**THE PRESENT AND FUTURE**

*JACC* STATE-OF-THE-ART REVIEW

# Coronary Microvascular Dysfunction Across the Spectrum of Cardiovascular Diseases

## *JACC* State-of-the-Art Review

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**ABSTRACT**

Coronary microvascular dysfunction (CMD) encompasses several pathogenetic mechanisms involving coronary micro-circulation and plays a major role in determining myocardial ischemia in patients with angina without obstructive coronary artery disease, as well as in several other conditions, including obstructive coronary artery disease, nonischemic cardiomyopathies, takotsubo syndrome, and heart failure, especially the phenotype associated with preserved ejection fraction. Unfortunately, despite the identified pathophysiological and prognostic role of CMD in several conditions, to date, there is no specific treatment for CMD. Due to the emerging role of CMD as common denominator in different clinical phenotypes, additional research in this area is warranted to provide personalized treatments in this "garden variety" of patients. The purpose of this review is to describe the pathophysiological mechanisms of CMD and its mechanistic and prognostic role across different cardiovascular diseases. We will also discuss diagnostic modalities and the potential therapeutic strategies resulting from recent clinical studies.  (J Am Coll Cardiol 2021;78:1352–1371)
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The term coronary microvascular dysfunction (CMD) has been used referring to the spectrum of structural and functional alterations at the level of coronary microcirculation, leading to an impaired coronary blood flow (CBF) and ultimately resulting in myocardial ischemia (1,2). As a result of the growing knowledge of the physiological

mechanisms of CMD and the new methods for its assessment, CMD is emerging as a major cause of myocardial ischemia in patients with angina without obstructive coronary artery disease (CAD) ("primary" microvascular angina) as well as in several other conditions, including obstructive CAD, primary cardiomyopathies, takotsubo syndrome (TTS), and heart

## HIGHLIGHTS

- CMD plays a pathophysiological role in various CVD states, influencing ischemic manifestations, symptoms, and prognosis, but its molecular, functional, and structural mechanisms have not been clarified.

- Various noninvasive and invasive techniques can be used to evaluate CMD in clinical practice, each of which has strengths and limitations.

- Better understanding of the physiopathology of CMD is needed to develop therapeutic strategies that ameliorate angina and improve long-term outcomes.

failure (HF), especially heart failure with preserved ejection fraction (HFpEF) (3). The purpose of this narrative review is to describe the pathophysiological mechanisms of CMD and its mechanistic and prognostic role across different cardiovascular diseases (CVD). We will also discuss diagnostic modalities and potential therapeutic strategies.

## PATHOGENETIC MECHANISMS OF ISCHEMIA CAUSED BY CMD

The coronary arterial system is composed of 3 uninterrupted compartments with decreasing size and distinct functions (4). The proximal compartment encloses the large epicardial coronary arteries, which have a capacitance function and offer little resistance to CBF; these vessels present a diameter that ranges from 5.0-0.5 mm with a 3-layered wall. The intermediate compartment comprises prearteriolar vessels (500-100 μm diameter) that offer significant resistance to blood flow resulting in a measurable pressure drop along its development. It can be further distinguished in 2 territories: the proximal (500-150 μm), more responsive to changes in flow, and the distal (150-100 μm), more sensitive to pressure variations. In general, their vasomotor actions are not directly governed by diffusible myocardial metabolites. The distal compartment is represented by intramural arterioles, with diameter <100 μm and with the function of matching myocardial blood supply with oxygen consumption. Arterioles are more responsive to changes in the intramyocardial concentration of metabolites and are mainly responsible for the metabolic regulation of CBF (5). Prearterioles, arterioles, and capillaries constitute the coronary microcirculation (Figure 1). The subset of disorders affecting the structure and function of the coronary microcirculation resulting in an inadequate coronary blood supply is defined as CMD.

**MOLECULAR MECHANISMS.** Although the mechanisms leading to CMD are not entirely clear, oxidative stress, caused by cellular reactive oxygen species (ROS) overproduction and accumulation together with the consequent inflammatory response, are considered key pathogenic mechanisms driving the development of CMD (6). Endothelial cells play a crucial role in regulating vasomotor activity by releasing vasoactive substances such as vasodilator nitric oxide (NO) and vasoconstrictor endothelin (ET)-1. Nicotinamide adenine dinucleotide phosphate oxidases (Nox) isoforms and mitochondria represent major systems accounting for the regulation of ROS production (7). The activation of Nox leads to ROS production and triggers p66$^{Shc}$ phosphorylation and translocation within the mitochondria. In mammals, p66$^{Shc}$ is a proapoptotic protein that further enhances ROS generation by altering the mitochondrial bioenergetic properties (6,8,9). In turn, p66$^{Shc}$ activation stimulates the activity of Nox, thus generating a vicious cycle of ROS augmentation. In vitro and in vivo studies showed that an increased concentration of intracellular ROS promotes the transformation of NO in peroxynitrite radicals and uncouple the endothelial NO synthetase, switching its activity from an NO- to an ROS-producing enzyme, leading to an impairment of NO-mediated vasodilation and an enhanced ET-1 vasoconstriction activity through activation of the RhoA/Rho-kinase pathway (10,11). Furthermore, epigenetic modifications, commonly detected in aging, further sustain oxidative stress by increasing ROS production, reducing the expression of antioxidant enzymes, and promoting proinflammatory cytokine production through activation of the nuclear factor kappa-light-chain-enhancer of activated B cells and expression of adhesion molecules (6).

The RhoA/Rho-kinase is another pathway strongly implicated in ROS synthesis, as well as in vascular smooth muscle cells (VSMCs) hypercontraction through the modulation of calcium sensitivity and phosphorylation of contractile myofilaments, regulating the force of smooth muscle contraction. It is

**FIGURE 1** Coronary Artery Circulation and Diagnostic Tools for CMD Assessment



The coronary arterial system is composed of large conductive vessels and the microcirculation (prearterioles and arterioles). Different invasive and noninvasive modalities can be used to characterize CMD. Notably, using noninvasive techniques, the diagnosis of CMD should be made only after the exclusion of obstructive CAD. CAD = coronary artery disease; CFR = coronary flow reserve; CFRV = coronary flow reserve velocity; CMD = coronary microvascular dysfunction; CMR = cardiac magnetic resonance; CT = computed tomography; HMR = hyperemic microvascular resistance; IMR = microcirculatory resistance index; MPR = myocardial perfusion reserve; MPRI = myocardial perfusion reserve index; PET = positron emission tomography.

**FIGURE 2** Role of CMD in Determining Ischemia

Ischemia may be cause by subtended by epicardial and/or microvascular structural and functional mechanisms. Epicardial causes determining ischemia include acute plaque disruption with lumen occlusion and epicardial coronary spasm, myocardial bridge, or progressive obstruction with vessel narrowing. CMD can result from an abnormal vasodilatory ability of the microvasculature, compressive external forces affecting the intramural microvessels, or microvascular spasm. CAD = coronary artery disease; VSMC = vascular smooth muscle cells.

therefore considered responsible for susceptibility of coronary vessels to spasm (11) and augments inflammation by inducing proinflammatory molecules both in VSMCs and endothelial cells.

