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First experience with *ex vivo* lung perfusion for initially discarded donor lungs in the Netherlands: a single-centre study

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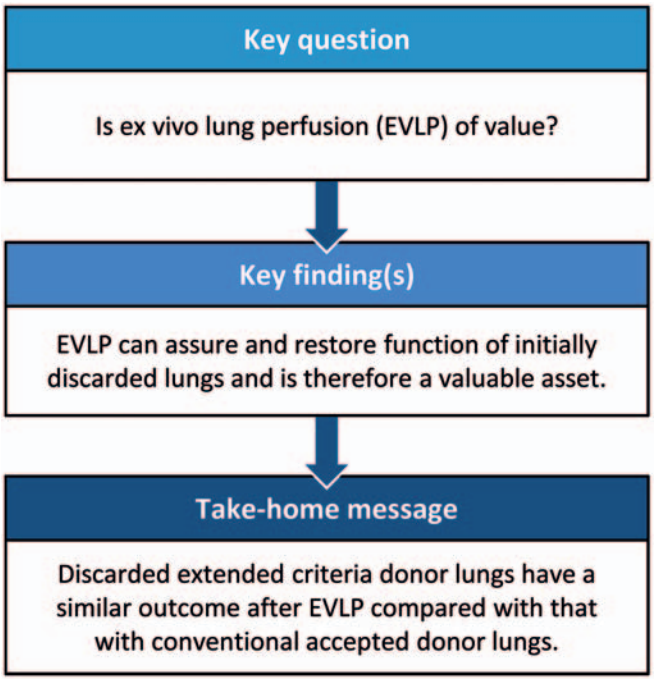
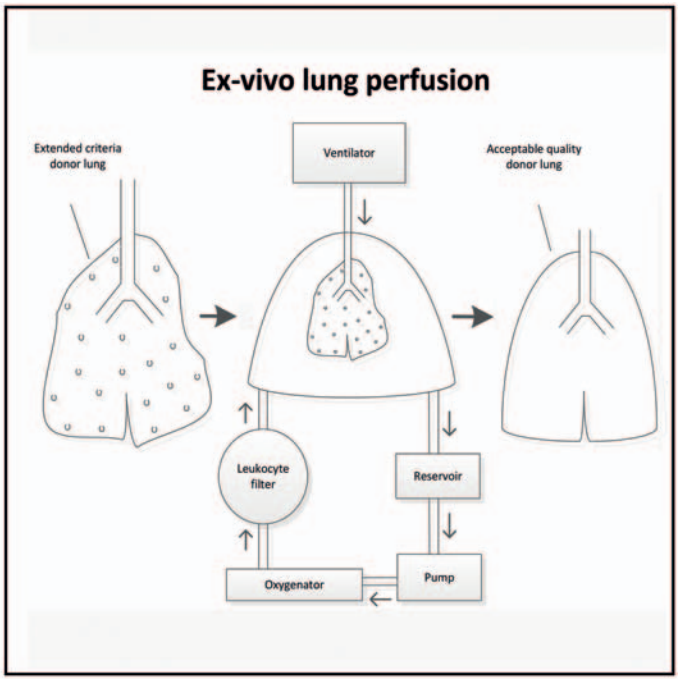




Abstract

OBJECTIVES: Despite progress in lung transplantation (LTx) techniques, a shortage of donor lungs persists worldwide. *Ex vivo* lung perfusion (EVLP) is a technique that evaluates, optimizes and enables transplantation of the lungs that would otherwise have been discarded. Herein, we present our centre's first EVLP experiences between July 2012 and June 2016, when we performed 149 LTxs.

METHODS: It was a single-centre, retrospective analysis of a prospectively collected database. The EVLP group ($n = 9$) consisted of recipients who initially received discarded donor lungs that were reconditioned using EVLP. The non-EVLP (N-EVLP) group ($n = 18$) consisted of data-matched patients receiving conventional quality lungs in the conventional way. Both groups were compared on primary graft dysfunction (PGD) grades 0–3, pulmonary function, chronic lung allograft dysfunction and survival.

RESULTS: In the EVLP group, 33% (3/9) developed PGD1 at 72 h post-LTx. In the N-EVLP group, 11% (2/18) developed PGD1, 6% (1/18) PGD2 and 11% (2/18) PGD3 at 72 h post-LTx. At 3 and 24 months post-LTx, forced expiratory volume in 1 s as percentage of predicted was

similar in the EVLP (78% and 92%) and N-EVLP groups (69% and 89%). Forced vital capacity as a percentage of predicted was comparable in the EVLP (77% and 93%) and N-EVLP groups (68% and 101%). Chronic lung allograft dysfunction was diagnosed in 1 N-EVLP patient at 2 years post-LTx. Three-year survival was 78% (7/9) (the EVLP group) vs 83% (15/18) (the N-EVLP group).

