Surgical Implications of Ischemic Preconditioning

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Background: Ischemic preconditioning (IP) has emerged as a powerful experimental method of ameliorating ischemic injury in a variety of organs. This systematic review examines the surgical implications of this phenomenon.

Data Source: A MEDLINE search was conducted to identify laboratory and clinical studies investigating IP-induced protection in a variety of organ systems. Particular emphasis was placed on uncovering evidence for the use of IP in the surgical setting.

Data Synthesis: Human clinical trials using IP have been successfully carried out in the fields of cardiac, hepatic, and pulmonary surgery. Epidemiologic data exist to support the existence of IP-induced neuroprotection in humans. Human skeletal muscle has been preconditioned experimentally, as have human proximal tubule (renal) cells. At present, there is no evidence for IP occurring in the human intestine, although animal studies attest to the possibility. Ischemic preconditioning appears to be effective even when applied to a site remote to the organ exposed to ischemia. However, these favorable effects are less evident in diabetic and elderly patients.

Conclusion: Ischemic preconditioning is safe for use in elective cardiac, hepatic, and pulmonary surgery. More studies with greater patient numbers need to be carried out in these areas to demonstrate the efficacy of IP in providing clinical benefit in terms of reducing morbidity and mortality. Although laboratory and experimental evidence is favorable, clinical studies using IP in orthopedic, vascular, reconstructive, transplantation, and gastrointestinal surgery are lacking.

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IN 1986, MURRY ET AL.1 REPORTED that brief periods of myocardial ischemia could confirm resistance to subsequent ischemia in the same tissue bed. The volume of an experimentally induced myocardial infarct was 70% smaller in preconditioned hearts compared with controls. This canine experiment was quickly reproduced in other animal models and different organ systems, giving rise to the concept of ischemic preconditioning (IP).2 Despite the abundance of animal and experimental data available, IP has been slow to enter the clinical arena. This systematic review examines the evidence for and possible uses of IP in humans with reference to each major organ. A MEDLINE search was conducted using the keywords ischemic preconditioning, myocardium, liver, brain, lung, intestine, kidney, and skeletal muscle. Additional articles were obtained from reference lists of recent topical reviews. In cases where human studies are lacking, key animal and experimental data are cited to identify possible uses for IP in the surgical setting.

PRECONDITIONING THE HEART

The first clinical study of IP reported the effects of 2 sequential 90-second coronary occlusions in 19 patients undergoing elective angioplasty of the left anterior descending coronary artery.3 The second episode of ischemia caused less chest pain and ST segment elevation in all patients, and in a further analysis of 7 of those patients, myocardial lactate production was also diminished. This study was soon followed by evidence for the protective effects of IP during surgery. Yellon et al.4 showed that IP had positive effects on reducing ATP utilization by cardiomyocytes during cardiopulmonary bypass. Measuring serum troponin T levels 72 hours postoperatively in a subsequent randomized trial of 33 patients undergoing coronary artery surgery, revealed that exposure to two 3-minute periods of myocardial ischemia prior to revascularization resulted in significantly less myocardial injury.5

The clinical correlate of myocardial IP—prodromal angina—appears to have a protective effect on patients who progress to acute myocardial infarction,6,7 although on closer scrutiny, the benefits were only manifest if angina occurred

