

Child-to-Adult Liver Transplantation With Donation After Cardiac Death Donors

Three Case Reports

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Abstract: Development of organ transplantation is restricted by the discrepancy between the lack of donors and increasing number of patients. The outcome of pediatric donors transplanted into adult recipients especially with donation after circulatory death (DCD) pattern has not been well studied. The aim of this paper is to describe our experience of 3 successful DCD donor child-to-adult liver transplantations lately.

Three DCD donors were separately 7, 5, and 8 years old. The ratio between donor graft weight and recipient body weight was 1.42%, 1.00%, and 1.33%, respectively. Ratio between the volume of donor liver and the expected liver volume was 0.65, 0.46, and 0.60. Splenectomy was undertaken for the second recipient according to the portal vein pressure (PVP) which was observed during the operation.

Two out of 3 of the recipients suffered with acute kidney injury and got recovered after renal replacement therapy. The first recipient also went through early allograft dysfunction and upper gastrointestinal bleeding. The hospital course of the third recipient was uneventful. After 1 year of follow-up visit, the first and second recipients maintain good quality of life and liver function. The third patient was followed up for 5 months until now and recovered well.

DCD child-to-adult liver transplantation should only be used for comparatively matched donor and recipient. PVP should be monitored during the operation. The short-term efficacy is good, but long-term follow-up and clinical study with large sample evaluation are still needed.

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Abbreviations: AKI = acute kidney injury, BL = body length, BSA = body surface area, BW = body weight, CMV = cytomegalovirus, CRRT = continuous renal replacement therapy, CsA = cyclosporine, DCD = donation after circulatory death, EAD = early allograft dysfunction, ELV = expected liver volume, IVC = inferior vena cava filter, MELD = model for end-stage liver disease, MMF = mycophenolate mofetil, OLT = orthotopic liver transplantation, PVP = portal vein pressure, SFSS = small-for-size syndrome.

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INTRODUCTION

Development of organ transplantation is restricted by the discrepancy between the lack of donors and increasing number of patients. Since 1994, the World Health Organization has encouraged organ donation after circulatory death (DCD) worldwide.¹ DCD donors appropriately mitigate the serious situation of organ shortage, but still could not meet the large demands. The application and efficacy of marginal donor liver as well as reduced-size graft despite significant size mismatch become important topics for liver transplantation.

The outcome of pediatric donors transplanted into adult recipients especially with DCD pattern has not been well studied. Weight of pediatric donor liver is considerably less than the standard liver weight of adult patient, the difference comes with excessive portal venous inflow and portal hypertension which could lead to small-for-size syndrome (SFSS).² And as DCD grafts, ineluctable warm ischemia time could cause more postoperative complications such as acute kidney injury (AKI),³ early allograft dysfunction (EAD),⁴ and more hepatobiliary complications.⁵ It is a big challenge for the surgeons to choose using such graft rather than discarded it. Here we describe the experience of three successful DCD donor child-to-adult liver transplantations in our center lately.

PATIENTS AND METHODS

DCD Donor Information

The DCD donor grafts were from 3 boys (Table 1). They all suffered with irreversible brain injury which was confirmed with the Maastricht categories of DCD type III.⁶ The donor grafts were harvested via double in situ perfusion with combined liver and kidney rapid resection technique.

The first donor is 7 years old. The body length (BL) and body weight (BW) were 140 cm and 30 kg with a 1.14 m² body surface area (BSA), respectively. The weight and volume of the first donor liver were separately 850 g and 800 ml. The warm ischemia time (time from arrest to cold flush or regional perfusion) was 8 minutes and the cold ischemia time of them was 6 hours.

The second donor is 5 years old. His BL and BW were 123 cm and 30 kg (BSA 1.03 m²). The donor liver weight 600 g and its volume was 560 ml. The warm and cold ischemia time were 10 minutes and 5 hours, respectively.

The third donor is 8 years old. He was 135 cm tall and weighed 27.5 kg (BSA 1.08 m²). The weight and volume of liver were separately 800 g and 730 ml, respectively. The warm ischemia time was 11 minutes and the cold ischemia time of them was 4 hours.

TABLE 1. Donor Information

DCD Donors	First Donor	Second Donor	Third Donor
Age	7	5	8
Cause of death	Brain trauma	Brain trauma	Brain trauma
Body length, cm	140	123	135
Body weight, kg	30	30	27.5
Body surface area, m ²	1.14	1.03	1.08
Weight of liver, g	850	600	800
Volume of liver, ml	800	560	730
Cold ischemia time, h	6	5	4
Warm ischemia time, min	8	10	11

DCD = donation after circulatory death.