CONCLUSIONS: These results are in line with the existing literature suggesting that transplantation of the previously discarded lungs recovered by EVLP leads to equal outcomes compared to conventional LTx methods.

Keywords: *Ex vivo* lung perfusion • Donation after brain death • Donation after circulatory death • (Chronic) lung (allograft) function/dysfunction • Lung transplantation/pulmonology • Patient survival

INTRODUCTION

For many end-stage lung patients for whom therapeutic options have been exhausted, lung transplantation (LTx) has proved to be an effective treatment [1]. However, constant demand forced research to develop new techniques and expand transplantation criteria, such as using extended-criteria donor lungs, donation after circulatory death (DCD) and the recent development of *ex vivo* lung perfusion (EVLP) [2, 3]. This has led to an increase in the number of LTxs and median survival [4]. Despite these advancements, a shortage of donor lungs persists, resulting in a waiting list mortality of 10.2% in the Netherlands [5]. Aimed at increasing the number of donor lungs, the Netherlands approved the use of DCD donors awaiting circulatory arrest (so-called controlled DCD, cDCD) for lung donation in 2005 [6]. These cDCD organs are procured after withdrawal of life-sustaining cardiorespiratory support. In addition, an EVLP programme was established at the University Medical Center Groningen (UMCG) in 2012. Implementation of EVLP allows previously discarded lungs to be assessed and treated within the transplantation window [7]. A transplantation window that accepts up to 12 h of cold ischaemic time (CIT) was upheld. The lungs treated on EVLP have to reach certain parameters to be eligible for transplantation, such as PaO_2 of >50 kPa. To be eligible for EVLP, the lungs must have a persistent low PO_2 despite optimization of donor management. The lungs that improved at retrieval after ventilation with open sternum were not used for EVLP. Furthermore, the lungs with aspiration, infiltration, bleeding or severe contusion in combination with a low PO_2 were not considered for EVLP. The low PO_2 of the included EVLP lungs were mostly due to lung oedema in combination with persistent large areas of atelectasis. As a reference, rejection criteria for conventional LTx are a consistent PO_2 of <40 kPa, lung oedema, lung haemorrhage, massive contusion, bronchoscopic proven aspiration or evidence of lung infiltrate. The primary aim of EVLP is to test and improve donation after brain death (DBD) and cDCD lungs that have been rejected for conventional transplantation due to lung oedema and subsequent low arterial oxygen pressure (PaO_2). The purpose of this study is to compare the outcomes of implanted discarded extended criteria donor lungs optimized by EVLP to those of implanted conventional donor lungs.

METHODS

Study group

One hundred and forty-nine LTxs were performed in the UMCG between July 2012 and June 2016. During that period, 14 EVLPs were performed of which 10 were done using initially discarded lungs. Nine of these were transplanted. Each of these 9 EVLP lungs was matched with 2 conventional donor lungs, which resulted in a study group of 27 patients. By matching 1:2, we aimed to increase our statistical power, even with a limited number of EVLP cases. To minimize differences between the procedures, all cases were matched in time as close as possible with selection based on the recipients' underlying lung disease and donor type (DBD or cDCD). Both patient groups received conventional postoperative care, including maintenance immunosuppression with tacrolimus, mycophenolate mofetil and prednisolone. The study protocol was approved by the Medical Ethics Review Board of the UMCG.

Donor protocol

Donor lungs were offered through Eurotransplant. Donor lungs that met any of the following indications were included in the EVLP procedure: (i) the lungs with a PaO_2/fraction of inspired oxygen (FiO_2) <40 kPa at a positive end expiratory pressure (PEEP) of 5 cmH_2O and 100% oxygen with clinically evident lung oedema and (ii) the lungs that had a persistent low PaO_2/FiO_2 <40 kPa after active lung recruitment without a clear reason (e.g. atelectasis). Donor lungs with any of the following were excluded from EVLP: pneumonia or persisting purulent secretions at bronchoscopy; significant lung trauma with bleeding or consolidation due to severe contusion; inadequately treated infection; aspiration; malignancy; HIV, persistent hepatitis B or C; lung diseases; and sepsis. Donor procedures were performed in the conventional manner in which an antegrade flush was first performed with Perfadex (50 ml/kg bodyweight; XVIVO Perfusion, Göteborg, Sweden). Subsequently, lung explantation was performed and followed by a retrograde flush with Perfadex until clear effluent on the back table. For cDCD donors, circulatory arrest was defined as the absence of peripheral pulsations and had to occur within 90 min after withdrawal of treatment [6]. For warm ischaemic time, a maximum of 60 min was adhered, defined as the time between circulatory arrest and start of antegrade flush [6].

