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REVIEW

# Ischemic preconditioning in solid organ transplantation: from experimental to clinics

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## Summary

This study reviews the current understanding of ischemic preconditioning (IP) in experimental and clinical setting, and the mechanisms that mediate the complex processes involved as a tool to protect against ischemia and reperfusion (I/R) injury, but is not intended as a complete literature review of preconditioning. IP has been mainly elucidated in cardiac ischemia. Recent reports confirm the efficacy of pre- and postconditioning in cardiac surgery and percutaneous coronary interventions in humans. IP utilizes endogenous as well as distant mechanisms in skeletal muscle, liver, lung, kidney, intestine and brain in animal models to convey varying degrees of protection from I/R injury. Specifically, preconditioned tissues exhibit altered energy metabolism, better electrolyte homeostasis and genetic reorganization, as well as less oxygen-free radicals and activated neutrophils release, reduced apoptosis and better microcirculatory perfusion. To date, there are few human studies, but recent trials suggest that human liver, lung and skeletal muscle acquire protection after IP. Present data address the potential therapeutic application of IP in the prevention of I/R damage specially aimed at clinical transplantation. IP is ubiquitous but more research is required to fully translate these findings to the clinical arena.

## Introduction: ischemic pre- and postconditioning

Ischemic preconditioning (IP) is a well-established phenomenon that describes tissue adaptation to stress by taking profit of intrinsic defence mechanisms that confers tissues a more resistant status. IP consists of a short period of ischemia followed by reperfusion, which protects from a subsequent severe ischemia/reperfusion (I/R) insult. The protective effects of IP were initially described in the heart by Murry *et al.* in 1986 [1]. Initial IP schedules in heart were unwieldy as authors usually designed four, five or six ultra short and alternative cycles of I/R. This did the procedure barely attractive and only few groups were encouraged to exploit it or to extrapolate it to other organs. In recent years, IP schedules have been adapted to one ischemic and one reperfusion window and so, it has been subsequently evaluated with success in other organs, including the liver and the kidney [2–9].

After almost 20 years of experimental progress and standardization of IP, the ischemic postconditioning (IPo) phenomenon was defined [10,11]. Postconditioning, defined as brief periods of reperfusion alternating with re-occlusion applied during the very early minutes of reperfusion, mechanically alters the hydrodynamics of early reperfusion. However, postconditioning also stimulates endogenous mechanisms that attenuate the multiple manifestations of reperfusion injury, similarly as IP. Postconditioning in clinical setting, out of organ transplantation, arises as a more realistic procedure than preconditioning, as post event intervention seems more rational. For true IP, to be applied clinically, the therapy must be carried out prior to the prolonged episode of ischemia and, for

 

instance, a myocardial or cerebral infarction are diseases that cannot be predicted. However, IP has found a well-recognized place in cardiac surgery [12] as the exact moment that the heart is placed on bypass is known. Yellon *et al.* [13] showed that brief intermittent aortic cross-clamping prior to coronary artery bypass surgery preserved adenosine triphosphate levels of myocardial biopsy specimens. Since this original observation, several other groups have verified the finding that the human heart undergoing cardiac surgery can be preconditioned [14–17]. A recent study demonstrates for the first time that postconditioning can protect against endothelial IR injury in humans [18].

## Experimental approaches of IP to liver and kidneys

Ischemic preconditioning phenomenon and its mechanisms have been mainly studied and characterized in the heart [1,11], but it has also been described in the liver [5–7], the small intestine [19,20] and the brain [21], and less frequently in the kidney [2], indicating that it is not a mechanism restricted to the myocardium.

The first report of liver protection by IP was done in 1993 by the group of Toledo-Pereyra in a warm ischemic model [22]. Later on, several groups [4,5,23] have extensively studied the reliability of preconditioning protection in the experimental ischemic liver. In this organ, one major advance was the introduction of one ischemic and one reperfusion windows of hepatic artery and portal vein as the IP schedule [4,5,23]. In particular, 5–10 min of ischemia followed by 10–15 min of reperfusion before either warm or cold ischemia significantly improved survival and liver injury in rat and mouse experimental models.

Hepatic steatosis is a major risk factor after liver surgery because steatotic livers tolerate poorly I/R injury with the occurrence of postoperative liver failure. In addition, the use of steatotic livers for transplantation is associated with an increased risk for primary nonfunction or dysfunction after surgery. Recent studies indicate that IP is able to confer protection in steatotic livers [24,25]. Authors showed that preconditioning, through IL-10 overproduction probably mediated by nitric oxide, inhibits IL-1β release and the ensuing hepatic I/R injury in normal and steatotic livers [26]. In a model of liver transplantation with cold ischemia, IP conferred protection against hepatic damage after both steatotic and nonsteatotic liver transplantation, attenuating transaminase increase and reducing the extent of necrotic areas. Thus, IP in clinical practice should be able to improve the tolerance of both fatty livers to I/R injury in normothermic conditions, donor livers with low steatosis but with deficient postsurgical results, as well as allow the use of donor livers with severe steatosis that are presently discarded for transplantation [27].

Concerning the kidney, a report in the early 1980s focused on the late acquisition of resistance against ischemic injury through the induction of intrinsic antioxidant enzymes by a previous episode of short ischemia [28]. This is a protein-dependent mechanism similar to the late phase of preconditioning described in the heart [29]. More recently, some studies concerning early protection of renal tissue by IP have been drafted [30–32] with contradictory results. All these studies used a four-cycle preconditioning schedule similar to that classically applied in the heart [29,33]. Using an easier one-cycle schedule, our group has shown that 15 min of warm ischemia and 10 min of reperfusion in the kidney is the most suitable schedule for IP as it protects from warm ischemia throughout a local production of nitric oxide [2]. The efficacy of this simple method with only one cycle of I/R offers further advantages and brings preconditioning closer to clinical organ harvesting, both in kidney and liver.

In the 2000ths, several reports have corroborated the efficacy of IP in kidney both in early and late preconditioning windows, implicating conventional mediators as nitric oxide, superoxide dismutase or iNOS [6,34–37]. Recently, more avant-gardist and attractive mechanisms of renal protection by renal IP have been reported, connecting with cell homing. Thus, immune cells are primed after renal IP and thereby lose the capacity to cause kidney injury during a second episode of I/R [38]. Late phase of IP is associated with the mobilization of the splenic pool of endothelial progenitor cells, forcing them to accumulate in the renal medullopapillary region [39]. Finally, several chemical and pharmacological measures as cyclosporine or FK506 low doses [40], sevoflurane [41], vitamin D3 [42], ozone [43] or tin-protoporphyrin IX [44] are capable of inducing ischemic tolerance, as effective as ischemic procedures. However the most stricking maneuver is the ischemic protection by preconditioning with erythropoietin [45].

Few experimental studies have assessed the efficacy of IP against cold ischemia in renal transplantation. Our group evidenced that preconditioning improved renal function during a 7-day follow-up after transplantation of cold ischemic kidneys and, more importantly, the renal structure was also preserved [2]. Although we only used 5 h of preservation with EuroCollins, previous studies showed that it caused severe acute renal failure [46]. Later on, other authors have confirmed this but with a prolonged cold ischemia time −42 h – by using Wisconsin solution [47].

