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Review Article

Coronary Microvascular Dysfunction in Ischemic Heart Disease: Diagnostic and Therapeutic Advances

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Abstract

Coronary microvascular dysfunction (CMD) has emerged as a key pathophysiologic mechanism underlying ischemic heart disease (IHD) in the absence or presence of obstructive coronary artery disease. CMD is characterized by structural and functional abnormalities of the coronary microcirculation that impair the ability to match myocardial blood flow to metabolic demand. Endothelial dysfunction, vascular remodeling, oxidative stress, and inflammation constitute the principal biological drivers of this condition. CMD manifests clinically as angina with non-obstructive coronary arteries (INOCA), persistent ischemia after revascularization, or as a contributing mechanism in heart failure with preserved ejection fraction. Diagnosis remains challenging because the microcirculation is invisible to standard angiography and requires advanced non-invasive or invasive physiological testing, such as coronary flow reserve, index of microcirculatory resistance, or perfusion imaging. Current therapeutic strategies rely largely on lifestyle modification, risk factor control, and empiric pharmacologic therapy targeting endothelial function or vasomotion. However, persistent symptoms and adverse prognosis in many patients highlight the need for novel approaches. Emerging therapies—including endothelin antagonists, Rho-kinase inhibitors, SGLT2 inhibitors, nitric oxide modulators, and regenerative or device-based interventions—offer potential to address the underlying vascular dysfunction rather than merely relieving symptoms. Future research should focus on standardizing diagnostic criteria, developing biomarkers, and conducting phenotype-directed trials to enable precision therapy. Recognition and effective management of CMD are critical to improving outcomes in patients with ischemic syndromes extending beyond epicardial coronary disease.

Keywords: coronary microvascular dysfunction; ischemic heart disease; endothelial dysfunction; coronary flow reserve; microvascular angina

1.Introduction

Ischemic heart disease (IHD) has long been defined as a condition resulting from an imbalance between myocardial oxygen supply and demand, traditionally attributed to obstructive atherosclerotic lesions in the epicardial coronary arteries. However, clinical observations have shown that a considerable number of patients with angina and objective evidence of myocardial ischemia do not have significant epicardial stenoses. This discordance has shifted attention toward the role of the coronary microcirculation, whose dysfunction can lead to ischemic syndromes even in the absence of large-vessel obstruction [1]. Coronary microvascular dysfunction (CMD) describes abnormalities in the small resistance vessels that regulate myocardial blood flow. These abnormalities may be functional, structural, or both, and result in inadequate vasodilatory capacity, inappropriate vasoconstriction, or microvascular spasm. CMD is increasingly recognized as a key contributor to ischemia in patients with non-obstructive coronary artery disease (INOCA) and in those with persistent angina despite revascularization [2,3]. The clinical importance of CMD lies in its high prevalence and prognostic implications. Up to half of patients with angina and non-obstructive coronary arteries demonstrate impaired microvascular function when investigated with advanced diagnostic tools [4]. CMD is particularly prevalent among women, possibly reflecting sex-related differences in endothelial function and hormonal influences [5]. Despite the absence of obstructive lesions, these patients are not free from risk; several longitudinal studies have shown that CMD is associated with an increased incidence of adverse cardiovascular events, including myocardial infarction, heart failure, and death [6,7]. The recognition of CMD as a distinct pathophysiologic entity has exposed major diagnostic and

therapeutic challenges. There is currently no single gold-standard test for CMD. Invasive measurements of coronary flow reserve and microvascular resistance, along with non-invasive modalities such as positron emission tomography and cardiac magnetic resonance imaging, provide valuable insights but remain underused due to cost, technical complexity, and limited availability. Furthermore, the heterogeneity of CMD, encompassing both structural remodeling and endothelial dysfunction, makes uniform diagnostic criteria difficult to establish. The result is underdiagnosis and empirical management based on conventional antianginal therapy rather than mechanism-specific interventions. Treatment of CMD remains an area of unmet clinical need. Conventional agents such as beta-blockers, calcium channel blockers, and nitrates often fail to provide adequate symptom control. Therapies that target endothelial dysfunction, including angiotensin-converting enzyme inhibitors, statins, and novel vasomodulatory drugs, show promise but require further validation in randomized trials. Beyond pharmacologic options, recent studies have explored device-based and regenerative approaches aimed at restoring microvascular function. In summary, CMD represents an important and underappreciated cause of myocardial ischemia in both obstructive and non-obstructive forms of IHD. It bridges the gap between traditional macrovascular disease and unexplained angina syndromes, with significant prognostic relevance. However, its diagnosis remains complex and its treatment largely empirical. The present review aims to synthesize current understanding of the pathophysiologic mechanisms, diagnostic approaches, and emerging therapeutic strategies for CMD, while highlighting ongoing challenges and future research directions.

