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Cardioprotection during the early reperfusion phase: Part II - clinical results of novel cardioprotective strategies

Results of animal experimentation (see part I) identified three main targets for reduction of a myocardial ischemic insult: the reperfusion injury salvage kinase (RISK) pathway, the protein kinase (PK) system either by activating the NO- cGMP- protein kinase G (PKG) pathway, or by inhibiting protein kinase C δ (PKC- δ) and interventions based on preconditioning, such as remote preconditioning, postconditioning, or application of preconditioning mimetics like adenosine or nicorandil (see part I).

In this article, part II, the translation of these different cardioprotective strategies into clinical therapy will be discussed. This was the main topic of the 5th Hatter Institute International workshop.¹

Clinical studies examining the cardioprotective effects of the RISK pathway activators erythropoietin and high-dose atorvastatin are underway. In the recently published J-WIND trial, atrial natriuretic peptide (ANP), which acts via the RISK and the NO- cGMP- PKG pathways (see part I), was given as adjunct to reperfusion in patients with AMI undergoing primary PCI. Whereas no differences in troponin T levels were present, total CK release over 72 hours indicated a reduction in infarct size by 14,7 % with a 2.2 % increase in the EF but without any change in the chamber dimensions, in survival or in cardiac events.² Thus, the maximum effect would be a small cardioprotective effect under clinical conditions—if present at all.

Interventions based on the preconditioning pathway are another promising approach. However, the preconditioning mimetic nicorandil, a mitochondrial K_{ATP} activator, was tested in the second arm of the J-WIND trial with a negative result.² Adenosine, which likewise activates pharmacologically preconditioning pathways, was investigated in the AMISTAD study. The drug was administered as a adjunct to reperfusion in patients with AMI, with a negative result altogether. A subsequent subgroup analysis revealed a benefit for patients with anterior STEMI treated within 3.17 h after onset of symptoms with a decrease in mortality after 39 days and 6 months of 4% and 3.9% respectively.³

Remote ischemic preconditioning by application of transient upper-limb ischemia with inflation of a blood pressure cuff is another possibility to initiate remote preconditioning. It was investigated in adults undergoing coronary artery bypass surgery. The intervention reduced overall serum troponin-T release at 6, 12, 24, and 48 h after surgery. The area under the curve was reduced by 43 % from 36.12 [μ g/L] in the control group to 20.58 [μ g/L] in the verum group. This difference was highly significant ($P=0.005$).⁴ In patients undergoing elective repair of an abdominal aneurysm with remote ischemic preconditioning by brief

episodes of lower limb ischemia, myocardial injury was evaluated by cardiac troponin I release and by the occurrence of AMI; furthermore, renal function was assessed by the serum creatinine levels. The intervention significantly reduced the incidence of myocardial injury by 27% ($P=0.005$), the occurrence of AMI by 22% ($P= 0.006$) and renal impairment by 23% ($P= 0.009$). According to a multivariable analysis, these beneficial effects of remote ischemic preconditioning were independent of other covariables.

A further approach based on the preconditioning pathway is ischemic postconditioning; it is a promising approach in clinical practice due to its easy application in patients undergoing primary PCI after AMI. It was tested in a randomized controlled trial comprising 30 patients with AMI. Infarct size was assessed by measuring the area under the curve of creatine kinase release. A 36% reduction in infarct size was found: in the intervention group 208 984 [arbitrary units] compared with 326 095 [arbitrary units]. In addition, blush grade, as a marker of myocardial reperfusion, was significantly increased in the postconditioning group compared with the controls (2.44 vs. 1.95; $P<0.05$). The beneficial effects are still preserved after 6 months with a reduction in infarct size of 39% determined by SPECT. Even after 1 year, LV ejection fraction determined with echocardiography was still improved by 7%.⁶

The difficulties in translating cardioprotective strategies from animal experiment into the clinical setting is evident from the metabolic intervention using glucose-insulin-potassium infusion in AMI. Despite beneficial effects in animal experiments and in smaller clinical studies, a high-powered clinical trial, the CREATE-ECLA trial, showed convincingly a negative result.⁵

Until now, the clinical data of cardioprotective interventions after AMI might be promising. They are, however, based on small studies including relatively few patients, and need confirmation in large controlled randomized trials before recommendations for routine clinical application can be given.

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