Living-donor liver transplantation for moderate or severe porto-pulmonary hypertension accompanied by pulmonary arterial hypertension: a single-centre experience over 2 decades in Japan

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Abstract

Background

Candidates for orthotopic liver transplantation (OLT) often have porto-pulmonary hypertension (PPHTN) with pulmonary arterial hypertension (PAH). Poor outcomes of PPHTN contraindicate OLT. There are no guidelines for living-donor liver transplantation (LDLT) in PPHTN patients.

Methods
We present our experiences of LDLT in six patients with moderate or severe PPHTN, along with our institutional guidelines. Three had liver cirrhosis and three were non-cirrhotic. Catheterization studies were undertaken before, during and after LDLT, and the mean pulmonary arterial pressure (mPAP), cardiac output (CO), pulmonary vascular resistance and total peripheral resistance (TPR) were monitored.
Results
The results showed significant differences in CO and TPR between cirrhotic and non-cirrhotic patients before, during and after LDLT. Cirrhotic patients showed systemic hyperdynamic state. Two cirrhotic patients showed poor responses to pre-transplant treatment, and continued to have increased PAH and poor clinical courses after LDLT. LDLT has an advantage of flexible timing of LT. Currently in our institution, PPHTN patients with mPAP <40 mmHg are registered for LDLT after treatment and catheterization. However, LDLT is performed when mPAP is ≤35 mmHg, leading to improved outcomes.
Conclusion
PPHTN patients with well-controlled PAH, or secondary PAH resulting from porto-systemic shunts, may be appropriate candidates for LDLT after careful considerations.
Keywords
Living donorLiver transplantationPulmonary arterial hypertensionPorto-pulmonary hypertensionLiver cirrhosis
Abbreviations
ACR Acute cellular rejection
AM Abernethy malformation
AVCT Acute volume challenge test
BSA Body surface area
BV Blood volume
CBA Congenital biliary atresia
CI Cardiac index
CO Cardiac output
DDLT Deceased-donor liver transplantation
ET-1 Endothelin-1
GRWR Graft-to-recipient weight ratio
HPS Hepato-pulmonary syndrome
ICU Intensive care unit

LDLT Living-donor liver transplantation
LNB Liver needle biopsy
NO Nitric oxide
OLT Orthotopic liver transplantation
MELD Model for end-stage liver disease
mAP Mean arterial pressure
mPAP Mean pulmonary arterial pressure
PELD Pediatric end-stage liver disease
PAH Pulmonary arterial hypertension
PCWP Pulmonary capillary wedge pressure
PGI_2 Prostaglandin I_2
POD Postoperative day
PPHTN Porto-pulmonary hypertension
PVR Pulmonary vascular resistance
RV Right ventricle
SPT Steroid pulse therapy
TPR Total peripheral resistance
UNOS Uited Network for Organ Sharing

Introduction

Advanced liver disease results in cardiopulmonary disorders, including porto-pulmonary hypertension (PPHTN) and hepato-pulmonary syndrome (HPS). In addition, eventration of the diaphragm because of intractable ascites, or easily broken ribs because of vitamin D deficiency, often disrupt ventilation. Hepatic failure and pulmonary arterial hypertension (PAH) may also be accompanied by congenital diseases such as Alagille syndrome. In immunocompromised patients with end-stage liver disease, such problems with the cardiopulmonary circulation result in increased mortality.

Previous studies have shown that (depending on the institutional definition) the frequency of cardiopulmonary disorders in patients with liver cirrhosis ranges between 5.3 and 8.4% [*1*, *2*]. Although PPHTN in patients with advanced liver disease was initially defined as PAH because of portal hypertension, the current definition of PPHTN includes secondary PAH because of porto-systemic shunts, as seen in patients with Abernethy malformation (AM). In other words, the presence of portal hypertension may not always be necessary for a diagnosis of PAH [*3*, *4*]. However,

HPS is defined as liver disease with abnormal pulmonary gas exchange and evidence of intrapulmonary vascular dilatation that results in a right–to–left intrapulmonary shunt. Therefore, PPHTN and HPS should be considered as different pathological states.

Several studies define the diagnostic criteria for PPHTN in association with portal hypertension as follows: (1) mean pulmonary arterial pressure (mPAP) >25 mmHg and pulmonary capillary wedge pressure (PCWP) <15 mmHg, (2) pulmonary vascular resistance (PVR) >120 dynes s cm^{-5} and (3) the exclusion of other causes, such as congenital cardiac disorders [*5–11*]. In pediatric patients, an mPAP of >20 mmHg is indicative of PPHTN. Previous studies show that 38–41% of PPHTN patients die within 15 months of diagnosis and that 50% of untreated PPHTN patients die within 6 months of diagnosis [*3*, *12*]. PPHTN causes right ventricular dysfunction, and 36% of PPHTN patients die during the early postoperative period after orthotopic liver transplantation (OLT) because of right ventricular dysfunction, acute respiratory distress syndrome, and cardiovascular collapse [*13*]. This, coupled with poor outcomes after OLT, led many physicians to believe that OLT was contraindicated in PPHTN patients with moderate (mPAP ≥35 mmHg) or severe (mPAP >50 mmHg) PAH [*10*, *14*, *15*]. However, some reports suggest that the outcome for OLT in PPHTN patients with mild PAH (mPAP <35 mmHg) has improved [*13*, *16*, *17*]. Successful OLT in PPHTN patients needs to be established, and some studies have focused on this [*10*, *13*, *17–26*]. However, the actual strategy for OLT in PPHTN patients with PAH is still unclear, especially with respect to living–donor liver transplantation (LDLT).

