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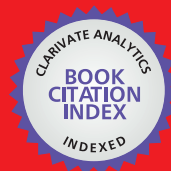
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# Initial Poor Graft Dysfunction and Primary Graft Non-Function After Orthotopic Liver Transplantation

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## 1. Introduction

Orthotopic liver transplantation (OLT) has become the effective treatment for end-stage liver diseases. Since the 1980s, the successful rate of liver transplantation has increased with the improvement of operative methods and the use of University of Wisconsin (UW) solution. Nevertheless, liver procurement and implantation are inevitably associated with allograft damage. Lack of donor liver hinders OLT and leads to an increase in the number of deaths on the waiting list and as a consequence the transplant community has greatly expanded the use of non-ideal donors to improve the rate of transplant (Delmonico et al., 2005). Donor pool expansion strategies such as the use of living donors, cadaveric split livers, and “extended criteria donors” (ECD)/marginal donors are being pursued. These may predispose recipients to graft dysfunction and increase long-term risk and survival in recipients.

Primary graft non-function (PGNF) is the most severe type of graft damage after OLT, followed by initial poor graft function (IPGF) (Chui et al., 2000). Emergency hepatic retransplantation is necessary because of the extreme high mortality of PGNF. Evaluation of IPGF is determined by a high level of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST). IPGF directly influences the survival in the hepatic graft. Ultimately, some grafts recover completely while others need to be retransplanted (Pokorny et al., 2000). IPGF and PGNF are associated with many factors, such as status of donor, quality of hepatic graft, long-term warm ischemia, cold ischemia, primary liver disease, status of liver function of recipients and operative techniques (Brokelman et al., 1999). For evaluation of the donor hepatic allograft with regard to pre-existing diseases, in particular macrovesicular steatosis and post-transplant evaluation of hepatic graft function, liver biopsy is the most challenging and valuable clinical practice. Recently, some progress has been made in the prevention and treatment of early hepatic graft dysfunction. The present review provides broad discussion in the relevant sections.

## 2. The definitions and clinical features

### 2.1 Definitions of IPGF and PGNF

The concept of primary graft dysfunction is not clear. In clinical liver transplantation, primary dysfunction is defined as IPGF or PGNF. The difference between IPGF and PGNF

considers the degree of dysfunction, the timing and length after liver transplantation and the need for urgent retransplantation.

The diagnostic standard for IPGF has not been set yet, and there are different opinions among some reported definitions (Table 1). The criteria of Ploeg et al (Ploeg et al., 1993) and Gonzalez et al (Gonzalez et al., 1994) are adopted by some earlier studies. The introduction of Nanashima et al's criteria (Nanashima et al., 2002), which is simpler, more convenient and dependable, for an ALT and/or AST level above 1500 IU/L within 72 hours after OLT means poor hepatic allograft function as early as possible and also puts us on guard to prevent PGNF.

Definitions of IPGF	References
Graded initial liver function	(Gonzalez et al., 1994)
Severe: sum of score 7-9	
Moderate: 5 or 6	
Mild: 3 or 4	
AST > 2000 IU/L and prothrombin time >16 s on days 2-7	(Ploeg et al., 1994)
ALT > 2500 IU/L within 3 days	(Ardite et al., 1999)
AST or ALT > 2500 IU/L within 24 hours	(Chui et al., 2000)
ALT or AST > 1500 IU/L within the first 3 days	(Nanashima et al., 2002)

Table 1. Diagnostic definitions of IPGF

PGNF is manifested by hepatic cytolysis and rapidly rising transaminases, absence of bile production, severe liver-related coagulation deficit, hypoglycemia, high lactate levels, and hepatic hemodynamic instability (Uemura et al., 2007). According to the United Network for Organ Sharing (UNOS), PGNF is defined as irreversible graft function requiring emergency liver replacement during the first 10 days after liver transplantation. It is characterized by an AST  $\geq$  5000 UI/L, an international normalized ratio of prothrombin (INR)  $\geq$  3.0, and acidosis (pH  $\leq$  7.3 and/or lactate concentration  $\geq$  2 $\times$  normal).

Silberhumer et al (Silberhumer et al., 2007) proposed four grades of initial graft function over the first postoperative 5 days as: (1) good function, AST maximal 1000 UI/L and spontaneous prothrombin time > 50%; (2) fair function, AST 1000-2500 UI/L, clotting factor support < 2 days; (3) IPGF, AST > 2500 UI/L, clotting factor support > 2 days; and (4) PGNF, retransplantation required within 7 days.

## 2.2 Clinical features

IPGF is a severe clinical complication after OLT, with elevation of serum aminotransferase. Some patients may further develop PGNF (Mor et al., 1992), which is manifested by hepatocellular necrosis, rapidly rising transaminases, absence of bile production, severe liver-related coagulation deficit, high lactate levels, systemic hemodynamic instability and acute renal failure (Pokorny et al., 2000).

Nevertheless, it is inconvenient to make the diagnosis of IPGF or PGNF due to the lack of precise to objective criteria in clinical practice. The great variability in the incidences reported in different series, which ranges from 2% and 23%. Ploeg et al reported the rates of IPGF and PGNF for 22% and 6%, respectively (Ploeg et al., 1993). Ardite et al's study showed the rates of IPGF and PGNF for 19% and 0% (Ardite et al., 1999) in contrast to 29.5%

and 0.93%, respectively in Chui et al's investigation (Chui et al., 2000). In the study by Chen et al, the rates of IPGF and PGNF were 36.25% and 1.3%, respectively (Chen et al., 2007). In The Scientific Registry for Transplant Recipients (SRTR) analysis enrolling 10545 deceased donors, adult first transplants, 613 (5.8%) cases of PNGF occurred (Johnson et al., 2007). In another single-center analysis of donors after cardiac death (DCD), PGNF occurred in 6.4% of brain dead donors (DBD) vs. 11.8% of DCD (Abt et al., 2004).

