LIVER TRANSPLANTATION 19:322–327, 2013

ORIGINAL ARTICLE

Liver Transplantation After Stage II Palliation for Hypoplastic Left Heart Syndrome

Flavia H. Feier,[1] Joao Seda Neto,[1] Gilda Porta,[1] Eduardo A. Fonseca,[1] Rodrigo Vincenzi,[1] Helry L. Cândido,[1] Marcel Benavides,[1] Bernardo Ketzer,[1] Renata Pugliese,[1] Irene K. Miura,[1] Vera Baggio,[1] Teresa Guimarães,[1] Adriana Porta,[1] Gustavo Foronda,[2] Enis Donizete,[3] Jose P. da Silva,[5] Lucilia Faria,[4] Mario Kondo,[1] and Paulo Chapchap[1]

[1]*Hepatology and Liver Transplantation Unit, Sírio-Libanês Hospital, São Paulo, Brazil*
[2]*Pediatric Cardiology, Sírio-Libanês Hospital, São Paulo, Brazil*
[3]*Anesthesia and Critical Care, Sírio-Libanês Hospital, São Paulo, Brazil*
[4]*Pediatric Intensive Care Unit, Sírio-Libanês Hospital, São Paulo, Brazil*
[5]*Cardiac Surgery Unit, Portuguese Charity Hospital of São Paulo, São Paulo, Brazil*

The association of biliary atresia (BA) with congenital heart diseases has been extensively described, and there are a number of reports on the outcomes of patients in this group who undergo liver transplantation (LT). The intraoperative management and the timing of LT for patients with end-stage liver disease are matters of debate, especially when complex heart diseases are involved. This report describes the outcome after LT for a pediatric recipient with BA and hypoplastic left heart syndrome. The patient underwent Norwood-Sano and Glenn procedures for heart palliation before LT. He was cyanotic, was severely malnourished, and had complications secondary to chronic liver failure. At the time of transplantation, the child was 16 months old and weighed 5175 g. Despite the critical clinical scenario and the long hospitalization period, there were no cardiac, vascular, or biliary complications after LT. At the age of 48 months, the patient was awaiting the final cardiac repair. In conclusion, the presence of complex cardiac malformations may not be a contraindication to LT. An experienced surgical team and a multidisciplinary approach are key to a successful outcome. ***Liver Transpl 19:322–327, 2013***. © **2013 AASLD.**

Received August 30, 2012; accepted November 25, 2012.

Biliary atresia (BA) is the main indication for liver transplantation (LT) in children,[1] and it can be associated with other congenital anomalies.[2] Case reports[3,4] and small series[1] have described the association of BA with other congenital heart diseases (CHDs), but to our knowledge, there is no report of the association of hypoplastic left heart syndrome (HLHS) with BA and LT. Patients with HLHS are usually diagnosed in utero. After birth, these patients can undergo a 3-stage surgical palliation treatment.[5] After stages I (the Norwood procedure) and II (bidirectional Glenn palliation), the patients continue to be cyanotic. During stage III (the Fontan operation), when the children are 2 to 3 years old, the final arrangement for the single-ventricle pathway is established.[6] The interstage period is associated with significant mortality.[7,8] These children are challenges for noncardiac surgical procedures because the single-ventricle physiology responds poorly to abrupt hemodynamic changes[6,8] such as those occurring in the setting of LT.[9] This report describes the association of BA and HLHS in an infant undergoing LT after successful stage II palliation for HLHS.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ao, aorta; BA, biliary atresia; CHD, congenital heart disease; FFP, fresh frozen plasma; HCT, hematocrit; HLHS, hypoplastic left heart syndrome; LA, left atrium; LDLT, living donor liver transplantation; LPA, left pulmonary artery; LT, liver transplantation; LV, left ventricle; MAP, mean arterial pressure; OLT, orthotopic liver transplantation; PA, pulmonary artery; PDA, patent ductus arteriosus; pO2, partial pressure of arterial oxygen; PRBC, packed red blood cell; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle; SaO2, arterial oxygen saturation; SVC, superior vena cava; SvO2, venous oxygen saturation. This protocol study has been approved by the institution's review committee.