Recipient selection

All recipients on our waiting list were candidates for both DBD and cDCD LTxs. Every recipient who signed an informed consent could have received an EVLP lung. Allocation was based on the Eurotransplant lung allocation score (LAS 0–100) [8]. Based on current medical information of the patient, such as type of lung disease and ability to perform daily tasks, a calculation is made. This calculation gives insight in the medical situation, and it also represents the chance of success in case of transplantation. All the LAS scores between 0 and 50 are considered as the low LAS scores, and medical information of these cases must be updated after 180 days. All scores of 50 or higher are considered high LAS

scores, and medical information of these cases must be updated every 14 days.

Ex vivo lung perfusion protocol

The lungs were placed in a perfusion dome (XVIVO Perfusion). Lung cannulas (XVIVO Perfusion) were sewn to the left atrium (LA) and the pulmonary artery. After opening the trachea, any secretions present were aspirated, and an endotracheal tube was placed and fixated. The LA cannula was then connected and deaired, and a retrograde flush (100 ml/min) was started until the outflowing perfusate became clear. Subsequently, the pulmonary artery cannula was connected, deaired and antegrade perfusion was started. During the procedure, maximum flow was set at 40% of the calculated cardiac output, in accordance with the Toronto Protocol [7]. The LA pressure (LAP) was maintained between 3 and 5 mmHg by changing the height difference between the lungs and reservoir. Ventilation was started when the outflowing perfusate temperature reached 32°C. A lung-protective ventilation strategy was applied, in which ventilation parameters were gradually increased over 10 min until a frequency of 7 breaths/min, a tidal volume of 7 ml/kg of donor bodyweight, a maximum airway pressure of 20 cmH_2O, a PEEP of 5 cmH_2O and an FiO_2 of 40% was reached.

Recruitment, if necessary, was performed by temporarily increasing the PEEP to 10 cmH_2O to optimize ventilation in the lungs and to achieve homogenous inflation and deflation. Perfusion was set to a maximum pulmonary artery pressure (PAP) of 15 mmHg, and if the calculated perfusion flow was not reached within this pressure limit, the lungs were rejected. If necessary, bronchoscopy was done to aspirate the sputa. The Lung Assist (Organ Assist BV, Groningen, the Netherlands) was used as perfusion machine. For ventilation, an Oxylog 3000 (Dräger BV, Zoetermeer, the Netherlands) was used. The circuit consisted of a reservoir, a leucocyte filter and an oxygenator. The system was primed with 2 l of STEEN solution (XVIVO Perfusion) and supplemented with heparin, cefuroxime and dexamethasone. STEEN solution is a crystalloid, buffered, extracellular solution containing human serum albumin and dextran 40 to provide an optimal colloid osmotic pressure.

Ex vivo evaluation

Lung quality was evaluated every hour for 4 h. The perfusate was deoxygenated with a gas mixture of 86% N_2, 8% CO_2 and 6% O_2, which was started 10 min before evaluation at a flow rate of 1–2 l/min. During evaluation, FiO_2 was set at 100%, tidal volume at 10 ml/kg of donor bodyweight and respiratory frequency at 10/min. Target parameters during pulmonary function evaluation were oxygenation capacity (PaO_2/FiO_2) >50 kPa; pulmonary vascular resistance (pulmonary vascular resistance = PAP-LAP/pump flow): decline <15% compared to baseline; peak airway pressure: decline <15% compared to baseline; and clinical suitability for transplantation. In general, if one or more of these criteria were not met, the lungs were discarded.

Baseline characteristics

Collected donor variables included age, gender, duration of mechanical ventilation, cause of death, smoking history, estimated total lung capacity, cDCD or DBD procedure and preretrieval PaO_2 after a minimum of 10 min of ventilation with 100% oxygen and a PEEP of 5 cmH_2O. Moreover, ischaemic times and duration of EVLP were registered. In recipients, the following variables were included: age, gender, LTx urgency, bilateral LTx, primary or secondary LTx, the need for extracorporeal circulation during transplantation, intensive care unit (ICU) stay, hospital stay and underlying diagnosis. The first CIT (CIT1) was defined as the time between the cross-clamp and the start of EVLP. The second CIT (CIT2) was defined as the moment the lungs were cooled on EVLP until the reperfusion of the last implanted lung [9]. We defined a total preservation time (TPT) from the cross-clamp to the reperfusion of the second lung in the EVLP group, including CIT1, EVLP time and CIT2. In the non-EVLP (N-EVLP) group, TPT only included CIT (time between the cross-clamp and the start of the last implanted lung reperfusion).

