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TOPIC HIGHLIGHT

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Strategies to optimize the use of marginal donors in liver transplantation

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Abstract

Liver transplantation is the treatment of choice for end stage liver disease, but availability of liver grafts is still the main limitation to its wider use. Extended criteria donors (ECD) are considered not ideal for several reasons but their use has dramatically grown in the last decades in order to augment the donor liver pool. Due to improvement in surgical and medical strategies, results using grafts from these donors have become acceptable in terms of survival and complications; nevertheless a big debate still exists regarding their selection, discharge criteria and allocation policies. Many studies analyzed the use of these grafts from many points of view producing different or contradictory results so that accepted guidelines do not exist and the use of these grafts is still related to non-standardized policies changing from center to center. The aim of this review is to analyze every step of the donation-transplantation process emphasizing all those strategies, both clinical and experimental, that can optimize results using ECD.

Key words: Liver transplantation; Extended criteria donors; Marginal donors; Results; Survival

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Core tip: This review analyzes the donation-transplantation process when using extended criteria donors. Every step, from donor selection to transplantation, is discussed emphasizing experimental and clinical strategies that can lead to optimize results.

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INTRODUCTION

Liver transplantation (LT) is the treatment of choice for patients with end stage liver disease. Due to improvement in surgical techniques, immunosuppressive strategies, and patient management, the number of candidates has dramatically grown in the last decades while the number of donors has remained stable. This gap has stimulated the development of innovative strategies to increase the donor pool. Currently, the ideal liver donor - younger than 40 years; trauma as the cause of death; donation after brain death; hemodynamic stability; without macrovescicular steatosis, infection(s) or chronic liver disease[1] - is less frequent due to demographic changes in the general population[2]. The concept of extended criteria donors (ECD) was introduced to indicate donors associated with a higher risk of primary non function (PNF) of the liver graft, delayed graft function (DGF), and a poorer prognosis after transplantation. Elderly donors (> 60 years), donors with malignancies, infections, macrovescicular steatosis > 30%, donors after cardiac death (DCD), hypernatremia, hemodynamic instability, prolonged cold ischemia time (CIT), split liver grafts, and living donor liver transplants (LDLT) are all included in this category[3-5].

Despite numerous studies, the impact of each donor variable on recipient outcome is still debated due to controversial results. Some authors reported that careful liver graft selection provides comparable results *vs* optimal donor grafts, and some recent studies confirm these findings[4-5]. Nevertheless, the reported results may be related to specific donor demographic characteristics (*i.e.*, healthier life styles) or to the experience of transplant teams with management of these donors[6]. The aim of the present review is to appraise all strategies that can be implemented in view of optimization of use of ECD in LT.

DONOR EVALUATION

Age

Old donors should be carefully evaluated as age is related to allograft failure and post-transplant death[7]. Nevertheless, the progressive aging of the population and the decreasing incidence of trauma-related deaths have made elderly donors a considerable resource in many countries. In our recent study the mean donor age was 70 years[5], and similar results were reported by the Spanish liver donor registry[8]. Old organs develop brown atrophy, show a decrease in weight and number of cells, thickening of endothelial cell lining, endothelial cell fenestrations, reduction of blood flow, reduced synthetic capacity resulting in a diminished response to external stressors and a limited regeneration rate[9-13]. Short term complications using these grafts include PNF - defined as an irreversible graft dysfunction requiring liver re-transplantation within 10 d - initial poor function (IPF) and vascular complications[14]. Long-term complications include reduced patient and graft survival, especially in HCV positive recipients, and ischemic type biliary lesions (ITBL)[14]. These grafts are extremely sensitive to hemodynamic instability, and an appropriate donor management is pivotal with adequate systemic blood (> 100 mmHg) and central venous pressures (> 10 cm H_2O), a hematocrit > 25%, normal body temperature, and diuresis greater than 1 mL/kg per hour in order to avoid hypoperfusion and low oxygen support to the liver graft[15]. A rapid procurement technique with minimal organ manipulation and double perfusion (aortic and portal) should be preferred[15]. In order to minimize the ischemia/reperfusion injury (I/R), CIT should be as short as possible[14,15]. Many series using graft older than 70 years showed optimal results when CIT is shorter than 8 h, whilst a CIT > 12 h is associated with a twofold risk of graft failure[16]. Thus, procurement in distant hospitals should be carefully evaluated and allocation to more stable patients who can better tolerate some degree of organ dysfunction should be warranted[16,17]. Older liver grafts are preferentially allocated to low biochemical model for end-stage (MELD) score patients and HCV-negative recipients with hepatocarcinoma[5,15].

