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# Ischemic Preconditioning Directly or Remotely Applied on the Liver to Reduce Ischemia-Reperfusion Injury in Resections and Transplantation

*Maria Eugenia Cornide-Petronio, Mónica B. Jiménez-Castro, Jordi Gracia-Sancho and Carmen Peralta*

## Abstract

Ischemia-reperfusion (I/R) injury is an important cause of liver damage occurring during surgical procedures. In liver resection, I/R causes post-operative transaminasemia and liver function failure. In liver transplantation, I/R causes graft dysfunction, ranging from biochemical abnormalities to primary non-function of the transplanted organ. Ischemic preconditioning is a surgical strategy to reduce the severity of I/R and improve post-operative outcomes by prior exposure to a brief period of vascular occlusion directly to the target organ or remotely to a distant vascular bed. This chapter aims to discuss the different ischemic preconditioning strategies in both liver resection surgery and liver transplantation. In addition, we will describe the differences of such surgical strategies in both steatotic and non-steatotic livers in both preclinical experiments and clinical practice. Such information may be useful to guide the design of the effective ischemic preconditioning methods in the surgery of hepatic resections and liver transplantation.

**Keywords:** ischemia-reperfusion injury, liver resections, liver transplantation, ischemic preconditioning, remote ischemic preconditioning

## 1. Introduction

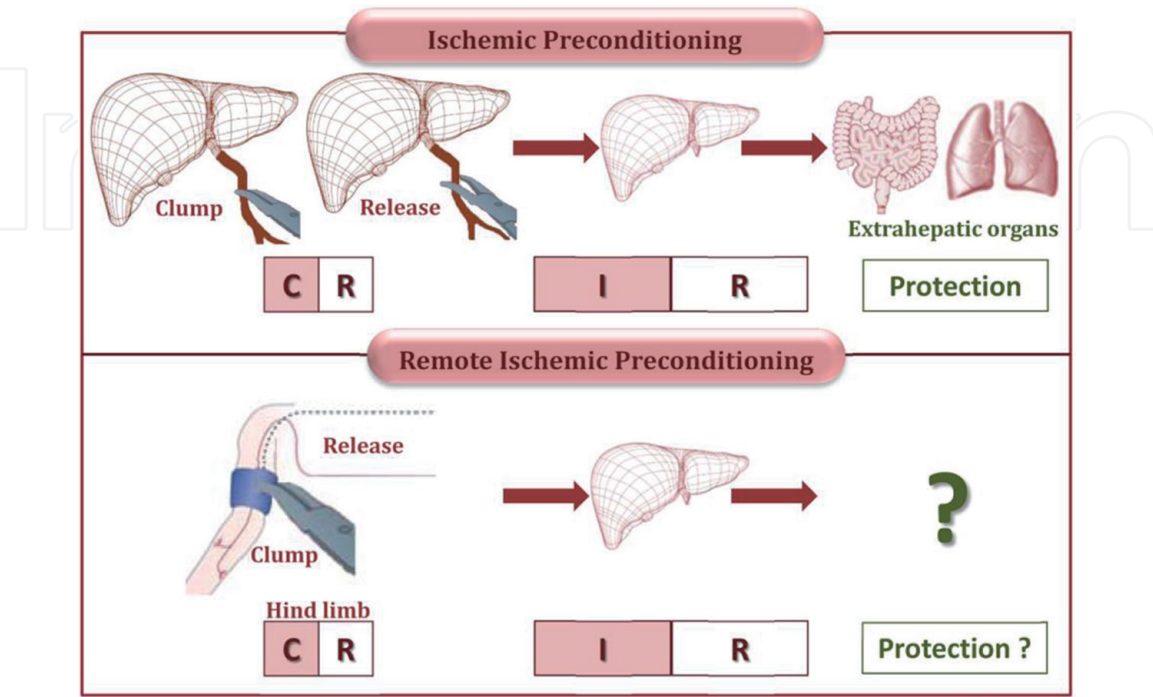
Ischemia-reperfusion (I/R) injury is a phenomenon in which cellular damage in a hypoxic organ is accentuated following the oxygen restoration [1–3], being a major pathophysiological event and cause of morbidity and mortality in liver resections and transplantation [4]. Despite the attempts to solve this problem, hepatic I/R is an unresolved problem. In addition, hepatic steatosis is a major risk factor for liver surgery, as it is associated with an increased complication index and postoperative mortality after major liver resection and transplantation, since steatotic livers show impaired regenerative response and reduced tolerance to I/R injury compared with non-steatotic ones. Of note, the prevalence of steatosis ranges from 24 to 45%