In partial liver transplantation, the biochemical profile of small for-size syndrome (SFSS) includes cholestasis with elevated conjugated bilirubin, mild to moderate elevation of transaminases, and prolonged prothrombin time. Approximately 50% of recipients with SFSS will die of sepsis within 4 - 6 weeks after septicemia (Heaton, 2003).

### **3. The impact of donor, recipient and factors associated with IPGF and PGNF**

Graft dysfunction can be a result of various factors including status of donor, quality of hepatic graft, organ harvesting, ischemia-reperfusion injury, SFSS, primary liver disease, status of liver function of recipients and operative techniques, etc. Although ECD from older donors or steatotic grafts provide a solution for the shortage of allografts, donor factors could still predispose recipients to IPGF and/or PGNF. With extended application of living donor liver transplantation (LDLT), SFSS has become the main problem. The occurrence of SFSS depends on a number of recipient, graft and technical factors.

#### **3.1 Recipient' factors**

##### **3.1.1 Child-Pugh classification and Model for End Stage Liver Disease (MELD) score**

In a retrospective study (Chen et al., 2007), Child-Pugh classification had no influence on the occurrence of IPGF, yet the ratio of Child-Pugh C in the IPGF group was higher than in the non-IPGF group. Their data suggested that Child-Pugh C of recipients was one possible risk factor leading to IPGF.

The MELD score, which combines the serum creatinine, bilirubin, and INR of recipient to predict waitlist mortality, has been considered to be controversial in evaluating the occurrence of PGNF. In the SRTR analysis by Johnson et al, MELD score as a compound of risk factors was not included in models to predict PGNF (Johnson et al., 2007).

Although MELD score at the time of transplantation showed only a trend of an association with recipient survival, it had no significant impact on initial graft function (Silberhumer et al., 2007).

##### **3.1.2 Other factors before transplantation**

Elderly recipient and urgent recipient status with the use of ECD graft were associated with an increased risk of death by 50% (Cameron et al., 2006). Although the recipient's age and clinical status before OLT were related to IPGF (Moreno Sanz et al., 1999), it was not confirmed in a recent study (Chen et al., 2007). In addition, the incidence of PGNF was more in male recipients receiving grafts from female donors than in patients with male donors (Marino et al., 1995).

Avolio et al considered that hyperbilirubinemia before OLT was associated with PGNF (Avolio et al., 1999). In the STRT analysis by Johnson et al, it was showed that by life support, mechanical ventilation, use of inotropes, hemodialysis, initial status 1 and use of a shared transplant were risk factors for PGNF by univariate analysis on recipients (Johnson

et al., 2007). In the multivariate model, only recipient serum creatinine, bilirubin, on life support and status 1 at transplant were significant risk factors for PGNF. For pediatric recipients, diagnosis of tumor, dialysis prior to transplant, recipient body weight  $\leq 6$  kg increased the risk of graft failure (Lee et al., 2008).

Controversies exist regarding the morbidity and mortality of patients undergoing OLT at the extremes of the body mass index (BMI). An extremely BMI is defined as a BMI  $< 18.5$  kg/m<sup>2</sup> or a BMI  $> 40$  kg/m<sup>2</sup>. In a study of the UNOS database, which reviewed 73,538 adult liver transplants, there was no significant impact of underweight or very severely obese on the occurrence of PGNF though these patients experienced significantly higher rates of morbidity and mortality compared with recipients with intermediate BMI range (Dick et al., 2009).

### **3.2 Donor's factors**

#### **3.2.1 Extended criteria donors and marginal donors**

The use of ECDs is associated with increased graft loss and decreased survival. At present, no consensus has been reached for the definition of ECD graft. However, several risk factors associated with an increased rate of IPGF or PGNF have been identified. These risk factors include donor's factors (age, gender, obesity, weight, height, BMI, elevated liver functions, hypotension/increased administration of vasopressor and hypernatremia, cause of donor death and graft steatosis) and transplant factors such as type of graft and cold ischemia time (CIT) (Müllhaupt et al., 2008).

Definition for ECD by the suggestion of Chung et al includes age  $> 65$  years, macrovesicular steatosis  $> 40\%$ , serum sodium  $> 155$  mmol/L, positive serological data, carcinoma outside the liver, DCD, and split-graft liver transplantation (Chung et al., 2010). In a large retrospective cohort study of 1153 OLT (Cameron et al., 2006), the ECD included donor age over 55 years, donor hospital stay  $>5$  days, CIT  $>10$  hours and warm ischemia time (WIT)  $> 40$  minutes.

Marginal donors were considered by Pokorny et al as follows (Pokorny et al., 2005): older than 60 years, a prolonged intensive care unit (ICU) stay  $> 4$  days with ventilatory support, a prolonged CIT  $>10$  hours, a high vasopressor support (high-dose dopamine or any other vasoactive amines), a donor peak serum sodium  $> 155$  mEq/L, a donor serum creatinine  $> 1.2$  mg/100 mL and BMI  $> 30$ . When patients had more than three cumulative marginal donor criteria, the rate of PGNF was 36% (Pokorny et al., 2005).

#### **3.2.2 Age**

Hepatic graft from old donor may increase susceptibility to cold ischemia-induced endothelial injury with impaired adenosine triphosphate (ATP) synthesis post reperfusion and result in decreased regenerative capacity and synthetic function (Gordon Burroughs & Busuttil, 2009).