Hemodynamic instability

Previous United Network for Organ Sharing (UNOS) data have shown that organs subjected to prolonged hypotension do not show any significant increase in post-transplant graft loss[17]. However, graft loss increased in transplants from donors receiving norepinephrine[17]. Some studies showed that dopamine dose > 10 μg/kg per minute[18], or 6 μg/kg per minute[19] had a significant impact on early graft function. Systemic blood pressure should be kept above 90-100 mmHg as low pressure is related to increased preservation injury[20]. The use of dopamine is indicated to increase the mesenteric and renal flows at doses of 2-5 μg/kg per minute. Higher doses can lead to renal impairment and a dopamine dose > 15 μg/kg per minute is considered a marginality criterion[21,22].

Hypernatremia

Hypernatremia is considered a risk factor for graft dysfunction, but the mechanism of hypernatremia-related injury to liver cells is not clear[23,24]. One hypothesis is that a sudden change in extracellular osmolality in a liver graft obtained from a hypernatremic donor might cause intracellular water accumulation and cell swelling[25]. However, high serum sodium concentrations may promote accumulation of osmoles within the liver allograft cells. Subsequent transplantation of these livers into recipients with normal serum sodium levels may promote intracellular water accumulation, hepatocyte lyses, and death[23]. Avolio *et al*[23] suggested that donor hypernatremia may adversely affect the outcome of LT and showed a direct correlation between the donor serum sodium concentrations and the recipient liver enzyme levels [aspartate aminotransferase (AST) and alanina aminotransferase (ALT)] after surgery[23]. González

et al[24] showed that donor hypernatremia correlates with hepatic allograft dysfunction, whilst Figueras *et al*[25] reported that donor hypernatremia is associated with high bilirubin levels post-operatively and graft loss within the first month post-transplantation. Totsuka *et al*[26] showed that both graft function and survival were improved by correction of donor hypernatremia and suggested that latent changes in hepatocytes induced by hypernatremia are reversible and might be attenuated by appropriate donor management. Recent studies have found that donor hypernatremia does not affect graft survival in liver and kidney transplantation[27].

Infections

Hepatitis B virus: In the presence of antibody to hepatitis B core antigen (anti-HBc) IgM-positivity or circulating hepatitis B virus (HBV)-DNA levels, some centers decline using these organs for donation. Anti-HBc IgG-positive donor grafts can be safely used, provided use of anti-HBV prophylaxis with oral antiviral agents in HBV naïve recipients[28-30]. The addition of anti-hepatitis B surface antigen immunoglobulin does not seem to provide superior protection rates *vs* oral antivirals alone[29].

In pediatric transplantation, organs from anti-HBc-positive donors are still used with caution after an individualized risk-to-benefit evaluation[28-30].

Hepatitis C virus: The use of hepatitis C virus (HCV)-positive donors for LT was originally debated and not widely practiced due to concerns about an increased risk of HCV-related graft failure after transplantation[31-34]. In the last decade, long-term follow-up data confirmed that use of HCV-positive donor grafts in HCV-positive recipients was safe and did not affect graft survival[31]. In this setting, post-transplant HCV recurrence rates were 55.54% *vs* 41.74% for recipients of HCV-negative grafts[32]. Patient and graft survival at 4 years post-transplantation are similar in recipients of either HCV-positive or HCV-negative liver grafts[32].