2. Pathophysiology of Coronary Microvascular Dysfunction

Coronary microvascular dysfunction (CMD) arises from an interplay of structural and functional alterations in the small resistance vessels of the heart. These changes degrade the ability of the coronary microcirculation to match myocardial perfusion to metabolic demand. The pathophysiology is multifactorial, involving endothelial dysfunction, smooth muscle cell dysregulation, inflammatory and oxidative pathways, microvascular remodeling, and disturbances in metabolic–vascular coupling.

Endothelial dysfunction is central. In normal physiology the endothelium modulates vasodilation via nitric oxide (NO) release, prostacyclin, and endothelium-dependent hyperpolarization. In CMD, bioavailability of NO is reduced by increased oxidative stress, uncoupling of endothelial nitric oxide synthase (eNOS), and reactive oxygen species (ROS) formation [8] [9]. Concurrent upregulation of vasoconstrictors such as endothelin-1 further disrupts basal tone regulation [10]. The balance shifts toward vasoconstriction, even at the microvascular level, limiting flow reserve and predisposing to microvascular spasm [11].

Structural changes accompany functional derangements. Persistent endothelial injury triggers remodeling in microvascular walls: hypertrophy of vascular smooth muscle cells, perivascular fibrosis, rarefaction (loss of capillary density), basement membrane thickening, and vessel lumen narrowing [12]. Some capillaries may regress (capillary drop-out), reducing overall microvascular cross-sectional area and increasing resistance. Pericyte loss or dysfunction further impairs microvascular integrity and responsiveness [13]. These structural alterations impose a fixed component of resistance unresponsive to vasodilators.

Another layer involves disturbed metabolic–vascular coupling. In a healthy heart, increases in myocardial demand trigger vasodilation via metabolic signals (adenosine, H^+, CO_2). In CMD, this coupling is disrupted, so metabolic signaling fails to elicit adequate vasodilatory response [11]. Microvascular autoregulation becomes less flexible. This is especially problematic during stress or increased demand, when microcirculation cannot further dilate, causing ischemia.

Inflammation and oxidative stress are additional contributors. Systemic factors (hypertension, diabetes, obesity, chronic kidney disease) foster a proinflammatory milieu, which induces endothelial activation, leukocyte adhesion, and microvascular injury. Activation of NADPH oxidase, xanthine oxidase, and mitochondrial ROS pathways amplifies oxidative stress, damaging microvascular endothelium [12]. Chronic low-grade inflammation contributes to microvascular remodeling and endothelial cell apoptosis [8].

Molecular signaling pathways are implicated: RhoA/Rho-kinase activation increases vascular smooth muscle contraction and impairs relaxation; the NO–cGMP axis is suppressed; signaling via MAP kinases, NF-κB, and TGF-β promote fibrotic changes [12]. Epigenetic modifications (microRNAs, histone modifications) are emerging as modulators that can "lock in" microvascular dysfunction phenotypes [13]. Cross-talk between microvasculature and systemic vascular beds suggests that CMD may reflect a systemic microvascular disease rather than isolated cardiac pathology [11].

In summary, CMD results from the convergence of endothelial failure, structural remodeling, impaired metabolic signaling, and persistent insults such as inflammation and oxidative stress. This multifaceted pathobiology helps explain why diagnosis is difficult and why a one-size-fits-all therapy is unlikely to succeed (Table 1).

Mechanism	Cellular / Molecular Basis	Consequence	Clinical Manifestation
Endothelial dysfunction	Reduced nitric oxide bioavailability, increased endothelin-1, eNOS uncoupling	Vasoconstriction, reduced coronary flow reserve	Exercise-induced ischemia, microvascular spasm
Oxidative stress	NADPH oxidase activation, excessive ROS production	Endothelial injury, perivascular fibrosis	Chronic angina, low CFR
Inflammation	Activation of NF-κB, IL-1β, TGF-β pathways	Capillary rarefaction, fibrosis	Progression to HFpEF
Structural remodeling	Smooth muscle hypertrophy, basement membrane thickening	Increased microvascular resistance	Persistent ischemia
Impaired metabolic–vascular coupling	Defective adenosine/H^+ signaling	Inadequate vasodilation during demand	Stress-induced ischemia

Table 1: Major Pathophysiological Mechanisms of Coronary Microvascular Dysfunction.

