

The Utility of Marginal Donors in Liver Transplantation

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The shortage of organs has led centers to expand their criteria for the acceptance of marginal donors. The combination of multiple marginal factors seems to be additive on graft injury. In this review, the utility of various marginal donors in patients requiring liver transplantation will be described, including older donors, steatotic livers, non-heart-beating donors, donors with viral hepatitis, and donors with malignancies. The pathophysiology of the marginal donor will be discussed, along with strategies for minimizing the ischemia reperfusion injury experienced by these organs. Finally, new strategies for improving the function of the marginal/expanded donor liver will be reviewed. (*Liver Transpl* 2003;9:651-663.)

Improvements in surgical techniques, immunosuppression, and patient management have led to the optimization of liver transplantation outcomes. Although over 4800 liver transplantations were performed in the United States in the year 2000, the waiting list for liver transplantation is increasing at a greater pace, with close to 17,000 patients registered for liver transplantation.¹ Furthermore, because of the Model for End-stage Liver Disease scoring system for liver allocation, which negates waiting time, those patients on the list are likely to be in critical need of liver replacement. To expand the potential donor pool, clinicians are continually modifying the criteria of an acceptable liver donor and are looking to marginal or expanded donors to meet the waiting list demands. Donors are generally considered marginal if there is a risk of initial poor function (IPF) or primary nonfunction (PNF), although those that may cause late graft loss are also included. Although the organs from marginal donors may not be optimal, they are a viable alternative to dying while waiting for transplantation, and their use needs to be pursued.¹

This review discusses donor risk factors associated with liver graft dysfunction and how the use of marginal donors will impact patient and graft survival. Clinical and new investigational strategies aimed at manipulating marginal donors to improve outcome will be covered, as well as approaches for marginal donor allocation.

Definition of Marginal Donors and Risk Factors Associated With Liver Graft Dysfunction

An accepted definition of marginal liver donors has not been definitively established within the liver transplan-

tation community. Among the most prominent donor characteristics that may influence the development of IPF or PNF in the recipient include increasing age, prolonged ischemia, hypotension and inotropic support, gender mismatch, non-heart-beating donors (NHBD), and steatosis (Table 1).²⁻⁷ More long-term determinants of poor patient and graft survival are malignancy or viral hepatitis in the donor.

Donor Age

Donor age has been steadily increasing over the past decade. In 1991, 13% of cadaveric liver donors were over the age of 50; 10 years later it is close to 30% (Fig. 1).¹ Initially donor age >50 years was thought to be associated with poor graft outcomes, but studies^{4,8-12} have shown that aged donors (>50 years) without additional risk factors have similar outcomes to younger donors and age itself should not be a contraindication to liver donation. Donor age of more than 70 years, however, was found to be associated with lower patient and graft survival.¹³

In contrast to other organs, the liver may be more immune to senescence, particularly in the otherwise healthy person. This is possibly because of the liver's large functional reserve, regenerative capacity, and dual blood supply, which exceeds its metabolic needs.¹⁴ On the other hand, older donor livers tend to be smaller and darker-colored, and may have developed fibrous thickening of the capsule.¹⁵ Whether these morphologic changes impact on organ function after transplantation should be elucidated. It has been shown that older

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Table 1. Potential Risk Factors Associated With Liver Graft Dysfunction

Donor	Perioperative	Recipient
Age	Warm ischemia	Age
Gender	Technical complications	Medical status
Race	Blood product use	Renal insufficiency
Weight		Retransplantation
Cause of brain death		Use of vasopressors
Intensive care unit length of stay		
Use of vasopressors		
Cold preservation		
High serum sodium		
Steatosis		
Partial liver grafts		

donor livers are more susceptible to endothelial cell injury from cold ischemia and show decreased adenosine triphosphate (ATP) synthesis after reperfusion, which may influence the decreased regenerative capacity¹⁶ and decreased synthetic function seen in these organs.¹⁷

Although older age, when controlling for other factors, may not adversely impact patient and graft survival, recipients of older donor livers seem to experience a greater degree of delayed function, with a notable cholestatic pattern after transplantation.¹⁸ However, over 75% of the recipients in this study did regain normal liver function.¹⁸ Furthermore, by maintaining cold ischemia time (CIT) to 8 hours or less, long-term graft function was shown to be equivalent in donors

greater and less than 50 years of age.¹⁸ Older donors also have an increased incidence of steatosis,^{8,19} which may potentiate cold preservation injury.²⁰ Therefore, older donors need to be carefully selected, and each organ requires an assessment based on other risk factors, especially steatosis and CIT.

Prolonged Ischemia

One of the major reasons for initial liver graft dysfunction is ischemic injury. Prolonged CIT is an independent risk factor for liver preservation injury, even more so than donor age.²¹ Grafts with more than 14 hours of cold ischemia have been associated with a two-fold increase in preservation damage resulting in prolonged postoperative course, biliary stricture, and decreased graft survival.²¹⁻²⁴ Furthermore, the length of cold preservation has been associated with sinusoidal cell damage and hypercoagulability.²⁵ Cold preservation decreases metabolic activity 10-fold, and increases anaerobic metabolism and lactic acidosis, therefore resulting in mitochondrial energy uncoupling. Decreases in ATP and build-up of hypoxanthine result in an increase of substrate for reactive oxygen species, which potentiates ischemia-reperfusion (IR) injury.

