Selection, preservation and evaluation of lungs from donors after circulatory death

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CHAPTER 7

Lung transplantation of an ex vivo conditioned unacceptable DCD lung followed by urgent liver transplantation.

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ABSTRACT

Lung transplantation is hampered by shortage of organ donors. Since 1995 the use of lungs from donors after circulatory death is a way to reduce this shortage. Ex vivo lung perfusion (EVLP) has recently been accepted as a method to condition lungs that are unsuitable for transplantation. We describe the case of a young recipient with cystic fibrosis and liver cirrhosis who received lungs from a donor after circulatory death that were deemed unsuitable for transplantation because of poor oxygenation. After conditioning for 4 hours via EVLP the PO_2 was 59.7 kPa with a FiO_2 of 1.0 and a PEEP of 5 cmH_2O. The lungs were transplanted successfully. Unfortunately he developed an acute-on-chronic liver failure for which he received a liver transplantation 19 days after the lung transplantation. He was ultimately discharged from Intensive care to the ward after 76 days for further revalidation and finally went home after another 38 days.

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 number of alternative pathways are currently used to reduce this shortage. The first is the use of extended criteria donor lungs, the so-called marginal donor lungs. There are no contraindications for the use of marginal donors for standard recipients. However, caution is necessary when allocating these lungs to high risk recipients [2].

Donation after circulatory death (DCD) and living-donor lobar lung transplantation are other options. The first lung transplantation in 1963 was performed with a DCD lung [3]. In the early 1990's there was a renewed interest in the use of lungs from DCD [4] and in 1995 four types of donors were identified [5]. Nowadays several centers have developed a successful DCD program. Living-donor lobar lung transplantation has been promoted as an alternative for patients who are not going to survive the long waiting time for deceased donor lungs. It can be applied in both pediatric and adult patients when size matching is acceptable and appears to provide similar or better survival than conventional lung transplantation [6].

EVLP has been advocated as a technique to condition and assess lungs that are deemed unsuitable for transplantation or are recovered from marginal donors [7,8]. In this case we report the use of EVLP to condition lungs from a donation after circulatory death donor that seemed unsuitable for transplantation followed by a successful lung transplantation and urgent liver transplantation.

CASE REPORT

A 20 year old male underwent bilateral lung transplantation with lungs conditioned via EVLP. The donor was a 41 year-old women with a no medical history who became unwell at home. Computed tomography scan of the brain demonstrated an intracerebral bleeding with an infaust prognosis. The criteria for brain dead where not fulfilled and the patient was consented for DCD. However the arterial blood gas showed a PO_2 of 24,9 kPa after ventilation with a PEEP of 5 cmH_2O and a FiO_2 of 1.0 during 10 minutes. There were no obvious signs of pulmonary oedema on chest X-ray (Figure 7.1).

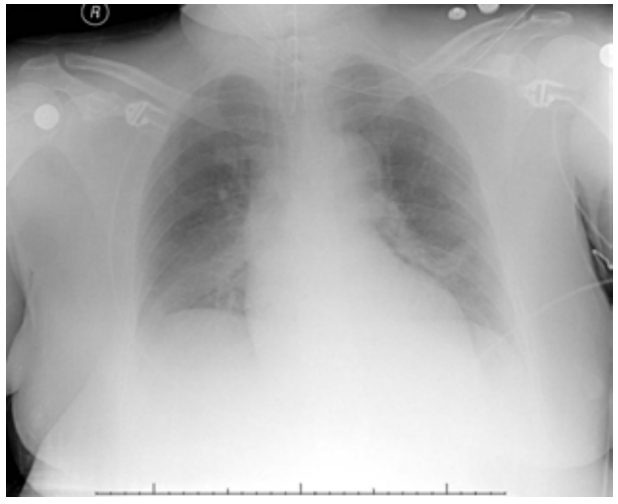

Figure 7.1: Donor chest x-ray with possible lung oedema in the lower lobes

Therefore it was decided to send a team to the donor hospital for evaluation. At procurement the lungs were a little bit heavy indicating pulmonary oedema, no other reason for poor function such as infection or atelectasis was observed (Figure 7.1, Figure 7.2A). After explantation the lungs were transported to the recipient hospital and evaluated ex vivo using the Lung Assist (Organ Assist BV, Groningen, The Netherlands) (Table 7.1). The system was primed with 1.5 l Steen solution. Reperfusion of the lungs was started, after retrograde flush of the tubing, with Steen solution at room temperature (20°C). The pulmonary artery flow was gradually increased up to a maximum calculated flow of 40% of the total cardiac output or a mean pulmonary artery pressure of 15 mmHg. When a temperature of 32°C was reached, ventilation was started with a FiO_2 0.4, a tidal volume of 7 ml/kg, a frequency of 7 breaths/min and a PEEP of 5 cmH_2O. Physiologic evaluation, with a tidal volume of 10 ml/kg, a frequency of 10 breaths/min and a FiO_2 1.0, was performed every hour and the function of the lungs was found to be excellent after 4 hours of EVLP (Table 7.2, Figure 7.2B). The lungs were then cooled to a temperature of 12°C and stored in buffered Perfadex (Table 7.1).