Abbreviations: NO: Nitric oxide; eNOS: Endothelial nitric oxide synthase; ROS: Reactive oxygen species; CFR: Coronary flow reserve; HFpEF: Heart failure with preserved ejection fraction; NF-κB: Nuclear factor kappa B; IL-1β: Interleukin-1 beta; TGF-β: Transforming growth factor beta.

3. Clinical Phenotypes and Epidemiology

Coronary microvascular dysfunction (CMD) is a heterogeneous condition that manifests across a wide spectrum of ischemic heart disease phenotypes. The clinical expression of CMD ranges from stable angina with non-obstructive coronary arteries to microvascular obstruction following myocardial infarction and the progressive development of heart failure with preserved ejection fraction (HFpEF). Recognition of these phenotypes has expanded the conceptual framework of ischemic heart disease beyond the epicardial vessel–centric model [5].

The most prominent phenotype is ischemia with non-obstructive coronary arteries (INOCA), in which patients present with angina, objective ischemia, and no flow-limiting epicardial stenosis on angiography. Epidemiologic studies have demonstrated that up to 60% of women and 30% of men undergoing coronary angiography for angina have non-obstructive disease, and approximately half of these exhibit evidence of CMD on invasive or imaging-based testing [4]. The Women's Ischemia Syndrome Evaluation (WISE) study and subsequent trials established CMD as a major mechanism underlying INOCA, particularly in postmenopausal women [14]. Hormonal withdrawal, endothelial dysfunction, and microvascular remodeling contribute to this sex-related predilection.

CMD also plays a critical role in the setting of obstructive coronary artery disease. In patients undergoing percutaneous coronary intervention (PCI), microvascular dysfunction frequently coexists with epicardial atherosclerosis and may limit post-revascularization flow recovery. Microvascular obstruction is a key determinant of infarct size, adverse ventricular remodeling, and long-term prognosis after acute myocardial infarction, even when epicardial reperfusion is successful [15]. The persistence of CMD following revascularization explains why some patients continue to experience angina and impaired perfusion despite patent stents.

Beyond angina and infarction, CMD contributes to the pathophysiology of heart failure with preserved ejection fraction. Systemic endothelial inflammation and microvascular rarefaction have been identified as mechanistic links between metabolic comorbidities, hypertension, obesity, and diabetes, and diastolic dysfunction [16]. In this context, CMD represents the cardiac manifestation of a generalized small-vessel disease that leads to myocardial stiffening and impaired relaxation. The prognostic importance of CMD is now well established. Patients with impaired coronary flow reserve or elevated microvascular resistance have a higher incidence of major adverse cardiovascular events, including myocardial infarction, hospitalization for heart failure, and cardiac death, even in the absence of obstructive CAD [17]. Longitudinal studies confirm that CMD is not a benign finding; rather, it identifies a high-risk subgroup whose outcomes parallel or exceed those with obstructive disease. The presence of CMD also correlates with reduced exercise capacity and impaired quality of life [18]. Despite increasing awareness, CMD remains underdiagnosed due to the absence of standardized criteria and the limited availability of advanced diagnostic testing. This diagnostic gap is particularly concerning given the high prevalence of CMD in women, diabetic patients, and individuals with metabolic syndrome. Recognition of CMD as a distinct entity has important implications for management, emphasizing the need for personalized diagnostic algorithms and mechanism-based therapy rather than uniform application of conventional antianginal drugs [19]. In summary, CMD spans multiple ischemic heart disease phenotypes, ranging from INOCA and myocardial infarction to HFpEF, each representing a clinical expression of impaired microvascular function. Its prevalence, prognostic significance, and under-recognition underscore the necessity for systematic evaluation and early intervention strategies targeting the microcirculation (Table 2).

