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CASE REPORT

A staged approach for a lung–liver transplant patient using *ex vivo* reconditioned lungs first followed by an urgent liver transplantation

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Abstract

Combined lung–liver transplantation is a logistically challenging procedure hampered by shortage of organ donors. We describe the case of a young patient with end-stage lung disease due to of cystic fibrosis and liver cirrhosis who needed combined lung–liver transplantation. The long waiting for this caused an interesting clinical dilemma. We decided to change our policy in this situation by listing him only for the lung transplantation and to apply for a high urgent liver transplantation if the liver failed after the lung transplantation. This strategy enabled us to use lungs treated with *ex vivo* lung perfusion (EVLP) from an unsuitable donor after circulatory death. After conditioning for 4 h via EVLP, the pO_2 was 59.7 kPa. The lungs were transplanted successfully. He developed an acute-on-chronic liver failure for which he received a successful liver transplantation 19 days after the lung transplantation.

Introduction

Worldwide, there is a disparity between the available donor lungs and the amount of patients on the waiting list. Overall, only 15% of all donor lungs are suitable for transplantation [1]. A combined lung–liver transplantation is a logistically challenging procedure even more hampered by organ shortage.

Donation after circulatory death (DCD) is an option to alleviate this shortage. The first lung transplantation in 1963 was performed with a DCD lung [2]. In the early 1990s, there was a renewed interest in the use of lungs from DCD [3], and in 1995, four types of donors were identified [4]. Nowadays, several centers have developed a successful DCD program. *Ex vivo* lung perfusion (EVLP) has proven to be a good technique to condition and assess lungs that are deemed unsuitable for transplantation or are from marginal quality [5,6].

The cumulative incidence for liver disease in cystic fibrosis ranges between 27% and 35%.

Although selection criteria for orthotopic liver transplantation and timing are not yet established, it is obvious that

in cystic fibrosis, other extrahepatic parameters should be considered when compared to chronic hepatic dysfunction [7]. Clear indications for liver transplantation are deterioration of pulmonary function, malnutrition, hepatopulmonary and portopulmonary syndromes, intractable variceal bleeding, ascites and jaundice, progressive hepatic dysfunction, and deterioration of quality of life.

In this case, we report the use of EVLP to condition lungs from a DCD donor that seemed unsuitable for transplantation followed by a successful urgent liver transplantation.

Case report

A 20-year-old man underwent bilateral lung transplantation with lungs conditioned via EVLP. The donor was 41-year-old woman with a medical history who became unwell at home. Computed tomography scan of the brain demonstrated an intracerebral bleeding with an unfavorable prognosis. The criteria for brain dead were not fulfilled, and the patient was announced for DCD. However, the arterial blood gas showed a PO_2 of 24.9 kPa after ventilation with a positive end-expiratory pressure of 5 cmH_2O and a fraction of inspired oxygen (FiO_2) of 100% during 10 min. There were no obvious signs of pulmonary edema on chest X-ray (Fig. 1). Therefore, it was decided to send a team to the donor hospital for evaluation. At recovery, the lungs felt heavy and pulmonary edema was visible in the lower lobes, no other reason for poor function such as infection or atelectasis was observed (Figs 1 and 2a). After explantation, the lungs were transported to the recipient hospital and evaluated with EVLP. The system was primed with 1.5 l Steen solution. Reperfusion of the lungs was started, after retrograde flush of the tubing, using the Toronto protocol [8]. However, we ventilated the lungs with a FiO_2 of 0.4. Physiologic evaluation was performed every hour, and the function of the lungs was found to be excellent after 4 h of EVLP (Table 1, Fig. 2b). The lungs were then cooled to a temperature of 12 °C and stored in buffered Perfadex (Table 2).

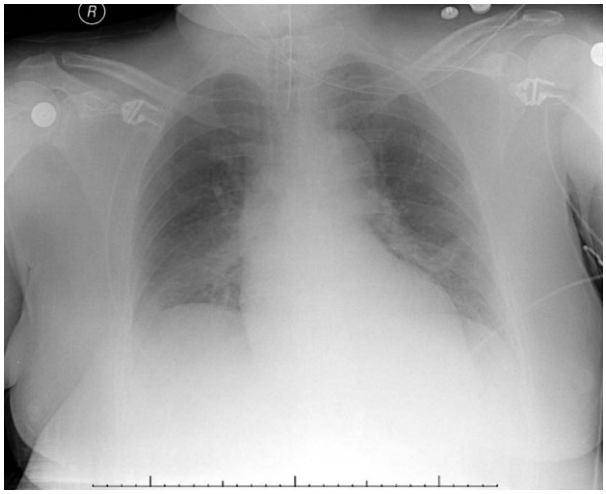

Figure 1 Donor chest X-ray with possible lung edema in the lower lobes.

