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Microvascular Angina: Evolving Diagnosis and Pharmacologic Treatments

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Abstract

Microvascular Angina (MVA), also known as Coronary Microvascular Dysfunction (CMD), is a condition in which structural abnormalities of the coronary artery microvasculature lead to impaired cardiac oxygen delivery and ischemia. There is a large population of patients, especially post-menopausal women, who present with persisting angina, but no angiographic evidence of obstructive coronary artery disease. There is also a sizeable population with persisting angina after successful coronary revascularization procedures. Currently, there are no clinical imaging studies that can display the health of the microvasculature of the myocardium which include the smaller pre-arterioles, arterioles, and capillaries. Studies show that patients with MVA are at high risk for MI, stroke, heart failure, and death. Numerous studies discussed in this paper have enhanced our understanding of MVA and how it can be diagnosed using the measure of Coronary Flow Reserve (CFR). CFR, the current gold standard for diagnosis, and criteria proposed by the Coronary Vasomotor Disorders International Study Group can assist in the diagnosis of coronary microvascular dysfunction. Traditional pharmacological treatment for angina is not effective in most patients with MVA. The current pharmacologic agents under investigation for treatment of MVA are also discussed in this paper.

Introduction

There are 3 to 4 million men and women in the U.S. who endure anginal chest pain despite normal coronary angiography. Many men and women with persistent episodes of chest pain who have undergone cardiac diagnostic testing without any evidence of obstructive CAD are thought to be enduring microvascular coronary dysfunction. [1-4]. Studies show that over 50% of patients with angina referred for nonurgent coronary angiography due to chest pain demonstrate nonobstructive coronary artery disease (ANOCA) [2-4]. Within this population, there is a preponderance of post-menopausal women [5]. There is also a sizeable population with persisting angina after successful coronary revascularization [6].

Nonobstructive coronary artery disease can be due to either coronary artery spasm Corcoronary Microvascular Dysfunction (CMD), also called Microvascular Angina (MVA). The Women's Ischemia Syndrome Evaluation (WISE) study demonstrated that patients with MVA are at higher risk for major adverse cardiac events, including MI, stroke, heart failure with preserved ejection fraction, and death [7-10]. Currently, there are guidelines for diagnosis; however, treatment options are evolving and under investigation.

Etiology and Pathophysiology

The coronary artery microvasculature can be described as the coronary arterioles that branch off from the larger epicardial coronary arteries [11]. Anatomically, the coronary vasculature is classified as large-diameter epicardial coronary arteries (≥500 μm) and smaller arteriolar vessels (≤500 μm) and capillaries. The coronary microcirculation includes pre-arterioles (diameter <500 Am), arterioles (<200 Am), and capillaries, which are below the resolution of current angiographic imaging [12,13]. These small vessels account for 70% of coronary resistance and are major determinants of coronary blood flow regulation [14].

Endothelial dysfunction of the microvasculature is the initial mechanism that occurs in the cascade of events that lead to MVA. The lack of vasodilation results from reduced nitric oxide bioavailability and increased vasoconstrictor responses to Endothelin-1 (ET-1), prostaglandin H2, and thromboxane A2 [15]. These mediators exert their vasoconstrictor effect mainly on the microcirculation and stimulate nociceptors [16]. In the structural remodeling of the coronary microvasculature, walls of the vessels thicken, leaving a narrowed diameter of the lumen, which increases microvascular resistance. Decreased microcirculatory conduction of blood flow leads to impaired oxygen delivery to the subendocardial tissue in MVA [17,18]. Thus, microvascular subendocardial ischemia is termed Ischemia with Non-Obstructive Coronary Artery Disease (INOCA), and for some persons, Myocardial Infarction with Non-Obstructive Coronary Artery disease (MINOCA) [12].

Risk Factors

Remodeling of the microvasculature in MVA occurs as a result of all known cardiovascular risk factors such as smoking, uncontrolled hypertension, hyperlipidemia, poorly controlled diabetes, insulin-resistant states, obstructive atherosclerosis, and aging [19]. It is theorized that an estrogen deficiency may also play a role in MVA, given the high prevalence of chest pain without obstructive CAD in post-menopausal women [20]. Cigarette smoking impairs endothelial-dependent vasodilation in chronic smokers. Uncontrolled hypertension is believed to lead to arteriolar thickening and reduced myocardial perfusion. Hyperlipidemia has been shown to reduce Coronary Flow Reserve (CFR). Reduced coronary flow reserve is strongly associated with an increased risk of all-cause Mortality and Major Adverse Cardiac Events (MACE). Uncontrolled diabetes and chronic hyperglycemia cause arteriolar endothelial injury, which reduces vasodilation [21]. When the heart is challenged by exercise or stress, these pathologic risk factors result in a decreased microvascular vasodilatory capacity, which limits blood and oxygen reserve to the subendocardium, causing angina.