**FUNCTIONAL ALTERATIONS.** CMD occurs as a consequence of functional alterations, structural alterations, or a combination of both (**Figure 2**). In particular, functional mechanisms responsible for CMD may be related to the presence of an impaired dilation (vasodilator abnormalities) and/or an increased constriction of coronary microvessels (microvascular spasm). Impaired vasodilation may be, in turn, caused by endothelium-dependent and/or endothelium-independent mechanisms (1-3,12). The reduced production and/or enhanced degradation of NO and other endothelial-derived relaxation factors result in a limited endothelial-mediated vasodilatory capacity. Of importance, the presence of CVD risk

factors has been shown to induce endothelial dysfunction, resulting in blunted CBF augmentation or vasoconstriction with frank reduction in CBF. Endothelium-independent mechanisms are less understood; attenuated vasodilator responses to papaverine, adenosine, or dipyridamole suggest that endothelial-independent vasodilatation likely involves an impaired relaxation of VSMCs. Moreover, an increased release of vasoconstrictor agonists (ie, ET-1), an enhanced susceptibility of VSMCs to normal vasoconstrictor stimuli, and an abnormal increase in sympathetic activity have also been questioned as potential mechanisms behind this phenomenon. Microvascular spasm is part of the spectrum of vasomotor abnormalities seen in patients with CMD, and it appears to be closely linked to the presence of endothelial dysfunction with prevailing vasoactive tone. Of note, the functional responsiveness of the microcirculation can be influenced by several variables, such as

**TABLE 1  Noninvasive Tools for Evaluation of CMD**

| Modality | Technique | Agent | Parameter | Diagnostic Threshold | Pros | Cons |
|---|---|---|---|---|---|---|
| Echocardiography | Pulsed-wave Doppler on the proximal LAD artery | Adenosine Dipyridamole Regadenoson | CFRV | CFRV <2 | • Inexpensive<br>• No radiation exposure<br>• No risks | • Limited to LAD region<br>• Extensive training<br>• Technical pitfalls (poor acoustic window in obese, lung diseases)<br>• Obstructive CAD needs to be excluded<br>• Very limited data with use in non-obstructive CAD |
| PET | Dynamic rest and vasodilator stress perfusion imaging | Adenosine Dipyridamole Regadenoson ¹³Nammonia, ⁸²Rb | MPR[a] MBF | MPR <2 | • Gold standard for noninvasive assessment of coronary microvascular function<br>• Global evaluation of microvascular function<br>• Low radiation exposure | • Limited availability<br>• Limited spatial resolution<br>• High costs<br>• Obstructive CAD needs to be excluded |
| CMR | Dynamic first-pass vasodilator stress and then rest perfusion images | Adenosine Dipyridamole Regadenoson Gadolinium-based contrast agents | MPR[a] MBF MPRI | MPRI <2 | • No radiation exposure<br>• Excellent spatial resolution<br>• All coronary territories can be evaluated at the same time<br>• Tissue characterization | • High costs<br>• Time-consuming<br>• Poor patient compliance<br>• Limited availability<br>• Limited ability for absolute quantification of MBF<br>• Obstructive CAD needs to be excluded<br>• Imaging artifacts<br>• Contraindicated in patients with severe renal disease, claustrophobia, arrhythmias, and implanted devices<br>• Still under research investigation |
| CT scan | Dynamic first-pass vasodilator stress and then rest perfusion imaging | Adenosine Dipyridamole Regadenoson Iodine-based contrast agent | MPR[a] | MPR <2 | • Combination of coronary anatomy and coronary perfusion data<br>• Evaluation of all coronary territories<br>• CTA-derived FFR | • Radiation exposure<br>• Risk of kidney disease<br>• Overestimation of MBF (caused by the vasodilatory effect of iodinated contrast)<br>• Limited ability for absolute quantification of MBF<br>• Still under research investigation |

[a]MPR is preferred to CFR when is not calculated invasively.

CAD = coronary artery disease; CFRV = coronary flow reserve velocity; CMR = cardiac magnetic resonance; CT = computed tomography; FFR = fractional flow reserve; LAD = left anterior descending artery; MBF = myocardial blood flow; MPR = myocardial perfusion reserve; MPRI = myocardial perfusion reserve index; PET = positron emission tomography.

heart rate, diastolic time, driving blood pressure, and left ventricular inotropism (1-3,12).

**STRUCTURAL ALTERATIONS.** Along with functional disorders, CMD may also be a consequence of structural alterations, particularly in patients with risk factors for CAD or with underlying cardiomyopathies. Structural abnormalities associated with CMD are mainly represented by luminal narrowing of the intramural arterioles and capillaries, perivascular fibrosis, and capillary rarefaction, often in the context of increased left ventricular mass (2). These phenomena are consistently documented in patients with hypertrophic cardiomyopathy (HCM) and hypertensive heart disease (13). In both of these conditions, the morphological changes observed are characterized by adverse remodeling of arterioles, resulting in medial wall thickening (mainly because of smooth muscle hypertrophy and increased collagen deposition) and variable degrees of intimal thickening, causing altered coronary physiology and CBF (13). An important common feature to these conditions is the diffuse nature of "microvascular remodeling," which extends to the whole left ventricle.

## ASSESSMENT OF CMD

Invasive and noninvasive techniques assessing the function and integrity of coronary microvasculature are required to evaluate the presence of CMD (Tables 1 and 2).

**NONINVASIVE TECHNIQUES.** Different noninvasive modalities can be used to characterize CMD. Notably, using noninvasive techniques, the diagnosis of CMD should be made only after the exclusion of obstructive CAD using computed tomography coronary angiography or invasive coronary angiography. Additionally, noninvasive techniques do not directly assess the inclination of coronary arteries to spasm, but do only test the vasodilator capacity of VSMC, allowing the identification of impaired vasodilatory capacity of the microcirculation.

Transthoracic Doppler echocardiography allows measurement of the maximal diastolic flow in the epicardial arteries during rest and adenosine/dipyridamole/regadenoson stress, known as coronary flow velocity ratio (CFVR) (14). It is often limited to the left anterior descending artery region, implicitly

**TABLE 2**   Invasive Tools for Evaluation of CMD

| Modality | Technique | Agent | Parameter | Diagnostic Threshold | Pros | Cons |
|---|---|---|---|---|---|---|
| Coronary angiography | Dynamic passage of angiographic contrast | Iodine-contrast agent | TIMI flow TFC | TIMI-2 TFC >25 frames | • Do not necessitate additional costs | • Do not provide information regarding the mechanism of CMD (impaired dilation vs microvascular spasm)<br>• Semiquantitative parameter<br>• Limited sensitivity<br>• Usually calculated after coronary angiography |
| Intracoronary temperature-pressure wire | Estimate of coronary blood flow using bolus (calculating the mean transit time) or continuous thermodilution techniques (does not need pharmacological agents to induce hyperemia) | Adenosine Papaverine Saline solution | CFR IMR | CFR <2- 2.5 IMR >25 U | • CFR and IMR allow a combined assessment impaired vasodilation and microvascular hyperconstrictive response<br>• IMR is specific for microcirculation and is not affected by resting hemodynamics<br>• HMR is independent of resting coronary flow<br>• FFR using the standard technique can be measured simultaneously | • CFR does not distinguish between microvascular and epicardial disease<br>• Cut-off values for IMR still debated<br>• Worse correlation with PET than HMR |
| Intracoronary Doppler flow-pressure wire | Direct measurement of coronary peak flow velocity | Adenosine | CFR HMR | CFR <2.5 HMR >1.7 mm Hg/cm/s | • CFR and HMR allow a combined assessment impaired vasodilation and microvascular hyper-constrictive response<br>• HMR is independent of resting coronary flow<br>• FFR using the standard technique can be measured simultaneously | • CFR does not distinguish between microvascular and epicardial disease<br>• Cut-off values for HMR still debated |
| Intracoronary provocative testing | Intracoronary infusion of vasoactive agents | Acetylcholine Ergonovine | — | — | • Easy to assess<br>• Evaluated at the time of coronary angiography<br>• Do not necessitate additional equipment | • Additional contrast and radiation<br>• Do not provide direct evidence of microvascular spasm<br>• Risk of arrhythmias<br>• Lack of availability |

