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Coronary Microvascular Dysfunction: A Comprehensive Review

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ABSTRACT

Coronary Microvascular Dysfunction (CMD) encompasses a range of structural and functional changes at the level of coronary microcirculation, eventually resulting in diminished Coronary Blood Flow (CBF) and, thereby, myocardial ischemia. It has been shown to be linked to high morbidity and mortality. While patients can have traditional cardiovascular risk factors, CMD may or may not be associated with coronary artery disease or other myocardial diseases. When present, the obstructive lesions can complicate the evaluation and management of CMD. Although various non-invasive techniques, including cardiac Positron Emission Tomography (PET) or Magnetic Resonance Imaging (MRI), can be incorporated into the evaluation of CMD, a complete evaluation is possible only with invasive methods. Different pharmaceutical agents can be utilized to assess endothelial-dependent and non-endothelial-dependent processes, as well as macrovascular (epicardial) and microvascular involvement, in order to distinguish abnormalities in the coronary circulation. The lack of standardized diagnostic criteria and limited effective therapeutic options contribute to the complexity of successfully treating CMD. Antianginals, statins, and other therapies that aggressively modify the risk factors have been the mainstay of treatment, with a goal to improve quality of life and event-free survival. Despite recent advances, there is still a considerable gap in the understanding of its pathophysiology, accurate diagnosis, and definitive treatment. This warrants further dedicated research and trials.

Keywords: Coronary microvascular dysfunction; Coronary blood flow; Cardiac magnetic resonance imaging; Coronary flow reserve; Coronary flow velocity ratio; Electrocardiogram; Index of microvascular resistance; Myocardial blood flow; Myocardial perfusion reserve; Positron emission tomography

INTRODUCTION

The coronary arterial system consists of epicardial arteries, pre-arterioles, and intramural arterioles. While they serve different functions, arterioles play a fundamental role in the metabolic control of Coronary Blood Flow (CBF). They have a high resting tone and dilate in response to the release of metabolites by the myocardium, brought on by an increase in oxygen demand. CBF, typically reported in milliliters per minute, is a measurement of the volume of

blood that flows through a specific coronary channel in a unit of time.[1] Although effective for determining flow *via* epicardial coronary arteries, CBF only gives a hazy indication of flow through the microvasculature. The degree of the increase in coronary flow from the resting state to the point of maximal coronary vasodilation is known as the Coronary Flow Reserve (CFR).[2] It provides an integrated assessment of flow through the big epicardial arteries and the coronary microcirculation.[3] Measurements are taken both at rest (base flow) and during maximal hyperemia, which is produced by intracoronary or intravenous infusions of adenosine or dipyridamole. Since the microvasculature plays a major role in determining the resistance of flow through the coronary circulation, CFR can be utilized as a substitute for the microvascular function.

The term Coronary Microvascular Dysfunction (CMD) has been used to describe a range of structural and functional changes at the level of coronary microcirculation that causes diminished CBF and eventually result in myocardial ischemia. The physiological mechanisms of CMD are becoming better understood, and new techniques for assessing them are being developed. As a result, CMD is now recognized as a significant contributor to myocardial ischemia in people who have angina without obstructive Coronary Artery Disease (CAD), or "primary" microvascular angina.[4] Nevertheless, despite considerable improvements in our understanding of Ischemia with No Obstructive Coronary Arteries (INOCA) and/or CMD, there are still knowledge gaps. CMD is linked to high morbidity, similar to other high-risk cardiac groups.[5] Accurate diagnosis of this disorder is important due to accumulating evidence that CMD represents a viable therapeutic target.[6]

