

# Hemodynamic Changes and Early Recovery of Liver Graft Function after Liver Transplantation

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## ABSTRACT

**Background:** Patients with liver cirrhosis experience a hyperdynamic circulation.

**Objective:** To investigate the association between early hemodynamic changes and graft function after liver transplant.

**Methods:** Those patients who underwent liver transplantation in 2016 were enrolled in the study. Liver function indices measured in postoperative days (POD) 1, 3, 5, 7, 9, and 11 along with hemodynamic indices including pulse rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and central venous pressure (CVP) measured q6h in the first 3 days after transplantation were recorded.

**Results:** 57 deceased-donor liver recipients with a mean±SD age of 41.4±11.8 years including 33 (58%) males were enrolled in the study. The mean±SD aspartate and alanine aminotransferases, alkaline phosphatase, and lactate dehydrogenase were significantly decreased from 1879±670.5, 369.2±40.5, 174.9±18.8, and 1907.6±323.1 U/L in POD 1 to 37.2±10.7, 243.4±37.3, 207.5±19.5, and 382.4±59.8 U/L in POD 3, respectively ( $p=0.028$ ,  $<0.001$ ,  $0.002$ , and  $0.001$ , respectively). During this period, the pulse rate of the patients was significantly ( $p<0.001$ ) decreased by a median (IQR) of 28.7 (8.5–39.7) beats/min; it was significantly correlated with a decrease in serum hepatic enzymes activities during this period. SBP, DBP, and CVP were significantly increased ( $p<0.001$  for all) during this period. Liver graft function improved significantly earlier in those patients with a mean pulse rate of 87 beats/min compared with others ( $p=0.03$ ).

**Conclusions:** There may be an association between changes of hemodynamic indices, especially reduction of pulse rate, and improved graft function early after liver transplantation.

**KEYWORDS:** Hemodynamics; Liver function tests; Liver transplantation

## INTRODUCTION

Patients suffering from liver cirrhosis, experience a hyperdynamic circulation characterized by decreased total peripheral resistance and blood pressure and increased cardiac output and pulse rate, which usually occurs in response to portal hyperten-

sion and cirrhosis [1, 2]. In response to hepatocyte injury, hepatic stellate cells are activated and converted to contractile hepatic myofibroblasts resulting in secretion of large amounts of extracellular matrix and inflammatory cytokines. Besides, the structural changes of endothelia of the sinusoids result in increased sinusoidal resistance followed by portal hypertension [3–5]. Moreover, increased levels of nitric oxide followed by systemic and visceral vasodilatation results in neurohumoral vasoconstrictive response mechanisms such as renin-angiotensin-aldosterone system, which

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**Table 1:** Distribution of characteristics studied in the 57 deceased-donor liver recipients

Variable	Statistics
Male sex	58%
Mean±SD age (yrs)	41.4±11.8
Mean±SD MELD score	20.8±5.5
Cigarette smoking	19%
Alcohol consumption	10%
Diabetes mellitus	10%
Etiology of liver cirrhosis	
Cryptogenic (including NAFLD)	28%
Autoimmune hepatitis	18%
Hepatitis B	12%
Primary sclerosing cholangitis	10%
Hepatitis C	9%
Primary biliary cirrhosis	5%
Hepatocellular carcinoma	4%

MELD: Model for end-stage liver disease; NAFLD: non-alcoholic fatty liver disease

aggravates the hyperdynamic circulation [6-8].

There are some studies investigating the hemodynamic alterations, especially during the period of weeks to months after liver transplantation. However, there is no consensus about the trend of postoperative hemodynamic changes after liver transplantation, time of liver graft recovery and their association. Some studies report that hyperdynamic circulation persists after liver transplantation for a while [9, 10]; others show that hemodynamic indices reverse to normal after liver transplantation [11, 12]. To the best of our knowledge, there is no study to show the strength of association of hemodynamic changes with liver graft function indices in early postoperative period after transplantation.

We therefore conducted this prospective clinical study to investigate the early hemodynamic changes after liver transplantation, the association between hemodynamic changes and liver function indices, and to find a probable cut-off point for the pulse rate reduction that may predict the improvement in liver function in early postoperative period after liver transplantation.