There are also data to suggest that the period of rewarming (warm ischemia time) intensifies cold ischemic injuries^{23,26} and that warm ischemia impairs liver function.²³ In one analysis, rewarming ischemia time was an independent determinant of graft survival, whereas CIT was not.²³

Hypotension and Inotropic Support

Previous United Network for Organ Sharing (UNOS) data have shown that donor organs subjected to prolonged hypotension have no significant increase in posttransplantation graft loss. However, graft loss was

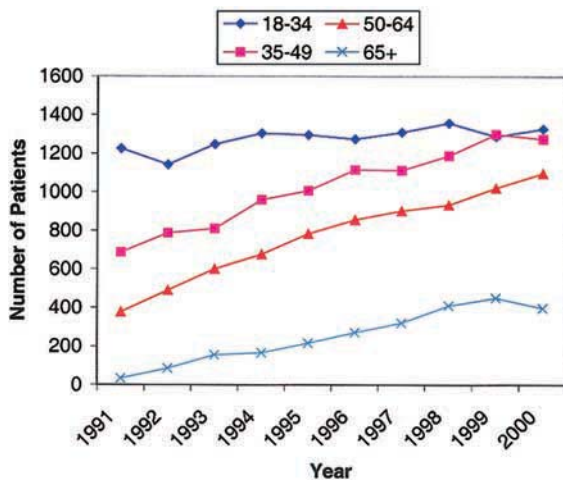


Figure 1. Relationship of donor age to the number of patients receiving organs. Donor age greater than 50 years has been steadily increasing over the last decade, whereas the number of donors ages 18 to 34 has remained constant. (Data from the UNOS 2001 annual report.)¹

increased in liver transplant recipients when donors received norepinephrine.²⁷ In other studies, dopamine dose $\geq 10 \mu\text{g}/\text{kg}/\text{min}$ ²⁸ or $6 \mu\text{g}/\text{kg}/\text{min}$ ²⁹ had a significant effect on early graft function. However, other factors such as age and fat content may modify these effects in either direction.

Gender

Transplantation of a female kidney donor into a male recipient leads to decreased graft survival.³⁰ Recently, a multivariate analysis of UNOS data from 1992 to 2000 showed that gender-mismatched liver transplant recipients had a higher likelihood of graft failure when compared with gender-matched liver transplant recipients (12.2% versus 11.3% respectively; $P = .013$). A female recipient receiving a liver from a male donor had no increased risk of graft failure (11.5%). However, the graft failure rate was worse in male recipients receiving female donor organs (12.9%; $P = .003$).³¹

NHBDs

Interest in using NHBDs has increased because of the lack of organ availability. In 1997, the Institute of Medicine determined that organs retrieved from NHBDs were medically effective and ethically acceptable.³² NHBDs are considered to be less than optimal for transplantation because of prolonged warm ischemia before cold preservation. Controlled NHBDs provide organs that are comparatively far less prone to ischemic damage and tend to offer superior posttransplant function. The controlled NHBDs undergo circulatory arrest after planned withdrawal of life support, most often in the operating room, with a donor surgical team available. Uncontrolled NHBDs sustain circulatory arrest and either fail cardiopulmonary resuscitation and/or arrive dead at the hospital. Death in this group is completely unplanned; as a result, the ischemic time for the organs is often extensive before recovery.³³ Liver allograft survival from uncontrolled NHBDs has been poor (17% to 41%).³⁴

Casavilla et al³⁴ from Pittsburgh University published a study on 24 recipients of NHBDs, both controlled and uncontrolled. Among the uncontrolled group ($n = 14$), the 1-year patient and graft survival was 95% and 86%, respectively. Mean serum creatinine in this group was 1.7 mg/dL. Among subjects in the controlled group ($n = 10$), the 1-year patient and graft survival rate was 94% and 82%. Mean serum creatinine in this group was 2.5 mg/dL. The data from these NHBDs showed similar 1-year patient survival rates when compared with data from heart-beating donors

from Pittsburgh showing a 93% survival rate. The results suggest that the use of controlled or uncontrolled NHBDs lead to acceptable graft function and patient survival, although there was a high incidence of acute tubular necrosis among the group.

In a series from the University of California at Los Angeles (UCLA), 29 NHBDs (16 uncontrolled and 13 controlled) were used for liver transplantation. In the uncontrolled group, 1 PNF occurred in a donor with 75 minutes of warm ischemia. One-year patient and graft survival in this group was 88% and 75%, respectively. In the controlled group, 1 PNF was seen in a donor who had 48 minutes of warm ischemia. Patient and graft survival was 85% and 77%. Based on this experience, a warm ischemia time of < 30 minutes did not adversely affect patient or graft survival (unpublished data).

