Coronary Microvascular Dysfunction: A Practical Approach to Diagnosis and Management

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Abstract

Purpose of Review The purpose of this review is to provide an overview of diagnostic and treatment considerations in patients with coronary microvascular dysfunction (CMD) in the absence of obstructive coronary artery disease (CAD).

Recent Findings The prevalence of obstructive CAD in unselected patient populations referred for evaluation of angina is less than 10%. A significant proportion of patients with angina and no obstructive CAD have CMD, a condition associated with impaired cardiovascular prognosis. Non-invasive and invasive evaluation of coronary microvascular function is feasible and widely available, yet CMD is underdiagnosed and undertreated. A patient-tailored treatment approach guided by coronary microvascular testing shows promising results for patient-reported outcomes of symptom burden and quality of life.

Summary Coronary microvascular testing should be considered in angina patients with no obstructive CAD, before other causes of chest pain are explored. A patient-tailored treatment approach guided by a complete evaluation of epicardial anatomy and macro-and microvascular function may help optimize treatment strategy and prevent unnecessary medical interventions. More research is needed to establish the long-term effect of patient-tailored therapies on risk reduction in CMD.

Keywords Coronary microvascular dysfunction · Microvascular angina · INOCA · Stable angina pectoris · Management · Coronary artery disease

Introduction

Angina pectoris affects approximately 112 million people worldwide, and obstructive coronary artery disease (CAD) has been accepted as the cause of angina for decades; however, up to 70% of symptomatic women and 30% of symptomatic men referred for diagnostic coronary angiography have normal or near normal epicardial arteries [1–3]. In many cases,

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a normal non-invasive test or coronary angiography with no obstructive CAD leads to diagnostic uncertainty and lack of treatment options. Accumulating evidence suggests that patients with angina and no obstructive CAD have increased cardiovascular morbidity and mortality compared with age- and sex-matched peers [4]. The symptom burden and lack of diagnosis and treatment options affects the mental health of these patients, resulting in more depression, anxiety, and vital exhaustion [5–7]. In addition to the human cost, the economic burden of the condition, including health-care costs and disabilities, is similar to patients with obstructive CAD [8, 9].

Angina caused by ischemia in the absence of obstructive CAD was recently coined INOCA—ischemia with non-obstructive coronary arteries. Ischemia may be caused by several mechanisms, and recently two INOCA endotypes were defined: microvascular angina and epicardial vasospastic angina. The two conditions can co-exist, which is associated with worse prognosis [10]. Microvascular angina is the clinical manifestation of myocardial ischemia caused by coronary microvascular dysfunction (CMD), a condition characterized by inability of microcirculation to regulate myocardial perfusion with increased myocardial oxygen demand due to

reduced arteriolar vasodilatory capacity and/or dynamic arteriolar obstruction (microvascular spasm) [10]. CMD is the frequent cause of ischemia and adverse prognosis in angina patients with no obstructive CAD [11–13]. The purpose of this review is to provide an overview of diagnostic and management strategies of CMD based on the existing evidence.

Epidemiology, Clinical Presentation, and Pathophysiology

The vast majority of angina patients undergoing diagnostic invasive coronary angiography do not have obstructive coronary lesions; however, non-obstructive anatomy does not rule out myocardial ischemia [3, 14, 15]. In fact, in a large cohort of patients with no history of CAD undergoing elective coronary angiography, the prevalence of obstructive CAD was less than 50% despite prior positive non-invasive stress testing [16]. The majority of angina patients with no obstructive CAD, with or without abnormal stress testing, are middle-aged women [2, 12].

Patients with CMD typically present with effort-induced chest pain or chest discomfort, and/or dyspnea, with or without occasional attacks of chest pain at rest. In some patients, symptoms can persist for several minutes after the exercise is interrupted and show poor response to short-acting nitrates [17]. Symptom burden and angina typicality are poor indicators of CMD and are often similar to patients with obstructive CAD. The imProve diagnOsis and treatment of Women with angina pEctoris and micRovessel Disease (iPOWER) study (*n* = 1.681) reported typical angina in only 34% of symptomatic women with no obstructive CAD, with no correlation between symptom characteristics and coronary microvascular function assessment [12, 18]. Similar results have been reported in other studies [19, 20]. Moreover, the iPOWER study showed that angina typicality and symptom burden were comparable between symptomatic women with CMD and symptomatic women with normal coronary microvascular function, suggesting that traditional stable angina classification is a poor indicator of CMD in this population [18].

