

# Intraoperative Serum Lactate Concentration and Central Venous Oxygen Saturation as Early Predictors for Early Graft Function during Liver Transplant



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## Abstract

**Background:** Initial poor graft function (IPGF) following living donor liver transplantation (LDLT) causes complications, result in poor prognosis. We evaluated that if intraoperative changes in blood lactate level and central venous oxygen saturation (ScvO<sub>2</sub>) after hepatic allograft reperfusion can reflect IPGF following LT.

**Methods:** 40(LDLT) recipients were studied. Patient State Index (PSI), monitored anaesthesia depth with Desflurane (Des) % and fentanyl altered accordingly. Transoesophageal Doppler (TED), invasive mean arterial blood pressure (MABP, mmHg) and heart rate (HR, beat/min) were monitoring; TED was used for fluid optimization. Intraoperative serum lactate and daily collection of serum and plasma samples to for routine biochemistry analysis, liver function test. Venous blood gases were collected from central venous catheter.

**Results:** IPGF occurred in 4 of the 40 patients (10%). Both serum lactate and ScvO<sub>2</sub> following reperfusion in the non-IPGF group was markedly lower than that in the IPGF group (p<0.001). Lactate clearance was positive in non-IPGF group in contrast to IPGF group in which lactate clearance was in a negative value, (p<0.001). Receiver operating characteristics curve (ROC) analysis resulted in an area under the curve of 0.65 for serum lactate and 0.46 for ScvO<sub>2</sub>, with a sensitivity and specificity of 83 % and 50 % for serum lactate and 94% and 25 % for SvO<sub>2</sub>. The optimum cut-off values for lactate and ScvO<sub>2</sub> predicting IPGF were 31.55% and 66.5 respectively.

**Conclusions:** Both changes in intraoperative blood lactate and ScvO<sub>2</sub> after hepatic allograft reperfusion served as good predictor of initial graft function during LT.

**Keywords:** Lactate; Central venous oxygen saturation; Predictors; Graft function

## Introduction

Adult living donor Liver transplantation (ALDLT) is currently considered to be the ultimate form of therapy for most patients with end-stage liver diseases. Liver transplantation represents a complex surgical procedure, in which several factors determine postoperative recipient and graft survivals. Three risk categories may be considered: namely, those related to the patient, to the organ to be transplanted and to the surgical procedure [1]. Early graft function after liver transplantation (LT) is an important prognostic parameter for the individual outcome. Initial poor graft function (IPGF) has been described as a borderline dysfunction with the potential to recover. IPGF is a multifactorial event, which is related to different risk factors, such as marginal donors, severe ischemia-reperfusion injuries, acute rejection episodes or vascular complications [2]. The diagnostic standard for IPGF has not been set yet, and there are different opinions among some

reported definitions. As, Silberhumer GR et al. [3] proposed four grades of initial graft function over the first postoperative 5 days as:

- Good function, AST maximal 1000 UI/L and spontaneous prothrombin time >50%;
  - Fair function, AST 1000-2500 UI/L, clotting factor support < 2 days;
  - IPF, AST >2500 UI/L, clotting factor support >2 days; and
  - PNF; Retransplantation required within 7 days.
- We designed this study to evaluate if intraoperative changes in blood lactate level and (ScvO<sub>2</sub>) after hepatic allograft reperfusion can reflect IPGF following LT.

## Patients and Methods

Approval was obtained from the local ethics and research committees of the Anaesthesia and Intensive Care Department of National Liver Institute, Menoufia University, Egypt (IRB 0100/2014). This observational analytical prospective cohort study of 40 ALDLT recipients from both sexes. A written informed consent was taken from each patient. Patients aged 18 to 60 yrs. had model of end stage liver disease (MELD) between 12 and 20 we enrolled in this , patients with extra hepatic malignancy, severe renal impairment, cardiovascular disorders and patients with severe pulmonary disorders were exclude. preoperative assessment and all patients were monitored by standard routine monitoring by the monitor of DatexOhmeda (GE, USA) which includes ECG, noninvasive blood pressure (NIBP), continuous invasive blood pressure (IBP) and arterial blood gas analysis, pulse oximetry (SaO<sub>2</sub>), capnography to monitor end tidal CO<sub>2</sub>, fractional inspired oxygen concentration (FiO<sub>2</sub>) ,neuromuscular blockade monitoring via accleromyography, NMT module, Dragger, USA), core temperature (nasopharynx probe) ,continuous Central venous pressure (CVP), trans-esophageal Doppler TED (CardioQ) parameter (Deltex Medical, Chichester, UK, FDA approved) for cardiovascular function (Cardiac output) and perioperative fluid optimization, Patient State Index (PSI), SEDLine (Masimo, Irvine, CA) monitored anaesthesia depth (25-50) with Desflurane (Des) % and fentanyl altered accordingly and rational Thromboelastometry. (ROTEM)(Pentapharm GmbH, Munich, Germany).