Address reprint requests to Joao Seda Neto, M.D., Ph.D., Hepatology and Liver Transplantation Unit, Sírio-Libanês Hospital, Rua Barata Ribeiro 414, cj 65, Bela Vista, Sao Paulo, Brazil 01308-000. Telephone: 55-11-32310800; FAX: 55-11-32310900; E-mail: joaoseda@gmail.com

DOI 10.1002/lt.23593
View this article online at wileyonlinelibrary.com.
LIVER TRANSPLANTATION.DOI 10.1002/lt. *Published on behalf of the American Association for the Study of Liver Diseases*

CASE REPORT

The child was born with HLHS (Fig. 1A) and BA. Four days after birth, he underwent the Norwood-Sano procedure (Fig. 1B), which created a systemic-to-pulmonary artery shunt in order to improve the pulmonary blood flow as well as an unobstructed systemic outflow through a neoaorta.[6] Five months later, he underwent the bidirectional Glenn procedure (Fig. 1C), which relieved the overload on the single ventricle with a cavopulmonary anastomosis. After the procedure, the patient remained cyanotic as expected.[6] Between these surgical repairs to his heart, he underwent portoenterostomy at the age of 3 months. The Kasai procedure failed, and the patient evolved with cirrhosis and portal hypertension and presented with recurrent episodes of cholangitis and gastrointestinal bleeding. Additionally, the patient was malnourished (height/age z score<-2.5) with hypoparathyroidism, osteopenia, and multiple pathological bone fractures.

Because of refractory gastrointestinal bleeding and sepsis, he was referred to our hospital at the age of 11 months to be evaluated for LT. His blood test results on admission were as follows: total bilirubin, 21.8 mg/dL; aspartate aminotransferase (AST), 430 IU/L; alanine aminotransferase (ALT), 819 IU/L; gamma-glutamyltransferase, 3106 IU/L; hematocrit, 47%; prothrombin time, 21.1 seconds; international normalized ratio, 1.7; and albumin, 2.5 g/dL. He was on mechanical ventilation with a fraction of inspired oxygen of 100% and a pulse oximetry of 92%. Echocardiography revealed a hypoplastic mitral valve and left ventricle (LV), a systemic ventricle with preserved contractile function, a patent neoaorta, and a patent cavopulmonary anastomosis. At a multidisciplinary meeting, LT surgeons, hepatologists, cardiologists, critical care specialists, and anesthesiologists discussed the feasibility of performing orthotopic liver transplantation (OLT) and decided to include the patient on the liver waiting list. A living donor was not available. After 5 months of hospitalization, he underwent OLT with a reduced size graft from a pediatric deceased donor.

The liver allograft was preserved with histidine tryptophan ketoglutarate solution at 4°C. The liver was reduced on the back table to a final weight of 280 g. The graft-to-recipient weight ratio was 5.4%, and the implanted graft included segments II, III, and IV and the caudate lobe.

At the time of transplantation, the patient was 16 months old and weighed 5175 g. His weight/age and height/age z scores were both equal to −3. The operative findings included extensive adhesions from the previous surgery, a moderate amount of ascites, and cirrhosis. The liver was removed without preservation of the retrohepatic vena cava (the standard technique). The decision to not use the piggyback technique was made intraoperatively because of technical difficulties, and the consequences of cross-clamping were weighed against the risk of additional bleeding. However, the patient tolerated the clamping period well. Graft implantation was accomplished in a standard fashion. After reperfusion and until the end of the surgery, even though the hepatic vein hemodynamics were not assessed, there were no concerns about liver congestion/perfusion beyond what occurs in other pediatric LT patients.

