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Microvascular Coronary Dysfunction—an Overview

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Abstract

Purpose of Review We will review the available data on the epidemiology, pathophysiology, diagnosis, and management of microvascular coronary dysfunction (MCD).

Recent Findings The study of MCD was pioneered by the Women's Ischemia Syndrome Evaluation (WISE) cohort. New techniques in the diagnosis of this condition, using invasive and noninvasive means, are helping to increase awareness of this condition as well as ways in which to treat it.

Summary Microvascular coronary disease without epicardial involvement has become an increasingly recognized cause of cardiac chest pain, particularly in women. Dysfunction of the microvasculature related to endothelium-dependent and endothelial-independent factors likely results in symptoms and/or evidence of ischemia. Although there is a growing body of research, there is still much about MCD that we do not understand.

Keywords Microvascular disease · Microvascular dysfunction · Women's heart disease

Introduction

In the last several decades, it has become increasingly evident that cardiovascular disease (CVD) is not just a "man's disease" but the leading cause of mortality in both men and women [1]. Population data suggest that approximately 1/3 of Americans have cardiovascular disease and the prevalence of CVD in women and men is at least comparable (54 vs 46% respectively) [2]. A greater emphasis has, therefore, been placed on not only improved community awareness but also on gender-specific cardiovascular research. This focus has led to the observation that women presenting with chest pain are more likely than men to have normal epicardial coronary arteries upon angiography [3, 4]. A subgroup of these women has evidence of ischemia on stress testing and/or very typical angina symptoms, arguing against noncardiac causes of chest pain. Research on this so-called Syndrome X suggests that microvascular dysfunction may be the cause of these chest pain syndromes that disproportionately impact women [5, 6]. In this review, we will discuss the epidemiology, diagnosis, management, and prognosis of microvascular coronary dysfunction (MCD) in the absence of epicardial coronary or myocardial disease.

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Microvasculature: Definitions and Physiology

The coronary vasculature can be divided into three components: the "conductance" or epicardial vessels, the "resistance vessels" or microvasculature, and the veins [7]. The epicardial vessels dilate during systole, increasing coronary blood flow, allowing for diastolic reopening of the intramyocardial vessels (arterioles) [8]. The coronary microvasculature, vessels too small to be seen by routine coronary angiography [9], is almost exclusively responsible for meeting the metabolic demands of the heart via regulation of coronary vascular resistance [7] and adjustments in vascular tone [10]. The microvasculature is comprised of the pre-arterioles and arterioles. The pre-arterioles (100–500 μm in diameter), similar to epicardial vessels, are under endothelial vasomotor control and are responsible for maintaining pressure within a narrow range despite hemodynamic changes [11]. Because of their position outside of the myocardium, they are not under the direct control of myocardial metabolites. The arterioles (< 100 μm in diameter), in contrast, are intramural in position. They directly

respond to metabolites released by the myocardium in response to oxygen demands and work to match myocardial blood flow with this demand [11]. They are largely regulated through endothelial-independent regulation of vascular smooth muscle [12], an important distinction given the arterioles are responsible for the majority of coronary vascular resistance [9].

Pathophysiology of Microvascular Coronary Dysfunction

The exact mechanisms by which MCD in the absence of epicardial disease can cause CVD have not yet been fully elucidated. There are several proposed mechanisms including endothelial dysfunction, smooth muscle dysfunction, and microvascular remodeling [8]. Both the endothelium and smooth muscle play a critical role in microvascular tone, regulating vasodilatation and vasoconstriction. The microvascular endothelium produces and releases nitric oxide (NO) and prostacyclin, major vasodilators, and decreased production, increased degradation, and/or an imbalance favoring the release of vasoconstrictive agents can result in endothelial dysfunction [13]. Although the role of smooth muscle in vasodilatation is not completely clear, it does appear that smooth muscle relaxation results from activation of pathways involving cyclic AMP and cyclic GMP (which are activated by the endothelial NO release) [14]. Given the complexity of these pathways, the causes of smooth muscle dysfunction likely vary by patient.

