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REVIEW

Coronary Microvascular Disease

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ABSTRACT

Coronary microvascular disease or dysfunction (CMVD) has been associated with adverse cardiovascular outcomes. Despite a growing prevalence, guidelines on definitive treatment are lacking. Proposed mechanisms of endothelial dysfunction and resultant inflammation have been demonstrated as the underlying cause. Imaging modalities such as echocardiography, cardiac MRI, PET, and in some instances CT, have been shown to be useful in diagnosing CMVD mainly through assessment of coronary blood flow. Invasive measurements through thermodilution and pressure sensor-guided Doppler microcatheters have also been utilized. Treatment options are directed at targeting inflammatory pathways and angina. In our review, we highlight the current literature on the background of CMVD, diagnostic modalities, and management of this disease.

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Key Summary Points

Coronary microvascular disease, despite its growing prevalence, has been a challenging diagnosis.

Current modalities involve imaging through PET, echocardiography, cardiac MRI, and CT.

Invasive measures such as thermodilution also assist with diagnosis.

Treatment options are mainly focused on anti-inflammatory and anti-anginal pathways.

INTRODUCTION

The prevalence of cardiovascular disease in adults is nearly 50% and growing [1]. Given this alarming statistic, the burden of chest pain in patients, especially women, who are found to have nonobstructive coronary artery disease has been appreciated to be around 81% in one study

[2]. In general, the prevalence of non-obstructive coronary artery disease has been noted to be as high as 50% in patients presenting with stable angina [3]. In 1967, Likoff et al. described patients with clinical presentation of ischemic heart disease but normal coronary angiograms thereby first bringing to awareness this unknown anomaly [4]. In 1973, Kemp described and coined the term "cardiac syndrome x" in patients presenting with chest pain and normal coronary arteries [5]. In 1988, Cannon et al. further coined the term "microvascular angina" or "Syndrome X" when studying the coronary flow and cardiac metabolic activity of patients who presented with normal coronary angiography but persistent angina [6]. Despite such a large prevalence, and the increasing number of studies since then, guidelines on definitive management of coronary microvascular disease or coronary microvascular dysfunction (CMVD) is lacking [7]. Furthermore, CMVD has been associated with an increase in morbidity and mortality from cardiovascular events [8]. The economic burden of CMVD is substantial, with patients reporting poor quality of life and productivity factors such as limitations in total productivity and increased worker absenteeism. This burden has been estimated to nearly $14,000 per patient annually [9]. In this review, we aim to provide insight into the background of CMVD, diagnostic imaging modalities, and management. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

ANATOMY AND PATHOPHYSIOLOGY OF CORONARY MICROCIRCULATION AND DYSFUNCTION

In a topological study of a post-mortem human heart, Schwarz et al. evaluated over 200,000 segments of the left coronary tree. Median diameter across all segments was 92.3 μm, with a median length of 441 μm. Diameter classes ranged from greater than 400 μm to 30 to 45 μm. The three most prevalent segments were 75–90 μm (16.6%), 60–75 μm (16.1%), and 90–105 μm (13.8%). In the subepicardium, midmyocardium, and subendocardium, the most prevalent diameter class was 60–75 μm, accounting for 27.4, 25.2, and 28.6%, respectively [10]. In regard to metabolic stimuli, arterioles with diameter of < 30 μm have been reported as being the most sensitive. Myogenic responsiveness has been appreciated in arterioles between diameters of 30 to 60 μm with flow sensitivity appreciated in arterioles of diameters from 120 to 150 μm [11].

Dysfunction of the coronary microvasculature has been appreciated to involve both impairment of dilation and contraction. Clinical chest pain associated with CMVD has been linked more closely to over-constriction and spasming of the vessels [12]. The two most appreciated mechanisms involving increased resistance in the microcirculation are poor vasodilation of the endothelium because of decreased nitric oxide, as well as decreased coronary blood flow responsiveness to acetylcholine. Primary impairment in the relaxation of smooth muscle cells is another purported mechanism of dysfunction, which has been reported as being non-dependent from classic vasodilatory chemicals [13].

EPIDEMIOLOGY, RISK FACTORS, AND ASSOCIATIONS

In a study of over 2000 low-to-moderate risk cardiac patients presenting with chest pain, 82% of patients with CMVD were found to be women. Even with coronary flow reserve being similar in both men and women with CMVD, woman were still reported to have dysfunction three times more likely than men when assessed through positron emission tomography (PET) and computed tomography (CT). Mean age of patients with CMVD in the study was 51.