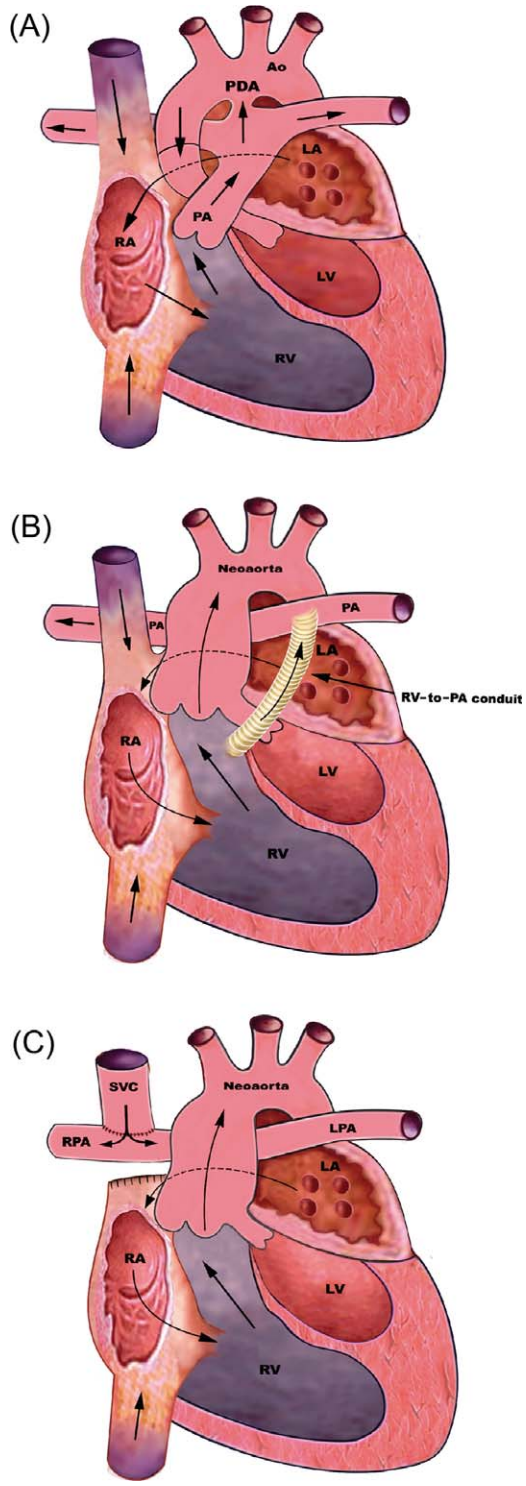
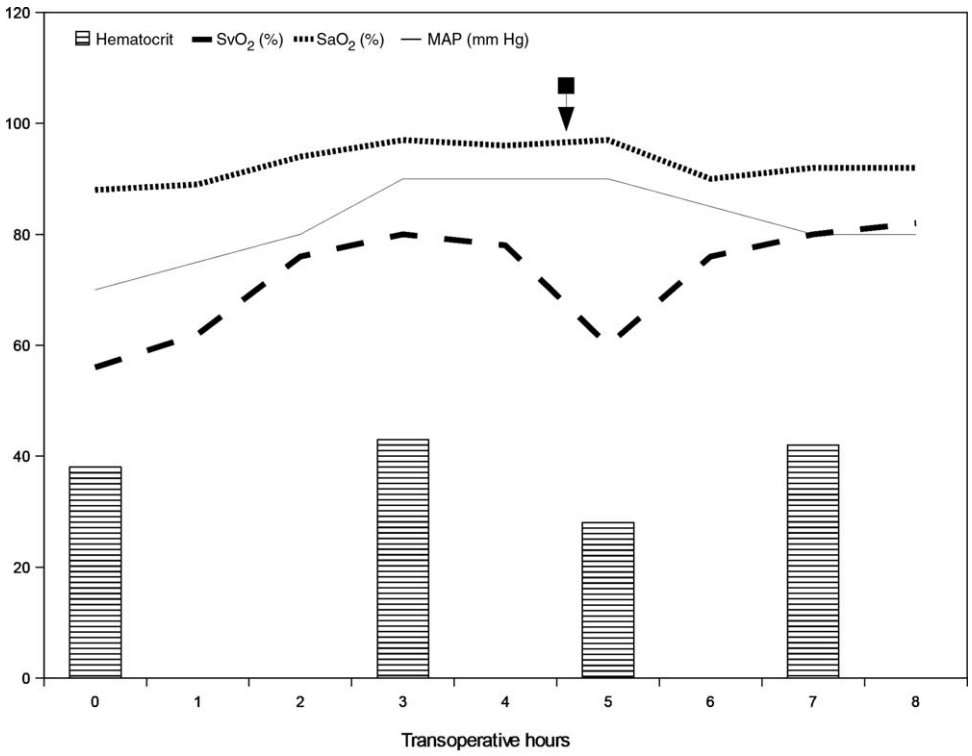