## PATIENTS AND METHODS

Patients who underwent deceased-donor liver transplantation in 2016 at Imam-Khomeini Hospital Complex, Iran, were enrolled in this study. Those patients aged <70 years who underwent primary deceased-donor liver transplantation due to chronic liver cirrhosis were included in the study. Recipients with obesity (defined as a body mass index >30 kg/m<sup>2</sup>), history of cardiac surgery, and neurological disorders, and those using beta-blockers or inotropic drugs or experienced sepsis, septic shock or death during their first 11 days after transplantation were excluded from the study.

### Study Protocol

All patients underwent transplantation under general anesthesia receiving invasive intraoperative monitoring by the same team of anesthesia specialists. All surgeries were performed by the same team of surgeons using modified piggyback technique and side-to-side cavocaval anastomosis without venovenous bypass or temporary portocaval shunt. Immunosuppression induction included 1000 mg methylprednisolone in an hepatic phase followed by a maintenance immunosuppression protocol with a triple regimen including corticosteroid, calcineurin inhibitor, and mycophenolate mofetil for almost all patients. Just a few received mammalian target of rapamycin inhibitors instead of calcineurin inhibitor due to drug intolerance or severe adverse events.

All patients were visited regularly by the same surgeon. The hemodynamic indices including pulse rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and central venous pressure (CVP), were measured with the same instruments and recorded accordingly every six hours in the first three postoperative days after liver transplantation. A 5-mL blood sample was taken from each patient at postoperative days (POD) 1, 3, 5, 7, 9, and 11 and were stored frozen at -20 °C under a similar condition. All samples were tested for aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total and direct bilirubin, and lactate dehydrogenase (LDH) on the day the sample

**Table 2:** Mean±SD of hemodynamic indices during the first three days post-transplantation. Values are significantly ( $p<0.001$ ) different among the three postoperative days.

Hemodynamic indices	POD 1	POD 2	POD 3
Pulse rate (beats/min)	103±2.7	82.8±2.3	72.6±2.1
SBP (mm Hg)	116±2.4	132±2.4	130±2.2
DBP (mm Hg)	74.6±1.6	85±1.5	84±1.5
CVP (cm H <sub>2</sub> O)	10±0.5	11.7±0.8	12.6±0.8

POD: Postoperative day; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CVP: Central venous pressure

was taken, using the same commercially available enzyme-linked immunoassay kit. Prothrombin time (PT) was also measured using tissue thromboplastin recombinant reagents.

### Ethics

The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences. The study was explained to the patients. Informed written consent was obtained from each patient prior to enrollment into the study.

### Statistical Analyses

Data analysis was performed with SPSS® for Windows® ver 16.0 (SPSS Inc, Chicago, IL, USA). Normally distributed variables were presented as mean±SD and tested by repeated-measures ANOVA; non-parametric variables were presented as median (IQR) and tested with Friedman test. Log-rank (Mantel-Cox) test and Kaplan-Meier survival analysis were used to show the correlation between the pulse rate reduction and the amount of improvement in liver function. A  $p$  value  $<0.05$  was considered statistical significant.