CFR = coronary flow reserve; ECG = electrocardiography; FFR = fractional flow reserve; HMR = hyperemic microvascular resistance; IMR = index of microvascular resistance; PET = positron emission tomography.

assuming that this is representative of global microvascular function. CFVR is a reliable measure of coronary microvascular function in absence of any epicardial flow limitation, and cutoff values ≤2-2.5 are commonly used as indicative for impaired coronary microvascular function (15). Transthoracic Doppler echocardiography is feasible, is relatively inexpensive, and does not expose patients to radiation; however, it requires extensive training and is associated with many technical pitfalls (16). Contrast echocardiography can also be helpful, but is less commonly used in clinical practice.

Positron emission tomography (PET) is now considered the gold standard reference for noninvasive assessment of CMD, because it allows the measurement of myocardial perfusion reserve (MPR), evaluating all coronary territories at the same time by quantification of myocardial blood flow (MBF) at rest and during pharmacologically induced maximal hyperemia (ratio of stress/rest MBF) (17). Presently, MBF can be quantified noninvasively using radionuclide imaging, cardiac magnetic resonance (CMR), or contrast echocardiography, but PET is the mostly commonly used and validated technique. However, its use is restricted in clinical practice caused by the limited availability and high cost (16).

CMR allows a simultaneous assessment of cardiac anatomy, morphology, functionality, and myocardial perfusion. CMR stress perfusion with vasodilator stress is becoming routinely used for the evaluation of myocardial ischemia in patients with suspected obstructive CAD, but also has diagnostic and prognostic value in patients with suspected CMD (18,19). As for PET, CMR allows the quantification of MBF at rest and during pharmacologically induced maximal hyperemia. Semiquantitative evaluation of the first-pass perfusion images can be used to calculate an indexed ratio of perfusion-time intensity curve upslopes as a measure of MPR index in response to vasodilator stress (20).

Myocardial first-pass dynamic computed tomography (CT) scan, similarly to CMR, allows a (semi-)quantitative assessment of MBF and MPR (21). Studies on perfusion CT in the setting of CMD assessment are still sparse, and in contrast to CMR, this method is associated with

substantial radiation. Nevertheless, CT imaging represents a promising technique that allows the combination of computed tomography coronary angiography and CT perfusion for the exclusion of epicardial CAD and assessment of microvascular function within 1 diagnostic tool (16).

**INVASIVE TECHNIQUES.** Coronary angiography is an invasive test that allows to exclude the presence of obstructive CAD. Moreover, the dynamic passage of angiographic contrast also provides information on coronary microcirculation. The "coronary slow-flow phenomenon" is an angiographic entity characterized by the delayed opacification of the distal coronary vasculature in the presence of nonobstructive CAD, and is considered a surrogate for the presence of CMD. The criteria used to define the coronary slow-flow varies among studies, some utilizing the Thrombolysis In Myocardial Infarction (ie, TIMI-2 flow) and others using the corrected TIMI frame count (>25 frames) (15).

A comprehensive invasive functional assessment of coronary microcirculation requires the investigation of the vasodilator as well as the vasoconstrictor microvascular response. For this purpose, coronary flow reserve (CFR) and microvascular resistance measurements by intracoronary Doppler or thermodilution along with intracoronary provocative testing have been introduced to obtain a combined assessment and diagnostic distinction of an impaired vasodilation of the microvasculature as well as an increased microvascular hyperconstrictive response.
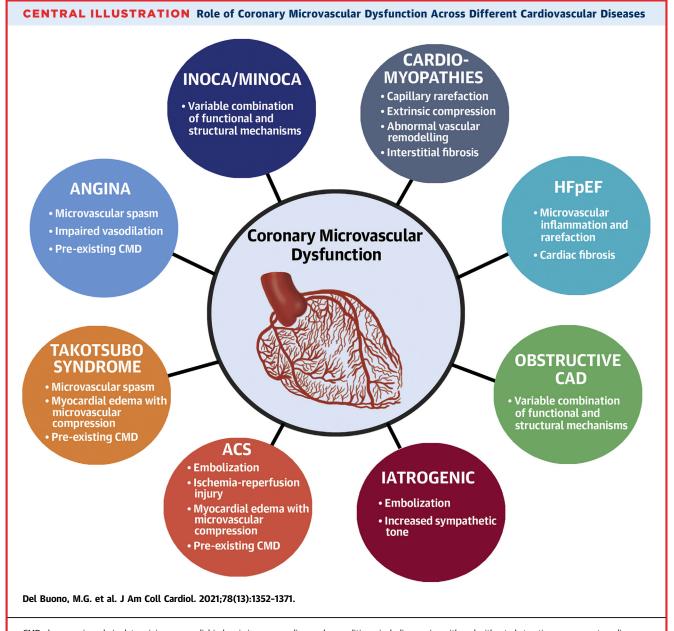
The vasodilator capacity of the coronary microcirculation is usually assessed by calculating the CFR as the ratio of maximum hyperemic to basal coronary flow velocity (with adenosine being the most used vasodilator for hyperemia) (1,2,16). It can be assessed by measuring coronary blood flow velocity by an intracoronary Doppler flow wire placed in the distal part of the studied coronary artery (usually the left anterior descending artery) or using a temperature sensor-tipped guidewire. The thermodilution technique estimates CFR indirectly via the saline bolus transit time, both of which are surrogates of true CBF. CFR can be reduced in patients with epicardial CAD as well as in patients with CMD who have an impaired hyperemic microvascular dilatory response; therefore, CFR can only serve as indicator of microvascular function in patients with unobstructed coronary arteries because it does not distinguish between microvascular and epicardial CAD. CFR is considered normal when values are >2.5 (1,2,16). The thermodilution-based index of microvascular resistances (IMR) has been introduced to selectively test microvascular dilatory function and is defined as the product of the distal coronary pressure and mean transit time of a saline bolus during maximal hyperemia (using adenosine or papaverine) (22). IMR is independent of epicardial vascular function and reproducible (22,23). Alternatively, hyperemic microvascular resistance incorporates Doppler flow velocity to estimate flow instead of thermodilution (24).

The diagnosis of a coronary vasospasm at the epicardial and/or microvascular level requires an intracoronary provocative test with pharmacological vasoactive agents (25). Microvascular spasm is defined as the concomitance of ischemic electrocardiographic changes along with reproduction of the typical symptoms (ie, chest pain) without angiographic evidence of epicardial spasm (26,27). In clinical practice, the most commonly used vasoactive provocative agents are acetylcholine (ACh) and ergonovine. ACh stimulates NO release from endothelium to vasodilate and directly induce VSMC contractility. Dependent on endothelial integrity and VSMC reactivity, the net effect of intracoronary ACh administration is either vasodilatation (healthy endothelium) or coronary spasm (26).