See Invited Critique at end of article
within 24 hours of infarction. Patients with angina within 24 hours of myocardial infarction had smaller infarct size, improved left ventricular function, and enhanced survival after reperfusion therapy. Preconditioning mimetics targeted at adenosine and bradykinin receptors have been used in coronary angioplasty clinical trials with encouraging results. Nicorandil, a new antianginal drug that has nitratelike vasodilator properties in addition to its effects on mitochondrial K<sub>ATP</sub> channels, has shown great promise. However, longer-term results of these interventions are necessary to fully appreciate their role in management of ischemic disease. On the other hand, IP has therapeutic limitations with diabetic and elderly patients. Furthermore, the salutary effects of an-I/R injuries were diminished after hepatic preconditioning and this protection could be enhanced by manipulation of apoptotic pathways. Translational studies by Clavien et al have given great momentum to bringing hepatic IP into the clinical arena. In 24 patients undergoing partial heptectomy under inflow occlusion, those receiving IP had a dramatic reduction in apoptotic cells in the ischemic liver bed. The IP-treated patients had half the levels of serum liver enzymes postresection. Similar results were achieved in a subsequent prospective randomized trial enrolling 100 patients. With the large sample size involved, Clavien et al were able to show that IP was particularly beneficial in younger patients (age <60 years), steatotic livers, smaller volume of resection (<50%), and longer duration of inflow occlusion (>40 minutes). Unfortunately, elderly patients did not receive the same degree of protection. A similar randomized study was carried out by Nuzzo et al on 42 patients undergoing hepatectomy. Hepatic transaminase levels were elevated postoperatively in both groups depending on the duration of operative ischemia (9 patients were subject to >60 minutes of continuous hepatic ischemia), but these levels were significantly less in the preconditioned group. Although use of IP in hepatic resectional surgery led to fewer cases of sinusoidal apoptosis and hepatocellular injury, it did not have a significant clinical effect on intensive care requirements, hospitalization, or mortality. While IP was a safe technique for use by Nuzzo et al, intermittent ischemia provided more effective protection of residual liver parenchyma and function than IP during prolonged ischemia of more than 75 minutes in a mouse model.

Organ transplantation was one of the greatest medical advancements of the 20th century, made possible because of huge strides in immunology and the development of meticulous surgical technique. Could there possibly be a role for IP in transplantation? Ischemic preconditioning of murine liver grafts before transplantation diminished oxidative stress, tumor necrosis factor α production, neutrophil recruitment, and pulmonary injury. Human liver transplant recipients from donors undergoing cardiopulmonary arrest prior to organ harvest had comparable graft survival in comparison with recipients of healthy livers. The short period of circulatory arrest, which might almost be regarded as a form of clinical IP, resulted in an overall longer organ ischemic time but did not appear to worsen the outcome of those liver transplants. In a matched-pair analysis, 40 grafts from cardiac arrest donors had similar results of liver chemistry analysis and histological results from postperfusion biopsies as nonarrest donors. Although brief preconditioning ischemia does not appear to be harmful in these retrospective studies, proper clinical trials using IP in human transplantation are needed. Perhaps IP may provide an additional dimension to the benefits observed with current methods of prolonging organ viability, such as the use of organ preservation solutions containing antioxidants, and transportation of donor organs under hypothermic conditions.

**LIVER**

The clinical importance of IP to liver surgery is 2-fold: resectional surgery, particularly cancer related, and transplantation. The topic of IP-mediated protection from hepatic ischemia/reperfusion (I/R) injury has been well studied in rodent and porcine models. Local and systemic I/R injuries were diminished after hepatic preconditioning and this protection could be enhanced by manipulation of apoptotic pathways. Translational studies by Clavien et al have given great momentum to bringing hepatic IP into the clinical arena. In 24 patients undergoing partial heptectomy under inflow occlusion, those receiving IP had a dramatic reduction in apoptotic cells in the ischemic liver bed. The IP-treated patients had half the levels of serum liver enzymes postresection. Similar results were achieved in a subsequent prospective randomized trial enrolling 100 patients. With the large sample size involved, Clavien et al were able to show that IP was particularly beneficial in younger patients (age <60 years), steatotic livers, smaller volume of resection (<50%), and longer duration of inflow occlusion (>40 minutes). Unfortunately, elderly patients did not receive the same degree of protection. A similar randomized study was carried out by Nuzzo et al on 42 patients undergoing hepatectomy. Hepatic transaminase levels were elevated postoperatively in both groups depending on the duration of operative ischemia (9 patients were subject to >60 minutes of continuous hepatic ischemia), but these levels were significantly less in the preconditioned group. Although use of IP in hepatic resectional surgery led to fewer cases of sinusoidal apoptosis and hepatocellular injury, it did not have a significant clinical effect on intensive care requirements, hospitalization, or mortality. While IP was a safe technique for use by Nuzzo et al, intermittent ischemia provided more effective protection of residual liver parenchyma and function than IP during prolonged ischemia of more than 75 minutes in a mouse model.

