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REVIEW

Coronary Microvascular Dysfunction
— Epidemiology, Pathogenesis, Prognosis, Diagnosis, Risk Factors and Therapy —

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Angina has traditionally been thought to be caused by obstructive coronary artery disease (CAD). However, a substantial number of patients with angina are found to not have obstructive CAD when undergoing coronary angiography. A significant proportion of these patients have coronary microvascular dysfunction (CMD), characterized by heightened sensitivity to vasoconstrictor stimuli and limited microvascular vasodilator capacity. With the advent of non-invasive and invasive techniques, the coronary microvasculature has been more extensively studied in the past 2 decades. CMD has been identified as a cause of cardiac ischemia, in addition to traditional atherosclerotic disease and vasospastic disease. CMD can occur alone or in the presence obstructive CAD. CMD shares many similar risk factors with macrovascular CAD. Diagnosis is achieved through detection of an attenuated response of coronary blood flow in response to vasodilatory agents. Imaging modalities such as cardiovascular magnetic resonance, positron emission tomography, and transthoracic Doppler echocardiography have become more widely used, but have not yet completely replaced the traditional intracoronary vasoreactivity testing. Treatment of CMD starts with lifestyle modification and risk factor control. The use of traditional antianginal, antiatherosclerotic medications and some novel agents may be beneficial; however, clinical trials are needed to assess the efficacy of the pharmacologic and non-pharmacologic therapeutic modalities. In addition, studies with longer-term follow-up are needed to determine the prognostic benefits of these agents. We review the epidemiology, prognosis, pathogenesis, diagnosis, risk factors and current therapies for CMD.

Key Words: Cardiac Syndrome X; Coronary flow reserve; Coronary microvascular dysfunction; Microvascular angina

Traditionally, the diagnosis of angina has focused on evaluating the patency of epicardial coronary arteries, as they are easily visualized on coronary angiography (CAG) and can be intervened upon when significant lesions are present. Nevertheless, some patients with anginal symptoms and ischemia on stress testing have a normal coronary angiogram. Historically, these patients were given the diagnosis of Cardiac Syndrome X. Initial studies suggested these patients had a good prognosis.[1,2] However, current evidence shows that a significant portion of these patients have coronary microvascular dysfunction (CMD), also known as microvascular angina. Patients with CMD have significantly higher rates of cardiovascular events, including hospitalization for heart failure, sudden cardiac death, and myocardial infarction (MI).[3–10]

In the past 2 decades, a large number of studies have used both invasive testing and non-invasive imaging to assess coronary microvascular function, which has led to further insight into the pathophysiology of CMD. CMD has now been shown to be another mechanism for angina and ischemia, in addition to obstructive coronary artery disease (CAD) and vasospastic disease.[11–13] Coronary flow reserve (CFR), defined as the ratio of coronary blood flow (CBF) at maximal dilation to CBF at baseline, is impaired in patients with CMD.

CMD encompasses various clinicopathologic changes that lead to functional and structural abnormalities in the coronary microvasculature. These changes disrupt the ability of the vessels to vasodilate and augment CBF in response to increased myocardial oxygen demand, causing angina and ischemia.[14]

Epidemiology

Various studies have shown that in patients who are undergoing clinically indicated CAG, up to 49% do not have significant stenosis.[15,16] Of these patients, up to 60% may have CMD. In one of the earliest studies, 59% (120/203) of the patients with anginal symptoms, but angiographically normal coronary arteries, were found to have abnormal response to vasodilator agents, adenosine and acetylcholine (ACh), suggestive of CMD.[17] Another study using transthoracic Doppler echocardiography (TTDE) found 40% (28/64) of the patients to have CFR <2.[18] In the Women's

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Table 1. Prevalence of CMD in Observational Studies With Various Testing Modalities

Author	Year	Test	Sample size	Prevalence of CMD (%)	Male (%)	Female (%)
Hasdai et al[17]	1998	Coronary reactivity test	203	59	–	–
Reis et al[19]	2001	Coronary reactivity test	159	47	–	47
Sade et al[18]	2009	TTDE (CFR <2.0)	68	40	–	40
Sicari et al[68]	2009	TTDE (CFR <2.0)	394	22	25	19
Cassar et al[127]	2009	Coronary reactivity test	367	63	61	65
Wei et al[61]	2012	Coronary reactivity test	293	49	–	49
Murthy et al[3]	2014	PET (CFR <2.0)	1,218	53	51	54
Sara et al[20]	2015	Coronary reactivity test	1,439	64	60	66
Mygind et al[37]	2016	TTDE (CFR <2.0)	919	26	–	26

CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; PET, positron emission tomography; TTDE, transthoracic Doppler echocardiography.