## CMD ACROSS DIFFERENT CVD

CMD is prevalent across different CVD, and may have a pathophysiological and a prognostic role in specific populations (Central Illustration).
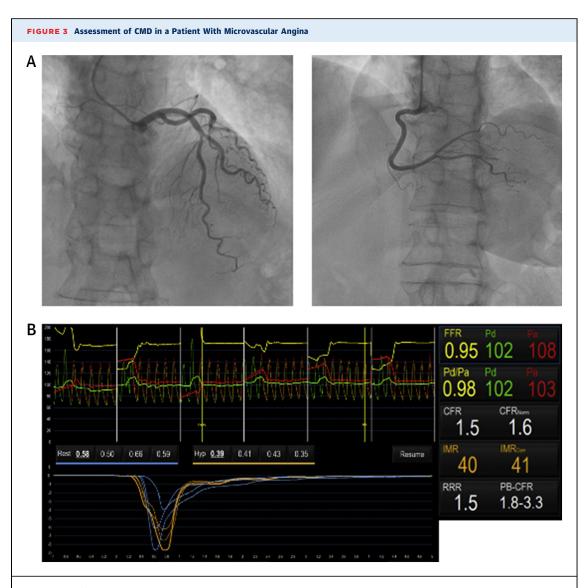
**CMD IN PATIENTS WITHOUT OBSTRUCTIVE CAD, MYOCARDIAL DISEASES, AND VALVULAR HEART DISEASES. Ischemia with nonobstructive CAD.** CMD, alone or in combination with CAD, is one of the mechanisms responsible for myocardial ischemia and symptoms in ischemia with nonobstructive coronary artery disease (INOCA) and can result in the clinical picture of primary microvascular angina (MVA), in which CMD is the principal alteration causing symptoms (15). MVA represents up to 40% of patients presenting with signs and symptoms of myocardial ischemia with normal or near-normal (<50%) coronary arteries at coronary angiography (1,15). The COVADIS (Coronary Vasomotor Disorders) study group proposed the following diagnostic criteria for MVA: signs and symptoms of myocardial ischemia, reduced CFR or microvascular spasm, and documented myocardial ischemia, which is not triggered by obstructive CAD but by functional or structural abnormalities at the site of the coronary microcirculation (Figure 3) (15). Of importance, in this subset of patients, the presence of CMD has also prognostic implications. Indeed, data from the National Heart, Lung, and Blood Institute-sponsored WISE (Women's Ischemia Syndrome Evaluation)

**CENTRAL ILLUSTRATION** Role of Coronary Microvascular Dysfunction Across Different Cardiovascular Diseases



**INOCA/MINOCA**
• Variable combination of functional and structural mechanisms

**CARDIO-MYOPATHIES**
• Capillary rarefaction
• Extrinsic compression
• Abnormal vascular remodelling
• Interstitial fibrosis

**ANGINA**
• Microvascular spasm
• Impaired vasodilation
• Pre-existing CMD

**HFpEF**
• Microvascular inflammation and rarefaction
• Cardiac fibrosis

**Coronary Microvascular Dysfunction**

**TAKOTSUBO SYNDROME**
• Microvascular spasm
• Myocardial edema with microvascular compression
• Pre-existing CMD

**OBSTRUCTIVE CAD**
• Variable combination of functional and structural mechanisms

**ACS**
• Embolization
• Ischemia-reperfusion injury
• Myocardial edema with microvascular compression
• Pre-existing CMD

**IATROGENIC**
• Embolization
• Increased sympathetic tone

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CMD plays a major role in determining myocardial ischemia in many cardiovascular conditions, including angina with and without obstructive coronary artery disease, myocardial infarction, nonischemic cardiomyopathies, takotsubo syndrome, and heart failure (especially HF with preserved ejection fraction). Many molecular, functional, and structural mechanisms may be involved and are related to the underlying disease. ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CAD = coronary artery disease; CMD = coronary microvascular dysfunction; HF = heart failure; HFpEF = HF with preserved ejection fraction; INOCA = ischemia with nonobstructive coronary arteries; MINOCA = myocardial infarction with nonobstructive coronary arteries; PCI = percutaneous coronary intervention.

study suggested that there is a worse prognosis in patients with INOCA, and low CFR was a robust independent predictor of MACE (28). These findings were then extended, and a reduced CFR (CFR <2) was found as a powerful incremental predictor of MACE in both women and men (29). Moreover, along with an adverse cardiovascular prognosis, INOCA patients have also a poor physical functioning and a reduced

quality of life (30). Recently, the CorMicA (CORonary MICrovascular Angina) trial provided proof-of-concept clinical evidence that a strategy of adjunctive invasive testing for disorders of coronary function linked with stratified medical therapy led to improvements in patient outcomes, including reduction in angina severity and better quality of life (31).

**FIGURE 3  Assessment of CMD in a Patient With Microvascular Angina**



Patient with effort angina and positive noninvasive stress testing. **(A)** Coronary angiography documented an angiographically normal right coronary artery **(right)** and intermediate coronary stenosis on mid-left anterior descending artery **(left)** without hemodynamic significance (FFR 0.95). **(B)** Microvascular function measured using a pressure wire coupled with thermodilution advanced into the distal part of the left anterior descending artery, at rest and during adenosine-induced maximal hyperemia, demonstrated an impaired coronary microvascular function (CFR 1.5 and IMR 40). Intracoronary provocative test with acetylcholine on left anterior descending artery was negative for epicardial and/or microvascular spasm, suggesting a mechanism of CMD caused by impaired vasodilation. CFR = coronary flow reserve; FFR = fractional flow reserve; IMR = index of microcirculatory resistance.

**Myocardial infarction with nonobstructive CAD.** Although CMD typically presents as stable ischemic heart disease, it is also considered a potential cause of myocardial infarction with non-obstructive CAD. The most common microvascular causes of myocardial infarction with nonobstructive coronary artery disease (MINOCA) are the obliteration of coronary microcirculation linked to thromboembolism (from left heart, paradox embolism caused by dx-sn shunt, or hereditary thrombophilic disorders) or microvascular spasm (32,33). In fact, although impaired vasodilation is the most common identifiable mechanism for symptoms in patients with effort angina, microvascular spasm is usually associated with angina at rest, and sometimes with an acute presentation as MINOCA (27). However, limited studies evaluated the role of CMD in these patients. MINOCA remains often an underdiagnosed and untreated condition, associated with a significant incidence of adverse events as well as impaired quality of life (34).

**Takotsubo syndrome.** CMD may also be involved in the pathogenesis of TTS (35,36). Sympathetic over-reactivity following a stressful event may trigger a local myocardial spillover of catecholamines resulting in an acute microvascular coronary vaso-constriction and myocardial stunning. Accordingly, clinical studies using serial Doppler transthoracic echocardiography or PET scan demonstrated a reduced microvascular blood flow and CFR in the acute phase of TTS (37,38). CMD is reversible in most patients with TTS in which a perfusion defect was observed in the dysfunctional segments with transient improvements after intracoronary adeno-sine infusion and with complete recovery at 1 month of follow-up (39). Of importance, the degree of CMD may also have prognostic implications, because patients with TTS presenting with *coronary slow-flow* at coronary angiography have a worse clinical presentation and a poor long-term clinical outcome (40).

