

# The Conundrum of Coronary Microvascular Dysfunction: A Case Report

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## Abstract

**Background:** Women with signs and symptoms of myocardial ischemia often have no obstructive coronary artery disease by invasive coronary angiography compared to men. Coronary microvascular dysfunction (CMD) is thought to be a key contributory mechanism for myocardial ischemia in women with chest pain and no obstructive CAD. The CMD diagnosis is challenging, and the disease management has so far been empirical because of its multifactorial pathophysiology.

**Case Illustration:** A 60-year-old woman with a history of hypertension and diabetes came to undergo elective diagnostic coronary angiography (DCA) related to complaints of chest pain and tightness that are often felt by patients. ECG examination shows an old myocardial anteroseptal and inferior infarction. Echocardiography examination showed left ventricular dysfunction (LVEF 26%) and right ventricular dysfunction (TAPSE 1.4 cm). From the DCA examination obtained, non-significant stenosis is 30% in mid LAD, whereas RCA, LMCA, and LCx show normal results. The patient is then discharged with optimal medical therapy advice.

**Discussion:** Structural and functional disorders that affect the entire coronary circulation, including microcirculation, are the cause of coronary artery disease symptoms. The subset of disorders that affect the coronary microcirculation itself is called coronary microvascular dysfunction (CMD). Cardinal manifestations of CMD include angina pectoris, dyspnea on exertion, and even heart failure. Patients generally experience a combination of these symptoms. A coronary vasomotor function analysis, both non-invasive and invasive approaches, is needed to diagnose CMD.

**Conclusion:** This case highlights the clinical importance and challenges of diagnosing CMD. In women with signs and symptoms of myocardial ischemia and no obstructive CAD, CMD may be a mechanism leading to symptoms. Therefore, it is important to identify and diagnose in the appropriate clinical setting, as CMD is associated with an increased risk of adverse cardiovascular events.

**Keywords:** Coronary microvascular dysfunction; Ischemic heart disease; Non-obstructive coronary artery disease

## Introduction

Since the early 1900s, cardiovascular disease has been the leading cause of mortality in developed countries (Benjamin *et al.*, 2018). However, no substantial obstructive coronary lesions were identified in several individuals with symptoms of cardiovascular disease who underwent cardiac catheterization (Maddox *et al.*, 2014). According to some studies, 40% of patients having coronary angiography fall into this category (Patel *et al.*, 2010).

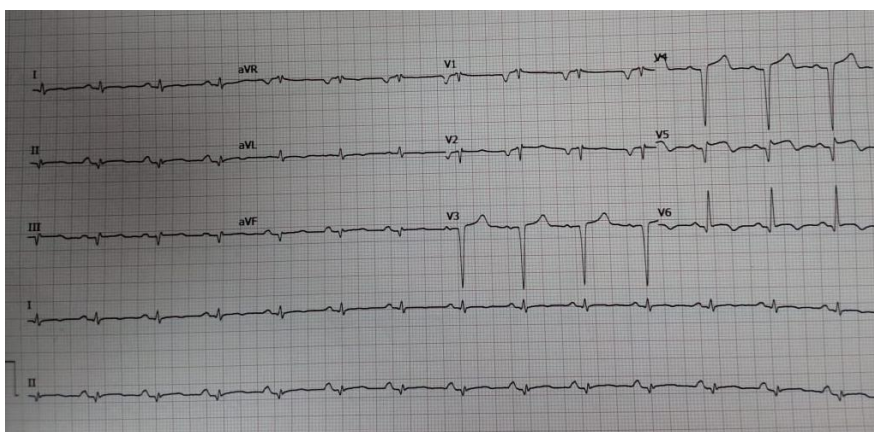
In 1985, Cannon and Epstein used the term “microvascular angina” to describe this patient population. They hypothesized that the pathogenic cause of this syndrome might be malfunctioning of the small intramural pre-arterioles arteries. A subset of disorders that impair the coronary microcirculation itself is called coronary microvascular dysfunction (CMD) (Cannon dan Epstein, 1988).

## Case illustration

A 62-year-old woman came to RSUD Dr. Soetomo for an elective diagnostic coronary angiography

(DCA) evaluation regarding complaints of chest pain and tightness that she frequently experiences when active and improves with rest. In 2019, she received coronary angiography, which revealed CHD with 30% non-significant stenosis in the LAD and MIINOCA. It is known from the disease's earlier history that she has had a history of hypertension since 15 years ago and diabetes mellitus since 5 years ago. She denies having ever had a stroke, kidney disease, or smoked.