The recipient was a 20-year-old man with cystic fibrosis and an Arnold-Chiari malformation (Fig. 3a). He had hepatomegaly, liver cirrhosis, and splenomegaly with esophageal varices and portal hypertension. Since 2010, there were several episodes of hemoptysis for which bronchial arteries were coiled. In September 2012, he was screened for liver–lung transplantation. Screening revealed a still reasonable liver function [mayo end-stage liver disease (MELD) 8, CHILD B] and no signs of pulmonary hypertension. To serve him the best, he was screened for combined transplantation. But, after weighing all options and possible problems, he was listed without liver transplantation to increase the chance of a lung offer. In December 2012, he was listed for high-urgency lung transplantation after a severe episode of untreatable hemoptysis.

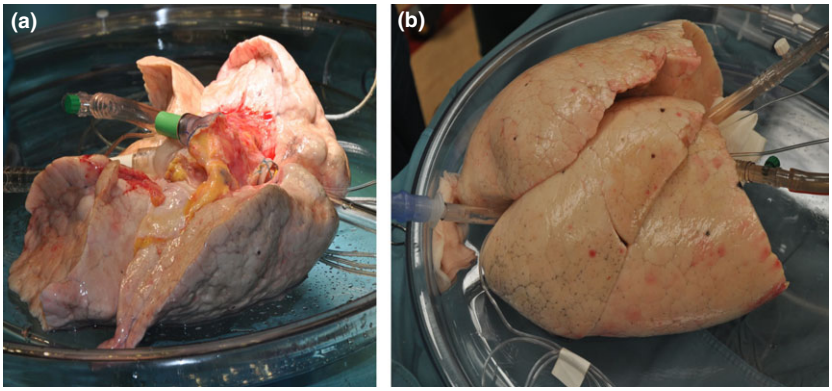

Figure 2 (a) Donor lungs before the start of the EVLP. (b) Donor lungs on the EVLP, at the end of the reperfusion.

Table 1. Functional parameters during EVLP.

	1 h	2 h	3 h	4 h
Flow rate (l/min)	2.5	2.7	2.7	2.7
PAP (mmHg)	12	11	12	13
LAP (mmHg)	8	6	2	1
PVR (wood units)	1.6	1.8	3.7	4.4
Plat AwP (cmH_2O)	16	17	21	20
Mean AwP (cmH_2O)	8	8	9	9
P/F ratio	57.1	46.6	58.8	59.7

PAP, pulmonary artery pressure; LAP, left atrial pressure; PVR, pulmonary vascular resistance; Plat AwP, plateau airway pressure; Mean AwP, mean airway pressure; P/F ratio, ratio of partial pressure of arterial oxygen/fraction of inspired oxygen (1.0).

Table 2. Time schedule.

Time	Action	
20:32	Switch off	
20:47	Hands off period (5 min)	Warm ischemia: 20 min
21:07–21:50	Flush with cold Perfadex and procurement	Cold ischemia: 3 h 48 min
0:55–4: 55	Functional assessment, bronchoscopy	
5:15	Start cold preservation	
12:05	Reperfusion right lung	Cold ischemia: 6 h 50 min
14:35	Reperfusion left lung	Cold ischemia: 9 h 20 min

Bilateral lung transplantation with the use of cardiopulmonary bypass was performed in January 2013. High perioperative pulmonary pressures necessitated the use of NO ventilation. This was stopped 2 days later. Hereafter, his respiratory function was stable with excellent blood gases (Fig. 3b). His postoperative stay on the intensive care unit was complicated. Four days after the transplantation, his liver function started to deteriorate (acute-on-chronic liver failure). Ultrasound of the liver showed a retrograde flow in the portal veins without thrombosis, but there was ascites. Microbiological investigation of the ascites showed infection with enterococcus faecium which was treated with antibiotics. He was accepted for high-urgency liver transplantation 12 days later (MELD 38.5). After 19 days, a full size liver of a donation after brain death (DBD) donor was implanted using a piggyback technique. The cold ischemia time was 8 h 29 min. There was a good function of the graft after the transplantation.

He developed acute tubular necrosis because of a hepatorenal syndrome and a systemic inflammatory response syndrome for which hemodialysis was started. Fortunately, his renal function recovered and after 52 days, dialysis was stopped.

He was extubated 4 weeks after transplantation, but after a short period of noninvasive ventilation, re-intubation was necessary. A tracheostomy was placed 34 days after transplantation to facilitate weaning from the ventilator. Seventy days after the transplantation, he was able to breathe without support. He was discharged to the ward after 76 days for further revalidation and finally home after another 38 days.

