

REVIEW ARTICLES

Cornary Microvascular Dysfunction: An Under-Appreciated Segment of Coronary Artery Disease

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Background:

Coronary artery disease (CAD) is predicted to be the most common cause of death and disability globally by 2020¹. Early detection and management of coronary artery disease can improve CAD related morbidity and mortality. Coronary angiogram remains the final diagnostic procedure for CAD. The current treatment strategy for CAD is confined mainly on disease of the epicardial coronary arteries. But, normal epicardial coronary arteries are found in 20% of cases undergoing coronary angiography for chest pain evaluation². Detection of normal coronary arteries in patients having angina pectoris does not exclude further coronary events; rather these patients bear more risk of future cardiac ischemic syndromes. Several studies tried to discover the dilemma of non-obstructive CAD.

They concluded with proposition of coronary microvascular dysfunction. Normal epicardial coronary arteries at angiography in patients with angina: Proposition of coronary microvascular dysfunction. Dysfunction of the coronary microcirculation was explained earlier by^{3,4}. Cannon and Epstein termed the condition as microvascular angina (MVA)⁵. Lanza and Crea described as Coronary microvascular dysfunction (CMVD) and demonstrated the pathophysiology with the following figure⁶:

Prognosis of Coronary microvascular dysfunction (CMVD):

Microvascular circulatory disease was previously considered not to confer elevated risk of future adverse cardiovascular events or early mortality^{7,8}. But recent data suggest that up to 30% of women diagnosed having

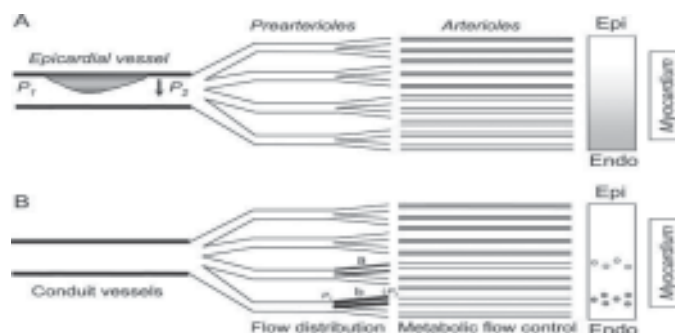


Fig.-1: Differences in myocardial ischemia caused by a significant coronary stenosis (A) or by CMVD (B). In the case of an epicardial (Epi) stenosis, myocardial ischemia diffusely involves the whole myocardial (usually subendocardial) territory supplied by the vessel (gray area), thus resulting in regional contractile dysfunction. In the case of microvascular alterations, myocardial ischemia is likely localized only in small myocardial areas, patchily diffused in the myocardium (small circles); this may not result in detectable contractile abnormalities because of the presence of normal contractile myocardial cells in the same territory. Also in this case, ischemia more easily occurs in subendocardial regions (more intense gray color of the small ischemic areas).

[Endo indicates endocardial. a and b indicate dysfunctional microvessels; P1 and P2- intracoronary pressure proximal and distal to obstructive vessels.]⁶

microvascular disease will develop clinically evident CAD within 10 year⁹. Women Ischemic Symptom Evaluation (WISE) trial found that more than two-fold increase in cardiovascular events in women with persistence of chest pain without obstructive coronary artery¹⁰.

Pathophysiological Mechanisms:

The pathogenesis of this dysfunction is still speculative. Some studies argued for functionally or anatomically abnormal coronary microcirculation^{4,11,12}. Structural abnormalities include smooth muscle hypertrophy³ and suggested functional abnormalities are primary impairment of vascular smooth muscle cell relaxation due to reduced endothelium-dependent (nitric oxide release) and endothelium-independent vasodilators (e.g., adenosine, dipyridamole, papaverine)¹³⁻¹⁵. Other studies suggest basal microvascular constriction¹⁶ and a blood steal phenomenon by normal microvessels¹⁷. This pathophysiology of microvascular disease explains slow flow at coronary microvascular bed. Abnormal pain perception¹⁸⁻²⁰ or a metabolic disorder affecting the handling of energy substrates by the heart muscle²¹ are also suggested explanations for pain in these patients.

Causes of CMVD

Common cardiovascular risk factors (e.g., hypertension, hyperlipidemia, diabetes mellitus, smoking) are thought to cause CMVD²² and Increased cardiac adrenergic activity can play a significant pathogenetic role in patients with stable MVA²³. Other potential causes of CMVD, reported in several studies, include increased insulin resistance, which may facilitate endothelial activation and dysfunction²⁴, estrogen deficiency in women²⁵, enhanced activity of the membrane sodium-hydrogen exchanger²⁶ and more recently, subclinical inflammation^{27,28}.

Diagnosis

At present, the diagnosis of MVA requires clinical suspicion and exclusion of epicardial abnormalities by coronary angiography⁶. In angina patients suspected to have MVA, however, attempts should be made not only to rely on this exclusion criterion for the diagnosis but to obtain objective evidence of CMVD.

Angina symptoms are often indistinguishable from those caused by obstructive CAD.