Though deceased–donor liver transplantations (DDLTs) make up the majority of OLTs in the USA and Europe, almost all OLTs performed in Japan are LDLTs. The indications for OLT as a treatment for end–stage liver disease are almost identical for DDLT and LDLT; however, each OLT has its own particular characteristics. For LDLT, donor selection and graft volume are more limited, but shorter cold ischemic times and more flexibility in the timing of OLT are an advantage. In this retrospective study, we focused on PPHTN patients who underwent LDLT in our institution within the last 2 decades. To our knowledge, this is the first study of the long–term experiences in a single centre performing LDLT in PPHTN patients with PAH. Based on our retrospective evaluations, we discuss the outcomes of LDLT in PPHTN patients with PAH, with the aim of establishing strategies for the successful use of LDLT as a treatment for this condition.

Patients and methods

Patients

A total of 1,421 recipients who underwent LDLT at Kyoto University Hospital between 1990 and 2010 were enrolled in the study. The median follow-up period was 6.9 years [range 1 day (patient died) to 20.5 years].
In our institution, all recipients received cardiac survey by Doppler ultrasound beforehand. Patients received advanced investigations including catheterization study if any abnormalities were detected or suspected. Patients with mild PAH, such as those with Alagille syndrome and suspicious cases identified during the survey, underwent LDLT without any intensive preoperative therapy for PPHTN. Six patients (3 male and 3 female; median age 8.3 years, range 5.0–21.0 years) with moderate or severe PAH underwent LDLT. The median body surface area (BSA) was 0.93 m^2 (range 0.67–1.67 m^2). The primary disease was congenital biliary atresia (CBA) in four cases and AM (one each of type Ib and II) in two cases (Table 1). The two cases of AM have been documented in detail elsewhere [*27*, *28*]. The protocol used in this study was approved by the Ethics Review Committee for Clinical Studies of Kyoto University Graduate School of Medicine (approval no.: E976).

Important parameters for the catheter studies before, during and after LDLT

Cardiac catheter studies were performed before OLT if required. All six patients in this study received detailed catheterization studies both before and after LDLT. Swan-Ganz catheters were used routinely both during OLT and in the intensive care unit (ICU), and cardiac parameters were closely monitored throughout the perioperative period.
mPAP (mmHg), mean arterial pressure (mAP, mmHg), cardiac output (CO, l/min) and PCWP (mmHg) values were collected retrospectively. The cardiac index (CI, l/min/m^2) was calculated as: CO/BSA. The PVR (dynes s cm^{-5}) was calculated using the following formula: PVR = (mPAP − PCWP) × 80/CO [*13*, *17*]. Previous studies have shown that the total peripheral resistance (TPR) and/or systemic vascular resistance (peripheral vascular resistance) reflects the peculiar systemic hemodynamics in cirrhotic patients [*29*–*32*]. TPR (dynes s cm^{-5}) was calculated using the following formula: TPR = mAP × 80/CO [*30*, *33*].

In our institution, to evaluate the function of the right ventricle (RV), an acute volume challenge test (AVCT) was performed during catheter study before LDLT. Normal saline of 10 ml/kg body weight was injected for 6–7 min via cardiac catheter.
We also evaluated the temporal changes in each of the parameters: (1) upon initial diagnosis of PAH (cardiac catheterization study); (2) after the induction of treatment (cardiac catheterization study); (3) during LDLT (via Swan–Ganz catheter after the induction of anesthesia); (4) after LDLT in the ICU (after weaning from respiratory ventilation); (5) up until discharge or the first cardiac investigation after discharge (catheterization study); and (6) the latest cardiac investigation after LDLT (catheterization study).

Immunosuppression

Immunosuppression after LDLT comprised tacrolimus and methylprednisolone. The trough level of tacrolimus was maintained at 8–15 ng/ml during the early postoperative period, based on the clinical findings in each case. Methylprednisolone was given intravenously (1 mg/kg) once daily from postoperative days (POD) 1–3 followed by 0.5 mg/kg once daily for the next 3 days. On POD 7, 0.3 mg/kg of methylprednisolone was given intravenously. Steroids were switched to oral prednisolone 0.3 mg/kg once daily on POD 8, and this dose was reduced to 0.1 mg/kg 4 weeks after LDLT. Thereafter, the immunosuppression was controlled according to each clinical course.

Histopathological analysis of native livers and liver needle biopsy results

Native livers were assessed macroscopically and microscopically by at least two experienced histopathologists. If necessary, liver needle biopsy (LNB) was performed after LDLT. Five of the six PAH patients underwent LNB. Liver tissues were fixed in neutral-buffered formalin, embedded in paraffin and sliced into sections (4 μ m thick). The histopathological findings were assessed after standard hematoxylin and eosin staining, and hepatic fibrosis was reconfirmed by Masson trichrome and reticulin staining. Liver fibrosis was scored using a five-grade scale (F0–F4) according to the METAVIR scoring system [*34*]: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa without cirrhosis; F4, cirrhosis.