Phenotype	Clinical Characteristics	CMD Prevalence	Predominant Patient Group	Prognostic Impact
INOCA	Angina with non-obstructive coronary arteries	40–60%	Women, postmenopausal	Increased MACE and MI risk
Post-obstructive CAD	Persistent ischemia after PCI or CABG	25–30%	Post-PCI patients	Larger infarcts, LV remodeling
HFpEF-associated CMD	Dyspnea, diastolic dysfunction	Up to 50%	Hypertensive, diabetic, obese	Higher mortality, HF hospitalization

Table 2: Clinical Phenotypes and Epidemiology of Coronary Microvascular Dysfunction.

Abbreviations: CMD: Coronary microvascular dysfunction; INOCA: Ischemia with non-obstructive coronary arteries; CAD: Coronary artery disease; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; MACE: Major adverse cardiovascular events; MI: Myocardial infarction; LV: Left ventricle; HFpEF: Heart failure with preserved ejection fraction.

4. Diagnostic Challenges

The diagnosis of coronary microvascular dysfunction (CMD) remains one of the most complex and debated aspects of ischemic heart disease evaluation. Unlike obstructive coronary artery disease, which can be visualized angiographically, CMD affects small resistance vessels beyond the resolution of standard coronary imaging. This limitation necessitates the use of functional and physiologic testing to detect abnormalities in microvascular flow regulation [20].

Non-invasive imaging techniques have become central to the evaluation of CMD. Positron emission tomography (PET) allows quantification of myocardial blood flow and calculation of coronary flow reserve (CFR), which reflects the vasodilatory capacity of both epicardial and microvascular compartments. PET remains the reference standard for non-invasive assessment of CMD, with reduced CFR (<2.0) serving as a diagnostic threshold associated with adverse outcomes [21]. However, PET's limited availability, high cost, and requirement for radiotracers restrict its widespread use. Cardiac magnetic resonance (CMR) with stress perfusion imaging provides an alternative method, offering high spatial resolution and the ability to assess myocardial perfusion reserve index (MPRI). Studies have shown good correlation between MPRI and PET-derived CFR, supporting its use in CMD evaluation [22].

Computed tomography (CT)-based approaches, such as CT perfusion imaging and CT-derived fractional flow reserve (CT-FFR), are emerging modalities that combine anatomical and functional assessment. CT perfusion imaging enables visualization of perfusion heterogeneity suggestive of microvascular disease, while CT-FFR allows evaluation of pressure gradients across the coronary tree. Although promising, these techniques are

still limited by radiation exposure and the need for standardization of analytical protocols [23]. Transthoracic Doppler echocardiography of the left anterior descending artery, while technically demanding, offers a non-invasive and inexpensive method to measure coronary flow velocity reserve (CFVR). A CFVR value below 2.0 indicates impaired microvascular function and has prognostic implications in both INOCA and heart failure populations [24].

Invasive coronary physiology testing provides the most direct and detailed assessment of microvascular function. Coronary flow reserve and the index of microcirculatory resistance (IMR) are commonly measured using a pressure–temperature sensor guidewire. IMR is calculated from distal coronary pressure and thermodilution-derived mean transit time during maximal hyperemia, providing a quantitative measure of microvascular resistance that is independent of epicardial disease. An IMR value ≥25 is typically considered diagnostic of CMD [25]. In addition, acetylcholine provocation testing is used to assess endothelium-dependent function and identify microvascular or epicardial spasm. Administration of incremental doses of acetylcholine under continuous ECG and angiographic monitoring allows the differentiation of microvascular spasm, characterized by ischemic ECG changes without visible epicardial constriction, from epicardial vasospasm [26].

Despite the availability of these tools, several challenges impede routine implementation. First, invasive testing requires specialized expertise and is limited to tertiary centers. Second, discrepancies between different diagnostic modalities complicate the establishment of universal thresholds for CMD. Third, many patients exhibit overlapping pathophysiologic endotypes, endothelial dysfunction, microvascular spasm, and structural remodeling, making single-parameter diagnosis inadequate [27]. Furthermore, symptom–ischemia dissociation is common: patients may have disabling angina with normal CFR or minimal symptoms despite marked CMD. This clinical variability underscores the need for integrative diagnostic strategies that combine hemodynamic, imaging, and biochemical parameters [28]. Standardization of diagnostic criteria remains a major unmet need. The 2019 European Society of Cardiology guidelines on chronic coronary syndromes formally recognized CMD as a diagnostic entity but did not provide universally accepted cutoffs for each modality. Variations in protocols, patient populations, and measurement techniques contribute to inconsistent results across studies. The ongoing effort toward harmonization, exemplified by the Coronary Vasomotion Disorders International Study Group (COVADIS), seeks to unify definitions and establish reproducible diagnostic algorithms [29].

