Protecting the heart by postconditioning

Coronary heart disease (CHD) is the leading cause of death in the UK (accounting for 105,000 deaths in 2004) and exerts a huge burden, both on our healthcare system (around £3,500 million in 2003) and on our economy (£7.9 billion per year). Following an acute myocardial infarction (AMI), the 30-day mortality remains significant at around 10%, despite successful reperfusion therapy, instituted by either thrombolysis or primary percutaneous coronary intervention (PCI), paving the way for novel cardioprotective strategies to be developed.

One such potential cardioprotective strategy was ischaemic preconditioning (IPC), which was first described in 1986 by Murry and colleagues, as the reduction in myocardial infarct size observed in canine hearts pre-treated with short bouts of non-lethal ischaemia.[1] Despite intensive investigation and the publication of nearly 4,000 studies, the clinical potential of IPC has not been realised in the clinical arena due, in part, to the limitation of having to intervene before the onset of the index ischaemic episode, which in the setting of an AMI is unpredictable. In scenarios where the onset of myocardial ischaemia can be reliably anticipated, however, such as in patients undergoing elective PCI, cardiac bypass surgery or in patients presenting with unstable angina, the potential for a form of intervention which can mimic the cardioprotective benefits of IPC may still be possible.

What is postconditioning?

For patients presenting with AMI, an intervention that can be administered at the same time as reperfusion therapy is instituted, offers a far more attractive and amenable strategy of cardioprotection. This can be delivered by the physician or the cardiologist at the time of thrombolysis or primary PCI. In this regard, ischaemic postconditioning, a phenomenon first described by Zhao and colleagues in 2003,[2] has caused much excitement in the field of cardioprotection. It offers an intervention which can be applied at the time of reperfusion in patients presenting with AMI. Ischaemic postconditioning describes the reduction in myocardial infarct size obtained from interrupting the myocardial reperfusion phase with short bouts of ischaemia.

A recent landmark clinical study by Staat and colleagues,[3] demonstrated that applying several low pressure inflations/deflations of the angioplasty balloon, immediately following the deployment of a coronary stent in an occluded coronary artery in patients undergoing primary PCI, resulted in a 36% reduction in myocardial infarct size as measured by creatine kinase (CK) release. Importantly, this was one of the first clinical studies to confirm the existence of lethal reperfusion injury as a distinct clinical entity, which can be protected against. For many years, controversy has surrounded the concept of reperfusion injury as an independent determinant of myocardial injury.

Clearly, in patients presenting with an AMI, the direct stenting of the occluded culprit artery results in an abrupt restoration of blood flow to the ischaemic myocardium, begging the obvious question – why should interrupting myocardial reperfusion with short bouts of ischaemia protect the heart? This is currently being addressed in ongoing preclinical studies. A straightforward 'haemodynamic' explanation is that ischaemic postconditioning simply reperfuses the ischaemic myocardium in a gradual manner, leading one commentator to describe postconditioning as "Old wine in a new bottle".[4] Preclinical studies had previously reported that gradual or low pressure or stuttered myocardial reperfusion reduced infarct size in animal hearts.[5]

Studies conducted by our group and others point to a more active process, and have implicated the recruitment of intracellular kinase signalling pathways, of which the main components are Akt and Erk1/2, in animal hearts subjected to ischaemic postconditioning.[6, 7] The mechanism through which these kinases actually reduce myocardial infarct size is unclear, although the inhibition of mitochondrial permeability transition pore (mPTP) opening has been implicated.[8] The mPTP is a channel of the inner mitochondrial membrane which, on opening at time of myocardial reperfusion, mediates myocyte death by uncoupling oxidative phosphorylation and compromising ATP production.[9]

Pharmacological postconditioning

The important implication from these preclinical studies raises the possibility that pharmacologically activating these kinase signalling pathways may actually mimic the protective effect conferred by ischaemic postconditioning. Interestingly, preclinical studies by our group and others, which predated the 'discovery' of ischaemic postconditioning, had already

reported that the pharmacological activation of these kinases, Akt and/or Erk1/2, at the time of myocardial reperfusion reduced myocardial infarct size in animal hearts (reviewed in reference [10]).

Pharmacological activation of these survival kinases at the time of myocardial reperfusion in the clinical arena by administering drugs such as insulin, erythropoietin, and 'statins', may provide the cardioprotective benefit of ischaemic postconditioning, without the need for serial angioplasty balloon inflations/deflations. This last point is particularly pertinent in patients treated post-AMI by thrombolysis, in which conventional ischaemic postconditioning using an angioplasty balloon would not be possible.

Further large-scale clinical studies are required to confirm the protective role of ischaemic postconditioning in patients presenting with AMI. Clinical trials are also required to determine the feasibility for the pharmacological activation of these survival kinases, so-called pharmacological postconditioning, using agents such as insulin, erythropoietin and 'statins'.

Conflict of interest

None declared.

References

1. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 1986;**74**:1124-36.
2. Zhao ZQ, Corvera JS, Halkos ME *et al*. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. *Am J Physiol Heart Circ Physiol* 2003;**285**:H579-H588.
3. Staat P, Rioufol G, Piot C *et al*. Postconditioning the human heart. *Circulation* 2005;**112**:2143-8.
4. Heusch G. Postconditioning: old wine in a new bottle? *J Am Coll Cardiol* 2004;**44**:1111-12.
5. Okamoto F, Allen BS, Buckberg GD, Bugyi H, Leaf J. Reperfusion conditions: importance of ensuring gentle versus sudden reperfusion during relief of coronary occlusion. *J Thorac Cardiovasc Surg* 1986;**92**(3 Pt 2): 613-20.
6. Tsang A, Hausenloy DJ, Mocanu MM, Yellon DM. Postconditioning: a form of "modified reperfusion" protects the myocardium by activating the phosphatidylinositol 3-kinase-Akt pathway. *Circ Res* 2004;**95**:230-2.
7. Yang XM, Proctor JB, Cui L, Krieg T, Downey JM, Cohen MV. Multiple brief coronary occlusions during early reperfusion protect rabbit hearts by targeting cell signalling pathways. *J Am Coll Cardiol* 2004:**44**:1103-10.
8. Argaud L, Gateau-Roesch O, Raisky O, Loufouat J, Robert D, Ovize M. Postconditioning inhibits mitochondrial permeability transition. *Circulation* 2005;**111**:194-7.
9. Hausenloy DJ, Yellon DM. The mitochondrial permeability transition pore: its fundamental role in mediating cell death during ischaemia and reperfusion. *J Mol Cell Cardiol* 2003;**35**:339-41.
10. Hausenloy DJ, Yellon DM. New directions for protecting the heart against ischaemia-reperfusion injury: targeting the Reperfusion Injury Salvage Kinase (RISK)-pathway. *Cardiovasc Res* 2004;**61**:448-60.

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