Effect of Portal Venous Pressure on Liver Function of Donors in Living Donor Liver Transplantation

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Background: We assessed the alterations in portal hemodynamics associated with donor right hepatectomy and its effects on functional regeneration of the remnant liver.

Material/Methods: This prospective study included 30 adult living donors who underwent right hepatectomy in the Liver Transplantation Unit, Faculty of Medicine, Cairo University from June 2015 to October 2016. During donor surgery, portal venous pressure (PVP) was measured using an antithrombotic catheter inserted into the main portal vein, and was measured before and after clamping of the right portal vein. Postoperatively, liver function tests were done daily until normalization. The outcome measures were the time to normalization of liver function tests and effect of residual volume and steatosis on PVP.

Results: All donors had normal PVP before clamping and changed significantly after clamping (p<0.001). After clamping, 25 donors (83%) had a PVP above 12 mmHg; i.e. had high portal pressure. The median percentage of change was 55%. There were obvious increases in liver enzymes and bilirubin after surgery, but albumin and international normalized ratio showed progressive decreases postoperatively. The percent change in PVP was positively correlated with the levels of liver enzymes, time to normalization of liver enzymes, albumin, and bilirubin, and with the degree of steatosis, bit it was negatively correlated with residual liver volume.

Conclusions: During living donor liver transplantation, PVP increases by over 50% after clamping of the right portal vein of the donor's liver. This increase is associated with temporary delay of normalization of liver function of the donors.

MeSH Keywords: **Liver Regeneration • Living Donors • Portal Pressure • Portal Vein**

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Background

Liver transplantation is now recognized as the only effective treatment of end-stage liver disease, acute liver failure, and hepatocellular carcinoma [1]. The shortage of cadaveric grafts hastened the progression of living donor liver transplantation (LDLT). In Egypt, deceased donor liver transplantation is not approved by the law, leaving LDLT as the only choice for liver transplantation in a country where chronic liver diseases are a major health problem. However, LDLT entails a major surgery in an otherwise healthy subject. Therefore, donor safety should be a primary concern and the primary obstacle to performing LDLT. It is reported that donor surgery is associated with a 25–35% morbidity rate in these previously healthy individuals [2,3].

Adequate liver regeneration in donors and recipients needs an adequate increase in portal venous pressure and flow. However, excessive portal hypertension and overperfusion have been shown to be associated with poor outcome [4,5].

In the present study we assessed alterations in portal hemodynamics that occur during donor right hepatectomy and its effects on functional regeneration of the remnant liver and its relation to remnant liver volume.

Material and Methods

This prospective study included 30 adult living donors who underwent right hepatectomy at the Liver Transplantation Unit, Faculty of Medicine, Cairo University during the period between June 2015 to October 2016. The study protocol conformed to the ethics guidelines of the 1975 Declaration of Helsinki and its amendments. The study was approved by the Institutional Review Board of the Faculty of Medicine, Cairo University. The procedure, possible complications, and purpose of the study were explained in detail to all participants, and they provided written informed consent for participation before enrollment in the study.

Inclusion criteria were age 2–50 years, residual liver volume ≥35%, and steatosis ≤10%. Exclusion criteria were donors with a body mass index >30 kg/m², positive viral serology (hepatitis B or C virus, IgM for Cytomegalovirus, herpes simplex, and human immunodeficiency virus), liver pathology (hemangioma, bilharzial fibrosis), or trifurcated portal vein on portal venography. Donors with malignancy, major medical disorders, hemophilia, or coagulopathy were also excluded.

Preoperative preparations

All donors were subjected to physical examination and laboratory and radiological investigations, including complete blood count (CBC), liver and kidney function tests, coagulation profile, and viral serology. Radiological investigations included chest x-ray, abdominal ultrasound, triphasic computed tomography (CT) of the abdomen to detect intra-abdominal pathology, and CT angiography to delineate the vascular anatomy of the hepatic artery, hepatic veins, and portal vein. Magnetic resonance cholangiopancreatography was done to delineate the biliary anatomy. CT volumetry was performed for all donors to calculate the graft weight recipient ratio and the residual liver volume of the donor. A percutaneous ultrasound-guided liver biopsy was done to assess hepatosteatosis. All donors were subjected to psychiatric and anesthetic consultation and they all signed informed consent for the procedure and its expected complications.