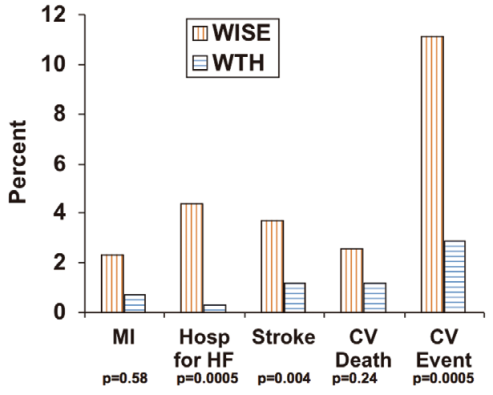

Figure 1. Comparison of cardiovascular event rates and deaths between WISE and WTH patients. CV, cardiovascular; HF, heart failure; MI, myocardial infarction; WISE, Women's Ischemia Syndrome Evaluation study; WTH, Women Take Heart study. Modified with permission from Gulati M, et al.[26]

Ischemia Syndrome Evaluation (WISE) study, 47% (74/159) of the women with chest pain but normal coronary arteries or minimal coronary luminal irregularities were found to have abnormal coronary microcirculation based on intracoronary reactivity test.[19] A large cohort study found that 64% (919/1,439) of the patients without obstructive CAD had CMD based on vasoreactivity testing, and no significant differences in the prevalence of CMD were observed between men and women (60% vs. 66%).[20] These results were consistent with a study of 1,218 patients showing CMD to be highly prevalent in both men and women undergoing positron emission tomography (PET) scan for suspected CAD, with no significant difference between sexes (51% men and 54% women).[3] This lack of a sex difference in CMD prevalence is in contrast to epicardial stenosis: women have been consistently found to have less obstructive CAD than men.[21–23] A summary of prevalence in these observational studies is shown in **Table 1**.

Prognosis

Studies now have consistently shown that CMD is associated with adverse cardiovascular outcomes, including MI, stroke, hospitalization for worsening angina and death. Suwaidi et al found that 14% of the patients with severe endothelial dysfunction (based on intracoronary Acetylcholine (ACh) testing) had cardiac events during the 28-month follow-up, compared with no cardiac events in patients with mild to moderate endothelial dysfunction.[4] Another study found that 18%, 10% and 5% of patients with severe, moderate and mild CMD, respectively, had adverse cardiovascular events.[24] In a study of 147 patients undergoing an assessment of coronary endothelial function, 30% of the patients with CMD developed obstructive CAD at the 10-year follow-up.[25] A comparison of cardiovascular events and death rates in the WISE study and St. James Women Take Heart (WTH) study found a more than 10-fold increase in heart failure rates and 5-fold increase in major cardiovascular event rates in symptomatic WISE patients compared with asymptomatic WTH patients[26] (**Figure 1**).

Both endothelial-dependent and non-endothelial-dependent CMD predict adverse prognosis. Endothelial-dependent dysfunction, as demonstrated by impaired coronary vasomotor response to ACh, is an independent risk factor for cardiac events regardless of the severity of a patient's CAD.[27,28] In the WISE study of 189 women with signs and symptoms of ischemia and no obstructive CAD, endothelial-independent dysfunction characterized by reduced CFR was also significantly associated with major adverse outcomes at 5-year mean follow-up. Statistical analysis identified CFR <2.32 as the discriminating threshold for predicting adverse outcomes (26.7% event rate vs. 12.2% event rate).[6]

