President's Page

From Preconditioning to Postconditioning in Clinical Practice

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Total acute occlusion of a coronary artery leads to necrosis of the myocardial region of the heart that it supplies. Opening of the artery by thrombolysis or angioplasty reduces the infarct size, prevents left ventricular remodelling and decreases morbidity and mortality.

In 1986, a group of investigators who were looking for intracellular changes in glycolytic products in different phases of ischaemia found that if short periods of ischaemia and reperfusion were applied before prolonged ischaemia, the resulting infarct was significantly smaller compared to controls.[1] The phenomenon was called "preconditioning" and it was confirmed in all species studied. The next step of the research was to investigate whether preconditioning could be applied in humans. The initial clinical studies were observational, and demonstrated that warm-up and pre-infarction angina, which were considered to be analogous to preconditioning, had a beneficial effect on patients with coronary artery disease. Subsequent studies of induced myocardial ischaemia, such as that during balloon inflations in angioplasty prior to the final inflation, or as a result of repeated exercise stress testing, also found it to be beneficial.[2-4] Once basic laboratory research had identified the appropriate receptors, stimulators, and intracellular mediators that promote ischaemic preconditioning,[5,6] clinical studies were performed to investigate the possibility of reproducing this phenomenon by pharmacological means. The multi-centre trials AMISTAD I[7] and AMISTAD II[8] confirmed the beneficial role of adenosine as well as acadesine,[9] while the CESAR 2,[10] IONA,[11] and SMART[12] trials did the same for nicorandil.

Despite the encouraging results of both multi-centre and smaller clinical studies, the problem with the application of preconditioning in clinical practice is that it is not possible to anticipate the timing of prolonged, potentially lethal ischaemia and thus appropriate stimuli cannot be supplied in advance. In 2003, another group of investigators using a dog model found that infarct size can be reduced by the application of very short periods of ischaemia-reperfusion, not before the prolonged ischaemia, but immediately after the opening of a closed artery.[13] This phenomenon was named "postconditioning" and the initial series of experimental studies was followed by studies in humans. Indeed, like preconditioning, postconditioning was applied successfully in small clinical studies.[14,15] Specifically, after successful angioplasty and stenting in acute myocardial infarction, short balloon inflations after opening of the artery resulted in smaller infarct size. Knowledge of the mechanism of preconditioning and recognition of the phenomenon of postconditioning led to the conclusion that these two protective mechanisms reduce the damage from reperfusion injury, which contributes significantly to the final size of the infarct. Reperfusion injury is due, among other things, to the development of specific proteins called mitochondrial permeability transition pores (MPTP).[16] These allow the entry of molecules up to 1500 d into the mitochondria, resulting in its destruction and thus the death of the cell. Both pre- and postconditioning activate some defensive kinases known as reperfusion injury salvage kinases (RISK), which prevent the MPTP production and hence protect the survival of the cell.[17] These kinases are ERKs and PI3. The research target is to use in clinical prac-

tice agents that will activate the RISK, or prevent the opening of mitochondrial pores, or do both at the same time. There are experimental data concerning these actions. Erythropoietin, atorvastatin, natriuretic peptide and others are among the agents that activate RISK, while cyclosporine directly prevents the opening of mitochondrial pores.[17] As can easily be understood, for practical and ethical reasons it is not possible to test in clinical practice all these substances that are used at the experimental level.

The easier use of postconditioning in everyday practice and the recognition of its common mechanism with preconditioning led to the knowledge that the final infarct size may be reduced significantly by limiting reperfusion damage. At the same time, these two intrinsic protection mechanisms also significantly reduce apoptosis. Multi-centre studies are expected to confirm the experimental findings and those of small clinical studies.

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