Donor surgery

We followed the routine surgical steps of donor right lobe hepatectomy in the form of mobilization of right lobe and hilar dissection to identify the portal vein, right hepatic artery, and right bile duct. Portal venous pressure was measured using a 16-, 18-, or 20-gauge antithrombotic catheter inserted into the main portal vein. The other end was connected through an extension-arterial line to a pressure transducer. Then, the right portal vein was clamped and the pressure was measured again. The normal range for directly measured PVP values was considered to be 7–12 mmHg.

Postoperative follow-up

In addition to the routine postoperative follow-up, CBC, liver function tests were done daily until normalization. Kidney function tests, coagulation profile, hemoglobin and bilirubin levels of the drainage, and abdominal ultrasound and duplex of the hepatic vessels were done daily. After discharge, all donors were followed up weekly for 1 month, then once every 3 months for 1 year by physical examination. Laboratory investigations, abdominal ultrasound, and duplex ultrasound examination for the hepatic vessels were done during follow-up visits. CT abdomen with intravenous contrast was done for all donors after 6 months to assess liver regeneration. Normal levels of AST, albumin, and total bilirubin are ≤47 U/L, >3.5 g/dL, and ≤1 mg/dL, respectively.

The primary outcome measure was the time to normalization of liver function tests in relation to PVP. The secondary outcome measures were the effect of residual volume and steatosis on PVP.

Table 1. Operative outcome and portal venous pressure before and after clamping and the percent change after clamping of the 30 studied donors.

	Value
Portal venous pressure (mmHg)	
Before clamping	9.9±1.2
After clamping	15.2±2.5
Percent change of PVP after clamping	53.6±14.7
Operative time (min.)	239±11
Graft weight (gm)	847±47
Residual volume (%)	40.2±1.7
Drain removal time (days)	4.6±1.2
Hospital stay (days)	7.6±1.3

Data are expressed as mean ±SD.

Statistical analysis

All statistical tests were performed using the software IBM© SPSS© Statistics ver-23 (IBM© Corp., Armonk, NY, USA). Presentation of quantitative data was done as mean and standard deviation or median and range, while qualitative data are expressed as frequency and percentage. Correlations between numerical variables were tested using Spearman-rho method.

Diagnostic accuracy of high PVP for prediction of abnormal levels of some of liver functions was calculated in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and total accuracy. A p-value <0.05 was considered significant.

Results

The mean age of the studied group was 29.7±5.4 years. There were 24 males and 6 females, with a mean body mass index of 24.4±2.4 kg/m^2. The operative outcome and the portal venous pressure (PVP) before and after clamping of the right portal are shown in Table 1. All donors had normal PVP before clamping. After clamping, 25 donors (83%) had a PVP above 12 mmHg; these cases were classified as having increased portal pressure. The PVP changed significantly after clamping (p<0.01). The median percentage of change was 55%, with a maximum of 80%.

Marked increases in liver enzymes and bilirubin were observed after surgery (Table 2). Albumin and INR progressively decreased postoperatively. All values of liver functions were normalized within the first 9 days after surgery.

Percent change of PVP was positively correlated with the levels of liver enzymes (ALT and AST) on day 1 after surgery, and it was positively correlated with the time to normalization of liver enzymes, albumin, and bilirubin. Also, the percent change of PVP was positively correlated with the degree of steatosis and negatively correlated with residual liver volume (Table 3).

Post-clamping PVP of 14.5 mmHg or more was predictive of increased levels of total bilirubin, with a sensitivity and specificity

Table 2. Liver function tests on day 1, 3, 5 after surgery and the time to normalization of their values.