End points

End points were primary graft dysfunction (PGD), pulmonary function, chronic lung allograft dysfunction (CLAD) and survival. PGD was only assessed at 48 and 72 h post-LTx (T48 and T72) to better discriminate for mortality [10, 11]. The PGD grades 0–1 (PGD0 and PGD1) were representative for adequate graft function. The PGD grades 2–3 (PGD2 and PGD3) represented compromised graft function [10]. Forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) as a percentage of predicted (FEV_1% and FVC%, respectively) were used to assess the pulmonary function. CLAD was defined as a persistent (≥3 months) decline in pulmonary function, expressed as FEV_1 <80% of baseline (average of the 2 best post-LTx values for FEV_1 obtained ≥3 weeks apart) [12]. The cut-off for post-LTx follow-up was 3 years.

Statistical analysis

Normally distributed continuous variables were analysed using the Student's *t*-tests. The Mann–Whitney *U*-tests were performed to compare non-normally distributed data. All data are expressed as mean ± standard deviation or as median and range, unless stated otherwise. For nominal variables, either the χ^2 test or the Fisher's exact test was used; variables are expressed in percentages and numbers. Overall survival and CLAD cases were visualized using the Kaplan–Meier method. Comparisons between groups were made using a log-rank test. No correction for multiple comparisons at different time points was performed. A statistical difference of *P*-value <0.05 was considered significant. All calculations were performed using the IBM SPSS Statistics 21.0 software (IBM Corp., Armonk, NY, USA).

RESULTS

The lungs of an 18-year-old donor were put on EVLP as doubts had arisen during quality assessment at retrieval. During EVLP, criteria were not met due to increasing lung oedema and ventilation peak pressures >30 cmH_2O in the first hour. Therefore, the lungs were not transplanted. Three conventional quality lungs were installed on EVLP for logistical reasons and, therefore, excluded from this study. The remaining 10 initially discarded lungs were evaluated on EVLP: 8 due to low PaO_2 and lung oedema, 1 with a low PaO_2 due to persistent atelectasis and 1

Table 1: Donor characteristics

	EVLP ($n = 9$)	N-EVLP ($n = 18$)	*P*-value
Age (years)	41 ± 12.7	52 ± 16.3	0.083
Female gender	56 (5)	50 (9)	1.00
cDCD	33 (3)	39 (7)	1.00
TPT (h)	15.7 ± 1.8	7.9 ± 2.7	<0.001
EVLP (h)	4 (3.5–4.2)		
Total CIT (h)	12.0 ± 1.4	7.9 ± 2.7	0.001
CIT1	4.3 ± 0.6	7.9 ± 2.7	<0.001
CIT2	7.7 ± 1.5		
Agonal phase time (min)	13 ± 2.6	15.3 ± 7.9	0.65
Warm ischaemic time (min)	19.3 ± 1.2	19.3 ± 6.9	0.99
Predicted TLC (l)	6.8 ± 0.8	6.8 ± 0.6	0.97
Time on ventilator (days)	4 (2.5–5.5)	4 (2–7)	0.66
PaO_2 at FiO_2 100% (kPa)	38.1 ± 13.3	60.2 ± 7.9	<0.001
Smoking history	44 (4)	44 (8)	1.00
Cause of death			
SAB	33 (3)	17 (3)	0.37
CVA	22 (2)	33 (6)	0.68
Cerebral anoxia	22 (2)	11 (2)	0.58
Trauma	11 (1)	17 (3)	1.00
SDH	0 (0)	11 (2)	0.54
Primary brain tumour	0 (0)	6 (1)	1.00
Miscellaneous	0 (0)	6 (1)	1.00

Data are presented as percentages (n), mean ± SD or median (IQR).

CIT: cold ischaemic time; CIT1: period between cross-clamp up to start EVLP; CIT2: period between cooling on EVLP up to reperfusion of last implanted lung; CVA: cerebral vascular accident; cDCD: controlled donation after circulatory death; EVLP: *ex vivo* lung perfusion (group); FiO_2: fraction of inspired oxygen; IQR: interquartile range; N-EVLP: conventional lung transplantation without EVLP-group; PaO_2: pre-retrieval arterial oxygen pressure; SAB: subarachnoid bleeding; SD: standard deviation; SDH: subdural haematoma; predicted TLC: predicted total lung capacity; TPT: total preservation time.

due to severe lung oedema although maintaining good PaO_2. The latter did not improve during EVLP and was discarded accordingly. This resulted in our group of 9 LTxs post-EVLP. Donor age in the EVLP group tended to be lower, although this was not statistically significant. The mean duration of EVLP was 3.8 ± 1.0 h (median 4.0 h). The EVLP group had an average total CIT (equals CIT1 + CIT2) of 12.0 ± 1.4 h compared to 7.9 ± 2.7 h total CIT in the N-EVLP group ($P = 0.001$). The EVLP group had a CIT1 of 4.3 ± 0.6 h and a CIT2 of 7.7 ± 1.5 h on average, and TPT was 15.7 ± 1.8 h (Table 1, donor characteristics). The preretrieval PaO_2 in the EVLP group (38.1 ± 13.3 kPa) was significantly lower compared to conventional donor procedure lungs (60.2 ± 7.9 kPa, $P < 0.001$). Thirty-three percent of the EVLP group and 39% of the N-EVLP group were cDCD donors.