A recent UNOS-based study on 1695 HCV patients transplanted with HCV-positive grafts has confirmed no difference in patient and graft survival *vs* HCV-positive recipients transplanted with HCV-negative liver grafts[33]. An European, multicenter study has also shown similar overall patient and graft survival rates in this category of patients[34]. HCV recurrence was reported to be more rapid in the group of patients who received anti-HCV-positive grafts, although it did not reach statistical significance ($P = 0.07$)[34]. The authors suggested appropriate use of anti-HCV-positive donor grafts, especially if HCV-RNA is positive, as their use might be associated with more rapid fibrosis progression[34]. The recent introduction of direct antiviral agents for treatment of HCV infection will likely reshape this practice.

Malignancies

According to the UNOS database, 2.7% of deceased donors have a history of cancer[35]. Between 2000 and 2005, more than 800 LT procedures were performed using grafts from donors with a history of malignancy, and only two donors transmitted a fatal disease[35]. The most common cancers were non melanoma skin neoplasms followed by central nervous system malignancies[35].

Melanoma is one of the most commonly reported donor-derived malignancies and might have one of the highest transmission rates and associated mortality if inadvertently transmitted to the recipient. As its biological behavior is complex and characterized by late recurrences (tumor dormancy) donors with an history of malignant melanoma should always be discarded also in case of cured disease[36]. Donors with central nervous system malignancies should be carefully evaluated as certain risk factors are associated with malignancy transmission; organs from donors having high grade (Ⅲ or Ⅳ) tumors, ventriculo-systemic shunts or history of extensive cranial surgery that disrupts the blood-brain barrier are associated with a transmission rate of 45% and should not be considered for transplantation; in cases where the underlying etiology of brain death is unclear, a rapid limited brain autopsy should be conducted[37].

Data derived from the United Kingdom Transplant Registry showed that 18 solid organ recipients developed cancer from 16 donors (0.06%): 3 were donor-derived cancer (0.01%) and 15 were donor-transmitted cancer (0.05%)[38]. Of the 15 donor-transmitted cancers, 6 were renal; 5 were lung; 2 were lymphoma; 1 was neuroendocrine, and 1 colon cancer[38].

Some recent Italian series have shown no disease transmission with use of grafts from donors with low-grade malignancies or neoplasms of low metastatic potential[39,40]. An accurate donor evaluation coupled with histological information of tumor grade allows to reduce to acceptable rates the risk of donor-to-recipient transmission[39,40]. Donors with a documented history of malignancy should not discarded *per se*, especially for low-grade central nervous system tumors and malignancies treated successfully with long-term disease-free survival rates. However, there is still variability in guidelines and practices across countries[39,40].

Steatosis

Steatosis is a very common chronic liver disease and it is estimated to occur in more than 65% of obese patients[41]. Microvescicular steatosis is accumulation of small fatty droplets not displacing the cell nucleus, and even if diffuse it does not entail a higher risk for graft loss after LT[42]. Macrovescicular steatosis is characterized by large droplets displacing the nucleus to the cell periphery and is associated with a significant risk factor for PNF[42,43]. It can be classified based on the proportion of hepatocytes affected, being mild < 30%, moderate from 30% to 60%, and severe > 60%[43]. Most transplant centers do not use grafts with more than 30% of macrovescicular steatosis. However, use of these latter grafts is suggested reducing cold storage within 6 h[44]. Steatotic livers show heightened sensitivity to I/R

injury and several mechanisms have been proposed to explain this. The liver might be more subjected to lipid peroxidation[45], and a more accentuated pro-inflammatory response with release of mediators, such as tumor necrosis factor (TNF)-α, and an increased neutrophil infiltration[46]. Animal models showed narrowed and tortuous microvessels with reduced hepatic and sinusoidal blood flow, mitochondrial dysfunction and decreased energy levels[47].