Donor age has been a well-recognized factor affecting PGNF. In the study by Feng et al, donor age over 40 years was associated significantly with the relative risk of graft failure (Feng et al., 2006). In the multivariate analysis by Lake et al, donor age over 40 was related with a 1.67 increased risk of graft failure in HCV-infected recipients and with 2.21 increased risk of graft failure when donor age was more than 60 years (Lake et al., 2005). In the SRTR analysis by Johnson et al, donor age more than 40 years was an independent factor for the prediction of PGNF (Johnson et al., 2007). Inversely, in other studies, donor age was not



confirmed to increase the incidence of PGNF (Busquets et al., 2001; Grande et al., 1998; Washburn et al., 1996). However, these studies were based on a much smaller scale.

### 3.2.3 Steatosis

Hepatic steatosis is more common in donors of advanced age, as well as in those with a history of obesity, dyslipidemia, metabolic disorders, or diabetes.

The decreased allograft survival rate after using fatty livers is seen in the early post-transplant period (Verran et al., 2003). In contrast to macrovesicular steatosis, livers with predominantly microvesicular steatosis show less injury and allograft survival rates are similar to those in nonsteatotic grafts (Fishbein et al., 1997). So, adoption of an allograft with microvesicular steatosis is safe and the pool of donors has expanded. However, macrovesicular steatosis is one of the important risk factors leading to IPGF (Selzner & Clavien, 2001). Macrovesicular steatosis may impair mitochondrial oxidation of fatty acids, increase synthesis and delivery of fatty acids to hepatocytes, reduce the removal of hepatocyte triglycerides, and microcirculatory disruption with narrowing of the hepatic sinusoids by enlarged, fat-laden hepatocytes (Reddy & Rao, 2006). Further more, macrovesicular steatosis may increase the oxidative injury of endothelial cell and hepatocyte and the vulnerability to secondary insults, including the cytokine surge associated with brain death as well as cold ischemic injury (Gordon Burroughs & Busuttil, 2009). In addition, the occurrence of IPGF or PGNF may be due to the release of free lipids from fatty hepatocytes, probably as a consequence of cold ischemia. Free lipids result in the production of reactive oxygen species after reperfusion initiating a cascade, which finally leads to sinusoidal endothelial cell damage (Selzner & Clavien, 2001; Kupiec-Weglinski & Busuttil, 2005). Severe fatty livers are more susceptible to warm and cold ischemia reperfusion injury than normal ones (Kukan & Haddad, 2001). The type of damage is not through the pathway of cellular apoptosis, but necrosis (Selzner & Clavien, 2000). Overexpression of the mitochondrial uncoupling protein 2 in fatty livers may contribute to decreased cellular ATP levels (Serviddio et al., 2008), which reduces the capacity for hepatic regeneration (Selzner et al., 2000). There are some other factors which may play a role in fatty livers after reperfusion, like the down-regulation of peroxisome proliferator-activated receptor- $\alpha$ , an important regulator of the hepatic inflammatory response to ischemia reperfusion, and overexpression of adiponectin, a fat cell-secreted hormone with antidiabetic and antiinflammatory activities (Massip-Salcedo et al., 2008).

Ureña et al considered that hepatic allografts with moderate macrovesicular steatosis (30% - 60%) can be used selectively in critical situations; mild macrovesicular steatosis (< 30%) is relatively safe, and severe cases (> 60%) enhance the rate of PGNF (Ureña et al., 1998; D'Alessandro et al., 1991). Canelo et al reported that PGNF can occur with donors having moderate macrovesicular steatosis. In this study, mild macrovesicular steatosis was 27.1% in the non-IPGF group and 13.8% in the IPGF group (Canelo et al., 2000). There was no significant difference between those groups.

In the study by Verran et al, 6% of patients receiving grafts with severe macrovesicular fat required retransplantation within 3 months versus 1.4% of those receiving mildly steatotic grafts (Verran et al., 2003). In another multivariate analysis by Salizzoni et al, cumulative adverse factors on the incidence of PGNF included donor age, recipient HCV viremia, and prolonged CIT by use of grafts with over 15% macrovesicular steatosis (Salizzoni et al., 2003).

### 3.3 Small-for-size syndrome (SFSS)

SFSS is a well-recognized complication that occurs primarily in living donor or reduced size liver transplantation. The principal pathogenesis of SFSS is the unbalance between the accelerated liver regeneration and the increased demand of liver function, leading to severe graft dysfunction with prolonged hyperbilirubinemia and increased ascites (Ikegami et al., 2008). SFSS is caused by multiple factors including graft quality, recipient conditions and technique problems. SFSS is seen most frequently when the graft volume/standard liver volume ratio (GV/SLV) is less than 30% or partial liver grafts with graft weight/recipient weight ratios (GW/RW) less than 0.8%. Another important factor leading to SFSS is portal venous hypertension (Shimamura et al., 2001). In recent study by Hill et al, GW/RW did not appear to be the only determinant of outcome after partial liver transplantation and the occurrence of SFSS was influenced not only by the graft size but also by other factors such as the degree of portal hypertension as well (Hill et al., 2009). For adult patient receiving right lobe graft, low intraoperative body temperature, graft size of < 35% of the estimated standard graft weight, and middle hepatic vein occlusion were significantly independent factors in determining hospital mortality (Fan et al., 2003). Other factors may impact the occurrence of SFSS (Emond et al., 1996; Yoshizumi et al., 2008): donor-related factors including advanced donor age and steatotic graft and recipient-related factors including higher MELD scores, septic complications, rejection and biliary complications. Donor age over 50 years is associated with reduced regenerative capacity, increased susceptibility to prolonged cold ischemia, increased rates of IPGF/PGNF and prolonged cholestasis. Fatty infiltration of 30% or more in grafts in splitting or auxiliary liver transplantation may increase incidence of SFSS (Heaton & Rela, 2001).