But suspicion should be made for MVA if-

- Chest pain persists for several minutes after effort is interrupted and/or shows poor or slow response to nitroglycerin^{29,30}.

- Induction of angina and ST segment depression, but not left ventricular contractile abnormalities, during stress echocardiography^{31,32}.
- An earlier appearance of ECG abnormalities and/or angina during an exercise test performed after sublingual nitrate administration³³.
- In case of vasospastic angina symptoms can be fully prevented by vasodilator therapy. Suspicion of co-existing MVA should be made when patients continue to experience typical effort angina despite full control of coronary artery spasm³⁴.

Available diagnostic modalities for CMVD and their limitations:

Various noninvasive as well as invasive modes were tried to assess microcirculation but failed to yield a consistent result and there is hardly any simple method available at present³⁵⁻³⁷.

Lanza and Crea (2010) described that exercise ECG changes were usually unremarkable for the diagnosis of CMVD. Tests to explore both the vasodilator and vasoconstrictor activity of coronary microcirculation are often proposed which can be done by invasive or non-invasively.

- A complete invasive evaluation, with intracoronary Doppler recording during CAG, would be complex and time-consuming and imposes unjustified adjunctive risks to patient.
- Whereas, a noninvasive tests, Transthoracic echocardiographic Doppler recording (TTE-DR) of coronary blood flow is easy to perform, reproducible, largely available, and, possibly, inexpensive³⁸. But TTE-DR cannot identify mild CMVD and cannot explore coronary territories other than LAD⁶

Contrast stress echocardiography is a promising method to detect CMVD in different myocardial territories. But there is scarcity of studies to support its applicability⁶.

Cardiac Magnetic Resonance (CMR) imaging with pharmacological stress tests and gadolinium (as a flow tracer) is perhaps the most promising method for noninvasive assessment of CMVD. At present, however, CMR seems to be too expensive, complex and time-consuming technique to use it in routine practice³⁸.

Myocardial perfusion imaging by scintigraphic stress test (SPECT, PET) is the most reliable tool available to diagnose myocardial perfusion and CMVD. But it is expensive and not easily available for routine use⁶.

The objective documentation of myocardial ischemia in patients with CMVD may be obtained with the use of certain other sophisticated diagnostic methods, which, however, cannot be proposed for routine application at present.

Assessment of lipid peroxidation products in the coronary sinus after stress tests seems to be sensitive³⁰; but it involves unjustified increased risk for the patient and are impractical for routine use.

CMR spectroscopy can detect ischemic abnormalities of phosphorus metabolism under stress tests⁴⁰; however, this technique is expensive, has scarce availability, and can only explore the anterior wall of the heart.

Coronary slow flow: a marker of CMVD

Presence of slow flow in coronary circulation in patients with angina and angiographically normal epicardial coronary arteries is evidenced by slow progression of angiographic dye^{41,42,43} showed higher TIMI frame count in all three coronary arteries in patients with syndrome X. On 2005⁴⁴ demonstrated impaired tissue level perfusion in patients with Syndrome X. But⁴⁵ found TIMI frame count & myocardial perfusion to be normal in patients with Syndrome X.

Sangareddi and Alagesan⁴⁶ proposed that the time delay between LAD opacification and filling of coronary sinus would indicate the transit time through microcirculation. On 2013⁴⁶ demonstrated significant difference in coronary sinus filling time (CSFT) but not TIMI frame count or TIMI myocardial perfusion (TMP) grade in patients with angina & normal coronaries compared with control group.

Therapeutic Approach

Treatment of patients with microvascular disease should focus on pathophysiologic mechanisms that contribute to endothelial dysfunction, with emphasis on smoking cessation, lipid and glycemic management and blood pressure control. Conventional anti-ischemic therapy may control symptoms in some patients, but overall results are usually mixed because the fact of the limited knowledge of its causes²⁹.

Traditional anti-ischemic drugs are the first step of medical treatment. β -Blockers seem rational approach because the dominant symptom is effort-related angina; particularly in patients with evidence of increased adrenergic activity (e.g., high heart rate at rest or during low-workload exercise). Calcium antagonists and nitrates have shown conflicting results in clinical trials and are more helpful in addition to β -blockers in the case of insufficient control of symptoms⁴⁷.

Short-acting nitrates can be used to treat anginal attacks, but often they are only partially effective^{29,30}.

In patients with persisting symptoms despite optimal anti-ischemic therapy, several alternative forms of treatment have been proposed.

ACEI (and possibly ARB) may improve microvascular function by counteracting the vasoconstrictor and pro-oxidant effects of angiotensin-II; particularly, in patients with hypertension or diabetes mellitus⁴⁸.

Statins⁴⁹ & estrogens²⁵ improve endothelial function, thus improve anginal symptoms. These drugs can be considered in patients with hypercholesterolemia and in menopausal women, respectively.

In patients with angina refractory to various combinations of the previous medications, significant enhanced cardiac pain sensitivity is likely to be present,^{19,20} which could benefit from some other forms of treatment viz. Xanthine derivatives (aminophylline- adenosine antagonists).¹⁷

Alternatively, the pure visceral pain inhibitor imipramine could be used to treat “refractory MVA”⁵⁰.

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