Adequate preoxygenation was done before the administration of any pharmacological agents. General anaesthesia was induced by rapid sequence induction with cricoid pressure using sleeping dose of Propofol titrated (approximately 20 mg every 10 seconds, 1-1.5 mg/kg) against the patient's response to both patient state index anaesthesia depth monitoring (SED-line, Masimo, Irvin, USA)and clinical signs. Rocuronium 0.9mg/kg to facilitate endotracheal intubation under neuromuscular nerve monitoring. Anaesthesia was maintained with Desflurane (Baxter, Erlangen, Germany) in O<sub>2</sub>/Air mixture (FIO<sub>2</sub> =0.4), fentanyl, and rocuronium to keep the patient state index anaesthesia depth monitoring between 25-50. Lactate and Scvo<sub>2</sub> data would be collected at the following times: The day before operation.

(T<sub>0</sub>); Base line data, one hour after induction.

(T<sub>1</sub>); Dissection phase, 30 min after clamping of the portal vein

(T<sub>2</sub>); Anhepatic phase, 10min after reperfusion of the portal vein

(T<sub>3</sub>); Reperfusion phase, 2 hours post reperfusion

(T<sub>4</sub>); Postoperative data collection include standard coagulation test: (International Normalized Ratio INR, PTT, PC), liver function tests (AST, ALT (U/L), Bilirubin Total and

Direct (mg/dl)), renal function tests (Urea and creatinene) (mg/dl), Lactate levels (mg/dl) and they would be collected postoperatively at the first post- operative dayPOD<sub>1</sub>

(T<sub>5</sub>), (T<sub>6</sub>); POD<sub>3</sub> and

(T<sub>7</sub>); POD<sub>5</sub>.

Lactate clearance calculated from the formula:

Lactate clearance= (lactate at anhepatic stage (T<sub>2</sub>) - (lactate at 2 hours post reperfusion stage (T<sub>4</sub>) divided by (lactate at anhepatic stage (T<sub>2</sub>) ×100%.

## Sample Size and Power of The Study

Patients were admitted to our National Liver Institute from 2013-2015 meeting the inclusion and exclusion criteria. Forty patients were involved in our study. In the present study  $\alpha$  was set to 0.05, and maximum accepted 20% with minimum power of study 80% of mean of predicted lactate.

## Statistical Analysis of the Collected Data

Results were collected, tabulated and statistically analyzed by an IBM compatible personal computer with SPSS statistical package version 20 (SPSS Inc. Released 2011. IBM SPSS statistics for windows, version 20.0, Armonk, NY: IBM Corp.). Descriptive statistics, was expressed in: Number (No), percentage (%) mean ( $\bar{x}$ ) and standard deviation (SD). Analytic statistics, student's t-test is a test of significance used for comparison of quantitative variables between two groups of normally distributed data, while Mann Whitney's test was used for comparison of quantitative variables between two groups of not normally distributed data. Wilcoxon test was used to compare between 2 consecutive means in the same group of not normally distributed data. Spearman correlation was used to study the correlation between two quantitative variables. p< 0.05 was considered statistically significant.

## Results

The two studied groups, patients with functioning graft group (non-IPGF) (n=36) and patients with initial poor graft function group (IPGF) (n=4). Patients' characteristics of both groups were comparable. Mean (MELD) values were (15.05±2.85 vs. 17.50±1.91) in non-IPGF group and IPGF group respectively, p=0.10. Sex distributions were comparable in the two studied groups. Concerning with the intraoperative date, there was statistically significant increase in mean operative duration (11.37±0.75 vs. 12.75±2.77 hrs. p= 0.01) in non-IPGF & IPGF group respectively. There were statistically significant increase in mean an hepatic, cold and warm ischemia times in IPGF group, The mean of graft body weight ratio (GBWR) was (1.02±0.15 vs. 0.97±0.06, p=0.40) in non-IPGF & IPGF group respectively, Table 1. In non-IPGF group, mean preoperative lactate was (T<sub>0</sub> 16.61±5.65) mg/dl.