of the population and consequently a further increase in the number of steatotic livers submitted to surgery is to be expected [5]. These observations highlight the need to develop protective strategies in liver surgical conditions.

The mechanisms involved in liver I/R injury are complicated, mainly including microcirculation failure and oxidative stress [4]. A wide range of strategies has been attempted in order to mitigate I/R injury, mainly pharmacological treatments focused on gene therapy, improvement of preservation solutions, among others. However, an effective treatment is still lacking [4] since is difficult to achieve by targeting individual mechanism. Surgical strategies such as the ischemic preconditioning (IPC) technique noted for its effectiveness, as it activates several protective pathways against I/R injury in experimental models should be considered. IPC can be either applied directly to the target organ [6] or remotely (RIPC) to a distant vascular bed [7]. The benefits of the IPC and RIPC observed in experimental models of hepatic warm and cold ischemia [8, 9] prompted human trials of ischemic preconditioning. However, controversial results have been showed in the clinical practice. Therefore, the present chapter aims to describe the current knowledge of the IPC and RIPC in liver resections and liver transplantation of both steatotic and non-steatotic livers. In addition, the scientific controversies regarding the possible beneficial effects of these techniques, in experimental, translational and clinical studies in the setting of liver surgery will be discussed.

2. Ischemic preconditioning

Preconditioning the liver with ischemia involves a brief period of portal triad clamping usually between 5 and 15 min followed by a brief period of reperfusion (10–20 min) before a prolonged period of ischemia [10] (**Figure 1**). The exact mode of action of the IPC in the prevention of post-operative hepatic complication has not yet been fully comprehended. The molecular basis for IPC consists of a sequence of events in which in response to the triggers of IPC, a signal must be generated and transduced into an intracellular message leading to the effector mechanism



**Figure 1.**  
*Schematic illustration of ischemic preconditioning and remote ischemic preconditioning.*

of protection [11, 12]. As in the pathophysiology of hepatic I/R, in the modulation of hepatic injury induced by IPC, there is a complex interaction between different mechanisms and cell types [13].

## 2.1 IPC in experimental models

Over the years, studies with experimental animal models have reported numerous positive effects of IPC on the alleviation of hepatic I/R injury and improvements of post-operative liver functioning. Various combinations of ischemia and reperfusion periods have been tested showing similar beneficial effects: lower aminotransferase levels, reduced hepatocellular injury, and higher survival rates [14]. IPC protected against mitochondrial ROS and thus reduce the oxidative stress-mediated damage in liver I/R injury [15–18]. However, Rüdiger et al. showed that IPC is beneficial in liver submitted to an ischemic period of up to 75 min, but not for more prolonged ischemia [19].

