

Review

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Coronary microvascular disease: diagnostic evaluation

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Abstract

The diagnosis of coronary microvascular disease (CMD) is vital in a subset of patients with symptoms of myocardial ischemia. The typical ischemic findings on resting electrocardiogram and echocardiogram are uncommon or absent in CMD. Therefore, a high clinical suspicion is essential. We aim to review the invasive and non-invasive diagnostic testing for CMD. The goal is to assess the endothelial dysfunction related to vasoconstriction or reduced coronary blood flow reserve. Non-invasive testing includes resting electrocardiogram, exercise electrocardiogram, transthoracic color Doppler echocardiography, myocardial contrast echocardiography, positron emission tomography, and cardiac magnetic resonance imaging. Comprehensive invasive assessment includes coronary angiography followed by fractional functional flow reserve assessment, coronary flow reserve testing with intravenous acetylcholine with or without intravenous adenosine.

Keywords: Coronary microvascular dysfunction, intracoronary acetylcholine, intracoronary adenosine, coronary flow velocity, coronary flow reserve, myocardial contrast echocardiography, positron emission tomography, cardiac magnetic resonance

INTRODUCTION

Coronary microvascular disease (CMD) is a structural and functional abnormality in the coronary microvasculature. CMD is usually secondary to vasospasm and endothelial dysfunction. However, there is accumulating evidence suggesting inflammation is playing an essential role^[1-3]. CMD is more common in



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females^[4]. A high index of clinical suspicion is necessary because CMD is associated with increased morbidity and mortality^[5]. The evidence of ischemic signs of CMD on a resting electrocardiogram (ECG) and resting transthoracic echocardiography (TTE) are usually not present or may be absent. Direct visualization of coronary microvasculature is beyond the resolution of conventional imaging such as fluoroscopy, echocardiography, or computed tomography. Hence, the assessment of CMD depends on techniques to interrogating the physiology of the coronary microvasculature. Among patients with non-obstructive coronary artery disease, the diagnostic evaluation of CMD is considered while ruling out other causes, which include myocardial infarction with normal coronary arteries such as Takotsubo cardiomyopathy, spontaneous coronary artery dissection, myocarditis, and coronary artery embolism. The underlying hypothesis in diagnosing CMD is to evaluate reduced coronary vasodilatation or increased coronary vasoconstriction by measuring coronary flow reserve (CFR)/coronary flow velocity (CFV). This review discusses non-invasive and invasive approaches used to diagnose CMD (summarized in [Table 1](#)).

NON-INVASIVE TESTING

Resting electrocardiogram

The resting ECG is universally available and an inexpensive test to evaluate myocardial ischemia. The resting ECG is usually normal in most patients with CMD. Therefore, ECG has poor sensitivity to establish the diagnosis of CMD. The absence of ECG changes does not exclude the diagnosis. If CMD is suspected, further workup must be pursued, as elaborated below.

Exercise electrocardiogram

Exercise ECG is a highly specific test and is an excellent test to evaluate coronary ischemia. Exercise ECG is performed by measuring ECG at rest followed by exercise (treadmill or bike). It is cheap, widely available with good reproducibility. It also provides prognostic information based on the duration of exercise, symptoms, and ECG changes. However, it is limited by its inability to provide hemodynamics in the coronary vasculature. Therefore, an exercise ECG could be a good screening tool supplemented by other diagnostic modalities. [Figure 1](#) shows typical ECG changes suggestive of myocardial ischemia in a patient with normal coronary arteriograms. Among 33 patients with angina of unknown cause, *Chen et al.*^[7] demonstrated ischemia-related changes in 17 patients during a treadmill exercise test. Compared to patients who did not have symptoms on treadmill exercise test, patients with symptoms on had a significantly lower maximum great cardiac vein flow (108.8 ± 47.0 vs. 146.4 ± 23.4 mL/min, $P = 0.007$), higher minimum coronary vascular resistance (0.94 ± 0.41 vs. 0.61 ± 0.09 mmHg/mL/min, $P = 0.003$), and lower corrected great cardiac vein flow reserve (great cardiac vein flow/rate-pressure product, 0.0087 ± 0.0036 vs. 0.0125 ± 0.0019 , $P = 0.001$) after dipyridamole infusion (0.56 mg/kg for 4 min). *Chen et al.*^[7] concluded that CMD was likely related to effort-related angina and ischemic ECG changes during treadmill exercise testing based on these findings.

