Review Article

Ex vivo lung perfusion prior to transplantation: an overview of current clinical practice worldwide

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Abstract: Lung transplantation is a lifesaving treatment in numerous forms of end-stage lung disease but organ shortage remains nowadays his biggest issue. Ex vivo lung perfusion (EVLP) has recently emerged as a solution to this problem and begins to be accepted is clinical practice. In this review, we will focus on his experience worldwide. We would like to describe the technique and the criteria used to select the donors and the transplantable lungs. We will also browse the acceptance rate described in literature as well as numerous other aspects of this new tool.

Keywords: Lung transplantation; machine organ perfusion; ex vivo lung perfusion (EVLP)

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Introduction

Since its first description in 1963 (1), lung transplantation is now accepted as a life-saving treatment in numerous forms of end-stage lung disease. But since the beginning of the experience, organ shortage has always been an issue. The large gap between patients waiting for transplant and the number of available lungs is responsible for a mortality rate on the waiting list of up to 30% (2).

Acceptance of extended-criteria donors, donation after circulatory death (DCD) donors, and single-lung and lobar lung transplantation have been the first responses to address the problem of organ shortage. Recently, a new solution has emerged in an effort to augment the number of acceptable lungs: ex vivo lung perfusion (EVLP). After procurement and cold flush, lungs are cannulated on an isolated circuit while perfused and ventilated at normothermia for several hours prior to transplantation. Compared to cold storage (CS) as the gold standard for lung preservation nowadays, EVLP permits continued evaluation, transportation, and reconditioning of the organ. The decision to transplant the lungs may be delayed until after final multidisciplinary evaluation. The lung transplant community is hopeful that EVLP in the future offers a platform to even repair lungs by immunomodulation or gene therapy, as a technique to prevent ischemia-reperfusion injury and primary graft dysfunction (PGD) (3).

In this article, we will focus on the worldwide experience with EVLP. We systematically reviewed all series reported in literature and aimed to compare these papers with regards to the technique and protocol used, inclusion and exclusion criteria of donors and recipients, lung acceptance rate after EVLP and reported outcome after transplantation.

General considerations

EVLP is a relatively new technique. The first center utilizing this new technology was the group of Stig Steen in Lund, Sweden in 2006 (4). The group of Toronto has

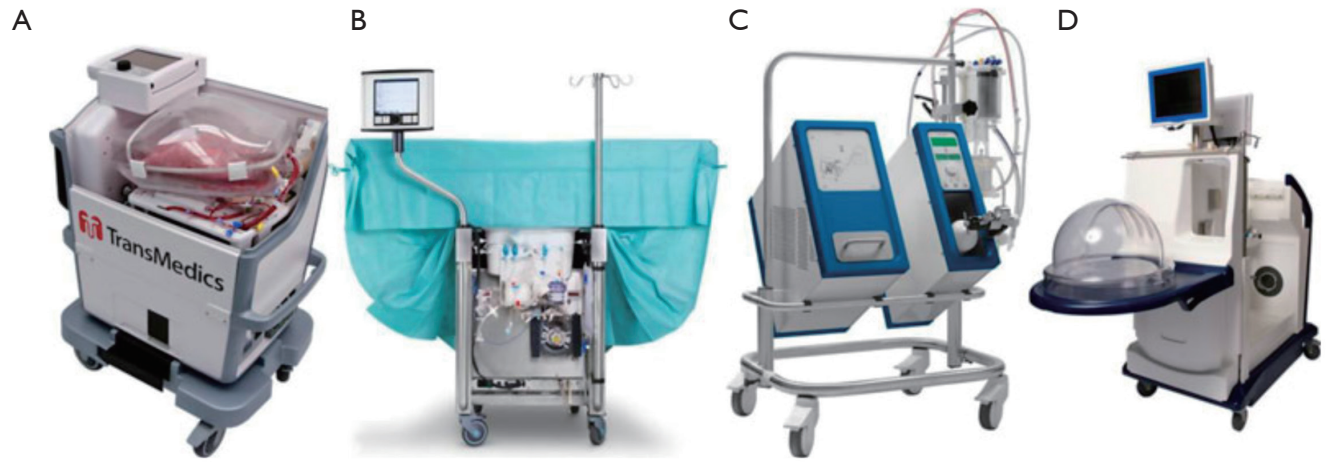

Figure 1 EVLP machines. Commercial devices for *ex vivo* lung perfusion. (A) OCSTM Lung (Transmedics); source: www.transmedics.com. (B) Vivoline LS1 (Vivoline Medical); source: www.vivoline.se. (C) Lung Assist (Organ Assist); source: www.organ-assist.nl. (D) XPSTM (XVIVO Perfusion AB); source: www.xvivoperfusion.com. EVLP, ex vivo lung perfusion. Reprinted from Van Raemdonck *et al.* (14) with permission.

thereafter largely contributed to the spreading of the technique worldwide, publishing their own technique and the first reports on its large-scale utilization (5-7). After extensive research, we identified 30 publications from 24 centers in 14 countries: UK, Canada, Australia, USA, Spain, Belgium, Brazil, Denmark, Germany, France, Sweden, Iran, Italy and Austria. This represent about 550 donors in whom the lungs were evaluated on an EVLP device. Papers from Iran (8) and Brazil (9,10), however, only described experience with lung cannulation and reconditioning on the EVLP circuit, but no transplantation followed. Their technique and results therefore will not be discussed in the present review.