Pathogenic mechanisms contributing to CMD can be categorized into two main categories, structural microcirculatory changes and functional arteriolar dysregulation, both of which can coexist in the same patient [10]. Structural microcirculatory changes include inward arteriolar remodeling (e.g., increased medial wall thickness, intimal thickening) causing reduction in wall/lumen ratio, perivascular fibrosis, and loss of myocardial capillary density [21]. These changes may occur secondary to cardiovascular risk factors (e.g., hypertension, diabetes, dyslipidemia, insulin resistance), atherosclerosis, left ventricular hypertrophy, or cardiomyopathies [22]. The potential consequences of structural microcirculatory changes over time are compensatory increases in basal myocardial blood flow and/or reductions of maximal microvascular vasodilatory capacity, leading to a mismatch between myocardial oxygen supply and oxygen demand. Furthermore, structural changes may lead to an increased sensitivity of smooth muscle cells to vasoconstrictor stimuli (e.g., endothelin-1, acetylcholine, serotonin) [21].

Similar to the underlying pathology of epicardial vasospasm, functional arteriolar dysregulation occurs secondary to endothelial dysfunction. Arteriolar endothelial dysfunction is characterized by one or more the following features: reduced flow-mediated dilation, with reduced nitric oxide response to increased shear stress, causing impaired smooth muscle cell relaxation; receptor-mediated dilation, with reduced nitric oxide response to acetylcholine, serotonin, histamine, bradykinin etc.; and even paradoxical vasoconstriction in response to increased myocardial oxygen demand [10, 21].

Assessment of Coronary Microvascular Function

Coronary microvascular vessels are beyond the spatial resolution of the angiography. Coronary microvascular function is therefore examined indirectly, using both non-invasive and invasive techniques (Fig. 1) [10, 23]. Non-invasive assessment can assess non-endothelial dependent coronary microvascular function but requires that obstruction of the epicardial vessels has been ruled out. In contrast to patients with obstructive CAD and regional perfusion defects, the pattern of hypoperfusion by myocardial perfusion imaging associated with CMD is either diffuse, affecting the whole ventricle, or patchy, with small ischemic areas interspersed among normal myocardium [24, 25]. While non-endothelial dependent coronary microvascular function can be assessed using both non-invasive and invasive techniques, the microvascular endothelial function can only be assessed invasively. Thus, a full clinical evaluation of coronary microvascular function currently requires invasive angiography [10].