Clinical Presentation

The clinical signs and symptoms of persons with microvascular angina are similar tothose with angiographically-proven CAD. Retrosternal pressure-like chest pain and dyspnea occurs with exertion. It can radiate into the jaw or back. Some persons report that the pain continues after exercise ceases or when they are at rest. These episodes of chest pain may vary in duration and can present as prolonged, oppressive discomfort or stabbing-like pain [22].

Also, compared to patients with obstructive CAD, patients with MVA angina respond less dramatically to the administration of sublingual or oral nitrates [23]. Although the clinical presentation can be similar in men and women with MVA, studies have consistently shown an increased female prevalence. Additionally, women have a higher prevalence of MINOCA-10.5% compared to 3.4% for men. Symptomatic women are generally older than men and are post-menopausal [20,24].

Diagnosis

The diagnosis of MVA cannot be established based on symptoms alone. A complete history, physical examination, resting Electrocardiogram (ECG), stress test, and coronary angiography are usually carried out in these patients. Angiography utilizes intracoronary adenosine and acetylcholine provocation testing to examine coronary artery reactivity. The diagnosis of MVA is considered after coronary angiography has shown no significant epicardial coronary artery disease. In some patients with MVA, transient ECG changes of ST-segment depression occur during anginal pain. However, many patients have no ECG changes during chest pain. On stress ECG, if ST-segment elevation is seen, vasospastic angina is usually diagnosed, not MVA.

The Coronary Vasomotor Disorders International Study (COVADIS) established the following criteria for the diagnosis of microvascular angina [25]:

presence of symptoms suggestive of myocardial ischemia
objective documentation of myocardial ischemia, as assessed by currently available techniques
absence of obstructive CAD (<50% coronary diameter reduction and/or fractional flow reserve (FFR) >0.80)
confirmation of a reduced coronary blood flow reserve and/or inducible microvascular spasm

Assessing Microvascular Function: Coronary Flow Reserve (CFR) The current gold standard for clinically assessing microvascular function is coronary flow reserve (CFR). CFR measurement is recommended by international guidelines as a diagnostic method for the identification of patients with microvascular angina who
could benefit from targeted therapy [26].

Coronary Flow Reserve (CFR) is defined as the ratio between coronary blood flow at maximal coronary dilation versus resting blood flow. It is the capacity of the coronary circulation to respond to a physiological increase in oxygen demand with a corresponding increase in blood flow. CFR assesses coronary circulation in terms of both the epicardial coronary artery territory and the microvascular coronary territory, which includes arterioles and capillaries [27].

When there is no significant epicardial coronary artery disease, CFR shows the degree of resistance to blood flow in the microcirculation. Maximal coronary blood flow should be at least two and a half times the resting blood flow. A key component of both the pathophysiology and diagnosis of MVA is a reduction in CFR. Depending on the methodology used, CFR values below or equal to 2 or 2.5 are indicative of coronary microvascular dysfunction [27].

Functional CFR can be investigated during angiography using intracoronary adenosine and acetylcholine. The latter is considered to be the gold standard for the assessment of endothelial-dependent coronary vasodilatation. Adenosine, a powerful endothelial-independent dilator of coronary microcirculation, is used to assess fractional flow reserve, CFR, and the Index of Microcirculatory Resistance (IMR) in the cardiac catheterization laboratory. CFR can be measured using non-invasive modalities, including transthoracic echocardiography, Positron Emission Tomography (PET), cardiac CT scan, Cardiac Magnetic Resonance (CMR), as well as invasively during angiography [28].

Potential Therapies for MVA

The management of MVA is currently under investigation, with numerous studies examining different medications. There currently are only potential therapies for MVA. Management of MVA begins with lifestyle recommendations in the same manner as obstructive CAD. The recommendations include daily exercise, no smoking, and a diet that is low in fat and sodium, high in fiber, and high in vegetable content. Persons need to control diabetes and blood pressure and treat hyperlipidemia if these exist. With the treatment of hyperlipidemia, statin medications are recommended as they have been shown to alter the progression and even promote the regression of atherosclerosis and improve vascular endothelial function. In hypertensive patients, ACE inhibitors, beta-blockers, and calcium channel antagonists are recommended. Each shows different results in investigations that promote their use in MVA. Antiplatelet agents, aspirin, and P2Y12 inhibitors are also recommended. Many investigators still recommend nitroglycerin, although proven ineffective in many patients with MVA. Currently, many different pharmacologic agents are being used empirically in attempt to enhance microvascular circulation (Table 1).