PATHOPHYSIOLOGY

Structural, functional, or a combination of both changes can lead to CMD. CMD leading to myocardial ischemia manifests clinically as Microvascular Angina (MVA). Myocardial ischemia in this clinical category may be caused by vasomotor diseases affecting the coronary arterioles (causing dynamic arteriolar obstruction) or structural remodeling of the microvasculature (resulting in fixed decreased microcirculatory conductance).[3] Impaired vasodilation and/or microvascular spasm may be associated with the functional processes for CMD. The clinical sign of myocardial ischemia caused by dynamic epicardial coronary stenosis brought on by a vasomotor dysfunction is known as Vasospastic Angina (VSA). CMD may also result from structural changes, particularly in patients with CAD risk factors or underlying cardiomyopathies. Luminal constriction of intramural arterioles and capillaries, perivascular fibrosis, and capillary rarefaction are the most common structural abnormalities linked to CMD.[4]

When patients without myocardial diseases or obstructive atherosclerotic lesions present with angina, this is commonly referred to as cardiac syndrome X. The most likely cause of angina in a subgroup of syndrome X patients with diminished CFR and metabolic evidence of myocardial ischemia is CMD. It is important to note that traditional risk factors may be present in these patients. In individuals with elevated blood levels of total cholesterol, a statistically significant inverse association between the measurement of CFR and levels of lipid sub-fractions has been described.[7] In asymptomatic smokers without signs of CAD, CFR was found to be 21% lower than in non-smoking controls, demonstrating CMD.[8] Another important risk factor is diabetes mellitus which has a direct

negative impact on endothelial and vascular function, particularly by raising the risk of thrombosis and vasoconstriction. Studies have consistently suggested that patients with diabetes have decreased CFR, which may be a precursor to atherosclerosis.[9] Similarly, despite having angiographically normal coronary arteries and no left ventricular hypertrophy, people with essential Hypertension (HTN) have been shown to have abnormal CFR.[1]

CMD with Concomitant CAD

CMD and epicardial vasospasm may cause myocardial ischemia either separately or in conjunction with CAD. These individuals continue to have recurrent angina with reduced quality of life, which results in repeated hospital stays, needless coronary angiography, and unfavorable short- and long-term cardiovascular outcomes. Even while obstructive CAD is a prevalent and well-known cause of myocardial ischemia, many stenoses that are visually assessed as significant may not actually restrict blood flow. Functional misclassification of obstructive lesions is common between 40 and 80 percent stenosis, with rates being especially high in patients with multiple coronary lesions.[3] When non-obstructive coronary atherosclerosis is present, CMD and/or epicardial coronary artery spasm may contribute to the mismatch between blood supply and myocardial oxygen demand in INOCA. Specifically, failure to identify epicardial CAD in a patient with known angina/ischemia should prompt further research into INOCA endotypes before looking into non-cardiac causes of chest pain. In individuals with concurrent obstructive CAD and atherosclerosis with outward remodeling, these processes may also generate ischemia, but these cases are not INOCA by definition.

The ischemic threshold in patients with stable angina is significantly influenced by CMD distal to coronary stenosis. After a successful percutaneous coronary angioplasty, coronary vasoconstriction has been observed. In addition, CMD in patients undergoing percutaneous procedures and coronary bypass surgery can also be caused by distal embolization of the coronary microcirculation. The "no-reflow" phenomenon (inability of a previously ischemic region to be reperfused) occurs in individuals with acute coronary syndromes with ST-segment elevation who have coronary microvascular dysfunction in the region of a recanalized infarct-related artery.[10]

CMD Associated with Other Myocardial Diseases

Microvascular dysfunction can be evident in the setting of various myocardial diseases. Some of the severe consequences of hypertrophic cardiomyopathy, such as ventricular arrhythmias, sudden death, progressive left ventricular remodeling, and systolic dysfunction, can be brought on by myocardial ischemia. As in individuals with hypertrophic cardiomyopathy, the degree of CMD in those with dilated cardiomyopathy has been demonstrated to be an independent predictor of cardiac events and is linked to a higher relative risk of death and subsequent development of heart failure.[1]