Figure 1. From inborn disease to the heart anatomy after stage II palliation: (A) HLHS, (B) Norwood-Sano procedure, and (C) bidirectional Glenn procedure. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



Input	Crystalloid	PRBC	FFP	Platelets	Albumin
	950 mL (190 mL/kg)	520 mL (104 mL/kg)	120 mL	0.5 IU	180 mL (7.2 g/kg)
Output	Urine				
	230 mL (3.2 mL/kg/hour)				

Figure 2. Intraoperative management. The arrow indicates reperfusion.

The cold and warm ischemia times were 465 and 37 minutes, respectively. The patient remained stable during the transplant and required the use of a single inotrope during the procedure (dopamine at a starting dose of 5 μg/kg/minute). The intraoperative management was based on venous oxygen saturation (SvO_2) and arterial oxygen saturation (SaO_2) monitoring, which was used to estimate systemic oxygenation and perfusion.[9,10] Figure 2 illustrates the intraoperative monitoring of the target parameters during the operation. The target hematocrit was 40%. The mean arterial pressure (MAP) was kept greater than 65 mm Hg. After reperfusion, there was a drop in the SvO_2 and hematocrit values because of bleeding from the graft's cut surface and blood redistribution. After the elevation of the hematocrit to the target level, there was an improvement in the SvO_2 value until the end of the procedure.

The patient remained stable in the immediate postoperative period and was maintained with a high hematocrit and a low positive end-expiratory pressure (<8 mm Hg) because of his single-ventricle physiology in order to ensure adequate tissue oxygenation and low pulmonary vascular resistance. The fraction of inspired oxygen was maintained at approximately 40% to 50%, SaO_2 was kept at 85% to 90%, and the hematocrit was 40%, as mentioned previously. The use of inotropic drugs was discontinued on postoperative day 5.

On postoperative day 10, the patient began to undergo a series of exploratory laparotomy procedures because of intra-abdominal bleeding and bowel perforations; there were 5 surgical interventions in all (Fig. 3). During the course of his hospitalization, he experienced 3 episodes of biopsy-proven mild acute cellular rejection, which were resolved with bolus steroid therapy. The rise in liver enzymes was correlated with these rejection episodes. Their levels had returned to normal ranges at the scheduled follow-up ambulatory visits. On the first biopsy sample (which was taken on postoperative day 11), there were signs of sinusoidal congestion. These signs were not found on liver biopsy samples taken later. Because of prolonged intubation and the presence of a tracheal granuloma, tracheostomy was performed on postoperative day 40. Postoperative echocardiographic examinations revealed a patent neoaorta and cavopulmonary shunt with preserved contractile function (ejection