Only two papers reported on a randomized control trial: INSPIRE trial (11) and VIENNA trial (12). The other 26 papers were retrospective controlled or prospective single-arm studies. The outcome of three others trials are still awaited (NOVEL, EXPAND and PERFUSIX trial) with interim results already presented at international meetings (13).

Technique

Four commercial systems are available on the market nowadays (*Figure 1*): OCS™ Lung (Transmedics, Andover, USA), Lung Assist™ (Organ Assist, Groningen, The Netherlands), XPS™ and LS™ (XVIVO, Göteborg, Sweden). In addition to these devices, some centers are using their own home-made system. Clinical experience with transplantation after EVLP using these devices has been published so far, even for the Lung Assist™ recently (15). Details of the technical aspects and functioning of all EVLP devices is beyond the scope of this review (*Table 1*). We would like to focus on some critical steps.

Basically, there are three EVLP protocols currently used worldwide: Toronto, Lund, and Organ Care System™ (OCS, Transmedics, Andover, MA, USA). These protocols differ by the perfusate used, target flow, pulmonary arterial pressure, left atrial pressure, and ventilatory settings.

Interestingly, some centers have reported a modification to these protocols. For example, in the DEVELOP-UK trial (16), the technique used for the first 22 donor lungs was a hybrid Toronto/Lund technique. The left atrium was left open, the perfusate was acellular and the flow was limited to 40% to 60% of donor cardiac output. After preliminary results in the first 22 EVLP patients and given the high number of extracorporeal support needed after transplantation, the investigators decided to switch entirely to the original Lund technique. At that time, the experience worldwide with the Vivoline device and the Lund protocol was growing and the hope was great that this would boost the conversion rate of lungs transplanted after EVLP reported to be >80% in other series.

The Gothenburg group (17-19) used the Lund technique, but included lots of minor differences (such as use of more careful ventilation and perfusion parameters during the reconditioning phase) derived from their own experiments.

Table 1 Techniques of EVLP

Parameter	Toronto	Lund	OCS*
Perfusion			
Target flow	40% CO	100% CO	2.0–2.5 L/min
PAP	Flow dictated	≤20 mmHg	≤20 mmHg
LA	Closed	Open	Open
Perfusate	Steen™ solution	Steen™ solution + RBCs hct 14%	OCSTM solution + RBCs hct 15–25%
Ventilation			
Start temp (°C)	32	32	34
Tidal volume (mL/kg bw)	7	5–7	6
RR (bpm)	7	20	10
PEEP (cmH_2O)	5	5	5–7
FiO_2 (%)	21	50	12

*, OrganCareSystem™ (Transmedics). EVLP, ex vivo lung perfusion; CO, cardiac output; FiO_2, inspired fraction of oxygen; hct, hematocrit; bw, body weight; LA, left atrium; PAP, pulmonary artery pressure; RBCs, red blood cells; bw, body weight donor; bpm, breaths per minute; RR, respiratory rate; PEEP, positive end-expiratory pressure; Temp, temperature. All parameters are listed for perfusion in steady state (preservation); values may vary during monitoring of the graft.

In total we counted 5 centers using the Toronto technique, 6 using the Lund technique, and 24 using OCS method. As already stated, some centers modified the originally described procedure to their own experience. Importantly, the vast majority of these reports didn't provide enough details to perform a real comparison between the procedures (*Table 2*).

Criteria for transplantation after EVLP (*Table 3*)

Most teams use the following combination of acceptance criteria after reconditioning to decide if the lungs are suitable for transplantation:

- ❖ Gas exchange at end of evaluation phase: several strategies are reported.
  - PaO_2/FiO_2 >350 mmHg with PaO_2 being measured in blood sample from the left atrium. This cut-off value varies between teams ranging from 300 to 400 mmHg. There is currently no universally accepted threshold;
  - Delta left atrium PaO_2 – pulmonary artery PaO_2 >350 mmHg;
  - (Perfusate left atrium PaO_2 – perfusate pulmonary artery PaO_2)/FiO_2 >300 mmHg;
  - PCO_2 <6 kPa (45.6 mmHg) and PO_2 >50 kPa (380 mmHg) at FiO_2 =1.0 or PO_2 >13 kPa (98.8 mmHg) at FiO_2 =0.21 as reported by the Danish team (20). These blood gas values are recorded after deoxygenation of the perfusate by the gas exchanger in the circuit.

These criteria may be used together as reported in the DEVELOP-UK and Manchester-Lund reports (21), where the authors used a combination of the arterial blood gas/ratio and selective pulmonary vein gas.