Studies have suggested that a number of cardiovascular risk factors can lead to MCD. Smoking, for example, releases free radicals that result in endothelial inflammation and oxidative damage. In asymptomatic smokers with no epicardial coronary disease, MCD may be a predictor of future CVD. In a twin study by Rooks et al., coronary flow reserve (CFR), to be discussed later in this review, was significantly lower in smokers than in nonsmokers (2.25 vs 2.75 respectively, $p = 0.03$). In smoking discordant twin pairs, CFR was significantly lower in the twin that smoked versus the nonsmoking twin (2.25 vs 2.67 respectively, $p = 0.03$). Similarly, there is evidence of decreased CFR in patients with hyperlipidemia [15] and some suggestion that initiation of lipid-lowering agents may improve coronary flow [16]. In the case of hypertension, extrinsic compression of the microvasculature, in the setting of hypertrophy, and excessive activation of the renin angiotensin system can lead to MCD [17]. Chronic inflammation in autoimmune disorders such as systemic lupus erythematosus and rheumatoid arthritis is also increasingly being recognized as a risk factor for MCD. In a study of 21 patients with typical chest pain and normal epicardial coronary vessels, elevated high-sensitivity C-reactive protein levels (particularly those greater than 3 mg/l) correlated with decreased CFR [18].

Epidemiology and Clinical Presentation

Given they disproportionately present with chest pain and normal epicardial coronary arteries, much of the research in this realm has focused on women. Approximately 70% of patients with MCD are women [19], although this may also be an underappreciated condition in men. In a study by Murthy et al. of 1218 patients referred for positron emission tomography (PET) stress testing, approximately 51% of men and 54% of women were found to have MCD, suggesting that men may be equally affected by this condition [20]. In this cohort, men were more likely to be smokers while women were more likely to be hypertensive. Women were also more likely to present with symptoms of chest pain and dyspnea. This does suggest that women may be more symptomatic from MCD than their male counterparts, and while this may be a condition that effects both genders, the pathophysiology may very well be different.

The initial Women's Ischemia Syndrome Evaluation (WISE) study of 159 women with typical chest pain and no obstructive coronary disease found that approximately half of these patients had an abnormal CFR [6]. The classic description of MCD is one perimenopausal or post-menopausal woman presenting in her 50s. These women experience recurrent chest pain with exertion or immediately after exertion that lingers for a lengthier period of time than would be expected in epicardial disease [21]. They may also present with atypical features not consistent with classic angina, and the chest pain may or may not be responsive to nitroglycerine [21]. These patients often have risk factors as mentioned above, but in some cases, no clear risk factors can be discerned. In an analysis of 883 women prospectively referred for angiography in the WISE study [22], approximately 67% of those with a positive stress test were found to have non-obstructive coronary arteries. While often deemed to be a "false positive," it is also possible that these stress tests are identifying patients with underlying MCD. It should be added that reproducible chest pain during stress testing or EKG evidence of ischemia in the absence of imaging evidence of ischemia may also suggest possible MCD. In general, it may be difficult to determine which patients should be evaluated for MCD. It is prudent to take a thorough medical history, identify potential risk factors, and assess all findings during stress testing in order to determine the utility of further evaluation.

Diagnosis of Microvascular Disease

Invasive Testing

The classic assessment of MCD during coronary catheterization used the myocardial blush grade. "Blush" describes the degree of opacification of the myocardium after dye injection

into an epicardial vessel as well as the time it takes for the dye to wash out. The myocardial blush grade is on a scale of 0–3, with 3 being both optimal opacification and optimal washout. This is a largely qualitative technique with great interobserver variability. While a suboptimal myocardial blush grade can be seen in MCD alone, this scoring system was largely used to identify the degree of MCD after percutaneous intervention. Currently, the gold standard for the diagnosis of MCD is coronary angiography with coronary vascular function testing. First, significant obstructive epicardial disease is ruled out. Then, both endothelial-dependent and endothelial-independent microvascular function is assessed. Endothelial function is assessed by acetylcholine, which, in normal endothelium, triggers endothelial-dependent vasodilation via the release of NO [23]. Patients should be off all vasoactive medications, such as nitroglycerine, for at least 48 h prior to testing. Intracoronary acetylcholine is injected into the left main coronary artery at escalating doses from 20 to 200 μg. The epicardial vessels are then assessed for vasodilation or, at the least, no vasoconstriction. Pathologic vasoconstriction is defined as > 20% reduction in coronary diameter. In some cases, a coronary Doppler wire is used to record the average peak velocity of blood flow after injection of acetylcholine, which should increase by at least 50%. After assessment with acetylcholine is performed, 200 μg of nitroglycerine is administered to assess the endothelium-independent macrovascular response.