In terms of race, Hispanics accounted for 21% and non-Whites accounted for 38% of patients with CMVD [14]. Although, in several other studies, prevalence of CMVD has not been shown to differ significantly between genders [15–18].

In terms of risk factors, notable associations have been found in women who have impaired coronary flow reserve and age, hypertension, smoking history, elevated heart rate, and low HDL [19]. Dyslipidemia has been appreciated to be an important association and cause of microvascular dysfunction. Some of the theorized mechanisms underlying dyslipidemia-induced microvascular dysfunction include abnormalities in production and destruction in endothelium-derived relaxing factor, alterations in dilatory response, and serotonin-potentiated vasoconstriction [20]. Diabetes mellitus has also been shown to be an associated risk factor [21]. CMVD has also been shown to play a major role in other cardiovascular conditions such as ischemia and no obstructive coronary artery disease (INOCA), myocardial infarction with nonobstructive coronary arteries (MINOCA), takotsubo cardiomyopathy, and heart failure with preserved ejection fraction (HFpEF) [22, 23]. The mechanism believed to be behind these diseases, especially HFpEF, is a chronic inflammatory state. The sub-mechanisms underlying this chronic inflammatory state include decreased nitric oxide with a resultant rise in reactive oxygen species and resultant inflammation and poor function of the endothelium. The inflammation is driven by inflammatory cytokines such as tumor necrosis factor-alpha and interleukins 1 beta and 6. Cytotoxicity as a result of poorly regulated interleukin 1 beta has also been associated. These mechanisms have been seen in patients with autoimmune rheumatic disease and CMVD [24].

CLASSIFICATION AND DIAGNOSTIC CRITERIA

In 2007, Camici et al. proposed a clinical classification for coronary microvascular dysfunction. This classification was divided into four major categories. The first category was coronary microvascular dysfunction in the absence of coronary artery and myocardial disease. The second category was in the presence of myocardial diseases such as hypertrophic cardiomyopathy, dilated cardiomyopathy, hypertension, aortic stenosis, and infiltrative heart disease. The third category was in the presence of obstructive coronary artery disease such as stable coronary artery disease and acute coronary syndromes. The fourth category was iatrogenic dysfunction seen in instances of distal emboli that form because of coronary recanalization [25].

The Coronary Vasomotion Disorders International Study Group (COVADIS) in their 2014 and 2015 summits, proposed the following criteria for coronary microvascular disease: "(1) presence of symptoms suggestive of myocardial ischemia, (2) objective documentation of myocardial ischemia, as assessed by currently available techniques, (3) absence of obstructive coronary artery disease defined as $< 50\%$ coronary diameter reduction and/or fractional flow reserve of > 0.80, and (4) confirmation of a reduced coronary blood flow reserve and/or inducible microvascular spasm." [26].

DIAGNOSTIC IMAGING MODALITIES

Echocardiography

Echocardiography, especially coronary flow velocity reserve assessment, has been noted to be a beneficial imaging modality in detecting disease of the microvascular system. Coronary blood flow velocity can be assessed with pulsed wave Doppler on transthoracic echocardiography of the mid to distal tract of the left anterior descending artery. Transesophageal echocardiography can also be used if assessing the proximal tract of the left anterior descending artery. Another modality is myocardial contrast echocardiography, which utilizes microbubbles and ultrasound. In this modality, coronary blood flow velocity is found to be enhanced during stress with opacification of the myocardium through microbubbles [27]. Vogel et al. also demonstrated the usefulness of echocardiography in determining myocardial blood flow [28].

