REVIEWS

Microcirculation as a target of myocardial reperfusion in acute coronary syndromes

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Abstract: Improving the outcomes of patients with acute coronary syndromes has become a matter of great importance, since worldwide coronary artery disease is still the leading cause of morbidity and mortality. Beginning with the reperfusion era, the goal of STEMI treatment is to restore blood flow to ischemic myocardium in order to reduce infarct size, but beyond the benefit of reperfusion, an important number of patients develop reperfusion injury and the "no-reflow" phenomenon. Taking these data into account and also the fact that coronary microvascular dysfunction increases the risk of cardiovascular events, we consider that an additional strategy in order to improve the outcomes of STEMI patients could be represented by the assessment of coronary microvascular functional and structural obstruction. Along with some issues related to the pathogenesis of coronary microvascular obstruction, some diagnostic methods as well as a few therapeutic options are been presented.
Keywords: microcirculation, coronary microvascular obstruction, repefusion injury.

Rezumat: Ameliorarea prognosticului pacienților post-sindrom coronarian acut este o temă de mare actualitate și interes, în contextul în care, la nivel mondial boala coronariană reprezintă încă principala cauză de morbiditate și mortalitate. Începând cu era reperfuziei, ținta tratamentului în STEMI este reprezentată de restabilirea fluxului sanguin în miocardul infarctat, în scopul reducerii zonei de infarct, dar, dincolo de beneficiile reperfuziei, un număr important de pacienți dezvoltă leziune de reperfuzie, precum și fenomenul "no-reflow". Pornind de la aceste premise, precum și de la faptul că disfuncția coronariană microvasculară determină o creștere a riscului de evenimente cardiovasculare, considerăm că o strategie adițională pentru ameliorarea prognosticului pacienților cu STEMI ar putea fi reprezentată de aprecierea obstrucției coronariene microvasculare, la nivel funcțional și structural. Alături de câteva repere legate de fiziopatologia obstrucției coronariene microvasculare, sunt prezentate câteva metode diagnostice precum și câteva opțiuni terapeutice ale acesteia.
Cuvinte cheie: microcirculație, obstrucție coronariană microvasculară, leziune de reperfuzie.

THE REPERFUSION INJURY AND THE "NO-REFLOW" PHENOMENON

Since worldwide coronary artery disease is still the leading cause of morbidity and mortality, improving the outcomes of patients with acute coronary syndromes is a matter of great importance[1-2]. The majority of deaths following acute coronary syndromes are determined by ST segment elevation myocardial infarctions (STEMI), the result of acute thrombotic occlusion of a coronary artery.

Beginning with the reperfusion era, first with fibrinolytic therapy and currently with primary PCI as gold standard, the goal of STEMI treatment is to restore blood flow to ischemic myocardium in order to reduce infarct size. The great challenge is to reduce time to reperfusion and the management of STEMI patients is now dominated by a principle that has became a fundamental one in coronary heart disease – "time is muscle"[3]. In practice, this principle is represented by a "door to balloon" time of 90 minutes, meaning the interval from the first ECG showing ST elevation segment to mechanical reperfusion of the occluded coronary artery.

Nowadays, the "door to balloon time" is a standard part of the European Society of Cardiology Guidelines for the management of STEMI patients, often used as a measure of quality performance[4]. However, even in the

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setting of an acceptable "door to balloon" time, the in-hospital mortality of STEMI patients is an important one (~10%) and also, two thirds of the surviving ones tend to develop chronic heart failure[5].

These findings suggest that additional strategies are needed in order to reduce in-hospital mortality and also in order to improve the outcome of STEMI patients. Also, it becomes clear that a review of the therapeutic objectives in the setting of an acute coronary syndrome may be of great interest, and that is why, beyond coronary reperfusion with subsequent restoration of myocardial oxygen supply, alternative approaches in order to improve survival and to reduce the burden of ischaemic heart failure are needed.

Reestablishing blood flow through epicardial coronary arteries after STEMI does not always lead to the end of myocardial damage, since an important number of patients develop reperfusion injury and necrosis of myocites from the infarcted area.

Some of the unsolved issues related to the treatment of STEMI patients are represented by the reperfusion injury and the "no-reflow" phenomenon. The term "no-reflow" refers to inadequate myocardial perfusion after successful repermeabilization of epicardial infarct related artery. It is estimated that 10 to 40% of patients undergoing reperfusion therapy may present the angiographic feature of "slow-flow" or even "no-reflow", both associated with impaired outcomes. The "no-reflow" phenomenon may be determined by a number of pathogenical compounds, among which: distal atherothrombotic embolization, ischemic injury, reperfusion injury, endothelial dysfunction, inflammation and myocardial oedema[6]. The presence of "no-reflow" may generate severe arrhythmia and important haemodynamic impaired function, with a great increase of clinical complications rate.