Steatotic Donors

Steatosis is frequent in donor livers and has been reported in 9% to 26% of donors.^{35,36} Causes are varied and include obesity, older age, alcoholism, diabetes mellitus, and postmortem nutritional changes. Histologic patterns in donor livers show two types of steatosis, a diffuse small droplet vacuolization or microsteatosis without macrovesicular deposit, and a combined pattern of large and small vacuole deposits or macrosteatosis.^{37,38} Fat accumulation in the cytoplasm of hepatocytes is associated with an increase in cell volume, which may result in partial or complete obstruction of the hepatic sinusoidal space.³⁹ Furthermore, animal studies have shown that fatty livers experience greater reduction in energy stores during cold storage and have a decreased capacity to restore ATP levels after reperfusion.⁴⁰ Additional factors contributing to the poor outcomes of fatty livers after transplantation may include Kupffer cell dysfunction, increased leukocyte adhesion, more vigorous lipid peroxidation, and ischemic necrosis of endothelial cells.⁴¹

Steatotic livers have been associated with increased primary nonfunction^{35,42,43} and initial poor graft function, although recoverable within the first week after liver transplantation.⁴⁴ Grafts that have more than 60% fat content should not be used, unless there is an urgent situation requiring them to be used as a bridge.³⁶ Transplantation of livers with mild steatosis ($< 30\%$) has similar results to transplantation with nonfatty livers, assuming there are no other donor or recipient risk factors. Recent studies have reported adequate function of livers with microvesicular steatosis.^{37,38,45,46} Clinically, recipients who receive grafts with moderate steatosis ($> 25\%$ to 30%) have impaired early graft function in the first 3 days as reflected by a higher peak

Table 2. Outcomes of Donor-Transmitted Malignancies in Liver Transplant Recipients

Tumor Types	N	Tumor Type	Outcome
Melanoma	5	Melanoma	Dead (n = 12)
Choriocarcinoma	3	Glioblastoma	5
Glioblastoma	3	Choriocarcinoma	3
Adenocarcinoma	3	Neuroendocrine	2
Kaposi's sarcoma	1	Kaposi's sarcoma	1
			Alive (n = 5)
Neuroendocrine	1	Adenocarcinoma	3
Squamous cell	1	Choriocarcinoma	1
		Squamous cell	1
Total	17	(Four patients were retransplanted)	

serum glutamic oxaloacetic transaminase, lower bile output, and increased intraoperative bleeding. Marsman et al⁴⁷ transplanted 59 livers with up to 30% fat and compared them to time-matched controls; the fatty liver group had a decreased 4-month graft survival and a decreased 2-year patient survival. In this study, graft survival was decreased if the recipient was more critical pretransplantation. Steatotic livers with <30% macrovesicular fat can be used to expand the donor pool as long as efforts are made to minimize other adverse donor and recipient factors. For livers with >30% macrovesicular steatosis, strategies to modify the graft, as discussed later, will need to be used for a consistent successful outcome.

Donors With Malignancies

Quantification or calculation of the true risk of donor-transmitted malignancies has been difficult because of underreporting to the Organ Procurement and Transplantation Network/UNOS registry. Although the Israel Penn International Transplant Tumor Registry has been collecting data on posttransplantation malignancies since 1968, the lack of a true denominator makes it difficult to calculate the frequency of cancer transmission from cadaveric donors. Thus far, there have been 17 documented cases of donor-transmitted malignancies to liver transplant recipients (Table 2).^{48,49} Based on these data, cancer histologies with prohibitively high transmission risk include melanoma and choriocarcinoma. The cancer-free interval must also be considered on evaluation of donors with a history of malignancy. However, tumors that may possess the potential of unpredictable recurrence include breast, colon, lung, melanoma, and renal cell carcinoma.⁴⁹

Donors with histories of primary central nervous system (CNS) tumors have also been evaluated.⁴⁸

Between January 1992 and December 1999, 397 of 42,340 cadaver donors had a history of CNS tumors. The 397 donors provided livers for 293 recipients, of whom 6 developed posttransplantation malignancies (two tongue, three skin, one posttransplantation lymphoproliferative disorder). The most common donor histological tumor types were medulloblastoma (2) and glioblastoma multiforme (17). Patient survival of the liver recipients from donors with CNS tumors and non-CNS tumors was similar. The risk of tumor transmission from donors with a primary CNS malignancy is small. Certain tumor types, such as glioblastoma and medulloblastoma, carry a higher risk of transmission and should be avoided unless the recipient status warrants the extra risk.⁴⁸ Donors who have had previous craniotomies and ventricular peritoneal shunts may have a greater risk of extracranial metastasis.