**Angina post-percutaneous coronary intervention or coronary artery bypass.** CMD may also play a role in determining recurrent or persistent angina even in patients treated with effective percutaneous coronary intervention (PCI) or coronary artery bypass (CABG). The mechanisms underlying angina in these scenarios are complex, are multifactorial, and involve both structural and functional causes (41). The presence of pre-existing CMD along with a predisposition to microvascular spasm and/or impaired vasodilatation may account for a significant proportion of cases. Indeed, the drug eluted by the stent after PCI has been shown to trigger vasoconstrictor disorders probably enhancing a pre-existing endothelial dysfunction (41). Importantly, a study by Ong et al (42) demonstrated that approximately one-half of patients undergoing coronary angiography for recurrent angina after PCI despite patent coronary arteries have functional causes of myocardial ischemia caused by microvascular or epicardial coronary spasm detected by ACh provocative test.

**CMD IN PATIENTS WITH OBSTRUCTIVE CAD. Chronic coronary syndrome.** In patients with obstructive CAD, CMD may coexist and determine myocardial ischemia in regions supplied by arteries without stenosis as well as synergistically contribute to magnify myocardial ischemia in regions with epicardial flow limitation (43). In fact, in patients with stable obstructive CAD, preserved coronary arteriolar vasodilator capacity in conjunction with the development of collateral flow may serve to prevent the occurrence of stress-induced myocardial ischemia (44-46). Furthermore, chronic adaptation of coronary microcirculation to a low perfusion pressure distally to a stenosis may negatively influence microvascular remodeling and capacity of maximal vasodilation after restoration of a normal basal CBF, with a variable time being required for coronary microcirculation to resume its normal vasomotility (47). At the same time, in the presence of CMD, fractional flow reserve may potentially underestimate the severity of an epicardial stenosis. This may also explain the discordance between lesion severity and the extent and severity of myocardial ischemia. Of importance, the presence of CMD among patients with obstructive CAD has also prognostic implications. Indeed, in patients undergoing elective PCI, an intracoronary Doppler-derived CFR <2.5 after PCI predicted recurrence of angina or ischemia within 1 month (48). Moreover, a reduced CFR was also associated with an adverse outcome in terms of cardiovascular death and readmission for HF independently of the presence of angiographic CAD and modified the effect of early revascularization, such that only patients with severely reduced CFR appeared to benefit from revascularization (in particular with CABG), underscoring the morbidity associated with CMD (43).

**Atherosclerotic acute coronary syndrome.** In patients with acute coronary syndrome, an acute CMD, namely microvascular obstruction (MVO), may occur (49). In particular, MVO refers to the inability to reperfuse the coronary microcirculation in a previously ischemic region, despite opening of the epicardial vessel. Pathogenic mechanisms underlying MVO are multiple and interacting, including distal atherothrombotic embolization, ischemia-reperfusion injury with endothelial cells death along with cardiomyocyte death, and myocardial edema and/or inflammation leading to microvascular compression ab-extrinseco. Extensive and severe MVO is associated with intramyocardial hemorrhage, an irreversible process of extravasation of erythrocytes caused by capillary destruction (49). Of note, in patients with ST-segment elevation acute myocardial infraction (STEMI), the occurrence of MVO (as assessed by different noninvasive modalities) has consistently been found to be a predictor of adverse events, with higher incidence of left ventricular remodeling, HF, and death (49). A recent meta-analysis showed that patients with an IMR >41 after primary PCI were more likely to have MVO at CMR (50). In addition, a high IMR (IMR >40) measured at the time of primary PCI for STEMI predicts longer-term clinical outcomes such as death and rehospitalization for HF (51).

**CMD IN PATIENTS WITH MYOCARDIAL DISEASES AND VALVULAR HEART DISEASES. CMD in HFpEF.** HFpEF is an umbrella term encompassing a clinical

heterogenous syndrome characterized by classic symptoms and signs of HF despite a normal or near-normal EF (52). Comorbidities, such as obesity, hypertension, metabolic syndrome, and type 2 diabetes mellitus (DM), are extremely common and, in fact, independent risk factors for HFpEF (52-54). Diastolic dysfunction, the key hemodynamic feature of HFpEF, is a multifaceted process of adverse LV remodeling, cardiometabolic dysfunction, and extracellular fibrosis. In animal models and patients with HFpEF, limited endothelial-dependent NO bioavailability has shown to promote proliferation of fibroblasts and myofibroblasts and affects energy-dependent cardiomyocyte relaxation through the hypophosphorylation of the cytoskeletal protein titin (55). Data from endomyocardial biopsy samples from patients with HFpEF showed that an inflamed microvascular endothelium allows monocytes' migration and transforming growth factor-β release, which promotes the differentiation of fibroblasts into myofibroblasts, collagen production, and cross-linking (54,56). Furthermore, this pro-inflammatory and pro-oxidative state may render the dysfunctional coronary microvasculature more vulnerable to repeat episodes of myocardial ischemia and microinfarcts, leading to interstitial fibrosis, shift in substrate metabolism, and reduced systolic reserve, ultimately leading to HFpEF in humans (56). Beyond the diastolic dysfunction, recently HFpEF has been reconceptualized more as a systemic disease, not limited at myocardium, and characterized by systemic multiorgan inflammation and microvascular dysfunction (57). The systemic multimorbidity-driven proinflammatory milieu may promote microvascular inflammation and rarefaction, and cardiac and extracardiac fibrosis (58-60). Whereas CMD exists also in heart failure with reduced ejection fraction (HFrEF), it is postulated to play a dominant role in the pathophysiology and outcomes of HFpEF (61,62). In a small prospective observational study, mean CFR was significantly lower and mean IMR was significantly higher in the HFpEF population compared with the control population, with over one-third of the HFpEF cohort exhibiting overt CMD, the latter associated with worse outcomes in terms of death or HF hospitalization at follow-up (63,64). The prevalence of CMD was the confirmed in a large series of patients with HFpEF undergoing direct intracoronary hemodynamic measurements using Doppler wire, the majority of which displayed CMD caused by both endothelium-dependent (an increase in CBF ≤0% in response to ACh) and independent mechanisms (CFR ≤2.5) (61). Recently, the multinational PROMIS-HFpEF (PRevalence Of MIcrovascular dySfunction in Heart Failure with Preserved Ejection Fraction) study showed that 75% of HFpEF patients have CMD (defined, using Doppler echocardiography, as CFR <2.5), and a prespecified exploratory analysis found that CMD was also independently associated with cardiovascular and HF-related events at follow-up (65,66). However, it remains to be determined whether CMD is the "primum movens" leading to ventricular remodeling/diastolic dysfunction and HFpEF, or alternatively, this myocardial remodeling property of HFpEF may secondarily lead to CMD. Previous studies suggested that women with CMD often have left ventricular diastolic dysfunction and are at increased risk of developing HFpEF (67). Recently, Taqueti et al (68) showed that the presence of both CMD and diastolic dysfunctions was associated with a markedly increased (>5-fold) risk of HFpEF hospitalization. Moreover, recently has been shown that exercise intolerance symptoms not only recognize reduced cardiac output as leading cause of limitation, but underscored the importance of peripheral contribution with impaired lung function and skeletal muscle diffusion capacity on the delineation of this clinical scenario. This capillarity alteration is probably linked to a systemic microvascular deregulation and inflammation, which progressively reveal to be the leitmotif of this tangled continuum (58).

