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Review Article

Liver graft preconditioning, preservation and reconditioning

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ABSTRACT

Liver transplantation is the successful treatment of end-stage liver disease; however, the ischaemia-reperfusion injury still jeopardizes early and long-term post-transplant outcomes. In fact, ischaemia-reperfusion is associated with increased morbidity and graft dysfunction, especially when suboptimal donors are utilized. Strategies to reduce the severity of ischaemia-reperfusion can be applied at different steps of the transplantation process: organ procurement, preservation phase or before revascularization. During the donor procedure, preconditioning consists of pre-treating the graft prior to a sustained ischaemia either by a transient period of ischaemia-reperfusion or administration of anti-ischaemic medication, although a multi-pharmacological approach seems more promising. Different preservation solutions were developed to maintain graft viability during static cold storage, achieving substantial results in terms of liver function and survival in good quality organs but not in suboptimal ones. Indeed, preservation solutions do not prevent dysfunction of poor quality organs and are burdened with inadequate preservation of the biliary epithelium. Advantages derived from either hypo- or normothermic machine perfusion are currently investigated in experimental and clinical settings, suggesting a reconditioning effect possibly improving hepatocyte and biliary preservation and resuscitating graft function prior to transplantation. In this review, we highlight acquired knowledge and recent advances in liver graft preconditioning, preservation and reconditioning.

1. Introduction

Liver transplantation (LT) is the ultimate treatment for end-stage liver disease, achieving substantial early and long-term results. However, the Ischaemia-Reperfusion Injury (IRI) profoundly influences outcomes after LT, representing still a considerable challenge.

The success of LT has created a new dilemma: the organ supply does not satisfy a steadily increasing demand; to overcome this limit, the criteria for organ donation have become less restrictive by including grafts of suboptimal quality, such as those from Extended Criteria Donors (ECD) (i.e. mainly those with significant macrosteatosis, old donor age or prolonged hospitalization) or Donation after Circulatory Death (DCD) [1]. Unfortunately, suboptimal grafts are more susceptible to IRI and carry an increased risk of organ failure after transplantation [2]. It is now clear that IRI represents a major hurdle we must deal with to further improve LT outcomes, thus satisfying patients' needs.

Living donation, minimizing the duration of cold ischaemia, may represent a solution to both IRI and shortage of donor grafts. The large experience accumulated by the Asian groups showed indeed that living donation can satisfactory replace a limited pool of deceased donors, achieving excellent survival [3,4]. However, Western experience is still far from reaching comparable numbers in terms of both LT performed and patient survival, and considerable concerns regarding donor safety and post-transplant graft failure still exist. Hence, researchers have consistently focused on reducing the severity of IRI with interventions that can be applied at different steps of deceased donor LT (Fig. 1).

The phase of procurement at the donor site offers the opportunity to treat the graft prior to the initiation of IRI, a concept known as organ *preconditioning*.

Maintaining the viability of the graft during the cold storage phase with dedicated solutions is probably the oldest attempt to reduce IRI, but the renewed interest in machine perfusion (MP) pushes towards new appealing scenarios in organ *preservation*.

Recent advances in experimental MP have prompted the possibility to assess graft viability and to resuscitate it immediately prior to LT, performing a real organ *reconditioning*.

Here, we review the acquired knowledge and highlight the emerging evidences on the effects of graft preconditioning, preservation and reconditioning in LT.

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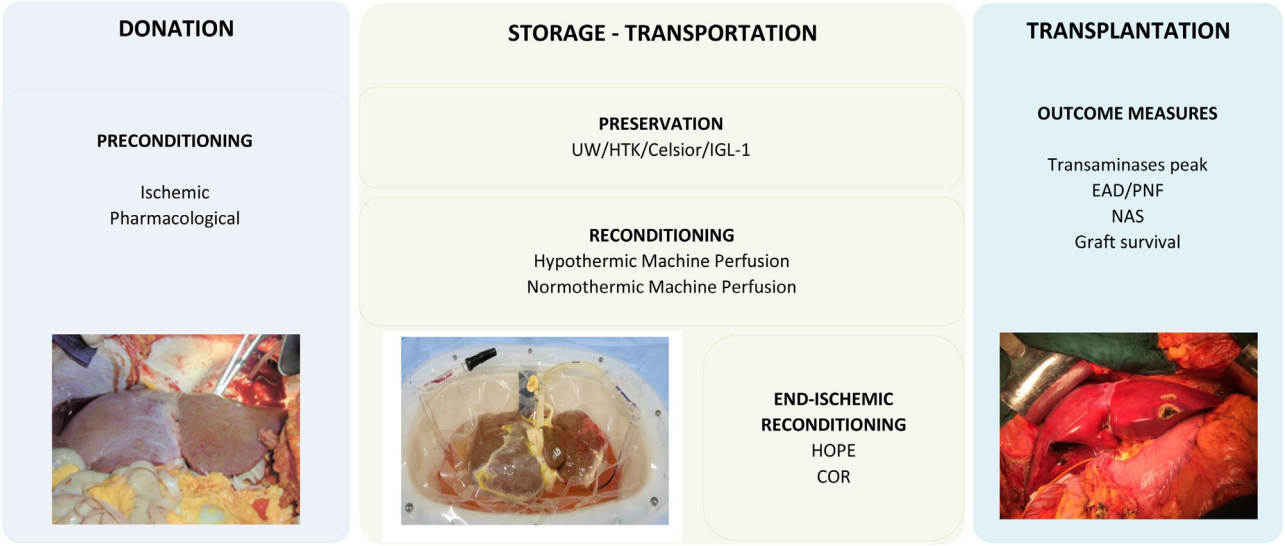