INTERVENTIONS

Several approaches have been suggested in order to reduce the sensitivity of livers to I/R injury. Physical exercise and dietary interventions are reserved to living donors, but it may take long before providing histologic changes in liver cells[48]. Drug schedules have been used to decrease liver cell lipid intake. Urso-deoxycholic acid was used in a clinical trial, but its results are controversial[49]. Pentoxifylline was used based on its effect on reducing TNF-α levels and increasing glutathione activity[50]. To date, only bezafibrate was reported in steatotic living liver donors before transplantation[51].

Ischemic preconditioning is based on intermittent clamping before cold flushing and has been shown to reduce lipid peroxidation, hepatic microcirculation failure and neutrophil accumulation when applied to steatotic livers[52]. Volatile anesthesia has been shown to be superior to the intravenous one in preventing liver injury after reperfusion in previous studies on liver resection[53], but a recent multicenter trial comparing propofol with sevoflurane in LT has shown no difference in terms of acute organ injury and clinical outcomes between the two regimens[54].

Several experimental strategies can be applied to either the donor or the graft. Pharmacological preconditioning was successfully used in rats with resulting reduced inflammatory responses, parenchymal dysfunction, and injury[55]. Heat-shock preconditioning is a method to induce endogenous protective heat-shock proteins by exposure to heat, and is applied 3-48 h before organ procurement[56]. This leads to a decrease in TNF-α, an increase in nitric monoxide and improvement of microcirculation and inhibited platelet aggregation[56]. Some pharmacological additives can be used during cold preservation to ameliorate metabolism and suppress inflammation, such as interleukin-6, pentoxifylline, L-carnitine, carvedilol, epidermal growth factor, and insulin like growth factor 1[57]. Venous systemic oxygen persufflation during static cold storage (SCS) preservation was described in the Nineties to supply gaseous oxygen to livers, and it utes was demonstrated that application for 90 min may rescue steatotic livers after extended SCS preservation[58]. The use of machine perfusion has recently been introduced in some centers and may preserve steatotic livers by continuous supply of nutrients, removal of waste products, and maintenance of ideal microcirculation conditions[59].

ALLOCATION STRATEGIES

In LT setting, several allocation policies have been proposed over the recent years, but none is complete in evaluating all clinical aspects of a liver disease patient. Patient based policies includes: Urgency principle and utility based principle. The urgency principle is based on MELD[60], and although widely practiced it has raised criticism over the years. The components of the formula are not always objective, due to inter-laboratory variability[61]; symptom-based exceptions may be under- or mis-scored, and extra-points are assigned almost arbitrarily[62]. The first-come-first-served principle did not take into consideration the individual patient gravity with the resulting risk of increased death on the waitlist of sickest patients. The utility based principle is based on survival benefit concept and was introduced as a way to balancing the risk of death after LT with the risk of mortality while on the list, thus avoiding futile transplantation[63]; survival benefit computes the difference between the mean lifetime with and without LT so that a graft goes to the patient with the greatest difference between the predicted post transplant lifetime and the predicted waiting list lifetime for this specific donor. Donor-based policies were introduced with the increasing use of ECD, as graft and patient survival was greatly reduced for some unfavorable donor-to-recipient matching categories[64,65]. Feng *et al*[1] introduced the concept of a donor risk index (DRI) assessing donor variables that can affect transplant outcomes, thus providing formal assessment to clinical donor-related variables. Main limitations of DRI are: First DRI was reported before introduction of MELD, second DRI is mainly related to donor age, third DRI takes into consideration only data at the time of procurement. Combined donor-recipient based systems have been proposed widely; balance of risks (BAR) score includes: MELD, recipient age, retransplant, life support dependence prior to LT, donor age and CIT thus establishing a threshold at 18 points. BAR score is mainly determined by MELD balanced by other factors both of recipient and donor[66]. Actually the ideal matching is still a theory based more on myth than reality. To date, every system that has been proposed appears to not be statistically robust enough[65].

