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Coronary Microvascular Dysfunction, Microvascular Angina, and Treatment Strategies

Mark A. Marinescu, MD,* Adrián I. Löffler, MD,* Michelle Ouellette, MD,* Lavone Smith, MD,* Christopher M. Kramer, MD,*† Jamieson M. Bourque, MD, MHS*†

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From the *Department of Medicine, Cardiovascular Imaging Center, University of Virginia Health System, Charlottesville, Virginia; and the †Department of Radiology and Medical Imaging, Cardiovascular Imaging Center, University of Virginia Health System, Charlottesville, Virginia. Dr. Kramer has received research support from Siemens Healthcare. Dr. Bourque has received research support from Astellas Pharmaceuticals. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABSTRACT

Angina without coronary artery disease (CAD) has substantial morbidity and is present in 10% to 30% of patients undergoing angiography. Coronary microvascular dysfunction (CMD) is present in 50% to 65% of these patients. The optimal treatment of this cohort is undefined. We performed a systematic review to evaluate treatment strategies for objectively-defined CMD in the absence of CAD. We included studies assessing therapy in human subjects with angina and coronary flow reserve or myocardial perfusion reserve <2.5 by positron emission tomography, cardiac magnetic resonance imaging, dilution methods, or intracoronary Doppler in the absence of coronary artery stenosis ≥50% or structural heart disease. Only 8 papers met the strict inclusion criteria. The papers were heterogeneous, using different treatments, endpoints, and definitions of CMD. The small sample sizes severely limit the power of these studies, with an average of 11 patients per analysis. Studies evaluating sildenafil, quinapril, estrogen, and transcutaneous electrical nerve stimulation application demonstrated benefits in their respective endpoints. No benefit was found with L-arginine, doxazosin, pravastatin, and diltiazem. Our systematic review highlights that there is little data to support therapies for CMD. We assess the data meeting rigorous inclusion criteria and review the related but excluded published data. We additionally describe the next steps needed to address this research gap, including a standardized definition of CMD, routine assessment of CMD in studies of chest pain without obstructive CAD, and specific therapy assessment in the population with confirmed CMD. (J Am Coll Cardiol Img 2015;8:210–20) © 2015 by the American College of Cardiology Foundation.

Patients with chest pain without obstructive coronary artery disease (CAD) have been a diagnostic and therapeutic challenge and have contributed to significant economic, social, and health care costs (1,2). At least 10% to 30% of patients presenting with angina have no significant CAD on invasive coronary angiography (3,4). As many as 50% to 65% of these patients with chest pain without obstructive CAD are believed to have coronary microvascular dysfunction (CMD), also known as microvascular angina (5–8). CMD is typically defined as impaired vasodilation of arterioles, leading to an inadequate increase in blood flow from rest to stress.

Patients believed to have CMD have a poor prognosis, with higher rates of hospitalization and increased rates of adverse cardiovascular events, including sudden cardiac death, myocardial infarction, congestive heart failure, and coronary revascularization (2,8–11).

Historically, the only practical methods available for the assessment of CMD have been invasive, such as intracoronary (IC) Doppler flow wire or thermodilution. This has likely impaired the objective evaluation of CMD in patients presenting with chest pain without obstructive CAD. Thus, the treatment of CMD has often been studied within imprecise clinical entities such as cardiac syndrome X (12). Moreover, a lack of consensus on diagnostic criteria and nomenclature for CMD has further obscured the evidence that sought to objectively define microvascular angina as a distinct clinical entity.

Given these challenges, it is unclear to what extent effective therapies have been identified in patients with CMD. Therefore, we performed a systematic review of the published data to evaluate treatment strategies for CMD using a rigorous definition with contemporary and accurate methods of microvascular assessment. We found little data that met these criteria. Accordingly, we analyze the challenges in studying therapies for CMD, present the results of our systematic review, discuss the excluded but related published data, and propose future research directions for this important field.