Hyperventilation and cold-pressor stress echocardiography

Hirano et al.^[8] described the hyperventilation and cold-pressor stress echocardiography to detect CMD among 43 patients suspected to have vasospastic angina. It was performed by hyperventilation for 6-min (30 respiration/min) and then right-hand immersion in ice water for 2 min, based on an earlier protocol by *Shimizu et al.*^[9]. The study demonstrated multivessel spasms in 26 patients by stress echocardiography and in 23 patients by angiography. This test's sensitivity, specificity, and diagnostic accuracy for detecting CMD were 48%, 100%, and 60%, respectively. However, with the recent advances in sensitive measurements of coronary physiology and imaging, this method is not frequently used.

Table 1. Coronary microvascular disease non-invasive and invasive diagnostic modalities with advantages and disadvantages

Test	Advantages	Disadvantages
Resting electrocardiogram	Universal availability Cheap to perform	Do not provide information during the activity
Exercise electrocardiogram	Universal availability Cheap to perform Physiological test	It does not provide information on hemodynamics in the coronary vasculature
Hyperventilation and cold-pressor stress echocardiography	Highly specific test Easy to perform Cheap to perform	Not convenient for the patient Needs technical expertise
Transthoracic Doppler echocardiography	Universal availability Cheap to perform	Need technical expertise Poor body habitus precludes accurate assessment
Myocardial contrast echocardiography	Universal availability Cheap to perform	Needs technical expertise Cannot rule out between myocardial bridging, coronary tortuosity, and CMD
Multislice detector computed tomography	Quick to perform	Ionizing radiation Limitation on accurate physiologic assessment of coronary microvasculature Expensive
Cardiac magnetic resolution imaging	High resolution Non-invasive No radiation exposure	Expensive Needs technical expertise Risk of nephrogenic systemic fibrosis in chronic kidney disease
Positron emission tomography perfusion imaging	Non-invasive Most-validated Provides prognostic data	Expensive Ionizing radiation Not universally available
Invasive coronary angiogram pharmacologic testing	Accurate assessment of coronary physiology using pressure wires	Invasive test associated with risk of ventricular arrhythmias during pharmacologic testing Expensive

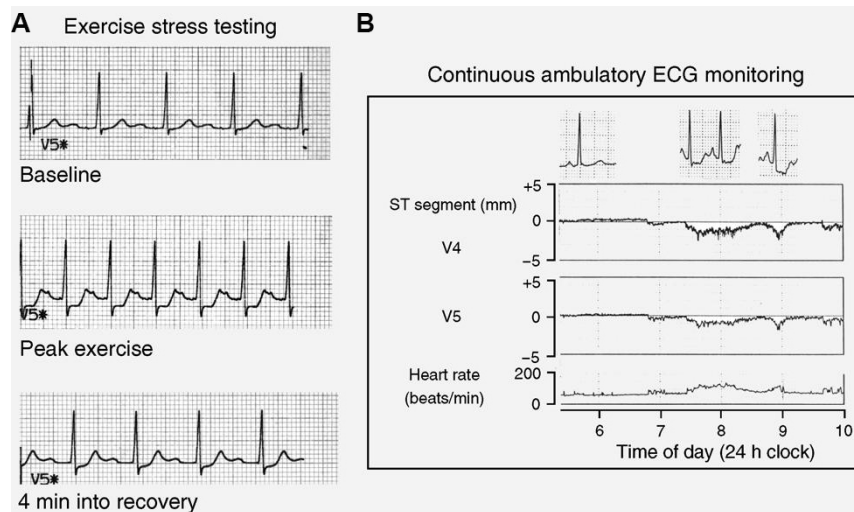


Figure 1. Electrocardiogram changes in a patient with normal coronary angiogram during exercise stress testing (A) and Holter monitor (B). Adapted from [6].

Transthoracic color Doppler echocardiography

TTE uses ultrasonic sound waves to characterize the cardiac structures. Using the Doppler principle, TTE provides a functional assessment of the valves, blood flow, and myocardium. TTE is widely available, inexpensive, and easily performed. The echocardiographic imaging of the distal left anterior descending artery was described originally by Voci *et al.*^[10] in 25 out of 33 study participants (with coronary artery disease) and Hozumi *et al.*^[11] in 23 participants in whom CFV was measured in the distal LAD by a Doppler