Whether IP works in large animals still remains controversial. It is now known that the occurrence of IP differs

between different species in any organ. For example, two studies, one using porcine kidneys [48] and one using dog kidneys [49], failed to identify warm or cold renal IP.

## Types and mechanisms of IP

Since initial description of IP in the heart [1], its mechanisms of action have progressively been elucidated and reviewed. Several features and pathways of the process are now clear but some elements still remain uncertain and speculative. All the – empiric – knowledge about mechanisms comes from studies on distinct organs and species and, despite assuming that they share common mechanisms, there are discrepancies in literature about differences attributed to species, tissue, and model.

From studies in myocardium, two windows of protection can be distinguished in IP: an early protective effect named classical IP and a delayed phase of resistance known as second window of protection (SWOP) also referred as delayed or late IP.

Classical or early IP protection was that described in 1986 by Murry in the heart [1]. It is transient, for about 2 h following the procedure, disappearing beyond 4 h [50–53]. This initial protective window is so potent that it has been defined as *the strongest form of in vivo* protection against myocardial ischemic injury other than early reperfusion [54]. This form of preconditioning as well as its intrinsic mechanisms of action is present in heart [1], skeletal muscle [55], intestine [56] and the kidney [2,3,57].

The SWOP was first described in 1993 by Kuzuya *et al.* [58] and Marber *et al.* [59] who discovered this delayed phase of myocardial protection. Late IP appears about 12 h after the IP stimulus, is not as powerful as the early phase and usually is long-lasting, persisting up to 72 h [60]. In the heart, both types of IP are found. In contrast, in other organs, as for instance the brain, SWOP is the sole type of IP acting [61].

For proposed physiopathological mechanisms, see Fig. 1 and Table 1. It is likely that adenosine throughout the A1 receptor, bradykinin and opioids released during the ischemia interval, interact with their respective receptors mobilizing the cell phospholipases, which induce the translocation of protein kinase C from the cytosol to the cell membrane. Protein kinase C plays an essential role in the mechanisms of protection. PKC initiates the activation of a complex kinase cascade that finally leads to the activation of mitogen-activated protein kinases (p38 MAPK and JNK).

## Local versus remote IP

Apart from local effects of IP in several organs, in 1993, Przyklenk *et al.* [96] showed that IP in one vascular bed could protect remote, virgin myocardium from

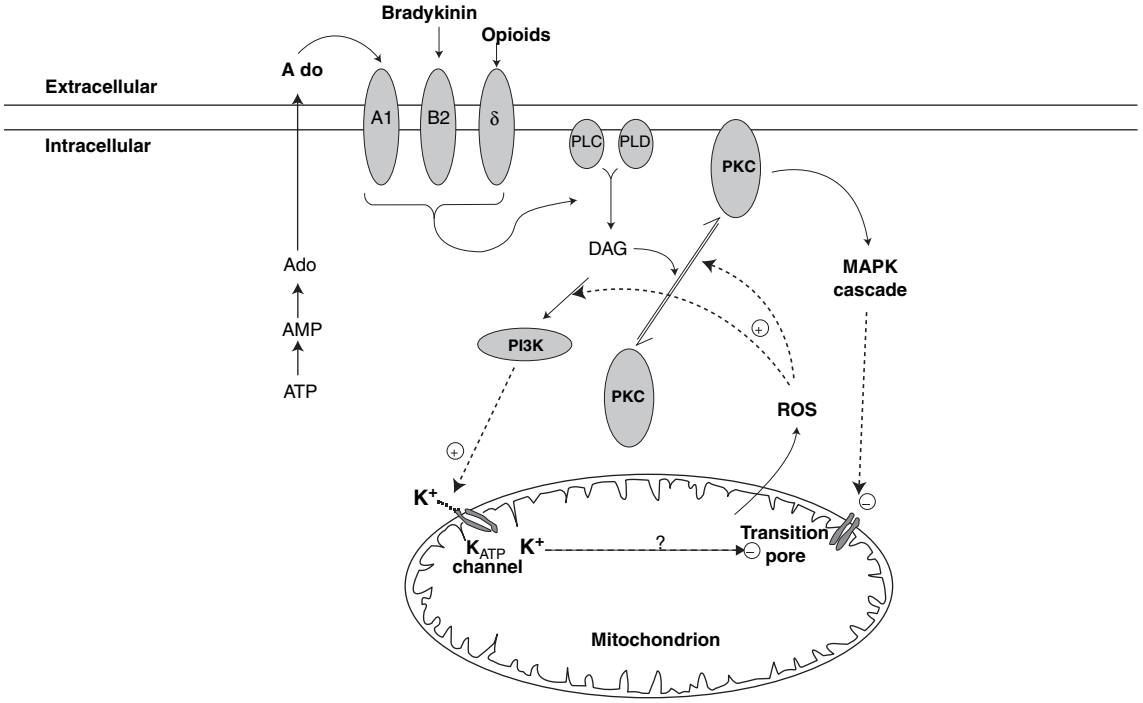


**Figure 1** Schematic representation of the proposed mechanism of classical ischemic preconditioning.

**Table 1.** Proposed mechanisms of classical and late ischemic preconditioning.

| | Classical ischemic preconditioning (IP) Specific mechanisms | Common mechanisms | Late IP or second window of protection Specific mechanisms |
|---|---|---|---|
| Triggers | | | |
| Sure | $G_i$-coupled receptors [62,63]<br>$Ca^{+2}$ influx [64]<br>Transient hyperthermia [65]<br>Transient hypoxia [66]<br>Rapid ventricular pacing [67] | Adenosine, bradikynin, opioids [81,87–91]<br>OFR [66,72–75,85,92] | Nitric oxide donors [62,66,69,92,99]<br>$K_{ATP}$ openers [66]<br>Cytokines [100]<br>TNF-α [92,100]<br>Exercise [92,101] |
| Controversial | Exogenous nitric oxide donors [68–70]<br>TNF-α [71] | Mitochondrial $K_{ATP}$ [62,70,72,73,78,81,93,94] | |
| Mediators | | | |
| Sure | $K_{ATP}$ [66,70,72–76]<br>OFR [73,77–79] | PKC [62,80,81,94–96] | Nitric oxide (eNOS early, iNOS delayed) [78,92]<br>Tyr kinases [80,95,94] |
| Controversial | Tyr kinases and JNK [80–82] | MAPKinases [79,80,81,95] | JAK-STAT [80,83,92,95,102,103]<br>AP-1, NF-kB [77,91,95,104,105] |
| Possible end-effectors | | | |
| Sure | | Mitochondrial $K_{ATP}$ [62,70,72–75,78,79,91,93] | Heat shock protein [59,90,94,106] |
| Controversial | Transition pore [83,84]<br>Na+/K+ exchanger [85,86] & Osmotic balance [62]<br>OFR [72,73,77,78]<br>Apoptosis [62] | Sarcolemma $K_{ATP}$ [70,73,74,91,97,98]<br>Heat shock protein (HSP70, HSP27), αβ-crystallin & cytoskeletal fragility [90,94] | Nitric oxide [62,94,103]<br>COX-2 [92,94] |

subsequent sustained coronary artery occlusion. This phenomenon was coined 'remote preconditioning' (RP). The protective effects of RP were also shown in the noncardiac organs including the kidney [114], intestine [115], and skeletal muscles [116].