Myocardial reperfusion was considered from the beginning of its use a "double-edged sword" due to the fact that, beyond restoration of blood flow to ischaemic myocardium, reperfusion also promotes cardiomyocyte death and microvascular damage through the so called "myocardial ischaemia reperfusion injury" process[7]. First, this process is determined by the fact that the occlusion of a coronary artery quickly determines uncoupled oxidative phosphorylation and reduced mitochondrial ATP synthesis. The decrease of ATP generation leads to the increase of intracellular calcium and lactate levels, with subsequent intracellular PH decrease. Beyond this, the reduction of ATP synthesis also determines the generation of reactive oxygen species (ROS) through a process known as "ROS-induced ROS release". Increased ROS levels may also lead to mitochondrial damage by opening a gap in the mitochondrial permeability transposition pore. Thus, reperfusion will indeed restore blood flow to the myocardium, but on the other hand it will also promote mitochondrial damage through the opening of the mitochondrial permeability transposition pore, a process that will further lead to necrosis and increased infarct size[5].

Therefore, finding an effective treatment approach in order to stop the myocardial injury related to coronary occlusion without sacrificing the benefit of reperfusion therapy would be the goal of STEMI therapy. Taking into account the data previously highlighted, we consider that an additional strategy in order to improve the outcomes of STEMI patients could be represented by the assessment of coronary microvascular functional and structural obstruction.

THE ROLE OF CORONARY MICROVASCULAR DYSFUNCTION

It has been demonstrated that traditional and non-traditional cardiovascular risk factors play an important role, both in epicardial as well as in microvascular endothelial dependent dysfunction[8]. Moreover, coronary microvascular dysfunction increases the risk of cardiovascular events[8]. Related to reperfusion, patients with pre-existent microvascular dysfunction will benefit less from reopening of the epicardial vessel. Also, a pre-existent impairment of myocardial microcirculation has been showed to be associated with a greater vulnerability to PCI related myocardial injury as well as with a poorer long term outcomes[9]. Thus, transient or permanent microvascular dysfunction influences the prognosis of acute coronary patients through the reduction of coronary blood flow with altered shear stress, impaired endothelial dysfunction of epicardial arteries and enhanced thrombus formation.

The pathogenesis of coronary microvascular obstruction is mainly influenced by four interacting mechanisms: ischaemia-related injury, reperfusion-related injury, distal embolization and individual susceptibility of the microcirculation to injury[10]. Ischaemic injury is influenced by the duration and the extent of ischaemia and is associated with severe capillary damage and myocardial cell swelling determined by sodium and calcium overload. The main determinants of reperfusion injury are represented by neutrophils, endothelin-1, thomboxane-A2, and platelets. Neutro-

phil-platelet aggregates may lead to obliteration of vessel lumen and is associated with release of vasoconstrictors and inflammatory mediators. As mentioned before, in cardiomyocytes, reperfusion increases the production of reactive oxygen species by the mitochondria. The consequence of this process is the aggravation of microvascular function. Infarct size may also be increased due to mitochondria swelling and cell rupture, phenomenon determined by the opening of the mitochondrial membrane permeability transition. The third mechanism, distal embolization of plaque and thrombus material may lead to microcirculation injury by mechanically obstruction, beyond the fact that it also represents a source of vasoconstrictors and procoagulant substances. Finally, the last mechanism taken into consideration is represented by individual susceptibility of the microcirculation to injury, mechanism influenced by genetic variability, diabetes, acute hyperglycemia, hypercholesterolemia and the lack of pre-conditioning[10].

DIAGNOSIS OF CORONARY MICROVASCULAR DYSFUNCTION

Diagnostic methods of microvascular dysfunction may be invasive or non-invasive (Table 1). When using these methods, the incidence of coronary microvascular dysfunction is variable, ranging from 10% when using angiographic assessment of thrombolysis in myocardial infarction (TIMI) flow, to 60% while using CMR or myocardial contrast echocardiography[11].

The gold standard method for invasive assessment of coronary microvascular dysfunction and obstruction assessment is the direct measurement of coronary flow reserve using intracoronary Doppler wire, with a typical flow pattern characterized by: systolic retrograde flow, diminished systolic anterograde flow, and rapid deceleration of diastolic flow[10]. Still, this method has some major disadvantages, such as the need for special equipment and the use of pharmacological interventions.

Other invasive methods are represented by the index of microvascular resistance and the hyperaemic microvascular resistance index. The first one is providing an assessment of microcirculation, independent of haemodynamic parameters whereas the hyperaemic microvascular resistance index is associated with ventricular recovery and clinical outcomes after acute coronary syndromes[12].