Fig. 1. Possible strategies to tackle Ischaemia-Reperfusion Injury throughout the liver transplantation process and proposed outcome measures in the recipient. COR, controlled oxygenated rewarming; EAD, early allograft dysfunction; HOPE, hypothermic oxygenated perfusion; HTK, histidine-tryptophan-ketoglutarate; IGL-1, Institute George Lopez 1; NAS, non-anastomotic biliary strictures; PNF, primary non function; UW: University of Wisconsin solution.

2. Ischaemia-reperfusion injury: pathogenesis and clinical implications

IRI inevitably occurs through the transplantation process from organ donation to graft revascularization. During the procurement, the graft is suddenly deprived of oxygen and cooled down with cold preservation solutions in order to slow metabolic processes. Yet, at 4 °C metabolism is not fully stopped, ATP is progressively depleted and mitochondrial function dysregulated. After reperfusion, the production of reactive oxygen species, cytokines secretion, neutrophil infiltration and the impaired hepatic microcirculation provoke inflammation, cell death, loss of functioning parenchyma and ultimately organ failure [5,6]. Additionally, cholangiocytes are more susceptible to IRI and extended damage of the biliary epithelium is visible at the end of preservation of virtually all grafts [7,8]. Peribiliary vascular plexus and glands (containing the precursor's niche) are also damaged by microthrombi and necrosis, leading to impaired regeneration of the biliary epithelium. The physiological systems buffering the detergent effect of bile salts are dysregulated during the preservation phase, hence a toxic damage superimpose to the injuries of the biliary tree [9]. All these mechanisms are responsible of the development of Non Anastomotic biliary Strictures (NAS), a troublesome complication characterized by multiple stenosis of the bile ducts. Histological features of IRI include hepatocytes swelling, apoptosis, necrosis, sinusoidal endothelial cells detachment and polymorphonucleate infiltration [10].

The clinical manifestation of IRI can vary from immediate graft function with minimal damage to Early Allograft Dysfunction (EAD), Primary Non Function (PNF) and NAS. EAD is the result of the hepatocellular necrosis and it is biochemically evident as highly elevated transaminases and/or impaired synthetic function (elevated total bilirubin, prolonged coagulation) within the 1st week post-LT [11]. PNF is a life threatening condition in which the liver graft immediately fails on sustaining the physiological metabolic demands but a uniformly accepted definition is currently missing. Both graft and patient survival are severely reduced by the occurrence of EAD or PNF. NAS also represents a common cause of graft loss especially after transplantation of DCD grafts [12].

Strategies preventing IRI should reduce the incidence of its manifestations; clinical studies evaluating the efficacy of such strategies should therefore focus on transaminases peak post-LT, incidence of EAD/PNF, incidence of NAS and graft survival.

3. Preconditioning (see Table 1)

Organ procurement offers a window for pre-treating the liver with several strategies. The most commonly attempted ones, are the Ischaemic Preconditioning (IP) and the pharmacological preconditioning, i.e. administering medications effective against IRI.

3.1. Ischaemic preconditioning

After the first report on the protective effect of transient run of IRI in the myocardium by Murray et al. [13], IP effect was evaluated and confirmed in different organs such as kidney and liver. The underlying protective mechanisms seem related to the increased production of protective mediators, antioxidants and inhibitor of apoptosis prior to the onset or IRI [14].

Different clinical trials have evaluated the effectiveness of IP applying different duration of ischaemia and reperfusion. Koneru et al. first performed IP using a protocol consisting of five minutes of ischaemia and five minutes of reperfusion before the beginning of cold ischaemia. In a randomized trial involving 60 LTs no differences were found in surrogate or pathological markers of IRI [15]. Azoulay et al. used a protocol of ten minutes ischaemia – ten minutes reperfusion and demonstrated a significant reduction of post-LT transaminase release. Despite this protective effect, IP significantly increased the incidence of EAD, although no impact on patient and graft survival was observed [16]. In our previous experience comparing the effect of IP (ten minutes ischaemia – thirty minutes reperfusion) in both optimal and ECD grafts, post-transplant transaminases release was significantly reduced, especially in ECD grafts treated by IP, and the severity of histological IRI was improved. However, no difference was observed in functional recovery or incidence of EAD, although a trend towards better graft and patient survival was observed in a short-term follow-up (6 months). We concluded that, even if IP in suboptimal grafts showed a protective effect, it was not able to prevent the functional impairment often observed after LT with ECD grafts [17]. Degli Esposti et al. partly confirmed our findings analyzing steatotic and non-steatotic grafts undergoing IP. Steatotic grafts displayed reduction of necrosis and enhancement of autophagy after IP while no significant impact in non-steatotic grafts was observed [18]. Finally, a recent meta-analysis detected no improvement in post-transplant

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