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Personal Viewpoint

Ischemic Preconditioning: Promises from the Laboratory to Patients—Sustained or Disillusioned?

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The pioneering discovery of a novel method of tissue protection in the kidney by Zager et al. (1) in 1984 and in the heart by Murry et al. (2) in 1986 paved the way for a new concept to minimize ischemia-reperfusion injury in other organs. This surgical approach requiring a short period of ischemia and reperfusion prior to the actual intervention was termed ischemic preconditioning (IP). This principle has been applied to other organs including the liver to explore whether it provides similar protection. Investigators have identified a number of molecules conferring protection after IP in steatotic (3) and nonsteatotic (4) livers in rodents. However, when that evidence was applied to human liver transplantation the expected protective effect was not obvious.

The protocol of IP is relatively standardized. Prior to extended ischemia during an operation, the blood supply to the liver is blocked for 10 min, followed by a short period of reperfusion for 5–10 min. Exceptionally, ischemia is maintained for only 5 min followed by a short reperfusion phase. Since IP is protective in hepatic surgery, e.g. resection, it was logical to extend this approach to liver transplantation during which ischemia-reperfusion injury is also a major issue (4,5).

Ischemia-reperfusion injury represents the most common cause of primary nonfunction of the liver graft, which is one of the main reasons for retransplantation. This situation has stimulated different types of strategies to prevent ischemic injury such as pharmacological treatment, use of novel preservation solutions and surgical strategies (6). The efficacy of IP in liver resection was first reported by our group (7). Since then, other clinical studies have corroborated the beneficial effect of IP, not only on warm ischemia, but also in liver transplantation requiring cold ischemia (8).

The clinical efficacy of IP on deceased donors was studied by Koneru et al. (9) in 2005. The authors applied 5 min of ischemia, while the majority of experimental and human studies demonstrated that 10 min of vascular clamping is required to obtain effective protection. In the same year, Azoulay et al. (10) compared the outcome of IP on the preservation and function of the graft to the principal of *ying* and *yang,* meaning a reduced injury to the liver, but also an early decrease of graft function. Another pilot study in 2005, presented by Jassem et al. (11), showed protective effects against ischemic injury as a reduction of the inflammatory response by decreased neutrophil infiltration. One year later, Cescon et al. (12) demonstrated that 10 min of IP has a protective effect against cold ischemia in deceased donor allografts. Nevertheless, this group concluded that IP has no apparent clinical benefit regarding patient and graft survival.

In the September issue of AJT, Amador et al. (13) reported that IP protects against ischemia-reperfusion injury after cold ischemia showing an improved liver function, a reduction in apoptotic cell death as well as in the need for reoperation (Table 1). This study enrolled 60 patients, without a stratified randomization, which could have an impact on the finding that IP may provide a positive outcome only in a subgroup of patients. Nevertheless, the authors showed an increasing HIF-α level, which suggests a beneficial effect of IP.

On the other hand, in the December issue of AJT, Koneru et al. (14) demonstrated on a randomized, controlled trial studying 101 deceased donors randomized to 10 min of IP in 50 patients and no IP in 51 patients. To date, this is the largest study looking at IP in patients undergoing liver transplantation. The investigators concluded that IP alone is insufficient to provide any demonstrable clinical benefit in deceased donor liver transplantation. In addition, this trial suggests that IP alone may worsen the reperfusion phase. However, while pro-inflammatory cytokines were unchanged, IP was accompanied by increasing systemic levels of IL-10, a potent anti-inflammatory cytokine. On the other hand, the authors suggest that IP combined with other strategies, like pharmacological methods, may have a potential benefit on deceased donor liver transplantation.

Although we are beginning to understand the basic pathways of IP, the role of IP and its protective effect on liver

Table 1: Ischemia preconditioning on deceased donor liver transplantation

Authors	Year	Total N patients (control/IP)	IP/Rp protocol (min)	IP protective effect (Y/N)	Markers assessed	Patient outcome	
						Positive	Negative
Azoulay et al. (10)	2005	91 45/46	10/10	Y	↓ Postoperative AST-ALT levels—IP group	Better tolerance to ischemia	Reduced early graft function
Koneru et al. (9)	2005	62 28/34	5/5	N	PT, total bilirubin and histology unchanged		IP does not reduce injury
Jassem et al. (11)	2005	23 14/09	10/10	Y	↓ Postoperative AST levels, ↓ neutrophil infiltration and platelet in liver tissue (postreperfusion)	Better tolerance to ischemia ↓ nonspecific inflammatory response	
Cescon et al. (12)	2006	47 24/23	10/15	Y	↓ Postoperative AST-ALT levels. PT, total bilirubin and histology (neutrophil infiltration, iNOS, apoptosis) unchanged	↓ Hepato cellular necrosis	No graft or patient survival benefit
Amador et al. (13)	2007	60 30/30	10/10	Y	↓ Postoperative AST levels, ↓ apoptosis, ↑ HIF-1α and uric acid in prereperfusion time, ↓ hyaluronic acid during reperfusion	↓ Apoptotic cell death ↓ need for reoperation	
Koneru et al. (14)	2007	101 51/50	10/39 (25–77)	N	↑ Postoperative AST levels. PT, bilirubin, histology unchanged	↑ IL-10 levels (postreperfusion) ↓ rejection in liver recipients	Increased reperfusion injury (IP paradox)

IP = ischemic-preconditioning; IP/Rp = ischemic-preconditioning and reperfusion time; PO = postoperative; AST = aspartate aminotransferase; ALT = alanine aminotransferase; I/R = ischemic-reperfusion injury; iNOS = inducible nitric oxide synthase; HIF-1α = hypoxia-inducible factor-1α; PNF = primary nonfunction; PT = prothrombin time; IL-10 = interleukin 10.

transplantation remains controversial (4), as the available data is still far from conclusive. In contrast to experimental models of liver transplantation, where all possible parameters are controlled by the investigator, in clinical studies parameters are much more heterogeneous, dictated by the degree of steatosis, types of protocol, underlying conditions such as portal hypertension as well as presence of cancer and other factors which may contribute to paradox findings.

Should we conclude that IP has no role in liver transplantation? We would suggest: not yet. While the current study provides interesting data suggesting that IP is not a beneficial strategy to protect the deceased donor liver transplantation, or may even have a paradoxical effect on reperfusion injury, IP has been shown to be protective against warm ischemia in patients undergoing liver resection, particularly in patients presenting with hepatic steatosis. In spite of the limited number of clinical trials bringing ambiguous results and the persistent problem of organ shortage, we still believe there is a lot to investigate. We believe further insight into mechanism of protection in animal models, and selective targeting of the protective pathways may reveal useful in patients undergoing liver transplantation. An important target may be non-heart-beating grafts, which are increasingly used with higher risk of ischemic injury, mostly due to the initial prolonged period of warm ischemia. IP is a good example of translational research, following the principle of *ping* and *pong,* i.e. going back and forth from laboratory to patients with the expectation of eventually reaching a significant impact in patients.

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