

# Combined heart-liver transplantation with extended cardiopulmonary bypass

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## ABSTRACT

**We report a case of combined heart and liver transplantation for familial amyloid polyneuropathy. This is the first such combined transplant performed in Asia, and differs from previously described cases, in that cardiopulmonary bypass was continued at partial flow during liver transplantation in our case. This was done in order to provide haemodynamic support to the cardiac graft and to protect it from the impending reperfusion insult that frequently accompanies liver transplantation. The utility of this management course is discussed, along with its actual and potential complications. We also describe the impact of a lung-protective ventilation strategy employed during cardiac transplantation.**

**Keywords: cardiopulmonary bypass, familial amyloid polyneuropathy, heart transplantation, liver transplantation, reperfusion injury**

*Singapore Med J 2011;52(3):e48-e51*

## INTRODUCTION

Our patient, a 57-year-old man, underwent combined heart and liver transplantation (CHLT) for familial amyloid polyneuropathy (FAP) non-transthyretin Met30 variant. This autosomal dominant disease is characterised by abnormal hepatic amyloidogenesis, with progressive amyloid deposition in the extracellular matrix of peripheral and autonomic nerves, and to a varying degree within the heart, gastrointestinal tract, kidneys and eyes. Life expectancy without transplantation is approximately ten years from the onset of symptoms.<sup>(1)</sup> This condition also carries the risk of subsequent cardiac failure despite isolated liver transplantation,<sup>(2)</sup> especially in patients with cardiac amyloidosis at the time of transplantation. Herlenius et al suggested that if cardiac involvement is present in patients with non-transthyretin Met30 FAP, then combined liver and heart transplantation may be justified.<sup>(3)</sup> We add our experience to the series of case reports of CHLT and detail the factors that compelled us to continue cardiopulmonary bypass (CPB) during

the liver implantation phase, along with its attendant implications for coagulation and witnessed benefits at the time of hepatic reperfusion.

## CASE REPORT

Our patient's first symptoms, diarrhoea and urinary incontinence, appeared in mid 2004 at the age of 52, followed by a gradual reduction in exercise tolerance over the next six months. He was a non-smoker, non-drinker, and his only medical history was that of childhood asthma. He was assessed by a neurologist in 2005. Physical examination revealed orthostatic hypotension and mildly reduced pinprick sensation in the extremities, and further questioning elicited a family history of paternal death due to a cardiomyopathy of unknown aetiology. Nerve conduction studies and electromyography showed a generalised sensorimotor and autonomic polyneuropathy. Congo red-stained prepares from neural biopsies exhibited birefringence in polarised light, denoting presence of amyloid fibrils. Subsequent genetic testing confirmed mutation of the transthyretin gene and a diagnosis of FAP was made. The patient was referred to our liver transplant service in September 2006. Cardiac biopsy revealed the presence of amyloid deposition. The decision was made in conjunction with the patient and his family to proceed with wait-listing for combined heart and liver transplantation.

Preoperative evaluation proceeded in accordance with local guidelines for heart and liver transplantation. Electrocardiography showed borderline low voltages in frontal leads, which was consistent with infiltrative heart disease. Plain chest radiography and spirometry were normal for age. Transthoracic echocardiography revealed mild concentric increase in left ventricular thickness, with ejection fraction of approximately 60% and pseudonormal filling. Right heart catheterisation revealed a central venous pressure of 11 mmHg, pulmonary arterial pressure 26/14 mmHg, mean pulmonary arterial pressure 19 mmHg, pulmonary artery capillary wedge pressure 18 mmHg, cardiac index 3.92 L/min/m<sup>2</sup> and systemic vascular resistance 978 dyne/sec/cm<sup>5</sup>. There was only mild derangement of hepatic transaminases. The patient's serum bilirubin concentration

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was 10  $\mu\text{mol/L}$ , plasma creatinine concentration was 71  $\mu\text{mol/L}$  and the International Normalised Ratio was 1, yielding a model for end-stage liver disease score of 2.<sup>(4)</sup> Modified polyneuropathy disability score was 1, based on the absence of peripheral motor impairment. On the day of transplantation, our patient weighed 45 kg, had an albumin of 32 g/L and was able to walk 500 metres on flat ground before becoming fatigued.