The recipient was a 20 year old male with cystic fibrosis (Figure 7.3A) and an Arnold Chiari malformation. He had hepatomegaly and splenomegaly with oesophageal varices and portal hypertension. Since 2010, there were several episodes of haemoptysis for which he received coilings of bronchial arteries. In September 2012 he was screened for liver- lung transplantation. Screening revealed a still reasonable liver function (MELD 8, CHILD B) and no signs of pulmonary hypertension. To serve him the best, he was accepted for combined transplantation. But, after weighing all options and possible problems, he was listed without liver transplantation to

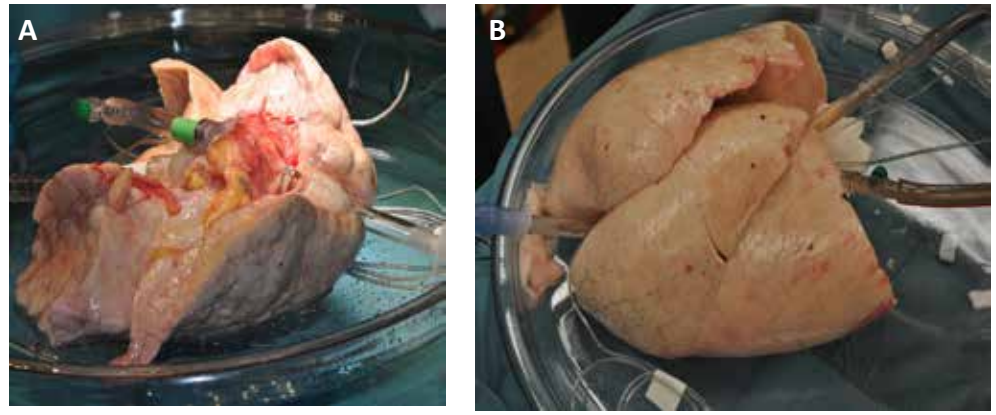

Figure 7.2: **A**: Donor lungs before the start of the EVLP. **B**: Donor lungs on the EVLP, at the end of the reperfusion.

increase the chance of a lung offer. In December 2012, he was listed for high urgency lung transplantation after a severe episode of untreatable haemoptysis (LAS only 33.95). Bilateral lung transplantation with the use of cardiopulmonary bypass was performed in January 2013. High peri-operative pulmonary pressures necessitated the use of NO ventilation. This was stopped 2 days later. Hereafter his respiratory function was stable with excellent blood gasses (Figure 7.3B).

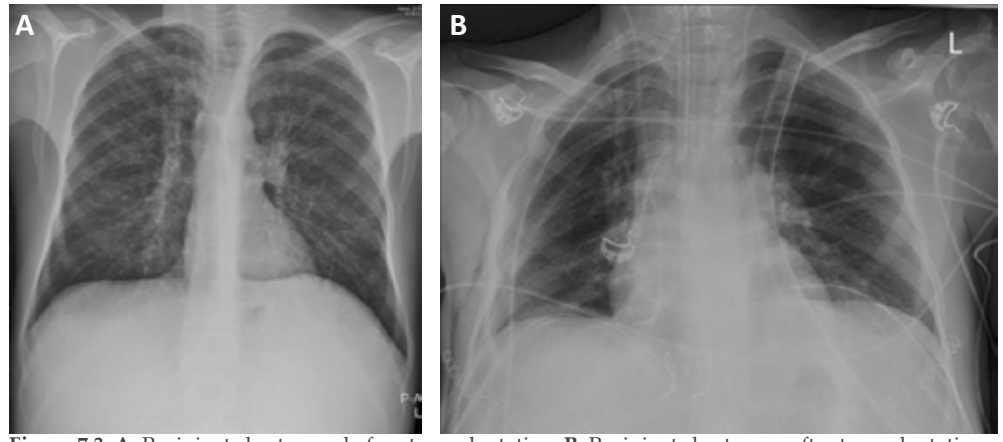

Figure 7.3: **A**: Recipient chest x-ray before transplantation. **B**: Recipient chest x-ray after transplantation

His post-operative stay on the intensive care unit was complicated. Blood analysis demonstrated progressive liver function deterioration (acute-on-chronic liver failure). Ultrasound of the liver showed a retrograde flow in the portal veins without thrombosis and ascites. Microbiological investigation of the ascites showed infection with Enterococcus faecium, which was treated with antibiotics. He was accepted for high urgency liver transplantation (MELD 38.5) and a full-size liver of a donation after brain death (DBD) donor was transplanted 19 days after his lung transplantation.