- ❖ Hemodynamic and ventilatory parameters: pulmonary artery and peak airway pressure, lung compliance and lung resistance. For most of the centers these parameters have to remain stable. However, a certain degree of deterioration is often permitted but a strict value or threshold for declining the organ for transplantation was never used. The group at the University of Alberta (22,23), the investigators of the HELP trial (5) and the Expand trial reported a threshold of maximum 15% of deterioration of these parameters as an acceptable criterion for transplantation.
- ❖ Macroscopic evaluation of the lungs: absence of oedema at palpation or bronchoscopy, purulent secretion, erythema of the bronchus (suggestive of aspiration), negative X-ray and satisfactory lung deflation after endotracheal tube disconnection (collapse test). Again, absolutely no strict guidelines

Table 2 Technique and various numerical values

Publication	Year	EVLP patients/ lungs	Standard patients/ lungs	EVLP no go patients/lungs	Conversion to transplantation (%)	EVLP/total transplantation (%)	Time in EVLP (min)	Type of machine	EVLP technique
Cypel *et al.* (Toronto)	Sep 2008–Dec 2011	60	265	8	86.67	18.46	240–360	XVIVO	Toronto
DEVELOP UK	Apr 2012–Jul 2014	53	184	35	33.96	22.36	Unknown	Vivoline	Hybrid Toronto/ Lund for 22 then Lund for 31
Luc *et al.* (Alberta)	Dec 2011–Nov 2015	7	4	0	100.00	–	210±101	OCS	OCS
Henriksen *et al.* (Danish exp)	May 2012–April 2013	8	36	1	87.50	18.18	146 [76–265]	Vivoline	Lund
Koch *et al.* (Essen)	May 2016–May 2017	11	41	2	81.82	21.15	240	XVIVO	Toronto
Sage *et al.* (French exp)	April 2011–May 2013	32	100	1	96.88	24.24	243 [124–460]	XVIVO	Toronto
Wallinder *et al.* (Gothenburg)	2011–2015	64*	290*	13*	79.69	18.08	208 [100–577]	Vivoline	Lund
Zeriou *et al.* (Harefield)	Jan 2007–Dec 2014	14	308	7	50.00	4.35	342±149	OCS	OCS
Zhang *et al.* (Groningen)	Jul 2012–Jun 2016	11	140	2	81.82	7.28	240 [210–252]	XVIVO + Lung Assist	Toronto
Lindstedt *et al.* (Lund)	2006–2007	6	15	Unknown	–	28.57	Difficult to evaluate	Medtronic, ECMO circuit	Lund
Manchester and Lund combined experience	Unknown	9	46	0	100.00	16.36	240	Unknown	Lund
Valenza *et al.* (Milan)	Mar 2011–Sep 2011	13*	42*	3*	76.92	23.64	Unknown	Home made	Lund
Schiavon *et al.* (Padova)	Jan 2014–Oct 2016	16	47	1	93.75	Not applicable, 47 patients transplanted but count of lungs not reported	410	OCS	OCS
Scandinavia experience	Jan 2011–Dec 2015	122*	529*	22*	81.97	18.74	Mean 200±94; median 175 [76–577]	Vivoline LS1	Lund

Table 2 (*continued*)

Table 2 (*continued*)

Publication	Year	EVLP patients/lungs	Standard patients/lungs	EVLP no go patients/lungs	Conversion to transplantation (%)	EVLP/total transplantation (%)	Time in EVLP (min)	Type of machine	EVLP technique
Boffini *et al.* (Turin)	Jul 2011–Feb 2013	11	28	3	72.73	28.21	–	Home made	Toronto
Aigner *et al.* (Vienna)	Mar 2010–Jun 2011	13	0	4	69.23	–	120–240	Home made	Toronto
Slama *et al.* (Vienna)	Oct 2013–May 2015	39	41	4	89.74	–	266 [245–329]	Home made	Toronto
HELP	Sep 2008–Jan 2010	23	111	3	86.96	17.16	240	XVIVO	Toronto
INSPIRE	Nov 2011–Nov 2014	150 PP; 141 ITT	169 PP; 165 ITT	0	Not applicable	–	Unknown	OCS	OCS
Mean	–	–	–	–	80.57	21.17	–	–	–

*, lung number. EVLP, ex vivo lung perfusion; ECMO, extracorporeal membrane oxygenation; PP, per protocol; ITT, intention to treat.

were found. The utilization of these criteria by the different teams that reported their experience is erratic.

The mean number of transplanted lungs after EVLP reported in the series was 80.57%. The acceptance rate varies from one center to another from 34% (DEVELOP-UK) to 97% in the French experience (24). However, many centers transplant more than 80% of the lungs reconditioned on an EVLP device (*Table 2*).

