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Coronary Microvascular Dysfunction, Microvascular Angina, and Management

Adrián I. Löffler, MD^a and Jamieson Bourque, MD, MHS^{*}

Adrián I. Löffler: al2ys@hscmail.mcc.virginia.edu; Jamieson Bourque: jbourque@virginia.edu

^aUniversity of Virginia Health System, Division of Cardiovascular Medicine, PO Box 800662, Charlottesville, VA, 22908, USA. Phone: 434.924.9001

^{*}University of Virginia Health System, Division of Cardiovascular Medicine and Radiology, Charlottesville, VA, 22908, USA. Phone: 434.243.9337

Abstract

Recent analyses have found that coronary microvascular dysfunction (CMD) portends a poor prognosis in patients with and without obstructive epicardial coronary artery disease (CAD). Chest pain in the absence of epicardial CAD is a common entity. Angina caused by CMD, microvascular angina (MVA), is often indistinguishable from that caused by obstructive epicardial CAD. The recent emergence of noninvasive techniques that can identify CMD, such as stress positron-emission tomography (PET) and cardiovascular magnetic resonance (CMR) myocardial perfusion imaging, allow improved identification of MVA. Using these tools, higher risk patients with MVA can be differentiated from those at lower risk in the heterogeneous population historically labeled as cardiac syndrome X. Likewise, MVA can be diagnosed in those with obstructive epicardial CAD who have persistent angina despite successful revascularization. There is little evidence to support current treatment strategies for MVA and current literature has not clearly defined CMD or whether therapy improves prognosis.

Keywords

coronary microvascular dysfunction; microvascular angina; therapeutics; prognosis

Introduction

When addressing angina pectoris, the majority of attention and research has focused on pathology of the epicardial coronary arteries. Although the importance of the coronary microcirculation in maintaining appropriate myocardial perfusion has been recognized for several decades, the substantial morbidity of coronary microvascular dysfunction (CMD) has

Address for correspondence: Jamieson M. Bourque, M.D., M.H.S., Assistant Professor of Medicine and Radiology, Cardiovascular Division, Department of Medicine, University of Virginia Health System, Box 800158, 1215 Lee Street, Charlottesville, VA 22908, Office: (434) 243-9337, Fax: (434) 982-1998, jbourque@virginia.edu.

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not been appreciated until recently. Traditionally, the assessment of risk severity in coronary artery disease (CAD) has focused on the presence and extent of epicardial coronary stenosis, the magnitude of inducible myocardial ischemia, and the degree of left ventricular dysfunction.[1] Recently, several studies have shown that CMD among patients with and without obstructive CAD denotes a poor prognosis with higher rates of MACE [1–7]. CMD can occur in four separate clinical settings: 1) in the absence of obstructive epicardial CAD and structural heart disease; 2) in the presence of structural heart disease; 3) in the presence of obstructive epicardial CAD; and 4) secondary to iatrogenic causes [8].

Chest pain without obstructive epicardial CAD is a common entity, occurring in up to 30% of patients undergoing invasive coronary angiography for chest pain. Patients who present with angina pectoris in the absence of apparent cardiac or systemic disease have traditionally been characterized as having cardiac syndrome X. This syndrome is heterogeneous, and different etiologies for cardiac syndrome X likely have different prognoses and optimal treatments. One potential pathophysiologic mechanism for symptoms in these patients is CMD, which results in microvascular angina (MVA) [9, 10]. Over the last two decades, noninvasive techniques for assessing CMD have evolved. Despite this, there is little data on what therapies are effective to treat the symptoms of MVA and alter the prognostic impact of CMD [11]. Furthermore, there is no standardized definition for CMD. In this review we will summarize the current literature on the definition and diagnosis of CMD, the prognosis of patients with CMD with and without concomitant CAD, and the treatment of CMD and MVA.

Clinical Presentation and Risk Factors of MVA and CMD

The clinical presentation of MVA is similar to chest pain with obstructive epicardial CAD. MVA is highly prevalent, encompassing an estimated 50% of patients with angina without obstructive epicardial CAD [11–14]. MVA should be suspected in patients presenting with typical chest pain who are found to have no obstructive epicardial CAD on coronary angiography, especially in those patients with stress testing indicative of myocardial ischemia. Patients with MVA have also been shown to have poor or slow response to short acting nitrates [9–15]. However, MVA is just one of several causes of chest pain in patients without obstructive epicardial CAD. The pathophysiology of chest pain without obstructive epicardial CAD can be divided into three groups: 1) non-cardiac; 2) cardiac non-ischemic; and 3) cardiac ischemic. There are multiple causes of non-cardiac chest pain, including gastrointestinal, pulmonary, musculoskeletal, and psychiatric. Cardiac non-ischemic pain can stem from pericardial pathologies and/or inappropriate pain perception. Cardiac ischemic etiologies include MVA, coronary spasm, and myocardial bridging [11]. Cardiac syndrome X is a clinical entity which most often pertains to women with chest pain, no obstructive epicardial CAD, and ST-depression on stress electrocardiography, although there is no standard definition. Cardiac syndrome X is a heterogeneous disorder with multiple pathophysiologic etiologies for chest pain within the non-cardiac and cardiac non-ischemic and ischemic groups. In contrast, MVA has an identifiable cardiac ischemic mechanism.