Overall, the diagnosis of CMD requires a multimodality approach integrating non-invasive and invasive assessments. Advances in physiological testing and imaging have improved understanding, yet practical and logistical barriers continue to limit clinical application. Early recognition of CMD is essential, as impaired coronary microvascular function is a strong predictor of adverse outcomes irrespective of the presence or absence of obstructive coronary artery disease [30] (Table 3).

Method	Type	Parameter	Diagnostic Threshold	Advantages	Limitations
PET	Non-invasive	Coronary Flow Reserve (CFR)	CFR < 2.0	Gold standard, strong prognostic value	Expensive, limited availability
Cardiac MRI	Non-invasive	Myocardial Perfusion Reserve Index (MPRI)	MPRI < 2.0	No radiation, high resolution	Technically demanding
Doppler Echocardiography	Non-invasive	Coronary Flow Velocity Reserve (CFVR)	CFVR < 2.0	Inexpensive, repeatable	Operator-dependent
IMR (Invasive)	Invasive	Index of Microcirculatory Resistance	IMR ≥ 25	Direct quantitative assessment	Requires expertise
Acetylcholine testing	Invasive	Vasomotor response	Ischemic ECG changes without epicardial constriction	Evaluates endothelial function	Potential risk, limited availability

Table 3: Diagnostic Modalities in Coronary Microvascular Dysfunction

Abbreviations: PET: Positron emission tomography; MRI: Magnetic resonance imaging; MPRI: Myocardial perfusion reserve index; CFVR: Coronary flow velocity reserve; IMR: Index of microcirculatory resistance; ECG: Electrocardiogram.

5. Current Management Strategies

Management of coronary microvascular dysfunction (CMD) remains a major clinical challenge because treatment is often empirical and not mechanism-specific. Conventional antianginal strategies developed for obstructive coronary artery disease have limited efficacy in CMD, since the underlying pathophysiology involves microvascular rather than epicardial abnormalities. Therapeutic approaches therefore focus on symptom control, improvement of endothelial and vascular function, and mitigation of risk factors that perpetuate microvascular injury [7].

Lifestyle and risk factor modification form the cornerstone of CMD management. Regular aerobic exercise improves endothelial nitric oxide bioavailability, augments coronary flow reserve, and reduces sympathetic tone. Structured exercise training programs have demonstrated significant improvements in both symptoms and perfusion in patients with microvascular angina [31]. Optimal management of hypertension, diabetes, and dyslipidemia is equally important. Antihypertensive therapy not only lowers afterload but also alleviates shear stress–induced endothelial injury. Strict glycemic control mitigates glycation-induced oxidative stress, while statins improve endothelial function independent of their lipid-lowering effect through anti-inflammatory and antioxidative mechanisms [32]. Smoking cessation and weight reduction are critical, as tobacco toxins and visceral adiposity promote systemic inflammation and microvascular remodeling [6].

Pharmacologic treatment for CMD can be divided into conventional antianginal drugs and agents targeting endothelial or metabolic dysfunction. Beta-blockers are often used as first-line therapy because they reduce myocardial oxygen demand and improve diastolic perfusion time; they are particularly useful in patients with elevated heart rates and hypertensive responses. However, their efficacy is limited in patients with vasospastic or predominantly endothelial dysfunction–mediated CMD. Calcium channel

blockers, such as amlodipine or diltiazem, are preferred in those with vasospastic components due to their potent vasodilatory effects on both epicardial and microvascular vessels [33]. Long-acting nitrates, while effective in relieving epicardial vasospasm, have inconsistent effects in CMD because tolerance and paradoxical endothelial dysfunction may develop with chronic use [34].

Drugs that improve endothelial and metabolic function show promise for CMD management. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) enhance endothelial nitric oxide production, reduce oxidative stress, and improve coronary flow reserve. Clinical trials have shown that ACE inhibition improves angina and perfusion in patients with microvascular angina [35]. Statins also contribute through pleiotropic effects, stabilizing endothelium and suppressing inflammatory cytokines [36]. Ranolazine, a late sodium current inhibitor, has demonstrated symptomatic improvement and increased exercise tolerance in CMD by improving diastolic relaxation and myocardial efficiency, though benefits vary among subgroups [37]. Trimetazidine, which shifts myocardial metabolism toward glucose utilization, enhances ischemic tolerance and may complement conventional antianginal therapy [38].

