ISCHEMIC PRECONDITIONING FROM MECHANISMS TO THERAPEUTICAL POSSIBILITIES

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Abstract: *Ischemic preconditioning (IPC) is a powerful endogenous form of cardioprotection of myocardial ischemia. The protective effect of ischemic preconditioning consists in diminishing the negative consequences of ischemia. Ischemic preconditioning increases myocardial resistance to ischemia, resulting in increasing the available time for applying the antiischemic therapy. During coronary permanent occlusion, or in severe permanent ischemia, preconditioning is inefficient and does not involve cardioprotection. Opening of the mitochondrial KATP channels seems to play a central part in the protective mechanism of preconditioning. Nicorandil, a selective mitochondrial KATP channel opener, has been extensively used in many experimental and clinical studies with very promising results.*

Keywords: *ischemic preconditioning; nicorandil; ischemia reperfusion; protection*

Rezumat: *Precondiţionarea ischemică este unul din mecanismele de protecţie a miocardului ischemic. Efectul cardioprotector constă în reducerea consecinţelor negative ale ischemiei miocardice. Precondiţionarea ischemică creşte rezistenţa miocardului la ischemie, astfel creşte timpul disponibil pentru aplicarea terapiei antiischemice. În cazul ocluziei coronariene permanente, precondiţionarea este ineficientă şi nu are efect cardioprotector. Deschiderea canalelor mitocondriale de K ATP dependente, se pare că are un rol central în mecanismul cardioprotector al precondiţionării. Nicorandilul, activator al canalelor de potasiu a fost folosit în numeroase studii experimentale şi clinice cu rezultate promiţătoare.*

Cuvinte cheie: *precondiţionare ischemică, Nicorandil, ischemie, reperfuzie, protecţie*

INTRODUCTION

In the ischemic cardiopathy, the myocardial metabolism is deeply depressed, the type and the severity of the occurred alterations depending on the form of the ischemic cardiopathy. In the case of myocardial ischemia, "compensatory" metabolic disorders also occur, represented by the paralysed myocardium, hibernated myocardium and by the ischemic preconditioning. These protection mechanisms are functional up to a certain limit of ischemia, in terms of severity and length. Over this limit, the ionic and metabolic consequences of ischemia become irreversible and may lead to cellular death, through necrosis or apoptosis.

Ischemic preconditioning – one of the protection mechanisms of the ischemic myocardium – was proved in the last 2 decades in numerous experimental and clinical studies. It consisted in the fact that the short myocardial ischemia episodes protect the heart from the next ischemic episodes. Ischemia preconditioning effect consists in lowering the consequences of ischemia: metabolic disorders, necrosis, electrophysiological disorders, cardiac performance lowering, pains, rhythm disorders, endothelial dysfunction, side effects of reperfusion. Preconditioning protection effects manifest only in the case of the coronary occlusions followed by reperfusion, or in case of transient coronary ischemia (1).
Ischemic preconditioning increases the myocardium resistance, allowing a larger period of time for the antiischemic therapeutic interventions. In the definitive coronary occlusions, or in the severe permanent ischemia, ischemic preconditioning is inefficient and does not provide protection to the ischemic myocardium (2). Preconditioning metabolic effects lead to the improvement of the energetic metabolism of the myocardium. Ischemic preconditioning brings about a reduction of the ATP consumption during the ischemic episodes, following the preconditioning episode.

The improvement of the energetic productivity derives from the decrease of the speed of using the ATP cellular reserves, secondarily to the reduction of the activity of the membranary pumps. The energetic reserve of the preconditioned hearts is superior to that of the unpreconditionned hearts (3,4).

Preconditioning mechanisms:

There are many hypotheses regarding the mechanisms of the ischemic preconditioning:

- The main preconditioning mechanism is the closing of the K+-ATP-dependent mitochondrial channels. The activation of these channels, through the depolarization of the mitochondrial membrane prevent the Ca+ charge of mitochondria;
- K+-ATP-dependent mitochondrial channels activation prevents or delays the occurrence of the osmotic inhibition of the myocytes (swelling). The

resistance of cytoskeleton to ischemia and rupture is enhanced through this mechanism;

- Actin polymerization is considered another end-factor of the ischemic preconditioning. The increase of the secondary actin preconditioning, of the kinase activation leads to the increase of the cytoskeleton resistance to rupture, increasing the length of the cellular viability;
- Through the opening of the K+-ATP-dependent mitochondrial channels, the swelling of the mitochondrial matrix will takes place, which would induce an improvement of the energy production, through a better coupling between the mitochondrial creatinkinase of the intermediary space and the adenine-nucleotid transferase at the level of the external mitochondrial membrane;
- Another hypothesis sustains that, as a result of the activation of the K+-ATP-dependent mitochondrial channels, an increase of the mitochondrial production of the species reactive to Oxygen will occur (oxygen free radicals), which activates C proteinkinase involved in predconditioning. The free radicals increase the expression of iNOS **(**inducible nitric oxide synthase) and the production of nitric oxygen during the prolonged ischemia. The free radicals would provide the protection against the oxidative stress mediated by the infiltration of the ischemic area with neutrophils.
- The activation of the sarcolemmal K+-ATP-dependent mitochondrial channels reduces the Ca+2 overload of the cells during ischemia, with the increase of the cellular viability. The opening of the the K+-ATP-dependent mitochondrial channels brings about the shortening of the action potential, which on one hand, inhibits Ca+2 entry into the cell and on the other hand, it reduces the possible rhythm disorders through the re-entry. The opening of these channels through the hyperpolarization of the cellular membrane decreases the myocytes' excitability (5-7).