CURRENT CHALLENGES IN CMD TREATMENT RESEARCH

CMD VERSUS OTHER CAUSES OF CHEST PAIN WITHOUT OBSTRUCTIVE CAD. There are multiple diagnoses that may cause chest pain without obstructive CAD. These diagnoses include microvascular angina, gastroesophageal reflux disease, musculoskeletal chest pain, cardiac syndrome X, cardiac syndrome Y (slow coronary flow), coronary

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CBF = coronary blood flow

CFR = coronary flow reserve

CMD = coronary microvascular dysfunction

CMR = cardiac magnetic resonance imaging

EECP = enhanced external counterpulsation

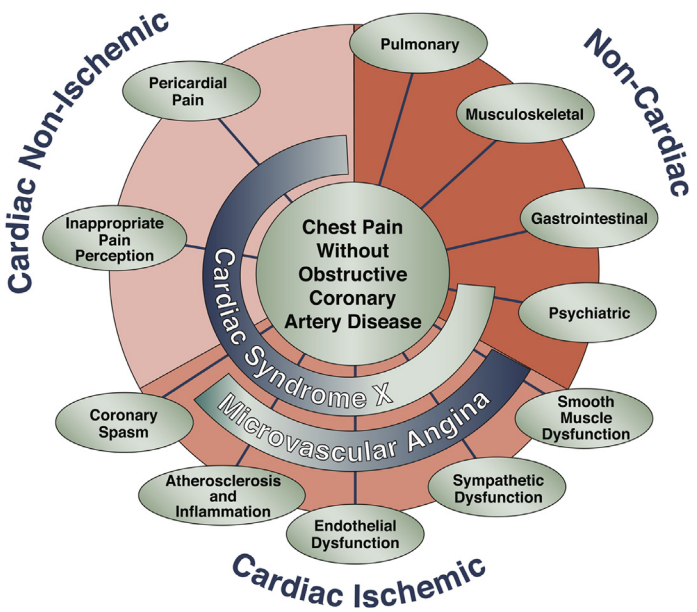
MPR = myocardial perfusion reserve

PET = positron emission tomography

spasm, and no reflow phenomena, among others. These entities derive from multiple different pathophysiological processes. These various pathophysiological causes can be described as causing noncardiac pain, cardiac ischemic pain, and cardiac nonischemic pain (13). Among the causes of cardiac ischemic chest pain in patients without obstructive CAD, CMD is likely common. However, the causes of CMD can be heterogeneous, and their relative contributions to pathologic microvascular angina are poorly understood. Among the leading contenders are endothelial and smooth muscle dysfunction, inappropriate sympathetic tone, and microvascular atherosclerosis and inflammation (14) (**Figure 1**).

Cardiac syndrome X is a well-known clinical entity that is often used as an inclusion criterion in treatment studies of patients with chest pain without CAD. Cardiac syndrome X most often pertains to women with angina, normal coronary arteries, and often evidence of ischemia, such as abnormal electrocardiographic findings or a positive nuclear stress test; however, there is no standard definition for this entity (15). There are numerous pathophysiological causes for chest pain in patients with cardiac syndrome X that likely range from noncardiac to CMD (16,17). Alternatively, microvascular angina is an identifiable pathophysiological mechanism and should be treated as a unique clinical entity (18,19) (**Figure 1**).

FIGURE 1 Etiologies of Chest Pain Without Obstructive CAD



The varying pathophysiologic mechanisms of chest pain without obstructive coronary artery disease (CAD) are grouped into 3 broad categories: noncardiac; cardiac ischemic; and cardiac nonischemic. The contribution of multiple potential pathophysiologies to cardiac syndrome X is highlighted. Microvascular angina overlaps partially with cardiac syndrome X as shown, but it has a narrower pathophysiological basis that is cardiac ischemic in nature.

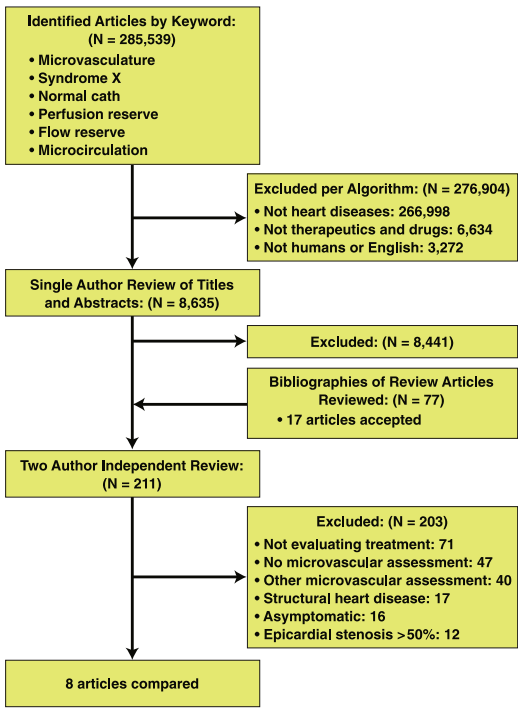
CMD DIAGNOSTIC CRITERIA. There has been significant variation in the diagnostic criteria used to define CMD. The current gold standards for clinically assessing microvascular function have been coronary flow reserve (CFR) using invasive testing and myocardial perfusion reserve (MPR) using positron emission tomography (PET) or cardiac magnetic resonance imaging (CMR) analysis. These values have gained acceptance in part due to the applicability of CFR or MPR across disparate diagnostic techniques (20).