From several reports that used EVLP with otherwise rejected lungs [Paris, Essen (25), Gothenburg and Copenhagen (26), Groningen, Lund (27), Milan (28,29), Turin (30) and Vienna 2012 (31)] we can also conclude that EVLP is a good tool to increase the number of lung transplants, with a mean increase of 21.17% (range, 7.28–28.57%). This brings hope that with greater acceptance of EVLP, mortality rate on waiting list will probably fall in the coming years. For example, the Foch Center in Paris reported a mean waiting time for patients of 3 weeks, which represent a dramatic decrease since the beginning of their EVLP program (*Table 2*).

EVLP donors (*Table 3*)

Two categories of donors were reported.

The vast majority of the studies that we found used an EVLP device for reconditioning of extended-criteria lungs or lungs that otherwise would have been rejected for transplantation. Needless to say, every team reporting their individual experience had different criteria to decide whether or not a lung is deemed suitable for transplantation. These criteria can be summarized as follows:

- Blood gases: best PaO_2/FiO_2 <300 mmHg, systemic arterial PaO_2 <300 mmHg, pulmonary vein gas <225 mmHg;
- Macroscopic evaluation: absence of oedema, contusion, atelectasis difficult to recruit, mass/nodules/edema on palpation, poor lung compliance, abnormal bronchoscopy, abnormal chest X-ray;
- Lungs from DCD donors: this criterion is used by some teams (e.g., Alberta group) as an absolute criterion to evaluate lungs on EVLP prior to transplantation. Other centers (e.g., Toronto group) used EVLP for DCD lungs at the start of their experience at the surgeon's discretion;
- Donor profile: multiple transfusion, history of aspiration, extended ischemic time, sepsis, age, smoking history, severe trauma, pulmonary

Table 3 Criteria and outcome

Publication	Criteria for transplantation (Tx)			EVLP donors					Recipient	Clinical outcome EVLP
	Blood gas	Haemodynamic/ ventilation	Macroscopic	Blood gases	Macroscopic evaluation	Hemodynamic/ ventilation pressure	DCD	History of the patient		
Cypel *et al.* (Toronto)	√	√		√	√		√	√	Single, double, redo included, ECLS excluded	No difference
	P/F ≥400 mmHg, stable PA/airway/compliance pressure (not much than 15% deterioration)			Best P/F less than 300 mmHg Pulmonary edema detected on the last chest X-ray or during clinical examination of the lungs Poor lung compliance during examination of the lungs during donor operation DCD High-risk history, such as multiple (>10 units) blood transfusions, questionable history of aspiration All DCD went to EVLP in the beginning (until Jan 2010) then at discretion						
DEVELOP UK	√	√	√	√		√		√	All patients >18 years old on waiting list, providing informed consent at time of inclusion and the day of transplant except: ❖ Lung retransplantation, heart-lung Tx, multiorgan transplantation, live lobar transplantation; ❖ Patients requiring invasive ventilation, ECLS, iLA at time of Tx; ❖ Patients enrolled in other studies or about to, 12 months prior the Tx (not absolute exclusion criteria)	More ECLS needed in patient with EVLP, study stopped
	All of the following: ❖ Any DBD or DCD donor lungs meeting previously stated criteria for standard transplant; ❖ PA pressure <20 mmHg, while achieving target perfusate flow; ❖ Oxygen capacity shown by ΔPaO_2 of >300 mmHg (perfusate left atrium PaO_2 – perfusate pulmonary artery PaO_2)/FiO_2; ❖ Selective pulmonary vein gas >225 mmHg on 100% FiO_2 and 5 cmH_2O PEEP; ❖ Stable or improving lung compliance and stable or falling lung resistance; ❖ No pulmonary oedema build-up in the endotracheal tube; ❖ Satisfactory assessment on inspection and palpation; ❖ Confirmed reconsent of potential matched recipient to receive an EVLP-reconditioned lung			Any one or more of the following: ❖ Warm ischaemic time >30 minutes for DCD donors; ❖ Withdrawal of life support between 60 and 90 minutes for DCD donors; ❖ Chest radiograph findings prohibitive of standard Tx; ❖ Systemic arterial PaO_2 <300 mmHg and/or selective pulmonary vein gas <225 mmHg on 100% FiO_2 and 8 cmH_2O PEEP; ❖ History of aspiration with bronchoscopic inflammation/soiling of the airway, or recurrent but not prohibitive secretions in the distal airway after adequate bronchial toilet; ❖ Difficult to recruit atelectasis; ❖ Sustained peak airway pressure >30 cmH_2O; ❖ Unsatisfactory deflation test on disconnecting endotracheal tube; ❖ Unsatisfactory palpation of the lungs identifying undetermined masses, nodules or gross oedema; ❖ Deterioration or cardiac arrest in the donor prior to retrieval such that uncertainty over assessment remains; ❖ Unsatisfactory inspection of the lung after administration of the preservation flush and procurement; ❖ Logistical reasons that will extend donor lung ischaemic time >10–12 hours and prevent donor organ use, such as: • Viral studies awaited; • HLA compatibility studies; • Pathology assessment of indeterminate mass in any donor; • Awaiting recipient admission						

Table 3 (*continued*)