Cardiovascular Magnetic Resonance Imaging

Cardiovascular magnetic resonance imaging (CMRI) has been established as a modality for assessing CMVD, with disease-specific protocol calling for repeat first pass perfusion or early gadolinium enhancement [29]. Thomson et al. evaluated 118 patients from the Women's Ischemia Syndrome Evaluation (WISE)-Coronary Vascular Dysfunction (CVD) study with 1.5T CMRI using first-pass gadolinium perfusion imaging and adenosine. Myocardial perfusion reserve index was compared with coronary reactivity testing. Results obtained from the study demonstrated that a threshold myocardial perfusion reserve index of 1.84 was predictive of CMVD with a sensitivity of 73% and specificity of 74% [30]. Kotecha et al. evaluated 50 patients with stable angina using adenosine stress 1.5-T CMRI with quantification of myocardial blood flood myocardial perfusion mapping in comparison to coronary angiography. In their study, they found that global stress myocardial blood flow of < 1.82 ml/g/min was able to differentiate between obstructive three-vessel disease and CMVD [31]. Rahman et al. evaluated 3-T CMRI in 75 patients using both visual and quantitative techniques such as stress myocardial blood flow, transmural myocardial perfusion reserve, and subendocardial myocardial perfusion reserve. In their study, subendocardial myocardial perfusion reserve was found to have a sensitivity of 95% and specificity of 72%. Myocardial perfusion reserve was found to have a sensitivity of 70% and specificity of 90% [32].

Positron Emission Tomography

PET has been an important modality in assessing coronary flow reserve. Through dynamic PET, myocardial blood flood, which helps to determine coronary flow reserve, can be evaluated at rest and with stress [33]. Coronary blood flow has been shown to be a useful tool in evaluating CMVD even in patients with normal PET [34]. Myocardial blood flow is acquired using 0–15 water, N-13 ammonia, or Rubidium-82 [35]. In a study of over 1000 patients to evaluate gender differences in coronary microvascular dysfunction, Murthy et al. found that although there were no gender differences, coronary flow reserve measured through PET was a strong predictor of major adverse cardiovascular events [16].

Computed Tomography

Although data are scarce in the use of CT in assessing CMVD, one of the main reported advantages is the ability to assess anatomy and functionality in one study. Risk factors of course include radiation and renal insult. Other concerns include misestimation of myocardial blood flow [36]. Grover et al., in their study of 30 patients with microvascular angina, demonstrated a lower mean total coronary lumen volume and mean myocardial mass compared to patients who were without angina [37].

INVASIVE ASSESSMENT

Invasive measures have also been proposed to be helpful in assessing for microvascular disease. Microvascular resistance can be measured through thermodilution. Hyperemic microvascular resistance can be measured as well through pressor sensor when utilized with guidewires that have Doppler capabilities [38].

TREATMENT AND FUTURE TRENDS IN MANAGEMENT

Treatment for CMVD is focused on targeting pathways that promote inflammation and thrombosis [39] and vasomotor dysfunction [40]. The main therapeutics are those that have been well established in targeting these pathways such as aspirin, statin therapy, and angiotensin-converting enzyme inhibitor or receptor blockers. Some proposed anti-anginal treatments have been beta-blockers, calcium channel blockers, nitrates, and ranolazine [39]. Vasomotor dysfunction is also regulated