We obtained blood pressure of 120/90 mmHg, pulse rate of 90 bpm, breath rate of 24 bpm, and oxygen saturation of 99% (O<sub>2</sub> nasal 4 lpm) during the assessment of the vital signs. The physical examination of the thoracic revealed fine rhonchi in 1/3 of the basal lung. We also obtained a warm acral without edema at both extremities. The electrocardiogram (ECG) revealed sinus rhythm at 90 bpm; frontal plane left axis deviation and horizontal axis clockwise rotation; and an image of an old myocardial infarction (OMI) of the anteroseptal + inferior (Figure 1). The lungs did not look abnormal and on the thoracic photos' examination obtained cardiomegaly with a CTR of 68% (Figure 2).



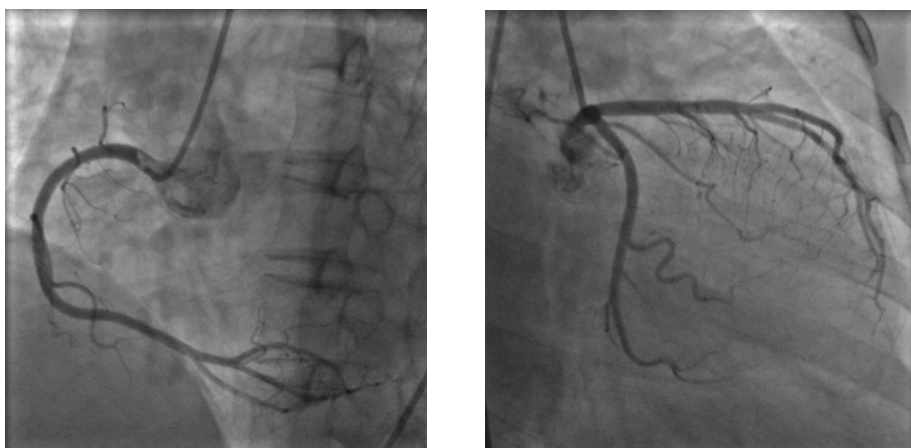
**Figure 1.** The patient's ECG examination when she entered the room.



**Figure 2.** The thoracic photos' examination obtained cardiomegaly (CTR 68%).

The patient's transthoracic echocardiogram (TTE) revealed the following findings: valves appeared to be dilated mitral annulus with moderate MR, mild TR, and mild PR; there was an LA and LV dilation (LVIDd 5.3 cm); no thrombus/intracardiac vegetation; systolic function LV decreased (EF by teich 26%, by biplane 28%); RV systolic function decreased (TAPSE 1.4 cm); there was akinetic segments in the anteroapical (B-M), septal (A), anterior (A), inferior (A), other hypokinetic segments; and there was an eccentric LVH. The results of the laboratory tests were within normal ranges.

Before elective DCA treatment, we treated the patient in a room with Furosemide Injection therapy 2 x 20 mg, Spironolactone 1 x 25 mg, ASA 1 x 10 mg, Lisinopril 1 x 10 mg, ISDN (if chest pain), Glimepiride 1 x 4 mg, and Metformin (delay before treatment). From the LMCA examination, we obtained a normal DCA result; there was non-significant stenosis of 30% mid LAD, while the LCx and RCA results were normal (Figure 3).



**Figure 3.** The DCA examination showed a normal RCA (A) result; 30% non-significant stenosis in the mid LAD; while the LMCA and LCx were normal (B)

Following the DCA treatment, our patient was treated in a low-care room, and after confirming her stable state, we returned her with recommendations for optimization of medicamentosa therapy.

## Discussion

Cardiovascular disease, often known as coronary heart disease (CHD), is conventionally defined anatomically as obstructive atherosclerosis involving epicardial coronary arteries. However, structural and functional abnormalities affecting the whole coronary circulation, including the microcircuit, are now recognized as the origin of the disease—symptoms of CHD. A subset of disorders that impair the coronary microcirculation itself is called coronary microvascular dysfunction (CMD). About 50% of women with persistent angina symptoms, evidence of ischemia, and presence of non-obstructive CHD are found to have CMD. CMD is prevalent among women with Triassic symptoms of chest pain, evidence of ischemia with a stress test, and non-obstructive CHD, according to the Women's Ischemia Syndrome Evaluation (WISE) (Reis *et al.*, 2001; Quyyumi, 2006).