The mechanisms of RP are not well understood [117]. It has been shown that some humoral mediators released by remote organs including bradykinin [118], adenosine [119] and opioids [120] play important roles. Kharbanda *et al.* [121] has shown that RP could prevent the reperfusion injury-induced endothelial dysfunction. Loukogeorgakis *et al.* [122] showed that RP protected against endothelial IR injury in humans via a neuronally mediated mechanism.

Several different strategies have been designed to take profit of RP, but there is no consensus on which procedure is the most desirable. Here, there are some examples. RP by infrarenal occlusion of the aorta protects the heart from infarction: a newly identified non-neuronal but PKC-dependent pathway [123]. It has been shown that RP produced by brief femoral artery occlusion could limit liver injury *in vivo* by inducing hepatic HO-1 expression [117]. Also, IP pretreatment reduced lipid peroxidation and lung injury caused by lower limb I/R [124]. Ischemic preconditioning at a distance altered the gene expression in mouse heart, kidney and lungs following brief occlusion of the mesenteric artery [125]. Systemic preconditioning by repeated hind limb ischemia protected against acute I/R injury of the lung, but not against all indices of reperfusion-associated systemic inflammation [126]. Brief ischemia in remote organs such as heart and liver protects gastric mucosa against gastric injury induced by I/R as effectively as gastric IP via mechanism involving both vagal and sensory nerves releasing vasodilatory mediators [127]. The beneficial effect of brief ischemia of liver on renal ischemia as a remote organ was confirmed by biochemical, histopathologic, and ultrastructural findings [124]. Finally, protection against ischemic kidney injury is afforded by 24 h of ureteral obstruction applied 6 or 8 days prior to ischemia [128].

A first clinical application in humans has been reported. In a randomized-controlled trial, the effects of remote IP on children undergoing cardiac surgery demonstrated the myocardial protective effects using a noninvasive technique of four 5-min cycles of lower limb I/R on common femoral artery [12].

## Preconditioning the human liver in transplantation

To date, studies on the effect of IP in liver of large-size animals (e.g. pigs) are less numerous and with more contrasting results than in rodents [129–131], but IP is mature enough to be assessed in humans. However, when evaluating efficacy of any protective measure, dissimilar endpoints are monitored. In experimental fields, researchers

usually assess well-controled injuries, always occurring on safety organs. In human transplantation, technical procedure is highly accurate and everything aims to achieve first-rate results. Thus, regular liver transplantation usually undergoes excellent outcomes, hard to ameliorate. Over 5% of liver allografts experience primary graft dysfunction following transplantation and this rate is expected to rise further because of the ever-increasing use of sub-optimal organs. I/R is the main mediator of allograft damage and contributes considerably to the development of primary graft dysfunction [132]. To our knowledge, very few studies have evaluated IP in clinical setting and only in optimal grafts.

The clinical efficacy of IP (by transient portal triad clamping) has been assessed in patients undergoing major hepatectomy [133,134]. These studies showed that IP patients suffered from less postoperative liver and endothelial cell injury but failed to demonstrate any advantage over the respective control groups in terms of postoperative liver function, morbidity, or mortality rate. In addition, the protective effect of preconditioning on ischemia–reperfusion injury was lost for the patients that *a priori* need it most, namely, those >60 years and those with liver steatosis [134].

Recently, a pilot study was performed to evaluate the effects of IP in orthotopic liver transplantation by comparing the outcomes of recipients of grafts from deceased donors randomly assigned to receive or not IP. Although hepatocellular necrosis was lower in the IP group versus the nonconditioning group on early postoperative days, bilirubin levels, prothrombin activity, iNOS expression, neutrophil infiltration, and apoptosis were not different. Importantly, incidence of graft nonfunction and graft and patient survival rates were similar between groups, suggesting that IP had no clinical benefits [135].

Another pilot study was simultaneously reported [136]. Authors evaluated nine IP cadaver livers prior to retrieval versus 14 control transplantations, using optimal donors and nonmarginal recipients. The selected procedure was performed by Pringle's maneuver (occlusion of porta hepatis) for 10 min, using a tourniquet technique. Reperfusion prior to cold preservation lasted for 30 min. Again, hepatocellular necrosis was lower in the IP group following transplantation. Furthermore, recipients of IP livers spent a significantly shorter time in mechanical ventilation or in the intensive care unit following transplantation compared with those nonpreconditioned allografts. To comprehend this, authors refer to the hypothesis from Peralta *et al.* [5] who showed that liver IP prevented remote events caused by the release of TNF-$\alpha$ after liver I/R that causes neutrophil infiltration in rat lungs. None of the IP allografts showed any tissue staining of platelet or neutrophil infiltration compared with diverse degree in nonpreconditioning allografts. Authors conclude that IP is a simple and effective method to protect cadaver donor allografts from cold ischemia and subsequent reperfusion injury and results in better graft function after transplantation.

A previous study by Koneru *et al.* in 2005 [137] showed no effects of IP on cadaver donor livers compared with controls. However, the study consisted of clamping the hepatic vessels for a period of 5 min, and, as the authors concluded, that may be insufficient to obtain beneficial effect from IP. Animal models [5–7] and human studies [94,96] have demonstrated that 10 min of vascular clamping is the ideal time to obtain an effective IP protection.

Finally, the group of Bismuth [138] found contradictory results in the first clinical application of IP in the liver and so, they referred IP in liver transplantation as the ying and the yang. In terms of hepatocellular necrosis, they concluded a protective effect of I/R. However IP was the only factor significantly associated with initial poor function a factor that compromises late success of liver transplantation. Surprisingly, it had no deleterious consequences on patient or graft survival rates. They concluded that IP, as performed via 10 min of warm ischemia, did neither improve nor compromise the outcome of cadaver liver transplantation.

## Preconditioning the human kidney in transplantation: present and perspectives

As far as we know, no studies on human IP renal protection have been reported. This is a rather surprising fact. Contrarily to liver transplantation, in kidney grafting, the rate of primary nonfunction is clearly high, within 20–30% depending on groups [139]. It is generally believed that hemodialysis easily controls this problem and that these patients are not at vital risk. However, clinical and experimental evidences support that I/R unchains a local inflammatory reaction [140,141], which conditions the onset and progression of chronic allograft nephropathy. So, in our group using a Fischer-to-Lewis model of kidney transplant, we found that ischemia added to the allogeneic background resulted in significant inflammatory injury, clearly activating and accelerating the cellular mechanisms involved in this process [141]. Introducing modifications to the immunosuppressive treatment, we showed that regimes incorporating rapamycin suppressed the inflammatory T-cell-mediated acute cellular changes associated with renal ischemic injury, improved long-term outcome, and attenuated chronic allograft nephropathy [142]. As IP has been proved to attenuate inflammatory response both in human liver transplantation [136] and experimental models [5,36–38], it is therefore reasonable

that preconditioning in human kidney should protect similarly this inflammatory response.