Discussion

Herein, we present a case performing high-urgency transplantation of EVLP conditioned DCD lungs followed by high-urgency liver transplantation.

There are two different protocols described for EVLP. The first technique was developed by Steen and resulted in successful single lung transplantation in 2000 with a lung from a DCD donor [6]. This protocol allows a pulmonary artery pressure (PAP) up to 20 mmHg with pump flow adjusted to the pulmonary artery pressure. The lungs were perfused with Steen solution mixed with red blood cells to a hematocrit of 15% [9].

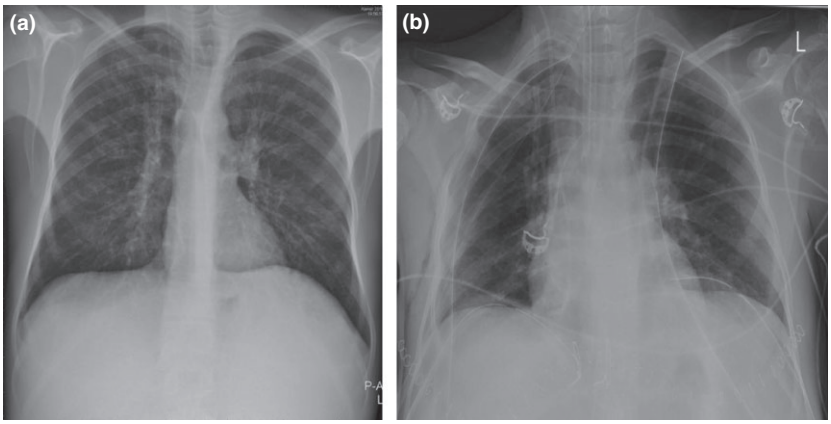

Figure 3 (a) Recipient chest X-ray before transplantation. (b) Recipient chest X-ray after transplantation.

Good results with the Steen protocol were reported by Wallinder *et al.* [10,11]. Eleven pairs of rejected donor lungs were subjected to EVLP. Eight double lung transplantations and three single lung transplantations were performed after improvement of the partial pressure of oxygen (pO_2). In two, EVLP succeeded to improve the oxygenation of one lung resulting in single lung transplantation. One pair of lungs was good after EVLP, but the recipient was listed for a single lung transplantation and this was performed.

In this case report, we used the protocol of the Toronto group. They describe a protocol with a lower PAP and a flow of 40% of the estimated cardiac output. The left atrial pressure is maintained between 3 and 5 mmHg. Perfusion is performed with an acellular Steen solution [5]. Recently, their experience with 50 EVLPs was published. Fifty-eight pair of lungs, 32 DBD and 26 DCD, were included in the EVLP trial, and 50 of 58 EVLPs resulted in lung transplantation. They also report similar outcome after comparison with a control group receiving standard donor lungs. However, approximately 50% of the DCD had acceptable oxygenation but were included as part of the study protocol. Therefore, it is difficult to interpret the results [12]. The Toronto technique is now used in several transplant centers. Aigner *et al.* report the evaluation *ex vivo* of 13 DBD lungs resulting in nine lung transplantations. Four lungs, from donors with a trauma history, deteriorated on the EVLP. Days on the ventilator, intensive care unit stay, hospital stay, and 30-day survival were comparable with patients receiving standard lung transplantation during the same time period [13]. Recently published results from the Harefield group report EVLP assessment of three DCD and nine DBD lungs. Six lungs (two DCD and four DBD) reached the criteria for lung transplantation [14]. Outcomes were similar to that of other published studies. The Sao Paulo group showed good functional results after assessment of nonacceptable DBD lungs [15].

In this case report, we describe the use of EVLP in an unsuitable DCD lung with PaO_2/FiO_2 of 24.9 kPa. After 1 h of EVLP, a pO_2/FiO_2 ratio of 57.1 kPa was reached. However, the decision to use the lungs was only made after 4 h of EVLP. The lungs were then accepted for transplantation and the recipient was informed. The active regular surgical program resulted in a by us accepted delay of 3 h between the end of the EVLP and the start of the operation.

In the reported case, the liver still had a reasonable function at the time of screening. However, because of his liver cirrhosis, the recipient met the criteria for a combined procedure and this caused an interesting clinical dilemma. Several possibilities were discussed. A combined organ transplantation would give him a higher priority than lung transplantation only. But there was an expected long waiting time for acceptable quality of organs for a combined procedure. In the Netherlands, almost a third of the lungs are coming from a DCD donor. There is a higher risk of liver graft failure [16] and biliary complications [17] in the DCD liver in a procedure with long ischemia time. This almost excludes the possibility to use both organs from a DCD donor.