### 3.4 Ischemia reperfusion injury

Hepatic ischemia reperfusion injury is an important factor related to IPGF (Mueller et al., 1997). During the course of clinical liver transplantation, warm ischemia, cold ischemia, rewarming ischemia, and reperfusion occur sequentially in the allograft. Severe ischemia reperfusion injury leads to immediate graft non-function and triggers irreversible ischemic biliary lesions.

#### 3.4.1 Warm ischemia

Hepatic warm ischemia occurs when the liver is maintained at body temperature but is inadequately perfused with blood. Although grafts from DCD increase the number of organs available, longer non-heart beating time and hypotension lead to warm ischemia, which may cause cell necrosis in the hepatic parenchyma after reperfusion and more easily result in IPGF or PGNF.

The process of warm ischemia reperfusion injury involves activation of immune pathways and is dominated by hepatocellular injury. There are 2 distinct phases: the early phase (less than 2 hours after reperfusion) is marked by activation of immune cells (CD4+T cells and Kupffer cells) and production of oxidant stress; the later injury (6 to 48 hours after reperfusion) is characterized by neutrophil-mediated inflammation and hepatocellular injury (Klune & Tsung, 2010). In addition, warm ischemia also damages endothelial cells (Selzner et al., 2003; Teoh & Farrell, 2003).

As prolonged WIT is common with uncontrolled DCD, standardized criteria in donor selection have not been established and limited data concerning its use have been reported. D'Alessandro et al reported that the average WIT was 16.4 minutes in 19 cases of OLT using a DCD and the rate of PGNF was 10.5% (D'Alessandro et al., 2000). Gomez et al also reported that with 5-15 minutes average WIT, IPGF occurred in 6 of 8 cases and PGNF in the other two cases (Gomez et al., 1997). In a matched-pair analysis, PGNF was occurred 5.1% in livers of DCD versus 0% in those of DBD (Pine et al., 2009). In another retrospective study, PGNF was presented 3.7% in livers of DCD versus 1.4% in those of DBD (Grewal et al, 2009). In the study of 141 patients by de Vera et al, the incidence of PGNF was 12% in livers of DCD versus 3% in livers of DBD. WIT over 20 minutes was associated with poorer DCD outcomes (de Vera et al., 2009). In the study by Chen et al, the average WIT was significantly longer in the IPGF group than in the non-IPGF (Chen et al., 2007). Changes after warm ischemia were seen in liver biopsies before OLT. Furthermore, WIT was 7 minutes in only one case who suffered from PGNF. From logistic regression analysis, the possibility of IPGF was enhanced significantly when WIT exceeded 3 minutes. These results suggested that extension of WIT is a direct risk factor in bringing on IPGF. Recently, an analysis of OPTN/UNOS data demonstrates donor age > 60 years, WIT > 30 minutes, CIT > 10 hours, retransplantation, and recipient cardiopulmonary support pre-OLT to be the most important predictors of significantly PGNF and patient survival after transplantation of a DCD graft (Mateo et al., 2006). Similarly, the University of California, Los Angeles (UCLA) reported with controlled DCD that PGNF occurred only in 2.6% of the recipients with about 30 minutes of mean WIT (Gordon Burroughs & Busuttil, 2009).

### 3.4.2 Cold ischemia

Although the cold preservation time of the allograft is extended greatly by the use of UW solution in clinical liver transplantation, cold ischemia is an important factor for IPGF and PGNF.

Some investigations showed that sinusoidal endothelial cells are damaged first in cold ischemia reperfusion, then hepatocellular cells, because of activation of Kupffer cells and neutrophilic leukocytes, and the release of inflammatory mediators, which leads to impairment of hepatic allografts (Jaeschke, 2006). During the phase of cold ischemia, loss of mitochondrial respiration and ATP depletion occur consequently though hypothermia reduces the metabolic rate and prolongs the time that anoxic cells can retain essential metabolic functions (Selzner et al., 2003). Energy-dependent metabolic pathways and transport processes deteriorate and proteinases and metalloproteinases are activated. These changes lead to the sinusoidal endothelial cells to be lifted away from the underlying matrix. Loss of sinusoidal microvascular integrity and function that occurs during cold preservation is attributable to the reperfusion phase. The degree of endothelial damage has been correlated with functional impairment of the liver following reperfusion.

Piratvisuth et al retrospectively summarized 230 cases of liver transplantation where the rate of IPGF was significantly higher when CIT was more than 720 minutes (Piratvisuth et al., 1995). In the study by Janny et al, AST level increased significantly after OLT if cold ischemia time was above 600 minutes (Janny et al., 1997). Adam et al thought that the possibility of hepatic allograft loss was significantly enhanced when cold ischemia time was



over 720 minutes (Adam et al., 1992). De Vera et al suggested that CIT over 8 hours was significantly related to the occurrence of PGNF (de Vera et al., 2009). In the study by Chen et al, the cold preservation time in all cases was within 1000 minutes, averaging 622 minutes in the IPGF group and 515 minutes in the non-IPGF group (Chen et al., 2007). A significant difference was shown by univariate analysis and not by multi-regression analysis. The results above suggested that extension of CIT is a potential risk factor for IPGF and PGNF.