Even when CFR or MPR has been used as the primary diagnostic criterion for CMD, the threshold for defining dysfunction has differed between studies. The current published data suggests that CFR and MPR are continuous variables, and thus, any cutoff used will have varying specificities and sensitivities. Several important prognostic studies have used thresholds of 1.5 to 2.3 to define cutoff values based on prognostic data (2,8). However, many treatment studies have included subjects with CFR or MPR values >3 in their analysis. This has likely resulted in a study population with disparate pathophysiologic mechanisms that may respond differently to treatment modalities.

In our systematic review, we have opted to maximize the sensitivity of our study by using the most liberalized cutoff for which there is supportive prognostic data among different diagnostic techniques. A CFR cutoff of <2.5 had been proposed more than 20 years ago in patients undergoing PET assessment of the microvasculature (6). Since then, it has been used in various other prognostic studies in both patients with and without CAD (21,22).

TECHNIQUES FOR CMD ASSESSMENT. Multiple techniques have been used to assess microvascular function. We considered PET, CMR, IC Doppler flow wire, and various dilution techniques as validated methods for inclusion. Dilution techniques use temperature gradient between the coronary arteries and the coronary sinus to estimate blood flow (23). Doppler tipped wires measure intracoronary blood velocity and arterial cross-sectional area to give an estimate of flow. Although these methods have proven to be safe and effective (24), the advent of

FIGURE 2 Study Design Flow Diagram



The search strategy for our systematic review is detailed. From the 285,399 subjects identified in an initial keyword search, only 8 papers met our strict inclusion criteria. The number of papers excluded and their reasons for exclusion are detailed.

noninvasive techniques such as PET and CMR increase the feasibility of diagnosing CMD while removing the risk associated with catheter based techniques.

PET perfusion imaging has become the gold standard of evaluation due to the linear relationship between myocardial blood flow (MBF) and radioisotope signal intensity, allowing highly accurate MBF quantification (25,26). The most commonly used tracers are $^{13}NH_3$, ^{82}Rb, and ^{15}O. MPR determination by these tracers can vary significantly based on characteristics such as first-pass extraction fraction, positron range, and half-life. Even when using the same tracer, the choice of methods for input function and myocardial extraction estimation can significantly affect the MPR value obtained for a patient (27).

CMR offers potential advantages over PET, such as superior temporal and spatial resolution, lack of ionizing radiation, and wider scanner availability. Semiquantitative upslope analysis was initially used, but it underestimates MPR due to differences in arterial contrast distribution, extracellular exchange, and incomplete and varying first-pass extraction (28). However, robust fully-quantitative tracer kinetic models using Fermi-deconvolution have been developed and validated (29-32). Lengthy offline post-processing and other technical issues have limited the application of CMR for CMD assessment to a few experienced centers (33,34). Multiple analyses using a variety of quantification methods have shown good

TABLE 1 Accepted Studies and Results

Treatment	Patients (n)	Mean CFR or MPR Baseline	Mean CFR or MPR With Therapy	Treatment Duration	Mode of Assessing CFR or MPR	Findings	First Author, Year (Ref. #)
ACE inhibitors							
Quinapril	13	2.2 ± 0.3	2.7 ± 0.5	4 months	IC Doppler	Improvement in angina and CFR	Pauly et al., 2011 (41)
Statins							
Pravastatin	6	0.97	N/A	6 months	IC Doppler	No improvement in CFR	Houghton et al., 2000 (49)
Nitric oxide inhibitors							
L-arginine infusion	12	2.0 ± 0.5	N/A	1-time infusion	PET scan	No improvement in MPR	Bøttcher et al., 1999 (56)
Sildenafil	12	2.1 ± 0.2	2.7 ± 0.6	1-time administration	IC Doppler	Improvement in CFR	Denardo et al., 2011 (55)
Calcium-channel blockers							
Diltiazem infusion	5	1.2 ± 0.1	1.3 ± 0.2	1-time infusion	Thermodilution	No improvement in CFR	Sutsch et al., 1995 (46)
Estrogens							
Norethindrone/ethinyl estradiol	18	<2.25	N/A	12 weeks	IC Doppler	Improvement in angina	Bairey Merz et al., 2010 (62)
Alpha-blockers							
Doxazosin	10	1.84 ± 0.55	NA	10 weeks	Thermodilution	No improvement in symptoms	Bøtker et al., 1998 (60)
Other							
TENS	8	1.59 ± 0.15	1.90 ± 0.1	4 weeks	PET scan	Improvement in angina and MPR	Jessurun et al., 2003 (64)

