Review Article

Ex vivo lung perfusion review of a revolutionary technology

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Abstract: Donor lung shortage has been the main reason to the increasing number of patients waiting for lung transplant. *Ex vivo* lung perfusion (EVLP) is widely expanding technology to assess and prepare the lungs who are considered marginal for transplantation. The outcomes are encouraging and comparable to the lungs transplanted according to the standard criteria. In this article, we will discuss the history of development, the techniques and protocols of *ex vivo*, and the logics and rationales for *ex vivo* use.

Keywords: *Ex vivo* lung perfusion (EVLP); *ex vivo*; lung transplant; lung reconditioning

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Introduction

Lung transplantation is the ultimate solution for patients with end stage respiratory failure. Lung organ procurement rates from deceased donors are considerably lower than other solid organ procurement rates. Lungs are harvested from only 15–20% compared with 30% of deceased donors for hearts (1-3). This low percentage of transplanted lung is likely due to the potential complications of the lung that might occur before and after donor brain death such as thoracic trauma, aspiration, ventilator associated barotrauma injury, ventilator associated pneumonia, and neurogenic pulmonary edema (4-7). However, 40% of rejected donor lungs may have been suitable for transplantation (6,8). The number of patients awaiting transplant is expanding, and waitlist mortality is increasing concern due to the donor lung shortage (3-5). Multiple ways are used to expand the donor pool as extended criteria donors, donation after cardiac death (DCD) (9,10), and aggressive use of ECMO post-transplantation for marginal lungs (6,11-13), lobar lung transplantations were used for patients with small thoracic volume as well (14). more marginal lungs are used after assessment by *ex vivo* lung perfusion (EVLP), these extra marginal lungs used will expand the donor pool. using EVLP may ameliorate lung injury in some cases and allow transplantation from donors previously deemed unsuitable (15,16).

Ex vivo and lung transplant development history

The first normothermic *ex vivo* organ perfusion was described by Carrel and Lindbergh (17) in 1935. When they explanted thyroid glands of cats and rabbits and perfused them up to a week.

The first human lung transplantation was performed in 1963, and the recipient survived 18 days (18). Over the subsequent two decades, around 40 lung transplantations were performed, with a very low survival rate, as the majority of recipients died preoperatively because rejection, infections and of bronchial anastomotic complications. The first successful heart/lung transplantation was performed for idiopathic pulmonary arterial hypertension in 1981 (19).

This was followed by successful single lung transplantation for idiopathic pulmonary fibrosis in 1983 (20), and double lung transplantation for emphysema in 1986 (21).

Normothermic EVLP was studied clinically in the 1980s by Hardesty, but it was abandoned due to lower outcomes (22).

Steen *et al.* in Sweden (9,23-25) developed a new method for *ex vivo* lung assessment in the mid 1990s allowing for objective evaluation for some hours to the lungs of non-heart-beating, this technique led to the first in human lung transplantation from a non-heart-beating donor in 2000 after successful evaluation by *ex vivo* (9). The same team performed in 2005 the first transplant of initially rejected lung after *ex vivo* lung "reconditioning" (26), this concept was proven in a study published in 2006 (27), by using EVLP on six lungs which were initially rejected then implanted with good outcomes. Same results were obtained by another team in the USA using a similar methodology (28). In 2009 Cypel *et al.* (16) proposed extended EVLP reassessment of lung function for transplant using a new protocol (Toronto protocol).

The rational and the indications of *ex vivo* use

EVLP will give a window of time to evaluate and recondition lungs of inferior quality outside the donor body before transplantation (27). During EVLP evaluation, the Lungs remain viable without additional injury during EVLP, as it is done at body temperature (37 ℃), this makes the lungs metabolically active and viable for hours, putting the lungs in cold static will decrease cellular metabolism and will lead to decrease in oxygen and nutrients requirements, this will keep lungs in physiologic conditions prior to transplantation. Early favorable outcomes have been reported in recipients who underwent transplantation after EVLP to those with conventionally selected and transplanted lungs (27,29-31).

The EVLP is used in high-risk donor lungs which meet any one of the following five criteria: (I) best ratio of the partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FIO_2) of less than 300 mmHg; (II) pulmonary edema, detected on the last chest radiograph; (III) poor lung deflation or inflation during intraoperative lung harvest; (IV) blood transfusions exceeding 10 units; (V) donor after cardiac death (DCD) (4,9,32).

EVLP should not be used if donor lungs have established pneumonia, severe mechanical lung injury including multi lobes trauma, and/ or gross gastric aspiration (9,32).

EVLP circuit and operating models

The EVLP system consists of multiple components available from the perfusion and respiratory departments. The basic components of an EVLP circuit include a ventilator, endotracheal tube, perfusion solution, reservoir, oxygenator, air filter, O_2 sensor, and pump. In addition, a tank of de-oxygenating gas, tubing pack, cannulas to be connected to the pulmonary artery and left atrial cuff (*Figures 1*,*2*) (33).

