Delayed Postconditioning: Cardioprotection at the Limit?
Lionel H. Opie and Sandrine Lecour

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Delayed Postconditioning
Cardioprotection at the Limit?

Lionel H. Opie, MD, DPhil, FRCP; Sandrine Lecour, PhD

The discovery of preconditioning was a landmark event in modern interventional cardiology. How could cardiomyocytes threatened by severe ischemia evade the inevitable damage? In one of the most quoted and influential articles in cardiac literature, the discovery of preconditioning by Murry et al gave a completely new view. With the use of repetitive short bursts of ischemia and reperfusion before coronary ligation, the infarct size was reduced at 45 minutes but not 3 hours after ligation. Because the ultimate infarct size was unchanged, the conclusion was that preconditioning did no more than delay the evolution of the inevitable infarct without decreasing its size. Of note, and often forgotten, Murry et al observed that the postligation evolution of the infarct was delayed by preconditioning (without any reperfusion); therefore, they did not study reperfusion injury.

Article see p 1330

Overall, the widely held view was that reperfusion merely accelerated the death of cells that would have died in any case versus the then avant garde, but eventually scientifically sound, view that reperfusion injury existed in its own right and newly damaged cardiomyocytes that otherwise would have survived intact. Many mechanisms conspired to cause this damage, including those already known for many years such as sudden exposure to oxygen, with formation of free radicals and rapid cytosolic calcium overload. It is a far leap from those early days to the present recognition of lethal reperfusion injury and the varieties of molecular cardioprotective tools currently available: preconditioning, postconditioning, remote conditioning, interorgan conditioning, and now delayed conditioning (Table), as described in the present issue.

In the first reported therapeutic reduction of postreperfusion infarct size by Verns et al, the active agent was allopurinol. Thereafter, a flood of studies on lethal ischemic/reperfusion injury led to the major new concept of molecular protection rescue pathways that reduce lethal ischemic/reperfusion injury, including the reperfusion injury salvage kinase and the survivor activating factor enhancement pathways.

The ultimate site of cell salvage is the mitochondrion, where opening of the mitochondrial permeability transition pore prompts the rapid influx of calcium ions that precipitate the demise of the cell through either apoptosis or necrosis. Preconditioning protects by closing the mitochondrial permeability transition pore, thereby saving the threatened cells from death. Both prosurvival signaling cascades, survivor activating factor enhancement and reperfusion injury salvage kinase, activated by preconditioning, converge on and act by closing the mitochondrial permeability transition pore.

Discovery of Postconditioning

To apply to acute myocardial infarction, the real revolution was that postconditioning was achieved by repetitive ischemia during early reperfusion after 60 minutes of left anterior coronary occlusion in dogs. The basic idea evolved from prior observations that stuttering reperfusion was better than sudden abrupt reperfusion.

Characteristic of this fast-moving field, the first clinical article with postconditioning appeared only 3 years after its discovery. The landmark study by Staat et al reported the effects of balloon postconditioning, applied by 4 cycles of 1 minute of inflation/deflation of the angioplasty balloon during the first minutes of reperfusion in acute myocardial infarction patients undergoing emergency percutaneous intervention (PCI). The result was reduced creatine kinase release over 72 hours with postconditioning. In 17 postconditioned patients at 1 year of follow-up, the ultimate infarct size decreased by 36% and left ventricular ejection fraction increased by 7% (P=0.04). Although we await larger trials, provisional clinical application of balloon postconditioning seems ethically acceptable. Pharmacological postconditioning was also rapidly translated to the clinical setting. In patients with acute ST-segment–elevation myocardial infarction, an intravenous bolus of cyclosporine (2.5 mg/kg), an immunosuppressor and inhibitor of the mitochondrial permeability transition pore opening, given immediately before undergoing percutaneous intervention reduced the infarct by 23%.

Delayed Postconditioning

Both balloon inflation/deflation and cyclosporine were started within minutes of the onset of reperfusion. However, many patients in remote areas do not have rapid access to PCI and are given thrombolysis before transfer to a regional hospital with PCI. Here, the development of delayed postconditioning, the subject of the present landmark article, may indirectly show the way forward. Roubille et al achieved substantial decreases in infarct size by postconditioning that was delayed up to 30 minutes after the onset of reperfusion. Roubille et al used 3 cycles of 1 minute of...
Remote Conditioning in the Ambulance

The Danish group in Aarhus tested remote conditioning of Danish patients with acute coronary syndromes on their way to the hospital to receive primary PCI. This process was called remote perconditioning because conditioning was given when the actual infarct was probably still in evolution owing to the rapidity of their ambulance services. The infarct size in the untreated group was only \( \approx 8\% \), reflecting the speed with which the ambulance system in Aarhus could bring patients to the hospital. The Danish group used 4 cycles of 5 minutes of inflation/deflation of the blood pressure cuff on the arm of 251 patients. Thirty days after reperfusion, the myocardial salvage measured by single photon emission computed tomography imaging was modestly increased by remote conditioning.