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Publication	Criteria for transplantation (Tx)			EVLP donors					Recipient	Clinical outcome EVLP
	Blood gas	Haemodynamic/ ventilation	Macroscopic	Blood gases	Macroscopic evaluation	Hemodynamic/ ventilation pressure	DCD	History of the patient		
Luc *et al.* (Alberta)	√	√	√				√		Unknown	In EVLP patients: ❖ PGD lower at 48 and 72 h; ❖ FVC lower at 3 months; ❖ Borg score better at 3 and 6 months
	Lung oxygenation capacity with a final P/F ratio of 350 mmHg or greater Deterioration of less than 15% from baseline levels of hemodynamic and respiratory variables (pulmonary vascular resistance, peak airway pressures, and lung compliance) Absence of clinical signs of lung injury (i.e., worsening edema, copious purulent secretion suggestive of infection, or bronchial erythema suggestive of aspiration)			All DCD						
Henriksen *et al.* (Denmark)	√		√	√	√			√	Unknown	No comparison done
	PCO_2 <6 kPa and PO_2 >50 kPa at FiO_2 =1.0 or PO_2 >13 kPa at FiO_2 =0.21 A collapse test is performed to evaluate possible oedema of the lung tissue			Donor lungs that were otherwise considered transplantable, but failed to meet the usual criteria due to: ❖ Possible contusions; ❖ Being from donors with sepsis; ❖ Being unable to pass the oxygenation test: PaO_2 <13 kPa at FiO_2 <0.4 or PaO_2 <40 kPa at FiO_2 =1.0, both with positive end-expiratory pressure (PEEP) <5 cmH_2O					
Koch *et al.* (Essen)	√			√					ECLS excluded single, double, redo, bilobar included	No difference
	ΔpO_2 between pulmonary venous and arterial gas analysis >350 mmHg			High-risk ECD lungs with P/F ratio <300						
Sage *et al.* (French exp)	√	√	√	√	√			√	High emergency excluded	No difference
	Left atrial P/F >400 mmHg and lung dynamic compliance and peak airway pressures stable or improving after a minimum of 2 h of EVLP			ECD (FNBA recommendations): ❖ Age (years): 56–70; ❖ P/F: (and/or) 200–400 mmHg; ❖ Chest X-ray: (and/or) abnormal; ❖ Smoking history: (and/or) yes; ❖ Gastric aspiration: (and/or) yes					

Table 3 (*continued*)

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Publication	Criteria for transplantation (Tx)			EVLP donors					Recipient	Clinical outcome EVLP
	Blood gas	Haemodynamic/ ventilation	Macroscopic	Blood gases	Macroscopic evaluation	Hemodynamic/ ventilation pressure	DCD	History of the patient		
Wallinder *et al.* (Gothenburg)	√	√	√	√	√		√	√	All on waiting list	No difference
	Lung oxygenation capacity with a P/F ratio of >40 kPa during the evaluation phase			P/F ratio <40 kPa and/or X-ray findings consistent with pulmonary edema						
	Stable or improving pulmonary vascular resistance, peak airway pressures, and lung compliance within the range that can be expected under EVLP (no absolute cutoff levels were used)			Then: ❖ When function was impossible to evaluate (i.e., a donor on ECMO); ❖ Suspected injury not possible to evaluate in the donor (i.e., pulmonary embolism or severe trauma as causes of death); ❖ Anamnestic, radiologic, or macroscopic findings suggestive of severely impaired lung function preventing the use of the lungs						
	Absence of macroscopic signs of pneumonic infiltrates or lung infarction									
	Normal collapse test			All DCD						
Zeriou *et al.* (Harfied)	Unknown			√	√		√	√	All on waiting list	FEV_1 3 and 6 months better in EVLP patients
				Abnormal parameters, such as: ❖ Donor smoking history of more than 20 pack-years; ❖ History of cannabis smoking; ❖ Prolonged mechanical ventilation; ❖ Pre-retrieval P/F ratio <300 mmHg; ❖ Abnormal bronchoscopy; ❖ Abnormal chest X-ray; ❖ History of cardiac arrest; ❖ Donors age higher than 55 years old						
				DCD donors on the condition that at least one trained retrieval surgeon and one trained perfusionist signed off for OCS were on call at the time of organ offer and an OCS kit was available						
				Only absolute exclusion criterion for normothermic preservation: mechanical lung damage (tears), i.e., after severe chest trauma						

Table 3 (*continued*)