### 3.4.3 Rewarm ischemia

The anhepatic phase was defined as the time from the physical removal of the liver from the recipient to the time of graft recirculation. During the anhepatic period, rewarming ischemia injury occurs because of the rise of allograft temperature. Strasberg et al considered that rewarming ischemia injury as the most important risk factor for IPGF can lead to increased AST level and decreased rate of allograft survival (Strasberg et al., 1994). The tolerance limits of allografts to rewarm ischemia time are not clear. In the study by Chen et al, although rewarming ischemia time was significantly longer in the IPGF group than in the non-IPGF group, shown by univariate analysis, multiregression analysis showed no significant difference between the two groups when rewarming ischemia time was above 45 minutes (Chen et al., 2007). In Nanashima et al's investigation, average rewarming ischemia time was about 110 minutes in both IPGF group and non-IPGF group (Nanashima et al., 2002). Platz et al reported that serum levels of ALT, AST, E-selectin and hyaluronic acid increased significantly if the anhepatic period was above 90 minutes (Platz et al., 1997). Delva et al thought that rewarm ischemia time should not exceed 60 minutes (Delva et al., 1989). Recently, in a logistic regression analysis by Ijtsma et al, the anhepatic phase over 100 minutes [odds ratio (OR), 4.28] was an independent predictive factor for graft dysfunction (Ijtsma et al., 2009). These results suggested that extended rewarming ischemia time is an important risk factor for IPGF.

## 4. Histopathological characteristics

For evaluation of the donor hepatic allograft with regard to pre-existing diseases, in particular macrovesicular steatosis and post-transplant evaluation of hepatic graft function, liver biopsy is the most challenging and valuable clinical practice.

### 4.1 Steatosis of donors

Excessively fatty liver, specifically macrovesicular (large droplet) fatty liver, is associated closely with risk for IPGF or PGNF. Microvesicular (small droplet) fat in the donor liver is not a contraindication for transplantation (Fishbein et al., 1997). As macroscopy is unreliable in the appraisal of the severity of steatosis, bioptical evaluation before transplantation is recommended in cases where significant steatosis is suspected. The percentage of steatosis should be determined by liver biopsy before transplantation.

### 4.2 Ischemia reperfusion injury

According to the experiences of Demetris et al, it is electron microscopy, not light microscopic examination, before transplantation which can be used to accurately assess the cold ischemia injury and post-transplant allograft function (Demetris et al., 2009). However,

after reperfusion, light microscopic examination is more informative. Reperfusion biopsies show the damage, with reasonable accuracy, can predict IPGF or PGNF during the first few weeks post operation.

Severe cold preservation reperfusion damage is one of the major reasons for PGNF. Histologically, it is characterized by massive necrosis, which becomes evident within the first 48 hours after transplantation (Chazouillères et al., 1993). The hepatic microenvironment involving in the pathogenesis of preservation injury includes lymphocytes, hepatocytes, bile duct epithelium, sinusoidal cells, Kupffer cells, neutrophilic leukocytes and platelets. Sinusoidal endothelial cells are the first affected then hepatic parenchymal cells (Clavien, 1998) and finally hepatic allograft function is impaired.

Most biopsy specimens were essentially normal before transplantation except for focal mild spotty acidophilic necrosis, a slight increase in sinusoidal inflammatory cells and mild hepatocellular swelling. It is important that the integrity of the sinusoidal lining cells could not be evaluated reliably with immersion fixed, paraffin-embedded and hematoxylin and eosin-stained slides of biopsy specimens before transplantation. By contrast to biopsy specimens before transplantation, various pathological findings after reperfusion are demonstrated. In severe cold ischemia reperfusion injury under the examination of light microscopy (Kakizoe et al., 1990), larger areas of necrosis appeared, which were classified as focal or zonal with periportal or bridging necrosis, and severe neutrophilic exudation. The focal or zonal necrosis was either centrilobular, periportal, or both in its distribution. In general, the degree of inflammation increased after revascularization and paralleled the degree of necrosis. For hepatocytes, microvesicular steatosis, focal hepatocellular cytoaggregation and mild hydropic cell swelling were detected. In more severe injury, if hepatocellular necrosis was mainly in zone 3, centrilobular hepatocyte dropout is seen. The adjacent viable zone 2 hepatocytes proliferate to restore the liver parenchyma, and mitoses are seen. If periportal necrosis and bridging necrosis are present, the parenchymal collapse triggers ductular reaction that can link adjacent portal tracts and distort the architecture. More severe injury is also usually accompanied by centrilobular hepatocellular swelling, and canalicular and cholangiolar cholestasis (Demetris et al., 1987).

Ultrastructural analysis by Kakizoe et al revealed that the sinusoidal microvasculature was more sensitive to organ procurement and cold preservation than the endothelium of larger vessels or hepatocytes (Kakizoe et al., 1990). These changes at the end of cold ischemia before transplantation included endothelial cell vacuolization and a partial or complete detachment of individual cells, resulting in denudation with loss of the space of Disse. The sinusoids contained cellular debris, presumably fragments of hepatocytes, detached endothelial cells and occasional inflammatory cells. The hepatocellular changes detected were relatively mild and included cytoplasmic fat vacuolization, a decrease in the mitochondrial matrix, formation of hepatocellular cytoplasmic blebs protruding into the sinusoids and occasional loss of hepatocyte microvilli on the sinusoidal surface. After reperfusion, increased sinusoidal cellular debris, focal sinusoidal endothelial cell denudation and occasional active appearing Kupffer cells that contained cytoplasmic vacuoles and electron-dense material are observed. Inflammatory cells were often clustered in areas of microarchitectural distortion and sinusoidal lining cell denudation. They were also seen near Kupffer cells and directly adherent to hepatocytes or amidst cellular debris. Hepatocyte alterations were relatively mild. The changes included an increase in lipid vacuolization, detachment of cytoplasmic blebs and, in some areas, formation of electron-dense material in the cytoplasm. The mitochondria in some cases showed mild

swelling, and the rough endoplasmic reticulum showed focal mild fusiform dilatation when compared with samples taken before transplantation.