More recent studies have utilized PET imaging to assess CFR for risk stratification. Patients with CFR <1.5 were associated with a 5.6-fold increase in risk of cardiac death compared with those with CFR >2.[5] Murthy et al showed that diabetic patients without known CAD but low CFR have yearly event rates similar to non-diabetic patients with CAD (2.8% vs. 2.0%).[8] Taqueti et al found that patients with low CFR had similar cardiac event rates as those with high angiographic scores, and those with both low CFR and high angiographic scores had the highest event rates.[7] In addition, patients with low CFR derive reduced benefit from revascularization.[5]

Pathogenesis

The coronary vasculature is composed of epicardial arteries, pre-arterioles and arterioles, with the latter two being the coronary microvasculature. Epicardial arteries offer little resistance when there is no significant stenosis. The branches

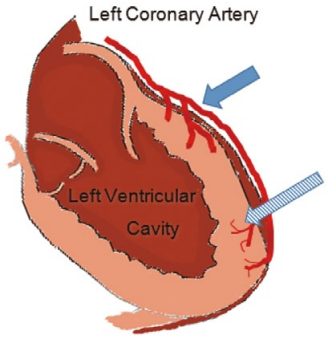

Figure 2. Anatomy of coronary macrovascular and microvascular circulation: epicardial coronary artery (solid arrow) dilates in response to nitroglycerin, acetylcholine, shear stress; intramyocardial arterioles (striped arrow) are responsive to local metabolites and responsible for metabolic regulation of coronary blood flow.

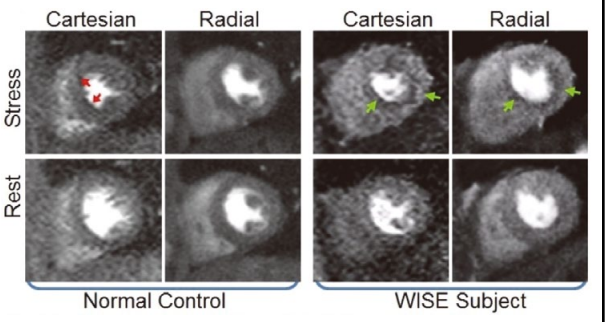

Figure 3. Cardiac magnetic resonance perfusion images demonstrating dark-rim artifact (red arrows) eliminated by high radial acquisition in a normal control subject, and improved subendocardial border delineation (green arrows) in a WISE subject. WISE, Women's Ischemia Syndrome Evaluation study.

divide into pre-arterioles located in the epicardial surface, with size ranging from 100 to 500 μm.[14] Finally, the pre-arterioles give rise to arterioles (<100 μm), which are intramyocardial and contribute to more than 50% of the total coronary vascular resistance.[29] The proximal and larger arterioles use the endothelial-dependent vasodilatory mechanism as a regulatory mechanism. Increased CBF causes vasodilation, whereas decreased CBF causes vasoconstriction.[30] The medium-sized arterioles have vascular smooth muscle cell stretch receptors that can detect the intraluminal pressure and respond to decreased intraluminal pressure by vasodilating. Lastly, the most distal arterioles are subjected to regulation by local metabolic activity (**Figure 2**). These various regulatory mechanisms interact with one another in order to match CBF to demand. If one fails, a different mechanism would compensate.

At the structural level, smooth muscle hypertrophy around the vascular wall, which results in increased vessel resistance, is seen commonly in hypertrophic cardiomyopathy (HCM) or left ventricular hypertrophy secondary to hypertension.[31] Functionally, CMD can occur because of disruption of the endothelial-dependent or endothelial-independent regulatory mechanisms.[32] Camici et al categorized CMD into 4 categories: CMD without myocardial disease or obstructive CAD, CMD with myocardial disease, CMD with obstructive CAD, and iatrogenic CMD.[14] Most recently, Herrmann et al proposed an additional category: post-cardiac transplant CMD.[33]

