *Ong P., Athanasiadis A., Sechtem U.*: Pharmacotherapy for coronary microvascular dysfunction. Eur Hear J — Cardiovasc Pharmacother. 2015; 1 (1): 65–71. doi: 10.1093/ehjcvp/pvu020
98. *Pizzi C., Manfrini O., Fontana F., Bugiardini R.*: Angiotensin-converting enzyme inhibitors and 3-hydroxy-3-methylglutaryl coenzyme A reductase in cardiac Syndrome X: role of superoxide dismutase activity. Circulation. 2004; 109 (1): 53–58. doi: 10.1161/01.CIR.0000100722.34034.E4
99. *Chen J.W., Hsu N.W., Wu T.C., Lin S.J., Chang M.S.*: Long-term angiotensin-converting enzyme inhibition reduces plasma asymmetric dimethylarginine and improves endothelial nitric oxide bioavailability and coronary microvascular function in patients with syndrome X. Am J Cardiol. 2002; 90 (9): 974–982. doi: 10.1016/S0002-9149 (02)02664-4
100. *Pauly D.F., Johnson B.D., Anderson R.D., et al.*: In women with symptoms of cardiac ischemia, nonobstructive coronary arteries, and microvascular dysfunction, angiotensin-converting enzyme inhibition is associated with improved microvascular function. Am Heart J. 2011; 162 (4): 678–684. doi: 10.1016/j.ahj.2011.07.011
101. *Kayikcioglu M., Payzin S., Yavuzgil O., Kultursay H., Can L.H., Soydan I.*: Benefits of statin treatment in cardiac syndrome-X1. Eur Heart J. 2003; 24 (22): 1999–2005. doi: 10.1016/S0195-668X(03)00478-0
102. *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; 94 (5): 652–655. doi: 10.1016/j.amjcard.2004.05.035
103. *Mehta P.K., Goykhman P., Thomson L.E.J., et al.*: Ranolazine improves angina in women with evidence of myocardial ischemia but no obstructive coronary artery disease. JACC Cardiovasc Imaging. 2011; 4 (5): 514–522. doi: 10.1016/j.jcmg.2011.03.007
104. *Tagliamonte E., Rigo F., Cirillo T., et al.*: Effects of ranolazine on noninvasive coronary flow reserve in patients with myocardial ischemia but without obstructive coronary artery disease. Echocardiography. 2015; 32 (3): 516–521. doi: 10.1111/echo.12674
105. *Villano A., Di Franco A., Nerla R., et al.*: Effects of ivabradine and ranolazine in patients with microvascular angina pectoris. Am J Cardiol. 2013; 112 (1): 8–13. doi: 10.1016/j.amjcard.2013.02.045

106. *Chen J.W., Lee W.L., Hsu N.W., et al.*: Effects of short-term treatment of Nicorandil on exercise-induced myocardial ischemia and abnormal cardiac autonomic activity in microvascular angina. Am J Cardiol. 1997; 80 (1): 32–38. doi: 10.1016/S0002-9149 (97)00279-8
107. *Nalbantgil S., Altintiğ A., Yilmaz H., Nalbantgil I., Önder R.*: The effect of trimetazidine in the treatment of microvascular angina. Int J Angiol. 1999; 8 (1): 40–43. doi: 10.1007/BF01616842
108. *Adamson D.L., Webb C.M., Collins P.*: Esterified estrogens combined with methyltestosterone improve emotional well-being in postmenopausal women with chest pain and normal coronary angiograms. Menopause. 2001; 8 (4): 233–238. doi: 10.1097/00042192-200107000-00003
109. *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; 14 (6): 1450–1453. doi: 10.1016/0735-1097 (89)90380-X
110. *Yoshio H., Shimizu M., Kita Y., et al.*: Effects of short-term aminophylline administration on cardiac functional reserve in patients with syndrome X. J Am Coll Cardiol. 1995; 25 (7): 1547–1551. doi: 10.1016/0735-1097 (95)00097-N
111. *Elliott P.M., Krzyzowska-Dickinson K., Calvino R., Hann C., Kaski J.C.*: Effect of oral aminophylline in patients with angina and normal coronary arteriograms (cardiac syndrome X). Heart. 1997; 77 (6): 523–526. doi: 10.1136/hrt.77.6.523
112. *Fukumoto Y., Mohri M., Inokuchi K., et al.*: Anti-ischemic effects of fasudil, a specific Rho-kinase inhibitor, in patients with stable effort angina. J Cardiovasc Pharmacol. 2007; 49 (3): 117–121. doi: 10.1097/FJC.0b013e31802ef532
113. *Mohri M., Shimokawa H., Hirakawa Y., Masumoto A., Takeshita A.*: Rho-kinase inhibition with intracoronary fasudil prevents myocardial ischemia in patients with coronary microvascular spasm. J Am Coll Cardiol. 2003; 41 (1): 15–19. doi: 10.1016/S0735-1097 (02)02632-3
114. *Olgin J.E., Takahashi T., Wilson E., Vereckei A., Steinberg H., Zipes D.P.*: Effects of Thoracic Spinal Cord Stimulation on Cardiac Autonomic Regulation of the Sinus and Atrioventricular Nodes. J Cardiovasc Electrophysiol. 2002; 13: 475–481.
115. *Hautvast R.W.M., Blanksma P.K., DeJongste M.J.L., et al.*: Effect of spinal cord stimulation on myocardial blood flow assessed by positron emission tomography in patients with refractory angina pectoris. Am J Cardiol. 1996; 77 (7): 462–467. doi: 10.1016/S0002-9149 (97)89338-1
116. *Murray S., Carson K.G.S., Ewings P.D., Collins P.D., James M.A.*: Spinal cord stimulation significantly decreases the need for acute hospital admission for chest pain in patients with refractory angina pectoris. Heart. 1999; 82 (1): 89 LP-92. doi: 10.1136/hrt.82.1.89
117. *Sharma U., Ramsey H.K., Tak T.*: The role of enhanced external counter pulsation therapy in clinical practice. Clin Med Res. 2013; 11 (4): 226–232. doi: 10.3121/cmr.2013.1169