Coronary Microvascular Dysfunction

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Abstract

In the last two decades, a number of studies reported that abnormalities in the coronary microcirculation function and structure may occur in patients without obstructive atherosclerosis, in patients with risk factors, with myocardial diseases, as well as in obstructive atherosclerosis. Coronary microvascular coronary dysfunction may be iatrogenic and is an important risk marker, contributing to the pathogenesis of cardiovascular and myocardial diseases. Due to its importance, it becomes a therapeutic target. This article presents an update on the clinical relevance of coronary microvascular dysfunction in different clinical situations.

Key words: Myocardial infarction; Coronary angiography; Atherosclerosis

Introduction

In patients undergoing coronary angiography, whose clinical data are indicative of coronary artery disease (CAD), normal coronary arteries can be found, i.e., without atherosclerotic obstruction. The literature reports that up to 40% of patients undergoing coronary angiography are in this category.

The use of the term microvascular angina (MVA) for this population of patients has been explained by the higher sensitivity of the coronary microcirculation to local vasoconstrictors, and its association with limited microvascular vasodilatory capacity. Over the past 20 years, studies used for assessing coronary physiology have brought information to enable the better understanding of coronary microvascular dysfunction (CMD) and microvascular ischemia. Specifically speaking, studies using positron emission tomography (PET) have allowed to establish the normal and absolute range of myocardial blood flow (MBF, mL/min/g) and coronary flow reserve (CFR). The availability of normal WSF and CFR values allowed the investigation of coronary physiology in individuals at increased risk for CAD and in different categories of patients with symptoms and signs suggestive of myocardial ischemia, despite normal coronary angiographies. Camici and Crea proposed a clinical and pathogenic classification of CMD into four types based on clinical data, which present the following: (I) CMD in the absence of myocardial and obstructive CAD disease; (II) CMD in myocardial diseases; (III) DMC with obstructive CAD; and (IV) iatrogenic CMD. They also proposed that several pathogenic mechanisms contribute to CMD and their importance varies in different clinical settings, many of which co-existing in the same condition (Chart 1).

The molecular pathways of CMD, particularly endothelial CMD, and smooth muscle dysfunction have been extensively reviewed in previous studies. The purpose of this article is to provide an update on CMD in different clinical situations.
Risk factors

The role of traditional risk factors and endothelial dysfunction imply a poor prognosis; moreover, studies indicate that the dilation of microvascular endothelium may be involved in functional and structural changes that lead to changes in CFR associated with aging, hypertension, diabetes, dyslipidemia, metabolic syndrome and insulin resistance^16-23^.

Promising markers include nitric oxide metabolism disorders, dysregulation of a number of inflammatory mediators, including cytokines, estrogen, adrenergic receptors and changes in the expression or production of local vasoactive substances such as angiotensin II and endothelin^24-26^.

Diabetes

Chronic hyperglycemia is associated with significant reduction in coronary endothelium-dependent vasodilation. Interventions aimed at improving insulin sensitivity are proven to improve endothelial function and decrease myocardial ischemia in artherosclerosis^27,28^.

Inflammation

High levels of C-reactive protein were found and associated with a greater number of ischemic episodes detected by the electrocardiogram (ECG) in patients with microvascular angina, suggesting a role of inflammation in the modulation of coronary microvascular responses in these patients^29^. There was a high prevalence of CMD in patients with systemic lupus erythematosus and rheumatoid arthritis^29,30^.

