Myocardial Small Vessel Disease and Endothelial Dysfunction

10

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10.1 Definition and Classification

Whereas CAD is defined as atherosclerosis in the epicardial coronary arteries, CMD is defined as abnormal or impaired blood flow in the coronary microcirculation. There are four previously proposed categories of CMD (Table 10.1) [2] as well as four physiologic categories related to responses of coronary blood flow to acetylcholine (endothelial-dependent mechanism) and adenosine (endothelial-independent mechanism) [8]. While CMD can occur in individuals with obstructive coronary disease, this chapter will specifically review CMD in those with nonobstructive CAD.

10.2 Prevalence

The true prevalence of CMD is unclear due to various definitions and because evaluation of the coronary microvascular is not routine. However, it is likely higher than reported. In the United States alone, the prevalence is believed to be at 3–4 million individuals [3]. Furthermore, CMD appears to be more prevalent in women and by some has been termed "female pattern ischemic heart disease" [9]. The cause for the higher prevalence in women is unclear, but is likely multifactorial given differences in hormones, genetics, and referral bias. In a group 917 women from the Women's Ischemia Syndrome Evaluation (WISE) cohort, researchers have found CMD in approximately 50% of women with chest pain and without obstructive CAD [10]. In a cohort of 405 men and 813 women with suspected CAD but with negative stress testing, Sara et al. found that two-thirds (predominantly women) of their cohort showed signs of CMD on physiologic testing of coronary blood flow.

Table 10.1 Classification of coronary microvascular dysfunction

Type 1	CMD with nonobstructive coronary artery disease
Type 2	CMD with myocardial diseases
Type 3	CMD with obstructive coronary artery disease
Type 4	Iatrogenic CMD

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10.3 Risk Factors

Traditional risk factors for epicardial atherosclerosis, including diabetes, hypertension, cigarette smoking, dyslipidemia, obesity, and increasing age, are also considered risk factors for CMD [2, 3]. However, evidence from the WISE cohort suggests that traditional risk factors, with the exception of age, do not completely account for the incidence of CMD [11], which suggests residual and unidentified causes. One proposed mechanism is chronic inflammation, which has been shown to correlate with atherosclerosis and CMD in rheumatologic diseases such as systemic lupus erythematosus [12, 13]. In a cohort of individuals with CMD but without traditional CVD risk factors, participants with an elevated high-sensitivity C-reactive protein (hs-CRP) (defined as >3 mg/L) had reduced coronary flow reserve (CFR) compared to those without elevated hs-CRP [14].

Just as diabetes has been linked to microvascular disease in the kidneys, eyes, and neurologic system, diabetes and chronic hyperglycemia are associated with both endothelial-independent and endothelial-dependent CMD. Diabetes-related CMD appears to be similar between type 1 and type 2 diabetics, indicating a shared mechanism despite inherent pathophysiologic differences between the two types of diabetes [15]. Dyslipidemia and tobacco smoking have both shown deleterious effects on CFR as well as a concomitant improvement in endothelial function with treatment and cessation, respectively [16–18]. Finally, some have reported a link between endothelial dysfunction and a family history of CAD [19, 20].

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10.4 Pathophysiology

Several pathophysiologic mechanisms have been reported with conflicting results [4], including the presence or absence of smooth muscle hypertrophy [21, 22]. However, no single mechanism entirely explains the microvascular dysfunction in patients with CMD, suggesting several mechanisms likely playing a role at the same time. Of the reported mechanisms, the most commonly accepted is endothelial-dependent dysfunction resulting in impaired vasodilation to nitric oxide [23, 24]. Recent studies have proposed decreased levels of endothelial progenitor cells, a repair mechanism for coronary endothelium, in those with CMD [25]. Numerous other studies have suggested an endothelial-independent mechanism and impairment in smooth muscle cell relaxation contributing to CMD [24, 26, 27]. Others have reported slow coronary flow secondary to inappropriate constriction in the microvasculature [28]. The end result of these heterogeneous and maladaptive functional abnormalities results in impaired subendocardial perfusion and microvascular angina (MVA).

10.5 Clinical Presentation

Those predominantly affected by CMD, women, frequently present differently than men with ischemic heart disease and, in particular, may not experience chest pain [29], which often leads to delay in seeking medical care [30]. Further, evidence from the WISE cohort indicates that typical vs. atypical angina is not helpful in distinguishing between obstructive and nonobstructive CAD [31]. Once found to have nonobstructive findings on angiography, which can lead to misdiagnosis, patients are often told that the source of their pain is non-cardiac in origin.