Statistical analysis

Results were expressed as the median and the range. Survival rates were calculated using the Kaplan–Meier method, and the log–rank test was used for between–group comparisons. The differences between unpaired continuous or discontinuous variables between two groups were analyzed by Student's t test. For individually, temporally and repeatedly measured data, the differences in changes over time between groups were analyzed by repeated measures ANOVA. Statistical calculations were performed using SPSS Software, version 17.0 (SPSS Inc., Chicago, IL, USA). A p value of <0.05 was considered to be statistically significant.

Results

Profiles before LDLT

All patients had a confirmed history of respiratory disturbances such as hypoxemia, lip cyanosis and puffing when breathing. The standard deviations in height and body weight were 0 (range 0.8–0.5) and −0.1 (range −0.9 to 0.3), respectively. Four of five recipients (aged <20 years) had a history of reduced growth. The United Network for Organ Sharing (UNOS) status was estimated to be III in five cases and IIB in one case. The median model for end–stage liver disease (MELD) or pediatric end–stage liver disease (PELD) score was 4.5 points (range 0–13 points). Grafts in five cases were from the father and in one case from the mother. Human leukocyte antigen typing indicated no barriers to LDLT. The ABO blood groups were identical in four cases, and compatible in two cases. The pre–transplant profiles are summarized in Table 1.

Surgical treatments before LDLT

Overall, 5/6 patients had undergone surgery before LDLT. All of the CBA cases had undergone Kasai's operation. Two of these cases received additional surgery after Kasai's operation: one for a distal spleno–renal shunt due to portal hypertension (case 1), and another underwent seven re–boring operations (case 3). One patient with AM type II underwent ligation of a porto–systemic shunt 4.2 years before LDLT (case 5). Surgery performed prior to LT is outlined in Table 1.

Treatment for PAH prior to LDLT

The interval from initial diagnosis of PAH to LDLT was 0.96 years (range 0.8–11.9 years). Continuous intravenous prostaglandin I_2 (PGI_2) was given to all patients before LDLT, and oxygen was given in 5/6 cases.

Catheterization studies before LDLT showed that 4/6 patients (cases 3–6) had a positive reaction to the loading tests and/or a negative response to the AVCT, though two patients showed low reactivity against the loading tests and a positive response to the AVCT (case 1 and 2). In case 2, PGI_2 treatment was discontinued 8.8 years after LDLT owing to a catheter-related infection, and deteriorations in quality of life and activities of daily living. Thereafter, PAH worsened temporarily. In retrospect, we feel that PGI_2 had a positive effect on reducing PAH in case 2. The period of PGI_2 treatment prior to LDLT ranged from 6 to 9 months.

Currently, in our institution, we determine the time point after induction of anesthesia at which LDLT should be performed. The cutoff level for mPAP (measured via a Swan-Ganz catheter) is 35 mmHg. If mPAP is >35 mmHg, we postpone LDLT and continue to manage the PAH. LDLT is performed when the mPAP after anesthesia is controlled at ≤35 mmHg. Although LDLT was postponed in two cases in the present study (cases 3 and 4), these patients received LDLT after further treatment for PAH. The mPAP and PVR values at the time of LDLT were 34.0 mmHg (range 23–54 mmHg) and 244.4 dynes s cm^{-5} (range 81.8–281.7 dynes s cm^{-5}), respectively. The treatments for PAH prior to LDLT are summarized in Table 2.

Profiles during LDLT

The median operation time was 628 min (range 484–931 min), and the median amount of intra-operative blood loss was 2965 ml (range 420–3,970 ml). Graft types were as follows: two extended lateral segment grafts, two left lobe grafts, one posterior segment graft and one right lobe graft without the middle hepatic vein. The median body weight was 26.0 kg (range 15.4–61.6 kg), and the median graft weight was 342.5 g (range 280–790 g). The median graft-to-recipient weight ratio (GRWR) was 1.30 g (range 0.95–2.24) (Table 1). A small-for-size graft is defined as a graft to GRWR <0.8 or a ratio of graft weight against standard liver volume <40%, and these grafts result in a high mortality and morbidity [*35*, *36*]. Our six cases in this study had appropriate graft size, though LDLT can not avoid inevitable insufficiency of allograft size. The median cold ischemic time was 73.5 min (range 26–346 min), and the median warm ischemic time was 30.5 min (range 22–61 min). The median anhepatic phase was 58.5 min (range 42–75 min). Though a side clamp of the inferior vena cava was performed

during LDLT, a total clamp could not be performed. Temporal portal-systemic shunt was made only in case 1, though we currently do not use temporal portal-systemic shunts. From 2006, an intentional control of portal venous pressure <15 mmHg was performed during adult LDLT in our institution. Retrospectively, portal venous pressure was monitored only in case 3.

Cirrhotic findings at LT

The Child-Pugh score was 6.5 points (range 5–10 points). Imaging studies prior to LDLT showed that 3/6 cases (cases 1, 2 and 4) had cirrhosis. The CO, CI and TPR values were 5.88 l/min (range 3.60–17.60 l/min), 5.49 l/min/m^2 (range 3.33–17.40 l/min/m^2) and 942.9 dynes s cm^{-5} (range 327.3–1361.3 dynes s cm^{-5}), respectively. Hepatic fibrosis in the native livers was assessed as follows: two at F3 and one each at F0, F1, F2 and F4 (Table 3).
Liver cirrhosis was apparent in three cases (cases 1, 2 and 4); the other three cases (cases 3, 5 and 6) did not seem to have signs of advanced liver cirrhosis. Statistical differences were found between cirrhotic and non-cirrhotic patients with regard to the Child-Pugh score ($p = 0.0023$), TPR ($p = 0.0164$) and the F score ($p = 0.0249$). Although the CO and CI values were higher in cirrhotic recipients than in non-cirrhotic recipients (Table 3), these differences did not reach statistical significance.