Review of the different studies that have met our strict inclusion criteria for coronary microvascular dysfunction in patients with angina and no obstructive epicardial coronary artery disease.
CFR = coronary flow reserve; IC = intracoronary; MPR = myocardial perfusion reserve; PET = positron emission tomography; TENS = transcutaneous electrical nerve stimulation.

TABLE 2 Studies Not Meeting Inclusion Criteria but With Assessments of Microvascular Function

Treatment	Baseline CFR <2.5	No CAD ≥50% Stenosis	Mode of Assessing CFR or MPR	Patients (n)	Findings	First Author, Year (Ref. #)
Renin/angiotensin/aldosterone inhibitors						
Eplerenone 25 mg	No	Yes	IC Doppler	25	Angina ↔, CFR ↔	Bavry et al., 2014 (44)
Candesartan 4–8 mg	NA	No	IC Doppler	14	CFR ↑	Iino et al., 2012 (74)
Enalapril 5 mg 2× daily	No	Yes	IC Doppler	10	Angina ↑, CFR ↑	Chen et al., 2002 (75)
Enalapril 10–20 mg/day	No	Yes	Argon dilution	15	Symptoms ↑, CFR ↑	Motz et al., 1996 (43)
Enalapril 5 mg 2× daily	No	Yes	PET	10	Exercise capacity ↑	Kaski et al., 1994 (42)
Statins						
Fluvastatin 40 mg	Yes	Yes	TTDE	23	Angina ↑, CFR ↑	Zhang et al., 2014 (50)
Atorvastatin 80 mg	No	No	IC Doppler	20	CFR ↔	Eshtehardi et al., 2012 (51)
Atorvastatin 20 mg	Yes	Yes	TTDE	20	CFR ↑	Caliskan et al., 2007 (52)
Nitric oxide modulators						
L-arginine 1-time infusion	No	Yes	IC Doppler	11	CBF ↓	Gellman et al., 2004 (58)
Tetrahydrobiopterin 1-time infusion	No	No	IC Doppler	23	CBF ↑	Setoguchi et al., 2001 (76)
L-arginine infusion 3 g 3× daily	No	No	IC Doppler	13	Angina ↑, CFR ↔	Lerman et al., 1998 (59)
L-arginine 1-time infusion	No	No	IC Doppler	8	CBF ↑	Egashira et al., 1996 (57)
Calcium-channel blockers						
Diltiazem 90 mg	No	Yes	TTDE	23	Angina ↑, CFR ↑	Zhang et al., 2014 (50)
Lidoflazine 240–360 mg	No	Yes	Thermodilution	11	Angina ↔, MBF ↑, Arrhythmias*	Cannon et al., 1990 (48)
Verapamil 80 mg 4× daily	No	Yes	Thermodilution	17	Angina ↑	Cannon et al., 1985 (47)
Nifedipine 10 mg 4× daily	No	Yes	Thermodilution	9	Angina ↑	Cannon et al., 1985 (47)
Alpha-blockers						
Doxazosin 2 mg	No	Yes	PET scan	11	Angina ↔, CBF ↔,	Rosen et al., 1999 (61)
Antianginal agents and nitrates						
Ivabradine 5 mg	Yes	Yes	TTDE	16	Angina ↑, CFR ↔	Villano et al., 2013 (68)
Isosorbide dinitrate 5 mg (SL)	NA	Yes	TTDE	29	Stress testing ↔	Russo et al., 2013 (69)
Ranolazine 500–1,000 mg	No	Yes	CMR	20	Angina ↑, CFR ↔	Mehta et al., 2011 (67)
Isosorbide dinitrate 10 mg (SL), 2 mg (IV)	NA	Yes	Thermodilution	11	Angina ↓, CBF ↓	Bugiardini et al., 1993 (70)
Estrogens						
17β-estradiol 1 mg + drospirenone 2 mg	No	NA	PET	27	MPR ↑	Knuuti et al., 2007 (63)
Devices						
EECP	Yes	Yes	TTDE	24	Angina ↑, CFR ↑	Luo et al., 2012 (65)
TENS	NA	Yes	IC Doppler	13	CBF ↓	Sanderson et al., 1996 (66)
Other						
Bariatric surgery	Yes	NA	TTDE	50	CBF ↑	Nerla et al., 2012 (72)
Cognac	No	NA	TTDE	18	CFR ↔	Kiviniemi et al., 2008 (77)
Vitamin C 3 g infusion	No	N/A	PET	19	CFR ↑ in asymptomatic smokers	Kaufmann et al., 2000 (78)
Exercise training	No	No	PET	13	CFR ↑	Czernin et al., 1995 (71)