Typical angina symptoms are present in roughly 50% of patients with CMD. Classically, CMD takes a prolonged period of time (>15 min) for resolution of chest discomfort and has a poor response to nitrates [32, 33]. Lanza et al. studied the response of nitrates during exercise stress testing in two groups, one with known CAD and the other with CMD. Whereas nitrates improved exercise tolerance and chest discomfort in individuals with CAD, participants with CMD had worsening of their exercise tolerance and lacked improvement in chest discomfort [34]. Patients with CMD undergoing stress testing who develop angina and ST-segment depression often lack echocardiographic wall motion abnormalities [35, 36].

10.6 Diagnosis

In 1910, Sir William Osler described the difficulty of distinguishing non-cardiac chest pain from "true" angina [37]. In the modern era, CMD is still difficult to diagnose, which is perhaps made more difficult by the existence of several chest pain syndromes (e.g., vasospastic or Prinzmetal angina) with normal or nonobstructive coronary arteries. Further, non-cardiac causes of chest pain must be ruled out when nonobstructive CAD is found on angiography [38]. These diagnostic uncertainties often lead to a delay in diagnosis as well as persistent chest pain in many of these patients [39, 40].

Diagnostic strategies for CMD include invasive and non-invasive studies. Through coronary angiography, coronary reactivity testing is the gold standard for diagnosis, and investigated with intracoronary infusion of endothelial-dependent (acetylcholine) and endothelial-independent (adenosine) stimuli [41]. Once these vasoactive agents are instilled, a Doppler flow wire inside the coronaries measures CFR. The risks and benefits of invasive coronary investigation need to be considered thoughtfully. Coronary reactivity testing has been estimated to carry a 0.7–2.4% risk of a non-fatal adverse event [42, 43] and argued by some to include unjustified risk [4]. However, others would disagree and argue the estimated lifetime cost for patients with CMD to be close to $800,000 due to repeated indeterminate exposures to the health-care system [44].

Several noninvasive modalities, including positron emission tomography (PET) [45], cardiac magnetic resonance (CMR) [27, 46], and transthoracic Doppler recording echocardiography (TTE-DR) [47], are available to aid in the diagnosis of CMD. Both PET and CMR are complex, time-consuming, expensive, and not widely available in clinical practice [4]. TTE-DR assesses diastolic coronary blood flow velocity after vasodilation with adenosine and coronary blood flow at rest as a ratio to evaluate coronary microvascular dilator function. CMD is suggested when this ratio is less than 2.0. Notably, only the left anterior descending artery is generally assessed, and mild CMD can be missed [4, 48].

10.7 Management

The mainstay of medical treatment for CMD is beta-blockers (Table 10.2), especially for patients with increased sympathetic activity (i.e., high resting heart rate) [4]. Beta-blockers have been estimated to provide chest pain relief in 19–60% of patients [49]. Of note, therapeutic studies for those with CMD, including with beta-blockers, have been small. In a crossover study of ten patients, atenolol showed less chest pain episodes when compared to amlodipine or nitrates [50]. Similarly, both atenolol (n = 22) and propranolol (n = 16) prevented exercise-induced ST changes when compared with verapamil and placebo [51, 52].

Calcium channel blockers have generally been used as second-line agents or in addition to beta-blockers for those with symptoms that were not well controlled [4]. However, studies have been conflicting, and most likely related to

Table 10.2 Treatment options by category for coronary microvascular dysfunction

Antianginal therapy
Beta-blockers
Calcium channel blockers
Nitrates
Nicorandil
Trimetazidine
Ivabradine
Ranolazine
Microvascular function therapy
Angiotensin-converting enzyme inhibitors
Statins
Metformin
Nitric oxide modulators
Sildenafil
L-arginine
Lifestyle therapy
Smoking cessation
Exercise
Diet (e.g., Mediterranean)
Miscellaneous
Xanthine derivatives (adenosine)
Imipramine
Estrogen
Alpha-blockers
Non-pharmacologic therapy
Spinal cord stimulation
Enhanced external counterpulsation

differences in patient selection and study design [49]. In a group of 26 patients with angina, normal coronary arteries, and abnormal coronary reserve, Cannon et al. found that those receiving calcium channel blockers had less angina and took fewer nitroglycerin tablets compared with placebo [53]. In contrast, Bugiardini et al. found no differences with verapamil compared to propranolol or placebo [52]. Nitrates have similarly been disappointing, but some report improvement in chest pain in roughly 50% of patients [49].