Patients with CMD have similar risk factors as those with epicardial CAD. Kaufmann et al. demonstrated that the noxious prooxidant effects of smoking extend beyond the epicardial

arteries to the coronary microcirculation [16]. Hypercholesterolemia has been shown to cause CMD in patients with normal coronary arteries [17, 18]. Hypertensive patients can develop CMD and MVA [19, 20]. Several studies have shown that patients with diabetes mellitus (DM) develop CMD, which may be an early marker for atherosclerosis and epicardial CAD in this population [7, 21–23]. Inflammation, such as in patients with systemic lupus erythematosus and rheumatoid arthritis has been associated with CMD [24].

CMD can be present in patients with and without obstructive epicardial CAD. Patients with CMD and obstructive epicardial CAD can present with angina that is prolonged or poorly responsive to sublingual nitrates. Concurrent CMD and MVA can also be suspected in patients with angina that appears to be more severe than expected by the degree of epicardial coronary stenosis [25]. Angina that persists despite successful revascularization may also be due to CMD. This is important to recognize because failing to do so can result in unnecessary revascularization procedures. The relative contribution of CMD and obstructive epicardial coronary stenosis to angina symptoms cannot currently be accurately discerned, and thus treatments must target both of these pathophysiologic mechanisms with risk factor reduction and anti-anginal treatment.

Diagnosis of MVA

Unlike epicardial coronary arteries, the coronary microcirculation cannot be directly imaged by coronary angiography [8]. Small coronary arteries may be visualized by endomyocardial biopsy, [26] but this is highly invasive and doesn't allow for functional assessment of the microcirculation. Several measurements relying on the quantification of blood flow through the coronary circulation have been used to describe function of the coronary microvasculature. Coronary flow reserve (CFR) is defined as the magnitude of increase in coronary flow that can be achieved from the resting state to maximal coronary vasodilation [8]. Since resistance of flow through the coronary circulation is primarily determined by the microvasculature, CFR can be used as a surrogate of microvascular function. CFR using invasive testing and MPR using positron-emission tomography (PET) or cardiovascular magnetic resonance imaging (CMR) are the current gold standard for clinically assessing microvascular function. The cut-off to use for CFR to define CMD is currently unclear especially since it has been shown that CFR among healthy individuals can vary according to age and sex [27]. An early study using PET suggested a threshold of 2.5 as the cut-off for "normal [12]." However, several contemporary prognostic studies among patients with and without CAD have found CFR to have prognostic benefit at thresholds of 1.5 to 2.6 (Figure 1) [1–6, 8].

Several invasive techniques to assess CFR exist, including thermodilution techniques and intracoronary Doppler ultrasonography [11]. Both of these techniques measure flow through one epicardial artery, thus interrogating only one coronary distribution. The development of non-invasive techniques has eliminated the need for invasive flow estimation.

Measurement of myocardial blood flow (MBF) noninvasively by PET [27] and CMR has allowed for noninvasive quantification of microvascular function with high precision [8]. PET perfusion imaging accurately quantifies MBF due to the linear relationship between

radioisotope signal intensity and MBF and has become the gold standard of coronary microvascular evaluation [11, 28, 29]. A disadvantage of PET MBF quantification is the short half-lives of the position emitters used, which require production at an onsite cyclotron with radiochemistry facilities or an expensive renewable generator. The risk from radiation should also be considered, although the effective dose received is minimal [27].

Alternatively, CMR can assess myocardial perfusion based on changes in the myocardial signal intensity of gadolinium. Quantitative perfusion reserve assessment is 83% and 77% accurate for the detection of coronary artery stenoses >50% and >70%, respectively [30]. CMR has high spatial resolution, wide scanner availability, and lacks ionizing radiation [11, 31]. However, it is limited by claustrophobia, body size too large for the machine bore, metallic hardware contraindication, and the risk of nephrogenic systemic fibrosis with gadolinium administration in patients with reduced GFR. Several studies have compared CMR to PET for perfusion quantification. CMR MPR values may be lower compared with PET, 2.5 ± 1.0 vs 4.3 ± 1.8 in one study [32]. However, in patients with known or suspected CAD, the diagnostic accuracy of MPR was similar, with an MPR by PET 1.44 predicting significant CAD with 82% sensitivity and 87% specificity, and an MPR by CMR 1.45 predicting significant CAD with 82% sensitivity and 81% specificity [31].