**CMD and diabetic cardiomyopathy.** In patients with DM, the evidence of myocardial dysfunction in the absence of apparent pathological substrates for cardiac damage (eg, arterial hypertension, CAD, valvular abnormalities) has been classically defined as "diabetic cardiomyopathy" (69). However, the presence of several concomitant and confounding factors such as CAD, aging, and comorbidities led to abandoning the use of the term "diabetic cardiomyopathy" and promoting the use of HFrEF and HFpEF as separate entities.
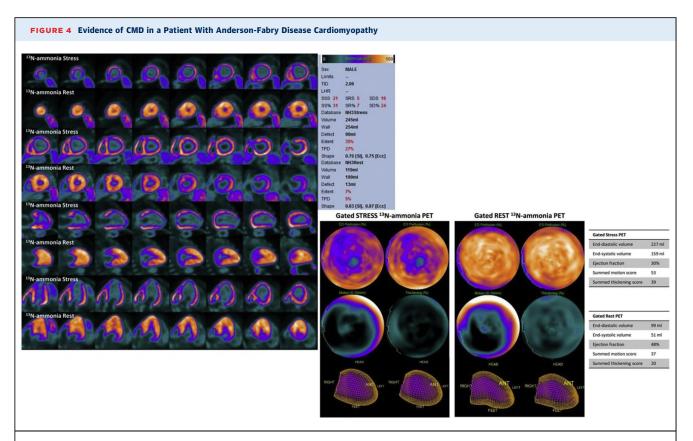
Impaired insulin signaling, hyperglycemia/glucotoxicity, and lipotoxicity are considered major pathophysiological drivers of DM-related diastolic dysfunction. These factors, as aforementioned, increase oxidative stress and contribute to create the proinflammatory substrate promoting microvascular dysfunction and HFpEF phenotype. Data from prospective and retrospective studies suggest that DM-HFpEF is associated with multimorbidity, poor functional status, lower exercise capacity, increased markers of inflammation, fibrosis, endothelial dysfunction, worse congestion, and increased morbidity and mortality supporting the existence of a distinct, high-risk, DM-HFpEF phenotype (70,71).

HFrEF phenotype is the result of sarcomere disappearance and cardiomyocyte cell death, followed by the extensive replacement fibrosis. Cell death is the principal mechanism caused by oxidative stress, tissue hypoxia induced by microvascular rarefaction, advanced glycation end-products deposition, and autoimmunity (69). The microvascular damage in DM patients is not only related to advanced glycation end-products deposition, vascular inflammation, and reduction in NO production, but also by a direct effect of the disease itself, which depletes endothelial cells and reduces capillary surface area (58).

**CMD in patients with aortic stenosis.** Up to 40% of patients with aortic stenosis (AS) experience angina that occurs frequently in the absence of epicardial CAD. The appearance of angina greatly increases the risk of sudden death, and when symptoms appear, the only effective treatment is surgical or transcatheter aortic valve replacement. Progression of AS is accompanied by discrepancies between blood supply and metabolic demand, with failing of the compensatory mechanisms because of structural and mechanical effects on the ventricle and coronary circulation (72). These patients have reduced MBF, impaired CFR, and reduced exercise capacity (73). A complex array of abnormalities in myocardial remodeling, coronary microvascular function, and pressure gradients are responsible for the distortion of coronary flow and symptoms developing, including the following: 1) reduced diastolic time of coronary filling (because of prolonged systole); 2) increased diastolic filling pressure (compressing the endocardium and leading to a selective hypoperfusion of the subendocardium); 3) delayed peak systolic forward flow and reduced velocity time integral; 4) disrupted backward expansion wave; 5) capillary rarefaction, arteriolar remodeling, and perivascular fibrosis; 6) reversal of normal endocardial-epicardial blood flow ratio at rest resulting in subendocardial ischemia; 7) low coronary perfusion pressure caused by Venturi effect when compared with intracavitary pressure; and 8) increased intramyocardial systolic pressure and delay in myocardial relaxation at the end of systole (which further reduces time of coronary filling and perfusion) (72). Of interest, 1 study found that low CFR was the only independent predictor of future cardiovascular events in AS patients (73). Percutaneous and surgical aortic valve replacement are associated with the restoration of myocardial perfusion and contractility and improved microcirculatory function by reducing LV wall stress (74), as shown by the reduced hyperemic microvascular resistance

values after transcatheter aortic valve replacement (75).

**CMD in patients with infiltrative heart diseases.** Anderson-Fabry disease is caused by an X-linked inherited deficiency of lysosomal a-galactosidase-A, determining a multiorgan glycosphingolipid deposition with renal, cardiac, and cerebrovascular damage. CMD has emerged as an important feature of Anderson-Fabry disease-associated cardiomyopathy and accounts for the considerable presence of angina in absence of obstructive CAD (**Figure 4**) (76-78). Myocyte hypertrophy, replacement fibrosis, hypertrophy, and proliferation of VSMCs and endothelial cells, narrowing intramural arteries, all contribute to raise coronary vascular resistance and increase myocardial oxygen demand (77-79). Moreover, although the typical hypertrophic phenotype is almost exclusively present in men, Tomberli et al (80) found that even women without hypertrophy had a significant degree of CMD as assessed by PET scanning, which could even represent an early sign of the disease. Recent findings have suggested that subtle abnormalities of microvascular function characterize a prehypertrophy phenotype and predetectable storage phase of cardiac involvement, providing a promising window for early therapeutic interventions (81).

Cardiac amyloidosis is characterized by the extracellular deposition of insoluble fibrils composed of misfolded proteins. Pathogenetic mechanisms of CMD in amyloidosis include structural changes of intramyocardial arteries (infiltration and thickening of the vascular wall with vessel lumen obstruction), functional abnormalities related to the imbalance of autonomic regulation and endothelial dysfunction, and extravascular factors (perivascular and interstitial amyloid deposits) resulting in increased left mass and extramural compression, decreased left ventricular compliance, and increased diastolic filling pressure (81). In the past decades, few studies have investigated CMD in a limited number of patients with amyloidosis experiencing chest pain. Al Suwaidi et al (82) demonstrated that patients with systemic amyloidosis can present with angina pectoris before the typical systemic manifestations of amyloidosis, and this presentation was associated with CFR abnormalities measured through intracoronary Doppler wire. Other clinical studies have confirmed a reduction of CFR in patients with amyloidosis and angina noninvasively, resorting to contrast echocardiography, PET, and CMR (81). Hitherto, no available study has investigated either the prognostic impact of CMD severity or the effects of specific therapies on microcirculation and symptom control.

**FIGURE 4**   Evidence of CMD in a Patient With Anderson-Fabry Disease Cardiomyopathy



**(Left)** 13N-labeled ammonia cardiac PET images show no significant perfusion defects at rest with a severe global subendocardial ischemia after pharmacological stress. Cardiac CT scan was previously performed to rule out obstructive CAD as the cause of angina. **(Right)** PET show abnormal left ventricular wall motions as well as a significant reduction in left ventricle ejection fraction from rest to peak stress. Reproduced with permission from Graziani et al (77). Abbreviations as in **Figure 1**.

Sarcoidosis is a multisystem noncaseating granulomatous disease. Up to 25% of patients with sarcoidosis have myocardial involvement, although only 5% of patients show clinical manifestations of cardiac disease; angina is a frequent symptom in sarcoidosis, whereas only a limited fraction of patients have obstructive CAD. Many studies, using noninvasive methods, demonstrated reduced CFR in patients with sarcoidosis; however, the underlying putative mechanisms are not well understood (83).