guidewire at the time of coronary angiography. The middle to the distal part of LAD was imaged by color Doppler. Once imaged, a pulse Doppler was used to measure coronary blood flow, peak and mean flow velocity, deceleration time, and deceleration rate. The authors concluded that CFV reserve from transthoracic Doppler echocardiography correlated highly with those from Doppler guide wire examinations (CFV: averaged peak velocity: $r = 0.97$; averaged diastolic peak velocity: $r = 0.97$; systolic peak velocities: $r = 0.97$; diastolic peak velocity: $r = 0.98$). Galiuto *et al.*^[12] studied this phenomenon in a small cohort of patients with cardiac syndrome X, another name for CMD, by using intravenous administration of adenosine (0.14 mg/kg/min for 90 s) followed by transthoracic echocardiography performed in the left lateral decubitus position at the cardiac apex to image the distal anteroseptal region; CFR was measured by Doppler echocardiography as an adenosine/rest velocity ratio and by myocardial contrast echocardiography as a microvascular volume, velocity, and flow adenosine/rest ratio. Compared with controls, patients with syndrome X demonstrated lower CFR, CFV, and microvascular flow reserves. Prognostically, the CFR by TTE has shown better outcomes among patients with normal CFR at 48 months follow-up^[13]. A good correlation has been demonstrated between echocardiographic Doppler measurements and positron emission tomography. However, compared to positron emission tomography, echocardiographic Doppler imaging is limited by echocardiographic challenges in visualizing coronary arteries, technical expertise, and poor echo windows in many patients^[14,15].

Myocardial contrast echocardiography

Myocardial contrast echocardiography (MCE) involves the intravenous administration of an ultrasound contrast agent [1.5 mL of Definity® 17 diluted in 28.5 mL of saline solution (0.09%) for a total volume of 30 mL, as a continuous intravenous infusion at a rate of 90 mL/h]^[16]. This is followed by TTE with a vasodilator stress agent (e.g., dipyridamole). Assessment of wall motion during rest and infusion of vasodilator was performed by measuring mean microbubble velocity and myocardial blood volume and computing myocardial blood flow (MBF)^[16]. The authors found that MBF reserve was significantly reduced in patients with CMD, which can be explained either based on increased resting MBF or inability of the resistance vessels to dilate during stress or both. Even though MCE measured hemodynamics in the coronary vasculature, this study was limited by requiring high technical expertise, limiting the study to imaging only the interventricular septum and inability to differentiate low MBF due to myocardial bridging and coronary tortuosity.

Multislice detector computed tomography with fractional functional flow assessment

Multislice detector computed tomography involves the intravenous administration of iodinated contrast and adenosine (0.14 mg/kg/min for 5 min) to image the coronary vasculature. Images are analyzed by measuring the attenuation over time in basal and hyperemic conditions and plotting time-attenuation curves. Fractional functional flow using multislice detector computed tomography has been established to evaluate epicardial coronary occlusions. However, the current imaging does not incorporate the influence of microvasculature^[17]. Therefore, multislice detector computed tomography is currently not used to evaluate CMD. Micro-optical coherence tomography, a relatively new application to visualize the endothelial cells in coronary arteries, has been described by Nishimiya *et al.*^[18]. This may help in better understanding the physiology of coronary micro-vasculature in the future.

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (CMRI) has emerged as a good option for the non-invasive evaluation of the heart. CMRI uses strong magnetic fields to generate images of the heart and blood vessels. CMRI is also used to evaluate cardiac hemodynamics by incorporating functional assessment techniques. In patients with CMD, magnetic resonance imaging can determine coronary blood flow (CBF) during maximal hyperemia by administering vasodilators such as adenosine^[19]. Panting *et al.*^[20] described subendocardial

perfusion defects after intravenous administration of adenosine in 20 patients with cardiac syndrome X. Lanza *et al.*^[21] confirmed the utility of magnetic resonance imaging with a dobutamine stress test in 18 patients with syndrome X by showing perfusion defects in LAD artery territory. Cardiac magnetic resonance imaging has the advantages of allowing high spatial resolution, lack of ionizing radiation, functional assessment of cardiac function while allowing assessment of microvascular blood flow. Contraindications for CMRI include the risk of nephrogenic systemic fibrosis in end-stage renal disease patients, the presence of non-MRI compatible hardware in the body, and gadolinium contrast allergy. Disadvantages of CMRI also include - not being universally widely available and necessitates relevant expertise in interpreting results.