Donors With Viral Hepatitis

Acquisition of the hepatitis B virus (HBV) remains a concern after liver transplantation because the majority of the infections occur via transmission by the donor liver.⁵⁰ Donors who are hepatitis B surface antigen negative (HBsAg⁻) but hepatitis B core antigen positive (anti-HBc⁺) have transmitted HBV infection to liver recipients who are HBsAg⁻ at a rate of 33% to 78%.⁵¹⁻⁵³

In a retrospective study by Prieto et al, HBV infection developed in 15 of 30 (50%) recipients of livers from anti-HBc⁺ donors compared with 3 of 181 (2%) livers from anti-HBc⁻ donors ($P < .00001$).⁵⁰ Eighteen anti-HBs grafts were transplanted into 10 patients, 6 anti-HBc⁺ recipients, and 2 anti-HBs⁺, anti-HBc⁺ recipients. None of these 18 developed HBV infection after a median follow-up of 24 months.⁵⁰ Recipients of anti-HBc⁺ livers are at high risk for acquiring HBV infection, whereas recipients of anti-HBs livers are sig-

nificantly less likely to acquire HBV infection, and this latter group may play a role in expanding the donor pool.

The use of hepatitis B immune globulin (HBIG) and lamivudine combination therapy has been investigated as a means of preventing recurrence of HBV in the recipient and viral transmission from donor to recipient. A study by Dodson et al reported that the use of this combination therapy in 15 anti-HBs⁻, HbsAg⁻ patients resulted in all patients remaining HbsAg⁻ at the average follow-up of 459 days.⁵⁴

In another study, the 1-year actuarial survival rate in 35 liver transplant recipients who received anti-HBc⁺ grafts was 88.6% with HBIG and lamivudine prophylaxis.⁵⁵ More recently, Joya-Vazquez et al showed that the use of anti-HBc liver grafts does not affect patient or graft survival.⁵⁶ With prophylaxis, patient survival was similar at 12 months (85% both groups) and at 60 months (68% anti-HBc⁺; 67% anti-HBc⁻; $P = \text{NS}$).

Transplantation because of hepatitis C (HCV) cirrhosis has increased because of the greater prevalence of the virus in the last 15 years.⁵⁷ HCV⁺ donors should only be used in HCV⁻ recipients under exceptional circumstances, whereas the organs may be implanted in HCV⁺ recipients, as shown by several studies.⁵⁸⁻⁶⁰

Testa et al reported their findings on the long-term effects of using hepatitis C–positive liver grafts. Of the 137 patients who underwent transplantation secondary to HCV, 115 received HCV⁻ grafts and 22 received HCV⁺ liver grafts. The HCV recurrence rate was similar in both groups (42% versus 55%; $P = \text{NS}$). Patient and graft survival at 4 years posttransplantation was 84% and 72% in the HCV⁺ donor grafts, compared with 79% and 76% in the HCV⁻ donor grafts.⁵⁹ Similar rates of HCV recurrence, patient survival, and graft survival have been reported by other centers using HCV⁺ liver grafts for patients requiring transplantation for HCV cirrhosis.^{60,61}

Data from the UNOS Scientific Registry showed that patient survival at 2 years was higher in 96 recipients of HCV⁺ than in 2,827 recipients of HCV⁻ grafts (90% versus 77%; $P = .01$).⁶² In the largest series from a single institution, the outcomes of 59 patients who underwent transplantation for HCV receiving HCV⁺ grafts were similar to those of 419 patients who did not receive a HCV⁺ graft.⁶³

Pathophysiology of the Marginal Donor

IR injury is the underpinning of graft dysfunction that is seen in the marginal organ. On restoring the blood supply, the liver is subjected to insult, aggravating

injury already caused by the initial ischemia (Fig. 2).^{25,64} IR injury to endothelial cells disrupts the sinusoidal microcirculation by up-regulating the attraction, activation, adhesion, and migration of neutrophils (polymorphonuclear cells [PMN]) causing local tissue destruction by release of proteases and oxygen-free radicals. IR in liver transplantation leads to PNF/IPF and increased rejection, and contributes to high morbidity.

Preservation injury in liver allografts occurs at four stages: (1) prepreservation injury, (2) cold preservation, (3) rewarming, and (4) reperfusion injury. Factors in the donor medical history may enhance prepreservation injury. They include a history of donor alcohol or drug abuse, presence of a fatty liver, cardiovascular instability after brain death, hypotension during the donor operation, and surgical trauma at the time of harvest.

Cold preservation is also associated with injurious effects. The Kupffer cells, endothelial cells, and Ito cells are more susceptible to cold IR injury as compared with hepatocytes. Sinusoidal endothelial cells undergo apoptosis and coagulative necrosis after cold storage followed by reperfusion of liver grafts.⁶⁵ The sinusoidal cell lining, which is most sensitive to cold ischemia, becomes deficient, exposing the hepatocyte microvilli.⁶⁶ White blood cells attach where the sinusoidal cells vacated and obstruct the sinusoids and liver blood flow. Additionally, PMNs release numerous mediators, amplifying the inflammatory response.⁶⁷⁻⁶⁹ Platelets, which adhere to the sinusoids, almost immediately on reperfusion aggravate the degree of preservation injury via a mechanism of procoagulant activity and cytokine release, which results in hepatocyte hypoxia.⁶⁹

Additionally, on reperfusion, Kupffer cells become activated, generating inflammatory mediators such as cytokines and oxygen-derived free radicals, which are injurious to endothelial cells and hepatocytes. The energy stores of the liver (e.g., ATP, glycogen) are depleted, severely compromising hepatocyte function.^{41,70} Furthermore, morphologic changes to the endothelial cells are observed, resulting in an endothelin/nitric oxide imbalance during the reperfusion period, which has been correlated with decreased liver blood flow.^{64,66,71}

Steatotic livers have been shown to be more susceptible to IR injury after transplantation. During cold ischemia, structural changes attributable to the disruption of hepatic microcirculation caused by fat droplets and hepatocellular swelling results in occlusion of the sinusoids. After reperfusion, loss of viable endothelial cells and activation of Kupffer cells are accentuated over the nonsteatotic graft.

