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**MODERN VIEW OF REPERFUSION INJURIES OF THE MECHANISM OF IN ACUTE
MYOCARDIAL INFARCTION**

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Abstract

The most effective treatment of blood flow in the infarct-related artery for acute myocardial infarction (AMI) is by angioplasty and stenting; it's currently a method of reduction of necrosis, but this tactic causes reperfusion syndrome, in further as damage to the myocardium. The reperfusion injury has recently become widely accepted like a phenomenon of lethal and the death of cardiomyocytes. There are many mechanisms of the death this type of cells. Important mechanism of reperfusion injury is the Calcium overload (which generates the myocyte hypercontraction), the rapid recovery of the physiological pH level, the neutrophilic infiltration in the area of ischemia and opening of mitochondrial permeability transition pores (mptp).

This article is about the main mechanisms in myocardial reperfusion injury of patients with acute myocardial infarction, as well as the clinical manifestations of reperfusion syndrome and myocardial protection mechanisms.

Keywords: Acute myocardial infarction, reperfusion injury, cardio protection.

Introduction

Reduction of infarct size and damaged cells is as a result of the rapid recovery of coronary blood flow and myocardial reperfusion, leading to decline in mortality. ST-segment depression comes to the isoline after angioplasty is in direct proportion to the improvement the reperfusion of the myocardium and ensures a favorable outcome of the disease [4]. In the cardiologic world long known, that is a strong determinant for the preservation of the myocardium (stunned myocardium).

In addition, it is well known the final size of AMI is the main determining factor of mortality and post-infarction left ventricular remodeling, consequently, the problem of reperfusion injury is relevant since directly affects the final size of infarction and the clinical outcome of acute myocardial infarction.

The classical dogma “the time it’s a muscle” had a significant impact on the treatment with acute myocardial infarction. Studies by Jennings and Reimer’s group in the early 1980s demonstrated that early reperfusion can save the ischemic myocardium. They also found out reperfusion efficiency mainly depends on the severity and duration of the preceding ischemia [14].

Paradoxically enough, but the process of blood flow recovery in ischemic area causes additional harm to myocardium (the so-called “ischemic/reperfusion injury”) [2], which reduces the beneficial effects of reperfusion. In this sense, the reperfusion injury can be treated as an inevitable damage associated with reperfusion process in ischemic myocardium. The reperfusion injury can be defined as the damage caused by recovery of blood flow after the ischemic episode, leading to the death of only those cells that have been damaged by the time of blood flow recovery.

The actual effect of the ischemic reperfusion injury on the myocardial infarction final size has not been clearly defined, generally because it also depends on the duration of ischemia. Animal studies, this indicator can reach 30-40% of the original size of the necrosis [1].

By now, the mechanisms of reperfusion injury well studied. It is important to bear in mind that all of these mechanisms are quite closely related, so it’s difficult to remove individually the "pure" effect of each of them.

The reperfusion injury occurs within a few minutes after the restoration of tissue and causes the death of viable cardiomyocytes. Death of myocytes happens in three forms: necrosis, apoptosis and autophagy; all they are interrelated, but the apoptosis is a specially regulated one. First pathological feature associated with reperfusion injury is the myocyte hypercontraction with the formation of contraction bands through the entire length of the myocardium, which leads to occurrence of reperfusion arrhythmias. The main mechanism of hypercontraction during reperfusion is not fully cleared up, but it is known that the overload with Ca^{2+} ions play a crucial role in process. Ca^{2+} homeostasis in the "healthy" myocytes is disturbed ischemic/reperfusion injury [20]. The degree of overload with calcium ions is controlled largely by metabolic disorders caused by ischemia. Increased the level of intracellular Ca^{2+} also subsequently leads to the opening of mitochondrial permeability transition pores (mptp) [19]. This is a large-hole pore that is formed in the inner mitochondrial membrane and allows free passage of all molecules of <1.5 kDa [5] into the mitochondrial matrix, causing thereby an osmotic swelling, damage and/or destruction of mitochondria. Experimental studies have shown that mitochondrial permeability transition pores remain closed during ischemia and open within the first minutes of reperfusion. Opening of mptp activates multiple apoptotic and

necrotic subcellular signaling mechanisms, including the release of cytochrome C, collapse of mitochondrial membrane potential, ATP depletion and caspase activation. The pathogenesis of this process is still understudied, however, it results of cell death [9].