Studies of therapies in patients who did not meet strict inclusion criteria nor had evidence of structural heart disease, heart failure, or untreated HTN, but which did assess coronary microvascular function. ↑ = improved with therapy; ↔ = not statistically different; ↓ = worse with therapy. *Treatment intervention associated with increased risk of arrhythmias.

CBF = coronary blood flow; CFR = coronary flow reserve; EECP = enhanced external counterpulsation; IV = intravenous; MBF = myocardial blood flow; N/A = not assessed; SL = sublingual; TTDE = transthoracic Doppler echocardiography.

correlation of MPR between CMR and PET. However, the absolute measures of rest and stress flow have not correlated well. Presumably, inconsistencies in quantification affect rest and stress equally and cancel out.

This systematic review excluded studies using transthoracic Doppler echocardiography as a method for assessing CMD. Myocardial contrast echocardiography suffers from excessive variability (35). Doppler echocardiography has gained some acceptance in the published data (36) as well as reproducibility in populations with known CAD (37). However, this technique also suffers from variability in patient anatomy and the inability to evaluate multiple coronary vascular territories. Other methods not specific to the coronary microvasculature, such as single photon emission computed tomography perfusion imaging and brachial artery flow reserve, were excluded. We have also excluded studies that induced hyperemia by rapid atrial pacing.

SYSTEMATIC REVIEW

We performed a Medline search using Ovid, last accessed in November 2014, to identify papers pertaining to the treatment of CMD (Figure 2). We used the multipurpose field search for the terms "microvascular angina," "microvascular," "syndrome X," "perfusion reserve," "microcirculation," "flow reserve," or "normal coronary." We excluded papers not pertaining to the exploded subject headings "heart disease" and "therapeutics and drugs (nonmesh) or therapeutics." We also limited our search to humans and the English language.

As "microvascular angina" was not added as a MeSH search term until 2005, and given the lack of standardized nomenclature referring to CMD, a more precise search strategy risked excluding relevant papers. We thus used a broad search strategy to yield a relatively large number of papers (n = 8,635). Single investigator review of title and abstract was then used to identify papers pertaining to the treatment of chest pain without obstructive CAD. This process identified 194 papers. Bibliographic review identified an additional 17 papers for inclusion. A detailed review by 2 independent investigators was performed on these 211 identified papers.

A rigorous definition of CMD was established using the following inclusion criteria: 1) human subjects; 2) evidence of CMD, as defined by a CFR or MPR <2.5 using PET, CMR, IC Doppler wire, or thermodilution methods; and 3) angina or symptom equivalent. We excluded papers based on the following exclusion criteria: 1) epicardial CAD with stenosis ≥50% or no evaluation of CAD (38,39); and 2) known structural heart disease or heart failure. No statistical meta-analytic techniques could be performed due to the significant heterogeneity in treatment modalities and endpoints studied.

Of the 211 papers that underwent 2-investigator review, 71 were excluded because they did not evaluate treatment. Additional exclusions from the remaining 140 papers are detailed in Figure 2. Only 8 papers, evaluating 84 patients, met strict inclusion criteria. Basic elements of the design and findings of these analyses are provided in Table 1. They represent 6% of the 139 studies on the treatment of CMD. The mean number of subjects per study was 10 ± 4. These studies evaluated pravastatin, sildenafil, quinapril, intravenous L-arginine, intravenous diltiazem, doxazosin, estrogen, and transcutaneous electrical nerve stimulation application in the treatment of CMD. Their endpoints encompassed different domains, including symptomatology, exercise capacity, markers of ischemia, and coronary blood flow (CBF). The studies evaluating sildenafil, quinapril, enalapril, estrogens, and transcutaneous electrical nerve stimulation application demonstrated benefits in their respective endpoints. No benefit was found with L-arginine, doxazosin, pravastatin, and diltiazem.