Despite the presence of angiographically normal coronary arteries, some of the alterations associated with the hypertrophic process also influence coronary circulation, and individuals with aortic stenosis have a lower CFR.[11] According to one study, the area of the aortic valve, hemodynamic stress imposed, and the duration of diastolic perfusion were more closely associated with the severity of CMD than the left ventricular mass.[12] Microvascular dysfunction can also occur in the setting of infiltrative heart diseases such as Anderson-Fabry disease, which is an

X-linked disorder that causes a deficiency of lysosomal a-galactosidase A. Myocytes, conduction tissue, vascular endothelium, and valvular tissue all exhibit glycosphingolipid deposition, which is a hallmark of the Anderson-Fabry disease cardiomyopathy. Endothelial accumulations cause endothelial dysfunction, and perivascular fibrosis can raise the microvascular resistance.[13]

EVALUATION

Reduced CFR is a sign of CMD after severe obstructive disease of the epicardial arteries has been ruled out. While non-invasive testing can be used to determine non-endothelial-dependent dysfunction, invasive angiography is required for a complete diagnostic evaluation of CMD.

Non-Invasive Techniques

Myocardial Blood Flow (MBF) can be measured noninvasively using Cardiac Magnetic Resonance (CMR), contrast echocardiography, or radionuclide imaging, but Positron Emission Tomography (PET) is the most widely used and well-validated method.[4] According to 2021 American College of Cardiology/ American Heart Association (ACC/AHA) chest pain guidelines, stress PET myocardial perfusion imaging or stress CMR with myocardial blood flow reserve can be reasonably considered to diagnose microvascular dysfunction and improve risk stratification for estimating the risk of major adverse cardiac events in patients with chronic stable chest pain and non-obstructive CAD (class IIa recommendation).[14] PET scan enables computation of the amount of blood flow per unit of mass (expressed as milliliters per minute per gram of tissue), which allows more direct and precise quantification of the function of the microvascular system. Because it allows for simultaneous evaluation of all coronary territories by measuring MBF both at rest and during pharmacologically induced maximal hyperemia, PET is now regarded as the gold standard reference for noninvasive assessment of CMD.[15] However, due to its limited availability and higher cost, its usage is constrained in the clinical practice. Similar to PET, CMR also enables the measurement of MBF both at rest and stress. Using quantitative imaging with high-resolution CMR, a precise diagnosis of CMD can be made. With a stronger preference for the sub-endocardial layer of the myocardium, CMD is associated with homogenous circumferential inducible ischemia and can be accurately detected with 3-T CMR with quantitative perfusion.[6]

A myocardial first-pass dynamic Computed Tomography (CT) scan enables a (semi-) quantitative evaluation of MBF and myocardial perfusion reserve (MPR).[16] The combination of CT coronary angiography and CT perfusion for the exclusion of epicardial CAD and the evaluation of microvascular function with a single diagnostic tool makes CT imaging a promising approach.[17] However, there are presently limited studies on perfusion CT for CMD assessment. Contrary to CMR, this approach also involves a significant amount of radiation. Transthoracic Doppler echocardiography can be used to measure the maximal diastolic flow in the epicardial arteries at rest and under adenosine/dipyridamole/regadenoson stress, which is also known as Coronary Flow Velocity Ratio (CFVR).[18] In the absence of any epicardial flow restriction, CFVR is a valid indicator of coronary microvascular performance, and cutoff values of 2-2.5 are frequently used as a sign of poor coronary microvascular function.[17]

Echocardiography is affordable and doesn't expose patients to radiation; however, its use is limited due to technical drawbacks.

Invasive Techniques

Currently, the gold standard for the diagnosis of CMD requires the exclusion of obstructive CAD through coronary angiography, followed by an assessment of microvascular coronary function using a Doppler guidewire in the cardiac catheterization lab. This involves endothelial function testing in response to intracoronary acetylcholine and CFR testing in response to adenosine or regadenoson.[19] In patients with persistent symptoms but angiographically normal coronary arteries (or non-flow-limiting moderate stenoses), guidewire-based measurement of CFR and/or microcirculatory resistance measurements should be considered, according to the 2019 European Society of Cardiology (ESC) chronic coronary syndromes (CCS) guidelines (class IIa recommendation).[3] Similarly, according to 2021 ACC/AHA chest pain guidelines, invasive coronary function testing is reasonable to consider for patients who have persistent stable chest pain, non-obstructive CAD, and imaging evidence of at least mild myocardial ischemia in order to diagnose CMD and to improve risk stratification (class IIa recommendation).[14]