Not only the intracellular Ca^{2+} overload, but also the reactive oxygen species (ROS) open the mptp. The relationship mptp between pH are complex. Removal of cytosolic Ca^{2+} is always regulated in cardiomyocytes under normal conditions. In ischemia, the normal sodium-calcium exchange changes in order to maintain the physiological intracellular pH. During reperfusion, extracellular pH returns to normal, whereas intracellular pH remains initially low, there is further H^+/Na^+ exchange, which aggravates an increase in cytosolic Ca^{2+} [12]. Intracellular Ca^{2+} causes changes in the mitochondrial sodium-calcium exchange with the influx of Ca^{2+} , which triggers the opening of the mptp [8].

The level of reactive oxygen during the ischemia is low and has no specific pathological significance. Nevertheless, there is strong evidence that the sharp activation of ROS during reperfusion is responsible for damage to the mitochondrial membrane. Oxidative stress during reperfusion reduces the availability of nitric oxide (NO), which is an intracellular cardioprotection mediator. Despite the clear connection with the infarction, the role of ROS in myocardial infarction is less defined, although they are involved in necrosis and apoptosis [24]. The pathogenesis of reperfusion injury is shown in Figure [2].

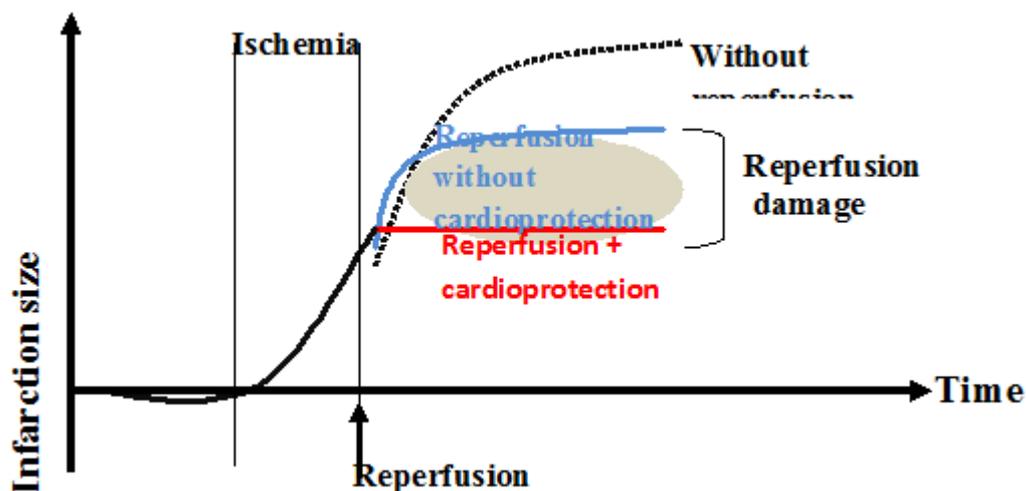


Fig. 1. Myocardial damage caused by ischemia and reperfusion. During coronary occlusion there occurs exponential death of cells. Size of AMI caused by coronary artery occlusion without reperfusion is represented by a dotted line. During reperfusion, the myocardial necrosis area decreases. Upon application of cardioprotection, the myocardial infarction size is represented only by the cells, died due to ischemia (Garcia-Dorado D, Piper HM., 2006).

optimal myocardial perfusion recovery. This leads to a reduced systolic function of the left ventricle (LV), dilation of heart chambers or aneurysm of the walls. The “no-reflow” syndrome also contributes to mortality, occurrence of ventricular tachycardia and heart failure. The clinical significance of non-optimal coronary blood flow is very high and manifested cardiovascular events and mortality during 1 year [17]. The presence of normal epicardial flow (TIMI-3) after stenting of the infarct-related coronary artery is a strong predictor of survival [7].