**Table 1:** Demographic and intraoperative data in the studied groups.

	Non-IPGF (n=36)	IPGF (n=4)	p value
	Mean ±SD	Mean ±SD	
Age(yrs.)	46.72 ± 6.75	43.75 ± 9.97	0.66 NS
BMI(kg/m2)	27.80 ± 2.48	28.00 ± 0.81	0.87 NS
MELD	15.05 ± 2.85	17.50 ± 1.91	0.10 NS
Gender	(n)(%)	(n)(%)	
Male	31 86.1	3 75.0	0.49 NS
Female	5 13.9	1 25.0	
ANT (h)	2.37 ± 0.7	3.20 ± 0.99	0.03
CIT(min)	45.00 ± 15.14	62.22 ± 18.73	0.03
WIT(min)	36.25 ± 7.49	45.00 ± 7.02	0.04
AGBWR	1.02 ± 0.15	0.97 ± 0.06	0.03
Operative Time(h)	11.37 ± 0.75	12.75 ± 2.77	0.40 NS

Demographic data were presented as mean ± SD, tested by Mannwhiteny test, while sex difference tested by chi square test p>0.05.

Body mass index: BMI; Model End Stage Disease: MELD.sOperative data were presented by mean ± SD using Wilcoxon test showing ANT: An hepatic Time; CIT: Cold Ischemia Time; WIT: Warm Ischemia Time; AGBWR: Actual Graft Body /Weight Ratio; OT: Operative Time.

Data was considered statistically significant, p< 0.05.

NS: Non significant, p> 0.05.

There were statistically significant increase in mean values of intraoperative lactate at the dissection & an hepatic phases, p =0.00, then followed by statistically significant decrease in mean lactate values at the reperfusion & 2hours post reperfusion phases, p=0.04. There were decreases in mean values of post -operative lactate. Regarding IPGF group, mean preoperative lactate was (T<sub>0</sub> 17.25±3.09) mg/dl. The mean values of serum lactate continue to increase all over the intra and post -operative period. Lactate

clearance was positive in non-IPGF group(30.64±15.57%) in contrast to IPGF group in which lactate clearance was in a negative value(-182.88±136.53%) and it was statistically significant, p<0.001, Table 2. In non-IPGF group, there were decreases in SCVO<sub>2</sub> values at their perfusion phase without reaching significant value, p= 0.26, then followed by significant decrease at 2hours post reperfusion phase, p=0.00.

**Table 2:** Lactate level (mg/dl) and Central venous oxygen saturation (Scvo<sub>2</sub>%) in the studied groups.

Serum lactate	Non-IPGF (n=36)		IPGF (n=4)
	Mean± SD	p value	
T0	16.61 ± 5.65		17.25 ± 3.09
T1	30.02 ± 13.43	0.001	33.50 ± 10.59
T2	80.41 ± 29.0	0.001	49.75 ± 30.24
T3	65.23 ± 32.58	0.04	69.00 ± 36.90
T4	53.46 ± 13.62	0.04	82.02 ± 14.16
T5	52.15 ± 36.52	0.84NS	104.20 ± 7.74
T6	43.46 ± 40.55	0.003	115.07 ± 11.51
T7	32.28 ± 29.09	0.003	119.00 ± 13.2
Lactate clearance	30.64±15.57%		-182.88±136.53%
Scvo2			
T0	74.82 ± 10.68		77.00 ± 6.16
T1	86.95 ± 3.47	0.001	86.25 ± 2.98
T2	87.00 ± 14.76	0.21NS	89.75 ± 1.89
T3	86.69 ± 6.58	0.26NS	90.72 ± 13.18
T4	79.89 ± 15.79	0.001	90.00 ± 12.08

Data were presented by mean ± SD using Wilcoxon test, and p<0.05 is considered statistically significant,

NS: non-significant,  $p > 0.05$ .