Also, another invasive tool for the assessment of microvascular dysfunction is the score grading system that describes the rate of blood flow in the epicardial vessels, the TIMI (thrombolysis in myocardial infarction) flow. The range of TIMI flow is quantified between grade 0 (no flow at all) and grade 3 flow (normal flow), while a TIMI flow <3 is considered as a marker of microvascular dysfunction[10]. Other invasive methods to be taken into consideration are the myocardial blush grade, that is assessing the intensity of contrast medium in the microcirculation and the TIMI myocardial perfusion grade that assesses microvascular clearance of contrast medium[10].

The non-invasive tools that allow us to assess myocardial dysfunction are the monitoring in a single lead of the ST segment resolution, myocardial contrast echocardiography, and cardiac magnetic resonance. Other methods are represented by myocardial scintigraphy and hybrid positron emission tomography-computed tomography. Among these methods, ST-segment resolution is a useful method for the assessment of coronary microvascular dysfunction, with an important prognostic value. Myocardial contrast echocardiography can also be used in order to assess coronary microvascular dysfunction, by the use of ultrasound to visualize contrast microbubbles, with a typical pattern that is represented by the lack of intra-myocardial contrast opacification. Cardiac magnetic resonance (CMR) is another non-invasive method that allows accurate quantification and localization of coronary microvascular dysfunction as well as of the infarct size relative to the entire left ventricle. Typical signs of coronary microvascular dysfunction and obstruction in CMR are represented by the lack of gadolinium enhancement during first pass and the lack of gadolinium enhancement within a necrotic region. Myocardial scintigraphy and the hybrid positron emission tomography are non-invasive techniques that may allow the assessment of inflammatory reactions after reperfusion[10].

Table 1. Diagnostic methods of microvascular dysfunction

Diagnostic methods of microvascular dysfunction
Invasive techniques
1.Coronary flow reserve
2.Index of microvascular resistance
3.Hyperaemic microvascular resistance
4.TIMI score
5.Myocardial blush grade
6.Thrombolysis in myocardial infarction myocardial perfusion grade
Non-invasive techniques
1. ECG (ST-segment resolution)
2. Myocardial contrast echocardiography
3. Cardiac magnetic resonance
4. Hybrid positron emission tomography/cardiac computed tomography

TREATMENT STRATEGIES

A few treatment strategies have been taken into consideration in order to ameliorate microvascular dysfunction. Therapies that have showed good results when used before catheterization laboratory are represented by ongoing statin therapy at the time of STEMI, with a better functional recovery of myocardial function after 6 months of follow-up in compare with patients without statin therapy[13]. Other therapies with evidences in the field of microvascular dysfunction that may be useful before catheterization laboratory procedures are the use of beta-blockers such as carvedilol or nebivolol, pre-hospital abciximab administration as well as remote ischaemic pre-conditioning[10]. Also before PCI, therapies with controversial results are represented by the use of the glucose–insulin–potassium (GIK) in the setting of STEMI as well as the chronic treatment with ACE inhibitors or nitrates[14,15]. No amelioration of microvascular dysfunction was found in association with the use of ticagrelor, COX inhibitors or hypothermia[10].

In the catheterization laboratory, there are several therapies with results tested in large trials with clinical endpoints. One of these is represented by the use of adenosine (the AMISTAD trial)[16]. Other therapeutic options are the use of atrial natriuretic peptide, cyclosporine and exenatide (a glucagon-like peptide-1 agonist), all known to have cardioprotective effects[10]. Controversial therapies in the setting of catheterization laboratory are represented by manual thrombus aspiration and the administration of vasodilators such as verapamil, diltiazem, and nitroprusside[17]. Inadequate therapies are the intracoronary administration of abciximab witch failed to improve the rate of MACEs (all-cause mortality, recurrent MI, and new heart failure) as well as the administration of nicorandil, a hybrid drug of ATP-sensitive K-channel opener[10].

Finally, a few therapeutic strategies in order to improve microvascular dysfunction and obstruction need to be taken into consideration after the catheterization laboratory. Among these, the aggressive risk factors modifications and rehabilitation measures had a significant impact on the recurrence of acute coronary syndromes and re-hospitalization rate[10]. Therapies that are still controversial and need further research are represented by the administration of cilostazol (for 1 month) to double antiplatelet therapy with aspirin and clopidogrel, as well as the use of vasodilators (calcium-channel antagonist, dypiridamole) or metabolic drugs (ranolazine)[18,19]. The use of intra-aortic balloon pumping (IABP) did not show favorable results in amelioration of microvascular dysfunction[20,21].

CONCLUSIONS

The role of the microcirculation in determining the outcomes of patients with acute coronary syndromes is still a matter of great debate. From the mechanisms by which reperfusion damage contributes to the microvascular abnormalities to novel aspects of the complex role of coronary microcirculation in acute coronary syndromes, future trials should explore the effects of integrated treatments aimed to ameliorate the outcomes of reperfusion strategies following primary PCI.

Conflict of interest: none declared.

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