ORGAN RETRIEVAL

Preservation solutions

A recent study was conducted on 42869 first liver transplants performed in Europe with the use of either University of Wisconsin solution (UW; n = 24562), histidine-tryptophan-ketoglutarate (HTK; n = 8696), Celsior solution (CE; n = 7756) or the Institute Georges Lopez preservation solution (IGL-1; n = 1855)[67]. The overall 3-year graft survival was higher with UW, IGL-1 and CE (75%, 75% and 73%, respectively), compared to HTK (69%) ($P < 0.0001$)[67]. The same trend was observed with a total ischemia time > 12 h or for grafts

used for patients with cancer ($P < 0.0001$)[67].

Retrieval techniques

During liver procurement for deceased donation, rapid *en bloc* procurement with minimal manipulation after clamping the donor aorta achieved better early graft function post-transplantation[68].

In DCD, most surgeons use some modification of the super rapid recovery technique[69]. The donor is prepared as well as the surgical instruments. After the declaration of death the surgeons expeditiously perform aortic cannulation. Thereafter, the thoracic or supraceliac aorta is cross-clamped, and the vena cava is vented into the right chest. The portal system can be flushed by *in situ* cannulation of the inferior mesenteric vein or on the back table. Organs can be removed separately or *en bloc.* Cannulating the donor pre-mortem may decreases warm ischemia time[69]. It is necessary to cannulate both femoral artery and vein before support withdrawl in order to perfuse with cold preservative solution immediately after declaration of death. Thereafter, a median sternotomy and midline abdominal incisions are made and the intra-abdominal organs are topically ice cooled and then removed *en bloc* or separately[69].

In donors from brain death, a randomized prospective study was performed to test the impact of the donor harvesting technique on post-transplantation outcomes in ECD. A modified double perfusion (MDP) technique was compared with the single aortic perfusion (SAP) technique. Thirty-five suboptimal grafts were randomly assigned to either technique (18 MDP livers *vs* 17 SAP livers). Variables were comparable in the 2 study groups. The SAP group presented higher blood transaminases and bilirubin levels after LT. Graft primary dysfunction was also significantly higher ($P = 0.01$) in the SAP group (35%) *vs* the MDP group (5%). In the SAP group, 5 cases required re-LT (< 30 d). Patient and graft survival rates were higher in the MDP (100% in both cases) than in the SAP group (68% and 58%, respectively) so that the study was stopped[70].

Perfusion with fibrinolytic drugs

Plasminogen activators have been tested in LT to prevent microthrombosis, improve microcirculation and oxygen supply[71]. Liver grafts from non-heart-beating donors (NHBD) are additionally affected by microvascular alterations, including erythrocyte aggregation and thrombi formation, which might hamper appropriate equilibration of the preservation solution to the graft microvasculature[71]. Streptokinase was used in experimental models to observe post-preservation viability in NHBD. Streptokinase preflush resulted in a relevant and significant improvement of structural integrity as well as functional and metabolic recovery[71,72].

ITBL have a multifactorial origin but I/R injury and microthrombosis are considered to be the most relevant[73]. In order to decrease its incidence, urokinase perfusion has been tested[74]. In a prospective study by Lang R *et al*[74], the arterial system of the donor liver was perfused twice with urokinase during cold perfusion and after trimming of the donor liver. The incidence of ITBLs resulted lower than in the control group[74].

CIT

Prolonged CIT is an independent risk factor for DGF and PNF[75]. The European Liver Transplant Registry survey showed a lower 5-year survival rate with CIT over 15 h if compared with CIT less than 12 h[76]. Similar results were reported in a United States survey[77].

Liver grafts from elderly donors and/or donors with steatosis are even more affected by prolonged CIT, which should be kept below 8 h[78]. In our previous series, we showed that, albeit not statistically significant, graft survival was lower for grafts > 80 years with a CIT > 8 h (3-year survival 82.6% *vs* 61.9%, $P = 0.078$)[5].