The use of antiplatelet and anti-inflammatory therapy is rational, as low-grade vascular inflammation contributes to microvascular injury. Low-dose aspirin is often prescribed, though evidence supporting its benefit in isolated CMD is limited and primarily extrapolated from macrovascular disease data. Agents targeting vascular inflammation and oxidative stress remain investigational but represent an active area of research. The anti-inflammatory effects of statins and renin–angiotensin system blockade are likely responsible for part of their benefit in CMD [39].

Despite the availability of these options, outcomes remain suboptimal. Many patients continue to experience angina and reduced quality of life despite apparently adequate medical therapy. The heterogeneity of CMD, encompassing functional and structural subtypes, means that treatment responses vary widely. Current management therefore emphasizes individualized therapy based on the predominant mechanism, whether endothelial dysfunction, vasospasm, or structural rarefaction. This phenotype-directed approach is supported by evidence from the CorMicA trial, in which invasive coronary function testing guided tailored therapy and led to significant improvement in angina and quality of life compared with standard empiric treatment [4].

In summary, CMD management currently relies on a multifaceted strategy combining risk factor optimization, lifestyle modification, and pharmacologic therapy aimed at improving endothelial function and alleviating ischemia. While traditional antianginal agents remain the mainstay, emerging mechanism-based approaches promise to refine treatment in the near future. The persistent symptom burden despite existing therapies highlights the need for novel treatments directly targeting the microcirculation (Table 4).

Treatment Category	Example Drug / Modality	Mechanism of Action	Evidence Level	Clinical Status
Lifestyle / risk modification	Exercise, weight loss, smoking cessation	Improves NO bioavailability, reduces inflammation	High	Foundational
Endothelium-targeted therapy	ACEIs, ARBs, statins	Enhance endothelial function, reduce oxidative stress	Moderate	Standard care
Metabolic modulation	Ranolazine, trimetazidine	Improves diastolic relaxation, energy efficiency	Moderate	In use
Novel pharmacologic agents	Endothelin receptor antagonists, Rho-kinase inhibitors, SGLT2 inhibitors	Promote vasodilation, anti-inflammatory action	Low–moderate	Investigational
Device / regenerative therapies	Coronary sinus reducer, EECP, cell-based therapy	Improves microvascular perfusion and angiogenesis	Low–moderate	Under clinical evaluation

Table 4: Current and Emerging Therapeutic Approaches for CMD

Abbreviations: ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; NO: Nitric oxide; SGLT2: Sodium–glucose cotransporter-2; EECP: Enhanced external counterpulsation

6. Novel and Emerging Therapies

The limited efficacy of conventional antianginal and vasodilator therapies in coronary microvascular dysfunction (CMD) has prompted the search for novel treatments targeting the underlying pathophysiology of microvascular disease. These emerging approaches aim to restore endothelial function, reverse microvascular remodeling, and modulate neurohumoral and inflammatory pathways contributing to impaired coronary flow. The current therapeutic landscape includes pharmacologic innovations, regenerative and cell-based strategies, and device-based interventions designed specifically to improve microvascular perfusion [40].

Several pharmacologic agents targeting microvascular tone and endothelial dysfunction are under active investigation. Endothelin receptor antagonists, such as zibotentan and atrasentan, have been evaluated for their potential to counteract endothelin-1–mediated vasoconstriction and inflammation in CMD. Endothelin-1 plays a central role in microvascular constriction and remodeling, and selective blockade may improve microvascular flow and reduce ischemic burden. Early-phase clinical trials have shown favorable hemodynamic effects, though larger outcome studies are required to determine clinical benefit [41]. The Rho-kinase pathway represents another therapeutic target, as its activation promotes vasoconstriction, endothelial dysfunction, and vascular smooth muscle hyperreactivity. Inhibitors such as fasudil have demonstrated improved coronary flow and symptom relief in patients with microvascular angina, highlighting their potential role in treatment-resistant cases [42].

