Delayed Postconditioning
Cardioprotection at the Limit?

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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.

**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.9 The basic idea evolved from prior observations that stuttering reperfusion was better than sudden abrupt reperfusion.10

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).12 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%.13

**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. Roumbille et al achieved substantial decreases in infarct size by postconditioning that was delayed up to 30 minutes after the onset of reperfusion. Roumbille 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.21 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.22

Remote Conditioning and Polyprotection

Thus, we propose that there is potentially a vast amount of cardioprotection and sending of protective messages and that (coming back to the article by Roubille et al3) 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

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

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.
protection if given combined with cyclosporine, which requires 1 simple injection, so far without significant side effects. Taking a cue from the pharmaceutical industry, polyprotection, eg, remote protection plus cyclosporine plus glucose-insulin, needs exploration. If such delayed polytherapy becomes possible, it might benefit those many patients throughout the world who, because of socioeconomic reasons, receive thrombolytic therapy rather than PCI for acute myocardial infarction. Delayed conditioning therapy does not necessarily mean no benefit, which is the essential message of the Roubille et al study. In addition, remote conditioning of the postinfarct rodent heart can be further enhanced when such conditioning is repeated daily for 28 days, thereby improving postinfarct survival in a dose-dependent manner.24

**Figure.** The powerful multigorgan protective effect of postconditioning. The time panel shows the effects of time delays on ischemic postconditioning in heart and brain, strongly suggesting that the onset of postconditioning does not need to occur immediately on reperfusion. The distance panel indicates that postconditioning can be performed either locally via the reperfused artery or remotely, often in the upper arm. The signaling panel indicates that 2 molecular signaling pathways, the reperfusion injury salvage kinase (RISK) and survivor activating factor enhancement (SAFE) pathways, inhibit opening of the mitochondrial permeability transition pore (mPTP) to protect the heart. The organ panel indicates 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 be the safest winning option to test in humans when such conditioning is repeated daily for 28 days, thereby improving postinfarct survival in a dose-dependent manner.24

A further speculation is that the benefit of conditioning may extend to nonischemic situations such as improving athletic performance.25 Bearing in mind that the brain can experimentally benefit from remote ischemic conditioning, we look ahead to better cognitive function.

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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