In some circumstances, the histological findings showed minimal alterations in some patients who experienced IPGF or PGNF. Biopsies after reperfusion may be performed too soon after reperfusion to detect morphological changes of irreversible ischemic injury.

#### 4.3 SFSS

The histopathologic features of SFSS had been summarized by Demetris et al (Demetris et al., 2006). The portal vein and sinusoidal injury could be divided into early, intermediate, and late changes. Early changes include focal endothelial denudation that is accompanied by hemorrhage into the portal connective tissue that occasionally dissects deeper into the hepatic parenchyma when it is severe. Denudation of portal vein and periportal sinusoidal endothelium, severe congestion with frank rupture and thrombosis of the periportal sinusoids may occur as early as 5 minutes after transplantation in grafts of less than 30% expected liver volume (Kelly et al., 2004). Intermediate and late portal venous changes are associated with repair of the early changes. Endothelial cell hypertrophy, subendothelial edema accompanied by an in-growth of myofibroblasts and endothelial cells resulting in focal fibrosis, and luminal obliteration or recanalization of thrombi may be present.

In addition, functional dearterialization could be observed because of arterial vasospasm and/or arterial thrombosis. The arterial lesions are invariably accompanied by large perihilar bile duct necrosis, cholangitic abscesses, leakage of bile in the surrounding connective tissue, and scattered parenchymal infarcts. The most characteristic triad of histopathologic findings present include centrilobular hepatocanicular cholestasis, centrilobular hepatocyte microvesicular steatosis, and a low-grade ductular reaction at the interface zone. The ductular reaction consisted of portal tract expansion because of an increase of ductal profiles at the interface zone accompanied by acute neutrophilic periductular inflammation.

Based on the above pathological manifestations, Demetris et al proposed the following sequence of SFSS (Demetris et al., 2006). First, portal venous hyperperfusion causes portal vein and sinusoidal endothelial cell injury which leads to intraparenchymal dissecting hemorrhage in severe cases. Second, portal hyperperfusion triggers the arterial buffer response (Marcos et al., 2000), hepatic arterial vasospasm, and decreased hepatic artery perfusion. Decreased hepatic arterial blood flow can also be presented in most reduced-size liver allografts (Marcos et al., 2000). Third, centrilobular microvesicular steatosis and infarcts in the periphery are caused by poor arterial flow and ischemia. In the hilum, it manifests as ischemic cholangitis in severe cases (Ludwig et al., 1992). Last, remnants of portal vein pathology often cause organizing mural thrombi or thickening in large branches portal vein branches and partial or complete luminal obliteration or recanalization in small portal vein branches.

However, the histopathologic and pathophysiologic manifestations of SFSS have not been depended completely on peripheral core needle biopsies (Demetris et al., 2006). Under the examination of peripheral core needle biopsies, affected grafts most commonly show the following triad: centrilobular hepatocanicular cholestasis, centrilobular hepatocyte microvesicular steatosis, and a ductular reaction at the interface zone. Venous pathology could not be detected by peripheral core needle biopsies in failed allograft though the presentation of venous changes is particularly helpful for the diagnosis of SFSS. In addition, it should be kept in mind that the changes in zone 3 and ductular reaction are not specific for SFSS. The detection should include suboptimal arterial flow as hepatic artery thrombosis

or bile duct stricturing are not related to the SFSS, and systemic causes such as sepsis with or without systemic hypotension.

## 5. The strategy for prevention and treatment

As PGNF is the most severe type of IPGF and a life threatening condition, there is growing need for early identification of IPGF and PGNF. This may help to determine further therapeutic interventions, changes in therapeutic protocols or additional diagnostic procedures aiming at preventing IPGF and PGNF.

### 5.1 Early diagnosis

At present, confirmation of IPGF and PGNF still depends on daily monitoring of liver function, renal function, blood coagulation function, hemodynamic and respiratory parameters, as well as liver biopsy. In order to reach a quick and accurate diagnosis, it requires careful interpretation of allograft biopsy and correlation of hepatic histopathological characteristics with clinical and laboratory findings. As laboratory tests may reflect later results of IPGF or PGNF, early biomarkers should be searched.

Recently, Dahaba et al assessed Bispectral index (BIS) monitoring as an early intraoperative indicator of living-donor or DCD graft function (Dahaba et al., 2009). BIS monitoring, an electroencephalographic (EEG)-derived parameter, is a useful measure for grading and monitoring the degree of central nervous system involvement in patients with chronic liver disease. BIS increase was associated significantly with non-IPGF but not with the occurrence of IPGF, which indicates predictive power of BIS monitoring as an indicator of the return of cerebral activity with the restoration of graft hepatic function.

In animal model of liver transplantation by using non-heart beating donor, the levels of serum  $\beta$ -galactosidase, IL-6, hyaluronic acid and redox-activate iron are closely associated with early confirmation of IPGF and PGNF (Monbaliu et al., 2007).

### 5.2 Donor-recipient matching models

As various donor and recipient risk factors influence graft function and survival after OLT (see Table 2), identifying the right set of donor and recipient matching characteristics may be very important, especially in the face of increasing use of DCD.