MICROVASCULAR ANGINA TREATMENT OPTIONS

This systematic review identified little evidence evaluating treatment strategies in patients with likely CMD. However, there are many analyses across multiple treatment modalities that have tangentially addressed this question and can inform future research design. The studies meeting inclusion criteria will be described in the following text. We will also discuss other studies that examined microvascular function in patients with chest pain but did not meet inclusion criteria. These studies have been summarized in Table 2. We have opted not to discuss studies pertaining to patients with structural heart disease, heart failure, or untreated hypertension. Although there are numerous other studies that have addressed therapies for CMD in other clinical settings, such as idiopathic dilated cardiomyopathy, hypertrophic obstructive cardiomyopathy, and Takotsubo cardiomyopathy, these studies were beyond the scope of this analysis.

THERAPEUTICS WITH STUDIES MEETING INCLUSION CRITERIA

RENIN-ANGIOTENSIN-ALDOSTERONE PATHWAY INHIBITION. It is well established that angiotensin II is a potent coronary vasoconstrictor. It has been proposed that angiotensin-converting enzyme inhibitors may directly modulate coronary microvascular tone (40). There was 1 study using angiotensin-converting enzyme inhibitors that met strict inclusion criteria. Pauly et al. (41) conducted a double-blind placebo-controlled trial of quinapril in 13 women with chest pain without obstructive CAD and with reduced CFR (≤2.5). They found significant changes in CFR with therapy (+0.55 ± 0.50) measured by IC Doppler (41). Two other studies by Kaski et al. (42) and Motz et al. (43), which were excluded from the systematic review, showed improved stress test parameters and, in the latter study, improved CFR. Bavry et al. (44) found no significant improvement in adding eplerenone to angiotensin II inhibition (44).

CALCIUM-CHANNEL BLOCKERS. Calcium-channel blockers have been shown to decrease microvascular tone and relieve spasm, thereby potentially

improving CFR or MPR in patients with CMD (45). Only 1 study met our strict inclusion criteria. Sutsch et al. (46) performed a case-controlled study of 16 patients to evaluate the effect of diltiazem on CBF. Five minutes after administration of intravenous diltiazem, there was a nonsignificant decrease in CBF from 178 to 170 ml/min in patients with microvascular angina. The study concluded that diltiazem failed to correct the impaired CFR (46). Verapamil, nifedipine, and lidoflazine have been shown to improve exercise stress test parameters, and lidoflazine has been shown to reduce coronary resistance but was associated with fatal arrhythmias (47,48). Multiple other studies have evaluated the role of calcium-channel blockers in patients with left ventricular hypertrophy or untreated hypertension. These patients were excluded.

STATINS. Statins may improve CMD through anti-inflammatory and antiatherosclerotic effects. A total of 10 studies have evaluated the role of statins in patients with chest pain without obstructive CAD. Only 1 study by Houghton et al. (49) met our inclusion criteria. This study evaluated pravastatin in 6 patients with an average baseline CFR of 0.97 ± 0.13. After 6 months of therapy, the CFR had increased to 1.60 ± 0.16 with administration of acetylcholine. However, there was no assessment of nonendothelial-dependent dilation or of symptoms of chest pain (49).

Zhang et al. (50) showed improvement in CFR and symptoms with fluvastatin, and Eshtehardi et al. (51) and Caliskan et al. (52) demonstrated CFR improvement in patients treated with atorvastatin; however, this was only significant in the study by Caliskan et al. (52). To further support the role of lipid-lowering therapies in the treatment of CMD, Nemes et al. (53) has shown that an inability to achieve cholesterol response on statin therapy is associated with worse CFR.

NITRIC OXIDE MODULATORS. Nitric oxide (NO) is a key player in endothelium-dependent mediation of coronary microvasculature tone through the activation of a guanylate cyclase signaling pathway preventing smooth muscle activation (54). Sildenafil works to inhibit the breakdown of cyclic guanosine monophosphate and, thus, promotes vascular smooth muscle relaxation. One study compared the role of a 1-time dose of sildenafil in symptomatic patients with CFR ≤2.5 or >2.5. Those patients with reduced CFR showed an increase in CFR from 2.1 ± 0.2 to 2.7 ± 0.6 ($p = 0.006$). There was no significant difference in CFR measurements in patients with CFR >2.5. The effect on symptoms was not evaluated (55).

L-arginine is a precursor of NO, and thus, its supplementation may improve microvascular function. One study evaluating L-arginine met our inclusion criteria. Bøttcher et al. (56) tested a 1-time infusion of L-arginine in 25 patients with chest pain without obstructive CAD and with CMD on PET. They noted no improvement in symptoms after infusion (56). Egashira et al. (57) and Gellman et al. (58) noticed improvement in CBF after a single infusion of L-arginine, whereas Lerman et al. (59) found improvement in symptoms but no change in CFR after 6 months of supplementation.