Positron emission tomography-computed tomography perfusion imaging

Positron emission tomography-computed tomography (PET-CT) is a non-invasive nuclear medicine technique involving administering a specific intravenous radio-isotopic tracer (such as $^{13}\text{NH}_3$, H_2^{15}O , and ^{82}Rb) to acquire sequential images using an x-ray computed tomography. This enables quantifying MBF per gram of tissue uptake during the rest and stress phase (induced with a vasodilator). PET-CT allows measuring MBF globally and regionally by the quantification of the myocardial radio-isotopic tracer uptake. CFR is calculated by the ratio of MBF in the hyperemic phase with a vasodilator and at rest. Murthy *et al.*^[22] assessed coronary microvascular endothelium-independent dysfunction in 405 men and 813 women by positron emission tomography. $\text{CFR} < 2.0$ in the absence of significant epicardial coronary artery stenosis was considered diagnostic of CMD. The role of positron emission tomography in patients with CMD and non-ischemic cardiomyopathies (such as dilated cardiomyopathy, hypertrophic cardiomyopathy, Fabry's disease, and amyloidosis) has been extensively studied to show lower CFR in these patients compared to controls^[19-22]. While PET is considered the future of nuclear cardiology, several limitations need to be acknowledged. First, PET is expensive and time-consuming. Second, it is not widely available and requires technical expertise. Third, the resolution of positron emission tomography is poor compared to CMRI. However, future studies evaluating the combined imaging using positron emission tomography with CT may improve the diagnostic capabilities.

Invasive testing

Coronary angiography is necessary for diagnosing CMD in terms of ruling out epicardial obstructive coronary artery disease (CAD). It is routinely performed in patients with angina and abnormal non-invasive cardiac stress test. In the absence of significant epicardial disease, a delayed distal vessel opacification of contrast may be noted. This is referred to as the coronary slow flow phenomenon^[23]. For further evaluation, patients with non-obstructive CAD with stenosis $< 80\%$ and fractional functional flow reserve (FFR) > 0.80 additional testings for coronary angiography are pursued. FFR is the most validated and the gold standard to identify non-obstructive stenosis. However, in recent years, non-hyperemic intracoronary pressure assessments have gained popularity. Instantaneous wave-free pressure ratio (iFR) was evaluated in the iFR SWEDHEART, and the DEFINE-FLAIR study revealed that iFR predicted outcomes like FFR. Less invasive quantitative flow ratio and diastolic hyperemia-free ratio also demonstrated good accuracy compared to FFR^[24,25]. During angiography, functional testing for CMD is performed by measuring the microvascular dysfunction with intracoronary acetylcholine and non-endothelial microvascular dysfunction with adenosine^[26]. Invasive provocative testing using acetylcholine has a small risk of major complications. In a review by Ciliberti *et al.*^[27], acetylcholine ($n = 6183$) administration was associated with a 1% risk of ventricular tachycardia/ventricular fibrillation and a 3% risk of transient bradycardia, 2% risk of paroxysmal or persistent atrial fibrillation. This small risk continues to limit the universal application of this test, at least in the United States.