T<sub>0</sub>: preoperative lactate and ScvO<sub>2</sub>,

T<sub>1</sub>: lactate and ScvO<sub>2</sub> in dissection phase,

T<sub>2</sub>: lactate and ScvO<sub>2</sub> in anhepatic phase,

T<sub>3</sub>: lactate and ScvO<sub>2</sub> in reperfusion phase,

T<sub>4</sub>: lactate and ScvO<sub>2</sub> in 2 hrs post reperfusion phase,

T<sub>5</sub>: lactate in POD<sub>1</sub>,

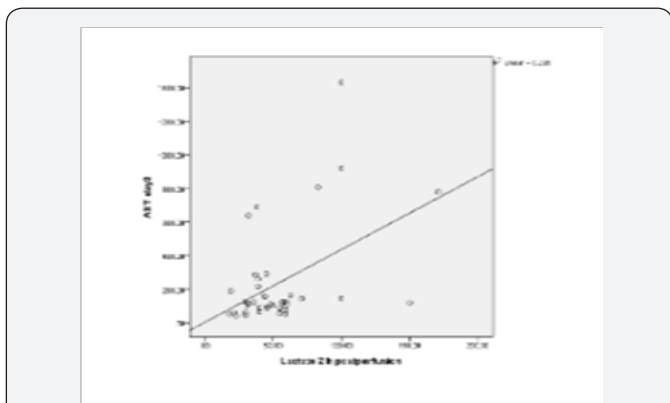


Figure 1: Spearman correlation of lactate at 2h post reperfusion phase showing positive correlation with peak AST at POD<sub>3</sub>.

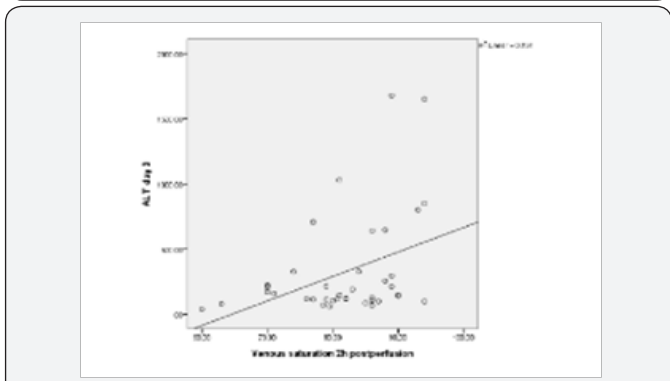


Figure 2: Spearman correlation of central venous saturation at 2h post reperfusion phase showing positive correlation with peak ALT at POD<sub>3</sub>.

Receiver operating characteristics curve (ROC) analysis resulted in an area under the curve of 0.65 for serum lactate and 0.46 for ScvO<sub>2</sub>, with a sensitivity and specificity of 83% and 50% for serum lactate, and 94% and 25% for ScvO<sub>2</sub>. The optimum cut-off values for lactate and ScvO<sub>2</sub> predicting IPGF were 31.55% and 66.5 respectively, as presented in Figures 3 & 4. (ROC) analysis for lactate clearance resulted in an area under the curve 92.4%, with a sensitivity and specificity 100% and 78% and cut-off value was 19.59%, presented in Figure 4. Regarding liver enzymes and coagulation, in non-IPGF group, there were increase in liver enzymes and coagulation postoperatively reaching peak level at post-operative day3 then tends to decrease. In contrast with IPGF group, liver enzymes continue to rise with persistant coagulopathy as presented in Table 3.

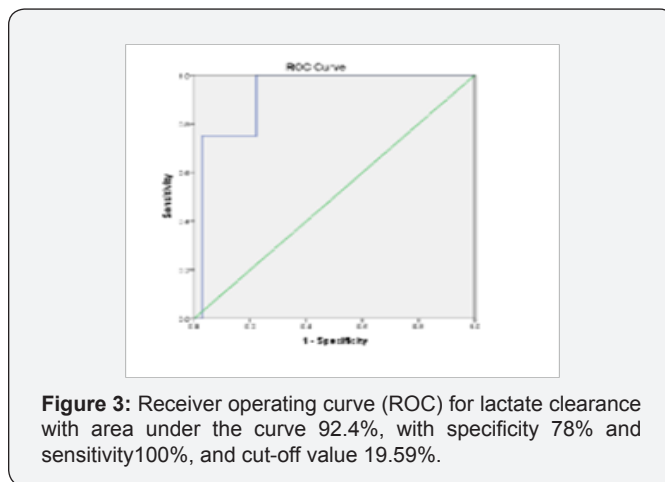


Figure 3: Receiver operating curve (ROC) for lactate clearance with area under the curve 92.4%, with specificity 78% and sensitivity 100%, and cut-off value 19.59%.

Table 3: ALT, AST levels (U/L) and INR in the studied groups.