Invasive Techniques

Evaluation of Non-Endothelial Dependent Coronary Microvascular Function

Guidewire-based evaluation of non-endothelial dependent coronary microvascular function, using either coronary flow reserve (CFR) or index of microcirculatory resistance (IMR), can be performed as an add-on examination to a diagnostic coronary angiography and is recommended by the European Society of Cardiology (ESC) guidelines (Class IIa; Level B) in angina patients with normal epicardial arteries or moderate CAD with preserved fractional flow reserve (FFR >0.80)
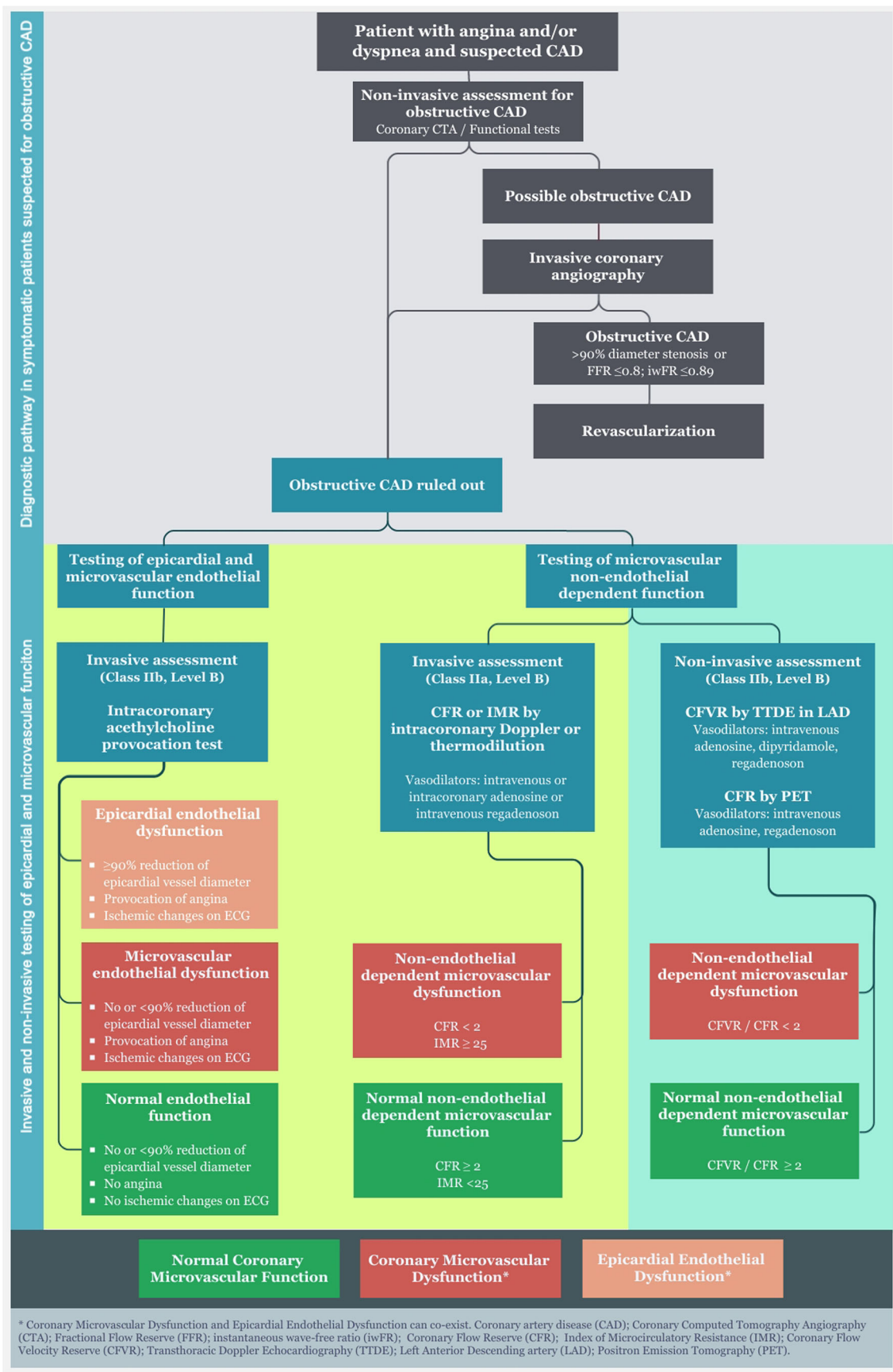
Fig. 1 Diagnostic flow in patients with angina pectoris and/or dyspnea suspected for CMD

[23]. The functional testing is traditionally performed in the left anterior descending artery (LAD); however, in patients with right or balanced coronary dominance, other coronary arteries may be used. CFR and IMR can be assessed by Doppler or thermodilution.

In thermodilution, the guidewire is equipped with two sensors allowing for estimation of temperature changes between proximal and distal segments of the coronary artery after injection of room-temperature saline. Coronary flow is estimated based on the time it takes for saline to pass between the two sensors (mean transit time; Tnm, s). Hyperemia is traditionally achieved using intravenous or intracoronary adenosine or intravenous regadenoson. CFR is then calculated as: $CFR = \frac{mean\ resting\ Tmn}{mean\ hyperemic\ Tmn}$. IMR, measured during peak hyperemia, is a product of hyperemic mean Tmn and distal intracoronary pressure: $IMR = T_{mn} \times P_d$, where P_d is mean distal intracoronary pressure [26].