Apart from the surgical procedures for IP, erythropoietin preconditioning has shown striking data, mimicking ishemic preconditioning. In its autocrine–paracrine roles, EPO mediates preconditioning tolerance and specifically limits the destructive potential of TNF-$\alpha$ and other pro-inflammatory cytokines in the brain, heart, kidney, and other tissues [45,143]. As local production of EPO is generally suppressed following injury, administration of exogenous EPO has been proved to be a successful therapeutic approach in preclinical and clinical studies, for example, following ischemia–reperfusion and toxin-induced injuries, and in human stroke [143,144]. The therapeutic time window of tissue protection by EPO is typically wide enough in experimental models, showing effectiveness when administered before, during, or after an insult and raising optimism for a high clinical potential. Pretreatment by EPO or its tissue-protective analogs provide significant protection in some tissues, for example, the heart, in which exposure either immediately (<1 h; activating acute preconditioning) or 24 h before (triggering delayed preconditioning) reduced subsequent ischemic–reperfusion injury [145]. EPO has been shown effective in attenuating also renal ischemia/reperfusion injury, and thus it may have several clinical applications, such as assisting in transplantation and in the treatment of renal injuries. Furthermore, EPO might also participate in the protective effects of IP in the kidney [146].

The surgical IP protocol appears to be feasible and safe by an expert surgeon and EPO has been safety used since more than 15 years ago in dialysis patients and in hemopoietic rescue in chemotherapy. Thus, either of the two maneuvers is mature enough to be evaluated in kidney transplantation in prospective randomized-blinded clinical trials. Furthermore, as IP is not easily applicable in vital organ surgery since for the first, the margin of safety of target organ might be damped; and the second, the time consumed to induce the preconditioning effect in the operation theater must be considered. Thus, using RP procedures, as for instance transient limb ischemia–reperfusion, seems more applicable for therapeutic advantages for it is safe and it could be a scheduled procedure before the surgery.

Heat shock proteins (HSP27, $\alpha\beta$ crystalin) that control the polymerization of actin filaments thus influencing the integrity of cytoskeleton are in turn activated by MAP kinases, which furthermore are somehow connected with potassium ATP channels ($K_{ATP}$). These channels are located in the inner membrane of both mitochondria and sarcolemma. Although the consensus about the role of sarc$K_{ATP}$ channels in IP protection is still controversial, that of mito$K_{ATP}$ is on the increase. There are different mediators released during ischemia as nitric oxide and signal transduction elements, as NF-kB which in spite of the fact that they are not completely allocated in the IP's protection pathway, are known to converge in the mitochondria. It is likely that the opening of mito$K_{ATP}$ channels protects from ischemia–reperfusion injury and apoptosis by regulating the mitochondrial K+ influx, reducing mitochondrial Ca++ overload and increasing ATP synthesis. Moreover, the opening of the mito$K_{ATP}$ channels generates oxygen-free radicals that again activates the survival kinases. This fact could account for the lapse between the IP event and SWOP, allowing for the possibility of new protein synthesis, post-translational modification and change in the compartmentalization of existing proteins [5,21,32,62–64,70,74–76,81,82,90–92,95,106–113].

Both, early and late IP, have distinct underlying mechanisms but share common physiopathological elements, classified as triggers, mediators and end-effectors. The IP signaling pathway begins with a trigger signal that induces physiological changes that provide tissue resistance to subsequent lethal ischemia. End-effectors are those causing the protection during lethal ischemia. All factors contributing to the signal transduction pathway between the trigger signal and the end-effector are classified as 'triggers' or 'mediators' depending on whether they exert their action respectively before or after the lethal ischemic insult. Some of those factors have been well established while others remain controversial.

Second window of protection can be stimulated by nonpharmacological stimuli as ischemia, heat stress, exercise,… as well as by pharmacological stimuli as adenosine receptor agonists, nitric oxide donors, cytokines,… Although sharing the same triggers as classical IP, what distinct SWOP triggers is their relative importance, being adenosine, opioids agonists, nitric oxide and OFR those maintaining the major significance. As in early IP, PKC activation is a key mediator of late IP as it seems that all the triggering signals, from either classical IP or SWOP, converge in this central kinase. Downstream of PKC, the role of survival kinases in late IP remains unsolved, although tyrosine kinases, MAP kinases, the JAK-STAT pathway through its activation of nuclear transcription factors (NF-kB), and the cAMP–PKA pathway have been implicated [62,63,73,81,82,94,5,103,105].