The coronary artery system is a continuous network of several functionally different segments of blood vessels with an increasingly narrowed size. Large proximal epicardial coronary arteries (> 400 µm) give way

to small pre-arterioles (100 to 400  $\mu\text{m}$ ) and smaller intramural arterioles. Coronary blood flow and myocardial perfusion are controlled by the coronary arteriolar tone in normal blood vessels. Through dynamic changes in blood vessel tone resistance, the coronary blood flow will stay constant at various coronary perfusion pressures (CPP). These dynamic changes are caused by a combination of somewhat exaggerated mechanisms, including adrenergic stimuli, changes in local oxygen pressure, and reactions to transmural pressure changes. Excessive control of coronary blood flow aids in the reduction of myocardial ischemia during the development of epicardial atherosclerosis. Because myocardial oxygen extraction is nearly maximum at rest, the delivery is almost entirely dependent on coronary blood flow. As a result, to prevent myocardial ischemia, the increased myocardial oxygen must be balanced by a proportional increase in coronary blood flow. In reaction to stress, the CMD reduces coronary flow augmentation, and if severe enough, it causes demand-supply mismatches and may result in sub-clinical or clinical myocardial ischemia (Camici *et al.*, 2007; Chilian *et al.*, 2007).

Some structural changes, or microvascular remodeling, have been linked to CMD. The spectrum of these diseases excludes atheroma, which occurs in the epicardial arteries but is likely exacerbated in the presence of atherosclerosis, particularly in patients with cardiovascular risk factors. These changes induce microvascular obstruction, with shrinking of arterioles and intramural capillaries' lumens and frequently result in an increase in LV mass. Numerous studies have shown evidence of microvascular remodeling, which is consistently related to several risk factors such as diabetes, hypertension, kidney diseases, or evidence of diffuse epicardial atherosclerosis (Amann *et al.*, 1992).

There is ample evidence that endothelial dysfunction of coronary blood vessels contributes significantly to CMD. By producing vasoactive substances such as nitric oxide, vascular endothelial plays an essential role in modulating smooth muscle function. In normal endothelial function, acetylcholine and physiological stimulation (e.g., physical activity) both produce epicardial coronary artery vasodilation and microvascular tissue, resulting in higher coronary blood flow and myocardial perfusion. Nonetheless, as cardiovascular risk factors and atherosclerosis develop, vascular endothelial dysfunction reduces the vasodilator response to pharmacological and physiological interventions, resulting in decreased coronary blood flow or vasoconstriction with a continuous drop in blood flow (Egashira *et al.*, 1993).

Furthermore, there is evidence that functional abnormalities of smooth muscle cells that control arteriole tone are found in many CMD patients. Weakened vasodilation response to papaverine, adenosine, or dipyridamole, mediated mainly by relaxation of vascular smooth muscle, has been observed in patients with diabetes, metabolic syndrome, dyslipidemia, hypertension, obesity, smoking habit, kidney disorders, and cardiomyopathy. Coronary spasm is a kind of spectrum vasomotor disorder that affects major and small coronary arteries in CMD patients. Epicardial or microvascular spasms resulting from acetylcholine have been reported in about 50% of patients with stable angina and non-obstructive CHD. Coronary spasm pathogenesis appears to be linked to atherosclerosis and endothelial dysfunction. Patients with coronary endothelial dysfunction and non-obstructive CHD are more likely to experience fatal and non-fatal cardiovascular events, such as sudden cardiac death, myocardial infarction (heart attack), and congestive heart failure (CHF) (Quericioli *et al.*, 2012).

Non-obstructive diffuse atherosclerosis in the epicardial coronary arteries is a common finding in most patients with CMD symptoms. In a study involving patients with angina symptoms and without obstructive CHD, nearly 70 – 80% of them showed evidence of non-obstructive diffuse atherosclerosis or coronary artery calcification with intravascular ultrasound (IVUS) examination. Cardinal manifestations of CMD include

angina pectoris, dyspnea on exertion, and even heart failure. Patients usually have a combination of these symptoms. CMD patients initially have a relatively prolonged asymptomatic phase during which they are diagnosed by coincidence with the disease. Angina occurs in approximately 30 to 60% of them. These symptoms are very similar to angina symptoms caused by obstructive CHD because they are usually triggered by activity and reduced by rest. Atypical angina, which includes episodes of chest pain when lying down, also happens frequently. The patients may also experience a progressive reduction in exercise tolerance or tightness when doing activities. The dyspnea on exertion can be caused by left ventricle systolic and diastolic dysfunction, as well as cardiopulmonary congestion (Lee *et al.*, 2015).