### 2.1.1 IPC in warm ischemia without liver resection

IPC modulates several molecular pathways involving in I/R. When long periods of liver ischemia occur in hepatectomy or transplantation, the lack of oxygenation induces the rapid ATP consume to generate energy for cellular metabolism, resulting in adenosine production. The accumulation of adenosine provokes its transformation to hypoxanthine and xanthine leading to ROS production. IPC (5 min of ischemia/10 min reperfusion) modulates oxidative stress since reduces the accumulation of xanthine and the conversion of xanthine dehydrogenase (XDH) to xanthine oxidase (XO). IPC (5 min of ischemia/10 min reperfusion) inhibits this ROS generating system, xanthine/XOD [11–13]. The activation of adenosine receptor A2 induced by IPC stimulates the activity of various intracellular kinases, like protein kinase C (PKC)-specifically PKC- $\delta$ - and p38 mitogen-activated protein kinase (p38MAPK) [20]. The activation of p38 and c-Jun N-terminal kinase (JNK-1) induced by IPC (10 min of ischemia/10 min reperfusion) is associated with increased cyclin D1 expression and entry into the cell cycle [21]. In addition to this, activation of p38 by different pharmacological strategies mimicking IPC effects, including agonists of the adenosine A2 receptor, carbon monoxide (CO), NO, and atrial natriuretic peptide (ANP) has been considered to be a crucial mechanism of hepatoprotection in the setting of liver surgery [22]. Moreover, autophagic flux is enhanced by liver IPC (10 min of ischemia/10 min reperfusion), since endothelial nitric oxide synthase (eNOS)-derived NO activates autophagy via phosphorylation of p38 MAPK [23]. On the other hand, the mechanism involved in the benefits of IPC might be different dependently of the type of the liver [1]. Indeed, in the presence of steatosis, IPC (5 min of ischemia/10 min reperfusion) reduces MAPK activation (JNK and p38), and this is associated with protection against hepatic I/R injury [24, 25]. The involvement of sirtuin-1 (SIRT1) induction in the benefits of IPC (5 min of ischemia/10 min reperfusion) on normothermic hepatic conditions has been reported [26]. Thus, SIRT1 inhibition decreased the expression of extracellular signal-regulated protein kinases (ERK) and augmented p38 protein levels [26]. ERK activation during IPC (5 min of ischemia/10 min reperfusion) protects against I/R injury in steatotic livers, by inhibiting apoptosis [27], whereas treatment with a p38 activator abolished the benefits of IPC on hepatic damage [24]. In addition, inactivation of GSK-3 $\beta$  by IPC (10 min of ischemia/10–15 min reperfusion) induces  $\beta$ -catenin signaling and subsequently up-regulates anti-apoptotic factors, such as Bcl-2 and survivin, leading to a significant amelioration of liver I/R injury [28, 29]. **Figure 2** shows some of the protective mechanisms of IPC in the hepatic I/R injury.

