CASE REPORTS/CASE SERIES

Combined heart and liver transplantation on cardiopulmonary bypass: report of four cases

Transplantation combinée du cœur et du foie sous circulation extracorporelle: compte-rendu de quatre cas

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Abstract

Purpose *Combined heart and liver transplant is a rare procedure to treat end-stage cardiac and liver disease. First performed during cardiopulmonary bypass and anticoagulation, subsequent concerns about increased bleeding changed the strategy to performing liver implantation following separation from cardiopulmonary bypass. Considering the overall decrease in transfusion requirements during liver transplant and the potential benefits to the transplanted heart to remain on cardiopulmonary bypass during liver implantation, we revised the strategy for combined heart and liver transplant. We report the clinical course of four consecutive patients who underwent this procedure in our institution.*

Clinical features *Patient 1 was a 53-yr-old male with familial hypertrophic cardiomyopathy and congestive cirrhosis. Patient 2 was a 57-yr-old male with hypertrophic restrictive cardiomyopathy and congestive cirrhosis. Patient 3 was a 48-yr-old male with dilated cadiomyopathy and hepatitis B cirrhosis. Patient 4 was a 57-yr-old male*
with ischemic cardiomyopathy and congestive cirrhosis. Each patient underwent combined heart and liver transplant, with liver implantation performed during cardiopulmonary bypass and anticoagulation. Estimated blood loss ranged from 1,000 to 3,000 mL. Intraoperative transfusion included 2-5 U of packed red blood cells, 4-12 U of fresh frozen plasma, 0-20 U of cryoprecipitate, and 5-23 U of platelets. All patients remain well 25-38 months after surgery.

Conclusion *Combined heart and liver transplant during cardiopulmonary bypass is a viable strategy that may confer benefit to this unique type of patient.*

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Résumé

Objectif *La greffe combinée du cœur et du foie est une intervention rare dont l'objectif est de traiter des maladies cardiaque et hépatique en phase terminale. Tout d'abord réalisée pendant la circulation extracorporelle et l'anticoagulation, des inquiétudes concernant l'augmentation du saignement ont plus tard poussé à une modification stratégique. Désormais, les greffes hépatiques sont réalisées après le sevrage de la circulation extracorporelle. En tenant compte de la réduction globale des besoins transfusionnels pendant la greffe hépatique et des bienfaits potentiels pour le cœur transplanté si l'on reste sous circulation extracorporelle pendant la greffe du foie, nous avons revu notre stratégie en matière de greffe combinée du cœur et du foie. Nous rapportons l'évolution clinique de quatre patients consécutifs ayant subi cette intervention dans notre centre.*

Éléments cliniques *Le patient no. 1 était un homme de 53 ans souffrant d'une cardiomyopathie hypertrophique héréditaire et d'une cirrhose congestive. Le patient no. 2 était un homme de 57 ans souffrant d'une cardiomyopathie hypertrophique restrictive et d'une cirrhose congestive. Le*

patient no. 3 était un homme de 48 ans souffrant d'une cardiomyopathie et d'une cirrhose due à l'hépatite B. Le patient no. 4 était un homme de 57 ans souffrant d'une cardiomyopathie ischémique et d'une cirrhose congestive. Chaque patient a subi une greffe combinée du cœur et du foie, la greffe hépatique étant réalisée pendant la circulation extracorporelle et l'anticoagulation. Les pertes sanguines estimées allaient de 1000 à 3000 mL. La transfusion peropératoire a consisté en 2-5 U de culot globulaire, 4-12 U de plasma frais congelé, 0-20 U de cryoprécipité et 5-23 U de plaquettes. Tous les patients sont encore en santé 25-38 mois après la chirurgie.

Conclusion *La greffe combinée du cœur et du foie sous circulation extracorporelle est une stratégie viable qui pourrait conférer des bienfaits à ces patients rares.*

The first combined heart and liver transplant (CHLT) was performed in a pediatric patient to treat end-stage heart disease secondary to homozygous familial hypercholesterolemia.[1] Although indications for this procedure have increased,[2] CLHT remains rare with fewer than 72 cases reported in the USA since 1998.[3] According to the few published reports, the preferred technique is transplantation of the liver, with or without veno-venous bypass, once the heart transplantation has been completed and the patient has been separated from cardiopulmonary bypass (CPB).[4-11] The purported advantages of this strategy include a shorter period of myocardial ischemia and a reduced length of CPB with its attendant problems of hemodilution, platelet dysfunction, and inflammation. Ostensibly, there is the benefit of improved cardiac function of the transplanted heart to support the considerable hemodynamic alterations associated with liver transplantation. In addition, after reversal of the heparin-induced anticoagulation, one may expect reduced blood loss and transfusion requirement during the implantation of the liver.