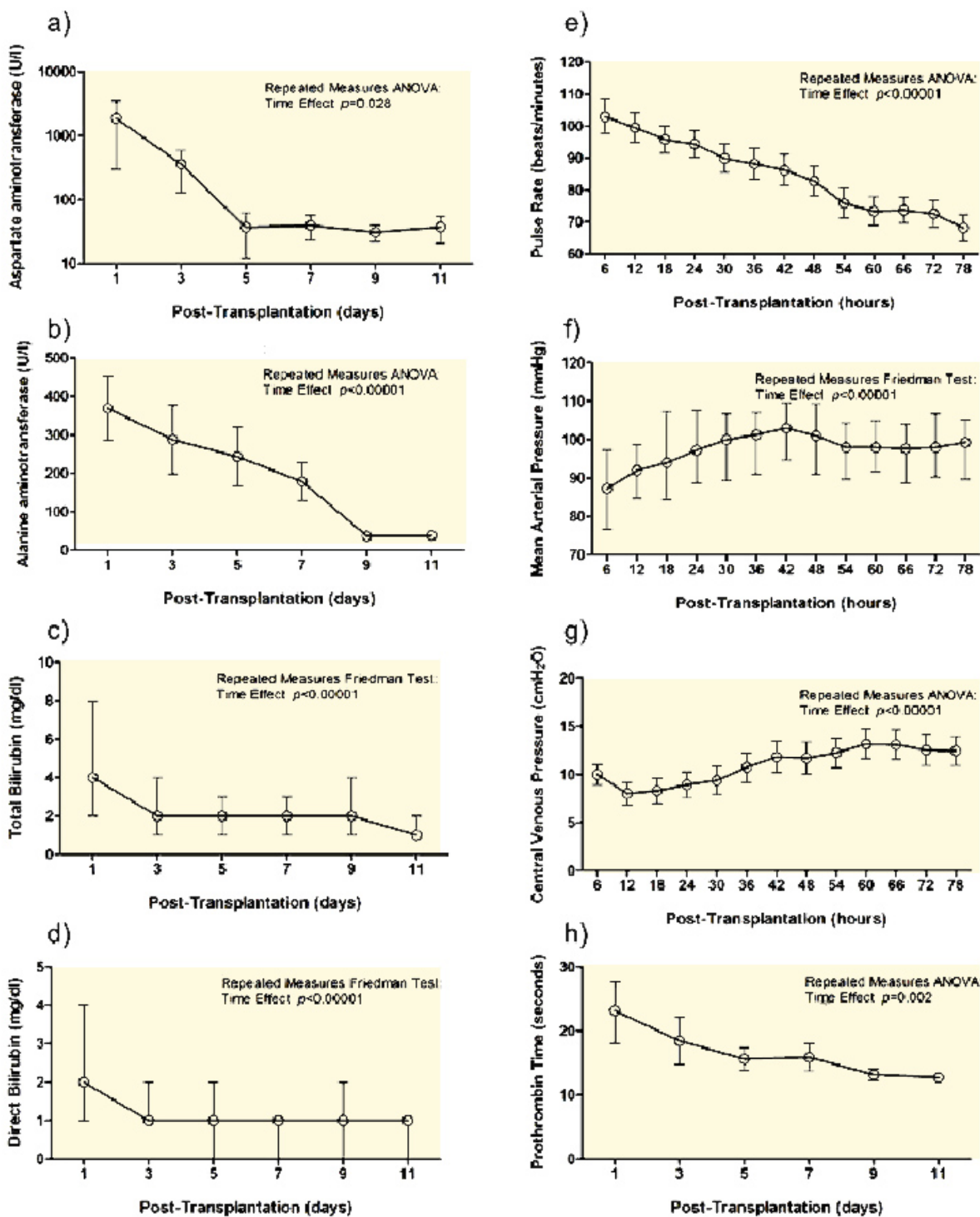
## RESULTS

Fifty-seven deceased-donor liver recipients were enrolled in the study. The data of the patients about demographics, status of cigarette smoking, history of alcohol consumption and diabetes mellitus and etiology of liver cirrhosis are shown in Table 1. Liver function indices were significantly decreased during the first 11 days after liver transplantation. The mean±SD AST, ALT, ALP, and LDH were significantly decreased from 1879±670.5, 369.2±40.5, 174.9±18.8, and 1907.6±323.1

U/L in POD 1 to 37.2±10.7, 243.4±37.3, 207.5±19.5, and 382.4±59.8 U/L in POD 3, respectively ( $p=0.028$ ,  $<0.001$ ,  $0.002$ , and  $0.001$ , respectively). The median (IQR) total and direct bilirubin decreased from 4 (2–8) and 2 (1–4) mg/dL in POD 1 to 2 (1–4) and 1 (1–2) mg/dL in POD 3, respectively ( $p<0.001$ ). The pulse rate of the patients significantly decreased during the first three postoperative days; there were concomitant significant increases in SBP, DBP, and CVP (Table 2). The changes in liver function and hemodynamic indices recorded in early postoperative period are shown in Figure 1.