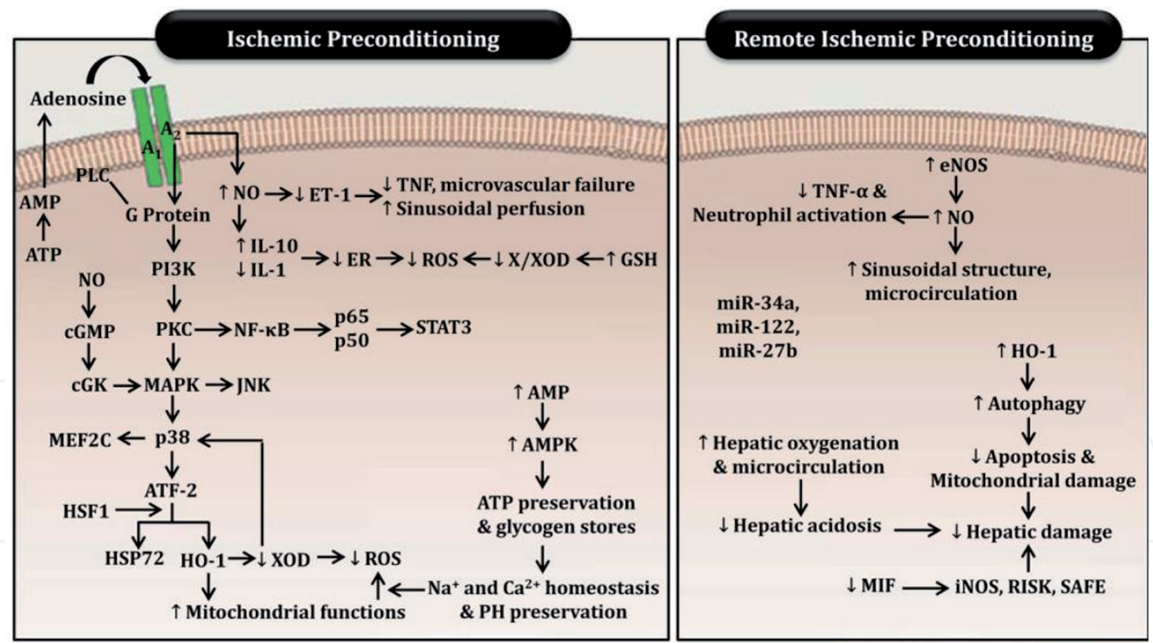


2.1.2 IPC in liver resections under warm ischemia

The beneficial effects of IPC (10 min of ischemia/5 min reperfusion) in liver partial hepatectomy (PH) have been shown to be linked to better ATP recovery, NO production, antioxidant activities, and regulation of endoplasmic reticulum stress. All of this limited mitochondrial damage and apoptosis. In addition, the ERK1/2 and p38 MAPK activation induced by IPC in PH favors liver regeneration [30]. Furthermore, IPC (10 min of ischemia/10 min of reperfusion) can initiate hepatocyte proliferation action by a signaling mechanism involving TNF- $\alpha$ /IL-6 signal pathway [31]. In contrast, Qian et al. found that IPC impaired residual liver regeneration after major PH without portal blood bypass in rats. In this case, IPC was of 5 min ischemia/10 min reperfusion [32]. Another study testing regenerative capacity of the liver after IPC (10 min ischemia/10 min reperfusion) and PH showed that, despite IPC decreased hepatic injury, it did not influence the regeneration up to 48 h [33].

2.1.3 IPC in reduced-size orthotopic liver transplantation

In a reduced-size orthotopic liver transplantation (ROLT) rat model, IPC (10 min ischemia/10 min reperfusion) has been suggested that potentiates hepatocyte proliferation via TNF- $\alpha$ /IL-6-dependent pathway [34]. In addition, authors described that IPC inhibits IL-1 through NO, increases HGF, and reduces TGF- $\beta$  to finally promote regeneration [34]. In addition, by another pathway independent



**Figure 2.** Protective mechanisms propose of ischemic preconditioning and remote ischemic preconditioning in the hepatic ischemia-reperfusion injury. A<sub>2</sub>-R: adenosine 2 receptor; AMP: adenosine monophosphate; AMPK: AMP-activated protein kinase; ATF-2: activating transcription factor-2; ATP: adenosine triphosphate; cGMP: guanosine 3',5'-cyclic monophosphate; eNOS: endothelial nitric oxide synthase; ER: endoplasmic reticulum; ET-1: endothelin-1; GSH: glutathione; HO-1: heme oxygenase-1; HSF-1: heat shock transcription factor-1; HSP72: heat-shock protein 72; IL: interleukin; iNOS: inducible nitric oxide synthase; JNK: jun N-terminal kinase; MAPK: mitogen-activated protein kinase; MEF2c: myocyte enhancer factor-2; MIF: macrophage migration inhibitory factor; NF- $\kappa$ B: factor nuclear factor-kappa B; NO: nitric oxide; PI3K: phosphatidylinositol 3-kinase; PKC: protein kinase C; PLC: phospholipase C; ROS: reactive oxygen species; STAT3: signal transducer and activator of transcription-3; TNF: tumor necrosis factor; X/XOD: xanthine/xanthine oxidase.

of NO, IPC induced over-expression of heat shock protein 70 (HSP70) and heme-oxygenase-1 (HO-1) [35]. HO-1 protects against I/R injury, whereas the benefits resulting from HSP70 are mainly related to hepatocyte proliferation [35]. In addition, when steatotic grafts from living donors were transplanted applying IPC, the incidence of necrosis was reduced and the expression of both pro-autophagic beclin-1 and LC3 was increased [36]. On the other hand, in a rat model of ROLT with 70 or 90% hepatectomy, IPC (10 min ischemia/15 min reperfusion) impaired hepatic proliferative response by decreasing IL-6 and blunting cell cycle progression through a mechanism at least partially independent of STAT3 [37].