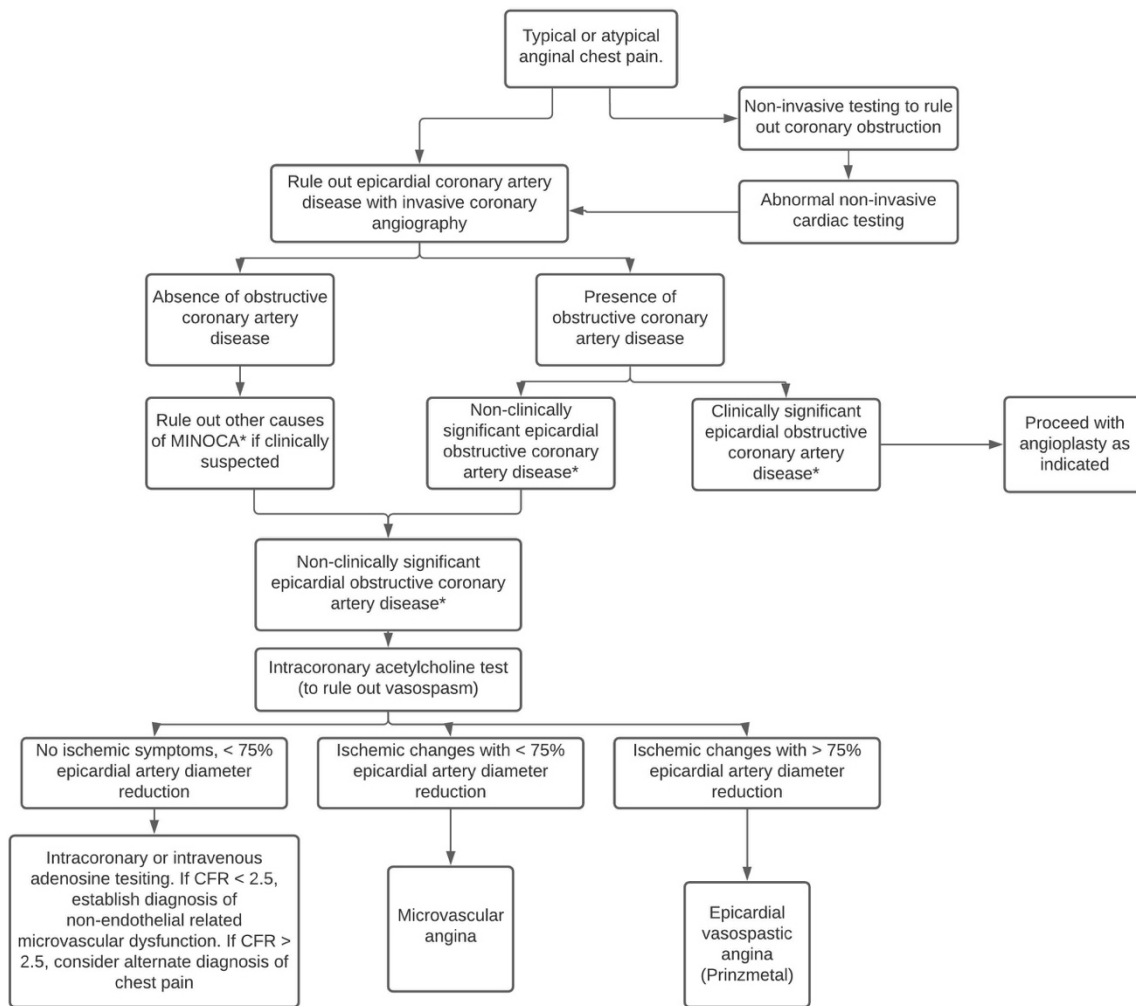


Figure 2. Flow chart for evaluation of coronary microvascular disease. It is adapted with permission from^[3].

Pharmacologic coronary endothelial and non-endothelial function testing

The pharmacologic testing for CMD involves performing a coronary angiography by administering vasodilator drugs in the coronary arteries and measuring coronary blood flow. During coronary angiography, the coronary endothelial function is assessed by injecting 50 µg acetylcholine by intracoronary route over 2 to 3 min^[26]. After each injection, coronary angiography is performed. Endothelial dysfunction is diagnosed if epicardial coronary artery diameter decreases by > 20% compared with baseline. If epicardial blood vessel narrowing greater than 25% is assessed along with ischemic changes on EKG, a diagnosis of epicardial coronary artery vasoconstriction is made. If the narrowing is less than 25% but associated with ischemic EKG, a diagnosis of coronary microvasculature vasospastic angina is made. If no coronary narrowing is noted with no ischemic changes, further testing with adenosine is performed to evaluate non-endothelial causes of micro-coronary vascular disease.

Intracoronary or intravenous adenosine is also used to measure the CFR. CFR measured during coronary angiography quantifies the CFV/CFR. Abnormal microcirculation is identified by administering adenosine during the angiogram^[28]. CBF normally increases 2.5 to 5 times with adenosine compared to baseline. When there is an obstruction in the microcirculation, the CFR is reduced when measured with an intracoronary Doppler wire. Reis *et al.*^[29] suggested a CFV reserve threshold of 2.25 as an indicator of endothelium-

independent coronary microvascular dysfunction with a sensitivity of 90% and specificity of 89%. Currently, a CFR value of 2.5 is used as a convenient threshold. Patients with abnormal CFR are considered to have endothelium-independent microvascular angina^[26]. According to Radico *et al.*^[30], patients with CFR > 2.5 after adenosine should be considered to have “true” cardiac syndrome X. [Figure 2](#) elaborates the flow chart for evaluation of CMD. In addition to doppler, intracoronary CFR measurement of thermodilution has shown to be reliable and safe. A good correlation ($r = 0.79$, $P < 0.0001$) has been demonstrated between Doppler and thermodilution derived CFR^[31].

CONCLUSION

CMD is suspected when a patient has typical anginal chest pain in the absence of obstructive lesion on coronary angiography. An accurate assessment of symptoms is warranted given the higher mortality and morbidity associated with CMD. The diagnosis of CMD can be aided solely by non-invasive testing. Cardiac MRI and PET enable us to identify coronary microvascular anatomy/physiology with high spatial resolution while avoiding the need for invasive studies. While the non-invasive modalities are yet to be standardized, future studies aimed at improving the diagnostic accuracy of non-invasive testing for CMD will enable accurate, prompt, and safe diagnosis.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Voruganti D, Mehta JL

Performed data acquisition and provided administrative, technical, and material support: Voruganti D, Mehta JL

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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