Our patient was admitted for surgery when a suitable multiorgan donor had been identified at a neighbouring hospital. Vascular access consisted of a 16 gauge peripheral intravenous cannula, a left radial arterial line and left internal jugular 12 French gauge triple lumen central venous catheter and 8.5 French gauge pulmonary artery catheter sheath. Once liver biopsy results and inspection of the donor heart confirmed suitability for transplantation, the patient was anaesthetised. General anaesthesia was induced with fentanyl, etomidate and atracurium, and maintained with isoflurane in oxygen/air along with infusions of fentanyl (3–5  $\mu\text{g/kg/hr}$ ) and atracurium (0.5  $\text{mg/kg/hr}$ ). Intraoperative monitoring included five-lead electrocardiography, capnography, oxygen saturation, ventilator functions, core and skin temperatures, urinary output, bispectral index monitoring and transoesophageal echocardiogram. A noradrenaline infusion (0.05  $\mu\text{g/kg/min}$ ) was commenced soon after surgery began, necessitated by vasodilatation produced by the general anaesthetic agents in the absence of intact autonomic responses.

Following mobilisation of the recipient's liver, the abdomen was packed and covered to facilitate heart transplantation. For CPB, vacuum-assisted venous drainage, non-pulsatile flow delivered via roller-pump, moderate hypothermia and haemoconcentration were employed. A loading dose of  $1 \times 10^6$  kallikrein inhibitor units of aprotinin was initiated before institution of CPB, and maintained at a background infusion rate of  $5 \times 10^5$  kallikrein inhibitor units per hour. Another  $1 \times 10^6$  kallikrein inhibitor units of aprotinin were added to the priming solution.

Restoration of sinus rhythm was achieved with a single 5 J direct current cardioversion. The donor heart function was assessed to be satisfactory as evidenced by direct observation and transoesophageal echocardiography. Upon initial weaning of CPB circuit flow to zero, infusions of noradrenaline at 0.15  $\text{mcg/kg/min}$ , adrenaline at 0.06  $\text{mcg/kg/min}$  and isoprenaline at 0.01  $\text{mcg/kg/min}$  were required to maintain mean arterial pressures of 50–60 mmHg and preserve organ perfusion. We elected at this point to reinstitute CPB flow at 10% of full flow, and continue it during liver

implantation. Partial CPB flow facilitated down-titration of noradrenaline to 0.03  $\text{mcg/kg/min}$  and adrenaline to 0.04  $\text{mcg/kg/min}$ , while maintaining an acceptable mean arterial pressure. In order to facilitate suturing of the inferior vena cava during liver transplantation, the inferior vena cava cannula of the CPB circuit was removed. Venous return from the CPB circuit was via the superior vena cava cannula, with the opening of the cannula turned and directed toward the right atrium. During this period of extended CPB, we continued mechanical ventilation at 4 breaths/min, with inspiratory pressure of 12  $\text{cmH}_2\text{O}$  and positive end-expiratory pressure of 5  $\text{cmH}_2\text{O}$ .

Liver transplantation utilised a modified piggyback technique (cavo-cavoplasty with partial caval cross clamping). The time from re-entering the abdomen to reperfusion of the hepatic graft was just over an hour, with a 55-minute anhepatic phase. While liver transplantation was proceeding on CPB, 1709 ml of packed red cells were transfused, which maintained haematocrit between 26% and 31%. Reperfusion of the liver graft, which had been flushed with histidine-tryptophan-ketoglutarate solution, resulted in hypotension (mean arterial pressure falling below 50 mmHg) and the appearance of peaked T waves on the electrocardiograph. Treatment consisted of an immediate increase in CPB flow, along with bolus doses of adrenaline (20  $\text{mcg}$ ), calcium chloride and sodium bicarbonate, resulting in rapid resolution of the disturbance. Complete weaning from CPB was achieved over the next 25 minutes. The total CPB duration was 271 minutes, with an ischaemic time of 174 minutes for the heart and 346 minutes for the liver (306 minutes cold).

Intravenous protamine was administered following decannulation of the superior vena cava. Coagulopathy, which was observable in the surgical field and which manifested on rotational thromboelastometry (ROTEM®, Pentapharm GmbH, Munich, Germany), was corrected with fresh frozen plasma, cryoprecipitate and tranexamic acid. Management of fluid therapy and transfusion of blood products were facilitated by the use of a temperature-regulated rapid fluid infusor (Fluid Management System®, Belmont Instrument Corporation, Billerica, MA, USA) and cell-saver device. The liver transplant was completed and the abdomen closed with the patient on stable doses of adrenaline (0.11  $\text{mcg/kg/min}$ ) and noradrenaline (0.12  $\text{mcg/kg/min}$ ). Sternal closure over a bloodless field was done 12.5 hours after commencement of the operation.