The migration of leukocytes and adherence to the

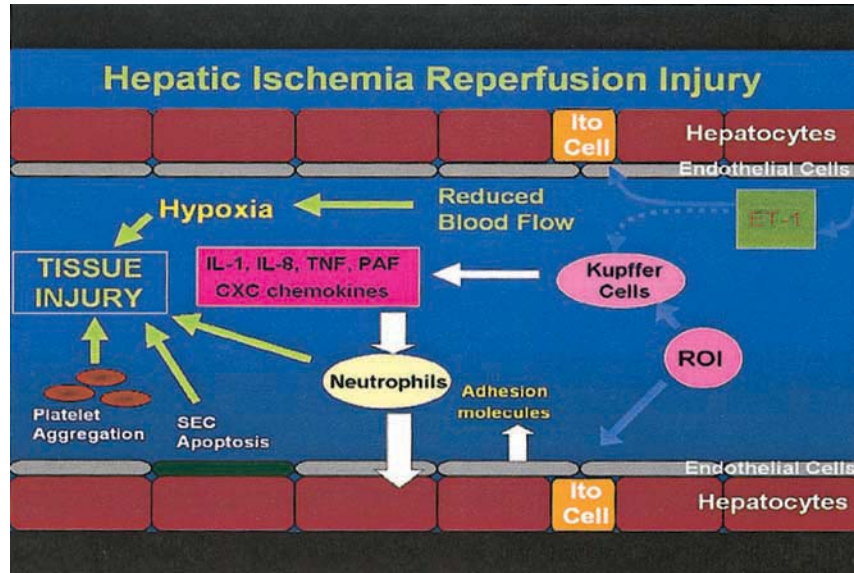


Figure 2. Mechanism of ischemia reperfusion injury. A hepatic sinusoid lined by endothelial cells. On the outer surface, hepatocytes line the sinusoid interspersed with Ito cells. The first step in the IR cascade is the liberation of endothelin-1 (ET-1), which activates Ito cells and results in constriction of the hepatic sinusoids. In addition, the Kupffer cells are activated and result in the release of reactive oxygen intermediates (ROI). The combination of these factors results in reduced blood flow through the liver. The second step involves up-regulation of the adhesion molecules (i.e., selectins, integrins, and immune globulins). The activation of adhesion molecules and liberation of chemokines from Kupffer cells stimulates avid rolling and sticking of neutrophils to endothelial cells in the hepatic sinusoid. In addition, platelet aggregation and sinusoidal endothelial cell (SEC) apoptosis result in tissue injury. This mechanism of IR injury is exacerbated in the steatotic liver.

vascular endothelium is an early and key step in IR injury and is mediated by three classes of adhesion molecules: the selectins, integrins, and immune globulins. Selectins mediate the initial sequence of events by recruiting leukocytes and platelets, which tether and roll on the vascular endothelium.⁷² There are various subclasses of selectins found on different cell types. P-selectin (CD62P) is expressed on activated platelets and endothelial cells.⁷³ Activated endothelial cells express both P-selectin and E-selectin (CD62E). L-selectin is expressed on all classes of leukocytes.⁷⁴ The three selectins have a high affinity for and bind a variety of carbohydrate ligands. One such glycoprotein expressed on the surface of leukocytes is P-selectin glycoprotein ligand-1 (PSGL-1), which can bind all three selectins.^{75,76}

IR injury is a dynamic process involving an interaction of all of the pathophysiologic and molecular events, including production of reactive oxygen species, Kupffer and Ito cell activation, release of chemokines and PMNs, and platelet and leukocyte adhesion. All of these in concert result in decreased sinusoidal blood flow, endothelial cell apoptosis, and necrosis, with eventual hepatocyte loss.