Recent advances in the perioperative management of patients undergoing liver transplantation led to a decrease in blood product transfusion, even in patients with uncorrected coagulopathy,[12,13] raising the possibility that liver transplantation during CPB is viable. The theoretical advantage of this approach is that hepatic ischemia time is minimized, and hemodynamic effects of liver transplantation on the newly transplanted heart are mitigated, particularly during hepatic reperfusion. Interestingly, this very strategy was adopted for the first CHLT[14] and has been used in only one other case.[15]

The purpose of this report is to describe four patients who underwent CHLT with liver transplantation performed during CPB. Written consent for publication was obtained from all patients.

Case descriptions

Patient characteristics

This analysis includes all four patients who underwent CHLT in our institution. The procedures were performed within the period April 2006 to June 2007.

Patient 1 was a 53-yr-old male with familial hypertrophic cardiomyopathy. His medical history included sino-atrial ablation and pacemaker placement for atrial fibrillation. He had severe right ventricular (RV) diastolic dysfunction and left ventricular ejection fraction of 65% with New York Heart Association (NYHA) class IV congestive heart failure. Child-Pugh grade C liver failure was determined to be secondary to chronic congestive hepatitis from RV failure. The electrocardiogram (ECG) showed a paced rhythm. Medications included furosemide 40 mg qd, spironolactone 25 mg qd, pantoprazole 40 mg qd, warfarin 2 mg qd, and alendronate 70 mg qwk. Indication for CHLT was progressive congestive hepatic dysfunction secondary to RV failure.

Patient 2 was a 57-yr-old male with hypertrophic restrictive cardiomyopathy and a left ventricular ejection fraction of 35% with NYHA class III heart failure, moderate mitral regurgitation, and severe tricuspid regurgitation. He also had atrial fibrillation, chronic renal failure, mild chronic obstructive pulmonary disease, and an implanted cardiac defibrillator. Child-Pugh grade C liver failure was determined to be secondary to chronic congestive hepatitis. The ECG demonstrated a paced rhythm. Medications included furosemide 160 mg bid, spironolactone 12.5 mg qd, warfarin 5 mg qd, docusate 100 mg bid, and allopurinol 200 mg qd. Indication for CHLT was progressive congestive hepatic dysfunction secondary to severe tricuspid regurgitation not amenable to surgical repair due to his hypertrophic restrictive cardiomyopathy.

Patient 3 was a 48-yr-old male with dilated cardiomyopathy. He had a left ventricular function of 10%, moderate mitral regurgitation, an implanted cardiac defibrillator, NYHA class IV congestive heart failure, and hepatitis B cirrhosis with Child-Pugh grade C liver failure. The ECG showed a paced rhythm. Medications included amiodarone 200 mg qd, pantoprazole 40 mg qd, ramipril 2.5 mg qd, spironolactone 25 mg qd, aspirin 81 mg qd, nitroglycerine patch 0.4 mg 12 hr qd, and carvedilol 6.25 mg qd. Indication for CHLT was severe hepatitis B cirrhosis in the setting of end-stage heart failure.

Patient 4 was a 57-yr-old male with ischemic cardiomyopathy. He had a left ventricular function of 20% with NYHA class IV congestive heart failure, severe mitral and tricuspid regurgitation, atrial fibrillation, an implanted cardiac defibrillator, and chronic renal failure. Child-Pugh grade C liver failure was determined to be secondary to