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## References


1. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 1986; **74**: 1124.
2. Torras J, Herrero-Fresneda I, Lloberas N, Riera M, Cruzado J, Grinyo J. Promising effects of ischemic preconditioning in renal transplantation. *Kidney Int* 2002; **61**: 2218.
3. Riera M, Herrero I, Torras J, *et al.* Ischemic preconditioning improves postischemic acute renal failure. *Transplant Proc* 1999; **31**: 2346.
4. Yin DP, Sankary HN, Chong AS, *et al.* Protective effect of ischemic preconditioning on liver preservation-reperfusion injury in rats. *Transplantation* 1998; **66**: 152.
5. Peralta C, Hotter G, Closa D, Gelpi E, Bulbena O, Rosello-Catafau J. Protective effect of preconditioning on the injury associated to hepatic ischemia-reperfusion in the rat: role of nitric oxide and adenosine. *Hepatology* 1997; **25**: 934.
6. Sindram D, Rudiger HA, Upadhya AG, *et al.* Ischemic preconditioning protects against cold ischemic injury through an oxidative stress dependent mechanism. *J Hepatol* 2002; **36**: 78.
7. Teoh N, Dela Pena A, Farrell G. Hepatic ischemic preconditioning in mice is associated with activation of NF-kappaB, p38 kinase, and cell cycle entry. *Hepatology* 2002; **36**: 94.
8. Arai M, Thurman RG, Lemasters J. Ischemic preconditioning of rat livers against cold storage-reperfusion injury: role of nonparenchymal cells and the phenomenon of heterologous preconditioning. *Liver Transpl* 2001; **7**: 292.
9. Hasegawa T, Malle E, Farhood A, Jaeschke H. Generation of hypochlorite-modified proteins by neutrophils during ischemia-reperfusion injury in rat liver: attenuation by ischemic preconditioning. *Am J Physiol Gastrointest Liver Physiol* 2005; **289**: G760. Epub 2005 Jun 30.
10. Zhao ZQ, Vinten-Johansen J. Postconditioning: reduction of reperfusion-induced injury J. *Cardiovasc Res* 2006; **70**: 200.
11. Zhao Z-Q, Corvera JS, Halkos ME, *et al.* Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. *Am J Physiol (Heart Circ Physiol)* 2003; **285**: 579.
12. Cheung MM, Kharbanda RK, Konstantinov IE, *et al.* Randomized controlled trial of the effects of remote ischemic preconditioning on children undergoing cardiac surgery: first clinical application in humans. *J Am Coll Cardiol* 2006; **47**: 2277. Epub 2006 May 15.
13. Yellon DM, Alkhulaifi AM, Pugsley WB. Preconditioning the human myocardium. *Lancet* 1993; **342**: 276.
14. Kloner R, Rezkalla SH. Preconditioning, postconditioning and their application to clinical cardiology. *Cardiovasc Res* 2006; **70**: 297.
15. Doi Y, Watanabe G, Kotoh K, Ueyama K, Misaki T. Myocardial ischemic preconditioning during minimally invasive direct coronary artery bypass grafting attenuates ischemia-induced electrophysiological changes in human ventricle. *Jpn J Thorac Cardiovasc Surg* 2003; **51**: 144.
16. Teoh LK, Grant R, Hulf JA, Pugsley WB, Yellon DM. The effect of preconditioning (ischemic and pharmacological) on myocardial necrosis following coronary artery bypass graft surgery. *Cardiovasc Res* 2002; **53**: 175.
17. Lu EX, Chen SX, Yuan MD, *et al.* Preconditioning improves myocardial preservation in patients undergoing open heart operations. *Ann Thorac Surg* 1997; **64**: 1320.
18. Loukogeorgakis SP, Panagiotidou A, Yellon D, Deanfield J, MacAllister R. Postconditioning protects against endothelial ischemia-reperfusion injury in the human forearm. *Circulation* 2006; **113**: 1015.
19. Osborne DL, Aw TY, Cepinskas G, Kvietys PR. Development of ischemia/reperfusion tolerance in the rat small intestine. An epithelium-independent event. *J Clin Invest* 1994; **94**: 1910.
20. Hotter G, Closa D, Prados M, *et al.* Intestinal preconditioning is mediated by a transient increase in nitric oxide. *Biochem Biophys Res Commun* 1996; **222**: 27.
21. Heurteaux C, Lauritzen I, Widmann C, Lazdunski M. Essential role of adenosine, adenosine A1 receptors, and ATP-sensitive $K^+$ channels in cerebral ischemic preconditioning. *Pharmacology* 1996; **92**: 4666.
22. Lloris-Carsi JM, Cejalvo D, Toledo-Pereyra LH, Calvo MA, Suzuki S. Preconditioning: effect upon lesion modulation in warm liver ischemia. *Transplant Proc* 1993; **25**: 3303.
23. Yadav SS, Sindram D, Perry DK, Clavien PA. Ischemic preconditioning protects the mouse liver by inhibition of apoptosis through a caspase-dependent pathway. *Hepatology* 1999; **30**: 1223.
24. Serafiin A, Rosello-Catafau J, Prats N, Xaus C, Gelpı E, Peralta C. Ischemic preconditioning increases the tolerance of fatty liver to hepatic ischemia-reperfusion injury in the rat. *Am J Pathol* 2002; **16**: 2.
25. Yamagami K, Yamamoto Y, Kume M, *et al.* Heat shock preconditioning ameliorates liver injury following normothermic ischemia-reperfusion in steatotic rat livers. *J Surg Res* 1998; **79**: 47.
26. Serafin A, Rosello-Catafau J, Prats N, Gelpi E, Rodes J, Peralta C. Ischemic preconditioning affects interleukin release in fatty livers of rats undergoing ischemia/reperfusion. *Hepatology* 2004; **39**: 688.
27. Fernandez L, Carrasco-Chaumel E, Serafin A, *et al.* Is ischemic preconditioning a useful strategy in steatotic liver transplantation? *Am J Transplant* 2004; **4**: 888.
28. Yoshioka T, Bills T, Moore-Jarret T, *et al.* Role of intrinsic antioxidant enzymes in renal oxidant injury. *Kidney Int* 1990; **38**: 282.
29. Bolli R. The late phase of preconditioning. *Circ Res* 2000; **87**: 972.


 

30. Islam C, Mathie R, Dinneeen MD, *et al.* Ischemia-reperfusion injury in the kidney; the effect of preconditioning. *BJU Int* 1997; **79**: 842.
31. Jefayri MK, Grace PA, Mathie RT. Attenuation of reperfusion injury by renal ischemic preconditioning: the role of nitric oxide. *BJU Int* 2000; **85**: 1007.
32. Lee HT, Emala CW. Protective effects of renal ischemic preconditioning and adenosine pretreatment: role of $A_1$ and $A_3$ receptors. *Am J Physiol (Renal Physiol)* 2000; **278**: F380.
33. Bolli R, Manchikalapudi S, Tang XL, *et al.* The protective effect of late preconditioning against myocardial stunning in conscious rabbits is mediated by nitric oxide synthase. *Circ Res* 1997; **81**: 1094.
34. Chien CT, Hsu SM, Chen CF, Lee PH, Lai MK. Hypoxic preconditioning reduces ischemia/reperfusion-induced apoptosis cell death in rat kidney. *Transplant Proc* 2000; **32**: 1653.
35. Yamasowa H, Shimizu S, Inoue T, Takaoka M, Matsumura Y. Endothelial nitric oxide contributes to the renal protective effects of ischemic preconditioning. *J Pharmacol Exp Ther* 2005; **312**: 153.
36. Chen CF, Tsai SY, Ma MC, Wu MS. Hypoxic preconditioning enhances renal superoxide dismutase levels in rats. *J Physiol* 2003; **552**: 561.
37. Park KM, Byun JY, Kramers C, Kim JI, Huang PL, Bonventre JV. Inducible nitric-oxide synthase is an important contributor to prolonged protective effects of ischemic preconditioning in the mouse kidney. *J Biol Chem* 2003; **278**: 27256.
38. Burne-Taney MJ, Liu M, Baldwin WM, Racusen L, Rabb H. Decreased capacity of immune cells to cause tissue injury mediates kidney ischemic preconditioning. *J Immunol* 2006; **176**: 7015.
39. Patschan D, Krupincza K, Patschan S, Zhang Z, Hamby C, Goligorsky MS. Dynamics of mobilization and homing of endothelial progenitor cells after acute renal ischemia: modulation by ischemic preconditioning. *Am J Physiol Renal Physiol* 2006; **291**: F176. Epub 2006 Feb 14.
40. Yang CW, Ahn HJ, Jung JY, *et al.* Preconditioning with cyclosporine A or FK506 differentially regulates mitogen-activated protein kinase expression in rat kidneys with ischemia/reperfusion injury. *Transplantation* 2003; **75**: 20.
41. Obal D, Dettwiler S, Favoccia C, Rascher K, Preckel B, Schlack W. Effect of sevoflurane preconditioning on ischaemia/reperfusion injury in the rat kidney *in vivo*. *Eur J Anaesthesiol* 2006; **23**: 319.
42. Kim YO, Li C, Sun BK, *et al.* Preconditioning with 1,25-dihydroxyvitamin D3 protects against subsequent ischemia-reperfusion injury in the rat kidney. *Nephron Exp Nephrol* 2005; **100**: e85. Epub 2005 Mar 17.
43. Barber E, Menendez S, Leon OS, *et al.* Prevention of renal injury after induction of ozone tolerance in rats submitted to warm ischaemia. *Mediators Inflamm* 1999; **8**: 37.
44. Kaizu T, Tamaki T, Tanaka M, Uchida Y, *et al.* Preconditioning with tin-protoporphyrin IX attenuates ischemia/reperfusion injury in the rat kidney. *Kidney Int* 2003; **63**: 1393.
45. Yang CW, Li C, Jung JY, *et al.* Preconditioning with erythropoietin protects against subsequent ischemia-reperfusion injury in rat kidney. *FASEB J* 2003; **17**: 1754.
46. Herrero I, Torras J, Riera M, *et al.* Prevention of cold ischemia-reperfusion injury by an endothelin receptor antagonist in experimental renal transplantation. *Nephrol Dial Transplant* 1999; **14**: 872.
47. Fuller TF, Freise CE, Feng S, Niemann CU. Ischemic preconditioning improves rat kidney graft function after severe ischemia/reperfusion injury. *Transplant Proc* 2005; **37**: 377.
48. Arend LJ, Thompson CI, Spielman WS. Dypiramidol decreases glomerular filtration in the sodium-depleted dog: evidence for mediation by intrarenal adenosine. *Circ Res* 1985; **56**: 242.
49. Kosieradzki M, Ametani M, Southard JH, *et al.* Is ischemic preconditioning of the kidney clinically relevant? *Surgery* 2003; **133**: 81.
50. Murry CE, Richard VJ, Jennings RB, Reimer KA. Myocardial protection is lost before contractile function recovers from ischemic preconditioning. *Am J Physiol Heart Circ Physiol* 1991; **260**: II796.
51. Sack S, Mohri M, Arras M, Schwarz ER, Schaper W. Ischemic preconditioning: time course of renewal in the pig. *Cardiovasc Res* 1993; **27**: 551.
52. Van Winkle DM, Thornton JD, Downey DM, Downey JM. The natural history of preconditioning: cardioprotection depends on duration of transient ischemia and time to subsequent ischemia. *Coronary Artery Dis* 1991; **2**: 613.
53. Burckhartt B, Yang X-M, Tsuchida A, Mullane KM, Downey JM, Cohen MV. Acadesine extends the window of protection afforded by ischaemic preconditioning in conscious rabbits. *Cardiovasc Res* 1995; **29**: 653.
54. Kloner RA, Bolli R, Marban E, Reinlib L, Braunwald E. Medical and cellular implications of stunning, hibernation and preconditioning: an NHLBI workshop. *Circulation* 1998; **97**: 1848.
55. Pang CY, Yang RZ, Zhong A, Xu N, Boyd B, Forrest CR. Acute ischaemic preconditioning protects against skeletal muscle infarction in the pig. *Cardiovasc Res* 1995; **29**: 782.
56. Ishida T, Yarimizu K, Gute DC, Korthuis RJ. Mechanisms of ischemic preconditioning. *Shock* 1997; **8**: 86.
57. Bonventre JV. Kidney ischemic preconditioning. *Curr Opin Nephrol Hypertens* 2002; **11**: 43.
58. Kuzuya T, Hoshida S, Yamashita N, *et al.* Delayed effects of sublethal ischemia on the acquisition of tolerance to ischemia. *Circ Res* 1993; **72**: 1293.
59. Marber MS, Latchman DS, Walker JM, Yellon DM. Cardiac stress protein elevation 24 hours after brief ischemia or heat stress is associated with resistance to myocardial infarction. *Circulation* 1993; **88**: 1264.