There are 4 commercialized devices for clinical EVLP use: Organ Care System™ Lung (OCS); XPS™ (XVIVO Perfusion AB); Lung Assist® (Organ Assist); and Vivoline® LS1. OCS™ Lung is the only pulsatile and transportable device, the assessment starts at the donor hospital, OCS™ Lung and XPS™ are available in both US and CE (Conformité Européene) market, the Lung Assist® and Vivoline® LS1 are only available in the CE market. There are diverse differences among these devices in design and in clinical use.

There are three different EVLP protocols used to prepare and assess the lungs: the Toronto protocol which is the most commonly used protocol; the Lund protocol which is the original protocol of *ex vivo*, and the OCS™ protocol. The first 2 protocols are similar in a way that after the cold pulmonary flush and the lungs harvest, the lungs are kept in static cold storage (ice) during the transportation time to the recipient hospital when the lungs are connected to the *ex vivo* device and being assessed, this transport time while on ice increases the overall cold ischemia time.

On the other hand, the OCS can provide lung assessment starting immediately after the cold pulmonary flush and the lung harvest; sub sequentially it reduces the cold ischemic time during transportation (34), *Table 1* summarize the most important variables among these three protocols.

Assessment during EVLP

The graft can be examined, palpated, and evaluated

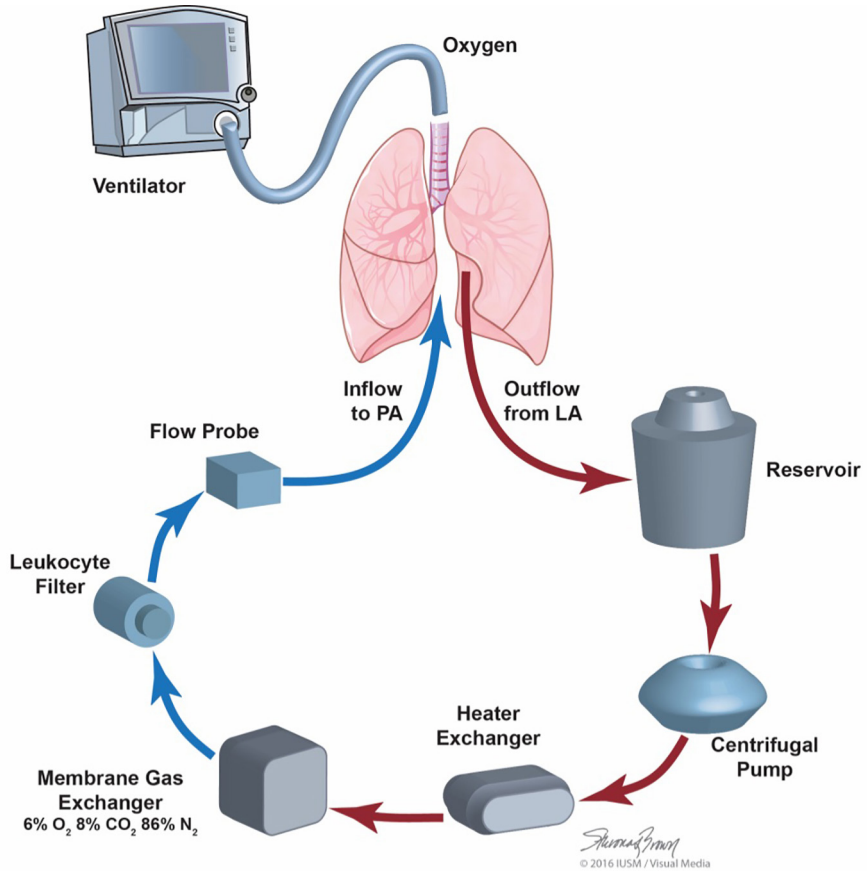

Figure 1 EVLP circuit with permission of Makdisi and Wozniak (33). O_2, oxygen; CO_2, carbon dioxide; N2, nitrogen; EVLP, *ex vivo* lung perfusion.

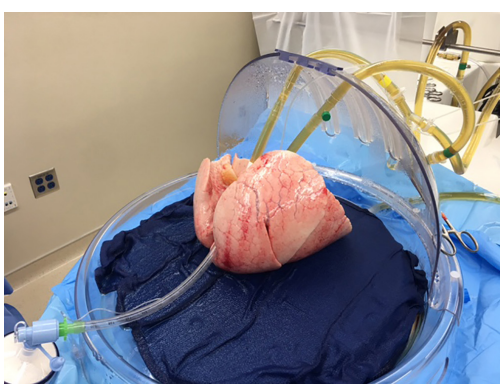

Figure 2 Lungs assessed by EVLP (Toronto protocol). EVLP, *ex vivo* lung perfusion.

clinically, bronchoscopically and radiographically allowing the surgeon to rule out tumors, areas of contusion, edema, infection, emboli, or other interstitial parenchymal abnormalities. Lung function including gas exchange, hemodynamics, and ventilatory mechanics is clinically evaluated for some hours (4,6). During these hours microbiologic, molecular, and morphological analysis are performed on any sampling obtained by bronchoalveolar lavage or any lung tissue specimens. These may help to guide the selection process of suitable organs in the future (35,36). Most important parameters monitored during assessment are listed in *Table 2*.