Table 1 Preoperative admission laboratory data

	Normal range or previous reports	Patient 1	Patient 2	Patient 3	Patient 4
Hemoglobin (g·L^{-1})	140-175	138*	131*	132*	107*
Platelets (109·L^{-1})	150-350	188	113*	174	143*
Urea (mmol·L^{-1})	2.9-8.2	8	23.7*	8.8*	17.9*
Creatinine (μmol·L^{-1})	53-106	95	216*	89	176*
INR	0.9-1.1	2.3*	3.21*	2.01*	3.54*
aPTT (sec)	25-40	39.6	53.9*	41.6*	55.3*
Albumin (g·L^{-1})	35-50	43	33*	31*	41
Total bilirubin (μmol·L^{-1})	5.0-21.0	39.4*	45.5*	62.4*	15.6
AP (U·L^{-1})	30-120	154*	175*	54	82
ALT (U·L^{-1})	10-40	22	24	20	22

* Abnormal values; INR = international normalized ratio; aPTT = activated partial thromboplastin time; AP = alkaline phosphatase; ALT = alanine aminotransferase

chronic congestive hepatitis. Medications included furosemide 160 mg bid, metolazone 2.5 mg qd, spironolactone 12.5 mg qd, warfarin 7.5 mg qd, allopurinol 200 mg qd, hydralazine 5 mg tid, ferrous sulphate 300 mg qd, darbepoetin alfa 30 μg qwk, carvedilol 3.125 mg bid, atorvastatin 20 mg qd, amiodarone 200 mg qd, and aspirin 81 mg qd. Indication for CHLT was progressive congestive hepatic dysfunction secondary to RV failure.

Baseline laboratory values are summarized in Table 1.

Anesthetic care

Intravenous access was achieved *via* catheters inserted into each upper extremity and the internal jugular vein. In addition to standard monitors (5-lead ECG, pulse oximetry, capnography, and nasopharyngeal and bladder temperature probes), invasive systemic arterial, central venous, and pulmonary arterial pressures were measured *via* catheters inserted into the radial artery and internal jugular vein, respectively. In addition to the standard 8.5 French central venous catheter in the right internal jugular (RIJ) vein, Patients 1 and 3 had three lumen central lines placed in the RIJ vein, and Patient 1 had a second 8.5 French central venous catheter placed in the left internal jugular vein. Cardiac function was further assessed by transesophageal echocardiography. The patients' temperatures were maintained using a water-heated mattress, the CPB heat exchange device, and warmed intravenous fluids. General anesthesia was induced with titrations of intravenous midazolam, sufentanil, and either pancuronium or rocuronium. Anesthesia was maintained with an infusion of midazolam 1.2 mg·hr^{-1} and sufentanil 30 μg.hr^{-1}, with additional boluses of sufentanil as indicated. Patient 4 also received 1% sevoflurane. The patients' lungs were ventilated with 50% air/O$_2$. Every patient received a bolus of 10^6 U aprotinin followed by an infusion of aprotinin 500,000 U·hr^{-1}. Immunosuppression was provided by methylprednisolone 500 mg. All patients were given heparin 400 U·kg^{-1} prior to introduction of CPB, and activated clotting time was maintained >500 sec with additional heparin as required. Anticoagulation was reversed with protamine 1 mg·100 U heparin^{-1} following completion of CPB. Vasoactive and inotropic drugs were utilized at the discretion of the anesthesiologist.

Surgical procedure

Sternotomy was performed, and the incision was extended to the upper abdomen using a bilateral subcostal approach. The liver was isolated, with exposure of the appropriate vasculature without completing the hepatectomy. Subsequently, CPB was initiated using bicaval cannulation *via* the superior vena cava and femoral vein followed by aortic cannulation. The recipient's heart was explanted followed by bicaval anastomosis of the donor heart. With the newly transplanted heart beating and kept on full CPB, the hepatectomy was completed and the donor liver was implanted. After completion of the liver transplantation and caval and portal unclamping, the patient was kept on CPB for five to ten minutes until the potassium surge subsided as evidenced by a normalization of the ECG and blood electrolytes. The patient was then weaned from CPB and the chest was closed. The biliary anastomosis was then completed and the abdominal incision closed. Red blood cells were transfused to maintain a hematocrit >25%. Platelets and clotting factors were transfused based on either the anesthetist's or the surgeon's clinical impression of bleeding. There is a list in Table 2 of the surgical, CPB, and organ ischemic times, as well as the inotropic and vasopressor support on arrival to the intensive care unit (ICU). In Table 3, there is a summary of the fluid and blood product requirements and the estimated blood loss.