ALPHA-BLOCKERS. Alpha-blockers decrease sympathetic activity and, thus, potentially decrease microvascular tone and improve microvascular perfusion. One study met inclusion criteria. In a double-blind, placebo-controlled, crossover study of 16 patients with microvascular angina given doxazosin daily for 10 weeks, Bøtker et al. (60) found no difference in exercise duration, time to angina pectoris, and exercise time to ≥0.1 mV ST-segment depression when compared with placebo. Rosen et al. (61) also showed no improvement in MBF or CFR.

ESTROGENS. Given the prevalence of chest pain without obstructive CAD in post-menopausal women, it has been theorized that an estrogen deficiency may play a role in CMD. One study by Bairey Merz et al. (62) met our inclusion criteria. This study showed an improvement in anginal symptoms but no improvements in myocardial ischemia or brachial artery flow-mediated dilation. Another study by Knuuti et al. (63) demonstrated improved average MPR after estrogen use.

SPINAL CORD STIMULATORS AND OTHER DEVICES. Spinal cord stimulators and enhanced external counterpulsation (EECP) have been examined in patients with chest pain without obstructive CAD. Spinal stimulation is believed to modulate pain-related nerve signals and increase MBF through effects on sympathetic tone. EECP increases diastolic blood flow to the heart. A single study by Jessurun et al. (64) met our inclusion criteria and found an improvement in symptoms after the use of transcutaneous spinal cord stimulator therapy. Their patients went from reporting 20 ± 3 chest pain episodes/week to reporting 3 ± 1 episodes/week ($p = 0.012$). There was also an improvement in MPR. Luo et al. (65) also found improvement in both CFR and angina symptoms in patients treated with EECP. Sanderson et al. (66), in contrast, found no improvement with transcutaneous electric nerve stimulators.

THERAPEUTICS WITHOUT STUDIES MEETING INCLUSION CRITERIA

BETA-BLOCKERS. Beta-blockers reduce myocardial oxygen demand and increase diastolic perfusion time; thus, they have a compelling potential role in the treatment of CMD. They were the most-studied intervention. Despite this, no studies met our strict inclusion criteria. Multiple studies evaluated the role of beta-blockers in the treatment of CMD in patients with nonischemic dilated cardiomyopathy and were excluded.

ANTIANGINALS AND NITRATES. Multiple drugs that reduce angina have been studied in chest pain without obstructive CAD, including ivabradine, ranolazine, mibefradil, nicorandil, and trimetazidine. However, no studies met our strict inclusion criteria. These agents use numerous different mechanisms, although most work to reduce myocardial oxygen demand and, thus, reduce ischemia. Of these interventions, ranolazine was best studied. Mehta et al. (67) found an improved MPR in the subgroup of patients with baseline CFR <3. Villano et al. (68) found improvements in various symptomatic and stress test metrics, but no improvement in MBF.

Nitrates increase smooth muscle relaxation and, therefore, produce a vasodilator effect on veins and arteries (54). Several studies have examined the role of nitrates in chest pain without obstructive CAD and have found no benefit. Russo et al. (69) showed no significant change in stress test parameters after use of isosorbide dinitrate. Bugiardini et al. (70) observed worse angina and reduced CBF with rapid atrial pacing.

OTHER THERAPIES. Adenosine receptor blockade with members of the xanthine family, such as theophylline, were assessed in 6 small studies, none of which assessed MVD. These studies had mixed results. However, the majority reported improved exercise capacity.

Nine studies have evaluated psychiatric pharmacological interventions, including tricyclic antidepressants such as imipramine as well as various relaxation and psychiatric interventions. Although many showed an improvement in symptoms, none of these studies evaluated microvascular dysfunction, resulting in a heterogeneous treatment population with limited applicability to CMD.

Czernin et al. (71) studied 6 weeks of aerobic exercise training versus a low cholesterol diet and relaxation techniques; they found an improvement in CFR in the exercise group. Nerla et al. (72) evaluated bariatric surgery and also found improvements in CBF; however, this was in patients without CMD.

Multiple other treatments have been evaluated, including metformin, vitamin C, anticoagulants, cognac, and traditional Chinese medical techniques. However, none of these studies limited their populations to patients with likely CMD.