The possibility of first a liver transplantation followed by a lung transplantation with the lungs preserved on EVLP during the liver transplantation was discussed as another option. It was thought that at that time, his liver function with a MELD of 8 was stable enough to survive the lung transplantation and might even improve after lung transplantation. There is a correlation between the MELD and the operative risk. In his situation, the 7-day mortality was 1.21% after major surgery. This is calculated with the postoperative mortality risk calculator of the Mayo Clinic.

Therefore, we listed him only for the lung transplantation. Another argument for a staged procedure was the development of severe hemoptysis requiring an urgent need for lung transplantation. Also, the assumed technical difficulty during transplantation with a long ischemic time for the liver played a role.

This case report demonstrates that EVLP of unsuitable DCD lungs is feasible and that recent lung transplantation is not a contraindication for urgent liver transplantation.

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Authorship

CVDW: wrote the paper and performed the EVLP. GD, EV and WVDB: contributed the paper and involved with patient care. IDH and MDB: contributed to the transplantation and to the paper. TK: contributed to the transplantation. AVDB: involved with patient care. MM: contributed to the paper. ME: performed the EVLP and contributed to the paper.

References

1. Hornby K, Ross H, Keshavjee S, Rao V, Shemie SD. Non-utilization of hearts and lungs after consent for donation: a Canadian multicentre study. *Can J Anaesth* 2006; **53**: 831.
2. Hardy JD, Webb WR, Dalton ML Jr, Walker GR Jr. Lung homotransplantations in man. *JAMA* 1963; **186**: 1065.
3. Egan TM, Lambert CJ Jr, Reddick R, Ulicny KS Jr, Keagy BA, Wilcox BR. A strategy to increase the donor pool: use of cadaver lungs for transplantation. *Ann Thorac Surg* 1991; **52**: 1113.

4. Kootstra G, Daemen JH, Oomen AP. Categories of non-heart-beating donors. *Transplant Proc* 1995; **27**: 2893.
5. Cypel M, Yeung JC, Liu M, *et al.* Normothermic ex vivo lung perfusion in clinical lung transplantation. *N Engl J Med* 2011; **364**: 1431.
6. Steen S, Sjoberg T, Pierre L, Liao Q, Eriksson L, Algotsson L. Transplantation of lungs from a non-heart-beating donor. *Lancet* 2001; **357**: 825.
7. Debray D, Kelly D, Houwen R, Strandvik B, Colombo C. Best practice guidance for the diagnosis and management of cystic fibrosis-associated liver disease. *J Cyst Fibros* 2011; **10** (Suppl. 2): S29.
8. Cypel M, Yeung JC, Hirayama S, *et al.* Technique for prolonged normothermic ex vivo lung perfusion. *J Heart Lung Transplant* 2008; **27**: 1319.
9. Steen S, Liao Q, Wierup PN, Bolys R, Pierre L, Sjoberg T. Transplantation of lungs from non-heart-beating donors after functional assessment ex vivo. *Ann Thorac Surg* 2003; **76**: 244.
10. Wallinder A, Ricksten SE, Hansson E, *et al.* Transplantation of initially rejected donor lungs after ex vivo lung perfusion. *J Thorac Cardiovasc Surg* 2012; **144**: 1222.
11. Wallinder A, Ricksten SE, Silverborn M, *et al.* Early results in transplantation of initially rejected donor lungs after ex vivo lung perfusion: a case-control study. *Eur J Cardiothorac Surg* 2014; **45**: 40.
12. Cypel M, Yeung JC, Machuca T, *et al.* Experience with the first 50 ex vivo lung perfusions in clinical transplantation. *J Thorac Cardiovasc Surg* 2012; **144**: 1200.
13. Aigner C, Slama A, Hotzenecker K, *et al.* Clinical ex vivo lung perfusion–pushing the limits. *Am J Transplant* 2012; **12**: 1839.
14. Zych B, Popov AF, Stavri G, *et al.* Early outcomes of bilateral sequential single lung transplantation after ex-vivo lung evaluation and reconditioning. *J Heart Lung Transplant* 2012; **31**: 274.
15. Pego-Fernandes PM, de Medeiros I, Mariani AW, *et al.* Ex vivo lung perfusion: early report of Brazilian experience. *Transplant Proc* 2010; **42**: 440.
16. Lee KW, Simpkins CE, Montgomery RA, Locke JE, Segev DL, Maley WR. Factors affecting graft survival after liver transplantation from donation after cardiac death donors. *Transplantation* 2006; **82**: 1683.
17. Foley DP, Fernandez LA, Leverson G, *et al.* Biliary complications after liver transplantation from donation after cardiac death donors: an analysis of risk factors and long-term outcomes from a single center. *Ann Surg* 2011; **253**: 817.