Clinical course and outcome after LDLT

The length of hospital stay was 55.0 days (range 51–97 days), and the follow-up LNBs were F0 and F1. One patient died on POD 12. The follow-up term in the surviving patients was 3.6 years (range 1.8–9.9 years) (Table 4). The survival curves after LDLT showed no statistical differences in survival rates between LDLT recipients with or without PPHTN ($p = 0.8114$). The results of long-term blood gas analyses after LDLT in 4/6 patients are shown in Table 4. Case 4 showed no respiratory discomfort after LDLT, so blood gas analysis was not performed in this case.
Catheter-related infections occurred in 5/6 cases (83.3%) during PGI_2 therapy. In four cases (cases 3–6), PGI_2 was successfully withdrawn after LDLT, and the patients were followed-up. In one case (case 2), PGI_2 was stopped 8.8 years after LDLT without stable mPAP. The time of PGI_2 withdrawal after LDLT was 1.9 years (range 0.9–8.8 years) in the surviving five cases (Table 2).

In one patient (case 1), PAH became worse after LDLT regardless of intensive care, causing cardiac failure and death. In case 2, PAH became worse 2 years after LDLT. A remnant from a spleno–renal shunt was detected, and we consider that this contributed to the increase in PAH. Splenectomy and ligation of the shunt were subsequently performed on POD 783. However, the resulting decrease in mPAP was not enough. Therefore, these two cases (cases 1 and 2) were considered to be PPHTN recipients with a poor clinical course and outcome after LDLT (Table 4).
In case 4, surgical hemostasis was performed on POD 1 and 12 because of intraperitoneal bleeding after LDLT. In this case, a hemorrhagic tendency was observed. Acute cellular rejection (ACR), which was observed in four cases, was successfully treated by steroid pulse therapy (SPT). Drug–induced liver dysfunction was also successfully treated (Table 4).

Changes of cardiac and Swan–Ganz catheter parameters before, during and after LDLT

The changes in mPAP, CO, SVR and TPR before, during and after LDLT are shown in Fig. 1.
The p values between cirrhotic and non–cirrhotic patients relating to changes in mPAP, CO, PVR and TPR were 0.1478, 0.0495, 0.4269 and 0.0030, respectively. The changes in CO and TPR in cirrhotic and non–cirrhotic recipients were significantly different (Table 5). The two patients (cases 1 and 2) with increased PAH after LDLT both had liver cirrhosis. The p values related to changes in mPAP, CO, PVR and TPR over time in recipients with or without a good clinical course were 0.0256, 0.7582, 0.3767 and 0.3789, respectively. The difference in mPAP between patients with or without a good clinical course after LDLT was statistically different (Table 5).

Discussion

The cirrhotic hemodynamic state is characterized by high CO or CI values, a large blood volume (BV), a reduced or normal central BV, a low TPR, mild tachycardia and low or normal aortic pressure [*30*, *37*–*39*]. In particular, TPR is considered to be the most reliable indicator of vascular alterations in cirrhotic patients [*30*–*32*]. The peculiar hemodynamics seen in cirrhosis are referred to as ‘hyperdynamic,’ and are indicated by a large BV, high CO and a low TPR [*33*, *40*]. Previous studies clearly show

that a systemic hemodynamic state persists in cirrhotic recipients after OLT regardless of the restoration of portal pressure [*33*, *37*, *41*, *42*] and that optimal systemic hemodynamics are required for excellent outcomes after OLT [*33*, *40*, *43*]. Even subtle disorders in systemic hemodynamics during the early postoperative period after OLT may result in decreased splanchnic flow [*33*, *40*], subsequently disrupting liver regeneration [*43*]. The two cases (cases 1 and 2) with persistently elevated PAH after LDLT both had liver cirrhosis. One patient died during the early postoperative period (case 1). Because the cirrhotic hyperdynamic state is one of several possible reasons for PAH in this case, postoperative management on the dry-side may be effective in controlling mPAP. However, maintenance of a hyperdynamic state during the perioperative period is important for excellent OLT results in cirrhotic patients because the collateral vessels do not disappear immediately, even after restoration of portal pressure [*33*, *40*, *43*]. Small BVs result in decreased portal flow and subsequent graft loss. Thus, the postoperative management of cirrhotic patients after OLT involves the dilemma of maintaining a low mPAP.

The etiology of PPHTN is still unclear, although several mechanisms have been suggested. One hypothesis is that the cirrhotic hyperdynamic state itself causes mild increases in pulmonary arterial pressure and shear resistance in the pulmonary vessels. Another is that some vasoactive substances impact on the pulmonary vascular bed, as patients with portal hypertension show increased concentrations of vasoactive substances such as endothelin-1 (ET-1), angiotensin II, norepinephrine, vasopressin, nitric oxide (NO), leukotriene, endotoxin and serotonin [*44*-*47*]. These vasoactive substances, which are usually metabolized in the liver via the portal flow, are not defused in cirrhotic livers, or do not flow into the liver because of the formation of collateral vessels [*45*, *48*, *49*]. Subsequently, these substances flow directly into the right side of the heart. This pathway may explain PPHTN in patients with porto-systemic shunts. In one case (case 1), a distal spleno-renal shunt was performed to control the portal pressure. We do not recommend this type of surgical treatment for PPHTN patients because of the risk of PAH caused by vasoactive substances, as porto-systemic shunts may exacerbate PAH.