#### *2.1.4 IPC in orthotopic liver transplantation*

IPC (5 min ischemia/10 min reperfusion) has protected liver grafts in an experimental model of orthotopic liver transplantation (OLT) by modulation of xanthine/XOD system [38]. IPC reduced cAMP generation, thus ameliorating hepatic injury and survival of recipients with steatotic grafts [39]. In addition, AMPK activation by IPC (5 min ischemia/10 min reperfusion) increased the accumulation of adiponectin in steatotic liver grafts. This increased resistin and activated PI3K/Akt pathway, thus protecting steatotic livers against damage that follows transplantation [40]. However, it should be noted that in experimental liver transplantation from cadaveric donors, brain death abrogates the benefits of IPC (5 min ischemia/10 min reperfusion) in both steatotic and non-steatotic liver transplantation [41, 42]. Indeed, in the setting of liver transplantation, the inflammatory response induced by brain dead, present in the liver before the induction of IPC, would interact with various mechanistic aspects of IPC and block the eventual IPC response. Thus, Jimenez-Castro et al. have demonstrated that the treatment with acetylcholine protected liver grafts from the deleterious effects induced by brain death [41]. Under these conditions, the application of IPC was useful to improve the post-operative outcomes after transplantation.

In addition to the liver, the benefits of IPC in experimental models of warm ischemia and liver transplantation have been observed in extrahepatic organs. Thus, IPC protects against lung damage associated with liver transplantation. The application of IPC in liver before I/R can prevent the release of both TNF and xanthine/XOD from the liver to the circulation. This regulated the P-selectin up-regulation and the neutrophil accumulation in remote organs such as lung and splanchnic organs [43].

#### **2.2 IPC in clinical trials**

The benefits of IPC observed in experimental models of hepatic resections and liver transplantation [8, 9] prompted human trials of IPC. The benefits of this surgical strategy have been evidenced in patients submitted to liver resections, protecting both steatotic and non-steatotic livers [44]. However, different results have been reported on the effects of IPC in the clinical practice of liver transplantation [45, 46].

##### *2.2.1 IPC in liver resections*

The first clinical trial testing IPC in patients undergoing major PH was reported by Clavien et al. [47]. Authors conclude that IPC (10 min ischemia/10 min reperfusion) is a protective strategy against hepatic ischemia in humans, particularly

in young patients requiring a prolonged period of inflow occlusion and in the presence of steatosis [44, 47]. Other clinical trials also suggest that IPC (10 min ischemia/10 min reperfusion) provides both better intraoperative hemodynamic stability and anti-ischemic effects compared with intermittent clamping [48, 49]. Regarding the molecular basis of IPC (10 min ischemia/10 min reperfusion) in clinical PH, its beneficial effects have been shown to be linked to the down-regulation of potentially cytotoxic functions of PMNLs elicited by the Pringle Maneuver [50]. In addition, IPC (10 min ischemia/15 min reperfusion) increased the generation of adenosine and attenuated the degradation of purines in patients undergoing PH. Moreover, IPC appeared to attenuate apoptotic response of the liver remnant after resection [51]. Other clinical trial revealed that IPC (10 min ischemia/10 min reperfusion) stimulated the expression of the IL-1-RA, inducible nitric oxide synthase (iNOS), and Bcl-2 which decreased the inflammatory response and abrogated liver I/R injury [52]. Interestingly, since the ischemic period and pathophysiology are similar in partial hepatectomy and living donor liver transplantation, IPC could reduce damage and improve liver regeneration failure, a relevant risk factor in living donor liver transplantation [34]. Moreover, IPC could be implemented as an appropriate surgical strategy for the use of suboptimal livers, such as steatotic ones, in the clinical practice. Different results indicate that in patients with liver cirrhosis, IPC (5 min ischemia/5 min reperfusion) has been a suitable method to decrease liver I/R injury [53, 54]. Recently, the protective mechanism of IPC in patients with liver cirrhosis subjected to PH has been associated with changes in MAPK pathways [54]. In contrast, IPC applied for 15 min followed by 5 min reperfusion did not improve liver tolerance to I/R injury after PH in patients with liver cirrhosis [55]. In fact, RIPC did not induce changes in the postoperative levels of transaminases, bilirubin, and albumin nor reduced the morbidity and mortality rates and the duration of hospitalization [55].