Recipient characteristics

The average age of patients was 53 years in the EVLP group and 50 years in the N-EVLP group. The majority (66.7%, 18/27) had chronic obstructive pulmonary disease as LTx indication. Additionally, all recipients were primary lung recipients and received bilateral transplants. Characteristics did not significantly differ (Table 2).

Survival

No significant difference in survival was observed between the 2 groups ($P = 0.73$) (Fig. 1). In the EVLP group, 2 recipients died during follow-up. One recipient died following candida empyema with subsequent pulmonary haemorrhage and hypovolemic shock (1 month post-LTx), and 1 recipient died due to metastatic lung cancer without evidence of a primary tumour in the implanted lungs (31 months post-LTx); this was most likely a lung carcinoma originating from the recipient. Of the total 135 recipients of conventional lungs, 22 (16.3%) patients died during the 36-month follow-up; 3 (16.7%) of these deaths were part of the 18 conventional/N-EVLP study cases in this study. One recipient died of brain herniation with meningitis (4 months post-LTx), 1 recipient died from respiratory insufficiency caused by lung fibrosis development post-LTx (23 months post-LTx) and 1 recipient died of urosepsis (26 months post-LTx).

Table 2: Recipient characteristics

	EVLP ($n = 9$)	N-EVLP ($n = 18$)	*P*-value
Age (years)	53 ± 13.3	50 ± 9.5	0.12
Female gender	56 (5)	56 (10)	1.00
Primary LTx	100 (9)	100 (18)	1.00
ECC use	33 (3)	33 (6)	1.00
ICU stay (days)	11 (4–26)	5.2 (3–13)	0.21
Hospital stay (days)	31 (27–46)	42 (25–50)	0.64
Diagnosis			
COPD	67 (6)	67 (12)	1.00
CF	22 (2)	22 (4)	1.00
Fibrosis	11 (1)	11 (2)	1.00

Data are presented as percentages (n), mean ± SD or as median (IQR).

CF: cystic fibrosis; COPD: chronic obstructive pulmonary disease; ECC: extracorporeal circulation; EVLP: *ex vivo* lung perfusion (group); ICU stay: intensive care unit stay; IQR: interquartile range; LTx: lung transplantation; N-EVLP: conventional lung transplantation without EVLP-group; SD: standard deviation.

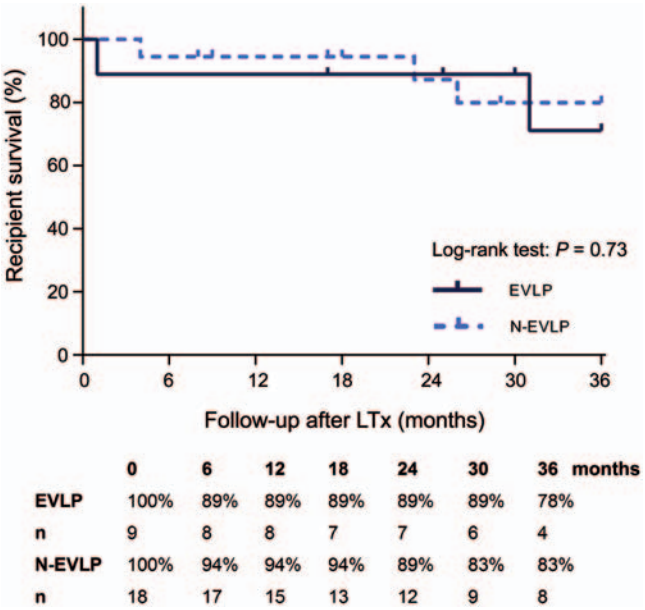


Figure 1: Survival curve of the EVLP and N-EVLP LTx recipients. EVLP: *ex vivo* lung perfusion; LTx: lung transplant; N-EVLP: non-EVLP.