Diagnosis

Typically, CMD is suspected in patients with angina and a normal-appearing coronary angiogram. Patients with CMD may have chest pain that can persist even after cessation of activity.[34] These patients may not have rapid or sufficient symptom relief with the administration of sublingual nitroglycerin. It is thought that nitroglycerin selectively dilates larger microvessels but may not have a significant effect on arterioles.[35] The WISE study found that typical or atypical chest pain does not differentiate between obstructive and non-obstructive CAD in women.[36] Symptom complexity is neither sensitive nor specific and may not always identify patients with CMD.[37] A recent study demonstrated that certain T-wave features on electrocardiography, when analyzed by computer, can predict the presence of abnormal CFR with 67% accuracy.[38] The association between an abnormal stress test and decreased CFR has also been studied and the results are conflicting. Mygind et al found that stress testing did not identify patients with CMD,[37] whereas Ong et al found that a pathologic exercise tolerance test is associated with ACh-induced CMD.[39] The difference in results is likely caused by the different testing modalities used to assess the coronary microvasculature.

Given there are no current techniques to directly visualize the coronary microvasculature, indirect assessment made through functional testing provides hemodynamic information about the coronary microvascular system, often represented by CFR in response to the vasodilator adenosine. CFR is calculated as the ratio of the CBF at maximal dilation to the CBF at rest and can be obtained through various imaging modalities. There is currently no consensus on the cutoff for the diagnosis based on imaging. Loffler et al proposed a 3-tiered characterization of CMD based on likelihood: CFR <1.5, definite CMD; 1.5–2.6, borderline CMD; and >2.6, no CMD.[40]

Cardiovascular Magnetic Resonance (CMR)

CMR imaging has been used to quantify myocardial perfusion and involves intravenous gadolinium injection. Tissue perfusion can be assessed based on the intensity of gadolinium in the myocardium. The myocardial perfusion reserve index is calculated using the ratio of the rates of contrast uptake during stress and at rest.[41] A decreased response to vasodilator is seen in the subendocardial region in CMD patients.[42] Results of CMR have correlated well with results from invasive measurement.[43] A drawback of CMR is the subendocardial dark-rim artifact, which lowers the diagnostic accuracy of ischemia, but optimized radial imaging has significantly reduced such artifact[44] (**Figure 3**). CMR is useful for assessing the prognosis of patients with ischemic heart disease.[45,46] It seems to be the most promising non-invasive imaging technique, given its high spatial resolution, lack of ionizing radiation, and good diagnostic accuracy and delineation between attenuation artifact and true myocardial infarcts or injuries.[47,48]

	Microvascular Dysfunction	Macrovascular Dysfunction
Non-Endothelial Dependent	CFR in response to adenosine ≤ 2.5	Change in coronary artery diameter in response to nitroglycerin < 20%
Endothelial Dependent	Change in CBF in response to acetylcholine < 50%	Change in coronary artery diameter in response to acetylcholine < 0%
Coronary Spasm	Chest Pain + EKG changes Change in coronary artery diameter in response to acetylcholine <90%	

Figure 4. Proposed diagnostic criteria of coronary dysfunction using reactivity testing. CBF, coronary blood flow; CFR, coronary flow reserve; EKG, electrocardiography.

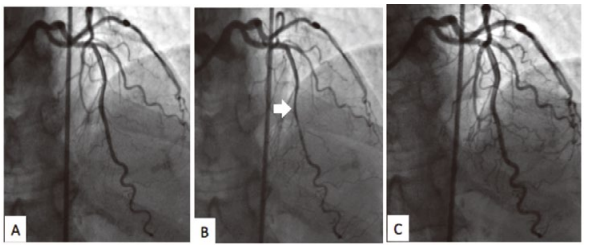

Figure 5. Coronary angiograms and coronary reactivity testing: baseline (**A**); severe abnormal vasoconstriction (arrow) in response to acetylcholine (**B**); resolution of vasoconstriction with intracoronary nitroglycerin (**C**).