Modulation of nitric oxide (NO) signaling also offers therapeutic promise. Agents that enhance the NO–cGMP pathway, including phosphodiesterase-5 (PDE5) inhibitors and soluble guanylate cyclase (sGC) stimulators, have shown endothelial protective effects in preclinical and early human studies. Sildenafil and related PDE5 inhibitors may improve microvascular vasodilation and myocardial perfusion, particularly in CMD associated with heart failure with preserved ejection fraction [43]. Similarly, the sGC stimulator vericiguat has been shown to improve vascular reactivity and myocardial energetics, suggesting potential benefit in CMD-related ischemia [54].

Sodium–glucose cotransporter-2 inhibitors (SGLT2i) have recently emerged as promising agents with pleiotropic vascular effects extending beyond glycemic control. By reducing oxidative stress, inflammation, and endothelial dysfunction, SGLT2i improve microvascular integrity and coronary flow reserve in both diabetic and non-diabetic populations. Clinical and imaging data indicate improved subendocardial perfusion and reduced myocardial oxygen demand following SGLT2 inhibition, suggesting that these drugs may exert cardioprotective effects partly through microvascular mechanisms [45].

Beyond pharmacotherapy, regenerative and cell-based strategies are being explored as potential approaches to restore microvascular density and function. Endothelial progenitor cell (EPC) therapy and mesenchymal stem cell–derived exosomes have shown the capacity to promote angiogenesis, attenuate fibrosis, and improve perfusion in preclinical models of CMD. Preliminary human studies indicate that intracoronary or transendocardial administration of cell-based products can enhance coronary flow reserve and reduce ischemic symptoms [46]. Although long-term safety and efficacy remain to be confirmed, these findings suggest a path toward biologically restorative therapy for CMD.

Device-based and neuromodulatory interventions represent another frontier. The coronary sinus reducer, a percutaneously implanted device that creates a controlled narrowing in the coronary sinus, has been shown to improve angina and quality of life in patients with refractory microvascular angina. The mechanism is thought to involve redistribution of coronary venous pressure, thereby enhancing subendocardial perfusion. Clinical trials, including the COSIRA study, demonstrated significant symptom and functional improvement in patients with refractory angina and no revascularization options [47]. Enhanced external counterpulsation (EECP), a noninvasive mechanical therapy that augments diastolic coronary perfusion and reduces afterload, has also been associated with improved endothelial function and angina relief in CMD patients [48]. Renal denervation, by reducing sympathetic overactivity, is being explored as a means to modulate neurovascular tone in CMD, although data remain preliminary [49]. Ongoing clinical research continues to expand the therapeutic possibilities. Trials investigating anti-inflammatory strategies targeting interleukin-1β, colchicine, and other inflammatory pathways may further clarify whether vascular inflammation is a modifiable driver of CMD. Similarly, therapies combining pharmacologic and device-based modalities hold potential for synergistic effects. The evolution of these treatments reflects a paradigm shift from symptom suppression toward microvascular repair and functional restoration.

In summary, novel therapies for CMD aim to address the root mechanisms of endothelial dysfunction, microvascular remodeling, and autonomic dysregulation. Although evidence remains early-stage, the cumulative data suggest that precision medicine approaches integrating pharmacologic, regenerative, and mechanical strategies may ultimately redefine the management of microvascular ischemia.

7. Future Directions and Research Gaps

Despite rapid progress in understanding coronary microvascular dysfunction (CMD), major gaps persist in diagnosis, risk stratification, and treatment. CMD remains a pathophysiologically complex and clinically heterogeneous disorder that straddles multiple disease spectra, from stable angina to heart failure with preserved ejection fraction (HFpEF). Future research must aim to refine diagnostic precision, define phenotypes, and develop mechanism-based, individualized therapeutic strategies [28].

A key unmet need is the standardization of diagnostic criteria. Although invasive coronary physiology testing provides detailed insight into endothelial and microvascular function, there is no consensus on diagnostic thresholds across modalities such as coronary flow reserve (CFR), index of microcirculatory resistance (IMR), or myocardial perfusion reserve index (MPRI). Variability in protocols, analytic methods, and patient characteristics limits interstudy comparability. The establishment of unified diagnostic frameworks, such as those proposed by the Coronary Vasomotion Disorders International Study Group (COVADIS), should be prioritized in large-scale, multicenter studies [26]. Standardization will not only improve diagnostic reliability but also facilitate stratified therapeutic trials targeting distinct CMD endotypes.