Biopsy

Biopsy can be a valuable tool to determine the utility in pursuing donation in ECDs, particularly with liver-only donors[79]. Nevertheless, there are still no guidelines on its routine use in this kind of donors. In our previous experience, we performed on demand biopsies based on surgical evaluation at procurement and discarded livers in the presence of macrovescicular steatosis > 30%, necrosis > 5%, fibrosis > 2% as per Ishak's score, severe micro and macroangiopathy, and severe inflammation[5]. In a recent review some authors stated that pre-transplant histopathological evaluation is a time-effective, accurate, and reliable tool to assess liver quality from candidate deceased donors[80]. Pre-transplant biopsies are of value in the selection of donor livers for transplantation, especially in case of ECD, and should be performed more frequently in order to avoid unnecessary loss of organs suitable for transplantation and transplantation of inappropriate organs[80]. Correlation of histopathological findings with clinical conditions is essential and requires excellent communication between pathologists, surgeons, and the other members of the transplant team.

Machine perfusion and machine preservation

Machine perfusion and/or preservation (PM) consists of a pump creating a flow of blood or preservative solution through the organ[81]. This continuous perfusion allows better preservation, oxygenation and removal of metabolites[81]. Another advantage is the possibility to monitor the performance of the graft and to provide adjuvant substances[81,82]. PM can be divided into 3 groups based on the temperature of preservation: Hypothermic (HMP) at 4 ℃; normothermic (NMP) at 37 ℃, and subnormothermic (SNMP) at 20 ℃-25 ℃. Different flow regimes and pressures (pulsatile *vs* unpulsatile), single (artery) *vs* dual perfusion (artery and portal vein), oxygenated *vs* nonoxygenated[82].

The HMP, by lowering the metabolism but providing metabolic substrates, is reported to protect grafts from ischemic insults related to reperfusion[83]. Guarrera *et al*[83] were the first to analyze the impact of this method in

humans observing an attenuation of biochemical markers of liver injury, less biliary complications and hospital stay. They concluded that HMP of donor livers provided safe and reliable preservation[83]. The addiction of oxygen to perfusion solution (hypothermic oxygenated perfusion) in animal models showed further improvements[84,85].

The SNMP lowers the liver metabolic demand in sub-physiological temperature conditions, however maintaining sufficient metabolism for viability testing and improvement of graft function[86,87]. In an animal model, a beneficial effect with lower transaminases was found, while rising total bilirubin levels suggested inadequate prevention of I/R or hypothermia-induced biliary damage[86].

This technique was tested on livers discarded from transplant and showed a preservation of liver function with minimal injury and an improvement in various post-ischemia hepatobiliary parameters[87].

The NMP system seems the most promising technique as it allows to maintain livers in an environment similar to human body with normal temperature and metabolite and oxygen supply[88]. Moreover, it allows to monitor liver function parameters such as pH, transaminases, and the bile output[88]. It has been recently tested on a human setting with optimal results showing favorable safety and feasibility profiles, whilst costs seems to limit its widespread applicability.

Back-table

The major back table concerns using ECD are related to arterial structure and anatomy. When using grafts from old donors, arterial evaluation plays a pivotal role as aneurysms or severe atherosclerosis may led to graft discharge[5]. Graft arterial reconstruction of a right replaced hepatic artery using a safe and rigorous technique does not enhance the risk of arterial complications or graft loss, and the technique using the GDA stump is to be recommended for routine use[89].

In order to reduce the incidence of ITBL, some authors reported on the use of back-table arterial pressure perfusion to achieve reliable perfusion of the capillary system of the biliary tract, which may be impaired by the high viscosity of UW solution[90]. A highly significant difference in the incidence of ITBL was found when this technique was used when compared to standard perfusion with lower peak AST and ALT levels[91]. The authors' conclusion was that arterial back-table pressure perfusion is an easy and reliable method for preventing ischemic biliary lesions in LT and suggested it should be standard in liver procurement[90,91].

Split liver grafts

Split liver transplant (SLT) is a technique used to increase the donor pool that creates two allografts from a single liver graft. Technical and logistical issues in both donors and recipients prevent its worldwide usage and it accounts for only 4% of LT in the United States. Splitting was originally performed as an *ex-vivo* bench procedure but it was after performed as an *in-situ* procedure as well in order to reduce CIT and prevent blood loss after reperfusion[92]. SLT in adults is associated with significant increase (10%) of graft failure and recipient morbidity. Results are notably better in children[93].