Positron Emission Tomography (PET)

PET scanning uses various radioactive tracers to determine absolute myocardial blood flow by continuously monitoring the tracer. The myocardium can be divided into segments in order to calculate regional blood flow in addition to global flow.[49] PET measurement of myocardial flow reserve can also be used to predict prognosis.[50] PET also has the advantage of assessing all 3 coronary distributions, thus allowing a more accurate assessment of microvascular dysfunction, as CMD has been shown to have a heterogeneous distribution over the 3 vessels.[51] Because computerized tomography is used during cardiac PET imaging, the coronary artery calcium score can be calculated to help with risk stratification and estimation of atherosclerotic burden.[52]

TTDE and Myocardial Contrast Echocardiography (MCE)

TTDE can measure the distal left anterior descending (LAD) artery CBF velocity (CBFV), which is a surrogate for CBF. CFR is measured as the ratio of peak CBFV after vasodilator to CBFV at rest.[53] TTDE measurements have been found to be highly reproducible.[54] In addition, CFR measured by TTDE has been shown to have excellent correlation with CFR measured by PET[54] and intracoronary testing.[55] TTDE is relatively cheaper compared with other imaging modalities, and can be done with relative ease and allows for the assessment of asymptomatic patients to establish reference CFR. However, assessment by TTDE is generally limited to the LAD artery.

MCE uses intravenously injected microbubbles, which have rheological properties similar to erythrocytes and allow myocardial opacification on ultrasound. Perfusion of the myocardium can be quantitatively assessed and results have correlated well with PET studies.[56]

Invasive Testing

The invasive diagnosis of CMD is based on coronary reactivity testing, which involves insertion of a Doppler guidewire into the LAD artery. Adenosine and ACh are used to assess endothelial-independent and endothelial-dependent dysfunction, respectively. Adenosine acts on the A2 receptor of the smooth muscle cell[57] and ACh causes the release of nitric oxide.[58] Intracoronary bolus injection of adenosine is administered in incremental doses to achieve maximal dilation. Flow velocity is measured before and after the drug administration. The CFR ratio is the ratio of peak flow velocity after adenosine administration to that at baseline. Intracoronary ACh is also infused in graded doses. CBF is calculated as the product of cross-sectional area and peak flow velocity divided by 2. Definitions of coronary vasomotor dysfunction by invasive testing are depicted in **Figure 4**.[59] CMD patients can be expected to have an attenuated hyperemic response or even possibly decreased CBF to these substances[60] (**Figure 5**). Coronary reactivity testing is invasive by nature, requires special expertise and can be time consuming. However, it allows direct injection of agents to cause maximal dilation. It has been shown to be safe and effective when performed by experienced interventional operators.[61]

Risk factors

Risk factors for CMD are similar to the traditional cardiovascular disease risk factors, including smoking, diabetes mellitus, aging, hypertension, and hyperlipidemia. One study showed smoking is associated with a 21% reduction in CFR based on PET, which was reversed with the administration of vitamin C, indicting oxidants are at least partially responsible for the dysfunction.[62] Another study demonstrated that smoking status is associated with CFR <2, with an odds ratio of 2.246 (95% confidence interval 1.078–5.618, P=0.033).[63] Diabetics have reduced CFR.[64,65] It is not surprising that hyperglycemia adversely affects the coronary microvasculature given the effect of diabetes on other microcirculations (i.e., retina, kidney and neuron). CMD in diabetic patients may be early progression of epicardial coronary disease.[66] Aging is associated with arterial remodeling[67] and has been shown to be a risk factor for CMD in numerous studies.[6,20,68,69] In patients with hypertension and reduced CFR, arteriolar remodeling, including increased medial wall thickness and periarteriolar fibrosis, are seen on biopsy.[70,71] Low-density lipoprotein (LDL)-cholesterol level has been found to inversely correlate with CFR.[72,73] Endothelial-dependent vasodilation was significantly increased after LDL apheresis in patients with hypercholesterolemia.[74] Interestingly, all these risk factors accounted for less than 20% observed data variability in the WISE study,[75] suggesting the presence of other unidentified risk factors.

Systemic inflammation now appears to be an important risk factor as well. Studies have found patients with systemic lupus erythematosus,[76] ankylosing spondylitis,[77] and rheumatoid arthritis[78] have lower CFR than control subjects.