He developed acute tubular necrosis due to a hepatorenal syndrome and a systemic inflammatory response syndrome for which haemodialysis 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 non-invasive 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.

Table 7.1: Time schedule

Time	Action	
20:32	Switch off	
20:47	Hands off period (5 minutes)	Warm ischemia: 20 min
21:07 – 21:50	Flush with cold Perfadex and harvesting	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

Table 7.2: Functional parameters during EVLP

	1 hour	2 hours	3 hours	4 hours
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: peak airway pressure, Mean AwP: mean airway pressure, P/F ratio: ratio of partial pressure of arterial oxygen/fraction of inspired oxygen (1.0).

DISCUSSION

Hypothermic static organ preservation is used worldwide to preserve donor lungs. EVLP was recently developed as a tool for assessing lung viability and for conditioning of marginal and unacceptable donor lungs.

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 [8]. This protocol allows a 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]. Wierup et all. reported the assessment of rejected DBD lungs and concluded that all but one met the blood gas criteria [10]. In 2005 Steen and colleagues performed the first lung transplantation of a rejected donor lung after ex vivo evaluation [11]. Between 2005 and 2006 the same group evaluated nine DBD donor lungs of which 6 were transplanted [12]. Compared to standard donor lungs, there was no significant difference regarding time on the ventilator, ICU time, in ward time and total hospital stay [13]. Good results with the Steen protocol were also reported by Wallinder et al. [14]. Six pairs of rejected donor lungs were subjected to EVLP. Four double lung transplantations were performed after improvement of the PO_2. In one, EVLP succeeded to improve the oxygenation of the right but not of the left lung resulting in single lung transplantation. However in one, transplantation of right lung led to impaired blood gases and the intended double lung transplantation was converted into single lung transplantation.

The Toronto group describes 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 [7]. Recently, their experience with 50 EVLP's was published. Fifty-eight pair of lungs, 32 DBD and 26 DCD, were included in the EVLP trial and 50 out of 58 EVLP's 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 [15]. There technique is now used in several transplant centers. Aigner et al. reports the evaluation ex vivo of 13 DBD lungs resulting in 9 lung transplantations. Four lungs, from donors with a trauma history, deteriorated on the EVLP. Days on the ventilator, ICU stay, hospital stay and 30 day survival were comparable with patients receiving a standard lung transplantation

during the same time period [16]. Recently published results from the Harefield group reports EVLP assessment of 3 DCD and 9 DBD lungs. Six lungs (2 DCD and 4 DBD) reached the criteria for lung transplantation [17]. Outcomes were similar to that of other published studies. The Sao Paulo group showed good functional results after assessment of non-acceptable DBD lungs [18].

Assessment of donor lungs with this technique can safely be performed in another center than the donor or transplant center [19]. This might be a future perspective.

In this case report we describe the use of EVLP in an unsuitable DCD lung with PO_2/FiO_2 of 24,9 kPa. The Toronto protocol was used. However lungs were ventilated with a FiO_2 of 40% instead of 21%. After 4 hours of EVLP a PO_2/FiO_2 ratio of 59,7 kPa was reached and the lungs were accepted for transplantation.

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 extra-hepatic parameters should be considered when compared to chronic hepatic dysfunction [20]. 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 the reported case the liver had still a reasonable function at the time of screening. Although the recipient met the criteria for a combined procedure we hoped that the liver function would remain stable enough to survive the lung transplantation and might even improve after lung transplantation. This decision was based on the expected long waiting time for acceptable quality of organs for a combined procedure, almost excluding the possibility to use organs from a DCD donor since the risk for liver graft failure [21] and biliary complications [22] is high in a procedure with long ischemia times. Another argument for a staged procedure was the urgent need for lung transplantation. Also the technical difficulty during transplantation with a long ischemic time for the liver played a role. Unfortunately he developed an acute-on-chronic liver failure and was listed for an urgent liver transplantation.

This case report demonstrates that EVLP of unsuitable DCD lungs is feasible and that recent lung transplantation is not a contra-indication for urgent liver transplantation. Next to that LAS allocation is not suitable in case of combined transplantation.

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