Table 2 Duration of cardiopulmonary bypass, aortic cross clamp, cardiac ischemia, surgery, and pharmacological support on arrival to the intensive care unit

	Normal range or previous reports*	Patient 1	Patient 2	Patient 3	Patient 4
CPB (min)		197	188	121	248
Aortic cross clamp (min)		73	53	43	76
Cardiac ischemia (min)	150 (12)*	185	201	86	83
Liver ischemia (min)	504 (24)*	288	300	167	135
Surgery (min)	786 (192)*	350	540	410	550
Norepinephrine ($\mu g \cdot min^{-1}$)		16	-	30	4
Epinephrine ($\mu g \cdot min^{-1}$)		5	5	6	-
Milrinone ($\mu g \cdot kg^{-1} \cdot min^{-1}$)		-	0.5	-	-

* Summary of surgical times in combined heart and liver transplant in seven patients with liver transplantation following CPB weaning.[6,7] Values are presented as mean and standard deviation. CPB = cardiopulmonary bypass

Postoperative course

Patient 1's trachea was extubated on postoperative day (POD) 1; he left the ICU on POD 5, was discharged from hospital on POD 14, and remains well 38 months later.

Patient 2's trachea was extubated on POD 1, and he left the ICU on POD 3. However, biliary stent occlusion with anastomotic leak resulted in abdominal sepsis and persistent fluid collections requiring repeated drainage. He was finally discharged on POD 176 and remains well 34 months later.
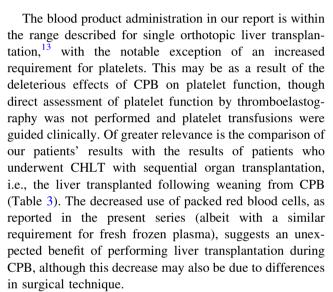
Patient 3 had a prolonged episode of hypotension on POD 1 followed by hepatic artery thrombosis necessitating a second liver transplantation. His course was complicated by acute renal failure requiring temporary continuous veno-venous hemofiltration. The patient recovered fully; he left the ICU on POD 12, was discharged 27 days after his original surgery, and remains well 30 months later.

Patient 4's trachea was extubated on POD 1, but he required continuous veno-venous hemofiltration for 48 hr. He left the ICU on POD 3, was discharged from hospital on POD 51, and remains well 25 months later.

Discussion

This report expands on the single case report from our institution[16] and summarizes the perioperative course of a case series of four patients who underwent CHLT. Rather than transplanting the liver following the heart transplant and weaning from CPB, which appears to be the standard approach, these cases are distinguished by the fact that both organs were transplanted during CPB.[4-11]

It is difficult to compare surgical strategies for CHLT because only scant data are provided in the literature. Bearing this caveat in mind, the following comparisons may be of interest.

The blood product administration in our report is within the range described for single orthotopic liver transplantation,[13] with the notable exception of an increased requirement for platelets. This may be as a result of the deleterious effects of CPB on platelet function, though direct assessment of platelet function by thromboelastography was not performed and platelet transfusions were guided clinically. Of greater relevance is the comparison of our patients' results with the results of patients who underwent CHLT with sequential organ transplantation, i.e., the liver transplanted following weaning from CPB (Table 3). The decreased use of packed red blood cells, as reported in the present series (albeit with a similar requirement for fresh frozen plasma), suggests an unexpected benefit of performing liver transplantation during CPB, although this decrease may also be due to differences in surgical technique.

With patients undergoing combined non-transplant cardiac surgery and liver transplantation, liver transplantation is performed primarily after the cardiac procedure.[17,18] While there can be no doubt that improved surgical and anesthetic techniques contribute to decreased blood transfusion requirements,[14] the use of high doses of aprotinin, as administered in our patients, mandates specific comment.