We performed LDLT in two patients with AM (cases 5 and 6). Because of the mechanisms involved and the malignant potential of this condition [*28*], OLT may become the definitive treatment for PPHTN patients with porto-systemic shunts. We suggest that PPHTN patients with PAH due to porto-systemic shunts are good candidates for LDLT, although ligation of the porto-systemic shunts should be the initial treatment for patients with AM type II.

Several therapies for PAH have been documented. Because of advances in diagnosis and treatment over the last 2 decades, the median survival rates for PPHTN patients with PAH have improved from 68 to 81.1% at 1 year, to 48–61.1% at 3 years, and 34–57.9% at 5 years [*50*]. PPHTN requires the correct treatment. Many agents, such as oxygen, nitric oxide, phosphodiesterase 5 inhibitors and ET-1 receptor antagonists are effective for the treatment of PPHTN patients with PAH [*5*, *51*–*53*]. However, some agents have side effects, such as increasing the effects of immunosuppressant drugs, hepatocyte toxicity and enhancement of the cirrhotic hyperdynamic state [*23*, *54*, *55*]. Thus, some agents cannot be used after OLT. After the introduction of epoprostenol (a synthetic analogue of prostacyclin, PGI_2), the outcome for PPHTN patients with PAH improved [*5*, *54*]. Currently, PGI_2 is considered a key drug for the control of PAH [*20*, *21*]. However, PGI_2 also has problems, including central line placement, drug preparation/handling, intensive patient education and the inhibition of platelet aggregation [*54*]. Hemorrhagic tendency is one problem during the early postoperative period, and 1/6 cases (case 4) required additional surgery after LDLT because of inhibited platelet coagulation caused by continuous PGI_2 administration. However, PGI_2 is only active for a short time and is chemically unstable [although the compound has adequate stability for 24 h in carbonate buffer (pH 10.0) at 0° C]. Also, a mobile device is required for continuous infusion, and a central venous catheter is needed to avoid painful vein irritation caused by peripheral administration [*56*]. The incidence of catheter-related sepsis has been reported as 0.1–0.6 cases per patient-year [*56*, *57*]. Immunosuppression after LDLT carries a risk of infection (the rate of catheter-related infections in our patients was high). Thus, quality of life and activities of daily living may be disturbed. Indeed, we had to discontinue PGI_2 treatment in one case for these very reasons (case 2). However, the effective control of moderate/severe PPHTN prior to OLT is associated with excellent outcomes [*19*], and we speculate that PGI_2 still plays an important role before, during and after LDLT. PGI_2 therapy was successfully withdrawn in four cases after LDLT. We found no significant differences in PVR between PPHTN patients, regardless of clinical course. However, unstable mPAP appeared to be associated with the clinical course. One possible explanation is that PGI_2 affected vasoconstriction and pulmonary vascular remodeling, even in PPHTN patients with unsatisfactory reductions in mPAP. In one case, PAH worsened 2 years after LDLT (case 2), and a remnant from a spleno-renal shunt was detected. At that time, we considered that this shunt may have caused the increase in PAH. Therefore, ligation of the shunt and splenectomy were performed. However, the decrease in mPAP was still insufficient. One possible explanation is that

organic consolidation within the pulmonary vessels had already occurred during the course of the disease. In this case, no signs of cardiac failure were detected 9.9 years after LDLT, though a temporal increase in PAH was observed after withdrawal of PGI_2. Previous studies show that only 29% of untreated PPHTN patients survive after OLT [*10*] and that patients with moderate/severe PPHTN (mPAP >35 mmHg and PVR >250 mmHg) have a >90% risk of death after OLT [*13*]. Effective pharmacological control of moderate/severe PPHTN prior to OLT is associated with excellent survival rates [*19*].

Our results showed that two recipients of LDLT (cases 1 and 2) had poor a response to treatment before LDLT, and their mPAP showed different courses after LDLT compared with the other four patients. The clinical course in these two cases were retrospectively consistent with the currently documented criteria prior to OLT [*13*, *16*, *17*] and illustrate the importance of intensive preoperative control of PAH for successful OLT [*19*]. The flowchart currently used in our institutional guidelines for LDLT in PPHTN patients is shown in Table 6. PGI_2 therapy was introduced when mPAP was >35 mmHg. Though we want to shorten the waiting times for LDLT, this therapy may be continued for 6–9 months prior to LDLT if necessary. Retrospectively, three cases (cases 1–3) did not fulfill the criteria set out in previous studies (mPAP >35 mmHg and PVR >250 mmHg) [*13*, *16*, *17*], and two cases (cases 1 and 2) did not conform to our own institutional guidelines. In PPHTN patients, the RV is well designed for volume transmission, but does not have the muscle power to deal with the increased work caused by an increased afterload unless the load develops very gradually to allow hypertrophy of the RV muscle. In the presence of decreased RV contractility, as seen in cases of cirrhotic cardiomyopathy, or dilatation from volume overload or increased afterload, the RV is even more sensitive to increases in work load and may become dysfunctional and fail. Right ventricular failure is commonly caused by acute increases in PVR. Once failure occurs, cardiac function declines at an accelerated pace. During OLT, temporal clamping of the inferior vena cava and hepatic vein, and the portal reflow after the anhepatic phase cause acute volume overload to the right side of the heart, and this stress may result in right heart failure. After the restoration of portal reflow, vasoactive substances may stimulate the pulmonary artery and subsequently cause the paroxysms associated with pulmonary hypertension. Our institution currently uses AVCT before LDLT to confirm RV function against acutely increased preloading. When mPAP is <40 mmHg, we perform AVCT. LDLT is considered if PAH is controllable and if cardiac function can be maintained during the clinical course. A decision is also based on the findings from