Recipient Information

Three adult recipients were well explained with all the details of the potential risks and surgical complications (Table 2). Operations were performed with the informed decision of the patients and their family and the approval of the hospital ethics committee.

All the patients accepted the orthotopic liver transplantation (OLT) and the second recipient received splenectomy at the same time. Hepatic artery anastomosis was performed between the common hepatic artery of donor and the bifurcation of gastroduodenal-proper hepatic artery with 7-0 Prolene suture. Duct-to-duct anastomosis was used to reconstruct the bile duct with a T-tube indwelled for biliary drainage. Portal pressure (PVP) was monitored as reported before.⁷ The first and second recipient received an immunosuppressive treatment with tacrolimus + mycophenolate mofetil (MMF) after surgical intervention and the third patient took cyclosporine (CsA) + MMF. ALL

TABLE 2. Recipient Information

Recipients	First Recipient	Second Recipient	Third Recipient
Age	41	41	64
Primary disease	Hepatitis B	Hepatitis B	Autoimmune hepatitis
Meld score	8	19	16
Child-Pugh score	7	12	11
Body length, cm	173	174	169
BW, kg	60	57	52
Body surface area, m ²	1.74	1.70	1.61
ELV, ml	1229.4	1204.9	1149.7
Donor liver volume/ELV	0.65	0.46	0.63
Donor liver weight/BW	1.42%	1.05%	1.54%
Anhepatic phase, min	49	67	82
Operation duration, h	5.25	8.75	7.0
Intraoperative blood loss, ml	1000	3500	4200

BW = body weight, ELV = expected liver volume.

of them underwent anticoagulation treatment using low-molecular-weight heparins followed by warfarin.

The first recipient is a 41-years-old male. His primary disease was hepatitis B cirrhosis. He once underwent upper gastrointestinal bleeding and splenectomy, and the model for end-stage liver disease (MELD) score and Child-Pugh score were separately 8 and 7. The BL and BW were 173 cm and 60 kg with a 1.74 m² BSA, respectively. The expected liver volume (ELV) which is calculated with the formula (ELV = 613 × BSA + 162.8) was 1229.4 cm³.⁸ The ratio between the volume of donor liver and ELV was 0.65. The ratio between donor graft weight and recipient BW were 1.42%. The anhepatic phase of the first recipient lasted 49 minutes. The PVP before and early after transplantation were separately 32 and 28 cmH₂O. The operation time was 5.25 hours and the amount of intraoperative bleeding was 1000 ml.

The second recipient is also a 41-years-old male and his primary disease was hepatitis B cirrhosis as well. With hepatic encephalopathy (HE, grade II), the MELD score and Child-Pugh score for the second recipient were 19 and 12, respectively. His BL and BW were 174 cm and 57 kg (BSA 1.70 m²). His ELV was 1204.9 cm³. The ratio between the volume of donor liver and ELV was 0.46. And the ratio between donor graft weight and recipient BW was 1.05%. The anhepatic phase of the second recipient was 67 minutes. The PVP before transplantation was 25 cmH₂O (decreased from 35 cmH₂O before splenectomy) and the early postoperative PVP was 20 cmH₂O. The operation time was 8.75 hours and the amount of intraoperative bleeding was 3500 ml.

The third recipient is a 64-years-old female whose primary disease was autoimmune hepatitis-related cirrhosis. The third recipient got the MELD score and Child-Pugh score of 16 and 11, respectively. She was 169 cm tall and weighed 52 kg (BSA 1.61 m²). Her ELV was 1149.7 cm³. The ratio between the volume of donor liver and ELV was 0.63. And the ratio between donor graft weight and recipient BW was 1.54%. The anhepatic phase of the third recipient was 56 minutes. The PVP before transplantation was 20 cmH₂O and the early postoperative PVP was 18 cmH₂O. The operation time was 7 hours and the amount of intraoperative bleeding was 4200 ml.

Outcomes and Follow-Up

The post-OLT course was complicated by EAD after transplantation for the first recipient with no bile drainage through the T-tube, prolonged liver cholestasis, and the peak transaminase was over 2000 U/L for days. The peak blood ammonia was 141 μmol/L. The liver function was recovered after thrice plasma exchange after Day 7 (Figure 1). Resistance index of hepatic artery and portal vein velocity were monitored by abdominal ultrasound examination² (Figure 2). He also suffered AKI and restored after continuous renal replacement therapy (CRRT), without notable water-sodium retention and electrolyte disorders. Pulmonary infection occurred on postoperative Day 7 and was controlled via antibiotic treatment. On Day 9, iliac vein thrombosis of double lower limbs was observed, and venacavography was performed with inferior vena cava filter (IVCF) placement. Twenty days following OLT, the patient unexpectedly returned to the intensive care unit for upper gastrointestinal bleeding and recovered after 2 days of conservative treatment. At 3 months post-OLT, tuberculosis was found and the patient was treated with combined anti-tuberculosis treatment (Rifampin 0.45 QD, Isoniazide 0.3 QN, Ethambutol 0.75 QD).