The next type of reperfusion injury - a rhythmic disturbance that is characterized by its diversity. Reperfusion arrhythmias: sinus bradycardia, ventricular tachycardia, atrial and ventricular fibrillation. They are clinically asymptomatic or manifested in arterial hypertension, angina, syncope attacks or acute heart failure.

Lethal reperfusion damage – death of cardiomyocytes that have not been irreversibly damaged during reperfusion – leads to a significant expansion of myocardial necrosis and as a consequence, to the heart failure.

Mechanisms and methods of protection against reperfusion injury.

Reperfusion protective kinases (RP-kinases) are a group of proteins that are activated during reperfusion, providing thereby cardioprotection [23]. Activation of protein kinases mediates a form of the programmed for cell survival and prevents reperfusion injury [22]. Pre Clinical interventions with pharmacological support have revealed a consistent decrease in the size of myocardial infarction under involvement of protective kinases.[11]. RE-kinase activation occurs during pre- and postconditioning, therefore, some authors believe that some of the beneficial effects on the zone of necrosis is associated with this factor [10]. RE-kinase activation ensures cardioprotection by inhibiting the mitochondrial permeability transition pores opening, and blocks calcium overload and regulates the anti-apoptotic paths. The most common method of cardioprotection is an ischemic postconditioning (endogenous cardioprotection), which is induced by short episodes of ischemia at the beginning of reperfusion. It is called endogenous because it does not require the administration of drugs or other means from outside. The protective effect of postconditioning is associated with a decelerated leaching of secondary metabolites, decreased oxidative damage, which maintains a signaling pathway NO- cGMP - protein kinase G and inhibits the Na^+/K^+ exchange [13]. Ischemic postconditioning is the first method of cardioprotection described in the literature, which is able to limit necrosis zone arising due to reperfusion injury.

The methods of cardioprotection have included many pharmacological agents, such as β -blockers, sodium uretic peptide, adenosine, cyclosporine, etc. The point of application of many pharmacological agents that have contributed to the preservation of viable myocardium was the activation of the protective protein kinases [1, 3].

Therapeutic hypothermia – has reserved the right to be called cardioprotector that has been confirmed by clinical studies. Use of hypothermia leads to a slower metabolism, reduces the inflammatory response and mitigates reperfusion injury, resulting in the reduction of myocardial necrosis by 38% as compared with the control group, and lowering the level of cardiac markers by 43% (according to RAPID-MI-ICE).

There are a lot of existing methods of cardioprotection against reperfusion injury, and each of them pursues only one goal – to reduce the myocardial necrosis zone and heart failure. Application of these methods will make it possible to fight against the reperfusion syndrome and weaken the adverse effects of acute myocardial infarction.

Conclusion

The fact of reperfusion myocardial injury in patients with AMI is becoming an increasingly recognized phenomenon among clinicians. This condition is characterized by a loss of cells, which were viable at the time of recovery of coronary blood flow which occurs immediately after reperfusion. Despite of all information about the existence of reperfusion injury, some authors still underestimate this cause of death of cardiomyocytes, because of the absence of a specific marker of damage. There are many interrelated mechanisms involved in this type of cell death. Activation of RP-kinases protects against reperfusion injury, primarily by inhibiting the opening of the mitochondria permeability transition pores; this mechanism is the basis for other methods of cardioprotection such as ischemic postconditioning and reducing myocardial necrosis. By slowing metabolism, the therapeutic hypothermia weakens the reperfusion damage, reducing thereby the final size of myocardial infarction. Thus, given the multifactorial nature of the mechanisms leading to reperfusion injury, only the measures aimed simultaneously at all the components of the pathogenesis will ensure success.

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