catheter examinations and the level of brain natriuretic peptides. In our institution, cardiopulmonary variables during LDLT are checked using a Swan–Ganz catheter, and LDLT may be postponed and internal treatments reconsidered if mPAP is >35 mmHg after the induction of general anesthesia. This strategy seems to work well, even though LDLT was postponed in two cases. We suggest that a hasty decision to perform LDLT will lead to worse results in PPHTN patients and that thoughtful decision making regarding the advantages of LDLT may be the key to successful LDLT in PPHTN patients. This is because OLT is based on the advantages of LDLT, as the timing of LDLT is more flexible than that of DDLT.

Previous researchers documented that the mPAP value should be decreased as <35 mmHg, preoperatively [*58*, *59*]. General anesthesia involves invasive factors and may affect mPAP values after the induction. Then, we agreed that preoperative mPAP <35 mmHg is an ideal. Actually, we still have some concerns about registering patients with 35–40 mmHg mPAP as LDLT recipients. Preoperative reactivity for pharmacological control of moderate/severe PPHTN is a key for excellent survival rates [*19*]. Though case 4 preoperatively showed marginal mPAP (mPAP 35 mmHg at LDLT) in comparison with previous documents and actually received a postponement of LDLT, this patient had well-kept RV function and a favorable course after treatment induction. Case 6 (mPAP 35 mmHg at LDLT) survived for 9.9 years after LDLT. Our cutoff level for LDLT registration (mPAP <40 mmHg) may seem higher than that in other institutions. The timing of LDLT is more flexible, and paradoxically the criteria of mPAP ≤35 mmHg after anesthesia induction seemed to work as a final check point before LDLT. Although we still do not have enough experience, we currently speculate that some patients with mPAP of 35–40 mmHg may have potential as LDLT candidates.

Treatment of PPHTN should be considered because non-treated patients have terrible outcomes. However, effective PPHTN treatment in candidates for OLT still requires well-designed prospective studies to establish formal guidelines [*18*]. Overall, we believe that, in some cases, PPHTN patients with PAH are potentially curable and that LDLT can achieve good results. PPHTN patients with well-controlled PAH, or secondary PAH due to porto-systemic shunts, may be appropriate candidates for LDLT after thoughtful consideration of the relevant factors, including the clinical course, results of catheterization studies and Swan–Ganz monitoring, the response to therapeutic agents and the findings of imaging studies. Close follow-up after LDLT are also crucial to establish good results in PPHTN patients.

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Table 1

Profiles of PPHTN patients with PAH before and during LDLT

Case	OLT	Age at LDLT (years)	Original diseases	Surgical treatments before LDLT	Respiratory disturbances[a]	Growth reduction[b]	UNOS status	MELD/PELD score (point)	ABO compatibility	GRWR
1	LDLT	17.9	CBA	Kasai' s operation Distal spleno-renal shunt	+	−	III	13	Identical	1.28
2	LDLT	6.5	CBA	Kasai' s operation	+	+	III	2	Identical	1.22
3	LDLT	21.0	CBA	Kasai' s operation Subsequent reoperations (seven)	+	N/A	III	11	Identical	1.29
4	LDLT	9.2	CBA	Kasai' s operation	+	+	IIB	3	Identical	0.95
5	LDLT	7.5	AM type II	Ligation of porto-systemic shunt	+	+	III	0	Compatible	1.57
6	LDLT	5.0	AM type Ib	−	+	+	III	6	Compatible	2.24

AM Abernethy malformation, CBA congenital biliary atresia, GRWR graft-to-recipient weight ratio, LDLT living-donor liver transplantation, MELD model for end-stage liver disease, N/A not applicable, OLT orthotopic liver transplantation, PAH pulmonary arterial hypertension, PELD pediatric end-stage liver disease, PPHTN porto-pulmonary hypertension, UNOS United Network for Organ Sharing

[a]Respiratory symptoms included hypoxemia, lip cyanosis and puffing when breathing

[b]The values in patients of age <20 years

Table 2

Treatments for PPHTN with PAH before and after LDLT

Case	Time up to LDLT[a] (years)	Treatments before LDLT[b]	Favorite reactivity against loading and challenging tests[c]	Treatment term with PGI_2 before LDLT (months)	At LDLT			Catheterrelated infection	Withdrawal of PGI_2 after LDLT (years)
					History of postponement	mPAP (mmHg)	PVR (dynes s cm^{-5})		
1	11.9	PGI_2 (20.0 ng/kg/min)	−	9	−	41	274.3	−	−
2	1.1	PGI_2 (6.0 ng/kg/min) O_2	±	8	−	54	281.7	+	+ (8.8)
3	0.9	PGI_2 (36.5 ng/kg/min) O_2	+	9	+	33	266.7	+	+ (1.3)
4	0.8	PGI_2 (20.5 ng/kg/min) O_2	+	8	+	35	81.8	+	+ (1.9)
5	4.4	PGI_2 (9.6 ng/kg/min) O_2	+	6	−	31	201.7	+	+ (2.2)
6	1.7	PGI_2 (1.9 ng/kg/min) O_2	+	9	−	23	222.2	+	+ (0.9)