Using intracoronary Doppler, a Doppler-tipped guidewire is used for estimation of coronary flow velocities (cm/s) during rest and peak hyperemia. CFR is calculated using formula: $CFR = \frac{mean\ hyperemic\ coronary\ flow\ velocity}{mean\ resting\ coronary\ flow\ velocity}$ [27]. Doppler-derived hyperemic microvascular resistance (HMR) index is calculated by dividing distal intracoronary pressure by hyperemic coronary flow velocity: $HMR = \frac{distal\ intracoronary\ pressure}{mean\ hyperemic\ coronary\ flow\ velocity}$ [28].

In patients without flow-limiting CAD, CFR <2 and IMR ≥25 are diagnostic for CMD [23]. Currently, there is no agreement regarding a HMR cut-off; however, HMR >2.5 has previously been reported to predict CMD, defined as CFR <2, assessed by positron emission tomography (PET) [29].

Evaluation of Coronary Endothelial Function

Invasive functional testing using intracoronary administration of acetylcholine (incremental doses of 10^{-6}, 10^{-5}, and 10^{-4} mol/L) is currently the only recommended method of assessment of coronary endothelial function [10, 23]. In healthy humans, intracoronary administration of acetylcholine causes vasodilation through release of nitric oxide from the endothelium. In the presence of endothelial dysfunction, the arterial and arteriolar response to acetylcholine is either blunted or involves a paradoxical vasoconstriction [21].

Arterial endothelial dysfunction (causing epicardial vasospasm) and arteriolar endothelial dysfunction (causing microvascular vasospasm) often coexist. Epicardial coronary artery spasm is another INOCA endotype with its own treatment pathway. Intracoronary acetylcholine provocation testing can be used to rule out epicardial vasospasm as the cause of symptoms and ischemia in patients suspected for CMD. According to the European Association of Percutaneous Cardiovascular Interventions (EAPCI) Expert Consensus Document on INOCA, an acetylcholine test with no or <90% reduction of epicardial vessel diameter, provocation of angina symptoms, and concomitant ischemic changes on ECG is diagnostic of CMD [10]. Severe epicardial vasospasm (≥90% diameter reduction), angina symptoms, and ischemic changes on ECG are diagnostic for epicardial vasospastic angina [10].

Cold pressor test has historically been used in the assessment of coronary endothelial function; however, due to its low sensitivity and modest correlation with intracoronary acetylcholine test, it is no longer recommended by the guidelines [23].

Non-Invasive Techniques

Evaluation of Non-Endothelial Dependent Coronary Microvascular Function

ESC recommended methods for assessment of non-endothelial dependent coronary microvascular function are coronary flow velocity reserve (CFVR) evaluation by transthoracic Doppler echocardiography (TTDE) in the LAD, myocardial blood flow reserve (MBFR) by PET, and evaluation of myocardial perfusion reserve (MPR) by cardiac magnetic resonance imaging (CMR).

In experienced hands, TTDE CFVR in the LAD is highly feasible, reproducible, and correlates well with CFR acquired using invasive techniques [30–37]. Using modified/ foreshortened parasternal or apical views, mid and distal segments of LAD can be visualized by 2D color Doppler, with or without the use of intravenous contrast enhancement. When coronary flow signal is identified and aligned as parallel to the ultrasound beam as possible, the biphasic coronary flow signal is visualized using pulsed-wave Doppler. Peak coronary flow velocity (m/s) is measured at rest and hyperemia, induced by adenosine, dipyridamole, or regadenoson. Similar to invasively derived CFR, TTDE CFVR is a ratio of basal to hyperemic peak diastolic coronary flow velocities: $CFVR = \frac{peak\ hyperemic\ coronary\ flow\ velocity}{average\ resting\ coronary\ flow\ velocity}$ (Fig. 2) [37]. Guidelines suggest a cut-off for CFVR <2 is diagnostic for CMD [23], but in reality there is a continuum of CMD.