From the data of SRTR, Feng et al identified seven donor characteristics that be independently used to predict significantly increased risk of graft failure and developed a quantitative donor risk index (DRI) using Cox regression models (Feng et al., 2006). By using DRI, the risk of donor liver graft could be assessed quantitatively. In another large analysis by using the data from the UNOS of 20,301 recipients, a comprehensive model that predicts survival after liver transplantation was developed and validated based on donor and recipient characteristics (Ioannou, 2006). These models could adequately predict survival after OLT in patients with or without hepatitis C virus and have a large effect on post-transplant survival.

By using the OPTN/SRTR data base on 21673 liver transplant recipients, Rana et al identified 13 recipient factors, 4 donor factors and 2 operative factors (warm and cold ischemia) as significant predictors of recipient mortality (Rana et al., 2008). The multivariate analysis in this study included all of the variables considered in the SRTR risk-adjusted model. The Survival Outcomes Following Liver Transplant (SOFT) score was evaluated by utilizing 18 risk factors to successfully predict 3-month recipient survival following liver

transplantation. Furthermore, the proposed SOFT risk score can be used to predict outcomes for a particular recipient and donor allograft prior to transplantation comparing against waitlist mortality predicted by the MELD score. However, the SOFT score addresses only 3-month mortality comparing other studies which look at longerterm outcome.

Study	Markmann	Cuende	Busuttil	Feng	Ioannou	Rana
References	(Markmann et al., 2001)	(Cuende et al., 2005)	(Busuttil et al., 2005)	(Feng et al., 2006)	(Ioannou et al., 2006)	(Rana et al., 2008)
Number in study	1393	5150	3200	20023	38811	21673
Year range of data	1992 - 1998	1994 - 2110	1984 - 2001	1998 - 2002	1994 - 2003	2002 - 2006
Data source	UCLA	Spain	UCLA	SRTR	UNOS	UNOS
<b>Donor factors</b>						
Age	•	•	•	•	•	•
Race				•	•	•
Gender					•	
Height				•		
Hypertension		•				
Cause of donor death				•		•
DCD				•		•
Length of donor hospital/ICU stay		•	•			
Serum sodium level	•					
Serum bicarbonate level		•				
Serum creatinine level						•
<b>Recipient factors</b>						
Age	•		•		•	•
Recipient urgency			•		•	•
Preoperative mechanical ventilation	•					
Serum creatinine level	•					
Serum albumin level					•	
Cause of recipient's liver disease			•		•	
Retransplantation			•			•
BMI					•	•
MELD score					•	•
<b>Transplant factors</b>						
Warm ischemia time			•			•
Cold ischemia time			•		•	•
Partial- or split-liver graft				•		

Table 2. Factors effecting graft function or graft survival

Given the importance of advanced donor age and graft quality, Halldorson et al developed a statistic, D-MELD, the product of donor age and preoperative MELD, calculated from laboratory values (Halldorson et al., 2009). Using a cutoff D-MELD score of 1600, they defined a subgroup of donor-recipient matches with significantly poorer short- and long-term outcomes as measured by survival and length of stay. It can be used to accurately



estimate the risk for various donor/recipient combinations and predict worse outcome in recipients after OLT if D-MELD  $\geq$  1600. In an observational cohort study that prospectively enrolled liver transplantations performed at 20 out of 21 Italian Transplant Centres, it was demonstrated that the liver donor population used for transplantation in Italy has a higher risk profile mainly because of older donor age (Angelico et al., 2011).

The models above are aimed to help clinicians balance waitlist mortality with posttransplant outcome and make right decisions on a particular allograft. Freeman (Freeman, 2008) suggested that the differences between statistical calculations and decision made for individual patients with various treatment options should be emphasized though these models have some useful information for donor-recipient matching.

### **5.3 Prevention and treatment**

#### **5.3.1 General consideration**

Recently, some progress has been made in the prevention and treatment of early hepatic graft dysfunction. In the clinical practice, limitation of the use of liver grafts from patients older than 50 years should be complied. For steatotic donor grafts, restricting the use of steatotic livers to those with less than 40% macrovesicular steatosis is recommended. Livers with large droplet fat in excess of 60% are at increased risk for primary graft dysfunction/nonfunction and are therefore typically excluded from transplantation (Trevisani et al., 1996/Ploeg et al., 1993). As with other ECD grafts, recipient matching should be based on the number and extent of recipient risk factors and the absence of other negative donor variables, such as advanced donor age and prolonged CIT, to minimize the negative impact on graft and patient's outcome. Determination of the BMI seems to be a helpful and non-invasive method to estimate the degree of liver steatosis, particularly in living donors (Rinella et al., 2001; Trotter, 2001). Individuals with normal BMI usually do not have steatosis (Rinella et al., 2001).