### *2.2.2 IPC in orthotopic liver transplantation*

Clinical trials in liver transplantation report different results on the effects of IPC against hepatic I/R injury. An IPC of 10 min ischemia/10 min reperfusion before liver transplantation reduced inflammatory response, improved ischemia tolerance, and decreased early graft function [56]. However, although the application of IPC (10 min ischemia/15 min reperfusion) reduced hepatocellular necrosis, it showed no clinical benefits [57]. In the largest prospective randomized trial of 10 min period IPC in liver transplantation from cadaveric donors, I/R injury was greater when IPC was applied [45], and it was called the “IPC paradox.” This was in accordance with the results obtained in experimental model of liver transplantation from cadaveric donors indicating that brain death abrogates the benefits of IP on post-operative outcomes [41, 42]. In fact, a microarray analysis in a randomized trial of 10 min IPC in deceased donor liver transplantation identified alteration of the expression of different antioxidant, immunological, lipid biosynthesis, cell development and growth transcripts, which are associated with hepatic damage [58].

## **3. Remote ischemic preconditioning**

RIPC is a surgical technique by which preconditioning of one organ or vascular bed provides protection to distant organs or vascular beds during a sustained period of ischaemia (**Figure 1**). Few experimental and clinical studies, most of them from the last years, have addressed the effects of RIPC in livers submitted to I/R.



### **3.1 RIPC in experimental models**

#### *3.1.1 RIPC in warm ischemia without liver resection*

When RIPC is applied in the hind limb, it reduced hepatic warm I/R injury of mice, rats, and rabbits. RIPC (5–10 min ischemia/5–10 min reperfusion) has been shown to improve hepatic oxygenation and microcirculation and to reduce hepatic acidosis and damage [59, 60]. RIPC (4 min ischemia/4 min reperfusion) induced eNOS activation, leading to NO production to preserve sinusoidal structure and blood flow [61]. In addition, RIPC (5 min ischemia/5 min reperfusion) regulated the expressions of iNOS and eNOS and the expressions of miR-34a, miR-122, and miR-27b injury related miRs in fatty livers, thus attenuating I/R injury [62, 63]. RIPC (10 min ischemia/10 min reperfusion) also induced the up-regulation of HO-1, induced autophagy, and then reduced the damaged mitochondria to inhibit apoptosis and eventually protect hepatic cells from I/R injury [64, 65]. Moreover, RIPC (5 min ischemia/5 min reperfusion) reduced neutrophil activation and adhesion and TNF- $\alpha$  [66]. Controversial results have been described in a rat model in which RIPC protocol included 3 cycles of 10 min ischemia interspersed with 10 min of reperfusion periods [67]. Regarding the hemodynamic and microcirculatory alterations, RIPC protocol had beneficial effect; however, the histopathological findings were paradox [67, 68]. In addition to RIPC in the hind limb, when RIPC (5 min ischemia/5 min reperfusion) is applied in kidney, it has also been shown to protect liver against I/R injury, improving blood flow, histology, and redox-state [69]. **Figure 2** shows some of the protective mechanisms of RIPC in the hepatic I/R injury.

#### *3.1.2 RIPC in liver resections*

A recent study in mice showed that RIPC (3 cycles of 5 min of ischemia each followed by 5 min of reperfusion) applied in the right femoral vascular bundle did not affect regeneration after 70%-PH [70]. However, of clinical interest, the same protocol of RIPC improved liver weight gain and hepatocyte mitoses after 90%-PH [70].