Correlation exists between disease activity measured by high-sensitivity C-reactive protein and the degree of microvascular dysfunction as measured by the CFR.[77,78] Most recently, a study also found CFR to be significantly lower during active inflammatory bowel disease.[79] One study observed a significantly higher prevalence of CMD in patients with polycythemia vera and essential thrombocythemia, and an association of abnormal CFR with Janus kinase 2 mutation.[80]

Treatment

Current approaches to treatment of primary CMD (**Table 2**) include the management of risk factors, use of antianginal and antiatherosclerotic medications and some novel agents. However, the current literature has little evidence for effective therapy for CMD for the following reasons: first, studies are often comprised of patients with cardiac chest pain that may be attributed to clinical entities other than CMD, such as Cardiac Syndrome X;[81] secondly, studies have used various CFR cutoff criteria for CMD, as there is no consensus definition to date.[82]

Management of risk factors includes control of diabetes and hypertension. Therapeutically lowering blood pressure can improve CFR, but excess lowering of diastolic blood pressure attenuates the benefit.[83] Insulin sensitizer, metformin, has been shown to improve endothelial function.[84] Lifestyle modifications include weight loss,[85] smoking cessation, high-fiber diet, fruit and vegetable consumption, and regular physical activity.[86–88]

Angiotensin-converting enzyme (ACE) inhibitors have been shown to improve exercise tolerance and anginal symptoms.[89] In the WISE control trial, the women who received quinapril had improved CFR after 16 weeks compared with the placebo group. In addition, the experimental group also had improvement in anginal symptoms based on the Seattle Angina Questionnaire.[90] Patients with essential hypertension had markedly improved CBF after 12 months of treatment with perindopril, with regression of periarteriolar fibrosis seen on biopsy.[91]

In patients already on an ACE inhibitor, the addition of an aldosterone blocker has not improved endothelial function.[92] In diabetics, the addition of spironolactone has been shown to improve coronary microvascular function.[93] The benefit of spironolactone is explained by the fact that mineralocorticoid receptor activation has been shown to cause vascular damage[94] and dysfunction.[95]

Few studies have addressed the use of β-blockers. The existing studies included patients with signs and symptoms of ischemia, but without a definitive diagnosis of CMD. Beta-blockers reduce myocardial oxygen consumption and increase the diastolic filling time. The use of atenolol has been shown to reduce the number of angina episodes[96] and also improve the ischemic threshold.[97] Carvedilol has been shown to improve endothelial function.[98]

Another class of vasodilator is calcium-channel blockers, which are a reasonable firstline treatment for CMD given the underlying pathophysiology. However, one study of intracoronary diltiazem did not show improved CFR in CMD patients, but rather it had a predominant vasodilatory effect on the epicardial artery.[99] Despite these findings, patients with abnormal vasodilator reserve had improved symptoms, less nitrate usage, and improved exercise tolerance after being treated with verapamil or nifedipine.[100]

Statins not only lower cholesterol, but also have antiatherosclerotic and antiinflammatory effects.[101] Data support the use of statins to improve CFR. Fluvastatin alone showed improvement in CFR and even greater improvement in combination with diltiazem.[102] Two small pilot studies have shown that administration of atorvastatin improved CFR after 2 months[103] and 6 months.[104]

Nitrates achieve their anti-anginal effect through venodilation to reduce the preload; in addition, they may have some coronary vasodilatory action. The use of nitrates may improve the patient's symptoms, but there is limited data on their effect on endothelial function.

Ranolazine is an antianginal that inhibits the late sodium channel, and overall reduces the intracellular calcium level in the cardiomyocytes, thus leading to improved ventricular relaxation.[105] Results for CMD have been conflicting. One pilot study showed improved symptoms in women with angina, evidence of ischemia but no obstructive CAD, and patients with low CFR demonstrated improved CFR with treatment.[106] A similar-sized study showed some improvement in symptoms but no effect on coronary microvascular function.[107] A recent large randomized trial of a 2-week course of ranolazine vs. placebo found no difference in symptoms or myocardial perfusion reserve.[108]

Ivabradine reduces the heart rate through its effect on the I_f current of the sinoatrial node. In patients with stable CAD, it is found to improve CFR.[109] Another study showed improvement in symptoms, but no effect on coronary microvascular function.[107] Ivabradine may have a therapeutic role in CMD patients.