Types of preconditioning

Early ischemic preconditioning was proved on an animal heart, as well as on a human heart, as a result of experimental and clinical studies. The early preconditioning is not dependent on the opening of the collaterals, of the inducement of certain antioxidant substances or of the synthesis of certain protective proteins. Preconditioning is a receptor-mediated process. The receptors may be stimulated by bradykinin**,** opioids (that are released during the preconditioning process) and by adenosine. Adenosine (as a result of the ATP degradation) stimulates the A1 adenosinic receptors at the surface of the myocardial and endothelial cells. Adenosine may mime the early preconditioning. As a result of the stimulation of the A1 adenosinic receptors, G protein is activated (intracellular messanger0, which induces the activation of phospholipase C. Phospholipase C. will activate proteinkinase C (PCK) and other kinases. Bradykinin may activate proteinkinase C, involved in preconditioning. Other kinases were also involved in preconditioning: tirozinkinase P38MAP – kinase (MAP = mytogen activated protein kinase), which increase during preconditioning (10).

Preconditioning occurs through certain end-factors that produce the alteration of the remodelling of cardiomyocytes, which become resistant to the toxic effort of the ischemic environment. The end-factors accomplish the heart protection for the following ischemic episodes. The ATP-sensitive potassium channels (K+-ATP) at sarcolemmal and mitochondrial level are most known end-factors – preconditioning makers. These channels are activated through proteinkinase C (PCK) or through other kinases (8,9).

Late preconditioning occurs 214 hours after the early preconditioning episode, lasting 72 hours, at the most. This is less intense and the production mechanisms partially differ from those of the rapid preconditioning. Late preconditioning provides antinecorsis protection, antiarrhythmic protection**,** and protection against the myocardial paralysis. Late preconditioning production mechanism is based on the production on endogenous nitric oxide, which is both, a trigger and an end-factor of preconditioning. Following the preconditioning episode, the transcription of NOS increases (nitric oxide synthase), as well as the increase of the endogen nitric oxide. This will accomplish iNOS transcription through proteinkinase C (PCK), tirozinkinase and through the necrosing factor kappa B and it is maintained up to 72 hours. This period of time corresponds to the late preconditioning. During a new episode of ischemia, the activity of the inducible NOS increases, as well as the production of nitric oxide, while the metabolic consequences of ischemia are reduced.

A number of authors consider that the adenosine A1 receptors play an important part in the late preconditioning, the mechanism being identical with that of the early preconditioning. It seems that these adenosine A1 receptors occur in the antinecrotic late preconditioning and not in the preservation of the myocardial contractions function (11,12).

Pharmacological preconditioning may be accomplished through the stimulation and modulation of trigger, receptors, through the activation of the intracellular signal and through the modulation of the end-factors. The most benefic pharmacological preconditioning is the modulation of the end-factors, which act even after ischemia has started.

Nicorandil (Ikorel, Adancor) is the first of the antiischemic agents, considered as activators of the K+ channels, which proved its efficacy in the treatment of the ischemic cardiopathy. Nicorandil way of action is double:

- Opens the potassium channels adenophosphate-sensitive;
- Nitrate-type mechanism.

Nicorandil holds an enhanced vascular selectivity, being capable of opening the K-ATP dependent channels of the cellular membrane or of extending their opening.

The vasodilatation of the smooth vascular muscle increases the blood flow in the ischemic area, thus raising the storage of myocardium with oxygen.

First of all, Nicorandil is an arterial vasodilatator, decreasing the post-load arterial resistances and as a result, the cardiac flow.

At the level of veins, Nicorandil induces a vento-dilatation through the simulation of guanylate cyclase with the increase of the intracellular levels of GTC-cyclic and the decrease of the concentration of the intracellular free calcium.

At the level of myocardium, through the activation of K-ATP's, their sensitivity decreases against the APT blocking action. Nicorandil drivers from the reduction of the pre and post load that brings about the decrease of the cardiac labour and of the energetic consequences of the heart.

Nicorandil has a strong vasodilatation action, both at the level of the undamaged and coronary arteries and of those with stenosis.

Nicorandil induces the pharmacological preconditioning through the modulation of the end-factors, increasing the resistance of myocardium to ischemia. It offers not only a safe antiischemic effect, but a direct cellular action as well, which protects the myocardial tissue, in case of a possible ischemia. (13,14).

CONCLUSIONS

- Ischemic preconditioning improves the energetic metabolism of the myocardium, having protective effects in the case of coronary occlusions, followed by reperfusion in the case of transient coronary ischemia, too.
- Nicorandil induces the pharmacological preconditioning through the modulation of the end-receptors, increasing the resistance of myocardium to ischemia.
- Introducing Nicorandil in the treatment of ischemic cardiopathy represented a visible therapeutic progress and led to a new vision in treating the disease.

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