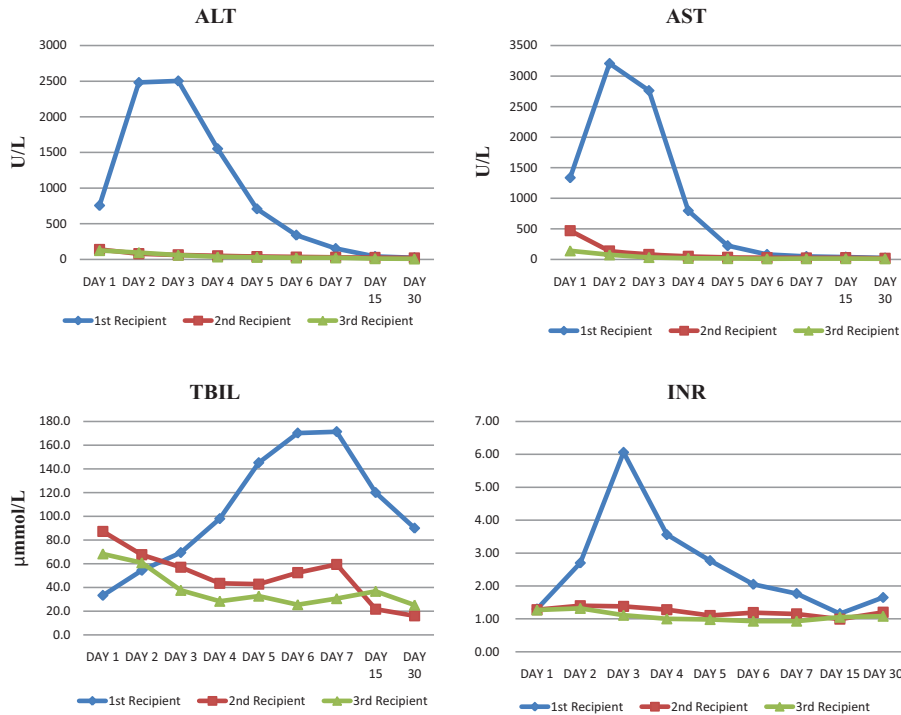


FIGURE 1. Liver function was tested after transplantation. The peak transaminase and total bilirubin (TBIL) for the first patient appeared on Days 2 and 7 post-OLT, respectively. The variation of International Normalized Ratio (INR) has the same trend with transaminase. The liver recovered with the help of plasma exchange therapy after Day 7 post-OLT. The liver function recovered well after transplantation for Patients 2 and 3.

Temporary renal function damage also occurred in the second recipient on Days 1 to 3 and was treated with CRRT. At 1 month following OLT, cytomegalovirus (CMV) DNA test shown positive result and he received Valcyte treatment for a month till the test result turned negative.

The hospital course was uneventful for the third recipient.

After 1 year of follow-up visit, the first and second recipients maintain good quality of life and liver function. T-tube was removed 2 months post-OLT and no vascular or biliary complication was found. The third patient was followed up for 5 months until now and she recovered well. The case report was approved of the Ethical Committee of the First Affiliated

Hospital of Xi'an Jiaotong University and approved of the patients consent.

DISCUSSION

Decades after liver transplantation been widely studied, organ shortage remains the main problem which restricts the qualitative advancement of this treatment. To save more patients on the waiting list, surgeons usually have to take chances to use organs from the expanded donor pool. As the proportion of adult recipients is much larger than that of pediatric recipients, donors from the pediatric age group are

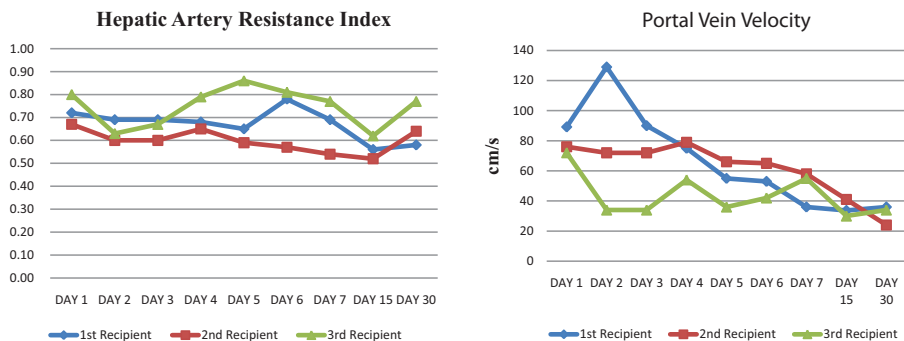


FIGURE 2. Unlike the other 2, the portal vein velocity for the first patient went through a rise and fall change which might lead to portal hyperperfusion and contribute to poor graft function after transplantation. No hepatic arterial vasoconstriction or hepatic artery thrombosis was found.