The ventilatory requirements were minimal postoperatively. Adequate oxygenation and gas exchange was achieved with synchronised intermittent mandatory

ventilation, inspired oxygen fraction of 0.4, positive end-expiratory pressure of 5 cmH<sub>2</sub>O, and pressure support of 10 cmH<sub>2</sub>O. The patient's chest radiograph taken after admission to the cardiothoracic intensive care unit revealed clear lung fields with a minimum of atelectasis. Total mediastinal tube drainage for the first 24 hours amounted to approximately 200 ml. By postoperative day (POD) 3, our patient had been extubated (in time to celebrate his 58th birthday), by POD 4, he was no longer dependent upon inotropic support and by POD 5, he could tolerate a soft diet. Two episodes of non-sustained ventricular tachycardia while on inotropes proved transient and no impediment to his rapid recovery. Myocardial biopsy performed on POD 7 showed evidence of focal ischaemia and the histology was graded as International Society of Heart and Lung Transplantation Grade I R.<sup>(5)</sup> The same histological grading was obtained on POD 15. The immunosuppression therapy regimen comprised prednisolone, mycophenolic acid and tacrolimus. An echocardiogram on POD 6 showed normal right ventricle size and function, left ventricular ejection fraction 55%–60%, no regional wall motion abnormalities and no pericardial effusion or thrombus. Serial Doppler ultrasonography of the liver showed sustained good graft perfusion with patent portosystemic veins and laboratory markers of hepatic function rapidly normalised after an initial transaminitis. No major postoperative complications were encountered, and the patient was discharged on POD 30, without any sign of cognitive dysfunction and was mobilising freely around the ward.

## DISCUSSION

There is no consensus in the literature with regard to the level of cardiac involvement that would allow for consideration of liver transplant alone in patients with non-transferrin receptor-related protein 30 familial amyloidosis. Our decision to proceed with combined transplantation of the heart and liver was based upon the presence of biopsy-proven cardiac amyloid deposits and the recognised risk of progressive cardiac disease and its implications for long-term survival.<sup>(6,7)</sup> The proposed surgical plan, which involved mobilisation of the liver prior to sequential heart and liver transplantation, was chosen to reduce the amount of dissection that would be required during the potentially coagulopathic state post CPB. The potential benefits have been described by previous authors,<sup>(8)</sup> as is the possible risk of prolonging cold ischaemia time for the allografts,<sup>(9)</sup> which mandated optimal coordination of the donor and recipient procedures.

Our decision to extend CPB at partial flow was

guided by the haemodynamic profile upon initial weaning following cardiac transplantation. Continuing CPB at only partial flow allowed ongoing assessment of the function of the cardiac graft, while still providing haemodynamic stability and recourse to return to full flow if necessary. With regard to protection of the grafts, the immediate haemodynamic stability afforded by CPB following hepatic reperfusion allowed the patient's physiological parameters to be assessed in turn and optimised. The improved flow at the time of reperfusion would have protected the cardiac graft from the direct effects of metabolites released from the hepatic graft and may have helped to avoid some of the well-documented risks of hepatic reperfusion to both remote organs and to the liver itself.<sup>(10,11)</sup>

Prolonging CPB mandated anticoagulation during a significant portion of liver transplantation. Considering all the factors that contribute to the precarious haemostatic balance of such patients, and in combination with meticulous surgical technique, the need for anticoagulation itself should not preclude the continuation of CPB during liver transplantation. Unfortunately, we have not been able to compare our transfusion requirements with those of others who have successfully performed simultaneous heart and liver transplantation on full CPB.<sup>(12)</sup> While active management was required for the coagulopathy encountered following prolonged CPB, the postoperative mediastinal chest tube drainage was minimal.

We continued mechanical ventilation of the patient's lungs and maintained positive end-expiratory pressure during liver transplantation. The low respiratory rate minimised distortion of the surgical field. This ventilation strategy was intended to limit the development of atelectasis and extravascular lung water that is associated with pulmonary dysfunction following cardiac surgery.<sup>(13)</sup> It is interesting to note that there was no evidence of acute lung injury in the postoperative period.

Thus, we have described the application of CPB at partial flow during the liver transplantation phase of CHLT. In this setting, with a cardiac graft that requires significant support and may be particularly susceptible to the effects of hepatic reperfusion, extending CPB is an option that proved valuable and consistent with a good short-term outcome.

## ACKNOWLEDGEMENTS

We would like to acknowledge the many nurses, pharmacists and allied health staff whose contributions ensured a successful outcome for our patient. In

particular, we are indebted to our heart and liver transplant programme coordinators Kerk KL, Tay CPG and Lee HL for their outstanding organisational roles.

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