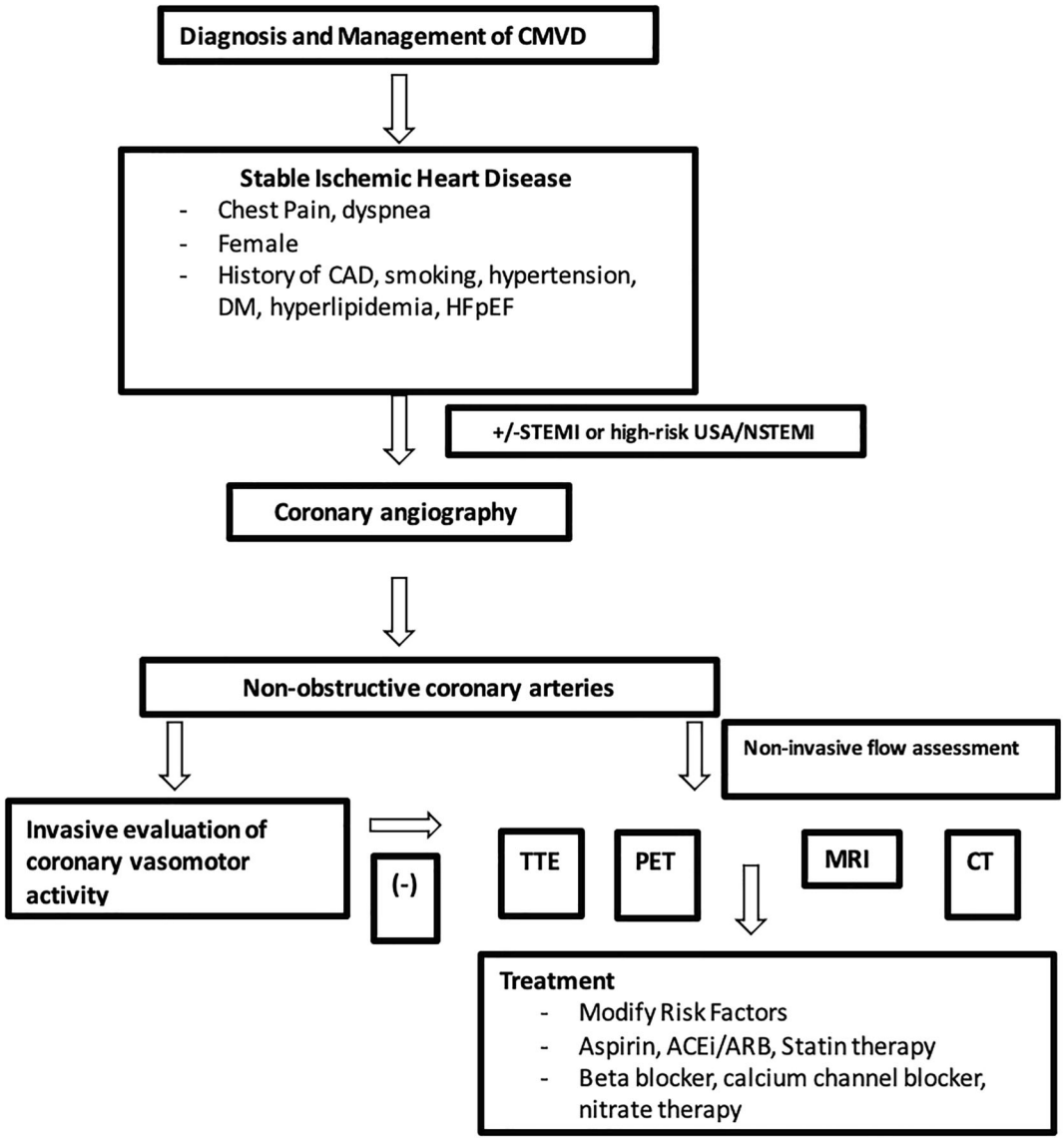

Fig. 1 Proposed algorithm for diagnosis and management of CMVD. CMVD (coronary microvascular disease), CAD (coronary artery disease), DM (diabetes mellitus), HFpEF (heart failure with preserved ejection fraction), STEMI (ST segment elevation myocardial infarction), USA (unstable angina), NSTEMI (non-ST segment elevation myocardial infarction), TTE (transthoracic echocardiography), PET (positron emission tomography), MRI (magnetic resonance imaging), CT (computed tomography)

through the above mechanisms through Quinapril, a type of angiotensin-converting enzyme inhibitor, that has been appreciated to be a novel therapy by targeting inflammatory pathways based off results from the WISE study [41]. Statin therapy is one of the first-line medications in the treatment of CMVD [42]. In a systematic review and meta-analysis by Yong et al., their study showed an improvement in coronary flow reserve in over 200 patients on statin therapy with a standard mean difference of 0.61 (95% confidence interval: 0.36–0.85). This improvement in coronary flow reserve was irrespective of a time period when evaluated up to 12 months of follow-up time [43]. Gliflozins have also been proposed as a possible treatment

modality through modulation of vascular endothelial cell activation and overall function of the endothelium, especially in patients with HFpEF, where microvascular dysfunction is believed to be an underlying cause [44]. Low-dose tricyclic antidepressants, through targeting of nociceptor activity, have also been demonstrated to be a potential target. Non-pharmacological treatment options include basics such as exercise, healthy diet, weight reduction, smoking cessation, stress reduction, and unique therapies such as enhanced external counterpulsation and spinal cord stimulation [45]. Data and guidelines are still lacking for definitive management of CMVD [7]. We provide a potential algorithm for diagnosis and management of patients presenting with concern for CMVD (Fig. 1).

CONCLUSIONS

CMVD, as outlined by our review, is a challenging diagnosis despite the growing literature of evidence. Prognosis is equally confounding with mixed results in terms of all-cause mortality, in-hospital mortality, and non-cardiac deaths [46]. Pending trials including the Women's Ischemia Trial to Reduce Events in Nonobstructive CAD (WARRIOR) trial may help provide further insight into this multifaceted disease [47].

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