Camici and Crea examined this issue in 2007 and suggested a categorization based on clinical and pathogenic CMD, dividing it into four main types: (1) CMD without myocardial and obstructive CHD diseases, (2) CMD with a myocardial disease, (3) CMD with obstructive CHD and (4) iatrogenic CMD. The enforcement of CMD diagnosis is quite challenging since coronary microvasculature cannot be directly seen during standard coronary angiography. Because CMD patients typically have normal physical examination findings. However, the specifics of clinical history and the presence of risk factors, which may overlap with their suffering from atherosclerotic CHD, might lead to a diagnosis. Typical signs of elevated filling pressure in patients with heart failure include jugular venous distention, rhonchi, and limb edema. The majority of them also have normal or non-diagnostic electrocardiograms (ECG) (Camici dan Crea, *et al.*, 2007; Ong *et al.*, 2012).

For those suspected of having CHD, an exercise stress test to identify myocardial ischemia is a Class I recommendation. Positive findings from the test have traditionally been used to confirm a diagnosis of CMD. Several extensive studies, however, comprising men and women with angina pectoris and non-obstructive CHD, discovered that positive results from such tests were insensitive and specific to CMD. The non-invasive diagnostic procedure for CMD relies on analyzing coronary vasomotor function by measuring regional and global myocardial blood flow during rest and stress, microvascular resistance, and coronary flow reserve (CFR). CFR, which is calculated as the ratio of absolute myocardial blood flow during hyperemic and rest conditions, is a coronary vasomotor dysfunction parameter that integrates the hemodynamic effects of focal, diffuse, and small blood vessels on myocardial tissue perfusion. CMD can be characterized realistically as a CFR disorder without the epicardial coronary artery flow disorder (obstructive), indicating vasomotor dysfunction of the distal coronary system (Ong *et al.*, 2012).

Positron Emission Tomography (PET) is the most reliable and accurate non-invasive technique for the quantitative assessment of coronary vasomotor function. The imaging protocols comprise studies of myocardial perfusion at rest and stress, with radiotracer injected into the bloodstream in each case. Post-image processing at rest and stress enables the quantification of localized and global myocardial blood flow as well as the calculation of CFR (such as myocardial blood flow ratio during stress and at rest). Cardiac Magnetic Resonance (CMR) may be used in the same way as PET to assess myocardial perfusion, albeit the technique takes longer. Imaging protocols, like PET, include studies of myocardial perfusion at rest and during stress, with each needing the injection of a gadolinium-based contrast agent. Doppler echocardiography of the anterior coronary artery left descendens can also be used to assess the pace of coronary blood flow at rest and during vasodilation stress. The coronary flow speed is assessed using pulsed-wave doppler and is graded as the peak diastolic flow speed at rest and the peak of hyperemia. The ratio of coronary flow velocity during hyperemic to coronary flow velocity at rest is used to determine Coronary Flow Velocity Reserve (CFVR) (Neglia *et al.*, 2002; Shimokawa *et al.*, 2014).

Invasive coronary angiography with the ability to eliminate obstructive CHD with complementary catheter-based techniques for analyzing epicardial and microvascular coronary physiology is an intriguing approach to evaluate patients with CMD. The most common method for assessing invasive coronary flow reserve (iCFR) is to use a doppler-tipped guidewire or thermodilution method to evaluate the speed of coronary blood flow at rest and in response to vasodilation to adenosine (Ado) or acetylcholine (ACh) (Egashira *et al.*, 1993). In a CMD setting, microvascular angina is defined as a symptom of myocardial ischemia, the lack of evidence of obstructive CHD and iCFR abnormalities, or the presence of acetylcholine microvascular spasms (Ong *et al.*, 2012).