Liver Preservation and Procurement

Several clinical measures can be taken to increase the liver's tolerance to IR injury. The use of improved preservation solutions allows extended ischemia and rewarming times. University of Wisconsin (UW) solution, considered the gold standard of preservation solutions, has proven itself to be effective in preventing organ damage during CIT and extending the threshold for prolonged storage.⁷⁷ UW achieves this by preventing the classic effects of hypothermia that include cell swelling, intracellular acidosis, impaired energy metabolism, and the accumulation of reactive oxygen intermediate precursors.⁷⁸ Cell swelling is prevented by two impermeants present in the UW, lactobionate and raffinose. Intracellular acidosis is diminished because UW does not contain glucose and also facilitates the resynthesis of ATP with the addition of adenosine.^{71,79} However, UW does have some qualities that hinder the preservation of the organ, such as its increased viscosity, preventing adequate perfusion of the donor organ, and elevated potassium levels, requiring the organ to be flushed before blood flow is established in the recipient.⁷⁷

An alternative preservation solution to UW is histi-

dine-tryptophan-ketoglutarate (HTK) or Bretschneider solution. Its formulation was compounded to retard acidosis (histidine), prevent membrane injury (tryptophan), and provide a substrate for energy metabolism (ketoglutarate).⁷⁸ Recent studies comparing the effectiveness of the two solutions have shown superior outcomes with the HTK solution when the cold ischemic times were below average.^{78,80} On the other hand, with long cold ischemic times, UW seems to represent a better solution for preservation purposes.⁷⁷

Tissue Matching

The role of human leukocyte antigen (HLA) matching in liver transplantation is not as clearly defined as with kidney transplantation. In a few studies, HLA matching did not impact graft survival but did decrease acute rejection episodes.⁸¹⁻⁸⁴ Conflicting results have also been published in which better matching decreased graft survival.^{85,86} The results of lymphocytotoxic cross-matches have been more reliable; positive cross-matches are associated with decreased graft survival and increased acute rejection.^{83,87-89} Dvorchik et al have recently have shown that two mismatches at the DR loci are associated with an increased rate of acute rejection compared with those with 0 or 1 mismatches. The length of time in the intensive care unit (ICU) further augmented acute rejection in those patients with two DR mismatches.⁹⁰ HLA matching at the DR loci may be useful in marginal liver grafts, with which the likelihood of a prolonged ICU stay is increased. However, the practicality of this approach, particularly when ischemia time may be prolonged, is questionable.

Recipient Factors Affecting Marginal Donor Function

The general condition of the liver recipient can have a major impact on graft function: the bad host effect. As an example, the incidence of PNF after transplantation for fulminant hepatic failure is higher than that observed for other indications.⁹¹ Thus, marginal donors and suboptimal recipients are a poor combination. Additionally, baseline renal insufficiency as seen in hepatorenal syndrome has been associated with increased primary dysfunction after transplantation,²⁴ longer ICU stays, greater hospitalization costs, higher rates of acute renal failure requiring dialysis, and a greater mortality rate.⁹²⁻⁹⁶ Recipient obesity (body mass index $> 30 \text{ mg/m}^2$) has also been reported to increase the risk of postoperative complications after liver transplantation, such as respiratory failure, systemic vascular

complications, and infections.⁹⁷ All of these factors negatively affect graft function, which has lead some investigators to recommend matching the graft to the recipient (i.e., marginal grafts for good-risk patients as opposed to placement in high-risk recipients).

The choice of immunosuppression may also influence postoperative complications in patients receiving marginal donor livers. In a study by Mueller et al,⁹⁸ no differences in the incidence of good, moderate, and poor initial graft function were observed in the cyclosporine (CsA)- or tacrolimus (TAC)-treated patients. However, patients with initial poor function treated with CsA had higher rates of steroid-resistant rejection compared with TAC-treated patients. The CsA patients with initial poor function had the highest rate of chronic rejection (9% compared with 4% in the TAC patients with initial poor function). Long-term patient survival was not influenced by initial graft function. However, the CsA-treated patients had higher rates of retransplantation and of acute and chronic rejection.⁹⁸

Allocation Decisions

Because of limited organ availability, the practice of using marginal donor livers has become arguably more accepted. However, there are no guidelines for the allocation of these organs as has been proposed by UNOS for kidneys. In this system, patients willing to accept a marginal kidney are noted on the waiting list and on the availability of a marginal organ, it is then distributed to those designated.⁹⁹ In the past, marginal grafts were transplanted into seriously ill patients with poor graft and patient survival.⁴² Recently, however, there has been a shift, and now these marginal donor organs tend to be allocated to more stable patients, yielding satisfactory results.⁴² This practice is not mandated by UNOS for livers, and only occurs when other centers refuse an organ for a particular patient, when it may then be used at the center's discretion.

Because the single and cumulative impact of donor risk criteria is unknown, one center sought to assess a scoring system that would determine the accumulation of donor risks on outcome of liver transplantation.⁴⁵ Donor criteria including donor age > 60 years, ICU stay > 4 days, CIT > 13 hours, hypotensive episodes, elevated bilirubin level, and elevated transaminase level was given a score of 1. Dopamine doses $> 10 \text{ } \mu\text{g/kg/min}$ and serum sodium $> 155 \text{ mEq/L}$ were given a score of 2. Recipients who underwent transplantation of marginal livers with a score of 3 or greater showed a decrease in graft survival at 6 months (92% liver score of 0 versus 60% liver score of 3; $P = .012$) and an increase

in the rate of delayed function (2% liver score of 0 versus 26% liver score of 3; $P = .03$).⁴⁵