AVCT acute volume challenge test, LDLT living-donor liver transplantation, mPAP mean pulmonary arterial pressure, PAH pulmonary arterial hypertension, PGI2 prostaglandin I2, PPHTN hypertension, PVR pulmonary vascular resistance

[a]Time from diagnosis to LDLT

[b]Medications at the time of LDLT

[c]Positive reactivity against loading test (PGI_2, O_2 and NO) and negative reactivity against AVCT

Table 3

Cirrhotic findings at LDLT

Case	Child–Pugh score (point)	Developed collaterals	Splenomegaly	CO (l/min)	CI (l/min/m^2)	TPR (dynes s cm^{-5})	Hepatic fibrosis[a]
1	8	+	+	7.00	4.19	765.7	F3
2	9	+	+	7.10	8.88	754.9	F3
3	5	−	−	4.50	3.33	1120.0	F2
4	10	+	+	17.60	17.40	327.3	F4
5	5	−	−	4.76	5.60	1361.3	F1
6	5	−	−	3.60	5.37	1288.9	F0

CI cardiac index, CO cardiac output, LDLT living-donor liver transplantation, TPR total peripheral resistance

[a]Histopathological assessment of removed native livers using the METAVIR score

Table 4

Episodes during LDLT and clinical course and outcomes after LDLT

Case	Complications and treatments	Discharge (POD)	Blood gas analysis (PaO_2, mmHg)[a]	Histopathological analysis[b]	Outcome (days or years)[c]
1	Confounded PAH, oversystemic PAH, cardiac failure	–	–	F0	Dead (12 days)
2	ACR (SPT), sepsis confounded PAH 2 years after LDLT. The remnant of spleno–renal shunt (splenectomy and the ligation of shunt at POD 783)	97	69.2	F1	Alive (9.9 years)
3	ACR (SPT)	51	–	F0	Alive (4.2 years)
4	Hemorrhagic tendency. Intraperitoneal bleeding (surgical hemostasis at PODs 1 and 12), ACR (SPT)	53	87.8	–	Alive (2.3 years)
5	Drug–induced liver dysfunction (the cessation of suspected drugs)	58	78.3	F0	Alive (3.6 years)
6	ACR (SPT)	55	100.5	F0	Alive (1.8 years)

ACR acute cellular rejection, LDLT living–donor liver transplantation, LNB liver needle biopsy, SPT steroid pulse therapy, PAH pulmonary arterial hypertension, POD postoperative day

[a]Long–term blood gas analysis of PaO2 levels after LDLT

[b]Histopathological assessment in LNBs after LDLT using the METAVIR score. The worst scores in each case are shown