High-quality imaging is critical to TTDE CFVR. Currently, there is no consensus on how the quality of the CFVR should be assessed. Based on a large, unselected sample of symptomatic women with no obstructive CAD ($n = 947$) investigated for CMD using TTDE ($n = 947$), the iPOWER research group has proposed a semi-quantitative quality score based on 4 main criteria: vessel identification, maintenance of probe positioning, visibility and configuration of coronary flow signal, and coronary flow signal characteristics [37]. A high-quality TTDE CFVR evaluation is characterized by a well-defined, single-vessel coronary signal, parallel alignment of beam direction to the coronary flow,
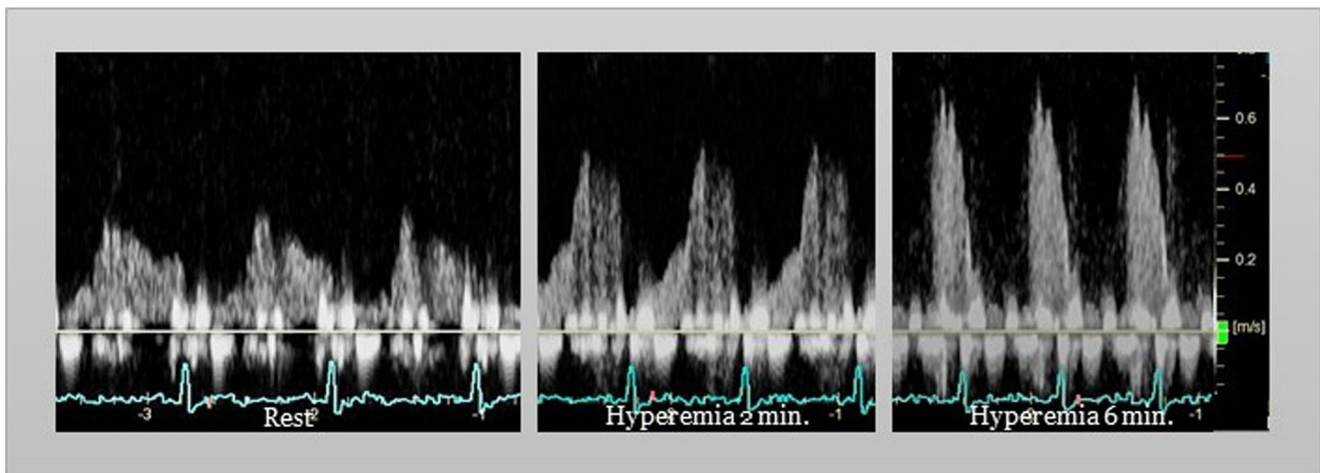
Fig. 2 Left anterior descending artery flow curves at rest and during adenosine-induced hyperemia imaged by transthoracic Doppler echocardiography

consistent measuring angle during rest and hyperemia, and well-defined biphasic flow curves gradually increasing during hyperemia.

Myocardial perfusion imaging by PET uses a dynamic imaging protocol to calculate the rate of radioactive tracer uptake into the left ventricular myocardium, allowing for an automated quantification of absolute global myocardial blood flow (mL/min/g) at rest and peak hyperemia. The most commonly used tracers are rubidium-82, oxygen-15 labeled water, and nitrogen-13 ammonia [38]. The scan protocol starts with a rest phase, followed by a stress phase acquired during adenosine- or regadenoson-induced hyperemia. When rubidium-82 or oxygen-15 labeled water tracers are used, the stress phase follows rest phase without a delay, resulting in a total examination time of approx. 30 min. When nitrogen-13 ammonia is used, the stress phase is delayed (minimum of 30 min) to allow for tracer decay, prolonging the total scan time to approx. 60–80 min [38]. Reported radiation exposure is approx. 4.3 mSv for rubidium-82 cardiac PET, 0.8 mSv for oxygen-15 labeled water cardiac PET, and 1 mSV for nitrogen-13 ammonia cardiac PET [38]. MBFR or CFR, terms that are used interchangeably in the PET literature, generally correlates well with invasively determined CFR and is defined using the formula: $MBFR/CFR = \frac{hyperemic\ absolute\ global\ myocardial\ blood\ flow}{resting\ absolute\ global\ myocardial\ blood\ flow}$ [39, 40].

In patients without flow-limiting CAD, MBFR/CFR <2 is regarded as diagnostic for CMD. There is a wide range of commercial software packages available for an automated quantification of both regional and global myocardial perfusion. Several studies have investigated the repeatability and reproducibility of rubidium-82 PET CFR, and results have been conflicting. Overall, an acceptable reproducibility between software packages can be achieved provided that the kinetic model used to conduct the data is the same [41–43]. Considering repeatability, a recently published study investigating test-retest properties of rubidium-82 PET using 3 commercially available software packages reported suboptimal findings with coefficient of variation (CoV) of approx. 20% in healthy individuals [41].

