Subcellular Control Mechanism of the Myocardial Reperfusion Injury

Nikolay V. Akulich, Head of Laboratory, e-mail: akulichn@gmail.com
Nikolay A. Efremov
Mogilev State University, Mogilev, Belarus

Coronary Heart Disease (CHD) has become main cause of death for adult population. The most dangerous sign of CHD is myocardial infarction (MI) with everyday lethality of 10%. The zone of myocardial ischemic damage is the main ending predicament for patients with acute myocardial infarction.

The optimal strategy is a direct approach to decrease acute myocardial infarction in fast and effective coronary reperfusion.

Improvement of coronary intervention technology and medical support has made possible to normalize epicardial blood flow for 95% of patients after first percutaneous coronary intervention.

Nonetheless the earlier and full recovery of epicardial blood flow into infarct-related artery, in 25% of events when it doesn't come to optimal tissue perfusion and contractile function normalization.

Most possible causes of unsatisfactory patient results by endovascular treatment with acute myocardial infarction and ST segment uprising could be microvascular dysfunction or lethal reperfusion injury.

An achievement in endogenouscardioprotection mechanism was an experimental work by Zhao L. Z. et al. (2003), which showed us that series of consecutive shortcycles which create occlusions/opening in coronaryarterylumen projected after modeled myocardial infarction and accomplished reperfusion of ischemic tissues, which leads to significant decrease of necrosis from 47% to 11%. This phenomena was titled an ischemicpostconditioning (IPC).

The differences in IPC conduction, researched in groups of patients without accounting comorbidities and drugs taken, and also experimental results of discrepancy and clinical research that won't let you analyze given data and are preventing the wide use of this strategy in clinic.

Knowing the importance and significance of AMI patient treatment problems, we are presented with an actual and significant research accomplishment, directed by development of interventionaltherapy for patients with AMI technology and ST segment uprising with purpose to augment closest and furthers treatment results.

Patients with acute myocardial infarction and ST segment uprising have the most unfavorable prognosis in all ACS cases. The hospital lethality of this group in countries of EU ranges 6-14%. According to the recommendations of American Heart Association and European Society of Cardiology, the main objective of this patient category treatment is early reperfusion therapy. Duration of coronaryischemia is the main determinant for necrosis prevalence and the bigger the zone of ischemicmyocardial damage is bigger risk of development ofleft ventricular remodeling, heart insufficiency and life-threateningarrhythmias. The zone decrease of ischemicmyocardial damage is the main mission in patient treatment with acute myocardial infarction.

A priori ischemia is the most important cause of irreversible myocardium damage, the main researchers efforts at the time of last three decades were directed on development of therapeuticstrategies for the most early coronaryreperfusion. We can suggest that reperfusion therapy has improved the results and prognosis for patients, with acute myocardial infarction and ST segment uprising, which could have reached it's maximum level of effectivness.

Despite for those positive effects of reperfusion therapy, reperfusion has singnificant threat for myocardium ("double-edged sword") and comes with its temporarycontractiledysfunction (stunning), microcirculation disturbance (phenomena «no-reflow») and life threatening rhythm disturbance (Yellon and Hausenloy, 2007) Those specific manifestations ofreperfusion can be characterized as functional and reversible myocardialreperfusion injury (MRI).

But irreversable forms of MRI, which count in microvascular obstruction and LRI (lethal reperfusion injury), give their contribution in ending sizes of myocardial infarction and negate the positive effects of early reperfusion. Irreversal LRI specifically for cell death after episodes of prolongedischemia which can be prevented by intervention during reperfusion. Size irreversible myocardial injury case, consists of two different types of damages -ischemia-reperfusion-induced and induced. Thus, the LRI can be considered one of the causes of death of cardiomyocytes, which is closely associated with reperfusion.

Mechanisms of ischemic preconditioning are considered as a complex of signaling cascade that includes three successive stages-a trigger, mediator and effector:

a) Preconditioning triggers:

1) receptor-dependent: adenosine, opioid peptides, bradykinin, catecholamines, etc.

2) receptor-independent: oxygen free radicals, ions, calcium oxide, nitrogen.

b) Preconditioning mediators: protein kinase C, G, A, B (Akt), tyrosine kinase , kinase, extracellular signal-regulated (ERK), PI3K, GSK–3β, etc.

c) Latest preconditioning effectors: (sarcolemmal Kchannel , mitochondrial channel.

Various biologically active substances like adenosine, bradykinin, endogenous opioids, IL 6,tumor necrosis factor and other are triggers and release at IPC process. They attach to G-protein-coupled receptors of cell membrane and other receptors and activate them. Those can activate protein kinases of phosphorylatingenzymes (PI3K)-Akt, ERK, end othelial NO-synthase and STAT3 protein family RISK and SAFE (Tsang et al., 2004), which leads to inhibition of the mitochondrial channel opening (Hausenloy and Yellon, 2003).

Some of the physiological effects, like the decrease of oxidative stress, reduction of intracellular calcium overload, prevention of apoptosis of cardiomyocytes and endothelium damage, deceleration of pH reneval and neutrophil accumulation in myocardial infarction zone and etc., they can show cardioprotective effects, which are independent from molecular mechanisms.

EndoG is a member of pantheon proteins that regulate apoptotic cell death in cardiovascular disease, including heart failure and ischemia/reperfusion. Attempts to define the specific role of ENdoG in either cell death or life in mammals have produced contradictory and controversial results. The purpose of this project is to analyze structural and functional role of EndoG in order to understand its mechanism in DNA fragmentation and degradation. In vivo investigation for the functional role of EndoG in Cardiomyocyte death after ischemic and pharmacologic postcondition will be investigated in Belorussian side. In vitro structural and functional analysis at the molecular level will be carried out in Korean side. The combined link between the in vivo and in vitro data analysis would help to understand the EndoG function as a whole on the DNA degradation and provide molecular basis for the development of its regulator in pharmaceutical application.

This research is to understand the mechanism and involvement of EndoG in chromatin condensation and degradation on apoptotic pathway by using the cellular and molecular biology techniques and crystallographic information based on protein structure. To do this:

1. We are to investigate the regulatory effect of EndoG in DNA degradation mechanism in molecular basis

2.We are to characterize the EndoG biochemical properties with respect to the placement and positioning in complex structures either with oligonucleotide substrate or with various interacting proteins that is involved in DNA fragmentation and condensation.

3.We are to analyze EndoG function in cellular compartment and visualize the EndoG activity by comparative assessment in vivo in the primary coronary angioplasty of 250 patients with heart failure.