ALT	Non-IPGF (n=36)		IPGF (n=4)	
	Mean± SD	p value	Mean± SD	p value
T0	43.69 ± 25.37		31.50 ± 21.30	
T5	162.34 ± 105.83	0.001	267.50 ± 110.21	0.005
T6	126.90 ± 99.66	0.03	320.50 ± 197.04	0.65 NS
T7	110.78 ± 93.76	0.03	293.33 ± 143.36	0.83 NS
AST				
T0	76.44 ± 39.33		75.75 ± 37.85	
T5	145.69 ± 138.00	0.02	263.25 ± 30.59	0.001
T6	128.02 ± 102.59	0.03	279.25 ± 19.43	0.41 NS
T7	118.91 ± 97.84	0.34NS	289.66 ± 97.04	0.84 NS
INR				
T0	1.58 ± 0.39		1.87 ± 0.42	
T5	1.87 ± 0.54	0.01	1.87 ± 0.42	0.73 NS
T6	2.01 ± 2.37	0.73NS	1.95 ± 0.18	0.22 NS
T7	1.68 ± 0.53	0.41NS	2.11 ± 0.15	0.15 NS

Data were presented by mean ± SD using Wilcoxon test, and  $p < 0.05$  is considered statistically significant,

NS: non-significant,  $p > 0.05$ .

ALT: Alanine amino transferase ,

AST: Aspartate amino transferase.

INR: International normalized ratio.

T<sub>0</sub>: preoperative ALT, AST and INR,

T<sub>5</sub>: ALT, AST and INR in POD<sub>1</sub>,

T<sub>6</sub>: ALT, AST and INR in POD<sub>3</sub>,

T<sub>7</sub>; ALT, AST and INR in POD<sub>5</sub>.

## Discussion

The main finding in our study was Lactate clearance was positive in non-IPGF group in contrast to IPGF group in which lactate clearance was in a negative value. Early graft function after liver transplantation (LT) is an important prognostic parameter for the individual outcome [4]. Initial poor graft function (IPGF) has been described as a borderline dysfunction with the potential to recover [5], which appears as a form of temporary/ reversible liver insufficiency. Among the parameters most frequently utilized for prediction of early mortality in OLT patients, the perioperative blood lactate levels, INR and the MELD post-OLT seem to be more precise. The serial blood lactate monitoring has been assessed in the critically ill patient in many situations [6] demonstrated that persistent elevation of blood lactate level in septic patients can be a reliable predictor of multiple organ failure syndrome and poor prognosis. Thus, in the ICU setting the study of the behavior of this metabolite in severe sepsis or septic shock is gaining terrain even more, since the reduction of elevated blood lactate level is considered to be the primary target of the treatment of the critically ill patient [7].

Hyperlactatemia has been shown to be associated with increased mortality and morbidity in a critical care setting in patients following liver resection [8]. Temporary absence of the liver during the anhepatic phase results in lactic acidosis until the graft liver is reperfused. Svensson et al. [9] reported similar blood lactate profiles in LT. They demonstrated that the inability of the hepatic graft to reduce lactate levels was associated with primary graft non function, as well as an increased incidence of mortality or morbidity during early postoperative periods. De Gasperi et al. [10] recorded that blood lactate appears to be a useful indicator of hepatic metabolic recovery of its functional capabilities in the immediate postoperative period of OLT. Nishimura et al. [11] & Orii et al. [12] conducted that the lactate clearance is associated to the size of the graft. Bernal et al. [13] reported that arterial blood lactate measurement rapidly and accurately identifies patients who will die from paracetamol-induced acute liver failure and its use can improve the speed and accuracy of selection of appropriate candidates for transplantation. Wu et al. [14] concluded that early postoperative lactate clearance can serve as a prompt and accurate bedside predictor of IPGF. Lactate clearance, especially early clearance as an important index in severe sepsis and septic shock, is reported to perform well in the prediction of prognosis with a high sensitivity and specificity.

We used ROC analysis to determine the best cut off of early lactate clearance rate and its sensitivity and specificity in liver transplant patients as a predictor of IPGF. Our study revealed that change in intraoperative blood ScvO<sub>2</sub> after hepatic allograft reperfusion served as good predictor of initial graft function during LT. The oxygen available to the tissues at every stage of the liver transplantation is dependent on the cardiac output and the arterial oxygen content (CaO<sub>2</sub>). Bleeding, vascular clamping, and hypotension are some of the factors that may adversely

affect the oxygen availability with undesirable consequences on graft viability in orthotopic liver transplantation [15]. Abnormal changes in total oxygen consumption are considered as an early indicator for the occurrence of primary nonfunction of the newly transplanted liver. Attempts to correlate changes in oxygen uptake with the function of the newly implanted liver have also had contradictory results [16]. Monitoring hemodynamic parameters during liver transplantation allows control of tissue oxygenation and allograft viability. The significance of oxygen transport and the role of oxygen consumption as a predictor of outcome in a variety of diseases have been discussed but ideal values for oxygen transport are difficult to maintain during liver transplantation.