Established guidelines do not exist from empirical evidence, thus, specific organ allocation policies have not been codified. However, based on the literature, which describes high-risk donor variables, it would be reasonable for transplant centers that use marginal donors to establish a "secondary list" of recipients who would be suitable for a marginal graft; at present this is only done for HBc+ and HCV+ donors. A more comprehensive screening procedure for other factors should be explored to maximally utilize marginal liver donors. A full disclosure and consent process regarding the marginal donor would be mandatory in this instance. The practice of having such an alternative list has proven to be successful in a large cardiac transplant program.¹⁰⁰ Over a 5-year period, 17 patients underwent transplantation at UCLA from the alternate waiting list. The early mortality rate for the patients on the alternate list was 12% versus 6% on the standard list ($P = NS$). The 1-year survival rate was 75% versus 83% for the alternate and standard groups, respectively ($P = NS$).¹⁰⁰ This list was able to provide heart transplants for patients who may have been turned down for transplantation (age > 65 or need for a third heart transplant) with similar outcomes to patients on the standard list.

Experimental Strategies for the Manipulation of Marginal Donors

Although transplantation should not be performed in the face of absolute risk factors for graft nonfunction, such as > 60% steatosis with prolonged ischemia, transplantation may be performed in the presence of a relative risk factor while controlling for other factors (Table 3). Strategies for manipulating marginal organs may reduce factors injurious to graft function, thus salvaging an otherwise discarded organ.

Reduction of hypothermic injury remains a desired good and is achieved by keeping CIT to a minimum. On the other hand, this injury has been shown to be lessened by the use of normothermic extracorporeal liver perfusion (NELP), which provides pulsatile perfusion with whole blood and an electrolyte solution. Additionally, NELP has the capability of providing continuous monitoring of hepatic viability. Results in porcine transplant models have shown NELP to be superior to cold perfusion via UW solution.¹⁰¹ For NHBD, machine perfusion with the addition of pentoxifylline or arginine to perfusion solutions may also improve the quality of these grafts by reversing ischemic damage.^{102,103}

Hypernatremia was shown by the UCLA group to

Table 3. Donor Risk Factors—Impact on Outcomes

Parameter	Relative Risk	Timing
High vasopressor support	+	Early
Longer intensive care unit stay	+	Early
Hypernatremia (> 155 mEq/L)	+	Early
Older age (> 50 y)	++	Early
Macrosteatosis (< 30%)	++	Early
Macrosteatosis (> 30%)	++++	Early
CIT (> 12 h)	++/+	Early/late
NHBD (controlled)	++/+	Early/late
NHBD (uncontrolled)	+++ / ++	Early/late
Female sex	+	Late
Viral carrier	+	Late

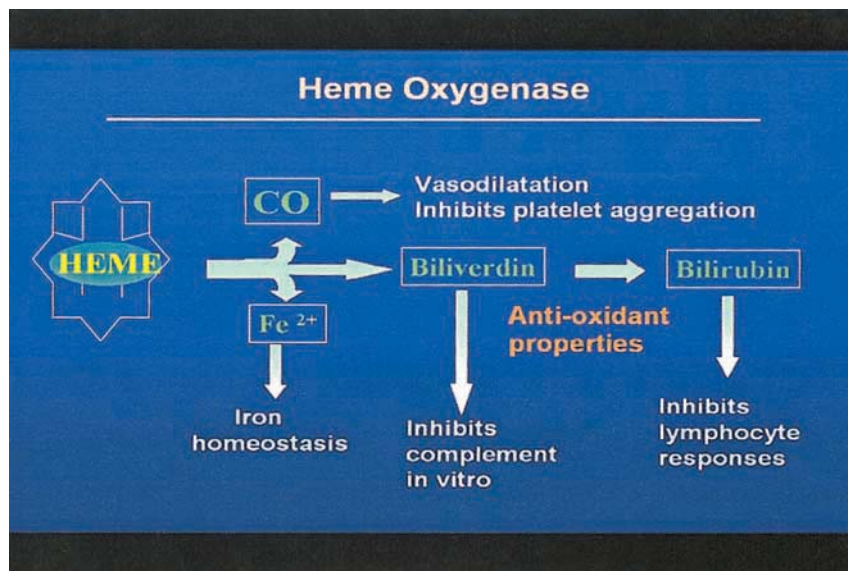
be one of five variables with prognostic value in predicting graft survival after transplantation.²⁸ The mechanism for the deleterious effect of elevated donor sodium on graft function is thought to be a result of cell swelling and exacerbation of reperfusion-mediated injury. A pilot study at UCLA examined the effects of infusing 5% dextrose in water through the inferior mesenteric vein before harvesting the organ if the donor sodium level was greater than 160 mEq/L. In the 17 donors that received the D₅W to decrease hypernatremia, the rates of recipient DNF/PNF were 0% compared with a group of historical controls that experienced a 60% incident of delayed non-function/PNF (unpublished data).

