The initial discovery of cardiac preconditioning has evolved into an exciting series of practical surgical applications. An enormous amount of evidence demonstrating both the safety and efficacy of ischemic preconditioning is available from animal studies. The challenging premise of intentionally subjecting patients and their organs to transient ischemia has acted as a formidable psychological and ethical impediment to the widespread clinical application of organ preconditioning. A more palatable alternative to ischemic preconditioning now involves approved medications designed to manipulate the cellular machinery mediating ischemic preconditioning. Pharmacologically induced preconditioning seems to confer equal organ protection. The relatively brief (but surgically relevant) window of protection provided by strategies such as ischemic preconditioning or adenosine agonists and potassium–adenosine triphosphate channel openers may, in the future, be extended. We have developed and reported the feasibility of liposomal delivery of heat shock protein to cardiac myocytes with subsequent protection against sepsis-induced dysfunction. Targeted strategies will ultimately broaden the therapeutic potential of organ preconditioning. 

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**SO WHAT IS ORGAN PRECONDITIONING AND WHY DO YOU NEED TO KNOW ABOUT IT?**

Organ preconditioning is a process whereby a brief antecedent event, be it transient ischemia, oxidative stress, temperature change, or drug administration, bestows on an organ a temporary tolerance to further insults by the same or similar stressors. Regardless of your surgical discipline, organ preconditioning is on the horizon and promises to reduce morbidity during coronary revascularization, to provide improved graft and patient survival after transplantation, to protect kidneys and intestines during vascular surgery, to improve skin and muscle flap survival, and perhaps even to protect the editors of this journal from the cerebrovascular ischemic ravages of old age. The purposes of this review are as follows: (1) to describe the evolution and mechanisms of organ preconditioning, (2) to examine the evidence that organ preconditioning is accessible and relevant to surgery, and (3) to discuss future implications for organ preconditioning.

**EVOLUTION**

Murry et al first recognized organ preconditioning. Paradoxically, while trying to create a larger myocardial infarction in a dog, they subjected animals to several brief episodes of myocardial ischemia and reperfusion prior to a protracted ischemic injury. To their surprise, the area of infarction in these stressed animals was reduced by up to 75% compared with animals not subjected to antecedent brief ischemia. In addition to limiting infarct size, ischemic preconditioning reduces myocardial functional “stunning,” postischemic arrhythmias, and accelerates the recovery of muscle function after ischemia. These counterintuitive findings have
Cardiomyocyte preconditioning may occur via transient ischemia, oxidants, heat shock, osmolar stress, or by ligation of adenosine, α-adrenergic, bradykinin, or opioid receptors. All of these signal through protein kinase C (PKC), which initiates a complex kinase cascade that ultimately opens mitochondrial potassium–adenosine triphosphatase channels (K-ATP), protecting the cell from subsequent injury. Gp indicates G-protein; PLC, phospholipase C; and Ca++, calcium.

been challenged, but confirmed in multiple organs across many species.

MECHANISM

Though the mechanisms of preconditioning have been best studied in the heart, these cellular protective strategies have been identified in other organs.7–9 Ischemic preconditioning is psychologically repugnant to the active surgeon; we are reluctant to clamp a carotid artery even transiently prior to performing a carotid endarterectomy. Fortunately, ischemic preconditioning can be replicated by pharmacologic agonists to adenosine, α-adrenergic, opioid and/or bradykinin receptors, suggesting that tissues have evolved multiple parallel endogenous means of self-protection.6,10–12 Intracellular signaling is a lot like the analog processing in a lap-top computer. In a computer, a fork in the network is transduced either yes/positive or no/negative. In a cell, kinases transmit the "yes" signal by phosphorylation, while phosphatases say "no" by cleaving a phosphate. A common theme among preconditioning receptors is that they are linked to protein kinase C,13 which is the first step in a complex cascade of phosphorylating (yes signal) kinases that activate the potassium–adenosine triphosphate (K-ATP) channel in the mitochondrial membrane (Figure). This K-ATP channel is the final common energy-producing pathway to organ preconditioning. We have reported that inhibition of this K-ATP channel completely abolishes the effects of ischemic preconditioning in the heart.14 Commonly prescribed drugs, such as oral hypoglycemic agents (inhibitors of the K-ATP channel) and L-type calcium channel blockers (inhibitors of the calcium "trigger"), compromise protective cardiac preconditioning and increase cardiac morbidity and mortality after an ischemic event.15,16 Conversely, the inhibition of bradykinin degradation in patients taking angiotensin-converting enzyme inhibitors may account for the reduced morbidity and mortality observed after a myocardial infarction.17

CARDIOTHORACIC SURGERY

After the description by Murry et al1 of myocardial ischemic preconditioning, a myriad of publications corroborated this initial discovery. Although many laboratory studies have confirmed the existence of ischemic preconditioning in animals, care must be taken in extrapolating these findings to humans.18 In vitro studies using human atrial muscle strips exhibit preconditioning but an in vivo clinical strategy to investigate ischemic preconditioning is both logistically and ethically challenging.