Liver function tests	Day 1		Day 3		Day 5	
ALT (U/L)	291	(153–701)	242	(99–511)	147	(58–230)
Time to normalization (days)	8	(5–9)				
AST (U/L)	249	(96–477)	158	(51–325)	60	(39–117)
Time to normalization (days)	5	(3–7)				
Albumin (g/dL)	3.8	(2.9–4.3)	3.5	(3.1–3.8)	3.6	(2.9–3.9)
Time to normalization (days)	5	(1–8)				
Total bilirubin (mg/dL)	1.5	(0.8–3.8)	2.6	(0.9–3.9)	1.7	(0.6–4.0)
Time to normalization (days)	7	(2–8)				
Direct bilirubin (mg/dL)	0.6	(0.3–1.8)	1.1	(0.4–2.3)	0.6	(0.3–2.5)
Time to normalization (days)	6	(3–8)				
INR	1.6	(1.0–2.7)	1.5	(1.2–2.3)	1.0	(1.0–1.5)
Time to normalization (days)	6	(4–9)				

Data are expressed as median (range). ALT – alanine aminotransferase; AST – aspartate aminotransferase; INR – international normalized ratio.

Table 3. Correlation between percent change of PVP and level of liver function tests and time to normalization, residual liver volume and degree of steatosis.

	Correlation coefficient	p-value
Liver function tests on day 1		
ALT	0.579	<0.01
AST	0.367	0.046
Albumin	0.000	1.00
Total Bilirubin	−0.177	0.35
Direct Bilirubin	−0.182	0.34
INR	−0.285	0.13

ALT – alanine aminotransferase; AST – aspartate aminotransferase; INR – international normalized ratio.

	Correlation coefficient	p-value
Time of normalization		
ALT	0.733	<0.01
AST	0.394	0.03
Albumin	0.396	0.03
Total Bilirubin	0.479	0.01
Direct Bilirubin	0.522	<0.01
INR	0.234	0.21
Residual volume	−0.524	<0.01
Steatosis	0.609	<0.01

Table 4. Diagnostic accuracy of portal venous pressure after clamping of the right portal branch and its percentage of change for prediction of increase of AST, and total bilirubin and decrease of albumin on day 5 after donor surgery.

	Sensitivity	Specificity	PPV	NPV	Accuracy
PVP ≥14.5 mmHg					
Increased AST	65.2%	42.9%	78.9%	27.3%	60.0%
Decreased albumin	92.9%	62.5%	68.4%	90.9%	76.7%
Increased total Bil.	90.5%	100.0%	100.0%	81.8%	93.3%
Percent change of PVP ≥48%					
Increased AST	69.6%	71.4%	88.9%	41.7%	70.0%
Decreased albumin	78.6%	56.3%	61.1%	75.0%	66.7%
Increased total Bil.	81.0%	88.9%	94.4%	66.7%	83.3%

PVP – portal venous pressure; AST – aspartate aminotransferase; Bil. – bilirubin; PPV – positive predictive value; NPV – negative predictive value.

Table 5. Correlation between age, residual liver volume and degree of steatosis and levels of liver function tests after surgery.

	Age		Residual volume		Steatosis	
	r	p	r	p	r	p
ALT	0.393	0.032	0.002	0.992	0.592	0.001
AST	0.466	0.009	−0.123	0.517	0.641	<0.001
Albumin	0.103	0.587	−0.415	0.023	−0.172	0.363
Total Bilirubin	−0.095	0.616	−0.205	0.277	−0.066	0.728
Direct Bilirubin	−0.082	0.668	−0.140	0.460	−0.076	0.689
INR	0.194	0.304	0.204	0.280	0.139	0.465

of 90.5% and 100%, respectively. It was also predictive of deceased albumin, with a comparable sensitivity but markedly lower specificity (Table 4).

Older age and higher steatosis grade were positively correlated with the levels of AST and ALT after surgery. Residual liver volume was negatively correlated with serum albumin level after surgery (Table 5). A residual volume ≤40% predicted low serum albumin, with a sensitivity of 64.3% but with a low specificity of 43.7%.

Discussion

Living donor liver transplantation has now become an accepted alternative for patients waiting for cadaveric liver transplantation [6]. In Eastern countries like Egypt, LDLT is commonly performed and deceased donor liver transplantation is rarely performed due to cultural, religious, and legal reasons [7]. At present, right-lobe grafts are commonly used in adult-to-adult LDLT programs, because it represents approximately 60% of the liver volume; thus, it can provide sufficient viable tissue for adult recipients of average size. The increasing popularity of LDLT highlights the importance of donor safety in this critical surgery [8]. In the majority of cases, the patient regains a normal liver mass within a few months during the postoperative period due to liver regeneration. However, despite adequate residual volumes, some donors decompensate to a greater extent. It has been proposed that a significant rise in portal pressures after donor hepatectomy can explain delayed functional regeneration in some patients [9].