The median (IQR) reduction in pulse rate were 28.7 (8.5–39.7) beats/min from POD 1 to 3 and 30.3 (11.8–42.2) beats/min from POD 1 to 4. There was a significant correlation between the amount of changes in hemodynamic indices and decrease in serum level of hepatic enzymes from POD 1 to 3. The median (IQR) pulse rate reduction of 22.5 (6.2–38.5) beats/min from POD 1 to 3 was associated with a reduction of 87.2% (80.0%–97.7%) in serum AST level during this period. The associations between the changes of hemodynamic indices and serum enzymes levels along with the changes in the pulse rate and serum AST level during the first three postoperative days are presented in Figure 2.

Log-rank (Mantel-Cox) test showed that the pulse rate of 87 in POD 2 was concomitant with an improvement in the graft function, defined as a serum ALT level of  $<180$  U/L in the fifth postoperative day. The graft function improved more quickly ( $p=0.003$ ) in patients with a pulse rate of less than 87 beats/min after a median of 54 (95% CI 5.7–62.3) hours post-transplantation than in those with



**Figure 1:** Variation in liver function and hemodynamic indices in early postoperative period

a pulse rate  $>87$  beats/min in whom the graft function improved after a median of 84 (95% CI 76.5–91.5) hours post-transplantation (Fig 3).

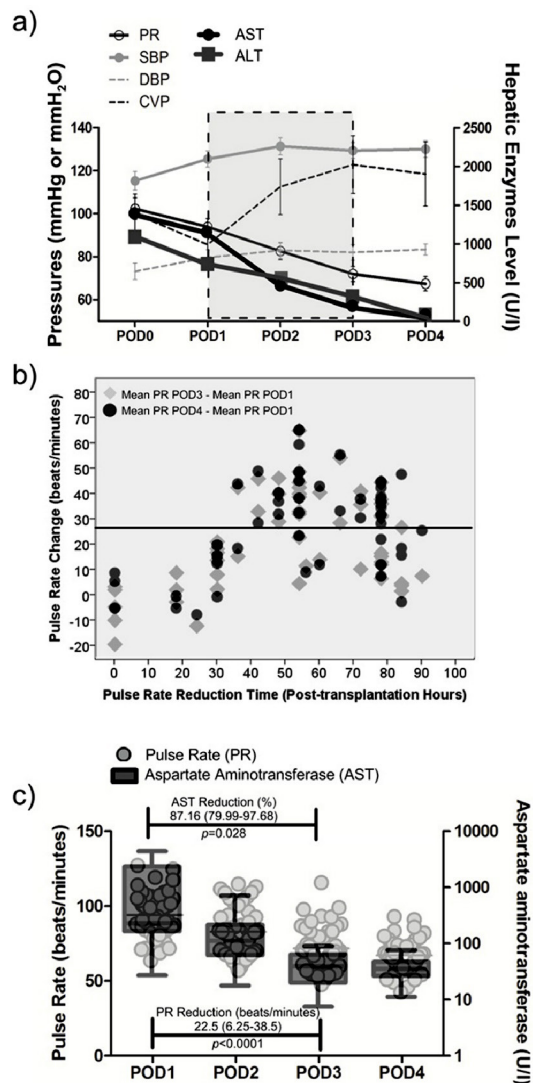
## DISCUSSION

We found that serum levels of AST, ALT, PT, and total and direct bilirubin significantly decreased during the first three post-transplantation days. Reportedly, serum levels of he-

patic enzymes—even in liver recipients with no postoperative complications—increase four to five times the upper limit of normal in the first postoperative day followed by a rapid reduction during the following days [13]. This increment may be due to ischemia-reperfusion damage; the consequent reduction in serum levels of hepatic enzymes may thus be used as an indicator of improvement of liver graft function [14]. Similar to our results, Kezazhi, *et al.*, show that serum levels of AST, ALT, PT, bilirubin, and fibrinogen return back to normal within one week of liver transplantation. However, a single peak may occur in any of the indices [15].

