Remote ischaemic pre-conditioning in cardiac surgery: benefit or not?

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This editorial refers to ‘Does remote ischaemic pre-conditioning with post-conditioning improve clinical outcomes of patients undergoing cardiac surgery? Remote Ischaemic Preconditioning with Postconditioning Outcome Trial’†, by D.M. Hong et al., on page 176

Hong et al.† report the results of a randomized controlled trial in which 1280 patients who underwent elective cardiac surgery were randomized into a group who received remote ischaemic pre-conditioning (RIPC) combined with remote ischaemic post-conditioning (RIPostC) or a control group. In the group who received remote pre-conditioning, four cycles of 5 min of ischaemia and 5 min of reperfusion were administered twice to the upper limb, before cardiopulmonary bypass or coronary anastomoses in patients who had beating heart surgery, and after cardiopulmonary bypass or coronary anastomoses. As compared with the control group, RIPC with RIPostC did not reduce the primary endpoint, a composite of major adverse outcomes, including death, myocardial infarction, arrhythmia, stroke, coma, renal damage, respiratory failure, gastrointestinal complications, and multiorgan failure. There was no difference in each major adverse outcome. Lengths of intensive care unit and hospital stays were similar in the two groups. Furthermore, in the off-pump subgroup, RIPC with RIPostC was associated with a significantly increased composite endpoint. These results are of importance in the debate regarding the potential interest in RIPC in cardiac surgery.

This clinical study has several strengths, including the randomization of a rather large population over a relatively short period of time and the inclusion of patients undergoing different cardiac surgical procedures, encompassing coronary artery bypass grafting, cardiac valve surgery, combined coronary and valvular procedures, ascending or transverse aortic surgery, and congenital heart defect repair, making it, to some extent, an ‘all-comer’ study. However, this heterogeneity probably introduced bias, as the authors correctly pointed out. Also, exclusion criteria were numerous; in particular, patients with poor left ventricular function who conceivably could benefit from pre-conditioning were excluded.

The authors discussed the possible effects of anaesthesia and of the addition of remote ischaemic post-conditioning to RIPC on their observations. Indeed, the use of propofol for anaesthesia maintenance could have influenced the results, as a recent study showed that propofol did abrogate the effect of RIPC.2 This, however, was, in contradiction to previous studies showing a cardioprotective effect of RIPC in patients who received propofol, but not volatile anaesthetics. Also, the study could possibly have yielded different results without the addition of post-conditioning to RIPC, although this appears unlikely.

This study should be placed into perspective with the literature, as RIPC has yielded conflicting and inconclusive results across several studies conducted in the last decade. In a small randomized trial of 57 patients, Hausenloy et al.3 showed that RIPC, applied through a similar protocol to that used in Hong’s study, significantly reduced serum troponin-T release up to 48 h after surgery. Of note, while the incidence of co-morbidities was similar, the population was older (67 vs. 60 years) but myocardial ischaemic (cross-clamp) time was significantly shorter (36 vs. 100 min) in the study of Hausenloy et al. as compared with the study reported by Hong et al.1,† Recently, D’Ascenzo et al.4 conducted a meta-analysis encompassing nine studies with a total 704 patients, showing that RIPC was associated with a significant decrease of troponin release, independent from anaesthetic and surgical techniques, while no differences in creatinine serum values and lengths of hospital stay were reported. It should be noted that all studies included in this meta-analysis were of small sample size, not powered to detect clinical differences in renal function or length of stay, and included heterogeneous protocols. In this context, the results of the large randomized controlled trial reported by Hong et al.† should have a significant weight in the balance, in dis-favour of RIPC.

To better understand the results of this study, it appears useful to summarize current knowledge on ischaemic pre-conditioning, applied locally or remotely.

Murry et al.5 first described myocardial pre-conditioning in a canine experimental model in 1986. They showed that exposure of the circumflex coronary artery territory to brief periods of ischaemia (four cycles of 5 min of ischaemia followed by reperfusion) before 40 min of complete ischaemia reduced the extent of infarction after restoration of blood flow. This finding showed that the heart could be rendered resistant to a clinically relevant ischaemia–reperfusion...
insult. Actually, this ability to undergo pre-conditioning is almost ubiquitous in tissues and is conserved across species. As the effects of pre-conditioning occur largely through modulation of reperfusion responses, the theory that the conditioning stimulus could be effective only when delivered before ischaemia was challenged. Indeed, local ischaemic post-conditioning where reperfusion is interrupted by further brief episodes of ischaemia followed by continued reperfusion also induced cardioprotection in experimental models. This provides some rationale for the addition of ischaemic post-conditioning to RIPC in the protocol of Hong et al., although applied remotely.