Even if procured from ideal donors these grafts should be considered as extended criteria as the volume is lower and may lead to hepatic failure in the post-operative course. Moreover non-optimal positioning in the recipients may lead to compromised venous outflow and complications as biliary leakage, hepatic artery thrombosis (HAT), IPF are more frequent than in whole organ LT[94].

SLT for two adults has been performed reporting worst results with the left segment and is actually considered a high risk procedure due to insufficient parenchymal volume and complex vascular anastomosis[94-96].

The use of left allografts should be primary considered for pediatric patients while the use of right allografts in adults marginally increases risks of graft failure so that SLT should be considered as a safe technique to expand the donor pool.

TRANSPLANTATION

At transplantation, the main strategies encompass the modality of graft reperfusion and use of temporary porto-caval shunts[97-100]. Graft reperfusion can be sequential or simultaneous. In the sequential mode, the liver graft is perfused first *via* portal vein or hepatic artery, while in the simultaneous technique the arterial anastomosis is fashioned during the anhepatic phase and both the porta and the hepatic artery are perfused simultaneously[97,98].

Sequential reperfusion is associated with a shorter CIT. However, if the porta is perfused first the delay of arterial revascularization is associated with more pronounced microvascular disturbances, while if the hepatic artery is perfused first this might cause an increased blood flow called reactive hyperemia[98]. Simultaneous graft reperfusion results in improved oxygenation but may entail a longer CIT[97-99].

The use of temporary porto-caval shunt (TPCS) is controversial. The hemodynamic and immunological consequences of portal vein clamping are poorly characterized. In animal models an interruption of portal flow for up to 90 min induces edema of the gut with mucosal damages. The use of TPCS was initially advocated for patient with acute liver failure without collaterals. It was thought to be useless in cirrhotic patients as the presence of collaterals resulted in little hemodynamic changes during portal clamping.

In a prospective randomized trials Figueras *et al*[101] demonstrated a beneficial effect of TPCS in terms of decreased blood transfusions especially in patients with severe portal hypertension and high portal flow.

Renal impairment is a common sequel to LT. Impaired renal perfusion, vascular instability and the release of cytokines at reperfusion contribute to a reduction in renal

function[102].

In a study by Ghinolfi *et al*[100] it has been shown to improve hemodynamic stability and renal function in patients undergoing orthotopic LT. Lower graft survival rates were reported in patients of high DRI liver grafts when a TPCS was not used[100]. TPCS improves the perioperative outcome, this being more evident when high-risk grafts are allocated to high-risk patients[100].

Another series by Pratschke *et al*[103] showed reduced hepatic injury and increased portal flow after reperfusion. Retransplantation rate was decreased and long term survival increased. This effect was more pronounced when using ECD[103].

POST-TRANSPLANT COMPLICATIONS

ITBL

Biliary complications continue to be a major issue in LT ranging between 10% and 30%[104,105]. Anastomotic strictures (AS) are mainly related to the surgical technique and to ischemia to the distal bile stump[104,105]. Non-AS (NAS) are thought to be caused by three different types of injuries: I/R, immune-mediated mechanisms, and cytotoxic injury from bile salts[106]. The highest incidence of NAS has been reported for DCD livers as they suffer from an additional warm ischemia time during organ retrieval[107]. NAS with a patent hepatic artery are generally referred to as ITBL. The incidence of ITBL in ECD is higher, due to a major vulnerability to I/R injury and to warm ischemia time and CIT, and are reported in up to 14% *vs* 3% for younger donors.

Several strategies have been suggested to reduce the incidence and severity of ITBL[108-111]. The relative importance of portal venous blood flow in developing ITBL was outlined by Farid *et al*[108] because these lesions were diagnosed in patients with a normal arterial flow but with portal thrombosis. In order to reduce the incidence of graft microangiopathy and thrombosis, back-table pressure arterial perfusion and the use of plasminogen activators have been proposed with favorable results. Simultaneous graft revascularization seems to be associated with a lower incidence of ITBL than sequential revascularization[109,110]. Viscous preservation solutions may negatively impact on efficacy of flushing of the bile ducts capillaries, resulting in residual bile crystallization and obstruction[111-113]. Use of less viscous solutions, like HTK, seems to provide better results in reducing the incidence of biliary tract injuries, despite the recent results of the European liver transplant registry data[67,112].