[c]Follow–up term

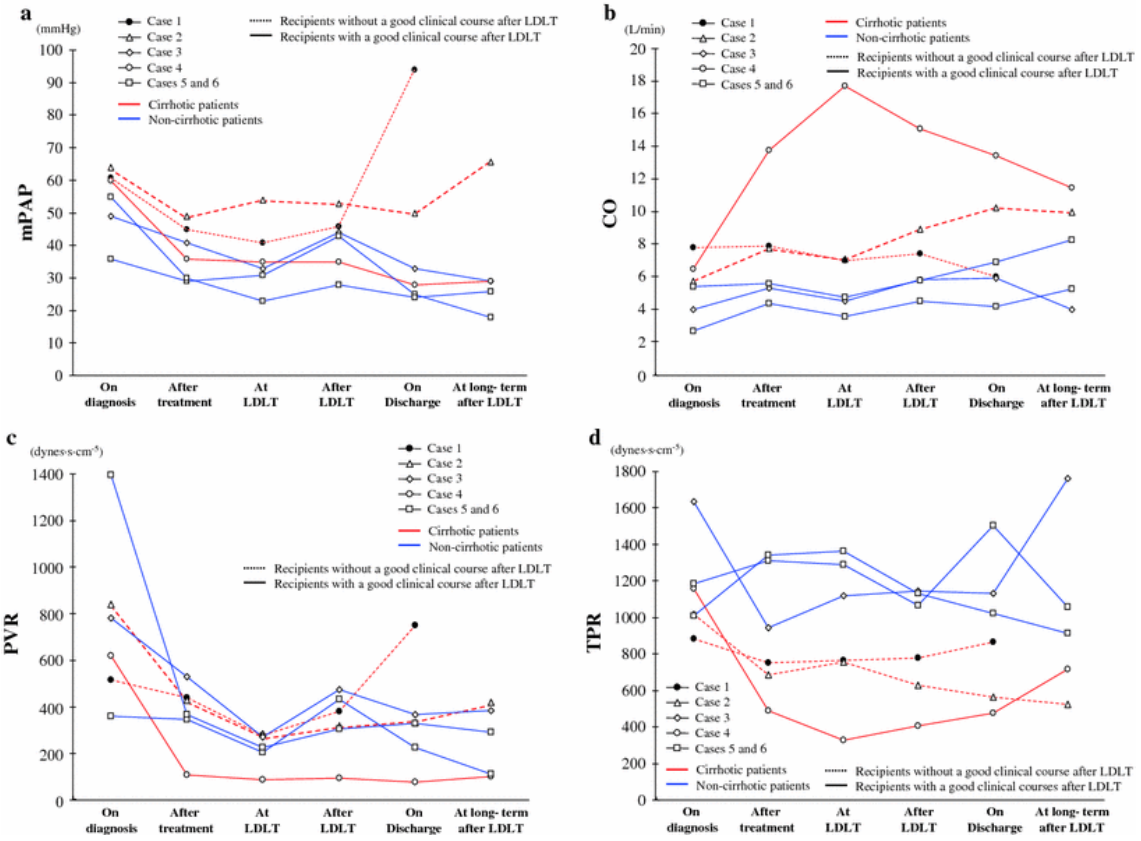


Fig. 1

Changes in mPAP, CO, PVR and TPR before, during and after LDLT. The mPAP, CO, PVR and TPR values are shown at each time point after LDLT. Filled circles, triangles, open circles and diamonds represent cases 1–4. Squares represent cases 5 and 6 combined. Red lines represent cirrhotic recipients (cases 1, 2 and 4) and blue lines represent non-cirrhotic recipients (cases 3, 5 and 6). The changes in CO and TPR between cirrhotic and non-cirrhotic recipients over time were significantly different. Dotted lines represent recipients with a poor clinical course (cases 1 and 2), and solid lines represent recipients with a good clinical course (cases 3–6) after LDLT. The changes in mPAP over time between recipients with poor or good clinical courses after LDLT were significantly different

Table 5

Statistical differences in the changes over time between groups for each variable before, during and after LDLT

	Statistical differences between cirrhotic and non-cirrhotic patients (cases 1, 2 and 4 vs. cases 3, 5 and 6)†	**Statistical differences between recipients with or without good clinical courses after LDLT (cases 1 and 2 vs. cases 3–6)†**
mPAP	0.1478	0.0256††
CO	0.0495††	0.7582
PVR	0.4269	0.3767
TPR	0.0030††	0.3789

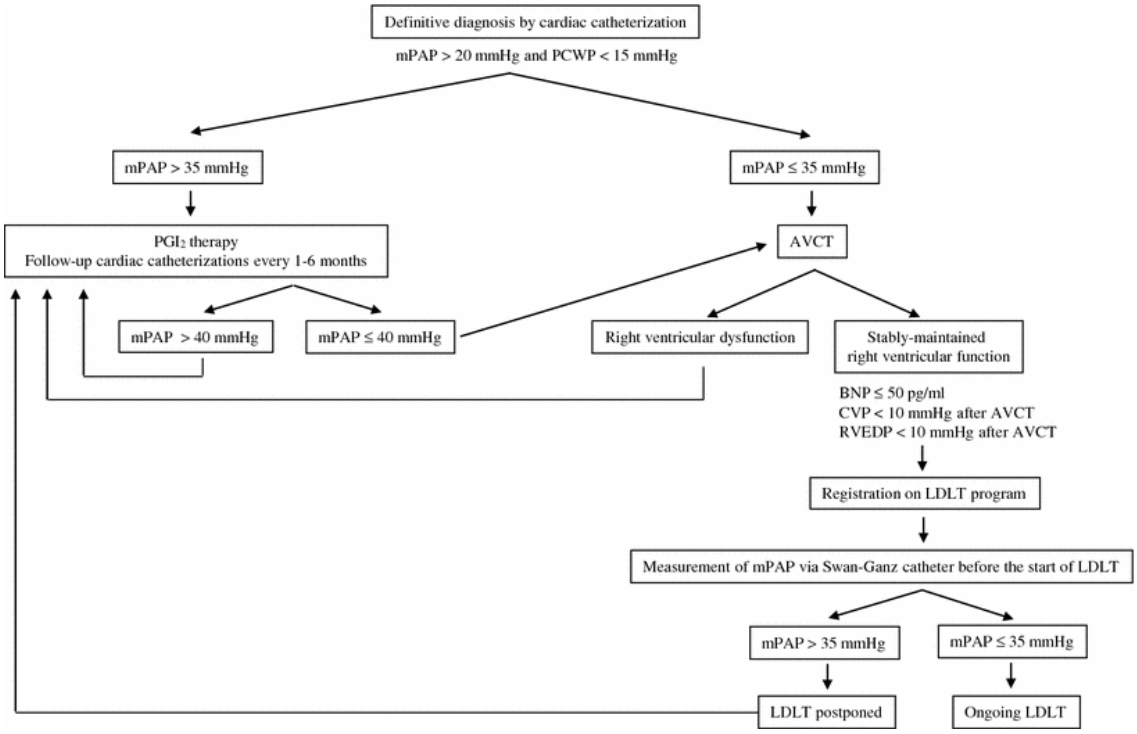
CO cardiac output, LDLT living-donor liver transplantation, mPAP mean pulmonary arterial pressure, PVR pulmonary vascular resistance, TPR total peripheral resistance

†The statistical differences between groups in the changes over time of each variable were analyzed by repeated measures ANOVA

††p value <0.05

Table 6

Flowchart of pre-transplant treatments for PPHTN patients with PAH



AVCT acute volume challenge test, BNP brain natriuretic peptide, CVP central venous pressure, LDLT living-donor liver transplantation, mPAP mean pulmonary arterial pressure, PAH pulmonary arterial hypertension, PCWP pulmonary capillary wedge pressure, PGI_2 prostaglandin I_2, PPHTN porto-pulmonary hypertension, RVEDP right ventricle end diastolic pressures