The Index of Microvascular Resistance (IMR) is calculated by measuring the pressure in the distal coronary divided by the opposite of the average transit time during maximal hyperemia. A pressure-temperature sensor-tipped coronary guidewire is required for this examination, which enables the measurement of coronary pressure and flows hyperemia simultaneously. Abnormal IMR values are related to worse cardiovascular outcomes in patients with stable non-obstructive atherosclerosis. By calculating the pressure ratio in the distal coronary arteries to aortic pressure during the hyperemia phase, fractional flow reserve (FFR) can offer an overview of impaired blood flow and a degree of coronary artery stenosis. The RCT study evidence supports that FFR examinations can help guide clinical decisions about coronary revascularization. However, FFR is not the primary modality for diagnosing CMD since pseudo-normalization of FFR might occur in this scenario. Instantaneous wave-free ratio (iFR) uses wave intensity analysis (WIA) to detect wave-free periods during the mid-late diastolic phase where the iFR is calculated. iFR is a degree of stenosis index calculated from pressure during the diastolic phase without the use of adenosine. This trans-stenotic pressure gradient (TPG) is a reliable measure of coronary stenosis degree and is highly associated with FFR. In a CMD setting, iFR has some of the same limitations as FFR (Halcox *et al.*, 2002; Lee *et al.*, 2015). WIA may also be used to evaluate coronary microvascular function. The primary metric is coronary blood flow augmentation caused by capillary re-expansion in the early diastolic phase. Because capillary density is a significant determinant of intramyocardial blood vessel capacity and backward suction that accelerates flow during the diastolic phase, quantifying microcirculation filling in the early diastolic phase with WIA can provide an overview of myocardial capillary density (Lee *et al.*, 2015).

Medicamentosa therapy for CMD has so far been empirical because of its multifactorial pathophysiology and overlapping phenotypes. CMD may be the main disease in some patients, but it may also be a subsequent clinical characteristic in others. There is presently no effective therapy for CMD. Existing therapeutic trials outcomes are hampered by the use of variables due to a lack of diagnostic standards, poor study designs, and small sample numbers. Because most CMD patients have a close relationship between risk factors for cardiovascular disease and atherosclerosis, aggressive management of comorbidities, such as quitting smoking, weight loss, blood pressure control, diabetes control, and related metabolic disorders, lipid management, nutritional improvement, and regular exercise, is an important goal of this disease management. Optimal medicamentosa therapy has been linked to a decrease in myocardial ischemia in patients with stable CHD, as well as improved coronary microcirculation function.

Low-dose aspirin (or an alternative antiplatelet drug if having an aspirin intolerance) remains a crucial component of patient management, even in patients with non-obstructive CHD. In addition to antiplatelets, statin therapy should be considered to be initiated and intensified in this group of patients since there is evidence that statin therapy improves myocardial ischemia and CMD. Traditional anti-ischemic medications, such as beta-blockers and short-acting nitrates, should be regarded as first-line therapies in managing CMD

symptoms. Calcium antagonists and long-acting nitrates may be used in addition to beta-blockers as supplementary therapies in situations of insufficient symptom control and are recommended when symptoms are caused by an increase in vasomotor tone or spasm. Angiotensin-converting enzyme (ACE) inhibitors (and perhaps angiotensin receptor inhibitors) can enhance coronary microvascular function by inhibiting angiotensin II's strong vasoconstrictor effect. Several medicines that help relieve angina symptoms in patients with CMD, including ivabradine, ranolazine, mibefradil, nicorandil, and trimetazidine, have been studied. Ranolazine, a well-studied medication, improves myocardial perfusion by lowering excess sodium and calcium, resulting in increased myocyte relaxation and diastolic stiffness. However, compared to placebo, the use of ranolazine in patients with CMD revealed no significant advantage in symptom improvement or changes in coronary microvascular function (Maddox *et al.*, 2014; Shah *et al.*, 2016).

Coronary revascularization of obstructive lesions also has the potential to improve symptoms and outcomes in patients with CMD, especially in the setting of severe myocardial ischemia or any evidence of coronary flow disorder. Cardiac rehabilitation can be started to reduce symptoms and has been found to help increase exercise capacity and relieve symptoms in these patients (Lee *et al.*, 2015).

## Conclusion

There has been a reported case of a 60-year-old woman with a history of hypertension and diabetes who came for an elective DCA evaluation because she was experiencing chest discomfort and tightness while doing activities. The thoracic physical examination obtained fine rhonchi in 1/3 of the basal lung, good perfusion without edema at the extremities, and vital signs within normal ranges. Anteroseptal and inferior OMI pictures were obtained during the ECG test. On echo examination, kinetic myocardial disorders were obtained with left and right ventricular dysfunction. Furthermore, she received a DCA and had non-significant stenosis in the LAD, whereas the RCA, LMCA, and LCx revealed normal findings. She was subsequently discharged with the recommendations for optimization of medicamentosa therapy.

In female patients with symptoms and signs of myocardial ischemia are frequently discovered to have non-obstructive CHD at coronary angiography examinations, and the CMD condition is the key to the mechanism that contributes to such condition. CMD diagnosis is difficult to enforce, and even now, the procedure is still empirical because of its multifactorial pathophysiology. Nonetheless, CMD must be identified and diagnosed in the appropriate clinical setting since it increases the risk of serious cardiovascular events.

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