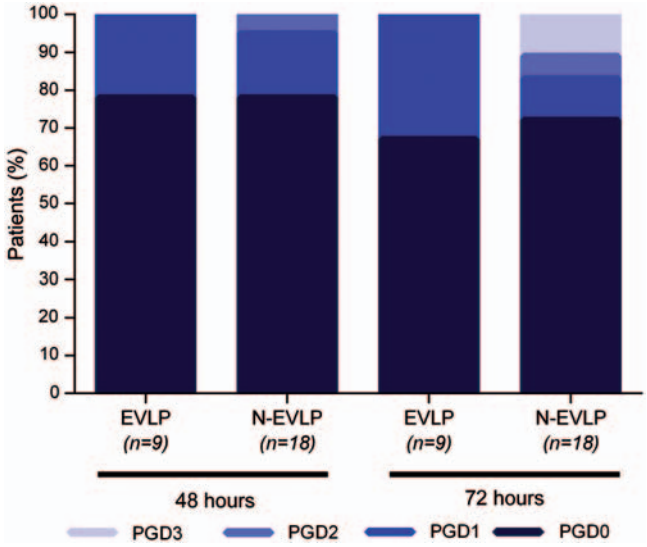
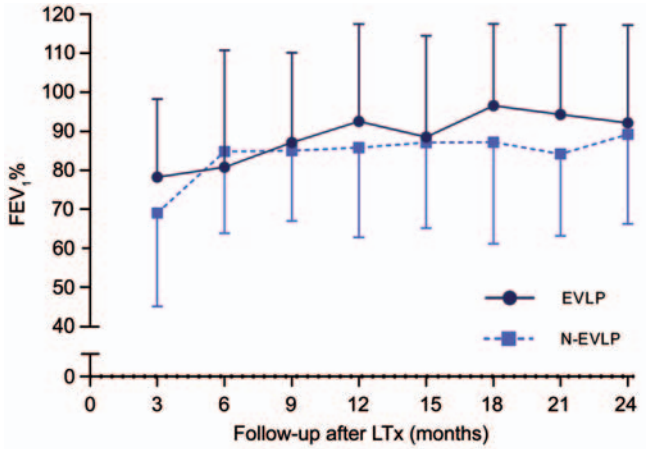


Figure 2: PGD grades 0–3 at 48 h (T48) and 72 h (T72) post-transplantation in the EVLP and N-EVLP groups. Percentages of the recipients in each PGD grade at different time points are shown. EVLP: *ex vivo* lung perfusion; N-EVLP: non-EVLP; PGD: primary graft dysfunction.

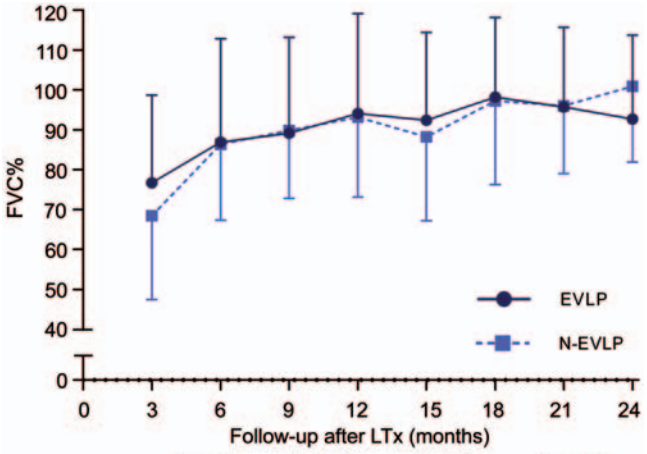


	3 months	6 months	9 months	12 months
EVLP FEV_1%, (n)	78% ± 20, (8)	81% ± 30, (8)	87% ± 23, (8)	93% ± 25, (8)
N-EVLP FEV_1%, (n)	69% ± 24, (18)	85% ± 21, (17)	85% ± 18, (16)	86% ± 23, (15)
	15 months	**18 months**	**21 months**	**24 months**
EVLP FEV_1%, (n)	89% ± 26, (8)	97% ± 21, (7)	94% ± 23, (7)	92% ± 25, (6)
N-EVLP FEV_1%, (n)	87% ± 22, (15)	87% ± 26, (13)	84% ± 21, (11)	89% ± 23, (9)

Figure 3: The mean forced expiratory volume in 1 s as a percentage of predicted (FEV_1%) in the EVLP and N-EVLP groups post-LTx is presented. The number (*n*) of patients at risk at every time point is presented. Data are presented as percentages (*n*), mean ± SD or median (IQR). EVLP: *ex vivo* lung perfusion; IQR: interquartile range; LTx: lung transplantation; N-EVLP: non-EVLP; SD: standard deviation.

Primary graft dysfunction

PGD differences were non-significant. Neither PGD2 nor PGD3 was observed in the EVLP group at either T48 or T72. In the EVLP group, PGD1 was observed in 22% of patients (2/9) at T48, with an increase to 33% (3/9) at T72 (Fig. 2). In the N-EVLP group, 6% (1/18) of patients had PGD2, at both T48 and T72. PGD3 was observed in 11% of patients (2/18) at T72. Additionally, PGD1 decreased from 17% (3/18) at T48 to 11% (2/18) at T72.