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Publication	Criteria for transplantation (Tx)			EVLP donors					Recipient	Clinical outcome EVLP
	Blood gas	Haemodynamic/ ventilation	Macroscopic	Blood gases	Macroscopic evaluation	Hemodynamic/ ventilation pressure	DCD	History of the patient		
Zhang *et al.* (Groningen)	√	√	√	√	√				All on waiting list	No difference
	P/F >50 kPa <15% change compared to baseline			Lungs with a P/F <40 kPa at PEEP of 5 cmH_2O and 100% oxygen with clinically evident lung oedema						
	Pulmonary vascular resistance (pulmonary vascular resistance = PAP – LAP/pump flow) <15% change compared to baseline			Lungs that had a persistent low P/F <40 kPa after active lung recruitment without a clear reason (e.g., atelectasis)						
	Peak airway pressure <15% change compared to baseline			Exclusion criteria: ❖ 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; ❖ Sepsis					
	Clinical suitability for Tx									
Lindstedt *et al.* (Lund)	√			√					Unknown	No difference
	PaO_2 on FiO_2 100% >50 kPa after reconditioning			DBD						
				Same criteria as for ordinary donor lungs except that lower PaO_2 values were accepted						
Fildes *et al.* (Manchester and Lund combined experience)	√	√	√	√	√	√		√	All on waiting list	Less CMV infection in EVLP patients at 12 months
	Oxygenation on the circuit is within standard criteria (systematic arterial PO_2 of >40 kPa on FiO_2 of 1.0 or equivalent on FiO_2 of 0.5 and selective PV gas >30 kPa on FiO_2 of 1.0)			Age <65 years with satisfactory chest X-ray						
	PA pressure <20 mmHg whilst achieving stable perfusate flow at 37 ℃			Systematic arterial PO_2 <40 kPa on FiO_2 of 1.0 and 8 cmH_2O PEEP						
	Peak airway pressure <25 cmH_2O whilst achieving adequate ventilation			Selective pulmonary vein gas <30 kPa on FiO_2 of 1.0 and 8 cmH_2O PEEP						
	No pulmonary edema in the endotracheal tube			Peak airway pressure >30 cmH_2O						
	Easily recruited atelectasis			Difficult to recruit atelectasis						
	Stable or improving lung compliance			Bronchoscopy-history of aspiration, inflammation/soiling of the airway, or recurrent but not prohibitive secretions in the distal airway after adequate bronchial toilet						
	Stable or falling lung resistance			Unsatisfactory palpation of the lungs identifying undetermined masses, nodules or gross edema						
	Satisfactory assessment on inspection and palpation			Unsatisfactory inspection of the lung after administration of the preservation, flush and procurement						
	Satisfactory deflation test on disconnection of the endotracheal tube			Unsatisfactory deflation test on disconnection of the endotracheal tube						

Table 3 (*continued*)

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Publication	Criteria for transplantation (Tx)			EVLP donors					Recipient	Clinical outcome EVLP
	Blood gas	Haemodynamic/ ventilation	Macroscopic	Blood gases	Macroscopic evaluation	Hemodynamic/ ventilation pressure	DCD	History of the patient		
Valenza *et al.* (Milan)	√	√		√					Only patients with clinical condition rapidly deteriorating included	No difference
	P[v-a] O_2 >350 mmHg on FiO_2 100%, in the absence of deterioration in pulmonary vascular resistance or lung mechanics over perfusion time			P/F <300 mmHg with 5 cmH_2O of PEEP after optimization of donor ventilation or if lung function was doubtful despite oxygenation >300 mmHg Donors with massive lung contusion, aspiration, pneumonia, or sepsis were excluded						
Schiavon *et al.* (Padova)	√	√	√	√	√		√	√	Unknown	No comparison done
	Visual and bronchoscopy inspection P/F ratio >300 mmHg Stable perfusion and ventilation parameters trends for PA pressure, PVR and PAWP (with no more than 20% rise in these trends throughout preservation)			Inclusion criteria: ❖ Donor P/F ≤300 mmHg at time of acceptance of lung despite active recruitment or proper sampling from left atrium or ❖ Expected ischemic time>6 hours or ❖ DCD or ❖ Donor age ≥55 years old ❖ Pulmonary edema, defined as bilateral interstitial infiltrates without evidence of infection, detected on the last chest radiography by the surgeon assessing the donor, or a major discrepancy between the patient clinical characteristics (e.g., young age, no smoking history) and lung function (low P/F) Exclusion criteria: ❖ Presence of moderate to severe traumatic lung injury with air and or blood leak; ❖ Presence of active confirmed pneumonia or persistent purulent secretions on repeated evaluation bronchoscopy; ❖ Previous history of pulmonary disease; ❖ Multiple transfusions of >10 pRBCs; ❖ ABO incompatibility; ❖ Recipient <18 years old						
Nilsson *et al.* (Scandinavian experience)				√	√			√	Reop excluded	ICU stay and time to extubation greater in EVLP patients
	Gothenburg: see Wallinder *et al.* Copenhagen: see Henriksen *et al.*			P/F <40 kPa and/or X-ray findings consistent with pulmonary oedema Later, criteria were expanded to also include donor lungs for which it was not possible to properly evaluate in the donor (patient on va-ECMO), or ones with suspected lung injury (donors with pulmonary embolism or severe trauma as cause of death), or donor history, radiological or macroscopic findings suggesting severely impaired lung function that prevents the use of the organs DBD only						

Table 3 (*continued*)