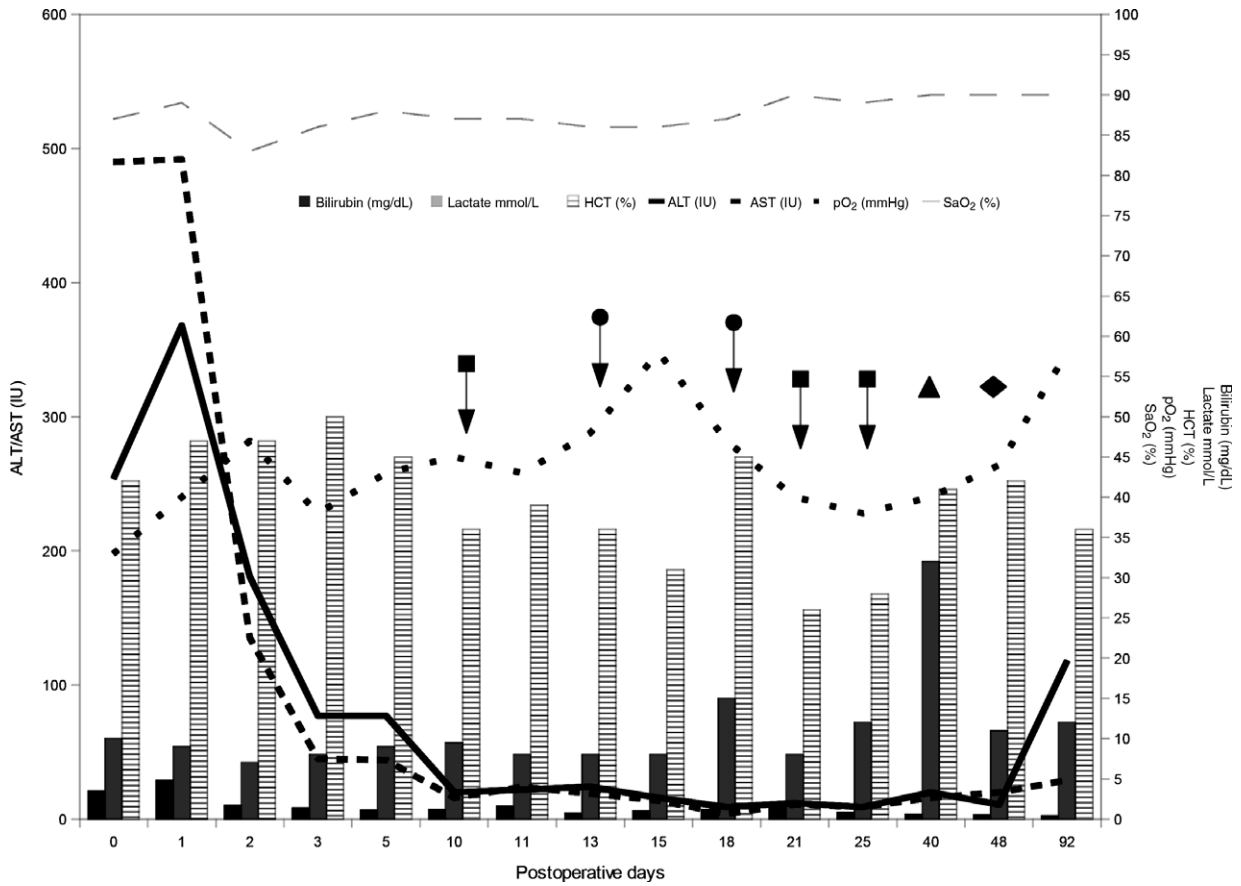


Figure 3. Postoperative events. The arrows with squares indicate laparotomy for abdominal bleeding, the arrows with circles indicate laparotomy for bowel perforation, the triangle indicates tracheostomy, and the diamond indicates gastrointestinal bleeding.

fraction=70%). There were no vascular or biliary complications. He was discharged home 4 months after LT with triple-therapy immunosuppression (tacrolimus, prednisolone, and mycophenolate sodium). At the age of 48 months, the patient's height/age and weight/age *z* scores were −2.5 and 0, respectively. He persisted with a tracheostomy and had moderate neuropsychomotor impairment. The patient's liver function tests were normal at the time of this writing, and he was awaiting the completion of the heart repair (the Fontan operation).