Aminophylline, a nonselective adenosine-receptor antagonist, blocks the mediation of nociception. It is postulated to benefit CMD by attenuating the excess dilation of the microvasculature in a relatively well-perfused area, thus shunting more blood to poorly perfused areas. Some improvement in symptoms and exercise capacity were seen with short-term intravenous[110] and oral aminophylline[111]

Table 2. Treatment of Subjects With Angina, Evidence of Myocardial Ischemia, and No Obstructive Coronary Artery Disease[126]

Microvascular coronary dysfunction
Abnormal endothelial function
Angiotensin-converting enzyme inhibitors
HMG CoA reductase inhibitors (statins)
L-arginine supplementation
Aerobic exercise
Enhanced external counterpulsation
Abnormal non-endothelial function
β-blockers/α-β-blockers
Nitrates
Antiangina
Ranolazine
Ivabradine
Xanthine derivatives
Abnormal smooth muscle function (Prinzmetal's angina)
Calcium-channel blockers
Nitrates
Abnormal cardiac nociception
Low-dose tricyclic medication
Spinal cord stimulation
Cognitive behavioral therapy

in patients with signs and symptoms of ischemia but normal coronary angiograms.

Fasudil, a rho kinase inhibitor, reduces smooth muscle cell hypercontraction[112] and is being researched currently and has potential for CMD. It has been shown to be effective for vasospastic angina. Preliminary studies showed patients pretreated with fasudil did not show evidence of ischemia with ACh infusion, compared with saline pretreatment.[113]

There may be a role in giving L-arginine supplementation to improve endothelial dysfunction, as L-arginine is the precursor of nitric oxide.[114] Two studies found improvement in CFR after one-time infusion of L-arginine.[115,116] However, Lerman et al found that after 6-months of oral supplementation, there was symptom improvement, decreased endothelin concentration, and improvement in CBF, but no improvement in CFR.[117]

Given that impaired cardiac nociception maybe involved in CMD, tricyclic antidepressants can be considered, as they are thought to have a modulatory effect on norepinephrine uptake and anticholinergic effect that can cause analgesia. Imipramine has been shown to reduce the frequency of pain,[118,119] but one of the studies did not show any improvement in quality of life,[119] likely because of its significant side effects.

Non-pharmacologic treatments have been found to be effective in controlling patients' symptoms. Spinal cord stimulation has been shown to normalize abnormal pain perception,[120] improve anginal symptoms and increase exercise tolerance.[121] Enhanced external counterpulsation uses pneumatic cuffs applied to the patient's legs. Sequential inflation and deflation synchronized to the cardiac cycle improves hemodynamics.[122] It has been shown to improve angina in a small case series.[123] Cognitive behavioral therapy has been shown to reduce symptoms severity and frequency.[124] Cardiac rehabilitation involves multiple sessions of cardiovascular exercise, psychological counseling and nutritional planning and can be helpful as it improves blood pressure, body mass index and exercise capacity.[125]

Conclusions

The diagnosis of CMD should be considered in patients with angina, and a normal coronary angiogram. In those with multiple cardiovascular risk factors, rather than reassurance, further evaluation of the coronary microvasculature should be pursued to determine the presence of CMD. Diagnosis is achieved through detection of an attenuated response of the CBF in response to a vasodilator agent. Imaging modalities such as CMR, PET, and TTDE have become more widely used, but not yet completely replaced the traditional intracoronary vasoreactivity test. CMD is not a benign diagnosis and carries an increased risk for adverse cardiac events, thus should be aggressively managed. Treatment of CMD starts with lifestyle modification and risk factor control. The use of traditional antianginal and antiatherosclerotic medications and some novel agents may be beneficial, but clinical trials are needed to assess the efficacy of the pharmacologic and non-pharmacologic therapeutic modalities. In addition, studies of longer-term follow-up are needed to determine the prognostic benefit of these agents.

Acknowledgments

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