Microvascular angina

It was observed that up to 40% of patients with signs and symptoms of myocardial ischemia undergoing coronary angiography do not have obstructive atherosclerosis^31^. After exclusion of non-coronary causes of chest pain, the presence of coronary vascular dysfunction, ischemia on stress tests and chest pain persisting after one-year follow-up can identify a subgroup of higher risk for adverse clinical outcomes identified from a database of 3-4 million patients in the United States who had signs and symptoms of ischemia despite no clinical evidence of obstructive arteriosclerosis. This was associated with poor quality of life,
psychological distress and worse follow-ups with health care.32-35

Contemporary studies document that most patients with angina and ST-segment depression during exercise test had myocardial regions with signs of ischaemia.36-39 Pathophysiological studies demonstrate coronary endothelial dysfunction in patients with signs and symptoms of ischaemia.40 They propose that dysfunction may not involve all coronary microvessels from a large coronary trunk uniformly, but may be distributed through the myocardium in a dispersed manner. This distribution of perfusion defects can provide a plausible explanation for the difficulties in obtaining objective evidence of myocardial ischemia. In fact, a sparse distribution of myocardial ischemia, though sufficient to produce ECG changes and myocardial perfusion in scintigraphy, may not result in contractile abnormalities detectable because of the surrounding normal function of the myocardial tissue. Similarly, the release in the coronary sinus of ischemic metabolites by ischemic myocardial foci may go unnoticed due to their dilution in the flow of larger normal myocardial areas.41

Patients with MVA have been considered of “low risk” even though this issue is still controversial. Invasive angiographic data showed that this group includes a more frequent women spectrum with higher risk of adverse cardiac events.42-46 The WISE study of 5.4-year follow-up showed adverse events, including cardiac death, stroke, early heart failure instead of myocardial infarction, particularly in women with reduced CFR.46

Although the relationship between the CMD and epicardial atherosclerosis is not fully understood, it has been proposed that intimal atherosclerotic lesion may vary and be related to sex differences in vascular remodeling and vascular reactivity, thus affecting women, preferably.46-49

**Stable microvascular angina**

There was a variable limit of physical activity that causes MVA; low heart rate activities such as mental excitement may trigger MVA in patients with obstructive atherosclerosis.50 In addition, in MVA, chest pain usually persists for several minutes after discontinuing efforts and shows an altered action of nitrates.51 Another characteristic that helps the differential diagnosis is the response to sublingual nitrates in stress ECG tests. The test results generally improve after sublingual nitrates in patients with atherosclerotic obstruction and remain unchanged or may even get worse in patients with MVA.52 Chest pain that persists for many years after angiography in women with apparently “normal” coronary arteries is associated with the future development of coronary atherosclerosis and adverse prognosis.53 The reduction of CFR assessed noninvasively using positron emission tomography, magnetic resonance imaging or transthoracic echo-Doppler can be useful for diagnosis.53-55 Furthermore, angina and ST-segment depression in the absence of regional motility abnormalities during adenosine infusion or dipyridamole in stress echocardiography represent a distinctive characteristic of MVA imaging studies.56 About half of patients with chest pain that reduced CFR in the absence of obstructive CAD resolution with drugs was associated with improved CMD.57,58

**Unstable microvascular angina**

Coronary angiographies defined as luminal smaller than 50% are reported relatively frequently in patients with ACS, including 10-25% of women and 6-10% of men.59 The ongoing investigation consists in addressing the paradox in which women have less severe obstructive CAD and less infarctions and even worse clinical outcomes. The higher mortality compared to men has been attributed to advanced age, comorbidities and underutilization of orientation care among women. The higher difference in mortality is observed in younger women, as evidenced by a series of studies.60-61

**Stable coronary artery disease**

Several lines of evidence suggest that the direct relationship between chronic obstructive coronary atherosclerosis and angina may be an oversimplified observation. In fact, many patients with angina and evidence of myocardial ischemia have coronary atherosclerosis detectable by angiography. On the other hand, a number of patients with severe coronary atherosclerosis do not experience angina. A recent study shows that patients with ACS as the first manifestation of CAD undergoing coronary angiography have multiarterial disease.62 This observation strongly suggests that the pre-existence of CAD obstruction was in a state of silence, probably because the microvascular function was preserved, and thus prevented angina and ischemia, despite obstructive CAD.

