No RISK, no... cardioprotection? A critical perspective

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This editorial refers to ‘Ischaemic postconditioning protects against reperfusion injury via the SAFE pathway’ by L. Lacerda et al., pp. 201–208, this issue.

Early reperfusion is today’s gold standard therapy for acute myocardial infarction. The underlying fundamental experiments that demonstrated salvage of myocardial tissue after prolonged coronary occlusion were published less than 4 decades ago1,2 and then subsequently confirmed in large-scale clinical trials such as the GISSI trial and many others. The notion that reperfusion may not only salvage infarcting myocardium but also induce damage itself dates back almost as long.3,4 The awareness of such potential reperfusion injury and the ambivalent character of reperfusion ischaemic preconditioning phenomenon, i.e. the reduction of infarct size following prolonged coronary occlusion by staccato reperfusion with a few cycles of re-occlusion,9 that the existence of lethal reperfusion injury became unanimously accepted.10–13 Ischaemic postconditioning protects from reperfusion injury.8 It was not until the detection of the ischaemic postconditioning phenomenon, i.e. the reduction of infarct size following prolonged coronary occlusion by staccato reperfusion with a few cycles of re-occlusion,9 that the existence of lethal reperfusion injury became unanimously accepted.10–13 Ischaemic postconditioning protects from infarction also in humans,14,15 as does cyclosporine A.16 The analogy of ischaemic postconditioning and of gentle reperfusion was emphasized, and it was proposed that ischaemic postconditioning is just another form of gentle reperfusion.17 The mechanistic relation between ischaemic postconditioning and gentle reperfusion is still unclear as is the question whether or not postconditioning provides protection beyond gentle reperfusion.

The signal transduction for protection from lethal reperfusion injury is still under intense debate.18 Yellon et al. have identified a concerted program of intracellular protein kinase activation which they have aptly termed reperfusion injury salvage kinases (RISK).19 Activation of both the phosphatidylinositol 3-kinase (PI 3-kinase)/Akt and the p42/p44 mitogen-activated kinase (ERK 1/2) pathways results from activation of sarcolemmal receptors by G-protein-coupled ligands or growth hormones and projects onto downstream kinases, such as p70S6 kinase and glycogen synthase kinase 3 β (GSK3-β), and ultimately to the mitochondria to affect cellular survival. The RISK concept goes back to experiments with a number of growth factors, notably insulin,20 and G-protein coupled ligands21, which, when given just at reperfusion, reduced lethal injury in isolated cardiomyocytes subjected to hypoxia/reoxygenation or isolated saline-perfused rodent hearts subjected to ischaemia/reperfusion. Subsequently, the RISK program was found to also contribute to ischaemic preconditioning22 and finally to ischaemic preconditioning in isolated perfused rat hearts.23 A postconditioning algorithm also protects human isolated atrial trabeculae through activation of the RISK program.24 Downey and Cohen emphasized the emerging pattern of salvage from reperfusion injury by RISK activation and ultimate prevention of the opening of the mitochondrial permeability transition pore that appeared to underlie ischaemic preconditioning, ischaemic postconditioning, and many pharmacological cardioprotective approaches.25

Now, is RISK activation truly mandatory for cardioprotection? Against a wealth of experimental data that confirm the RISK concept, some studies do not fit: increased phosphorylation/activation of Akt and ERK 1/2 was seen at 30 min reperfusion following 30 min coronary occlusion with postconditioning by three cycles of 30 s re-occlusion and 30 s reperfusion, but there was no reduction of infarct size in anaesthetized pigs.26 Conversely, infarct size was reduced by postconditioning with four cycles of 30 s re-occlusion and 30 s reperfusion in isolated rabbit hearts27 or three to six cycles of 10 s re-occlusion and 10 s reperfusion in isolated mouse hearts,28 but only the ERK and not the Akt pathway was activated. Again in anaesthetized pigs, we found the RISK program activated to the same extent with immediate full reperfusion or a postconditioning protocol of six cycles of 10 s re-occlusion and 10 s reperfusion; moreover, infarct size was reduced by postconditioning and this protection was not abrogated by concomitant pharmacological blockade of both the PI 3-kinase/Akt and the ERK pathways.29 Likewise, the reduction of infarct size by gentle reperfusion in this model was not abrogated by pharmacological RISK blockade.30

Transgenic approaches to the role of RISK in cardioprotection have also revealed ambiguous results: the same strain of transgenic mice with an inactive mutant of GSK3-β...
Alternative pathways of cardioprotection include the borders of an existing paradigm and challenge it, thus promoting the development of a broader, more comprehensive view:

Ich bin der Geist, der stets verneint...

Mephistopheles in: J.W. Goethe, Faust, Studierzimmer

References

25. Downey JM, Cohen MV. We think we see a pattern emerging here. Circulation 2005;111:120–121.