If there is evidence of what appears to be mild to moderate epicardial disease, it is prudent to also measure fractional flow reserve (FFR) in order to objectively show hemodynamically insignificant epicardial coronary disease. A pressure wire is used to measure the pressure distal to the stenosis while the pressure at the tip of the guide catheter is used to measure the pressure proximal to the stenosis. The pressure distal to stenosis is divided by the pressure proximal to the stenosis to determine the FFR, which is clinically normal at > 0.80. Attention is then turned to assessment of myocardial CFR. CFR measures the capacity of the coronary vasculature to dilate and increase flow in response to increased metabolic demands. The widely accepted cutoff for normal CFR is 2 [23]. Both thermodilution and Doppler techniques have been used, but Doppler is more commonly used. Adenosine is most commonly administered to achieve maximum hyperemia, as it has a direct, non-endothelium-dependent effect on the microvasculature and little effect on the epicardial vessels. The average peak velocity via Doppler is measured at baseline as well as after infusion of adenosine. This ratio of the average peak velocity at maximum hyperemia to baseline determines the CFR. It should be noted that CFR can be greatly affected by baseline hemodynamics. The index of microcirculatory resistance (IMR) is thought to be a more specific measure of microvascular function and less influenced by hemodynamics [24]. The pressure in the distal artery is multiplied by the mean transit time at maximal hyperemia, with an IMR greater than

25 being abnormal. By better determining the cause of MCD, endothelial-dependent or non-endothelial-dependent, using these provocative maneuvers, one may be able to tailor drugs that will relieve the patient's symptoms more effectively.

Noninvasive Testing

There are a number of promising noninvasive means by which to identify MCD. Stress echocardiography has been evaluated largely in the research setting. Pulsed-wave Doppler is placed over the left anterior descending (given the greater ease of visualizing this vessel) and the peak diastolic flow velocity or mean diastolic flow velocity is measured [8]. The same is done after induction of maximum hyperemia, provoked by adenosine or dipyridamole. The ratio of coronary flow at maximum hyperemia to coronary flow at rest determines CFR. While this technique is relatively cost-effective and noninvasive and does not require radiation, it is almost exclusively experimental at this time and only reliable in the hands of experienced technicians. As previously mentioned, stress testing is also useful in the evaluation of ischemia, and if the epicardial vessels are found to be normal, it could suggest ischemia driven by MCD.

Advanced imaging with PET, computed tomography (CT), and magnetic resonance imaging (MRI) has also been studied [8]. Cardiac MRI is particularly useful, given the safety of gadolinium outside of end-stage renal disease and the lack of radiation exposure. Perfusion cardiac MRI uses the concept of first-pass kinetics in which gadolinium diffuses into the interstitial space from the microvasculature, leading to a signal intensity proportional to the structural and hemodynamic capabilities of the vasculature [8]. In the normal myocardium, this leads to a homogenous increase in signal activity followed by uniform contrast washout. A delay in signal increase or areas without signal activity may suggest hypoperfusion. A vasodilatory agent such as adenosine is used in conjunction with gadolinium for evaluation of perfusion during stress followed by gadolinium alone for resting images. In one WISE study evaluating this technique, 118 women with suspected MCD underwent perfusion MRI [25]. They found that women with MCD based on invasive testing also had a statistically significant reduction in their myocardial perfusion reserve index (MPRI) as compared to matched controls, suggesting that MRI may be a useful noninvasive tool in the diagnosis of MCD. Other studies have shown a sometimes patchy although often homogenous perfusion abnormality of the subendocardial myocardium that may be suggestive of MCD [26].

Treatment of Microvascular Disease

It should be noted that often, these patients present with a baseline angiogram that has ruled out epicardial coronary

disease, but certainly, this should be the first step. If the clinical picture appears consistent with MCD, it is reasonable to proceed with treatment without invasive or noninvasive vascular function testing. If empiric treatment of symptoms is not effective, then one can consider vascular function testing for further evaluation. Certainly, control of risk factors such as tobacco abuse, hyperlipidemia, hypertension, and uncontrolled diabetes mellitus is important in the treatment of these patients. There is limited data in terms of the best management of MCD, but a summary of potential medications and their utility is outlined below.

Aspirin There is no clear evidence for the benefit of low-dose aspirin in these patients. However, aspirin may decrease microvascular "plugging" in patients with comorbidities associated with atherosclerosis. Certainly, if non-obstructive coronary disease is seen by angiogram or the patient's atherosclerotic cardiovascular disease (ASCVD) risk is greater than 10%, one could consider initiating an aspirin after weighing the risks and benefits.

