“From bench to bedside” is a favorite aphorism for the scientifically inclined cardiologist. When the powerful antiischemic effects of preconditioning were discovered in 1996, it was a revolutionary concept: Repetitive brief ischemia could beget protection instead of the logically anticipated increased myocardial damage. The 75% reduction in histological infarct size was truly astounding. Early laboratory and clinical studies with concordant mechanisms strongly suggested that this powerful tool would soon have practical application. It has been a long road (Table) to clinical application, and consistently an elusive goal until the landmark study by Staat et al in this issue of Circulation. The major problem has been that the protection provided by preconditioning is a relatively short-lived phenomenon, so that to reduce infarct size it would have to be instituted just before the patient experienced an unannounced myocardial infarction. Furthermore, the recent experimental emphasis on reperfusion-induced cell death seems a far cry from clinical reality because there has been no convincing demonstration of major reperfusion injury after revascularization for acute myocardial infarction. The animal experiments show extensive reperfusion damage resulting in large infarcts of up to half of the area at risk after only a relatively short period of ischemia. Clinicians argue that if such large infarcts were produced by reperfusion, then why does early reperfusion within 1 hour afford such good clinical recovery?

A Simple, Clinically Applicable Procedure to Improve Revascularization in Acute Myocardial Infarction

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Discovery of Postconditioning
Reperfusion remains the definitive treatment for ischemic myocardium. Although reperfusion salvages myocardium that would ultimately die in its absence, restoring blood flow to myocardium carries the potential to exacerbate injury from that present at the end of ischemia (ie, reperfusion injury). Reperfusion injury potentially offsets the optimal salvage of myocardium achieved during cardiac surgery, percutaneous coronary intervention, or cardiac transplantation.

Early strategies to attenuate reperfusion injury applied concepts derived from cardiac surgery, in which protecting the myocardium from ischemia-reperfusion injury was a mainstay of the operative strategy. Surgical cardioprotective strategies were centered on modifying the conditions of reperfusion (cardiopulmonary bypass, reperfusate pressure, pulsatility, temperature) or the composition of the reperfusate (pH, osmolality, substrates such as glucose, amino acids, and adjunct drugs). Reperfusion achieved with cardiopulmonary bypass (modified conditions) and cardioplegia (modified composition of reperfusate) delivered at low pressures reduced infarct size after a fixed period of ischemia. This strategy of modifying the conditions and composition of reperfusion describes the approaches used some 20 years later to reduce various aspects of reperfusion injury. Such a broad spectrum approach is, in fact, necessary to address a problem with a complex cause. All strategies initiated before or at the onset of reflow including the administration of drugs at reperfusion can be classified as a modification of reperfusion.

A critical early observation was that reperfusion damage could be modified by slowly initiating reflow. This “gentle” or “ramped” reperfusion reduced infarct size, restored postischemic contractile function, reduced edema in the area at risk, and avoided blood flow defects characterized as a “no-reflow” response. Postconditioning is a strategy that can modify reperfusion-induced adverse events. It arose from lateral thinking and through the simple application of preconditioning, suggested by Zhi-Qing Zhao more than 10 years ago, by moving the preconditioning “stimulus” to the beginning of reperfusion, and thereby ostensibly modifying reperfusion (Figure 1). Initial experiments in which several cycles of 5 minutes’ reperfusion and 5 minutes’ coronary occlusion preceded complete reperfusion failed to reduce infarct size. The experiments were terminated and the concept was filed in storage for nearly 10 years; we now know that the protocol applied in these early experiments was suboptimal. This incubation time turned out to be fortunate because the science...
Some Key Events in Evolution of Postconditioning
From Preconditioning

Phenomenon of preconditioning discovered in dogs
Similar phenomenon in humans during percutaneous intervention
Infarct size reduction in small animals; preconditioning can be mediated by adenosine
Second window of protection
Direct proof of preconditioning in human heart
Many experimental observations delineate mechanisms of preconditioning
Postconditioning first described in dog heart
Postconditioning confirmed in rat and rabbit hearts and mechanisms delineated

Postconditioning of human heart rapidly following revascularization of acute myocardial infarction.

- The group of Vinten-Johansen had in mind that postconditioning could conceptually be applied to the clinical situation because it was initiated at the time of reperfusion. Its application in patients presenting for percutaneous coronary interventions had been suggested in implications to several experimental publications, but questions were immediately raised regarding potential injury to the target coronary artery from repeated balloon inflations, possible dislodgement of atheromatous material, or dissection of the coronary artery. The prospective, randomized, multicenter study by Staat et al is the first to test the concept of postconditioning in humans. In a select group of patients, postconditioning was acutely safe; no adverse poststenting events were reported. In addition, postconditioning attenuated enzyme release, which is strongly suggestive of infarct size reduction, a paramount aim in patient treatment.