Evaluation of coronary microvascular function by CMR myocardial perfusion in angina patients with no obstructive CAD is recommended by ESC guidelines; however, only a few studies have explored and validated CMR as a diagnostic tool for CMD, and the reported results have been inconsistent [44–50]. Moreover, there is currently no diagnostic CMR MPR threshold for CMD, which limits the clinical applicability of the method. Compared with typically well-defined rest-to-stress regional hypoperfusion defects seen in patients with flow-limiting CAD, the diffuse and patchy pattern of myocardial hypoperfusion associated with CMD is difficult to evaluate qualitatively [25, 51].

Perfusion abnormalities consistent with CMD can be detected using a semi-quantitative approach. CMR uses rest to stress changes in myocardial signal intensities using an extracellular-based contrast agent, gadolinium, to assess MPR. Hyperemia is traditionally achieved using adenosine, regadenoson, or dipyridamole. MPR is calculated as a ratio of myocardial signal intensity upslope at peak hyperemia and rest, normalized to the arterial input function: $MPR = \frac{relative\ upslope\ at\ peak\ hyperemia}{relative\ upslope\ at\ rest}$, where relative upslope is defined as the ratio between the maximum upslopes of the first-pass time-intensity curve of the myocardium compared to the LV cavity [46, 50]. Alternatively, MPR can be assessed quantitatively as a ratio of absolute myocardial blood flow (mL/min/g) at peak hyperemia and rest. For this technique, resting values of myocardial blood flow are corrected for the rate pressure product, an index of myocardial oxygen consumption, to account for cardiac workload [48].

MPR by CMR has shown to correlate with invasive CFVR by Doppler [52]. Reproducibility data for first-pass myocardial perfusion CMR are sparse. One study reported higher reproducibility of MPR for the semi-quantitative values (CoV 5.4 %) compared with the quantitative values (CoV 12.7%)

[53]. A study investigating test-retest differences in CMR perfusion measurement reported acceptable repeatability coefficients for global myocardial blood flow values and MPR [54].

Vasodilators

Assessment of non-endothelial dependent coronary microvascular function is traditionally performed using adenosine, dipyridamole, or regadenoson. All three vasodilators can be used interchangeably. Of note, although the effect of these vasodilators is predominantly non-endothelial dependent, a minor part is mediated by endothelial release of nitric oxide [55]. Intravenous (0.14 mg/kg/min; 4–6 min) or intracoronary (<200 µg) adenosine induces arteriolar dilatation through activation of A2$_A$ receptors, resulting in smooth muscle relaxation and a 3–4-fold increase in coronary blood flow in healthy individuals [56]. Adenosine has a short half-life (<10 s), requiring no antidote. The most common side effects are shortness of breath, chest tightness, and flushing. Less common but more serious side effects are transient atrioventricular block and bronchospasm [57]. Intravenous dipyridamole (0.84 mg/kg; 4–6 min) increases coronary blood flow by inhibiting reuptake of endogenous adenosine. Dipyridamole has a significantly longer half-life compared with adenosine, and administration of an antidote (aminophylline; 50–250 mg) is often necessary. The most common side effects are chest and abdominal discomfort, headache, and dizziness [58]. Similar to adenosine, intravenous regadenoson (0.4 mg; rapid injection) is a selective A2$_A$ receptor agonist acting on arteriolar smooth muscle cells. Common side effects are shortness of breath, headache, and flushing. Persisting adverse reactions can be attenuated using aminophylline.

Patient Preparation

The use of non-endothelial dependent vasodilators requires 24-h abstinence from food and drinks containing a significant amount of methylxanthines (e.g., coffee, sodas, chocolate, banana etc.), which block adenosine receptors [59]. Medications containing dipyridamole should be paused for 48 h. Medications affecting myocardial perfusion or cardiac workload (e.g., nitrates, β-blockers, antihypertensives) should be paused for 24 h.

