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Cardioprotection during the early reperfusion phase: Part I - novel experimental cardioprotective strategies

In April 2008 the 5th Hatter Institute International workshop on cardioprotection was held in South Africa, devoted to the translation of cardioprotective strategies into clinical therapy. A summary has recently been published.¹

For cardioprotection to limit reperfusion injury, several salvage pathways have been identified. One of the most important is the reperfusion injury salvage kinase (RISK). Endogenous cardioprotective mechanisms, such as ischemic preconditioning and postconditioning, are assumed to act via this pathway. In animal experiments it was able to be shown that the RISK pathway can be activated by erythropoietin and high doses of atorvastatin. These pharmacological agents reduce infarct size by 25% to 50%.² The RISK pathway acts by preventing the opening of the mitochondrial permeability transition pore (mPTP), a nonspecific channel, which is closed during ischemia, but opens during reperfusion, resulting in uncoupling of oxidative phosphorylation and mitochondrial swelling, with the ultimate consequence of cell death. Cyclosporin-A (CsA) is an inhibitor of the mPTP and can reduce infarct size in animal models by 25% to 50%.³ The incretin, glukagon-like peptide 1, reduces likewise myocardial infarct size in experimental studies by activating the RISK pathway. According to animal experiments, however, the pharmacological activators of the RISK pathway must be given prior to or immediately at the onset of myocardial reperfusion.

Other important reperfusion injury salvage pathways include TNF- α , a pro-inflammatory cytokine, and STAT-3, which belongs to the STAT protein family and mediates the expression of a variety of genes in response to cell stimuli and plays a key role in many cellular processes, especially in cell growth and apoptosis. Preconditioning with TNF- α acts via STAT-3 and not via the RISK pathway.

According to experimental studies, natriuretic peptides reduce infarct size also by 25% to 50%. This is partially due to activation of the RISK pathway and especially due to a further distinct reperfusion injury salvage pathway mediated by nitric oxide (NO), activating soluble guanylate-cyclase, which exerts cytoprotective effects via a downstream pathway of the protein kinase G (PKG).⁴

Other members of the protein kinase (PK) family are likewise the target for cardioprotective measures, such as inhibition of protein kinase C δ (PKC- δ).

Ischemic preconditioning is the most powerful endogenous cardioprotective mechanism. It can be activated by brief ischemia and reperfusion applied even in remote organs, such as the upper or lower limb (remote ischemic preconditioning). Another promising clinical approach to protect the heart is postconditioning, ie, the application of brief ischemic and reperfusion periods immediately at the onset of reperfusion. Adenosine is an activator of the preconditioning pathway and has been shown to reduce infarct size in animals. This effect is mediated through the receptor subtypes A2A, A2B and A3, which are all possible candidates for pharmacological cardioprotection in the clinical setting. New adenosine receptor agonists are, therefore, "in the pipeline."

In clinical studies in patients with STEMI the situation is more complex than under experimental conditions, as infarct size depends in addition on the ischemic load on collateral flow, duration of ischemia, area at risk, and local myocardial energy demands. It can be expected that patients with larger ischemic zones may gain most benefit from cardioprotective interventions. These are mainly patients with anterior myocardial infarcts or inferior infarcts due to occlusion of a dominant right or circumflex coronary artery. In addition, TIMI flow grade should be 0 in order to exclude non quantifiable effects of collateralization.

In summary, there are three main targets for reduction of a myocardial ischemic insult in patients: the RISK pathway, the PK system, either by activating the NO-cGMP-PKG pathway, or by inhibiting PKC- δ , and interventions based on ischemic preconditioning such as remote preconditioning, postconditioning, or application of preconditioning mimetics like adenosine or nicorandil. The translation of these different cardioprotective strategies into clinical therapy will be discussed in part II.

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