A systematic review of local ischaemic pre-conditioning in patients undergoing cardiac surgery pooled data from 22 trials with a total of 933 patients, showing significant reductions in inotrope requirements, ventricular arrhythmias, and length of intensive care unit stay. Outcome measures were usually biomarkers of myocardial injury, the positive effects being limited to patients in whom cardioprotection was achieved with cardioplegia. In addition, most studies were not powered for clinical endpoints, and there was substantial heterogeneity and bias regarding outcomes. Evolution of cardioprotection techniques, effects of some anaesthetics on cardioprotection, and changes in surgical methods have confounded the translation of these results to regular clinical practice. In addition, since a local ischaemic pre-conditioning protocol usually cross-clamps the aorta, it implies unnecessary aortic manipulations with potential associated morbidity. For these reasons, it has not gained significant popularity for clinical application.

A less invasive approach to cardioprotection might be achieved by RIPC, whereby brief ischaemia in one region or organ protects distant tissue or organs from a sustained episode of ischaemia. Twenty years ago, Przyklenk et al. showed that brief ischaemia of the circumflex artery reduced infarct size in the territory of the left anterior descending coronary artery, a phenomenon called intraorgan pre-conditioning. Subsequently, experiments demonstrated that brief ischaemia of several non-cardiac tissues such as the kidney, the intestine, or skeletal muscle could also protect the heart against subsequent ischaemia—reperfusion injury. More recently, Birbaum et al. showed that RIPC by transient limb ischaemia can reduce the infarct size in animals. The invasive stimulus consisted of a partial reduction in femoral artery flow applied in conjunction with an electrical stimulus to the leg muscle. Subsequently, a far less invasive and simpler procedure for inducing transient upper limb ischaemia by blood pressure cuff inflation was used in humans.

Overall, RIPC shows an equivalent level of protection to local pre-conditioning and probably induces similar intracellular kinases and changes in mitochondrial function, with however significant mechanistic differences between local and remote pre-conditioning. With intraspecies and interspecies variations in triggers, subcellular mediators, and effector pathways, the final common pathway is induction of a cascade of intracellular kinases and subsequent modifications of mitochondrial function, through opening of ATP-sensitive potassium channels and closure of mitochondrial permeability transition pores.

The technique of RIPC is thought to have systemic protective effects on distal organs, including the heart, lungs, kidneys, and brain, although the results are controversial for all organs examined. The exact nature of signal transduction from remote tissue to the target organ has been the subject of significant research. Three mechanisms (neurogenic, humoral, and systemic) are probably involved, interacting with each other and, therefore, not being mutually exclusive (Figure 1).

**Figure 1** Possible mechanisms for signal transduction from remote ischaemic tissue (upper arm) to target organ (heart).
The neurogenic pathway, abolished by the ganglion blocker hexamethonium or the pre-treatment of sensory nerves with capsaicin, involves an afferent signal from the remote organ stimulating the efferent limb of the reflex in distant tissues. Adenosine, bradykinin, and calcitonin gene-related peptide have been shown, in animals, to be mediators in the afferent loop of the reflex, while adenosine probably plays a role in the efferent limb. The neural pathways to the organ where the pre-conditioning stimulus is applied need to be intact but apparently not those of the target organ.

The nature of the substances involved in the humoral pathway probably varies with stimulus and species, but could function through opioid, endocannabinoid, or angiotensin II receptors, considering the inhibiting effects of naloxone, cannabinoid CB2 receptor blockade, or losartan. The role of nitric oxide is controversial, although inducible nitric oxide synthase is likely to play a significant role in delayed-phase conditioning. Also, RIPC has been shown to reduce platelet reactivity and therefore thrombogenic burden.

Finally, RIPC induced by transient limb ischaemia has been shown to have a systemic anti-inflammatory influence through suppression of the expression of proinflammatory genes in leucocytes and reduced neutrophilic adhesion. It appears to modify myocardial gene expression by up-regulation of cytoprotective genes and suppression of proinflammatory genes potentially involved in the pathogenesis of ischaemia–reperfusion injury.

In summary, although several small size clinical studies have reported some potential benefit of RIPC mainly on surrogate endpoints such as elevation of serum cardiac enzymes, the results of the randomized controlled trial reported by Hong et al.1 appear to weight against RIPC. Even more, RIPC could induce some harm in patients undergoing off-pump coronary artery bypass grafting. Therefore, further large studies are needed before a complete appraisal of RIPC in cardiac surgical patients can be achieved.

Conflict of interest: The author has received honoraria for participation in advisory boards and lecturing at symposia for AstraZeneca and B. Braun.

References