DISCUSSION

In 20% of BA cases, there is an associated anomaly (also called polysplenia syndrome),[2] and the results of the Kasai procedure in this subset of patients have been proven to be poorer.[2] A number of cardiovascular anomalies have already been described in association with BA,[2-4,11] and LT has already been performed in these patients.[1,3,4,11] An increased incidence of complications with greater morbidity and mortality is expected in such cases. This is the first report describing the association of BA with HLHS and LT.

The unique physiology of this syndrome, in which pulmonary and systemic circulations run in parallel and result in cyanosis and ventricular volume overload,[6] puts newborns and infants at a high risk of death. Thirty years ago, comfort care was the only option, but because of the development of 3-stage palliation, the rate of survival to the age of 5 years currently approaches 70%.[12] After stage I (the Norwood procedure), children still have a considerable risk of death with an interstage mortality incidence of 9% to 16%.[7] Noncardiac surgery during this period should be avoided and restricted to emergent procedures.[6] Gastrostomy with fundoplication is one of the frequently performed procedures after stage I palliation, and the reported mortality rate is 0% to 19%.[8,13] In this case, the decision to perform the Kasai procedure was made before the patient was transferred to our center. Even though the mortality rate is greater with noncardiac surgeries between stages I and II of palliation and the results of the Kasai procedure are worse when there are associated malformations,[2] we believe that it is the only chance for avoiding LT, as illustrated in previous publications.[14,15] In these reports, however, the Kasai procedure was performed before 60 days of age when there was a greater chance of success.

After stage II, the patient is expected to remain cyanotic, but the partial cavopulmonary anastomosis relieves the parallel circulation and volume overload and creates a favorable condition for elective

TABLE 1. Case Reports and Small Series of LT Patients With Complex CHD

Study	CHD	Age	Indication	OLT/LDLT	Cardiac Repair
Feierman et al.[3] (2006)	Single atrium, single atrioventricular valve, incomplete interventricular septum	13 months	BA	OLT	Before LT
Garbanzo et al.[1] (2006)	Aortic stenosis	9 years	Alagille syndrome	LDLT	After LT
	Double-outlet RV, pulmonary stenosis	7 months	BA/polysplenia	LDLT	Before LT
	PDA	2 years	BA	LDLT	During LT
	Ventricular septal defect, pulmonary stenosis	9 months	BA	LDLT	After LT
	Tetralogy of Fallot	9 months	BA	LDLT	Before LT
Kimura et al.[11] (2007)	Corrected transposition of great arteries, ventricular septal defect, ostium secundum	2 years	BA	LDLT	After LT
Singhal et al.[4] (2009)	Ventricular septal defect	4 years	BA	LDLT	None

noncardiac surgeries. The incidence of complications in this phase drops to 6%.[7] At this point, the patient is hyperdynamic and well perfused with a systemic saturation in room air of 80% to 85%.[6] Increases in pulmonary vascular resistance do not affect systemic perfusion, but an adequate preload must be ensured. This type of patient has a poor response to hypovolemia and impaired venous return.[6] During noncardiac surgery, great care should be taken intraoperatively[16] to maintain a low pulmonary vascular resistance and avoid excessive positive end-expiratory pressure and prolonged inspiratory times. Inotropes should also be avoided. It is advisable to choose small doses of dopamine if it is needed.[6] For intraoperative management, we used SaO_2 and SvO_2 monitoring, which can allow the early identification of decreased cardiac output and poor oxygen delivery. The high hematocrit level was paramount in order to accomplish the anesthetic plan. Indeed, this is the strategy commonly used during surgery in patients with a single-ventricle physiology.[9,10] It was used during the transplant and during the series of exploratory laparotomy procedures performed in this child.

Torres et al.[13] reported the prevalence of noncardiac surgeries performed in patients with HLHS, but there is no report of a procedure such as LT that challenges the volume status. There are continuous changes in the preload and vascular resistance during the several phases of LT, which starts with the clamping of the vena cava, when an adequate preload should be ensured, and during reperfusion, when there is usually ventricular volume overload as well as a drop in the systemic vascular resistance.[3] The piggyback technique should be preferred, although in this case, because of technical difficulties, we chose the standard technique to avoid additional bleeding. A prepared and experienced anesthesiologist and a cardiologist are warranted because volume status changes are the rule in the setting of LT.