Aprotinin and lysine analogues have been shown to reduce transfusion compared with placebo in cardiac surgery and liver transplantation, although there have been more trials with aprotinin.[19,20] No increased risk for hepatic artery thrombosis, venous thromboembolic events, or perioperative mortality has been documented for either of these drugs after liver transplantation, although aprotinin has been identified as a risk factor for severe renal dysfunction within the first week post liver transplantation.[21,22] Recently, aprotinin has been withdrawn from marketing because of safety concerns.[23] Thus, at our institution we have switched to using tranexamic acid for those patients at

Table 3 Fluid and blood product transfusion requirements, estimated blood loss, and laboratory data on arrival in the intensive care unit

	Normal range or previous reports*	Patient 1	Patient 2	Patient 3	Patient 4
EBL (mL)		2,600	3,000	1,000	2,000
Crystalloid (mL)		3,000	3,500	7,500	4,700
Pentaspan (mL)		750	750	750	750
PRBC (U)	14.9 (2.9)*	3	2	4	5
FFP (U)	7.4 (2.8)*	12	8	4	8
Platelets (U)		10	23	10	5
Cryoprecipitate (U)		10	20	-	-
Fibrinogen (U)		2	-	-	-
Hemoglobin (g·L^{-1})	140-175	106**	77**	69**	103**
Platelets (10^9·L^{-1})	150-350	177	192	152	149**
Na (mmol·L^{-1})	136-142	140	136	135**	147
K (mmol·L^{-1})	3.5-5.0	3.5	3.1**	4.0	4.9
Ionized Ca (mmol·L^{-1})	1.15-1.27	0.98**	1.03**	1.07**	1.11**
Glucose (mmol·L^{-1})	3.9-6.1	10.6**	12.6**	14.2**	5.4
Creatinine (µmol·L^{-1})	53-106	84	131**	103	199**
INR	0.8-1.1	1.61**	1.42**	3.11**	2.46**
aPTT (sec)	25-40	44.3**	53.7**	81.3**	103.2**
Albumin (g·L^{-1})	35-50	25**	24**	15**	21**
Total bilirubin (µmol·L^{-1})	5-21	134**	31**	44**	71**
AP (U·L^{-1})	30-120	70	56	29	50
ALT (U·L^{-1})	10-40	124**	127**	242**	2100**
Lactate (mmol·L^{-1})	0.6-1.7	4.7**	2**	9.2**	3.4**

* Summary of blood product administration in combined heart and liver transplant in seven patients with liver transplantation following cardiopulmonary bypass weaning.[6,7] Values are presented as mean and standard deviation. ** Abnormal values; EBL = estimated blood loss; PRBC = packed red blood cells; FFP = fresh frozen plasma; INR = international normalized ratio; aPTT = activated partial thromboplastin time; AP = alkaline phosphatase; ALT = alanine aminotransferase

risk of severe intraoperative blood loss, including liver transplantation.

Three of the four patients had serious postoperative complications. Patient 2 had biliary stent occlusion with an anastomotic leak resulting in intra-abdominal sepsis. However, post liver transplantation biliary strictures have an overall incidence ranging from 5-23%, and the incidence does not appear to be affected by the type of surgical anastamosis.[24] Furthermore, the biliary anastomosis was performed off CPB, so it would be difficult to attribute this complication to the decision to perform the liver transplant while the patient remained on CPB. On POD 1, Patient 3 had a prolonged episode of hypotension of unclear etiology, which led to hepatic artery thrombosis necessitating a second liver transplantation that was further complicated by acute renal failure. While we do not have an explanation for the hypotensive episode, it is possible that the use of aprotinin may have contributed to the episode of acute renal failure, though it would be difficult to separate the contribution of aprotinin from the renal insult, the

hypotensive episode, as well as the repeat orthotropic liver transplantation. Also, the acute renal failure suffered by Patient 4 could be attributed in part to the use of aprotinin or prolonged CPB. Despite these complications, our patients have a 100% two-year survival rate compared with published one-year and five-year survival rates of 84.8% and 75.6%, respectively.[11]

Performing the liver transplantation during CPB provides a considerably shortened liver ischemia time compared with the sequential approach (Table 2). In addition, the adverse effects of unclamping the vena cava and hepatic reperfusion on the transplanted heart, i.e., fluid overload, acidosis, and hyperkalemia, are blunted. Improved hemodynamic and metabolic stability may help to explain the modest use of vasopressor and inotropic drugs in our patients.

In summary, we describe the perioperative course of four consecutive patients undergoing CHLT with the liver transplanted during CPB. Compared with patients undergoing liver transplantation following weaning from CPB, this approach may confer benefits to this unique patient

population, such as decreased blood transfusion and a shortened hepatic ischemia time.

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