60. Baxter GF, Goma FM, Yellon DM. Characterisation of the infarct-limiting effect of delayed preconditioning: time course and dose-dependency studies in rabbit myocardium. *Basic Res Cardiol* 1997; **92**: 159.
61. Kirino T. Ischemic tolerance. *J Cereb Blood Flow Metab* 2002; **22**: 1283–1296.
62. Yellon DM, Downey JM. Preconditioning the myocardium: from cellular physiology to clinical cardiology. *Physiol Rev* 2003; **83**: 1113.
63. Goto M, Liu Y, Yang X-M, Ardell JL, Cohen MV, Downey JM. Role of bradykinin in protection of ischemic preconditioning in rabbit hearts. *Circ. Res* 1995; **77**: 611.
64. Miyawaki H, Ashraf M. Ca2+ as a mediator of ischemic preconditioning. *Circ Res* 1997; **80**: 790.
65. Yamashita N, Hoshida S, Taniguchi N, Kuzuya T, Hori M. Whole-body hyperthermia provides biphasic cardioprotection against ischemia/reperfusion injury in the rat. *Circulation* 1998; **98**: 1414.
66. Kolar ÁŘ, Ostadal B. Molecular mechanisms of cardiac protection by adaptation to chronic hypoxia physiol. *Res* 2004; **53**: S3.
67. Koning MMG, Gho BCG, Vanklaarwater E, Opstal RLJ, Duncker DJ, Verdouw PD. Rapid ventricular pacing produces myocardial protection by nonischemic activation of KATP_channels. *Circulation* 1996; **93**: 178.
68. Liu P, Hock CE, Nageler R, Wong PY. Formation of nitric oxide, superoxide, and peroxynitrite in myocardial ischemic–reperfusion injury in rats. *Am J Physiol* 1997; **272**: H2327.
69. Nakano A, Liu GS, Heusch G, Downey JM, Cohen MV. Exogenous nitric oxide can trigger a preconditioned state through a free radical mechanism, but endogenous nitric oxide is not a trigger of classical ischemic preconditioning. *J Mol Cell Cardiol* 2000; **32**: 1159.
70. Wang Y, Haider HK, Ahmad N, Ashraf M. Mechanisms by which KATP channel openers produce acute and delayed cardioprotection. *Vasc Pharm* 2005; **42**: 253.
71. Lecour S, Suleman N, Deuchar GA, *et al.* Pharmacological preconditioning with tumor necrosis factor-α activates signal transducer and activator of transcription-3 at reperfusion without involving classic prosurvival kinases (Akt and extracellular signal-regulated kinase). *Circulation* 2005; **112**: 3911.
72. Oldenburg O, Cohen MV, Yellon DM, Downey JM. Mitochondrial K channels: role in cardioprotection ATP. *Cardiovasc Res* 2002; **55**: 429.
73. Garlida KD, Dos Santos P, Xiec ZJ, Costa AD, Pauceka P. Mitochondrial potassium transport: the role of the mitochondrial ATP-sensitive K+ channel in cardiac function and cardioprotection. *Biochim Biophys Acta* 2003; **1606**: 1.
74. Suzuki M, Sasaki N, Miki T, *et al.* Role of sarcolemmal KATP channels in cardioprotection against ischemia/reperfusion injury in mice. *J Clin Invest* 2002; **109**: 509.
75. Wang L, Cherednichenko G, Hernandez L, *et al.* Preconditioning limits mitochondrial Ca2+ during ischemia in rat hearts: role of KATP channels. *Am J Physiol Heart Circ Physiol* 2001; **280**: H2321.
76. Herrero I, Torras J, Bover J, *et al.* Effect of ETA/ETB receptor antagonist administration on iNOS gene expression in a rat renal transplantation model. *Transplant Proc* 1999; **31**: 2344.
77. Das DK, Maulik N. Preconditioning potentiates redox signaling and converts death signal into survival signal. *Arch Biochem Biophys* 2003; **420**: 305.
78. Otani H. Reactive oxygen species as mediators of signal transduction in ischemic preconditioning, antioxidants & redox signaling. *Antioxid Redox Signal* 2004; **6**: 250.
79. Knight RJ, Buxton DB. Stimulation of c-Jun kinase and mitogenactivated protein kinase by ischemia and reperfusion in the perfused rat heart. *Biochem Biophys Res Commun* 196; **218**: 83.
80. Amstrong SC. Protein kinase activation and myocardial ischemia/reperfusion injury. *Cardiovasc Res* 2004; **61**: 427.
81. Cohen MV, Baines CP, Downey JM. Ischemic preconditioning: from adenosine receptor to $K_{ATP}$ channel. *Annu Rev Physiol* 2000; **109**: 62.
82. Miki T, Cohen MV, Downey JM. Opioid receptor contributes to ischemic preconditioning through protein kinase C activation in rabbits. *Mol Cell Biochem* 1998; **186**: 3.
83. Hausenloy DJ, Maddock HL, Baxter GF, Yellon DM. Inhibiting mitochondrial permeability transition pore opening: a new paradigm in myocardial preconditioning. *Cardiovasc Res* 2002; **55**: 534.
84. Dos Santos P, Kowaltowski AJ, Laclau MN, *et al.* Mechanisms by which opening the mitochondrial ATP-sensitive K(+) channel protects the ischemic heart. *Am J Physiol Heart Circ Physiol* 2002; **283**: H284.
85. Xiao X-H, Allen DG. Activity of the Na+/H+ exchanger is critical to reperfusion damage and preconditioning in the isolated rat heart. *Cardiovasc Res* 2000; **48**: 244.
86. Kandasamy RA, Yu FH, Harris R, Boucher A, Hanrahan JW, Orlowski J. Plasma membrane Na_/H_ exchanger isoforms (NHE-1, −2, and −3) are differentially responsive to second messenger agonists of the protein kinase A and C pathways. *J Biol Chem* 1995; **270**: 29209.
87. Gross GJ. Role of opioids in acute and delayed preconditioning. *J Mol Cell Cardiol* 2003; **35**: 709.
88. Headrick JP. Ischemic preconditioning: bioenergetic and metabolic changes and the role of endogenous adenosine. *J Mol Cell Cardiol* 1996; **28**: 1227.
89. Schultz JEJ, Hsu AK, Gross GJ. Morphine mimics the cardioprotective effect of ischemic preconditioning via a glibenclamide-sensitive mechanism in the rat heart. *Circ Res* 1996; **78**: 1100.
90. Dana A, Skarli M, Papakrivopoulou J, Yellon DM. Adenosine A1 receptor induced delayed preconditioning in rabbits: induction of p38 mitogen-activated protein kinase activation and Hsp27 phosphorylation via a tyrosine kinase- and protein kinase C-dependent mechanism. *Circ Res* 2000; **86**: 989.