In patients with chronic liver failure, peripheral vasodilation, mainly in the splanchnic circulation, and a compensatory increase in cardiac output and hence oxygen delivery exist. Severe intrapulmonary and extrapulmonary arterial-venous admixing characterizes this group of patients, [17] and a rightward shift in the ODC is usually observed in patients with cirrhosis. One quarter of whole-body O<sub>2</sub> consumption (VO<sub>2</sub>) in awake humans is due to splanchnic (liver) metabolism, and this fraction increases during general anesthesia, under which extra splanchnic O<sub>2</sub> metabolism is selectively inhibited with relative preservation in the splanchnic bed. The liver remains a major contributor to VO<sub>2</sub> even in the presence of end stage disease, as evidenced by the marked decrease in VO<sub>2</sub> after hepatectomy during liver transplantation (OLT). Our study showed that there was a decrease in central venous saturation in the immediate reperfusion phase as the neohepatic graft start to consume oxygen but if a graft fails to function, there was failure to decrease central venous saturation as there was no oxygen consumption by the neohepatic graft.

This agreed with Takaya et al. [18] & Scalea TM et al. [16], showed that in addition to increased lactate or metabolic acidosis, ScvO<sub>2</sub> may indicate inadequate oxygen delivery earlier. The occurrence of IPGF is associated with many factors, but confirmation has not yet been made [20]. IPGF is a serious clinical complication after OLT, with elevation of serum aminotransferase. Some patients went to primary graft non function PGNF, [21] which was 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 [22]. Varotti et al. [23] vascular complications represent a second group of early complications after LT associated with high morbidity and mortality. The clinical pictures of these complications may vary considerably, but if not promptly treated they can also lead to graft failure. How to avoid IPGF is the crucial problem that the transplant surgeon must deal with. Gruttadauria S et al. [24] described a condition that we defined as early graft dysfunction (EGD) which could be identified preoperatively and concluded that EGD could be identified preoperatively and was associated with increased morbidity after LRLT.

A prompt recognition of EGD can trigger a timely treatment. Salvalaggio et al. [25] created a grading system for EGD. Lee et

al. [26] concluded that donation after cardiac death (DCD) liver allografts have been associated with increased morbidity from primary non-function, biliary complications, early allograft failure, cost, and mortality. Early allograft dysfunction (EAD) after liver transplantation has been found to be associated with worse patient and graft survival. Siniscalch et al. [27] demonstrated that patients with and without post transplantation complications had slightly different mean MELD scores. Filho et al. [28] concluded that the MELD post-OLT performed better in predicting early mortality of patients after orthotopic liver transplantation. Wagener et al. [29] demonstrated that the MELD score could be a useful tool not only for pretransplant graft allocation but also for postoperative risk stratification. We noticed in our current study that the duration of anhepatic phase, cold and warm ischemia times were prolonged in patients with IPGF more than patients with non-IPGF. During the anhepatic phase, cytokines, metabolites, and other toxins accumulated in the splanchnic system. Ijtsma et al. [30] concluded that the anhepatic phase duration over 100 minutes to be an independent predictor of graft dysfunction, which was associated with significantly lower patient survival.

Microcirculation of grafted liver could be gradually resumed normal after reperfusion when WIT was less than 30 min, which indicated that hepatic cells held the recovery potency and could regain normal microcirculatory structure after reperfusion if the WIT was less than 30 min. After 45 min of warm ischemia, most hepatic sinus was unobstructed, but there were still some sinus filled with cytoplasm blebs, reticular fibrosis and hemocytes. So 45 min may be the deadline of hepatic warm ischemia. When WIT was more than 60 min, microcirculatory structure of liver graft presented irreversible injuries. [31] During the phase of cold ischemia, loss of mitochondrial respiration and ATP depletion occur consequently though hypothermia reduce the metabolic rate and prolongs the time that anoxic cells can retain essential metabolic function [32]. In agreement with, Totsuka et al. [33] revealed that cold-ischemia time appears to be a good predictor of not only PNF but also of patient and graft survival. There are several limitations in our study. First, continuous monitoring of Scvo<sub>2</sub> intraoperatively by a new fibro-optic technology was not available in our study. Second, the unavailability of Swan Gaunaz catheter for collection of mixed venous saturation for good estimation of oxygen consumption by the neograft.

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