Hyperdynamic circulation of the patients suffering from liver cirrhosis reversed during the 3–5 postoperative days in our study. Particularly, SBP, DBP, and CVP significantly increased during the first three days post-transplantation in concomitant with a significant reduction in the pulse rate.

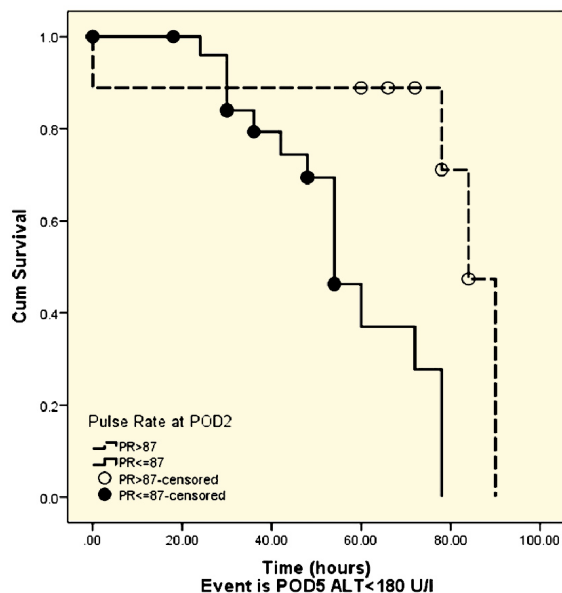
Limited studies have examined the hemodynamic alterations after liver transplantation. Some studies, like ours, suggest that hemodynamic circulation is restored after liver transplantation, probably because of the restoration of normal liver function and portal pressure or administration of immunosuppressive drugs and endothelin activation within the first days after liver transplantation [16]. Navasa, *et al.*, show that the hyperdynamic circulation and increased levels of aldosterone, renin and glucagon in patients suffering from liver cirrhosis return back to normal levels within two weeks of liver transplantation [17]. In a study by Glauser, *et al.*, the hemodynamic indices progressively improved during the first four days after liver transplantation in 21 patients [18]. Soresi, *et al.*, showed that the hemodynamic indices in patients suffering from liver cirrhosis progressively improve during 12 months after liver transplantation [19]. In contrast, some studies show that the hyperdynamic circulation persists during immediate or early postoperative period [20–22]. The possible explanation for this discrepancy could be the effect of antihypertensive or antirejection medications on blood pressure, total peripheral resis-



**Figure 2:** a) Hemodynamic indices of liver recipients determines the serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) from postoperative days (POD) 1 to 3. b) The changes observed in the mean pulse rate of patients from POD 1 to 3 and 4. c) Reduction in the pulse rate and the concomitant decrease in AST during the first three postoperative days.

tance, and consequently pulse rate and cardiac index, besides liver graft quality and ischemia times [12].

Our observations showed that the graft function and hyperdynamic circulation in patients with a pulse rate <87 beats/min in POD 2 were significantly improved earlier than those in other patients. This cut-off point may therefore be used as one of the predictors of reversal of hyperdynamic circulation after liver



**Figure 3:** The Kaplan-Meier survival curve regarding the pulse rate (PR) reduction during the postoperative day (POD) 2 and the event of liver function improvement defined as an alanine aminotransferase (ALT) <180 U/L on POD 5.

transplantation. Aggressive intravenous fluid replacement in addition to the increment of CVP, pulmonary capillary wedge pressure and systemic vascular resistance, may result in pulmonary edema, the most common cardiovascular complication during the immediate period post-transplantation [23, 24]. Application of a convenient and noninvasive predictor of restoring hyperdynamic circulation, such as the pulse rate in our study, may be a useful guide for intravenous fluid management in the early postoperative period.

A major shortcoming of our study was lack of data that could have influenced our results including circulatory data about pre- and post-operative complications.

In summary, it seems that there is an association between changes of hemodynamic indices, especially reduction in pulse rate, and decrease in serum level of hepatic enzymes during early post-transplantation period.

**CONFLICTS OF INTEREST:** None declared.

**FINANCIAL SUPPORT:** None.

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