Future work must also focus on developing reliable biomarkers of CMD. Circulating indicators of endothelial dysfunction, oxidative stress, and inflammation, such as asymmetric dimethylarginine (ADMA), endothelin-1, and high-sensitivity C-reactive protein, have shown promise as surrogates of microvascular health. Metabolomic and proteomic profiling may uncover novel molecular signatures that reflect microvascular injury or remodeling [50]. Integration of these biomarkers with advanced imaging and physiologic data may enable non-invasive diagnosis and monitoring of treatment response. The development of composite diagnostic scores incorporating clinical, imaging, and biomarker data represents an important step toward precision medicine in CMD [51].

Therapeutically, the next decade is likely to see a shift from symptomatic management toward disease-modifying strategies. This includes agents targeting vascular inflammation, fibrosis, and endothelial senescence, key drivers of microvascular dysfunction. Anti-inflammatory drugs such as colchicine or interleukin-1β inhibitors, already validated in macrovascular disease, warrant evaluation in CMD-specific populations. Similarly, antifibrotic and mitochondrial-targeted therapies hold potential to reverse the structural component of CMD [52]. Ongoing work exploring SGLT2 inhibitors, Rho-kinase inhibitors, and nitric oxide–modulating agents may further define the most effective pharmacologic strategies for restoring microvascular function [45].

Another major research frontier is the translation of regenerative and cell-based therapies into clinical practice. Early studies using stem cell–derived products and endothelial progenitor cells have shown improvement in coronary flow reserve and symptomatic relief, but robust evidence on long-term efficacy and safety is lacking. Understanding the mechanisms of benefit, whether through direct angiogenesis, paracrine signaling, or modulation of vascular inflammation, will be essential to optimize such approaches [46]. Future trials should also address patient selection, dosing, and delivery methods to ensure reproducibility and durability of clinical benefit.

Finally, CMD should be increasingly recognized as part of a systemic microvascular disorder rather than an isolated cardiac pathology. Its overlap with other small-vessel diseases, such as renal microangiopathy and cerebral small-vessel disease, suggests shared mechanisms involving endothelial inflammation and vascular rarefaction. Collaborative, interdisciplinary studies linking cardiology, vascular biology, and neurology could yield insights into the systemic nature of CMD and its implications for cardiovascular and cognitive health [20].

In summary, advancing CMD research requires coordinated efforts to standardize diagnosis, refine phenotyping, and develop mechanism-specific therapies. Future directions lie in integrating molecular biomarkers with

physiologic and imaging data to enable personalized management. A paradigm shift from empiric symptom control to targeted microvascular restoration represents the ultimate goal for improving outcomes in patients with CMD.

8. Conclusion

Coronary microvascular dysfunction (CMD) represents a central yet often underrecognized contributor to ischemic heart disease. It challenges the traditional paradigm that attributes myocardial ischemia primarily to epicardial atherosclerotic obstruction. By disrupting the regulation of coronary blood flow at the microvascular level, CMD produces ischemia, angina, and functional impairment even when angiography appears normal.

Over the past two decades, scientific advances have clarified the complex mechanisms underlying CMD, encompassing endothelial dysfunction, vascular remodeling, inflammation, and autonomic imbalance. These discoveries have reframed CMD as a systemic microvascular disorder with cardiac manifestations rather than a purely localized vascular problem. Diagnostic progress, through physiological testing and high-resolution imaging, has enabled identification of CMD phenotypes that carry substantial prognostic risk.

Despite this progress, CMD remains difficult to diagnose and treat. Current management largely depends on empirical therapy derived from macrovascular disease, and many patients continue to experience persistent angina and reduced quality of life. The lack of standardized diagnostic criteria and limited availability of specialized testing further impede effective clinical care.

The emerging era of mechanism-based treatment offers cautious optimism. Advances in pharmacologic modulation of endothelial pathways, regenerative and device-based therapies, and integration of precision diagnostics hold promise for transforming CMD management from symptom control to disease modification. Achieving this transition will require coordinated research, standardization, and multidisciplinary collaboration.

In conclusion, CMD lies at the intersection of vascular biology and clinical cardiology. Recognizing and targeting microvascular dysfunction is essential for improving outcomes in patients with both obstructive and non-obstructive ischemic syndromes. Understanding CMD not as a secondary finding but as a core mechanism of myocardial ischemia will define the next phase in the evolution of cardiovascular medicine.

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