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Publication	Criteria for transplantation (Tx)			EVLP donors					Recipient	Clinical outcome EVLP
	Blood gas	Haemodynamic/ ventilation	Macroscopic	Blood gases	Macroscopic evaluation	Hemodynamic/ ventilation pressure	DCD	History of the patient		
Boffini *et al.* (Turin)	√	√	√	√	√				Unknown	No difference
	Delta pO_2 >350 mmHg (perfusate LA pO_2 – perfusate PA pO_2)			P/F <300 at initial donor referral or at final graft assessment before retrieval						
	Left atrial pressure from 3 to 5 mmHg			And/or evidence of pulmonary oedema at chest X-ray or CT scan						
	Pulmonary artery pressure stable or <15 mmHg			And/or presence of wet lung at surgical inspection in the absence of significant infection and/or contusion						
	Airway pressure stable or decreased									
	Pulmonary vascular resistance stable or decreased									
	Compliance stable or decreased									
	Bronchoscopy negative									
	Lung X-ray negative									
Aignier *et al.* (Vienna)	√	√		√	√				All on waiting list	No comparison done
	Difference in oxygenation between the arterial inflow and the venous outflow >350 mmHg at FiO_2 of 100%			All donors presenting with PaO_2 values <300 mmHg at FiO_2 1.0 and at PEEP5 despite active donor management strategies and without medical or logistic contraindication						
	No deterioration of other functional parameters			DBD						
Slama *et al.* (Vienna)	√	√	√	√	√			√	All recipients on waiting list were considered for study inclusion except for patients presenting with any of the following pre-defined exclusion criteria: ❖ Consent not given; ❖ Pediatric recipient <18 years old; ❖ Diagnosis of primary pulmonary arterial hypertension (Dana Point classification group 1.1); ❖ Patient ventilated or on mechanical support before Tx; ❖ Previous Tx of any solid organ; ❖ Need for combined heart-lung Tx, lobar lung Tx, or single-lung Tx	No difference
	All lungs showing stable or improving functional parameters with a delta PO_2 >350 mmHg and a satisfactory macroscopic evaluation at the final evaluation			DBD						
				P/F >300 mmHg						
				Donor age >18 years						
				Clear chest X-ray						
				No major purulent secretions found during bronchoscopy						
				No major mechanical lung trauma						
				No gross gastric aspiration						
				No evidence of significant infection						
				No evidence for human immunodeficiency virus, hepatitis B virus, hepatitis C virus, or any other relevant viral disease						
				No history or evidence of malignant disease						

Table 3 (*continued*)

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Publication	Criteria for transplantation (Tx)			EVLP donors					Recipient	Clinical outcome EVLP
	Blood gas	Haemodynamic/ ventilation	Macroscopic	Blood gases	Macroscopic evaluation	Hemodynamic/ ventilation pressure	DCD	History of the patient		
HELP	√	√		√	√		√	√	Candidates for combined heart-lung Tx excluded	No difference
	P/F ≥350 mmHg			Best P/F <300 mmHg						
	Deterioration from baseline levels pulmonary vascular resistance, dynamic compliance, and peak inspiratory pressure <15%			Pulmonary edema						
				Poor lung deflation or inflation during direct intraoperative visual examination at the donor site						
				Blood transfusions exceeding 10 units						
				DCD						
INSPIRE	Unknown			√				√	Recipients excluded if they were: ❖ A single lung recipient; ❖ Had undergone a previous solid organ, bone-marrow, or multiorgan transplant; ❖ Were diagnosed with end-stage chronic renal dysfunction; ❖ Had undergone chronic use of haemodialysis	Less PGD 3 within 72 h in EVLP and EVLP and OCS Solution patients in PP analysis
				<65 years old						Patient survival at day 30 and freedom from primary graft dysfunction grade 3 within 72 h after lung Tx better in: ❖ EVLP patients (in PP analysis); ❖ EVLP and OCS Solution patients (PP and ITT analysis)
				P/F>300 mmHg						
				No active primary pulmonary disease						
				Suitable for preservation with OCS or the current cold storage standard of care						

Table 3 (*continued*)

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Publication	Criteria for transplantation (Tx)			EVLP donors					Recipient	Clinical outcome EVLP
	Blood gas	Haemodynamic/ ventilation	Macroscopic	Blood gases	Macroscopic evaluation	Hemodynamic/ ventilation pressure	DCD	History of the patient		
										Patient survival at day 30 and throughout the initial hospital admission and freedom from primary graft dysfunction grade 3 within 72 h after lung Tx (post hoc analysis) better in: ❖ EVLP patients (PP and ITT analysis); ❖ EVLP and OCS Solution patients (PP and ITT analysis)

EVLP, ex vivo lung perfusion; DCD, donation after circulatory death; P/F, PaO_2/FiO_2 ratio; DBD, donation after brain death; ECLS, extracorporeal life support; ECD, extended criteria donor; FNBA, French National Biomedicine Agency; pRBC, packed red blood cells; PA, pulmonary artery; iLA, interventional lung assist; PGD, primary graft dysfunction; FVC, forced vital capacity; FEV_1, force expired volume in one second; CMV, cytomegalovirus; PP, per protocol; ITT, intention to treat.

embolism, prolonged mechanical ventilation, history of cardiac arrest.