becoming more likely to be directed to adult recipients. As a small-for-size liver for an adult, the most important potential risk is SFSS. It is reported by previous studies that grafts must be greater than 0.8% of the recipient BW or >40% of ELV to avoid postoperation SFSS.^{9–11} To reach such standard, we carefully choose recipients with low BW when allocated the liver. To our certain knowledge, the second boy in this paper is the youngest DCD donor whose liver is successfully transplanted to an adult. But even the 3 cases in this report are all well match with the standard mentioned above, EAD still occurred in the first recipient. We believe that plasma exchange and molecular adsorbent recirculating system could be useful in such situation and help the grafts to recover.^{12,13}

Another reason which may cause the EAD for the first recipient is relatively high PVP after transplantation. Yagi et al found a poor outcome for the graft early postoperative PVP elevation to 20 mmHg.¹⁴ Zhou et al⁷ found the improvement in esophageal varices could be observed in the whole liver transplantation group 2 weeks post-OLT, whereas no change was observed in the living donor liver transplantation group. This may explain the upper gastrointestinal bleeding for the first recipient. The following report by Feng et al shown the advantage of splenectomy which could prevent the occurrence of SFSS by leading a decrease in the portal flow and PVP and a significant increase in the arterial flow.^{15,16} Nevertheless, there is also considerable increase of surgical risk and infection for splenectomy.^{17,18} On the other hand, recent studies suggest spleen plays an important role in regulating the immune system, metabolism, and endocrine function.¹⁹ But the main reason which increases the morbidity and mortality in asplenia or postsplenectomy states comes from immunological and infectious complications.²⁰ We recommend intraoperative monitoring of PVP and splenectomy which is necessary only if the patient has portal hypertension to protect the donor graft and prevent postoperative gastrointestinal bleeding. Long-term risk of overwhelming post-splenectomy infections should be aware and immediate medical attention is needed in response to every febrile episode.²¹

The outcomes of the Child-to-Adult liver transplantation have not being well studied. But both Ruud and Emre research suggested a greater incidence of vascular complications and worse 1-year graft survival.^{22,23} They both considered the discrepancies in the size of the donor as compared with the recipient might be the main reason caused the bad prognosis. Size mismatch is not only the risk for hyper-perfusion injury but also causes blood stream slow at the first hepatic portal which could induce thrombosis. They suggested using donor-to-recipient BSA ratio to be the evaluation criteria before OLT. Based on above reasons, they both suggested anticoagulation therapy to the recipient to prevent vascular complications, especially hepatic artery thrombosis. We applied an anticoagulation protocol with short-term low molecular weight heparin right after transplantation followed by warfarin for about half a year and no vascular complication has been found yet. However, long-term following-up is still needed.

These 2 papers above found a relationship between ischemia time and vascular complications. Both cold and warm ischemia time have significant impact on the prognosis post-OLT. In this study, we first report DCD Child-to-Adult liver transplantation with a good short-term efficacy. Since March 2010 when the Chinese organ donation system been developed, the ratio of DCD liver transplantation have stepwise become dominate.²⁴ The main challenge of current DCD practice is prolonged warm ischemia time which could lead to a series of

post-OLT disorders, such as AKI and hepatobiliary complications.²⁵ Two out of 3 of our patients suffered with AKI and needed CRRT treatment. Leithead et al³ reported that DCD liver transplantation is associated with an increased frequency of AKI. There is no evidence that AKI is related to pediatric or size mismatched grafts. CRRT could help renal function recovery, maintaining a stable blood volume and removing inflammation factors.²⁶ Although usage of T-tube to prevent biliary complication remains controversial, it is recommended when the bile duct diameter is less than 7 mm.^{27,28} In the size mismatch situation of Child-to-Adult liver transplantation, T-tubes are used in the duct-to-duct anastomosis biliary tract reconstruction in all 3 cases of this study with good outcomes. We also believe that the ischemia time and donor graft injury could be minimized with rational intensive care unit management and lead to a good recovery for the recipient.²⁹

CONCLUSIONS

In conclusion, we suggest DCD pediatric donor liver could only be used for comparatively matched adult recipient. PVP should be monitored during the operation. The short-term efficacy is good, but long-term follow-up and clinical study with large sample evaluation are still needed.

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