Use of various portal flush solutions before reperfusion to minimize the effects of cold ischemia has also been investigated. One such solution, Carolina rinse solution, contains cytoprotective components such as glutathione, adenosine, and allopurinol. In an uncontrolled trial, use of the Carolina rinse before transplantation was found to prevent endothelial cell death, decrease Kupffer cell activity, and prolong graft survival.¹⁰⁴⁻¹⁰⁶

Recently, studies have been conducted to target in a systematic fashion the various components of the IR cascade. Several novel molecules have been studied to minimize IR injury and are in preclinical development. These include interfering with one of four components of IR injury: (1) endothelin receptor blockade, (2) adhesion molecule blockade, (3) endothelial cell apoptosis, (4) and up-regulation of the heme-oxygenase system.

An early stage endothelin (ET) receptor blocker, tezosentan, has been studied in the rat model. This agent is a substrate for ET α receptors, found on Ito cells, and ET β receptors, found on endothelial cells and Kupffer cells.¹⁰⁷ In rats given tezosentan before reper-

Figure 3. Heme oxygenase-1 offers protection against oxidative stress. The heme oxygenase system catalyzes the conversion of heme into carbon monoxide (CO) and ferrous and biliverdin. CO causes vasodilatation and inhibits platelet aggregation, the ferrous cation is involved with iron homeostasis, and biliverdin has been found to inhibit complement in vitro. Biliverdin is further broken down into bilirubin, which inhibits lymphocyte responses.



fusion, serum glutamic oxaloacetic transaminase release was significantly lower, and at 24 hours, histology was markedly improved over that of controls. There was also a reduction in chemokines (interleukin-1 β and MIP-2) released from the Kupffer cells.¹⁰⁷

Soluble forms of the adhesion molecule receptor blockers prevent neutrophils and platelets from adhering to endothelial cell surface. Brain death increases sensitivity to IR injury and CIT and may contribute to immunogenicity. Transcription of proinflammatory cytokines significantly increases in brain-dead donor (cytokine storm) compared with living donor transplants.¹⁰⁸ In a series of ex-vivo liver perfusions of > 50% steatotic liver grafts and in a group of orthotopic liver transplants between steatotic Zucker and lean Zucker rats, blockade of selectins by P-selectin glycoprotein ligand-1 (PSGL1-Ig) significantly improved liver function over control animals. Ex-vivo livers perfused with PSGL1-Ig had lower transaminase release, increased portal venous flow, and increased bile production compared with controls. Histologic architecture of the liver after 2 hours of perfusion showed minimal changes in the PSGL1-Ig-treated grafts versus severe centrilobular disruption, drop-out, and necrosis in controls. Survival of lean rats who underwent transplantation with steatotic livers in the control group was only 40% compared with 90% in the same combination treated with PSGL1-Ig at harvest and before reperfusion.¹⁰⁹

Evidence suggests that overexpression of heme oxygenase-1 (HO-1), also known as hsp32, exerts potent cytoprotective effects.^{110,111} HO-1 belongs to a family of enzymes involved in the catabolism of heme into bilirubin, free iron, and carbon monoxide (CO) (Fig.

3). HO-1 confers protection against oxidative stresses such as hyperthermia, hypoxia, and radiation, and is considered to be one of the most sensitive indicators of cellular injury.¹¹⁰⁻¹¹² HO-1 prevents the deleterious effects of heme, which promotes lipid peroxidation and free radical formation.¹¹⁰ The mechanisms underlying HO-1's beneficial effects against IR injury have yet to be elucidated, but may be related to the production of CO. CO, released directly from heme, may act as a regulatory molecule in cellular and biologic processes, including endothelium vasodilatation,¹¹³ inhibition of platelet aggregation,¹¹⁴ suppression of inducible nitric oxide synthase,¹¹² down-regulation of procytokines via the mitogen-activated protein kinase pathways,¹¹⁵ and inhibition of endothelial apoptosis.¹¹⁶ Investigations in which HO-1 is up-regulated through pharmacologic induction (cobalt protoporphyrin) or gene therapy have shown promising results in attenuating IR injury and prolonging graft survival.^{112,117,118}

Summary

Based on this review, the following recommendations can be made. Marginal liver grafts from donors that are > 60 years old, have > 30% or < 60% steatosis, experience an ICU stay > 5 days, or require > 1 vasopressor should be maximized by keeping CIT < 8 hours and selecting a good-risk recipient. Donors with serum sodium > 160 mEq/L should be pretreated with D₅W to lower sodium to < 155 mEq/L. Gender matching and cross-matching, although theoretically described, is not practical in the current allocation scheme. The use of donors with prior malignancy must be individualized depending on tumor type, length of

time from detection, or treatment. Hbc-positive and HCV-positive donors are acceptable with prophylactic therapy and matched patient selection, respectively.

Conclusions

With the increasing waiting time for liver transplantation, donor organs remain in short supply. Criteria for marginal donors vary from center to center, however, because of the lack of organs, more centers are transplanting livers that were previously considered unacceptable. The deleterious effects on graft function seem additive with the presence of multiple marginal characteristics and can contribute to the etiology of IR injury experienced by the organ. Multiple methods are currently being investigated to minimize the effects of IR injury to allow the use of marginal organs. Until there are enough donors to meet the needs of the transplant waiting list, marginal donors may be a viable option to expand the donor pool.

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