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**LUNG**

Reduction of neutrophil infiltration, parenchymal injury and edema in IP-protected lungs has been shown in canine, rabbit, and guinea pig models. In addition, pulmonary compliance and gas exchange was better in preconditioned lungs prior to prolonged ischemia and reperfusion in other animal studies. In a randomized trial of 20 patients undergoing pulmonec- tomy, those receiving IP by clamping of the main pulmonary artery for 10 minutes prior to resection had significantly higher levels of superoxide dismutase. In another study, 8 patients underwent isolated lung perfusion with doxorubicin intraoperatively for unresectable cancer. Although there were no mortalities in either group, patients receiving prior IP had significantly fewer cases of pulmonary edema, inflammatory cell infiltrate, focal hemorrhages, and alveolar disruption.

**BRAIN**

Both early and delayed cerebral ischemic tolerance have been demonstrated in murine models. Mitochondrial K<sub>ATP</sub> channels, an important gateway for protection from I/R injury in the heart, have also been identified in the rat brain. Ischemic preconditioning 24 hours prior to an I/R insult can decrease the degree of cerebral infarction by more than half when compared with control rats. This protection is partly owing to better perfusion of the cerebral microcirculation in preconditioned animals. The normally hypoxia-sensitive rat brain can undergo genetic reprogramming after IP to enhance survival during further ischemia. In a review of 148 patients with stroke, Weih et al suggested that a favorable outcome and poststroke independence were significantly associated with prior transient ischemic attack (TIA). In another retrospective study, Moncayo et al found that patients who sustained cerebral infarction within 1 week of a TIA had more favorable neurologic recovery. These
findings hint that a second period of cerebral ischemia is better tolerated when applied close to the preceding one, raising issues about the optimal timing of carotid endarterectomy after a TIA—should surgery be carried out within 1 week?

Two more studies from Germany have raised the possibility of brain preconditioning. Sitzer et al analyzed 332 patients with TIA preceding anterior circulation infarction. This multicenter study had a denominator of 4465 patients. A robust association was found between a preceding TIA and better outcome after stroke. Even after correction for the degree of disability on admission, preceding TIA was associated with a 1.5-fold higher probability of favorable outcome. A study by Wegener et al suggested the existence of endogenous neuroprotection in the human brain. Magnetic resonance imaging performed within 12 hours of stroke onset revealed smaller infarct volumes (associated with milder clinical deficits) in patients with a history of TIA, despite similar size and severity of the perfusion deficit.

**SKELETAL MUSCLE**

The first demonstration of the protective effect of IP in skeletal muscle was in a porcine latissimus dorsi muscle flap model. Further studies in rodent latissimus dorsi flaps and rodent and porcine hind limb muscle showed a reduction of infarct size of 44% to 62% in IP-treated animals following I/R injury. This protection extended to free myocutaneous and skin tissue transfer, increasing the area of preconditonned flaps that survived prolonged ischemia of up to 14 hours by 2 to 5 times. Not only does IP provide protection from infarction, it also maintains good skeletal muscle function. Maximum contractile force, endurance, and recovery were better in preconditioned rodent hind limb muscle subjected to prolonged ischemia. The protective effects of IP extend to both fast and slow twitch muscle fiber types. Kharbanda et al demonstrated that human skeletal muscle can be preconditioned. Ischemic preconditioning reduced endothelial dysfunction and neutrophil activation in forearms of healthy volunteers subjected to tourniquet-induced I/R injury. Similar protection was observed after remote preconditioning, when the IP stimulus was applied to the contralateral forearm.