#### **5.3.2 Surgical strategies**

For reduction of severe ischemia reperfusion injury of graft, surgical strategies have been undertaken. It is recommended that the time from pronouncement of cardiac death until liver perfusion with preservation solution and CIT should be between 20 minutes to 12 hours. For the use of uncontrolled non-heart-beating donors, normothermic extracorporeal membrane oxygenation (NECMO) were adopted in a prospective case-control study on adult patients undergoing OLT, and the results are encouraging (Jiménez-Galanes et al., 2009). Prior to major hepatectomy, ischemic preconditioning (IP) of the liver has been successfully employed to protect against subsequent prolonged periods of ischemia (Clavien et al., 2000). The aim of IP is to induce resistance to a subsequent longer episode of ischemia by a short episode of ischemia reperfusion. The development of hepatic preconditioning can be differentiated into 2 phases. An early phase of protection occurs immediately after IP. The subsequent phase (late preconditioning) begins 12-24 hours after the stimulus and the induction of cytoprotective genes, including HSP70, HSP27, and HSP32/heme oxygenase 1. Hepatic preconditioning is not limited to parenchymal cells but also ameliorates sinusoidal perfusion, prevents postischemic Kupffer cell activation, neutrophil infiltration, and decreases the production of proinflammatory cytokines, oxidative injury and apoptosis (Carini & Albano, 2003). In a prospective randomized study on 100 patients undergoing major liver resection to the impact of ischemic preconditioning was evaluated (Clavien et al.,

2003). Postoperative serum transaminase levels were significantly lower in preconditioned group than in control group, with even more benefits in younger patients, longer duration of inflow occlusion, where resected volume <50%, and in the presence of steatosis (Clavien et al., 2003). Recently in experimental settings, graft preservation by normothermic machine perfusion has proven superiority over static cold storage. Normothermic perfusion could preserve extended criteria grafts for long periods, assess the viability of these grafts during perfusion and improve the condition of the grafts (Vogel et al., 2010). However, the feasibility and the device of the normothermic machine perfusion should be introduced and evaluated in human livers.

### 5.3.3 Pharmacological strategies

Pharmacological treatments include (Bahde & Spiegel, 2010): first, antioxidant therapy aiming at supporting endogenous antioxidants and inhibiting ROS generation; second, vasoactive mediators, such as ET, angiotensin II, thromboxane A<sub>2</sub>, NO, carbon monoxide, prostaglandin E<sub>1</sub> and prostacyclin, can ameliorate the hepatic microcirculation; third, anti-inflammatory drugs in order to reduce ischemia reperfusion injury via selectin, cyclooxygenase 2 and protease inhibition, cytokines (including TNF- $\alpha$  and IL-1) and chemokine blockade; fourth, antiapoptotic strategies, including mitochondrial permeability transition inhibitors (cyclosporin A, trifluoperazine), anti-Fas or anti-Fas ligand antibodies, antiapoptotic proteins, caspase inhibitors and others; fifth, pharmacological preconditioning imitating the protective mechanisms induced by IP; finally, glucose infusion, by supplying glucose for ATP generation. A total of 14 RCTs were identified for evaluating these pharmacological measurements. Although some pharmacological strategies showed promising results with improved hepatic function and clinical outcome, but there is still not solid evidence to recommend its application in clinical. However, methylprednisolone (Aldrighetti et al., 2006; Pulitanò et al., 2007) and sevoflurane (Beck-Schimmer et al., 2008) are the most promising drugs for reduction of ischemia reperfusion injury.

### 5.3.4 SPSS

For prevention of SFSS in partial liver transplantation, several interventions should be considered. First, selection of grafts from healthy donors without advanced age. Second, graft steatosis of 30% or more should preclude. Third, sufficient graft volume should be guaranteed. In the pediatric population, the recipient receives an adult lateral left segment or left lobe. In adult-to-adult LDLT, an extended right lobe graft with or without middle hepatic vein can increase graft volume though the donor is relatively small (Lo et al., 2004; Cattral et al., 2004). Finally, ischemic preconditioning may also be of benefit in partial liver transplantation to protect SFSS grafts, as it has been shown to maintain the hepatic microcirculation and decrease the activation of Kupffer cells (Franco-Gou et al., 2004; Vajdová et al., 2004).

### 5.3.5 Retransplantation

Early retransplantation is the only choice of treatment in patients with PGNF. It was reported by Grande et al that the third postoperative day is a crucial time in making the decision of retransplantation in patients with IPGF (Grande et al., 1992). It is because that the improvement of liver function began on the third day in almost all patients whose graft dysfunction spontaneously ameliorated. Upon the diagnosis of PGNF, rescue hepatectomy

of the non-functioning liver can achieve a dramatic temporary clinical improvement as failing graft causes the pathophysiology of this disorder and extrahepatic sequelae. Retransplant after PGNF in the initial transplant can achieve relatively good long-term survival (Uemura et al., 2007). However, a second or third transplant after PGNF did not demonstrate long-term survival, and hospital mortality was 57% (Uemura et al., 2007). In addition, the patient's and graft's survival were lower in recipients with hepatitis C virus infection who received retransplantation when compared with those without HCV infection as HCV was an independent predictor of mortality after retransplantation (Yoo et al., 2003).

## 6. Conclusion

IPGF is a severe complication after OLT while PGNF is a life-threatening event. The factors of donor, recipient and operation contribute to the occurrences of IPGF or PGNF. For evaluation of the donor hepatic allograft and post-transplant evaluation of hepatic graft function, liver biopsy as well as with clinical and laboratory findings are important for early diagnosis in clinical practice. For prevention of IPGF or PGNF, it is necessary for careful consideration of donor and recipient factors before OLT. Surgical and pharmacological interventions should be undertaken cautiously.

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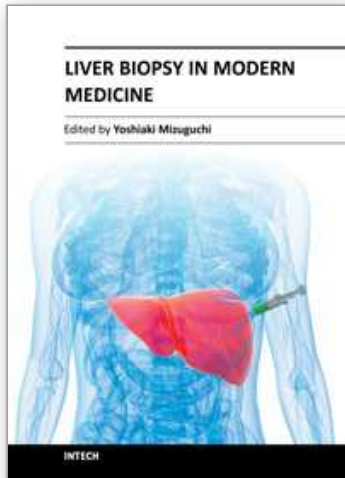
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