NEXT STEPS IN CMD RESEARCH

Given its unique pathophysiology and prognosis, it is important that microvascular angina be studied independently of other causes of chest pain without obstructive CAD, such as cardiac syndrome X, coronary spasm, and noncardiac causes of chest pain. Our review highlights the lack of evidence evaluating therapies to relieve angina and reduce risk in this morbid population. We propose a blueprint to promote more consistency in defining research populations for future treatment studies.

The first necessary step is to develop a universal definition of CMD. Variations in blood flow estimates due to the imaging modality, stress agent, and quantification method are partially abated by the use of CFR or MPR. However, differences remain, and these parameters affect the relationship between CFR or MPR and clinical endpoints such as mortality (27). Further research to precisely identify the optimal cut point for the diagnosis of pathologic CMD across varying patient populations and estimation methods will be essential. Standardized protocols will allow for refined estimates of prognosis and the development of optimal therapies.

In the interim, we propose a 3-tiered characterization of the likelihood of CMD based on the available prognostic data. Multiple studies examining prognosis in CMD have demonstrated that there are increased events in patients with reduced CFR or MPR, using disparate cutoffs ranging from 1.5 to 2.5. Murthy et al. (8) demonstrated a 5.6-fold increased risk of cardiac death in patients with suspected CAD and CFR <1.5. Thus, it seems likely that patients with a CFR <1.5 have CMD. Multiple other studies have used cutoffs that ranged from 1.5 to 2.5 to identify cohorts at increased risk due to presumed CMD. Therefore, it is likely that patients with a CFR or MPR >2.5 are unlikely to have CMD, and an alternative pathophysiologic mechanism for chest pain should be pursued. Those with a CFR or MPR between 1.5 and 2.5 fall in an indeterminate range and may have CMD. In patients without obstructive CAD (Pepine et al. [2]) and with CAD (Fukushima et al. [11]), cutoffs of 2.32 and 2.11, respectively, identified CMD. Other studies have used 2.0 as their cutoff (10,73). Suwaidi et al. (22) used a cutoff

of <1.5 for endothelial-dependent dilation and <2.5 for endothelial-independent dilation in patients without obstructive CAD.

The second necessary step is a transition to the routine assessment of CMD using validated imaging techniques in patients with chest pain without obstructive CAD. Definitive diagnosis of microvascular angina allows for validation of patient symptoms, differentiation from other clinical syndromes with potentially different therapeutic and prognostic implications, and initiation of more aggressive risk factor reduction (if a benefit is confirmed by future research).

The third step is to assess for effective therapies specifically in patients with microvascular angina. Future research should assess for improvements in symptoms, quality of life, and prognosis using both drug classes effective in microvascular angina and therapies that exploit the unique pathophysiology of CMD. Commonly used antianginal therapies, such as beta-blockers, calcium-channel blockers, nitrates, and statins, have not been adequately examined in the CMD population. Novel approaches could include treatment of metabolic syndrome and intensive exercise.

CONCLUSIONS

Chest pain without obstructive CAD is a heterogeneous entity in which a subset of patients experiences microvascular angina. In contrast to the favorable prognosis of most patients with chest pain without obstructive CAD, the presence of CMD is associated with poor outcomes. However, there is no standardized approach to defining CMD. The lack of standardized definitions has made the evaluation of treatment strategies for microvascular angina challenging. Only recently have advancements in PET and CMR allowed for widespread evaluation of microvascular function in patients with chest pain without obstructive CAD. However, even with these advances, the optimal strategy for diagnosing CMD is not clear.

After reviewing the published data, we found that there is little evidence to support current treatment strategies for objectively-defined CMD. Current practice is to use traditional antianginal and risk-reduction therapies targeted at epicardial CAD. However, these may not be effective in the management of CMD, as exemplified by the paradoxical effects seen in the data exploring the use of nitrates in chest pain without obstructive CAD.

Both prognostic and treatment studies suggest that those patients with the lowest CFR or MPR values have the worse prognosis. This group also seems to derive the most benefit from therapy. This suggests that CFR and MPR are important clinical indicators of physiologic dysfunction and should be used to guide therapy.

There is still considerable work needed to definitively address optimal therapy for CMD. After common definitions are adopted and CMD is routinely assessed in patients with chest pain without obstructive CAD, traditional and novel treatment strategies can be assessed to reduce symptoms, improve quality of life, and reduce risk in this prevalent and morbid disease.

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REPRINT REQUESTS AND CORRESPONDENCE: Dr. Jamieson M. Bourque, Cardiovascular Division, Department of Medicine, University of Virginia Health System, Box 800158, 1215 Lee Street, Charlottesville, Virginia 22908. E-mail: jbourque@virginia.edu.

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