91. Fryer RM, Hsu AK, Nagase H, Gross GJ. Opioid-sensitive cardioprotection against myocardial infarction and arrhythmias: mitochondrial versus sarcolemmal ATP-sensitive potassium channels. *J Pharmacol Exp Ther* 2000; **294**: 451.
92. Adam B, Stein MD, Tang X-L, *et al.* Delayed adaptation of the heart to stress. Late Preconditioning *Stroke* 2004; **35**: 2676.
93. Vetter SY, Elsässer A, Tutdibi O, *et al.* Brief antecedent anoxia preserves mitochondrial function after sustained undersupply: a subcellular correlate to ischemic preconditioning. *Mol Cell Biochem* 2006; **285**: 191.
94. Baines CP, Pass JM, Ping P. Protein kinases and kinase-modulated effectors in the late phase of ischemic preconditioning. *Basic Res Cardiol* 2001; **96**: 207.
95. Hausenloy DJ, Yellon DM. Survival kinases in ischemic preconditioning and postconditioning. *Cardiovasc Res* 2006; **70**: 240.
96. Przyklenk K, Bauer B, Ovize M, *et al.* Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation* 1993; **87**: 893.
97. Gumina RJ, Pucar D, Bast P, *et al.* Knockout of Kir6.2 negates ischemic preconditioning-induced protection of myocardial energetics. *Am J Physiol Heart Circ Physiol* 2003; **284**: H2106.
98. Ghosh S, Standen NB, Galinanes M. Evidence for mitochondrial KATP channels as effectors of human myocardial preconditioning. *Cardiovasc Res* 2000; **45**: 934.
99. Guo Y, Jones WK, Xuan YT, *et al.* The late phase of ischemic preconditioning is abrogated by targeted disruption of the inducible NO synthase gene. *Proc Natl Acad Sci USA* 1999; **96**: 10953.
100. Smith RM, Lecour S, Sack MN. Innate immunity and cardiac preconditioning: a putative intrinsic cardioprotective program. *Cardiovasc Res* 2002; **55**: 474.
101. Yamashita N, Hoshida S, Otsu K, Asahi M, Kuzuya T, Hori M. Exercise provides direct biphasic cardioprotection via manganese superoxide dismutase activation. *J Exp Med* 1999; **189**: 1699.
102. Ananthakrishnan AR, Hallam K, Li Q, Ramasamy R. JAK-STAT pathway in cardiac ischemic stress. *Vascul Pharmacol* 2005; **43**: 353.
103. Bolli R, Dawn B, Xuan YT. Role of the JAK–STAT pathway in protection against myocardial ischemia/reperfusion injury trends. *Cardiovasc Med* 2003; **13**: 72.
104. Xuan YT, Guo Y, Han H, Zhu Y, Bolli R. An essential role of the jak-stat pathway in ischemic preconditioning. *Proc Natl Acad Sci USA* 2001; **98**: 9050.
105. Li XC, Ma YF, Wang XH. Role of NF-_B as effector of IPC in donor livers before liver transplantation in rats. *Transplant Proc* 2006; **38**: 1584.
106. Guay J, Lambert H, Gingras-Breton G, Lavoie JN, Huot J, Landry J. Regulation of actin filament dynamics by p38 map kinase-mediated phosphorylation of heat shock protein 27. *J Cell Sci* 1997; **110**: 357.
107. Thornton JD, Liu GS, Olsson RA, Downey JM. Intravenous pre-treatment with A1-selective adenosine analogues protects the heart against infarction. *Circulation* 1992; **85**: 659.
108. Kaiser RA, Liang Q, Bueno OF, *et al.* Genetic inhibition or activation of JNK1/2 each protect the myocardium from ischemia– reperfusion-induced cell death *in vivo*. *J Biol Chem* 2005; **23**: 32602.
109. Samavati L, Monick MM, Sanlioglu S, Buettner GR, Oberley LW, Hunninghake GW. Mitochondrial K(ATP) channel openers activate the ERK kinase by an oxidant-dependent mechanism. *Am J Physiol Cell Physiol* 2002; **283**: C273.
110. Eaton P, Awad WI, Miller JIA, Hearse DJ, Shattock MJ. Ischemic preconditioning: a potential role for constitutive low molecular weight stress protein translocation and phosphorylation? *J Mol Cell Cardiol* 2000; **32**: 961.
111. Garlid KD, Paucek P, Yarov-Yarovoy V, Sun X, Schindler PA. The mitochondrial KATP channel as a receptor for potassium channel openers. *J Biol Chem* 1996; **271**: 8769.
112. Kowaltowski AJ, Seetharaman S, Paucek P, Garlid KD. Bioenergetic consequences of opening the ATP-sensitive K+ channel of heart mitochondria. *Am J Physiol Heart Circ Physiol* 2001; **280**: H649.
113. Pain T, Yang XM, Critz SD, *et al.* Opening of mitochondrial K(ATP) channels triggers the preconditioned state by generating free radicals. *Circ Res* 2000; **87**: 460.
114. Ates E, Genc E, Erkasap N, *et al.* Renal protection by brief liver ischemia in rats. *Transplantation* 2002; **74**: 1247.
115. Gho BC, Schoemaker RG, van den Doel MA, *et al.* Myocardial protection by brief ischemia in noncardiac tissue. *Circulation* 1996; **94**: 2193.
116. Addison PD, Neligan PC, Ashrafpour H, *et al.* Noninvasive remote ischemic preconditioning for global protection of skeletal muscle against infarction. *Am J Physiol Heart Circ Physiol* 2003; **285**: H1435.
117. Lai IR, Chang KJ, Chen CF, Tsai HW. Transient limb ischemia induces remote preconditioning in liver among rats: the protective role of heme oxygenase-1. *Transplantation* 2006; **81**: 1311.
118. Shoemaker RG, Van Heijningen CL. Bradykinin mediates cardiac preconditioning at a distance. *Am J Physiol* 2000; **278**: H1571.
119. Liem DA, Verdouw PD, Ploeg H, *et al.* Sites of action of adenosine in interorgan preconditioning of the heart. *Am J Physiol* 2002; **283**: H29.
120. Patel HH, Moore J, Hsu AK, Gross GJ. Cardioprotection at a distance: mesenteric artery occlusion protects the myocardium via an opioid sensitive mechanism. *J Mol Cell Cardiol* 2002; **34**: 1317.
121. Kharbanda RK, Mortensen UM, White PA, *et al.* Transient limb ischemia induces remote ischemic preconditioning *in vivo*. *Circulation* 2002; **106**: 2881.