Statin Statins may improve microvascular function through lipid lowering as well as anti-inflammatory effects [27]. A recent study assessed the CFR of 56 hypertensive patients before and after initiation of rosuvastatin 10 mg daily. They found a statistically significant improvement in CFR after 12 months of therapy (3.16 ± 0.44 to 3.31 ± 0.42, $p < 0.001$) [28]. While this is intriguing, further systematic evaluation of statins in this population is needed. At this time, there is no recommendation for uniform initiation of statins in patients with MCD. As with aspirin, those with an elevated ASCVD risk and/or evidence of atherosclerosis should initiate statin therapy per current prevention guidelines.

Angiotensin-Converting Enzyme Inhibitors Angiotensin-converting enzyme and angiotensin II promote oxidative stress and vasoconstriction. By inhibiting production of these molecules and blocking degradation of bradykinin (which releases NO), angiotensin-converting enzyme inhibitors (ACEIs) increase NO bioavailability and, thereby, endothelial-dependent vasodilation [29, 30]. The release of NO may also have antiproliferative effects in the vascular smooth muscle [30]. A double-blinded, randomized study by the WISE group evaluated the CFR of 61 women with MCD before and after initiation of a 16-week course of quinapril. They found a statistically significant improvement in CFR in the ACEI-treated group versus the placebo group [31].

Calcium Channel Blockers Calcium channel blockers (CCBs) lead to endothelium-dependent relaxation and reduce smooth muscle constriction via reduction of endothelin-1. They also inhibit the effects of platelet-derived growth factor preventing further vascular deposition of platelets. Small studies of both non-dihydropyridines and dihydropyridines have shown mixed results [32, 33]. However, given their mechanism of action, this class of drugs does appear to benefit a group of MCD patients. CCBs are not considered first-line therapy and are often used in conjunction with other agents such as beta blockers.

Beta Blockers These drugs reduce myocardial oxygen demand and increase diastolic perfusion time. In a comparison of nitrates versus CCBs versus beta blockers, atenolol was the only medication found to reduce chest pain episodes in a small group of patients with MCD [33]. Based on this, some consider beta blockers as first-line agents in these patients. Nebivolol is a particularly intriguing drug as it is a highly selective beta-1 agonist and also stimulates endothelial release of NO. A small study of 10 patients suggested it may increase CFR as compared to controls [34].

Nitrates These medications lead to smooth muscle relaxation. Their benefit varies and some patients may have paradoxical worsening of chest pain. However, if chest pain is responsive to nitrates, a long-acting nitroglycerine may be helpful in preventing further episodes.

Other Drugs Ranolazine, an inhibitor of late sodium currents, improved physical functioning, angina, and quality of life in a small pilot study of women with myocardial ischemia and no evidence of epicardial disease. There was also a trend towards increased MPRI by cardiac MRI [35]. There has also been evaluation of hormone therapy, spinal cord stimulation, and L-arginine that are beyond the scope of this review. There is some suggestion that a subset of patients may have abnormal nociception, without clear evidence of MCD, which could potentially be treated with tricyclic antidepressants such as amitriptyline.

Prognosis and Conclusions

Although historically MCD without obstructive epicardial disease was considered a benign condition, there is increasing suggestion that MCD may predict future cardiovascular risk [27, 36, 37]. In a study of 157 patients with mild epicardial coronary artery disease, patients with severe endothelial dysfunction, based on their response to invasive assessment with acetylcholine, had statistically significantly greater cardiovascular events as compared to those with normal endothelial function or mild endothelial dysfunction [38]. In a study of 11,223 patients with stable angina pectoris and no evidence of obstructive epicardial disease, when compared to a cohort of control patients, these patients had an increased risk of major adverse cardiovascular events (hazard ratio of 1.52, confidence interval 1.27–1.83) [36]. In the WISE study, women

with a low CFR had an increased risk of major adverse cardiovascular outcomes as compared to those who had a normal CFR (hazard ratio 1.16, 95% confidence interval 1.04 to 1.30; $p = 0.009$) [39]. While one must be cautious in the way these data are presented to patients with MCD, these are important findings that require further exploration. We must continue to grow the body of research evaluating the etiology, diagnosis, and treatment of microvascular disease. Given that it appears to disproportionately impact females, it is also important to assess how sex biology may play a role in this condition.

Compliance with Ethical Standards

Conflict of Interest   Sahar Naderi declares no conflict of interest.

Human and Animal Rights and Informed Consent   This article does not contain any studies with human or animal subjects performed by the author.

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