Prevalence of CMD by Modality

The reported prevalence of CMD in patients with angina and no obstructive CAD varies significantly depending on patient selection and the method of assessment. One-stop evaluation of both microvascular angina and epicardial vasospastic angina is typically performed as an add-on investigation to a diagnostic coronary angiography, using either intracoronary Doppler or thermodilution and acetylcholine test, with reported CMD prevalence as high as 64% [60]. Testing for non-endothelial dependent CMD can be performed non-invasively and is therefore more accessible, cost- and time-efficient, can be done repeatedly with no radiation exposure, and is associated with fewer procedure complications compared with the functional testing in the catheterization laboratory.

Among the non-invasive modalities, intracoronary Doppler and TTDE measure coronary flow velocities, while PET and CMR measure myocardial perfusion. Thus, the reported prevalence of CMD in studies using either flow- or perfusion-based methods is often different, suggesting that the methods are not interchangeable [36]. Furthermore, the reported prevalence of CMD depends on the cut-off applied. Up until recently, TTDE CFVR cut-offs <2 and <2.5 were frequently used to define non-endothelial dependent CMD [61, 62]. In a large study of patients with angina and no obstructive CAD ($n = 1.498$; 65% women), non-endothelial dependent CMD (intracoronary Doppler; CFR cut-off <2.5) was reported in 12% of participants, epicardial and/or microvascular endothelial dysfunction (abnormal coronary blood flow response to acetylcholine) in 33% of participants, and both in 19% of participants [60]. In the smaller WISE cohort of symptomatic women with no obstructive CAD, non-endothelial dependent CMD (intracoronary Doppler CFR cut-off <2.5) and abnormal epicardial response to acetylcholine (vasoconstriction or lack of vasodilation) were reported in 43% and 50% of women, respectively [62]. In the iPOWER cohort of 1.684 symptomatic women with no obstructive CAD, the prevalence of non-endothelial dependent CMD assessed by TTDE using a CFVR cut-off <2 was 25% [18]. The reported prevalence of non-endothelial dependent CMD in other TTDE studies using CFVR cut-off <2 ranges between 22 and 40% [63, 64]. In a large study of patients with angina and no previous history of CAD ($n = 1.218$; 67% women), non-endothelial dependent CMD assessed by PET (CFR cut-off <2) was found in 53% of participants with similar prevalence in men and women [19].

Prognostic Significance of CMD

A meta-analysis assessing the prognostic value of impaired coronary microvascular function in symptomatic patients with no obstructive CAD concluded that the presence of non-endothelial dependent CMD, evaluated by PET or TTDE, was associated with a 2- to 4-fold higher risk of adverse cardiovascular outcomes. Abnormal vasomotor response to acetylcholine was associated with a 2-fold higher risk of adverse cardiovascular outcomes [11].

It is important to acknowledge that historically there has not always been a clearly defined diagnostic threshold for non-endothelial dependent CMD, and that the accepted modality-specific thresholds are constantly challenged by the accumulating prognostic data. In the published literature, TTDE/PET CFVR/CFR associated with increased risk of cardiovascular events in patients with no obstructive CAD have ranged between 1.6 and 2.6 [12, 13, 65, 66]. Recently published prognostic data from the iPOWER cohort ($n = 1681$), followed for a median of 4.5 years, showed an independent inverse association between TTDE CFVR and adverse cardiovascular outcomes (HR 1.05 [95% CI 1.01–1.09] per 0.1 unit decrease in CFR), primarily driven by an increased risk of myocardial infarction and heart failure. The study suggested an optimal TTDE CFVR threshold of 2.25, which was associated with nearly a 2-fold increase in cardiovascular risk (1.94 [95% CI 1.29–2.91]) [12•].

CMD in Different Clinical Settings

From a clinical perspective, individuals with CMD constitute a heterogeneous group of patients, presenting with a spectrum of symptoms and clinical findings. In addition to being a highly prevalent condition in patients with angina and no obstructive CAD, CMD has been documented in other clinical settings, including cardiomyopathy (hypertrophic, dilated cardiomyopathy, and takotsubo syndrome), aortic valve stenosis, and obstructive CAD [22]. Furthermore, coronary microvascular function is known to decline with age, and CMD has been associated with conventional cardiovascular risk factors, including hypertension, diabetes, dyslipidemia, and smoking [13, 60, 61, 63, 67–69]. Interestingly, several studies have shown that conventional risk factors account for little of the variation in coronary microvascular function, suggesting that other, not yet identified factors may play a role in the development and progression of CMD [60, 61, 70]. A few studies have suggested a link between inflammation and CMD [71–74]. A recently published iPOWER study has reported an association between specific pro-inflammatory biomarkers and CMD, confirming the potential role of inflammation in the pathophysiology of CMD [75].