	3 months	6 months	9 months	12 months
EVLP FVC%, (n)	77% ± 22, (8)	87% ± 26, (8)	89% ± 24, (8)	94% ± 25, (8)
N-EVLP FVC%, (n)	68% ± 21, (18)	86% ± 19, (17)	90% ± 17, (16)	93% ± 20, (15)
	15 months	**18 months**	**21 months**	**24 months**
EVLP FVC%, (n)	92% ± 22, (8)	98% ± 20, (7)	96% ± 20, (7)	93% ± 21, (6)
N-EVLP FVC%, (n)	88% ± 21, (15)	97% ± 21, (13)	96% ± 17, (11)	101% ± 19, (9)

Figure 4: The mean FVC% of the EVLP and N-EVLP groups post-LTx. The number (*n*) of patients at risk at every time point is presented. Data are presented as percentages (*n*), mean ± SD or median (IQR). EVLP: *ex vivo* lung perfusion; FVC%: forced vital capacity as a percentage of predicted; IQR: interquartile range; LTx: lung transplantation; N-EVLP: non-EVLP; SD: standard deviation.

Pulmonary function

In the EVLP group, the mean FEV_1% changed from 78% to 92% between 3 and 24 months post-LTx compared to 69–89% in the N-EVLP group ($P = 0.62$.). The mean FVC% in the EVLP group changed from 77% to 93% between 3 and 24 months, compared to 68% and 101% in the N-EVLP group ($P = 0.39$) (Figs 3 and 4).

Chronic lung allograft dysfunction

During 3 years of follow-up, 1 N-EVLP case was diagnosed with CLAD at 24 months post-LTx ($P = 0.45$).

DISCUSSION

This study reports the first experiences with EVLP in the Netherlands. Our results did not present any significant differences in PGD, pulmonary function, CLAD or survival between our 2 groups.

Using our strategy of only accepting the lungs with oedema or the lungs that should be of good quality but have an unexplainably low PaO_2 for EVLP, we achieved a favourable conversion rate of 90% (9 of 10). Established conversion rates vary between 34% and 97% (Table 3). Because of the high cost of EVLP and the extra demands it places on personnel, we might have been more selective in accepting the lungs as compared to other EVLP lung transplant centres. With more centres starting to use EVLP, it is important to note that extended criteria lungs can still be successfully transplanted without EVLP [21]. This includes the lungs with a PO_2 of <40 kPa [22]. However, in those cases, one might imagine that there is a smaller comfort zone in accepting and using extended criteria lungs.

Table 3: Overview of the study results in the literature

Group	UMCG (present study)		Sage *et al.* [13]		Wallinder *et al.* [14]		Fisher *et al.* [15]		Boffini *et al.* [16]		Henriksen *et al.* [17]		Valenza *et al.* [18]		Sanchez *et al.* [19]		Tikkanen *et al.* [20]
Method	Toronto		Toronto		Lund + red blood cells		Toronto + Lund		Toronto		Lund + red blood cells		Toronto		Toronto		Toronto
Year	2017		2014		2016		2016		2014		2014		2014		2014		2014
EVLP grafts transplanted	9		31		27		18		8		7		7		42		63
Control grafts transplanted	18		81		145		184		28		36		28		42		340
Conversion rate	90%		97%		84%		34%		73%		88%		88%		55%		86%
	EVLP	N-EVLP	EVLP	N-EVLP	EVLP	N-EVLP	EVLP	N-EVLP	EVLP	N-EVLP	EVLP	N-EVLP	EVLP	N-EVLP	EVLP	N-EVLP	EVLP	N-EVLP
PGD3 T72 (%)	0	11	9.50	8.50	14[a]	12[a]	27.80	22.50	0	25	NA	NA	28	32	9[b]	4[b]	NA	NA
Single LTx (%)	0	0	0	0	19	22	11.10	13	0	43	NA	NA	14	50	NA	NA	23.80	13.20
ICU stay (days)	11	5	9	6	4	3	NA	NA	NA	NA	7	NA	10	5.5	3	2.5	NA	NA
Hospital stay (days)	31	42	37	28	NA	NA	NA	NA	NA	NA	39	NA	NA	NA	13	11	NA	NA
1 year survival (%)	89	94.40	93.30	91.50	92	79	67	80	NA	NA	NA	NA	71[c]	86[c]	90	95	79	85
CLAD (%)	0[d]	5.6[d]	NA	NA	11	19	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

[a]PGD > 1.
[b]At any time point.
[c]400 days.
[d]After 2 years.
CLAD: chronic lung allograft dysfunction; EVLP: *ex vivo* lung perfusion; hospital stay; ICU: intensive care unit; LTx: lung transplantation; NA: not available; N-EVLP: non-EVLP; PGD3: primary graft dysfunction category 3; UMCG: University Medical Center Groningen.