Pharmacologic Agent	Action	Investigational Study results
ACE inhibitor (quinapril)	Anti-hypertensive, blockade of renin-angiotensin-aldosterone cycling	Pauly, et al. [29] showed that quinapril improved angina symptoms in patients treated for 12 weeks. Cardiac PET imaging showed a 42% improvement in their CFR.
Beta blockers (carvedilol and nebivolol)	Beta adrenergic and some alpha adrenergic blockade	Galderisi, et al. [30] showed that third-generation beta-blockers (e.g. carvedilol and nebivolol), have vasodilating capacity and improve CFR. Microvascular resistance reduced which can be attributed to alpha-adrenergic blockade and/or a nitric oxide-mediated effect.
Calcium antagonist (sublingual nitrendipine)	Exert an arterial vasodilatory effect	Ong, et al. [22] recommends calcium antagonist, sublingual nitrendipine, for those who cannot tolerate beta blockers.
Nitroglycerin (sublingual)	Coronary vasodilation, systemic arterial vasodilation, and venodilation	Sublingual NTG is not effective for all patients with MVA. Wu, et al. [31] and Russo, et al. [32] showed improvement with sublingual nitrates in about 40 percent of patients with MVA.
Ranolazine	Inhibits late sodium current and reduces intracellular calcium levels in cardiac myocytes which improves ventricle relaxation and oxygen consumption	Hasenfuss & Maier [33] recommend ranolazine together with other medicines (eg, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers, nitrates, antiplatelets, or lipid-lowering medicines). Rambarat, et al. [33] showed ranolazine improved CFR.
Nicorandil	An antianginal drug called n-(2-hydroxyethyl) nicotinamide nitrate. It has the effect of nitrates to dilate blood vessels, improve coronary blood flow and reduce the preload and afterload of the heart.	In animal and clinical trials, nicorandil has been shown to improve microvascular perfusion, relieve microvascular spasms, and reduce platelet aggregation. There is a lack of high-quality randomized controlled trials on the clinical effectiveness and safety of nicorandil [34].
Phosphodiesterase type 3 inhibitors (cilostazol) Phosphodiesterase type 5 inhibitor (sildenafil)	Vascular smooth muscle relaxation; vasodilation	Yoo, et al. [35], found in combination with calcium antagonists, cilastazol effective in MVA. Denardo, et al. [36] showed efficacy of sildenafil to increase CFR.
Rho-kinase inhibitors (fasudil)	Rho kinase is an intracellular enzyme for excitation-contraction coupling in smooth muscle; it contributes to Ca ++ -sensitization of smooth muscle.	Intracoronary fasudil is effective not only in patients with epicardial coronary spasms but also in approximately two-thirds of those with MVA [37,38].
Endothelin-1 (ET-1) receptor antagonist (atrasentan)	ET-1 is produced by the endothelium to cause potent vasoconstriction.	Using atrasentran in a randomized clinical trial in patients with MVA, microvascular coronary endothelial function improved after 6 months [39].

Table 1: different pharmacologic agents are being used empirically in attempt to enhance microvascular circulation.

Implications for Primary Care of the Patient with MVA

Evidence gathered over the past 30 years has made it clear that functional and structural mechanisms affecting pre-arterioles, arterioles, and capillaries represent yet another major cause of myocardial ischemia; termed Microvascular Angina (MVA). MVA occurs in the absence of angiographic evidence of obstructive CAD. Chest pain with normal coronary arteries was once considered to be noncardiac in origin with a benign prognosis. Confusion about its pathophysiology resulted in the use of a variety of terms, such as "noncardiac," "atypical," "angiographically negative," and "chest pain of undetermined origin." In the past, clinicians have attributed chest pain without evidence of obstructive CAD to irritable esophagus, anxiety due to stress, and coronary vasospasm (atypical angina) [40]. However, investigations, such as the WISE study and Coronary Vasomotor Disorders International Study, have shown that angina in the absence of obstructive CAD is common and associated with major adverse cardiovascular events such as MI, heart failure, and stroke.

Clinicians are now beginning to recognize that many persons do have persisting angina despite normal angiographic imaging. Also, many persons have persisting angina after coronary reperfusion procedures. These patients may be enduring MVA which is challenging to diagnose.

Investigation of Coronary Flow Reserve (CFR) is key in patients with MVA. There is an evolving availability of tests to investigate CFR and coronary microcirculation. Traditional antianginal drugs are only effective in about half of MVA patients. Several drugs with different mechanisms of action are under scrutiny for symptom control in this patient population. There is evolving evidence for effective pharmacologic treatment.

Key Concepts

Many patients have persistent angina despite no angiographic evidence of obstructive coronary artery disease. There is also a sizeable population with persisting angina after successful coronary revascularization procedures. This is called non-obstructive coronary artery Disease or Microvascular Angina (MVA).
Post-menopausal women make up a large percentage of these patients with MVA.
Currently, there are no clinical imaging studies that can display the health of the microvasculature of the myocardium.
Studies show that patients with MVA are at high risk for MI, stroke, heart failure, and death Coronary Reserve Flow (CFR) is the major method of diagnosis. CFR can be measured using non-invasive modalities, including transthoracic echocardiography, Positron Emission Tomography (PET), cardiac CT scan, Cardiac Magnetic Resonance (CMR), as well as invasively during angiography.
Currently, many different pharmacologic agents are being used empirically in attempt to enhance microvascular
circulation. No one agent has proven more effective than another. Studies of MVA are evolving.

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