Management

Currently, there is no guideline-recommended treatment strategy of CMD [23]. A systematic review of 80 studies on pharmacological (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, statins, beta-blockers, calcium channel blockers, antihyperglycemics, diuretics, hormone replacement therapy) and non-pharmacological (exercise and weight loss) interventions, investigated for the purpose of improving the coronary microvascular function, concluded that the existing knowledge is not sufficient to point toward any specific treatment strategy of CMD [76]. The current knowledge is based on small study cohorts investigating heterogeneous populations (various risk factor profiles and CAD severity) using different methodology (assessment of either non-endothelial dependent CMD and/or endothelial function using various techniques and diagnostic cut-offs), which results in conflicting findings and makes it difficult to compare results across the studies. Large, randomized, placebo-controlled trials, investigating homogeneous patient populations, targeting a specific CMD pathology, using reproducible method of assessment and an unambiguous diagnostic threshold for CMD, are needed to provide more knowledge on the effect of the available interventions on symptom burden, microvascular function, and risk reduction.

The recently published CORonary MICrovascular Angina (CorMicA) trial, a randomized, placebo-controlled trial investigating the effect of an invasive coronary angiography and microvascular function testing, followed by a patient-tailored treatment strategy (antianginal therapy, risk factor management, and lifestyle modification) in patients with angina and no obstructive CAD ($n = 151$; 74% women) has reported a marked and sustained reduction in angina severity and better quality of life at 6 months and 1 year compared with standard care [77, 78]. Importantly, patients with CMD, ischemia, vasospastic angina, and non-cardiac chest pain each followed different treatment pathways with de-escalation of inappropriate therapy. In a recent randomized trial, the iPOWER group have found that weight loss and risk factor optimization in symptomatic women with CMD were associated with a significant improvement in symptom burden, although not accompanied by improvement in coronary microvascular function [79]. These results underline the importance of coronary microvascular function testing to optimize treatment strategy to a specific diagnosis, rather than treating all patients with angina and no obstructive CAD using a "one size fits all" approach. An approach that ignores endotypes will often lead to unnecessary re-evaluations due to treatment failure or side effects in patients with causes of chest pain other than CMD. Larger trials are awaited to evaluate the value of treatment management guided by the coronary function testing.

According to the EAPCI Expert Consensus Document on INOCA, optimizing the risk factors associated with CMD (hypertension, dyslipidemia, diabetes), combined with lifestyle factor modification (weight loss, stress coping, smoking cessation), should be considered in patients with CMD. Furthermore, antianginal therapy with beta-blockers, calcium channel blockers, and/or angiotensin-converting enzyme inhibitors can be considered [10]. Evidence on treatment of CMD in the setting of myocardial disease or obstructive CAD is largely lacking.

Conclusion

CMD is highly prevalent in patients with angina and no obstructive CAD. Despite the condition being a strong marker of poor cardiovascular prognosis, patients with CMD are often underdiagnosed and undertreated. Coronary microvascular function can be assessed using both invasive and non-invasive techniques. Complete assessment of non-endothelial CMD and microvascular endothelial dysfunction can only be performed invasively; however, the potential risk of an invasive procedure should always be weighted against the benefit for the patient in terms of available treatment options and long-term risk reduction [10]. Modality-specific thresholds for CMD are challenged by the accumulating prognostic data. Currently, there are no guideline-recommended treatment strategies. Patient-centered approach guided by coronary microvascular testing, focusing on risk factor optimization, lifestyle modification, and targeted antianginal therapy, has shown promising results. Existing knowledge on CMD pathophysiology, prognosis, and treatment management is predominantly based on female-focused studies. Given that CMD is highly prevalent in both sexes, future research initiatives should include an equal distribution of men and women [19, 60].

Compliance with Ethical Standards

Conflict of Interest   The authors declare no competing interests.

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

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