Other risks that should be kept in mind are hepatic artery thrombosis, emboli, and infectious endocarditis. Because of hypoxemia, these patients develop very high hematocrits,[6] and after stage II, there is a well-described prothrombotic state.[5] Because pediatric transplant patients have a higher risk of hepatic artery thrombosis than their adult counterparts,[17] the hematocrit is usually kept at or lower than 30%.[3] However, in the cyanotic patient, there is a need to keep the hematocrit greater than 45%. High hematocrits have already been proven to be a risk factor for hepatic artery thrombosis.[13] Hypoxemic patients also are at risk of developing biliary complications.[18] The reported rates of posttransplant bile leaks are up to 26% in patients with hepatopulmonary syndrome.[19] Our patient, despite hypoxemia (Fig. 2), had no biliary or vascular complications following the transplant.

Another concern with intracardiac shunts is the risk of paradoxical emboli, which is increased during reperfusion.[3,20] Postoperatively, because of immunosuppression and a lower threshold for infection, patients with intraventricular shunts are at greater risk for infective endocarditis.[6] Sequential echocardiography after the transplant did not show vegetations on the heart valves.

The majority of reports on LT and CHD involve patients with Alagille syndrome, and the usual CHDs are pulmonary stenosis and aortic stenosis.[21] Other centers have performed deceased donor LT and living donor liver transplantation (LDLT) for patients with CHD (Table 1), and some have not found an increase in morbidity or mortality.[20,22] In a case-control study,[20] however, no correction of the heart condition was attempted before LT, and there were no intraoperative cardiac complications; this suggested that every patient had compensated heart disease at the time of LT.

When CHD and end-stage liver disease are combined, it is a matter of debate whether LT should come first, cardiac repair should come first, or the 2 procedures should be performed at the same time.[3,20] Raichlin et al.[23] reported the results of combined heart and liver transplantation and found no

difference in survival in comparison with heart transplantation alone. However, when combined heart and liver transplantation is not an option or an indication, deciding what comes first should take into consideration the risks of worsening liver function after a cardiac repair versus the development of the aforementioned complications in a patient with heart disease.[3,20] In our case, the cardiac malformation demanded early intervention.

In conclusion, patients with complex CHD are at greater risk of developing postoperative complications related to LT and to the heart condition itself. However, LT can be safely performed in such patients as long as the physiology of the specific CHD is studied and the therapeutic plan is established. A multidisciplinary and experienced team is paramount for the success of the procedure.