Assessment of Coronary Microcirculation

Contrary to epicardial coronary arteries, coronary angiography cannot directly assess the coronary microcirculation. Endo-myocardial biopsy may reveal pathologic small coronary arteries with fibromuscular hyperplasia, hypertrophy of the media, swollen endothelial encroaching on the lumen, and myo-intimal proliferation; however, it cannot visualize the vessels between 200 and 500 μm and may underreport CMD that may be patchy.[19] The study of the human coronary microcirculation is therefore indirect and relies on evaluating parameters, such as CBF and CFR, which reflect its functional status rather than morpho-histologic evaluation. Hence, anatomical or morphologic approaches to evaluate coronary microcirculation are quite limited.

There are several invasive methods for evaluating CFR, such as intracoronary Doppler ultrasound and thermodilution methods. The current gold standard for clinically evaluating microvascular function is CFR utilizing invasive testing and MPR using cardiovascular CMR or PET.[2] It is deemed abnormal if the coronary flow reserve is less than 2.0. The substantial between-study heterogeneity may be explained in part by the diverse techniques and cutoffs.[20] The Thrombolysis in Myocardial Infarction (TIMI) frame count, another invasive method for measuring CBF, does not quantify the flow but still can be relevant for comparisons.[1]

Enhancing CBF is a typical physiological reaction to an increase in cardiac demand. This is accomplished by vasodilating epicardial and resistance vessels, which are mediated by endothelium-dependent and non-endothelium-dependent processes, respectively (Table 1). These processes along with macrovascular (epicardial) and microvascular involvement, can be used to categorize abnormalities in the coronary circulation and CFR.[19]

Table 1: Coronary Microvascular Function Testing.

	Endothelial dependent	Non-endothelial dependent
Epicardial	Acetylcholine	Nitroglycerine
Microvascular	Acetylcholine	Adenosine

Endothelial-Dependent Microvascular and Macrovascular Function

Acetylcholine is frequently utilized to assess endothelium-dependent vasomotor tone modulation. Both the micro- and macro-vasculature are uniformly dilated in response to the acetylcholine receptor stimulation.[21] Approximately 3- to 4-fold increase in coronary blood flow in response to acetylcholine indicates normal coronary endothelial function.[19] A significant attenuation of the increase in CBF in response to intracoronary acetylcholine, no change, or even a decrease in CBF can all be signs of coronary endothelial dysfunction.[22]

Non-Endothelial-Dependent Microvascular Function

Even in the presence of normal epicardial endothelial function, the administration of adenosine may identify aberrant CFR and allows for an endothelium-independent assessment of the coronary microvasculature. Through activation of the adenosine A2 receptor on smooth muscle cells, adenosine mostly affects coronary arteries less than 150 μm in diameter.[23] It primarily evaluates changes in the coronary resistance vessels as shown by alterations in the coronary flow, thereby determining CFR.[22]

Non-Endothelial-Dependent Macrovascular Function

Nitroglycerin administration enables an endothelium-independent assessment of the coronary macro-vasculature. Nitroglycerin causes a dose-related dilatation of coronary vessels more than 200 μm in diameter and no action on smaller coronary vessels because the coronary microvasculature lacks the enzyme required to convert nitroglycerin to its active form, nitric oxide (NO).[22,23]

In summary, in individuals with angina and non-obstructive CAD, impaired coronary vasomotor tone modulation may include one or more processes. Usually, a CFR ratio of >2.5 in response to adenosine and a >50% increase in CBF over baseline is regarded as normal.[22] When a patient's reactivity to acetylcholine and adenosine is impaired, epicardial and resistance vessels may be deemed to be dysfunctional, with endothelium-dependent and non-endothelium-dependent processes, respectively. A non-endothelium-dependent mechanism for CMD is indicated by an aberrant response to adenosine and a normal response to acetylcholine. Endothelium-dependent pathology is indicated by a reduced response to acetylcholine and a normal response to adenosine.[19] Finally, a lack of sensitivity to nitroglycerin indicates that the epicardial arteries are dysfunctional independently of the endothelium.[22] The clinical diagnostic pathway for CMD is summarized in **Figure 1**.