Routine orthopedic or peripheral vascular surgery is unlikely to benefit significantly from any use of IP, as skeletal muscle is able to withstand short periods of ischemia (1-2 hours) with little clinical effect on the patient. However, prolonged ischemic times which are likely during complex thoracoabdominal aortic/mesenteric reconstructions and trauma may be rendered safer by the use of preconditioning ischemia, although applying this in the emergency situation may have practical limitations. In experimental rabbit and rodent models, IP has been shown to reduce the incidence of spinal cord infarction after prolonged aortic occlusion. Another possible use of IP is for reconstructive surgery. Kuntscher et al and Addison et al have demonstrated in rodent and porcine models that this preconditioning can be effected on the opposite limb or at a site distant from the muscle in question. A muscle flap could be raised at the same time as a tourniquet placed on the same or opposite limb with equivalent protective effect, making IP a potentially simple technique to improve outcome after microsurgical free tissue transfer.

**KIDNEY**

Murine renal morphology and function measured by glomerular filtration rate, fractional excretion of sodium and lithium, and serum analysis of urea and creatinine have all been shown to be protected by IP after I/R injury. Murine kidneys subjected to 40 minutes of ischemia have demonstrated consistently better renal excretion in the preconditioned group up to 9 days after reperfusion. A recent study suggested this protection may persist for up to 12 weeks. Unfortunately, these favorable effects have not been reproduced in the porcine model. On the other hand, human proximal tubular epithelial cells have been shown in vitro to adopt a protective phenotype to hypoxia following IP. No formal studies on human kidneys have been carried out, but the advantage of enhancing resistance to ischemia cannot be overstated, as ischemic renal failure is a serious and not uncommon complication following major surgery, with significant attendant patient morbidity and mortality.

**INTESTINE**

In murine and canine intestinal models, IP has been shown to reduce acidosis, neutrophil recruitment and oxidative stress, and to maintain villous height after I/R injury. Gastric preconditioning in rats significantly reduced the size of mucosal lesions, induced by not only prolonged ischemia but also irritants such as 100% ethanol. Prostaglandins and intrinsic neural pathways appear to play an important role in the gastroprotective effects of IP. While endogenous opioid peptides released after IP such as leuenkephalin were responsible for mediating protection from I/R injury in rat small intestine, nuclear factor κB-related adaptive mechanisms were initiated within 1 hour of preconditioning ischemia in a canine model with the response peaking at 3 hours. In a comparison of ischemic and adenosine preconditioning in a rodent jejunal flap model, both forms of preconditioning were found to be highly protective against I/R injury in terms of oxidative stress, apoptosis, and histopathological damage. These results augur well for the use of IP during intestinal free tissue transfers and transplantation.

**CAN IP MAKE THE JOURNEY FROM BENCH TO BEDSIDE?**

Ischemic preconditioning provides ischemia protection by a variety of physiological mechanisms. Energy requirements are reduced, conserving substrates and diminishing metabolism. Acid base and electrolyte homeostasis is therefore better controlled. Preconditioned tissues also demonstrate reduced oxidative stress, neutrophil activation, and cytokine production and apoptosis. However, an important observation from Murr et al in their original study, which is often overlooked, is that IP did not have any protective effect when myocardial ische-
mia was extended from 40 minutes to 3 hours. This implies that preconditioning merely allows organs to withstand marginally longer periods of ischemia than nonpreconditioned tissues. The conversion to a hypoxia-tolerant phenotype is incomplete at best. Hard objective evidence such as reduction in major morbidity and mortality after preconditioning is scarce which may be due to the lack of sizeable randomized controlled trials to date.

In most branches of surgery, specific techniques have been developed to reduce operative ischemia. In addition, the excellent anesthetic and intensive care support available today has led to a dramatic reduction of complications in most elective surgical procedures. The one subset of patients who may benefit most—those who present with acute ischemic events—unfortunately find their window of opportunity for preconditioning already closed. In this climate, it is not unexpected that IP has not revolutionized modern clinical practice as envisioned more than a decade ago. However, as Yellon et al, Clavien et al and Chen et al have shown, IP can be performed in a safe and elegant manner as an adjunct to major surgery in a variety of organ systems. As more complex operative procedures are developed, IP may still find its niche and therefore should be available to any surgeon seeking to push forward the frontiers of clinical practice.

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