REFERENCES

1. Garbanzo JP, Kasahara M, Egawa H, Ikeda T, Doi H, Sakamoto S, et al. Results of living donor liver transplantation in five children with congenital cardiac malformations requiring cardiac surgery. Pediatr Transplant 2006;10:923-927.
2. Tanano H, Hasegawa T, Kawahara H, Sasaki T, Okada A. Biliary atresia associated with congenital structural anomalies. J Pediatr Surg 1999;34:1687-1690.
3. Feierman DE, Yudkowitz FS, Hojsak J, Emre S. Management of a cadaveric orthotopic liver transplantation in a pediatric patient with complex congenital heart disease. Paediatr Anaesth 2006;16:669-675.
4. Singhal A, Srivastava A, Goyal N, Vij V, Wadhawan M, Bera M, Gupta S. Successful living donor liver transplant in a child with Abernethy malformation with biliary atresia, ventricular septal defect and intrapulmonary shunting. Pediatr Transplant 2009;13:1041-1047.
5. Bailey PD Jr, Jobes DR. The Fontan patient. Anesthesiol Clin 2009;27:285-300.
6. Walker SG, Stuth EA. Single-ventricle physiology: perioperative implications. Semin Pediatr Surg 2004;13:188-202.
7. Carlo WF, Carberry KE, Heinle JS, Morales DL, McKenzie ED, Fraser CD Jr, Nelson DP. Interstage attrition between bidirectional Glenn and Fontan palliation in children with hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 2011;142:511-516.
8. Watkins S, Morrow SE, McNew BS, Donahue BS. Perioperative management of infants undergoing fundoplication and gastrostomy after stage I palliation of hypoplastic left heart syndrome. Pediatr Cardiol 2012;33:697-704.
9. Barnea O, Santamore WP, Rossi A, Salloum E, Chien S, Austin EH. Estimation of oxygen delivery in newborns with a univentricular circulation. Circulation 1998;98: 1407-1413.
10. Tweddell JS, Hoffman GM, Mussatto KA, Fedderly RT, Berger S, Jaquiss RD, et al. Improved survival of patients undergoing palliation of hypoplastic left heart syndrome: lessons learned from 115 consecutive patients. Circulation 2002;106(suppl 1):I82-I89.
11. Kimura T, Hasegawa T, Ihara Y, Mushiake S, Kogaki S, Dono K, Fukuzawa M. Successful living related liver transplantation in a case with biliary atresia associated with corrected transposition of the great arteries. Pediatr Transplant 2007;11:540-542.
12. Feinstein JA, Benson DW, Dubin AM, Cohen MS, Maxey DM, Mahle WT, et al. Hypoplastic left heart syndrome: current considerations and expectations. J Am Coll Cardiol 2012;59(suppl):S1-S42.
13. Torres A Jr, DiLiberti J, Pearl RH, Wohrley J, Raff GW, Bysani GK, et al. Noncardiac surgery in children with hypoplastic left heart syndrome. J Pediatr Surg 2002;37:1399-1403.
14. Imamura M, Dyamenahalli U, Sachdeva R, Kokoska ER, Jaquiss RD. Hypoplastic left heart syndrome, interrupted inferior vena cava, biliary atresia. Ann Thorac Surg 2007;84:1746-1748.
15. Becker DJ, Islam S, Geiger JD. Biliary atresia associated with hypoplastic left heart syndrome: a case report and review of the literature. J Pediatr Surg 2004;39:1411-1413.
16. Sümpelmann R, Osthaus WA. The pediatric cardiac patient presenting for noncardiac surgery. Curr Opin Anaesthesiol 2007;20:216-220.
17. Tisone G, Gunson BK, Buckels JA, McMaster P. Raised hematocrit—a contributing factor to hepatic artery thrombosis following liver transplantation. Transplantation 1988;46:162-163.
18. Urahashi T, Mizuta K, Sanada Y, Umehara M, Wakiya T, Hishikawa S, et al. Pediatric living donor liver transplantation for biliary atresia with hepatopulmonary syndrome: the gift of a second wind. Pediatr Surg Int 2011;27:817-821.
19. Taillé C, Cadranel J, Bellocq A, Thabut G, Soubrane O, Durand F, et al. Liver transplantation for hepatopulmonary syndrome: a ten-year experience in Paris, France. Transplantation 2003;75:1482-1489.
20. Concejero A, Chen CL, Liang CD, Wang CC, Wang SH, Lin CC, et al. Living donor liver transplantation in children with congenital heart disease. Transplantation 2007;84:484-489.
21. Kasahara M, Kiuchi T, Inomata Y, Uryuhara K, Sakamoto S, Ito T, et al. Living-related liver transplantation for Alagille syndrome. Transplantation 2003;75:2147-2150.
22. Manzoni D, D'Ercole C, Spotti A, Carrara B, Sonzogni V. Congenital heart disease and pediatric liver transplantation: complications and outcome. Pediatr Transplant 2007;11:876-881.
23. Raichlin E, Daly RC, Rosen CB, McGregor CG, Charlton MR, Frantz RP, et al. Combined heart and liver transplantation: a single-center experience. Transplantation 2009;88:219-225.