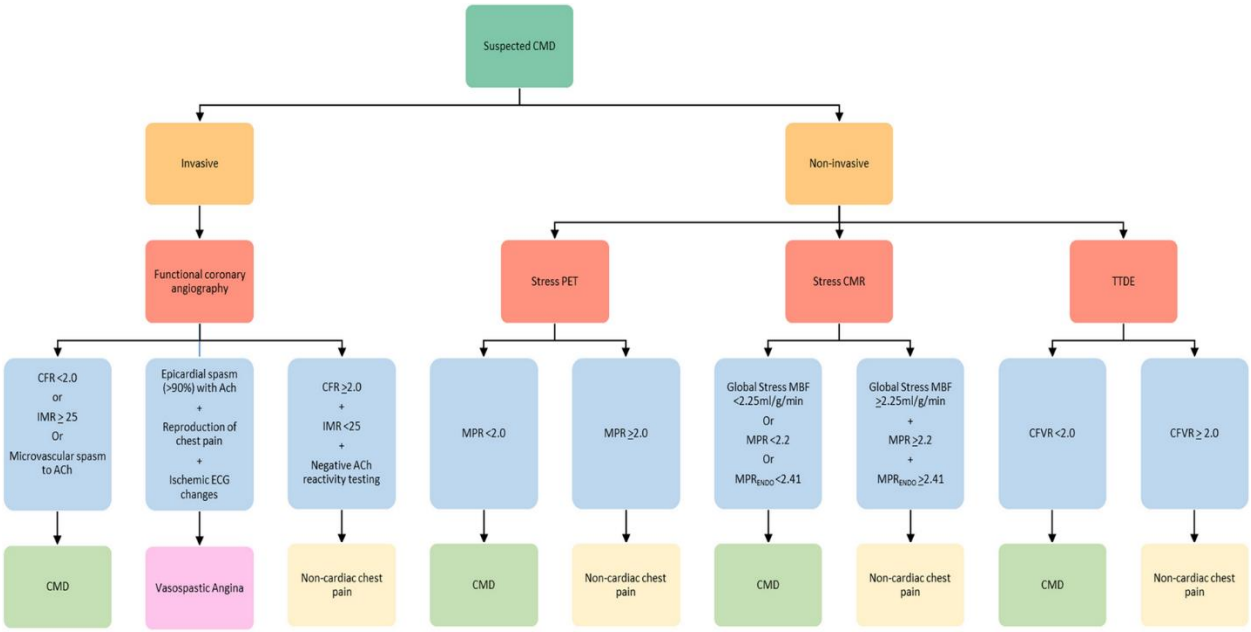

Figure 1: Diagnostic Pathway for CMD. Ach- Acetylcholine, CFR- Coronary Flow Reserve, CFVR- Coronary flow velocity ratio, CMD- Coronary Microvascular Dysfunction, CMR- Cardiac Magnetic Resonance Imaging, ECG- Electrocardiogram, IMR- Index of Microvascular Resistance, MBF- Myocardial Blood Flow, MPR- Myocardial Perfusion Reserve, PET- Positron Emission Tomography, TTDE- Transthoracic Doppler Echocardiography. Image reprinted without changes from C. Bradley and C. Berry[24] under the Creative Commons Attribution 4.0 International License (CC BY). https://creativecommons.org/licenses/by/4.0/