122. Loukogeorgakis SP, Panagiotidou AT, Broadhead MW, *et al.* Remote ischemic preconditioning provides early and late protection against endothelial ischemia-reperfusion injury in humans role of the autonomic nervous system. *J Am Coll Cardiol* 2005; **46**: 450.
123. Weinbrenner C, Nelles M, Herzog N, Sarvary L, Strasser RH. Remote preconditioning by infrarenal occlusion of the aorta protects the heart from infarction: a newly identified non-neuronal but PKC-dependent pathway. *Cardiovasc Res* 2002; **55**: 590.
124. Olguner C, Koca U, Kar A, *et al.* Ischemic preconditioning attenuates the lipid peroxidation and remote lung injury in the rat model of unilateral lower limb ischemia reperfusion. *Acta Anaesthesiol Scand* 2006; **50**: 150.
125. Huda R, Chung DH, Mathru M. Ischemic preconditioning at a distance: altered gene expression in mouse heart and other organs following brief occlusion of the mesenteric artery. *Heart Lung Circ* 2005; **14**: 36.
126. Waldow T, Alexiou K, Witt W, *et al.* Protection against acute porcine lung ischemia/reperfusion injury by systemic preconditioning via hind limb ischemia. *Transpl Int* 2005; **18**: 198.
127. Brzozowski T, Konturek PC, Pajdo R, *et al.* Importance of brain-gut axis in the gastroprotection induced by gastric and remote preconditioning. *J Physiol Pharmacol* 2004; **55**: 165.
128. Park KM, Chen A, Bonventre JV. Prevention of kidney ischemia/reperfusion-induced functional injury and JNK, p38, and MARK kinase activation by remote ischemic pretreatment. *J Biol Chem* 2001; **276**: 1870.
129. Garcia-Valdecasas JC, Tabet J, Valero R, *et al.* Liver conditioning after cardiac arrest: the use of normothermic recirculation in an experimental model. *Transpl Int* 1998; **11**: 424.
130. Schulz R, Walz MK, Behrends M, Neumann T, Gerken G, Heusch G. Minimal protection of the liver by ischemic preconditioning in pigs. *Am J Physiol Heart Circ Physiol* 2001; **280**: H198.
131. Ricciardi R, Meyers WC, Schaffer BK, *et al.* Protein kinase C inhibition abrogates hepatic ischemic preconditioning responses. *J Surg Res* 2001; **97**: 144.
132. Clavien PA, Rudiger HA, Selzner M. Mechanism of hepatocyte death after ischemia: apoptosis versus necrosis. *Hepatology* 2001; **33**: 1555.
133. Clavien PA, Yadav S, Sindram D, Bentley RC. Protective effects of ischemic preconditioning for liver resection performed under inflow occlusion in humans. *Ann Surg* 2000; **232**: 155.
134. Clavien PA, Selzner M, Rüdiger HA, *et al.* consecutive patients undergoing major liver resection with versus without ischemic preconditioning. *Ann Surg* 2003; **100**: 843.
135. Cescon M, Grazi GL, Grassi A, *et al.* Effect of ischemic preconditioning in whole liver transplantation from deceased donors. A pilot study. *Liver Transpl* 2006; **12**: 628.
136. Jassem W, Fuggle SV, Cerundolo L, Heaton ND, Rela M. Ischaemic preconditioning of cadaver donor livers protects allografts following transplantation. *Transplantation* 2006; **81**: 169.
137. Koneru B, Fisher A, He Y, *et al.* Ischemic preconditioning in deceased donor liver transplantation: a prospective randomized clinical trial on safety and efficacy. *Liver Transpl* 2005; **11**: 196.
138. Azoulay D, Del Gaudio M, Andreani P, *et al.* Effect of ischemic preconditioning of the cadaveric liver on the graft's preservation and function: the ying and the yang. *Ann Surg* 2005; **242**: 133.
139. Lechevallier E, Dussol B, Luccioni A, *et al.* Posttransplantation acute tubular necrosis: risk factors and implications for graft survival. *Am J Kidney Dis* 1998; **32**: 984.
140. Araki M, Fahmy N, Zhou L, *et al.* Expression of IL-8 during reperfusion of renal allografts is dependent on ischemic time. *Transplantation* 2006; **81**: 783.
141. Herrero-Fresneda I, Torras J, Lloberas N, Vidal A, Cruzado JM, Grinyó JM. Reduction of post-ischemic renal inflammation: an effective strategy to attenuate chronic allograft nephropathy. *Transplantation* 2005; **79**: 165.
142. Herrero-Fresneda I, Torras J, Cruzado JM, *et al.* Do alloreactivity and cold ischemia cause different elementary lesions on chronic allograft nephropathy? *Am J Pathol* 2003; **162**: 127.
143. Brines M, Cerami A. Discovering erythropoietin's extrahematopoietic functions: biology and clinical promise. *Kidney Int* May 2006; **70**: 246.
144. Ates E, Yalcin AU, Yilmaz S, Koken T, Tokyol C. Protective effect of erythropoietin on renal ischemia and reperfusion injury. *ANZ J Surg* 2005; **75**: 1100.
145. Benjamin B, Ebert L, Bunn HF. Regulation of erythropoietin gene. *Blood* 1999; **94**: 1864.
146. Baker JE. Erythropoietin mimics ischemic preconditioning. *Vascul Pharmacol* 2005; **42**: 233.

 