Two important observational studies have provided strong evidence for the existence of ischemic preconditioning in human myocardium, and have thus paved the way for further clinical investigation of preconditioning as a therapeutic strategy. Patients undergoing coronary angioplasty experienced less pain and exhibited only mild S-T segment depression during sequential balloon inflation after an initial 90-second coronary artery occlusion.19 Similarly, patients experiencing preinfarction angina during the 24 hours preceding a myocardial infarction suffered smaller infarcts and enjoyed improved survival.20 Subsequent investigations revealed that adenosine antagonists and K-ATPase inhibition prevent protective preconditioning during angioplasty, confirming that the mechanisms of myocardial preconditioning are similar in animals and humans.21,22

Jenkins et al23 provided the first clinical evidence that ischemic preconditioning resulted in myocardial protection. During routine coronary artery bypass grafting (CABG), they applied two 3-minute periods of ischemia (aortic cross-clamping) followed by 3 minutes of reperfusion before the more extensive ischemia (10–15 minutes) obligatory for a coronary vascular anastomosis. Preconditioned patients released lower levels of serum troponin T at 72 hours postbypass.23

Despite these promising findings, the unnerving thought of intentionally inducing myocardial ischemia in patients is too difficult for many clinicians to bear, thus hindering the widespread clinical application of ischemic preconditioning. Fortunately, pharmacologic strategies have evolved that seem to mimic the mechanisms of ischemia while reaping the benefits of preconditioning without the actual ischemia (Figure). We and others have reported that adenosine administered prior to routine CABG decreases postoperative atrial arrhythmias,24 and a multi-institutional trial confirmed that adenosine administered immediately prior to cross-clamping the aorta improves ventricular function following CABG.25

TRANSPLANT SURGERY

Transplant surgery offers the perfect opportunity for preconditioning as it requires a scheduled, transient ischemic period during organ procurement and storage. Strong support for the application of organ preconditioning has been established in animals. In the rat, 2 short periods of ischemia and reperfusion, or administration of diazoxide (a K-ATP channel opener) prior to explantation and cold storage, improved postreperfusion left ventricular compliance and reduced creatine kinase leak.26
Yin et al. have reported that rat livers subjected to ischemic preconditioning or adenosine administration prior to harvest prompted improved survival and reduced aspartate transaminase (AST) release after 16 hours of cold storage and transplantation. A clinical correlate to this study, again counterintuitively, reported that livers procured from donors suffering a brief cardiopulmonary arrest prior to procurement enjoyed similar graft function and host survival but lower posttransplant AST levels compared with the nonarrest group. Any rational surgeon would logically predict impaired posttransplant hepatic function in the cardiopulmonary arrest donor group. Liver preconditioning, therefore, is the only plausible mode of protection.

Lung transplantation is associated with a 20% incidence of severe graft dysfunction in the early postoperative period. In animals, ischemic preconditioning of lungs prior to prolonged hypothermic storage is protective of both compliance and gas exchange.

**VASCULAR SURGERY**

Elective vascular surgery also offers a unique opportunity for organ preconditioning, as it too involves an obligate period of transient ischemia. Preconditioning may improve functional recovery of skeletal muscle during peripheral vascular procedures and may also protect renal function during complex pararenal aortic aneurysm repair. Animal evidence has been overwhelming in showing that antecedent transient ischemia will protect the brain during carotid endarterectomy; however, the psychological hurdles for the surgeon who must intentionally clamp the carotid (of a university dean or even a trial lawyer) remain daunting.

Lee and Emala have reported that ischemic preconditioning prior to a 45-minute ischemic event resulted in improved renal function and morphological structure in rats. Moreover, these investigators found that A-1 adenosine agonists and A-3 adenosine antagonists reproduced the benefits of ischemic preconditioning. This study delineates and confirms the role of the various adenosine receptors in organ preconditioning.

**NEUROSURGERY**

Analogous to the study by Ottani et al correlating preinfarction angina with reduced morbidity after a myocardial infarction, several groups have reported that patients suffering transient ischemic attacks (TIA) experience a more favorable outcome after a subsequent ischemic stroke. Animal investigations have confirmed similar benefits with protective ischemic preconditioning in reducing neuronal damage after subsequent prolonged ischemia.

**PLASTIC OR RECONSTRUCTIVE SURGERY**

Despite a better understanding of vascular anatomy and improved flap design, the devastating complication of partial or complete myocutaneous flap necrosis following reconstructive surgery still occurs. Zaher et al. have reported that ischemic preconditioning reduces the incidence of skin and free-muscle flap necrosis in rats. Preliminary clinical trials using ischemic preconditioning have shown improved survival rates of both transverse rectus abdominis flaps and groin flaps.

**FUTURE IMPLICATIONS**

Despite the enormous amount of evidence demonstrating the safety and efficacy of ischemic preconditioning in animal studies, the challenge of intentionally subjecting patients to transient ischemia has acted as a formidable impediment to its widespread clinical application. The development of approved medications designed to replicate the cellular machinery involved in preconditioning offers a more palatable alternative to ischemic preconditioning. Moreover, the relatively brief window of protection provided by strategies such as ischemic preconditioning, adenosine agonists, and K-ATP channel openers may, in the future, be extended. For instance, we have developed and reported the feasibility of liposomal delivery of heat shock protein to cardiac myocytes, with subsequent protection against sepsis-induced cardiac dysfunction. Strategies such as this may ultimately broaden the therapeutic potential of organ preconditioning even further.

**REFERENCES**