CLINICAL IMPLICATIONS

CMD and/or coronary spasm are present in about half of patients who do not have obstructive coronary artery disease. Female patients are known to have a higher prevalence of CMD.[20] In the multivariable analysis of a study, body mass index and glomerular filtration rate were the two clinical factors that best predicted the definitive CMD.[5] In individuals with moderate or severe renal impairment, the degree of coronary vascular dysfunction, as shown by PET, is an independent predictor of cardiovascular death. Noninvasive evaluation of coronary vasodilator function among patients with moderate to severe renal dysfunction provides additional risk stratification beyond standard clinical risk measures.[25] The quality of life of individuals with CMD is positively impacted by objective evidence of the source of their chest discomfort and tailored therapy.[20] According to data from the WISE trial, women who have evidence of myocardial ischemia but no obstructive CAD had a relatively worse prognosis than those who do not.[26] The rate of adverse cardiac events among CMD patients is 2.5% annually and includes myocardial infarction, congestive heart failure, stroke, and sudden cardiac death.[27] Also, the activity limitations that patients with INOCA experience, which can lead to a significant economic effect, cannot be overlooked.[5] The identification of CMD or

coronary spasm as the source of symptoms spares these patients from repetitive invasive diagnostic tests, which may lower healthcare costs and enables the optimization of medical therapy in accordance with a particular diagnosis.[20]

As the trend is shifting towards atherosclerotic heart disease being seen as a global disease burden rather than focusing on individual plaques, zero Coronary Artery Calcium (CAC) scores may not be helpful for people who smoke, have diabetes, HIV, or history of CAD.[28] Even after correcting for clinical risk, across all CAC score levels, the presence of aberrant CFR (indicating the effect of widespread atherosclerosis, as well as epicardial and microvascular dysfunction) was persistently associated with a greater incidence of adverse cardiac events. Although the amount of coronary calcium deposits and the presence of coronary vascular dysfunction are linked to an increased risk of adverse cardiac events, after adjusting for clinical risk, only coronary vascular dysfunction improved the risk evaluation.[29] Assessment of coronary vasodilator function offers incremental risk stratification beyond conventional clinical risk measures, including estimates of LV systolic function and the extent and severity of myocardial ischemia and scar, and results in a meaningful risk reclassification of 1 in 3 patients with known or suspected CAD. This also applies to patients with and without diabetes mellitus. Diabetes patients without overt CAD who had aberrant CFR were shown to have a cardiac death rate at least equal to (and possibly higher than) that of non-diabetic patients with known CAD.[30]

MANAGEMENT

Due to the lack of standardized diagnostic criteria, the numerous molecular pathways that contribute to the pathophysiology, and the frequently ineffective empiric therapeutics, treating CMD can be difficult. The objectives of treatment are to reduce the frequency of hospitalization and repeated invasive testing, to improve quality of life, and to increase event-free survival. The cornerstone of treatment involves adopting therapeutic lifestyle modifications to aggressively decrease risk factors in patients with angina, evidence of ischemia, and no obstructive CAD due to a high burden of cardiac risk factors and coronary atherosclerosis. Since cardiac rehabilitation has been shown to be successful in these subjects for increased exercise capacity and symptom relief, it can be advised for patients who have restricted their physical activity to reduce their symptoms.[31]

Definitive pharmacological therapeutic options are limited in the management of CMD. Beta-blockers are beneficial in reducing anginal symptoms in up to two-thirds of patients.[32] Beta-blockers help to lessen the frequency and severity of anginal episodes and enhance functional ability in CMD patients. In a randomized controlled experiment, Lanza et al. evaluated amlodipine, atenolol, and nitrate and found that only atenolol was more efficient at treating these patients.[33] Beta-blockers alone can increase symptoms in a small percentage of individuals with coronary spasms due to unopposed alpha-1 adrenergic stimulation; thus newer generation beta-blockers with alpha-blocking qualities may provide further benefits. For e.g. Carvedilol, a vasodilatory beta blocker, has been shown to improve endothelial-dependent microvascular function.[34] Nebivolol, a highly selective beta-1 blocker that suppresses the production of endothelin-1 (ET-1) and activates the eNOS pathway, also has vasodilatory effects. Erdogan et al. demonstrated that Nebivolol enhanced CFR (from 2.02 to 2.61) in patients with CMD by increasing hyperemic CBF after a month of therapy.[35] Nebivolol therapy for 12 weeks improved treadmill exercise capacity and time to 1 mm