Transthoracic Doppler echocardiography has also been studied in CMD but is not as robust. This technique measures coronary blood flow velocity, an indirect measurement of coronary blood flow. This technique has only been shown to be reliable when assessing blood flow in the left anterior descending artery [33, 34] in patients with good echocardiographic windows. It is also highly operator dependent. Myocardial contrast echocardiography has also displayed excessive variability [11, 35].

Coronary Flow Reserve (CFR) and Prognosis

Several studies have assessed prognosis in CMD among patients with obstructive epicardial CAD. Among patients with epicardial CAD who underwent PCI, an intracoronary Doppler-derived CFR <2.5 after angioplasty predicted recurrence of angina or ischemia within one month after PCI [3]. Fukushima et al. demonstrated that patients with CAD and a global CFR < 2.11 were at higher risk of a composite of cardiac death, MI, invasive angiography, or hospitalization for heart failure [5]. Murthy et al. demonstrated a 16-fold increased risk of cardiac death in patients with suspected CAD and CFR <1.5 compared to patients with a CFR > 2 [1]. A recently published study assessing patients referred for coronary angiography after stress PET showed an association between CFR and outcomes independent of angiographic disease score [6]. In this study, a CFR < 1.6 predicted benefit from revascularization. Lower CFR was associated with increased morbidity independent of angiographic scores, including admissions for HF.

Similar ranges in CFR have been seen in studies assessing patients without obstructive epicardial CAD. Pepine et al. demonstrated an increase in the composite outcome including death, nonfatal MI, nonfatal stroke, or hospitalization for heart failure in women without obstructive CAD but with a CFR <2.32 [2]. Likewise, Suwaidi et al. demonstrated an increase in cardiac events (MI, percutaneous revascularizations, CABG, and or/cardiac death in patients with non-obstructive CAD and a mean CFR of 2.6 measured by intracoronary

Doppler [4]. Diabetic patients without known CAD who have an impaired CFR have a risk of cardiac death comparable to and possibly higher than nondiabetic patients with known CAD [7]. It has been suggested that impaired CFR may be a more powerful biomarker for diffuse atherosclerosis than diabetes mellitus alone [6].

Figure 1 illustrates the multiple studies examining prognosis in CMD. Given that the literature doesn't clearly define an optimal cut point for the diagnosis of pathologic CMD we propose the following 3-tiered characterization of the likelihood of CMD: <1.5 definite CMD, 1.5–2.6 borderline CMD, and >2.6 no CMD.

Therapies for Microvascular Angina

A recent systematic review by Marinescu et al. assessed the literature on treating MVA and the underlying CMD [11]. Studies were included in the review if they met the following inclusion criteria: 1) human subjects; 2) evidence of CMD defined by CFR or MPR <2.5 using PET, CMR, invasive intracoronary Doppler, or invasive intracoronary thermodilution; and 3) angina or an anginal equivalent. Studies that included patients with epicardial CAD with a stenosis $\geq 50\%$, no evaluation of CAD, or known structural heart disease or heart failure were excluded. CMD therapy in patients with dilated cardiomyopathy, hypertrophic cardiomyopathy, and Takotsubo cardiomyopathy has also been studied but was beyond the scope of this review. Strict inclusion criteria were only met in 8 papers evaluating 84 patients, highlighting the limited evidence available to support current treatment strategies for MVA and CMD. Table 1 highlights these findings.

Nitric oxide modulators, angiotensin-converting enzyme (ACE) inhibitors, estrogens, and transcutaneous electrical nerve stimulation (TENS) were the only drug classes/treatment modalities that met strict inclusion criteria and demonstrated benefits in their respective endpoints. We will briefly review the potential mechanism for each class and the studies that showed benefit. Guanylate cyclase activation by nitric oxide leads to increased cyclic guanosine monophosphate (cGMP). Likewise, PDE-5 inhibitors, such as sildenafil, inhibit breakdown of cGMP. The net effect is smooth muscle relaxation. A small study with sildenafil showed improvement in CFR but did not assess symptoms [36]. A study using a one time L-arginine infusion did not show an improvement in MPR [37]. Angiotensin II is a potent coronary vasoconstrictor. It has been proposed that ACE inhibitors may directly modulate coronary microvascular tone [11]. One small placebo-controlled trial involving quinapril showed improvement in angina and CFR [38]. Chest pain in the absence of obstructive epicardial CAD has high prevalence in post-menopausal women. Thus it has been theorized that an estrogen deficiency may play a role on CMD [11]. One small study using norethindrone/ethinyl estradiol showed an improvement in anginal symptoms [39]. Spinal stimulation is thought to modulate pain-related nerve signals and increase myocardial blood flow through effects on sympathetic tone [11]. A small study assessing TENS in MVA showed improvement in myocardial perfusion reserve and angina [40].