**CMD in patients with HCM.** The hallmark of HCM is the massive hypertrophy, which is generally asymmetric and develops independently of hemodynamic or systemic triggers. Along with cardiomyocyte hypertrophy, HCM phenotype involves a complex interplay of myocyte disarray, interstitial fibrosis with thickened fibers encasing myocytes, mitral valve and subvalvular abnormalities, and coronary microvascular remodeling. These structural abnormalities are considered the most relevant substrate of CMD that, in the presence of increased oxygen demand, ultimately exposes to recurrent myocardial ischemia and its sequelae (13). Several studies have shown that CFR is more blunted in the subendocardium and the more hypertrophied areas, but is also impaired in the nonhypertrophied ones, in line with the evidence of a widespread remodeling of intramural arterioles at autopsy (84-86). CMD over time may also lead to recurrent ischemia and myocyte death leading to foci of replacement fibrosis, as shown by the presence of areas of late gadolinium enhancement at CMR. Furthermore, CMD assessed by PET has been shown to be a long-term predictor of adverse remodeling, systolic dysfunction, clinical deterioration, and death in HCM (84-86).

**CMD in patients with dilated cardiomyopathy.** Previous studies have identified myocardial perfusion abnormalities in patients with dilated cardiomyopathy with moderate or severe adverse remodeling. Myocardial ischemia attributable to CMD is an independent contributor in the progression of the disease (87,88). However, further work is required to elucidate the temporal relationship between perfusion abnormalities and ventricular dysfunction in dilated cardiomyopathy. The degree of CMD has been shown to be an independent predictor of CVD events and is

associated with increased risk of death and further progression of HF (87).

## IATROGENIC CMD

Iatrogenic CMD may occur after percutaneous or surgical coronary revascularization, limiting their clinical benefit. In patients undergoing PCI, the mechanisms underlying CMD are distal embolization of plaque material during the stenting procedure or functional alterations, which may overlap a pre-existent CMD. Ischemia caused by balloon inflations and the stretch of the artery may in fact elicit a reflex sympathetic increase of α-adrenergic constrictor tone in the microcirculation (89). This complication often results in troponin elevation, which occurs in one-third of patients and is associated with an increased risk of subsequent major CVD events, death, myocardial infarction, and re-PCI. In patients with stable CAD undergoing elective PCI, IMR (IMR ≥25) measured immediately after PCI predicts adverse events independently of fractional flow reserve, indicating the prognostic importance of CMD despite successful epicardial coronary revascularization (90). In patients undergoing CABG, a number of factors can influence microvascular function, including cardioplegia, extracorporeal circulation, periprocedural ischemia, and inflammatory response. Similarly, the prognostic impact of myocardial damage following CABG is as clinically relevant as the one following PCI, suggesting that patient prognosis is eventually driven by the extent of necrosis regardless of the mechanisms responsible for its occurrence (91). A potential explanation is that myocardial damage might lead to increased mortality as a result of electrical instability or of persistent myocardial ischemia associated with CMD.

Furthermore, CMD is also common in heart transplant recipients with cardiac allograft vasculopathy (CAV). Of importance, CMD has been shown to be independently associated with the onset of epicardial CAV and associated with a higher risk of death, regardless of CAV onset (92).

## TARGETING CMD

To date, there are no specific therapeutic strategies targeting CMD validated by large-scale randomized clinical trials, and therefore, treatment of patients with CMD should be targeted on the risk factors and specific phenotypic presentation.

Physical training, smoking cessation, and intentional weight loss (in obese patients) have consistently been shown to be beneficial in improving CFR, exercise capacity, cardiorespiratory fitness, and CVD outcomes (93-96) (**Table 3**).

In patients with high levels of low-density lipoprotein cholesterol or at high CVD risk profile, statin therapy exerts significant off-target effects as a consequence of its anti-inflammatory and antioxidant properties, and previous studies have confirmed its efficacy in improving CFR (97).

Third-generation beta-blockers, such as nebivolol and carvedilol, and dihydropyridine-type calcium-channel blockers have been shown to modify endothelial function along with their effect on reducing myocardial oxygen demand and increasing diastolic perfusion time (98,99). Beta-blockers are the cornerstone of therapy in HFrEF patients; they have also been shown to improve angina symptoms in MVA patients with effort-induced angina and evidence of increased adrenergic activity, and are considered as first-line therapy in this patient population (98,99). However, currently there is no evidence of benefit for beta-blocker use in patients with HFpEF (100). Non-dihydropyridine calcium-channel blockers are effective in patients with MVA often triggered by microvascular spasm, as well as in patients with documented epicardial coronary spasm (101).

The large TREND (Trial on Reversing ENdothelial Dysfunction) (102) provided evidence that angiotensin-converting enzyme inhibitors, in particular quinapril, was able to reverse endothelial dysfunction, and these beneficial effects have been replicated by several other studies involving angiotensin II receptor blockers. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are the first-line therapy in patients with HFrEF (99) but failed to improve overall morbidity or mortality in patients with HFpEF (100). In patients with INOCA, enalapril improved CFR as well as exercise parameters in patients with MVA in a cohort of 20 Taiwanese patients compared with placebo (103). In another randomized study of women with INOCA and CMD, quinapril treatment improved CFR in response to adenosine as well as angina pectoris symptoms after 16 weeks of treatment when compared with placebo (104).

Sacubitril-valsartan has been approved by the U.S. Food and Drug Administration for patients with symptomatic chronic HFrEF to reduce CVD mortality and hospitalization for HF compared with enalapril (105). Conversely, sacubitril-valsartan failed to meet a statistical difference on the primary composite endpoint (total HF hospitalizations and cardiovascular death) in the HFpEF population when compared with valsartan (106). The ongoing PRISTINE-HF (Study of Sacubitril/ValsarTan on MyocardIal OxygenatioN and Fibrosis in Heart Failure with

**TABLE 3  Nonpharmacological Treatments Targeting CMD**

| Class of Intervention | Study Design | n | Major Inclusion Criteria | Primary Endpoints | Main Findings | Ref. # |
|---|---|---|---|---|---|---|
| Aerobic interval training and weight loss | CUT-IT trial Randomized clinical trial (12 weeks aerobic interval training or low-energy diet) | 70 | Obese patients with stable CAD | CFR assessed by transthoracic Doppler echocardiography on the LAD | ↑ CFR after aerobic interval training and after low energy diet without significant between-group difference | (94) |
| Smoking cessation | Rooks et al Twins Heart Study Investigation of psychological, behavioral and biological risk factors for subclinical cardiovascular disease using twins | 360 | Smoking and nonsmoking middle-aged male twins | CFR assessed as response to adenosine with PET | CFR was significantly lower in smokers compared with nonsmokers ($P < 0.01$) | (95) |
| Exercise training | Hambrecht et al Randomized clinical trial (exercise-training group n = 10 and control group n = 9) | 19 | Obstructive CAD and a noncritical stenosis in another coronary vessel with signs of endothelial dysfunction (defined as constriction or no change in response to acetylcholine) | Changes in vascular diameter in response to the intracoronary infusion of increasing doses of acetylcholine | ↑ endothelium-dependent vasodilatation ($P < 0.01$) | (96) |

CFR = coronary flow reserve; ECG = electrocardiogram; LAD = left anterior descending artery.

Preserved Ejection Fraction; NCT04128891) will investigate the effects of this drug on microvascular function and ischemia, as assessed by oxygen sensitive-CMR at rest and after stress.