Several drugs, including renin-angiotensin-aldosterone inhibition, statins, and metformin, have targeted microvascular function [54]. Angiotensin II has been shown to stimulate oxidative stress in the endothelium, vascular remodeling, and be a potent vasoconstrictor [54, 55]. Several studies have demonstrated improvement in CFR and ST-segment depression on stress testing with angiotensin-converting enxyme inhibitors (ACE-I), but without additional benefit from aldosterone antagonism such as eplerenone [56–58]. Similarly, statin therapy, through putative pleiotropic and anti-inflammatory effects, has been shown to improve CRF in several studies in those with CMD [59–62]. In a group of 33 nondiabetic women with CMD, women randomized to metformin showed improvement in ST-segment depression on stress testing, Duke score, and chest pain incidence compared with placebo [63].

Two newer antianginals, ranolazine and ivabradine, have shown promise in the treatment of CMD. Mehta et al. found that ranolazine, compared with placebo, decreased anginal episodes and improved quality of life in a group of women with CMD [64]. In a group of 46 patients with persistent CMD symptoms, Villano et al. showed both ranolazine and ivabradine decreased angina compared with placebo. Ranolazine appeared to be superior to ivabradine in this small study of 46 patients and also showed improved time to 1-mm ST-segment depression on stress testing [65].

Non-pharmacologic options for patients with multidrug-"resistant" CMD include spinal cord stimulation (SCS) and enhanced external counterpulsation (EECP). The exact mechanism for improvement in CMD from SCS is unknown. However, SCS is thought to provide improvement in microcirculatory function and perhaps abatement of increased pain perception seen in those with CMD [66–69]. After long-term follow-up with a mean of 36 months, Sgueglia et al. found improvement in angina symptoms, quality of life, and stress test parameters in those receiving SCS [70]. Luo et al. similarly found improvement in angina and CFR in those treated with EECP [71]. While some evidence shows that these treatment options are helpful in those with resistant CMD, it must be noted that they are typically more costly and carry risks of several serious complications.

While beta-blockers are the mainstay of medical therapy, non-pharmacologic lifestyle changes are just as important. Although not studied directly in those with CMD, tobacco cessation has been shown to improve endothelial-dependent dilation [72]. Klonizakis et al. found a Mediterranean diet when combined with regular exercise has also shown endothelial-dependent vasodilation [73]. A low-fat diet with exercise training and exercise training alone has also showed improvement in CFR [74, 75].

10.8 Case Studies

10.8.1 Case 1

A 52-year-old woman visits your office for the third time in the last 2 months. She has a distant history of tobacco smoking as well as hypertension and dyslipidemia. During this time, she has also been to the emergency department twice for chest pain with the first episode resulting in admission to the hospital. She was found to have nonobstructive coronary disease and told the source of her chest pain was likely noncardiogenic. She reports nearly daily chest pain described as substernal, associated with exertion, and relieved with rest over 10–15 min. She denies reflux symptoms, shortness of breath, and wheezing.

She has a pulse of 87 beats/min and a blood pressure of 147/83 mm Hg. Her lungs are clear and cardiovascular exam

unremarkable. An EKG is obtained and unremarkable. Due to the reassuring coronary angiography and negative noncardiac workup, you suspect CMD. The patient would like a more definitive answer for her symptoms, but would prefer not to undergo another invasive procedure. What noninvasive options are available to aid your diagnosis?

Several noninvasive options are available or are being studied, including transthoracic echocardiographic Doppler records (TTE-DR), positron emission tomography, and cardiac magnetic resonance. Given availability and reliability, you order a TTE-DR, which measured the diastolic coronary blood flow in the left anterior descending artery at peak vasodilation and at rest. The ratio returns <2.0 and you make a diagnosis of CMD.

10.8.2 Case 2

A 63-year-old woman with a history of hypertension, type 2 diabetes mellitus, and obesity presents to your office for follow-up of her exertional angina. She was diagnosed with CMD after several episodes of chest pain prompting visits to the emergency department. She was found to have nonobstructive coronary disease and microvascular dysfunction on coronary angiography. Once diagnosed, she was placed on beta-blockers in addition to aspirin, statin, metformin, and titrated to maximum doses. A calcium channel blocker was tried, but the patient self-discontinued the medication due to side effects. Sublingual nitroglycerin does not provide relief of her chest pain.

Her pulse is 62 beats/min and blood pressure 127/82 mm Hg. Her lungs are clear to auscultation, and heart sounds are regular without murmurs. Her EKG shows a normal sinus rhythm with nonspecific T-wave flattening in the precordial leads. While she reports that her anginal events have decreased, she is still experiencing 2–3 episodes weekly. What is the next appropriate step in the management of this patient?

The next best option would be to try ranolazine. She has received maximum doses of beta-blockers and has a well-controlled heart rate and blood pressure. Calcium channel blockers are often considered second line, but this drug class was tried and discontinued by the patient. Ranolazine has been shown to be helpful in chronic stable angina and also for CMD in small studies.

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