Most reports agree that coronary artery bypass grafting improves symptoms in patients with severe and
multivessel obstruction, but in many patients with angina, the pain recurs after 2-3 years, while myocardial infarction and death are not mitigated, as clearly shown in a recent meta-analysis.35

These observations certainly do not deny the usefulness of coronary artery bypass grafting in patients with ACS when coronary artery bypass grafting is needed to avoid irreversible damage or impending death, but the authors raise questions about whether coronary artery bypass grafting should continue to be considered a final treatment for obstructive atherosclerosis in stable patients. Thus, in patients with stable angina who have a large area at risk of myocardial ischemia, the main goal of treatment is to control risk factors and antianginal treatment directed to large epicardial coronary arteries and coronary microcirculation.

Acute coronary syndromes

The temporal association between the events that occur in large epicardial vessels, such as erosion of the plaque or fissure associated with thrombus formation and microcirculation with paradoxical vasoconstriction, does not allow establishing the causal relationship between these two events. It is believed that epicardial events precede and cause microvascular events. A more extreme view is that at least in a proportion of patients, CMD has a causal role in determining the formation of thrombi in coronary and epicardial arteries.64

In acute myocardial infarction with ST-elevation (STEMI), some pathophysiological condition is represented by CMD, which occurs after successful recanalization of the infarct-related artery. Mechanical reperfusion by percutaneous coronary intervention (PCI) is the treatment of STEMI. However, in a considerable proportion of patients, primary PCI reaches epicardial coronary artery recanalization, but not myocardial reperfusion, a condition known as no-reflow, now more commonly defined as microvascular obstruction (MVO).65,66

MVO may be caused by four mechanisms: (1) distal atherothrombotic embolization; (2) ischemic lesions; (3) reperfusion injury; and (4) the individual susceptibility of coronary microcirculation to the lesion.67,68. Ischemic pre-conditioning seems to have a beneficial effect on microvascular function.69

Pericutaneous coronary interventions

The clinical relevance of post-PCI distal embolization resulting in CMD is considerable. In a recent meta-analysis, the authors evaluated the occurrence and impact of the prognosis of troponin elevation in patients with normal basal levels undergoing PCI. Troponin elevation after PCI occurred in approximately 1/3 of patients, and the most severe atherosclerotic process was associated with an adverse prognosis due to increased risk of cardiovascular events.70

There is evidence that in patients with stable CAD and exercise-induced ischemia undergoing elective PCI, non-recovery of CFR immediately after the procedure despite successful recanalization, suggests CMD.69

Surgical interventions

Surgical trauma and cardiopulmonary bypass may contribute to a systemic inflammatory response, which is measurable by circulating cytokines, and promote CMD.67,72. This may result from several factors including blood contact with the bypass circuit, myocardial ischemia during bypass, aortic clamping and reperfusion. Perioperative myocardial infarction results in higher inflammatory markers.73-76. By measuring the basal metabolite rate (BMR) and the coronary flow reserve in patients undergoing coronary artery bypass grafting (CABG) using PET, it was found that hyperemia BMR and CRF improve steadily over six months after coronary artery bypass grafting suggesting persistent CMD.77

A study using images of CMD and Tnl measurement found that about 1/3 of patients undergoing coronary artery bypass grafting had a new myocardial infarction demonstrated by CABG, and a Tnl cut-off point of 5 mg/L (limit above normal of 0.6 mg/L) in 1 hour had 67% sensitivity and 79% specificity for detecting the new myocardial infarction. In this study, the predictive value of CK-MB for diagnosing myocardial infarction was lower than that of Tnl using a cutoff point of CK-MB of 25 mg/L; sensitivity was 44% and 89% specificity for detecting the new infarction. Substantial elevations of biomarkers after CABG have demonstrated implications in prognosis.78,79

The fact that different mechanisms of lesion after PCI and CABG have similar prognostic implications suggests that the prognosis is occasionally driven by the extent of necrosis regardless of the mechanisms responsible for its occurrence. The prognostic impact of myocardial damage after coronary artery bypass grafting assessed by elevation of enzymes is clinically relevant.80

Future efforts should be directed to achieve a better understanding of the pathophysiological mechanisms that contribute to coronary microvascular dysfunction.
in different clinical situations and forms of prevention and treatment in its various forms of presentation.

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References


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