ST depression in patients with cardiac syndrome X, according to Erdamer et al.[36] Verapamil and diltiazem may be helpful as they reduce myocardial oxygen consumption by inducing vascular smooth muscle cell relaxation.[37] Although the first-line treatment for vasospastic (Prinzmetal's) angina is Calcium Channel Blockers (CCBs), there is currently insufficient evidence to justify regular use of CCBs for CMD management. Though nitrates could be helpful for many people, they can have unpredictable effects on the frequency and duration of angina in CMD patients.[19]

Patients who have risk factors, signs of atherosclerosis, and/or endothelial dysfunction may benefit most from statin therapy. Due to their anti-inflammatory, antioxidant properties, and potential to increase vascular nitric oxide (NO) availability, statins may enhance endothelial function through lipid-independent pathways.[38] Since the majority of these patients have diffuse coronary atherosclerosis, it may be appropriate to utilize antiplatelet medications like aspirin in patients who have signs of ischemia but no obstructive CAD.[19] A pro-inflammatory molecule called Angiotensin II may contribute to the inflammatory response linked to atherosclerosis and HTN. By increasing the availability of NO, angiotensin-converting enzyme inhibitors and angiotensin-renin blockers have been shown to enhance endothelium-dependent relaxation of coronary resistance arteries.[38,39] The aberrant MBF response to cardiopulmonary test (CPT) that is linked to type 2 diabetes mellitus can be greatly addressed by proper glycemic management. A direct negative impact of elevated plasma glucose concentration on diabetes-related coronary vascular disease is suggested by the strong relationship between the drop in plasma glucose concentration and the improvement in coronary vasomotor performance in response to CPT.[40,41]

L-arginine (2 g, three times daily), a precursor to NO, improved endothelial function and angina symptoms in patients without obstructive CAD after four weeks of treatment.[42] The anti-anginal drug ranolazine works by preventing calcium overload in the ischemic myocytes by blocking the late sodium current.[43] Additionally, ranolazine encourages the transition from inefficient fatty acid metabolism to oxygen-sparing glucose oxidation, thereby lowering oxygen demand.[44] According to a study by Bairey-Merz et al., ranolazine enhanced myocardial perfusion (on CMR imaging) and reduced angina frequency in patients with INOCA and CFR<2.5.[45] Some of the other drugs that are currently under investigation include Rho-kinase inhibitors, endothelin receptor antagonists, nicorandil (mitochondrial ATP-sensitive potassium channel activator), ivabradine (sinus node selective inhibitor) and trimetazidine (fatty acid oxidation inhibitor).[37]

CONCLUSION

The functional analog of conventional coronary risk factors in the absence of obstructive CAD is coronary microvascular dysfunction. A subset of people has CMD that is severe enough to result in myocardial ischemia. The presence of concomitant obstructive CAD complicates the evaluation of CMD. The no-reflow phenomenon, which is known to be associated with a worse outcome in patients with acute myocardial infarction, is also caused by CMD.

The diagnosis of microvascular angina can be aided by tests that focus on documenting coronary or microvascular flow abnormalities, and there is strong evidence that evaluating flow alterations enhances the risk classification.

Vasospasm, as well as non-endothelial-dependent and endothelium-dependent microvascular reactivity, can be assessed *via* invasive coronary reactivity testing. The innovative contribution of PET MBF techniques is supported by prognostic data; multiple studies also highlight the benefit of CMR and echocardiographic methods. However, further research is warranted to fill the gaps in our understanding of complete evaluation, risk stratification, and effective management of coronary microvascular dysfunction.

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