In a large study, a CIT > 10 h was found to be associated with a higher incidence of ITBL and every effort should be made not to exceed this limit[113].

Vascular complications

HAT represents more than 50% of all arterial complications following LT and it is divided into early (< 4 wk from LT) and late HAT (> 4 wk from LT)[114-116]. Early HAT is generally related to technical problems and can have serious consequences[115]. Emergent interventions are usually needed with early HAT because of its related ischemia/necrosis of the bile duct system[114]. Although urgent re-transplantation is considered the main treatment for early HAT, endovascular interventions including percutaneous transluminal angioplasty (PTA), intra-arterial thrombolysis (IAT) in selective cases, and stent placement may be alternative treatments[117,118]. Currently many centers consider interventional radiology as first choice for the management of early HAT[118,119]. IAT can be considered but is related to high risk of hemorrhage in patients with recent (< 2 wk) surgery[120]. Late HAT can be silent in up to 50% of patients with only mildly elevated liver function tests[116]. Symptomatic patients often present with biliary complications with recurrent cholangitis, abscess and biliary leakage or stricture, and the presentation may be insidious[116]. Late HAT is usually due to ischemic or immunologic injuries and can be treated with biliary stenting and/or endovascular interventions[116,117].

Hepatic artery stenosis (HAS) has been treated both with PTA and stent placement with comparable results[117-120]. The use of PTA for HAS can reduce the rate of HAT[120]. Solitary stenosis are usually treated with PTA while angioplasty is used for tandem lesions[117-120]. These procedures are related to complications and risks that have to be taken into consideration and moreover are, in some cases, ineffective so that surgical intervention such as anastomotic reconstruction or re-transplantation must be applied[120].

Aneurysms and pseudoaneurysms of the hepatic artery are very rare complications after LT, but they are associated with high mortality rates (> 50%)[121]. Both can be treated by either surgical or endovascular procedures[121].

A series from the UNOS database reported that the risk of HAT with loss of the graft increases progressively with each decade of donor age > 50 years, such that a 61% risk was associated with use of donors older than 70 years[122]. A recent experience with donors older than 70 years showed a lower incidence of HAT (4.7%) and improved results were attributed to better management[123]. Ghinolfi *et al*[5] in their series showed a 3.6% of severe vascular complications: 10 (1.2%) HAT and 7 HAS (0.8%) with no differences across all donor age groups. There were no differences in terms of donor age for the 11 (1.3%) cases of portal thrombosis as well[5].

Venous complications are more frequent in LDLT[124]. Compared with the arterial complications, venous adverse events usually have a better response rate to endovascular interventions, such as angioplasty or stent placement[124,125]. Endovascular procedures are considered as the first choice for post-transplant portal vein complications with high success rates[125].

CONCLUSION

The imbalance between the number of potential

recipients and available donors still represents a major concern in LT so that the expansion of donor pool continues to be a priority.

Improvements have been made in order to better define ECD but many lacks still exist regarding their use. Some centers routinely use ECD but their results seem to be related more to their practical experience and can be reproduced with difficulties.

Some ethical considerations should also be carried out; the use of ECD can constitute a risk for recipients in terms of PNF, DGF and surgical complications so that some authors advocate the use of an informed consent about allograft specific risks. Moreover some combinations such as ECD with HCV recipients have been proved to be dangerous in terms of recurrence and survival but they have never been clearly censored by the scientific community.

It has finally to be taken into consideration that this is an expanding field in LT so that applying too strict rules on ECD use may preclude further advancement. Many efforts should be carried out in order to establish an international consensus on ECD use and to create guidelines that could be largely adopted.

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