The following drug classes met inclusion criteria and but did not show improvements in their respective endpoints: alpha-blockers, statins, and calcium channel blockers. Alpha-blockers are thought to decrease microvascular tone by decreasing sympathetic activity [11], but a

small study using doxazosin did not show any improvement in symptoms [41]. Statins have both anti-inflammatory and antiatherosclerotic effects that could theoretically improve CMD, but a small study of pravastatin did not show a statistically significant improvement in CFR and did not assess symptoms [42]. Calcium-channel blockers are potent vasodilators and thus may decrease microvascular tone. Only one small study using intravenous diltiazem met strict inclusion criteria and failed to show an improvement in CFR [43].

Several of the classes of medications most typically used for angina pectoris in known obstructive CAD lack any data in MVA and CMD, including beta-blockers, anti-anginals, and nitrates. Beta-blockers treat ischemia by reducing myocardial oxygen demand and increasing diastolic perfusion time. Although well studied in obstructive epicardial CAD and in CMD in patients with structural heart disease, there is no currently published study that met our inclusion criteria in patients with MVA. Anti-anginals such as ranolazine are commonly used for refractory angina pectoris, but no study met strict inclusion criteria for MVA. Nitrates increase smooth muscle relaxation and cause arterial vasodilation. These are also commonly used in angina pectoris but have not been well studied in MVA [11].

As illustrated by Marinescu et al. there is little evidence to support current treatment strategies for MVA and CMD [11], and yet most clinicians treat MVA with traditional antianginal therapy. There are several limitations to the current studies assessing therapeutics in microvascular angina. First, they have typically had small sample sizes and short-term follow-up periods. Second, there is not a clearly defined definition of CMD based on CFR cut-offs. Finally, no studies have assessed whether improving CMD leads to an improved prognostic benefit, although it's well known that impaired CFR in itself is a poor prognostic indicator.

Conclusions

This review summarized the current literature on the definition and diagnosis of CMD, the prognosis of patients with CMD with and without concomitant CAD, and the treatment of CMD and MVA. CMD and MVA are highly prevalent and clinicians need to be aware of their clinical implication. Noninvasive techniques such as CMR and PET have emerged that can accurately assess coronary microvascular function. However, a standardized definition for CMD has not yet been established. Patients with CMD with and without epicardial CAD have been shown to have a poor prognosis including an increase in cardiac death, nonfatal MI, and hospitalizations. Diabetics with CMD and without known CAD have been shown to have a similar prognosis to patients with known obstructive epicardial CAD. Ideal treatment for CMD is unknown as there is little evidence to support current therapies for MVA. Future research needs to focus on developing a universal definition for diagnosing CMD using validated techniques, and on assessing effective therapies that improve angina relief and prognosis among patients with CMD.

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Figure 1.

This figure illustrates the coronary flow reserve (CFR) cutoffs that have been used in studies showing a worse prognosis among patients with coronary microvascular dysfunction (CMD) with (red font) and without (black font) obstructive coronary artery disease (CAD). A proposed definition of CMD is illustrated that shows ranges of CFR that represent definite CMD, possible CMD, and the absence of CMD.

Table 1

Therapies studied in microvascular angina.

Treatment	Patients (n)	Treatment Duration	Mode of Assessing CFR or MPR	Findings	Authors
Quinapril	13	4 months	IC Doppler	Improvement in angina and CFR	Pauly et al. 2011 [38]
Norethindrone/ethinyl estradiol	18	12 weeks	IC Doppler	Improvement in angina	Bailey Merz et al. 2010 [39]
L-Arginine infusion	12	one time infusion	PET Scan	No improvement in MPR	Böttcher et al 1999 [37]
Sildenafil	12	one time administration	IC Doppler	Improvement in CFR	Denardo et al. 2011 [36]
TENS	8	4 weeks	PET Scan	Improvement in angina and MPR	Jessurun et al. 2003 [40]
Pravastatin	6	6 months	IC Doppler	No improvement in CFR	Houghton et al. 2000 [42]
Diltiazem infusion	5	one time infusion	Thermodilution	No improvement in CFR	Sutsch et al. 1995 [43]
Doxazosin	10	10 weeks	Thermodilution	No improvement in symptoms	Bøtker et al. 1998 [41]

Table is modified from the systematic review: Marinescu et al. [11]. CFR = coronary flow reserve, MPR = myocardial perfusion reserve, PET = positron emission tomography, TENS = transcutaneous electrical nerve stimulation