- Most important, the study by Staat et al compellingly supports the notion that reperfusion damage is a clinical entity rather than a laboratory curiosity. Indeed, the positive outcome poses the question of just when cardiac muscle dies, a question that was asked nearly 20 years ago, and shows that reperfusion contributes to lethal injury. Moreover, the positive outcomes resulting from applying postconditioning to patients supports a role for reperfusion therapy to reduce infarct size and attenuate other aspects of reperfusion injury, such as endothelial dysfunction, postischemic blood flow defects, and contractile dysfunction shown in experimental studies. On another broader scale, the concept of postconditioning reveals an aspect of nature’s endogenous cardioprotective armamentarium that has heretofore escaped widespread appreciation. This will generate interest in mechanisms of reperfusion injury and in opportunities for therapy.

Mechanisms Common to Pre- and Postconditioning

Although Heusch described ischemic postconditioning as “old wine in a new bottle,” maybe it is excellent wine with a winning taste. The present article by Staat et al justifies the years of research that have gone before and will stimulate much more research to achieve optimal clinical cardioprotection. Any fully cardioprotective strategy applied at the time of reperfusion must provide protection against the known mediators of lethal reperfusion injury, which include cellular and mitochondrial calcium overload, a burst of oxidative stress, endothelial dysfunction, and reduced nitric oxide production. Yellon’s group provided mechanistic insights, showing that it is now possible to protect the reperfused myocardium by activating prosurvival kinase signaling pathways (reperfusion injury salvage kinase pathway). Both pre- and postconditioning activate the same key pathways, which include phosphatidylinositol 3-kinase-Akt and extracellular signal-regulated kinase. Upstream may be activation of G-protein coupled receptors, and the many downstream events include key phosphorylations of endothelial nitric oxide synthase and inhibition of the apoptosis promoters (Figure 2). To activate these and other prosurvival pathways requires rapid institution of a series of ischemia-release cycles starting within 30 seconds of reperfusion in experimental studies. Whether similar pathways are activated within 1 minute of direct stenting, as in the clinical study by Staat and colleagues, needs verification.

As in the case of ischemic preconditioning, protective pathways activated by postconditioning appear to converge...
on the mitochondria, in particular the mitochondrial permeability transition pore. This opens during the first few minutes of reperfusion, in response to mitochondrial calcium overload, oxidative stress, and adenosine triphosphate depletion. Both preconditioning and postconditioning protect the heart through the inhibition of mitochondrial permeability transition pore opening. Furthermore, the protective effect of postconditioning may directly or additionally be related to beneficial antiinflammatory or antioxidant effects, decreased extracellular levels of noxious metabolites such as protons and lactate, or delayed washout of adenosine, a well-established mediator of preconditioning.

Pharmacological activation of the reperfusion injury salvage kinase pathway at the time of reperfusion should also be considered. The postconditioning protocol of Staat and colleagues, carefully applying intermittent episodes of myocardial ischemia/reperfusion at the moment of reperfusion to a patient undergoing an acute myocardial infarction, may require expert skills to implement. Based on the molecular mechanisms mediating postconditioning, appropriate pharmacological agents that can be given at reperfusion should now be tested in patients at the time of revascularization. Experimental agents that activate this path include insulin or glucagon-like peptide-1, erythropoietin, and statins. Should these “postconditioning-mimetics” be administered as a constant infusion at the onset of or even before reperfusion, or are intervening periods of drug-free perfusion (similar to the “washout” periods in preconditioning only displaced in time) necessary to trigger postischemic protection?

Ready for Clinical Application?
The present study was powered and designed to test the safety and efficacy of postconditioning in a select population of patients undergoing angioplasty and stent deployment. The conclusions are 3-fold. First, a simple procedure that any interventional cardiologist can apply is potentially powerful in reducing infarct size. Second, reperfusion damage does occur in humans, and it is clinically significant, although not typically sought. The third issue is that enzyme release re-enters the scene as an index of the severity of acute myocardial infarction.

What are the implications for the future? First, before there is a general application of postconditioning, we do not need a large double-blinded multicenter study but rather additional studies to confirm the efficacy of postconditioning in a larger and more diverse group of patients. Was the protocol used (4 cycles of 1-minute reperfusion-reooclusion) optimal? Such trials are already being planned or are under way. In addition, studies should look sufficiently beyond the interventional event (ie, 1 to 5 years) to ensure that more subtle adverse events do not surface. Thereafter, we anticipate that postconditioning will become part of the standard care of acute myocardial infarction. Protection of other organs such as brain and liver is the next challenge to overcome. Now that revascularization is applied to early thrombotic cerebral infarcts in humans, it will be equally logical clinically to test postconditioning of the brain.

In summary, the article by Staat et al has brought the bench to the bedside, albeit nearly 20 years later, and made relevant all of the intense work of the many basic researchers who have helped to define the signaling paths involved, the role of the mitochondria, the importance of reduction of reperfusion damage, and the creation of hypotheses for additional clinical trials. This landmark study may well galvanize the scientific/clinical community to appreciate that reperfusion injury exists in humans and is a new therapeutic target.

References


**Key Words:** Editorials ■ myocardial infarction ■ reperfusion ■ stents ■ ischemia
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