These criteria are usually combined, but may also be used alone (especially for the DCD criterion and the blood gases).

Some teams also reported a modification of their use of EVLP over time. For example, in the Scandinavian experience, at the beginning, the authors only used blood gases and X-ray findings to accept EVLP lungs. Later, the criteria were expanded to also include patients bridged to lung transplantation on extracorporeal life support (ECLS), injured lungs and severely impaired lungs on macroscopic and radiological evaluation. In the Toronto experience, all DCD donors' lungs were included for EVLP then at the surgeon's discretion.

Two studies evaluated the use of EVLP for normothermic preservation of standard-criteria lungs compared to CS (Vienna 2017 and INSPIRE trial).

Donor inclusion criteria used were:

- Blood samples: best PaO_2/FiO_2 >300 mmHg, no viral infection (HIV, hepatitis B/C, …);
- Macroscopic evaluation: clear chest X-ray, normal bronchoscopy, no evidence of lung infection/malignant disease;
- Donor age (>18 and <65 years);
- No history of aspiration, neither trauma.

Exclusion criteria to prevent useless EVLP therapy were:

- Mechanical lung damage (tears) leading to air/blood leaks;
- Massive lung contusion;
- Pneumonia;
- Sepsis or aspiration;
- Multiple RBC transfusion;
- Recipient <18 years;
- ABO incompatibility.

The description of the EVLP donors is generally well reported by the teams worldwide.

EVLP recipients (*Table 3*)

Patients who may benefit from a lung transplantation after reconditioning with EVLP are poorly described and usually not discussed in the different reports we examined.

The Toronto and Essen group included patients receiving single, double or even redo lung transplantation. Only patients under ECLS and patients requiring heart-lung transplantation were excluded.

In DEVELOP-UK, EVLP was reserved for adult patients >18 years requiring no lung/heart assistance and no redo/multiorgan/lobar/living donor lung transplantation.

The Paris team excluded high emergency patients while the Milan team (25,26) choose to include only patients with rapidly deteriorating clinical status.

Only Gothenburg and Harefield (32,33) teams included all patients on waiting list.

Concerning the studies evaluating standard lungs with EVLP, recipients were excluded if they were pediatric patients (<18 years), suffered from pulmonary arterial hypertension, need for heart/lung assisting device prior to transplantation (VIENNA 2017) or if they presented with severe renal dysfunction (INSPIRE). Both studies included double-lung transplantation only and excluded patients with previous transplant.

EVLP outcomes (*Table 3*)

In most of the reports, outcome was compared with a control group showing no major difference between reconditioned and standard lungs except in the experience reported from Denmark, Padova (34) and Vienna 2012. In many reports total cross clamp time (including cold and warm ischemic times) in EVLP transplants was greater compared to cold stored lungs. Lungs on EVLP are however fed with nutrients and constantly ventilated. Therefore, these lungs are not exposed to the risk of ischemic damage while stored outside the body.

Clinically, the Alberta team (evaluating EVLP only for DCD lungs) demonstrated a significantly lower rate of PGD at 72 h after transplant for the lungs undergoing EVLP compared to standard lungs (0.4±0.5 *vs.* 2.1±0.7, P=0.003). Three months after lung transplantation, FVC% and Borg Dyspnea Score was worse in patients transplanted with EVLP lungs. The authors stated that the explanation for such results is unknown and should be validated in a larger prospective study. In the Scandinavian experience, the patients treated with EVLP lungs were found to have longer ICU stay and time to extubation compared to recipients of standard lungs. The explanation could be that the EVLP lungs are in worse condition than the standard lungs and that the time from retrieval to transplantation was also longer.

Manchester and Lund experience reported that patients with EVLP lungs were more prone to symptomatic CMV infection 90 days from the transplantation. However, all patients developing a CMV infection in these studies were high/intermediate risk patients from a serologic point of view. This probably explains these negative findings better than the EVLP process itself.

Conclusions

EVLP is certainly a useful technique for the future. We have seen that, in numerous centers, this tool permits to really expand the number of lungs available for transplantation and to decrease the waiting time for patients. The clinical outcomes of EVLP treated lungs are as good as favorable lungs in terms of PGD and overall survival and the new perspective of treating lungs while on EVLP is a promising research field for the future.

However, there is a need to standardize the procedure. The techniques, the criteria for recipient and donor lung selection and the duration of EVLP are very different from one study to another making them difficult to reproduce. Several study reports are thus difficult to compare because of the potential bias in the inclusion criteria. To our knowledge this review represents the most complete overview of the worldwide utilization of EVLP nowadays.

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Footnotes

Conflicts of Interest: D Van Raemdonck is a member of the scientific advisory board of Transmedics. The other authors have no conflicts of interest to declare.

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