Interorgan Conditioning

Not only the heart but also the brain, liver, lungs, muscle, and kidneys can benefit from various forms of conditioning. The marked extent of interorgan protection is shown in the Figure. Indeed, every organ seems potentially capable of communication with most of the other organs, giving the impression of a vast network with various threatened organs potentially being protected by repetitive transient ischemia in others.

Remote Conditioning and Polyprotection

Thus, we propose that there is potentially a vast amount of interorgan chatter and sending of protective messages and that (coming back to the article by Roubille et al.3) the exact timing of the induced ischemia that triggers these multiple protective systems might be more flexible than previously thought.

Looking ahead, the crucial issue is whether different types of cardioprotection can be additive. Does pharmacological protection by cyclosporine add to ischemic preconditioning? That seems unlikely because the ultimate site of action of both therapies is the mitochondrial transition pore. What about combining metabolic protection and conditioning? Because the activity of mitochondrial hexokinase II is required for ischemic preconditioning23 and hexokinase is stimulated by glucose metabolism, logic would say that glucose-insulin infusions could be added to remote perconditioning in the ambulance for maximal protection.

Could postconditioning be pushed to the limit to combine a practical protocol with maximal protection in a clinical setting? Remote ischemic postconditioning merits serious consideration as a basis of future clinical trials because it is safe, noninvasive, cheap, and practical. Indeed, remote conditioning would potentially add neurogenic to mitochondrial

Table. Evolution of Concepts in Cardiac Conditioning

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PCI, percutaneous intervention; AMI, acute myocardial infarction; RISK, reperfusion injury salvage kinase path; SAFE, survivor activating factor enhancement path.

miscellaneous.

ischemia/1 minute of reperfusion, but different timing might give the optimal postconditioning protocol for maximal protection. That would lead to clinical testing of the hypothesis that patients undergoing thrombolytic therapy followed by delayed PCI could still benefit from balloon postconditioning. Another organ for clinical testing is the brain; delayed postconditioning in the rat brain can be achieved for up to 6 hours with 6 cycles of 15 minutes of occlusion/15 minutes of reperfusion.14

Remote Conditioning and Its Human Application

After the remarkable discovery of cross-talk between coronary arteries,15 the first evidence for the phenomenon of remote interorgan conditioning was that transient ischemia of the intestine protected the rat heart16; in humans 6 years later, ischemic limb conditioning was shown to protect the contralateral limb.17 Soon thereafter, the same group studied children undergoing repair of congenital heart defects in whom remote ischemic preconditioning was induced by four 5-minute cycles of lower-limb ischemia and reperfusion with a blood pressure cuff.18 Postoperatively, troponin I was lower, inotropic stimulation was less frequently required, and airways resistance fell with remote preconditioning. From there, it was a small but significant step to show that remote upper-limb preconditioning in adults likewise reduced troponin I release after coronary artery bypass grafting.19 Next, similar benefit was found for elective PCI by prior remote limb ischemia.20 Troponin release was less, ECG changes were fewer, and the protected patients experienced much less chest discomfort.

Looking ahead, the crucial issue is whether different types of cardioprotection can be additive. Does pharmacological protection by cyclosporine add to ischemic preconditioning? That seems unlikely because the ultimate site of action of both therapies is the mitochondrial transition pore. What about combining metabolic protection and conditioning? Because the activity of mitochondrial hexokinase II is required for ischemic preconditioning and hexokinase is stimulated by glucose metabolism, logic would say that glucose-insulin infusions could be added to remote perconditioning in the ambulance for maximal protection.

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...results suggest that the protection afforded by postconditioning potentially extends to all vital organs and peripheral muscle.

The Future

These observations on repetitive postinfarct remote conditioning considerably support and extend the observations of Roubille et al., namely that the onset of postconditioning could be delayed. The hope is raised that repeated daily postconditioning after acute myocardial infarction would certainly be practical and would be the cheapest clinical option to assess in the near future. The first conditioning cycles could ideally be performed within the delayed window of protection suggested by Roubille et al. This may seem to be in the distant future, but let us remember that there has been an amazing speed progress as molecular studies, often on rodents, have delineated therapeutic principles that have jumped rapidly to human testing.

A further speculation is that the benefit of conditioning may extend to nons ischemic situations such as improving athletic performance. Bearing in mind that the brain can afford in the distant future, but let us remember that there has been an amazing speed progress as molecular studies, often on rodents, have delineated therapeutic principles that have jumped rapidly to human testing.

We conclude by speculating that delayed repeated remote postconditioning would be the safest winning option to test in humans and that the conditioning protocol (such as the number of cycles) still needs to be tuned to reach the maximal limit of protection. Furthermore, the protocol may have to be adapted to the patient (ie, sex, age, other diseases). Optimistically, we predict that eventually there will be guidelines for the use of conditioning in various clinical settings.

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Disclosures

None.

References


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