Of great interest was the observation that our EVLP lungs did not develop PGD3. PGD is an acute lung injury that can arise in transplanted lungs within the first 72 h post-LTx [10]. Since the standardization of PGD in 2005, studies have shown that PGD3 occurrence at T72 compared to PGD0 at T72 leads to significantly higher risk of 30-day mortality [11, 23]. Diamond *et al.* [23] also showed that PGD3 at T48 or T72 after regular LTx was associated with increased mortality in the first 90 days compared to PGD0 (23% vs 5%, $P < 0.001$), as well as a higher 1-year mortality (34% vs 11%, $P < 0.001$). Various studies report differences in PGD3 incidence within the same groups (EVLP or N-EVLP) (Table 3). For example, Boffini *et al.* [16] had a PGD3 percentage of 0% at T72 post-LTx (the EVLP group) but others as high as 28% [18]. Considering that PGD3 at T72 tends to be higher in a conventional single LTx, we hypothesized this might be due to the difference in the number of single LTxs in each study. This tendency could be explained by the influence of the native lung on PGD grading through ventilation–perfusion mismatch, as reported by Oto *et al.* [24]. This mismatch may lead to worse PGD grades but yields equal results in ICU stay and survival. Studies indeed appeared to have an incidence of PGD3 numerically related to the number of single LTxs in each group (Table 3). As PGD3 is strongly correlated with early post-transplant mortality, we propose to correct for single and bilateral LTxs in future EVLP studies to more precisely value EVLP [25].

Another important finding was that prolonged out-of-body times with increased CIT using EVLP was not harmful. This was shown by the absence of PGD3 at T48 and T72 post-LTx in the EVLP group, despite the fact that the EVLP group had significantly longer CIT and TPT (total CIT = 12 h and TPT = 15.7 h) compared to our N-EVLP group (7.9 h CIT/TPT). Our results were comparable to a study by Yeung *et al.* [26], in which they split their cohort of 906 patients into 2 groups: TPT > 12 h ($n = 97$ of which 95% underwent EVLP) and TPT < 12 h ($n = 809$ of which 5% underwent EVLP). PGD3 at T72 post-LTx was 10% in both of their groups. Although each phase (CIT1, EVLP and CIT2) was significantly longer for their EVLP lungs in the TPT > 12 h group compared to their EVLP lungs in the TPT < 12 h group, the results of these EVLP lungs (PGD grade, ICU stay, hospital stay and survival) did not show significant differences. In our study, TPT and total CIT in the EVLP group were both ≥12 h, whereas TPT (which equals total CIT) in the N-EVLP group was 7.9 h. Arango Tomas *et al.* [27] found a greater PGD risk (36% PGD3 at 72 h) and higher 1-year mortality (45%) to be associated with CIT2 > 5 h. Interestingly, all our CIT2 times were ≥6 h and 25 min, so prolonged CIT time in our group did not impair outcome. We speculate that non-apparent protocol differences, such as the ventilation strategy during EVLP, might cause these differences in outcome.

When considering our 12-month survival and trends in the FEV_1% and FVC% function over 24 months post-LTx, the EVLP group again showed good performance. This finding is comparable to what Fisher *et al.* [15] presented on their FEV_1% results over 12 months: at 3 months post-LTx, both the EVLP and the N-EVLP groups had an FEV1% of 71%. At 12 months, this increased to 93% for the EVLP group and 78% for the N-EVLP group. Our FEV_1% increased from 78% to 93% in the EVLP group and from 69% to 86% in the N-EVLP group at 12 months post-LTx. The FVC% presented in the study by Fisher *et al.* increased by 20% (the EVLP group) and 31% (the N-EVLP group). Our FVC% at 3 months in the EVLP and N-EVLP groups were 77% and 68%, which increased to 94% (17% increase) and 93% (25%

increase) at 12 months post-LTx, respectively (Fig. 4). As this was our first experience with EVLP, the selection of the lungs was executed with a high level of caution, focusing on the lungs that would offer the best chance of improvement.

Limitations

Our relatively strict selection criteria may be a limitation of this study. Another limitation may have been the small sample size, as well as our learning curve with EVLP, even though no differences were noticeable between the earlier and later EVLP cases.

CONCLUSION

In conclusion, this study describes the Dutch experiences with EVLP over the recent 4 years. By accepting discarded lungs for EVLP, the addition of this single-centre EVLP procedure increased the number of LTxs by 6.4% (9 EVLP/149 LTxs). Despite the small number of EVLPs performed, these yielded excellent results in terms of PGD, pulmonary function and survival. We conclude that EVLP provides a reliable platform to evaluate LTx suitability of donor lungs with oedema and/or bad oxygenation.

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