In the present study, the PVP increased significantly after clamping (p<0.001), by a median of 55%. About 83% of donors developed high portal venous pressure (i.e., a PVP above 12 mmHg). After a marked increase of liver enzymes and bilirubin, all values were normalized within the first 9 days after surgery. However, the percent change of PVP was positively correlated with the time to normalization of liver enzymes, albumin, and bilirubin, and it was positively correlated with the degree of steatosis and negatively correlated with residual liver volume. High PVP predicted abnormal levels of total bilirubin and albumin after surgery.

After hepatectomy, the time to recovery of the donor depends on sufficient regeneration of the residual liver. It takes about 3–5 days for initial regenerative events to start after the resection [10]. In humans, hepatocyte replication usually starts within 1 day of major hepatectomy, while replication of non-parenchymal cells begins later [11]. Liver regeneration involves several molecular events and gene expressions. It has been hypothesized that an increase in PVP is necessary for liver regeneration to occur after hepatectomy [12]. However, portal hyper-perfusion after liver resection can cause a decrease in hepatic arterial blood flow. Many studies have reported a reduction in hepatic arterial blood flow after small-for-size liver transplantation [13,14].

There have been few published studies on changes in portal hemodynamics occurring during donor hepatectomy and their effect on remnant functional regeneration. Hepatectomy modifies liver hemodynamics, with increased resistance to blood flow of the organ. It has been shown that high portal pressure [15], high portal flow [16,17], and high hepatic venous pressure gradient [18] are associated with post-hepatectomy liver failure. A recent study investigated the hemodynamic changes after partial hepatectomy using a closed-loop lumped model during 12 surgeries in pigs. The authors reported that during 75% hepatectomy, hepatic artery tree resistance increased without hepatic arterial buffer response. Portal venous flow decrease by 30% on average, mainly due to blood loss and PVP increase by about 45% [19].

In the present study, we recorded a post-clamping increase of PVP by a median of 55%. However, normalization of liver function shortly after surgery indicates that the adverse effect of high PVP is generally temporary. Audebert et al. [19] have shown that portal pressure increase is compensated by 3 mechanisms: interaction with the rest of the circulation, the reduced increase in portal venous tree resistance due to dilation, and blood loss.

A previous study, conducted at our center in 2014, aimed to correlate the portal hemodynamic changes in the recipients with liver functions. It concluded that the rise in PVP significantly influenced the indices of liver function after LDLT [20].

In 2012, a prospective study by Gupta and colleagues studied the effect of portal hemodynamic changes on liver functions of 50 donors donating their right lobe, with residual liver volume ≥30%. They reported a mean rise in pressure during the procedure of 3.24 mmHg (p<0.05). In their series, the portal pressure was positively correlated with postoperative serum bilirubin and ALT, as well as with the duration of normalization of serum bilirubin [9].

A study using animal models found that sequential liver resection decreased the hepatic artery flow and increased the portal venous flow and PVP, which led to a poorly oxygenated blood supply and high pressure in the liver [21]. The study focussed on normal livers subjected to hepatectomy. On the other hand, in patients with severe fibrosis or cirrhosis undergoing major hepatectomy, post-hepatectomy PVP was found to be an independent predictor of post-hepatectomy liver failure, and the authors found that a value of PVP 21 mmHg was the best cut-off value for predicting liver failure [15]. Therefore,

the increase in PVP after clamping of the right portal vein in donors with normal pre-clamping pressure is expected to have only a temporary effect on liver functions. This is confirmed in the present study, as well as by previous studies. This increase in PVP seems to be a compensatory mechanism to enhance liver regeneration. This viewpoint is supported by our finding of a negative correlation between the percent change of PVP and the residual liver volume.

Conclusions

We found that during the process of LDLT, portal venous pressure increases by over 50% after clamping of the right portal vein of the donor's liver. This increase is associated with temporary delay of normalization of liver function of the donors, provided that the residual liver volume is 35% or more and the degree of steatosis is within 10%.

Conflict of interest

None.

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