The effects of several other antianginal drugs, such as ivabradine, ranolazine, nicorandil, and trimetazidine, all cooperating in reducing oxygen demand, have been investigated in patients with CMD (101). Ranolazine has been extensively used in small-cohort randomized clinical trials, with contrasting efficacy results in terms of CFR, symptom control, and stress test metrics (107,108). Ivabradine improved angina in patients with MVA without changing coronary microvascular function, suggesting that symptomatic improvement could be attributed to a heart rate–lowering effect. However, it has also been shown to improve CFR in patients with stable CAD even after heart rate correction, suggesting a potential role in microvascular function (101).

Nitrates have shown inconclusive effects in patients with CMD in multiple studies, probably burdened by bias in patient selection and inclusion criteria. However, short-acting nitrates can be useful to treat anginal attacks (especially in those patients with abnormal vasodilator reserve), but they are often only partially effective (101,107).

Phosphodiesterase type-5 inhibitors, such as sildenafil, enhance the effect of NO by inhibiting the breakdown of cyclic guanosine monophosphate favoring smooth muscle relaxation. The positive effects of sildenafil in CMD were first investigated by Denardo et al (109) who demonstrated a significant increase in CFR after the administration of the drug in patients with impaired microvascular function (109).

Fasudil, a specific Rho-kinase inhibitor, is highly effective in preventing ACh-induced coronary spasm and consequent myocardial ischemia in both patients with epicardial and microvascular spasm (110,111) (**Table 4**).

In patients with MVA, the findings of elevated circulating concentrations of ET-1 led to conducting 2 small trials with ET-1 receptor antagonists (atrasentan and darusentan; NCT00271492; NCT00738049) with favorable profiles in patients with MVA. However, following neutral results from phase III trials relating to their primary indications, they were no longer investigated for application in MVA. A randomized controlled trial in patients with MVA with zibotentan (NCT04097314), a potent inhibitor of the $ET_A$ receptor with no "off-target" binding to the $ET_B$ receptor, is now ongoing (**Table 4**).

Recently, 2 classes of drugs, the sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1-receptor antagonists, have consistently been demonstrated to reduce rates of major adverse CVD events in subjects with DM at high risk for CVD (112). SGLT2i and glucagon-like peptide 1-receptor antagonists could exert their effects by targeting several mediators of macrovascular and microvascular pathophysiology, such as cytokines and inflammation mediators, oxidative stress-induced endothelial dysfunction, and vascular smooth muscle cell proliferation, all etiological features of CMD (112). These data are further supported by the results recently published by Adingupu et al (113), who investigated the effects of SGLT2i on coronary microvascular function and cardiac contractility in a prediabetic mice model, showing

**TABLE 4  Upcoming Pharmacotherapies for Treating CMD**

| Drug Compound | Pharmacological Class | Beneficial Mechanisms in CMD |
|---|---|---|
| Fasudil | Rho-kinase inhibitor | Rho-kinase pathway is involved in endothelial dysfunction, vascular smooth muscle hypercontraction, vasospasm, and inflammatory cell accumulation in blood vessel adventitia |
| Atrasentan Darusentan Zibotentan Sitaxentan | Endothelin receptor antagonists | ET-1 contributes to coronary endothelial dysfunction |
| Dichloroacetate | Inhibitor of all isoforms of PDK kinase | Activation of PDK maintains myocardial ATP and glycogen, improving hypoxic tolerance and reversing microvascular dysfunction |
| Amiodarone Dronedarone | Cardiac K+ channel blockers | Potent coronary vasodilation, antiremodeling, and myocardial protectant actions |
| Colchicine Anakinra Rilonacept Canakinumab Tocilizumab | Tubulin inhibitor IL-1r antagonist IL-1 trap IL1 β inhibitor IL-6 inhibitor | Block coronary endothelial dysfunction Anti-ischemic, antiatherosclerosis actions |
| Empagliflozin Dapagliflozin Canagliflozin | SGLT2-channel inhibitors | Block coronary endothelial dysfunction Probable pleiotropic effects |
| Evolocumab Alirocumab | PCSK-9 inhibitors | Improvement in lipidic profile Reduction of ROS production Block coronary endothelial dysfunction |
| NPY receptor inhibitors | | NPY is a potent vasoconstrictor and inhibitor of cardiac vagal activity inducing transient ischemia by microvascular constriction NPY has a role in adverse differentiation of mesenchymal stem cells |
| TT-10 | Fluorine substituent | Promotion of cardiomyocyte proliferation, with antiapoptotic and antioxidant effects in vivo and in vitro |
| Vorinostat | Histone deacetylase inhibitor | Prevention of NF-kβ activation, endothelial NO synthetase uncoupling, and vascular oxidative stress |
| Apabetalone | Epigenetic regulator targeting bromo-domain and extraterminal proteins | Modulation of vascular inflammation |
| Bone-marrow-derived CD34+ cells | | Release of growth and differentiation factors Promotion of neovascularization and endogenous repair of damaged myocardium Improvement of bioenergetics Prevention of fibrosis |

ATP = adenosine triphosphate; CD = cluster of differentiation; ET-1 = endothelin-1; IL = interleukin; NF-kB = nuclear factor kappa-light-chain-enhancer of activated B cells; NPY = neuropeptide Y; PCSK-9 = proprotein convertase subtilisin/kexin type 9; PDK = pyruvate dehydrogenase kinases; ROS = reactive oxygen species; SGLT-2 = sodium–glucose cotransporter 2.

improvement in CFVR and fractional area change. The encouraging results by the EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) trial led to a focus on the effects of empagliflozin on CMD. It has been shown that empagliflozin directly restores the beneficial effect of cardiac microvascular endothelial cells on cardiomyocyte function, suggesting their potential role to improve CMD (114). Ongoing clinical trials are examining the effects of SGLT2i in HFpEF (EM-PEROR-PRESERVED [EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction; NCT03057951], DELIVER [Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure; NCT03619213] trial), which may recognize CMD as pathological substrate (**Table 4**).

The coronary microcirculation may also represent an important therapeutic target in patients presenting with myocardial infarction (49). In STEMI patients, no definite therapies have consistently been shown to be effective in improving MVO (4). Future research efforts should be directed toward evaluating the potential benefits of therapies aimed at improving coronary microcirculation in high-risk subgroups (ie, those with evidence of high microvascular resistances). Furthermore, the current guidelines do not address the management of patients with MINOCA, because of the lack of randomized control trials so far in this patient population (33). The "one-size-fits-all" approach uniformly applied to patients presenting with MI-CAD should be replaced by a personalized therapeutic approach guided the underlying pathophysiological mechanism responsible for the clinical presentation. Finally, CMD has been demonstrated to play a pathogenetic role in most myocardial diseases. Therefore, future studies specifically assessing the effect of therapy on CMD across different CVD are warranted.

## CONCLUSIONS

CMD represents a combination of structural and functional abnormalities affecting the coronary

microcirculation. It is prevalent across a broad spectrum of CVD risk factors and diseases. CMD significantly contributes to determine the clinical manifestations in all of these conditions and has a significant impact on prognosis. The limited knowledge about CMD across different cardiovascular diseases precludes providing clarity concerning the underlying pathophysiological mechanisms. This extends also to therapy, where, to date, no treatment specifically targets CMD. However, because of the emerging role of CMD as a key player in different clinical phenotypes, additional research in this area is warranted to fill knowledge gaps and provide personalized treatments in these "*garden variety*" patients.

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