

Coronary microcirculation: the new frontier in coronary artery disease

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A large body of evidence challenges the common view which attributes myocardial ischemia entirely and exclusively to atherosclerotic obstructions of large epicardial coronary vessels. In animal model as well in man, altered vasomotor control at the microvascular level may aggravate the effects of epicardial obstructions and/or hinder myocardial perfusion even in the absence of a proximal obstruction.

However, based on the assumption that atherosclerotic obstructions of the coronary vessels are the only cause of myocardial ischemia, thousands of surgical and percutaneous revascularization procedures are performed worldwide. Unfortunately, these procedures do not reduce the risk of death or myocardial infarction and even the symptomatic benefit has been limited. Randomized trials comparing revascularization with medical therapy have consistently shown that one third of patients remained symptomatic for angina after a successful procedure.

The prevalence and relevance of angina persisting after PCI need to be assessed in prospective trials, and the pathogenetic mechanisms clarified. Microvascular dysfunction is likely to play a major role in persisting angina and the development of therapeutic strategies directed to restoring microvascular function appear of paramount importance in order to consistently improve symptoms and prognosis in patient with IHD.

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Introduction

Over the past 3–4 decades, the view has evolved that coronary syndromes are caused by epicardial coronary plaques that can undergo rupture, with subsequent thrombus formation. The pathophysiology of ST-segment elevation myocardial infarction (STEMI) is believed to differ from the pathophysiology of unstable angina or non STEMI in the presence of a more stable and occlusive platelet-rich thrombus, less collateral circulation, and, generally, a more severe and prolonged imbalance between myocardial oxygen supply and demand in the culprit vessel territory, causing more prolonged and severe ischemia [1].

However, autopsy studies do not support the concept that the extent of intimal vessel injury determines the

magnitude and stability of the intraluminal thrombus [2], and the findings of prospective clinical trials do not support a relevant role for platelet-rich thrombi in unstable angina and non Q-wave infarction [3].

The behavior of the entire coronary vascular tree in relation to the pathogenesis of ischemic syndromes deserves further investigation. Classical concepts, often derived from animal models, do not fit with clinical observations. Focal increases in resistance at the coronary epicardial level, regardless of the causative mechanism, are expected to result in compensatory vasodilatation at the microcirculatory level [4]. Conversely, several studies have shown that this is not the case, and that a paradoxical microvascular vasoconstriction may be associated with stable or unstable angina [5,6].

Coronary microvascular dysfunction in the pathogenesis of myocardial ischemia

We have measured trans-stenotic and microvascular coronary resistances to flow in patients with tight left anterior descending (LAD) coronary artery stenosis, at baseline, after the intracoronary administration of adenosine, and during ischemia [6]. The major finding of that study was the recognition of an increased coronary microvascular resistance at a time when the traditional view would predict maximal vasodilatation of the coronary vascular bed. This observation strongly supports the hypothesis that abnormalities in coronary vasomotion can contribute to the precipitation and maintenance of ischemia in man. Endothelial dysfunction may impair microvascular adaptation to ischemia, and constrictor response to reduced intraluminal pressure has been described in isolated microvessels [7].

A large body of evidence challenges the common view that attributes myocardial ischemia entirely and exclusively to atherosclerotic obstruction of large epicardial coronary vessels. Altered control of distal coronary tone may aggravate the effects of epicardial obstructions or hinder myocardial perfusion, or both, even in the absence of a proximal obstruction.

Evidence of a prominent role of the coronary microcirculation in ischemic heart disease

Thousands of surgical and percutaneous revascularization procedures are performed every year, on the assumption that removal of coronary obstructions may improve symptoms and prolong survival. Unfortunately, available evidence does not support this popular opinion. In the Randomised Intervention Treatment of Angina (RITA)-2 trial, after a median 7 years of follow-up, death or myocardial infarction occurred in 14.5% of patients who underwent percutaneous transluminal coronary angioplasty (PTCA) and in 12.3% of patients treated medically. In addition, the prevalence of angina remained increased in both groups, with 70% of patients undergoing PTCA and 83% of those treated medically receiving at least one antianginal drug at 5 years [8].

The findings of a meta-analysis [9] confirmed that PTCA may lead to a reduction in angina, although the magnitude of the effects varies considerably, but it is unlikely to reduce non fatal myocardial infarction and death. In a critical review of the literature, it was concluded that PTCA of flow-limiting stenosis in chronic coronary artery disease does not reduce the rate of subsequent myocardial infarction or mortality. PTCA results in superior symptomatic relief of angina and improved exercise tolerance compared with medical therapy, but the difference narrows with time; however, only a minority of patients are free from

angina and antianginal medication after a revascularization procedure [10].

The recently published Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial has demonstrated conclusively that percutaneous coronary intervention does not reduce the risk of death, myocardial infarction, or other major cardiovascular events when added to optimal medical treatment [11].

Pathogenetic mechanisms for “persistent” angina

On the basis of current pathogenetic concepts, it is not easy to understand the limited prognostic benefit deriving from removal of obstructive coronary lesions – and even more puzzling is the persistence of ischemia in the absence of visible obstructions in the large epicardial coronary branches. Several hypotheses may be considered, including incomplete revascularization, graft/PTCA failure, and disease progression, but none of these provides a satisfactory explanation.

Incomplete revascularization may be a planned choice in patients with acute coronary syndromes and multivessel coronary disease. In several circumstances, operators may find it appropriate to limit treatment to the culprit lesion. Incomplete revascularization may be inevitable in patients with chronic disease who have obstructions that are not amenable to dilatation, such as lesions in small vessels or in the distal portion of larger vessels. Nevertheless, it appears unlikely that incomplete revascularization has contributed, to any significant extent, to the findings of studies in which patients were carefully selected for being amenable to multivessel revascularization.

Failure of a graft or PTCA is certainly possible, but is today a rare occurrence, all techniques claiming success rates close to 100%.

Disease progression in native coronary arteries has been observed during the time interval between the diagnostic angiogram and the PTCA procedure, and following bypass operations. Reported rates of disease progression, however, are far too low to explain persistent angina early after the procedure, which can be estimated as being present in close to one-third of patients who have undergone revascularization.

Thus, even accounting for the additive effects of several pathogenetic mechanisms, it remains difficult to understand why so many patients suffer from persistent angina after “successful” revascularization procedures, unless we take into consideration another mechanism, namely persisting microvascular dysfunction.

It has long been known that removal of coronary obstructions is not consistently followed by recovery of coronary blood flow reserve. Several investigators, using different techniques, have reported that coronary blood flow reserve remains markedly impaired in

New therapeutic approaches

Coronary microvascular dysfunction

a large proportion of patients after balloon angioplasty or stent implantation.

Conclusions

Microcirculatory dysfunction is emerging as a relevant pathogenetic mechanism for ischemic heart disease. It manifests as a paradoxical increase in resistance to flow in response to reduced perfusion pressure, and contributes to the precipitation of ischemic attacks in both stable angina and acute coronary syndromes. The limited impact of revascularization procedures on patients' prognosis, and the persistence of angina in a large number of patients after removal of coronary obstructions strongly support this hypothesis. A better understanding of the role of microvascular dysfunction and the development of therapeutic strategies directed to restoring microvascular function appear to be of paramount importance in the improvement of symptoms and prognosis in patients with ischemic heart disease. ■

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