#### *3.1.3 RIPC in orthotopic liver transplantation*

In an experimental model of OLT, RIPC based on 4 cycles of 5 min of ischemia and 5 min of reperfusion was applied on the infrarenal aorta. The results suggested that RIPC might confer potent protection against the detrimental effects of I/R injury including apoptosis and inflammation [71]. In addition, authors suggest that HO-1 overexpression could play an orchestrating role in RIPC (5 min ischemia/5 min reperfusion)-mediated organ protection [71]. In addition, a recent study showed that the same protocol of RIPC also exhibits protective effects, as indicated by increased portal venous flow and microcirculation, as well as decreased AST and ALT levels and a reduced Suzuki score in a model of OLT [72]. Authors suggest that the RIPC inhibited the macrophage migration inhibitory factor (MIF), which resulted in the modulation of further downstream pro-survival mechanisms (iNOS, RISK-, SAFE-pathways), protecting graft injury [72].

### **3.2 RIPC in clinical trials**

Only three studies dated in 2017 and 2018 have addressed the effects of RIPC in the clinical liver surgery.



### *3.2.1 RIPC in liver resections*

In major HP, RIPC was shown to reduce liver I/R injury as indicated by a reduction in post-operative transaminases and increased ICG clearance [73]. To induce RIPC, a tourniquet was inflated to induce 10 min of ischemia and then deflated for 10 min to reperfuse the leg. This was repeated twice prior to commencing the operation. RIPC has potential to reduce liver injury following PH [73]. In addition, other clinical trial where RIPC was induced by three cycles of 5 min of ischemia of right upper limb followed by 5 min of reperfusion showed hepatic cytoprotective effects assessed by cholinesterase and bilirubin levels during liver resection [74]. Authors suggest that a shorter protocol of RIPC is safe and of equal effect, although the mechanisms of this effect must be investigated in future studies [74].

### *3.2.2 RIPC in orthotopic liver transplantation*

The first trial to investigate the feasibility of RIPC in liver transplant recipients was addressing by Robertson et al. [75]. The trial involved randomization of adult recipients undergoing deceased donor liver transplantation. To induce RIPC, a tourniquet was inflated for 5 min and then deflated for 5 min to reperfuse the leg. This was repeated twice and completed prior to the transplant procedure. Authors demonstrated that RIPC is feasible, acceptable to patients and safe in this group of patients but clinical benefits within the first 3 months post transplantation were not detected [75]. Authors suggest that 5 min cycles are insufficient to create localized ischemia in the limb [75].

## **4. Conclusion**

Surgical strategies such as the induction of IPC or RIPC could be of clinical interest in human liver resections and liver transplantation in both steatotic and non-steatotic livers. Both IPC and RIPC are easy to apply, inexpensive and does not require the use of drugs with potential side effects, but it requires a period of pre-ischemic manipulation for organ protection. These preconditioning techniques have been demonstrated to be promising tools for the reduction of hepatic I/R injury in different warm and cold ischemia models. Therefore, the potential applications of IPC and RIPC in human liver surgery are numerous. The benefits of IPC and RIPC have been evidenced in patients submitted to partial hepatectomy in both steatotic and non-steatotic livers. In our view, IPC and RIPC could resolve, at least partially, the lack of liver grafts available for transplant, since it can improve the post-operative outcome of liver grafts from extended criteria donors. However, controversial results on the effects of IPC and RIPC have been reported in the clinical practice of liver transplantation. It should be considered that the underlying mechanisms of both IPC and RIPC and their relevance in liver surgery remain poorly understood. Indeed, as stated along this chapter, most of the experimental studies have been focused on the molecular changes occurring during IPC and RIPC in non-brain-dead donors. Moreover, most of the experimental studies of IPC and RIPC have been performed only in I/R injury models, without hepatic resections or liver transplantation. The tolerance to I/R injury induced by either IPC or RIPC is dependently of the number of cycles of I/R and their duration as well as the surgical procedures. The clinical application of strategies designed at benchside will depend on the use of experimental models of IPC and RIPC that resemble as much as possible the clinical conditions. Multidisciplinary research groups should devote additional efforts to better understand the molecular mechanisms of IPC and RIPC

during the different clinical liver surgery setting to ultimately develop useful surgical strategies aimed at reducing I/R damage.

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## Conflict of interest

The authors declare that they have no conflict of interest.

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