EVLP evidence-based

The role of EVLP for assessment and reconditioning of questionable donor lungs was investigated in multiple studies and currently ongoing trials. The results from the first prospective clinical trial the "HELP" trial was published in 2011, in this trial a group of 23 high-risk

Table 1 Comparison between the three different protocols of EVLP

Parameters	Lund	Toronto	OCS
Perfusion			
Target flow	40% of CO	40% of CO	2–2.5 L/min
Pressure			
PA	Flow dictated	≤20 mmHg	≤20 mmHg
LA	3–5 mmHg (closed)	0 mmHg (open)	0 mmHg (open)
Perfusate	Steen TM solution	Steen TM solution and RBCP Hct 14%	OCS TM solution and PRBC Hct 15–25%
Pump	Roller	Centrifugal	Piston (pulsatile)
Ventilation			
Start temp (℃)	32	32	34
Tidal volume	7 mL/kg	5–7 mL/kg	7 mL/kg
RR	7	20	10
PEEP	5 cmH_2O	5 cmH_2O	5–7 cmH_2O
FiO_2 (%)	21	50	12
Sweep gas flow	Titrate to PA pCO_2 34–38 mmHg	Titrate to PA pCo_2 34–38 mmHg	
Temperature (℃)			
Start of ventilation	32	32	32
Start of perfusion	15	25	32
Start of evaluation	37	37	37

EVLP, *ex vivo* lung perfusion; OCS, Organ Care System; CO, cardiac output; PA, pulmonary artery; LA, left atrial; RBCP, red blood cell products; Hct, hematocrit; RR, respiratory rate; PEEP, positive end expiratory pressure; FiO_2, fraction of inspired oxygen.

Table 2 Multiple parameters need to be monitored during assessments period

Gross anatomy: direct evaluation by the surgeon (weight, inspects of atelectasis, consolidation, dynamic compliance etc.), airway pressure
Radiologic CXR: assessment of lung improvement (reduction of lung edema)
Bronchoscopy: checking for clear secretions, edema, contusion
ABGs: the numbers, the tendency & curves, along with pO_2/FiO_2 less than 350 mmHg
Other factors: monitored are any decline of pulmonary vascular resistant, significant changes of peek inspiratory pressure

pO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; CXR, chest X-ray; ABG, Arterial blood gas.

donors underwent EVLP and among these; 20 sets of lungs (87%) were considered suitable for transplantation. These were compared to a group consisting of 116 patients underwent transplantation according to the standard criteria. The study group didn't observe any significant differences in terms of primary graft dysfunction (PGD), days on mechanical ventilation after transplant, ICU stay, hospital stay, and 30-day mortality (32).

Aigner *et al.* (30) reported 9 double-lung transplants with EVLP assessment, compared to 119 standard preservation transplants with similar short term results between the 2 groups including days on mechanical ventilation, ICU stay,

hospital stay and 30-day mortality.

Same results were obtained by Zych *et al.* (37) at 3 and 6 months comparing a group of 6 implanted lungs after EVLP assessment with second group of 86 patients transplanted according to the standard criteria.

At the ISHLT meeting in 2013, the Toronto, Paris and Vienna groups presented their EVLP experience combined (125 transplantation after EVLP assessment). The overall transplantation rate of 82.5% of. Comparable to earlier reports, the occurrence of PGD at 72 hours was at 5%, the 12-month mortality at 12% (38).

The NOVEL Lung Trial, which is a FDA-mandated multicenter, non-randomized comparing 2 groups of reconditioned EVLP lungs versus standard-criteria lungs, the study included 76 EVLPs resulting in 42 lung transplants compared to 42 controls, early results and 1-year survival were comparable (39,40).

Fisher *et al.* (41) reported the outcomes of DEVELOP-UK which is a nonrandomized Reconditioned extended-criteria lungs versus standard-criteria lungs, among 53 donors with EVLP, only 18 (34%) were subsequently transplanted. The study concluded the estimated survival over one year was lower than in the standard group, but this was not statistically significant. Patients receiving these additional transplants experienced a higher rate of early graft injury and need for unplanned ECMO support, at increased cost.

Most recently, Yeung *et al.* (42) presented retrospective study comparing the outcomes between 2 groups the first combined of transplanted patients who received lungs preserved for more than 12 hours including EVLP time (97 patients) with the second group with total preserved lung less than 12 hours (809 patients). The average preservation time for group one was 14.6 hours for 97, and 6.7 hours for group 2. Early post-transplant outcomes were similar between the two groups despite high-risk lungs. No differences were seen in PGD or length of hospital and ICU stay between the two groups. These results are extremely encouraging, as lifesaving transplants can now be performed across larger geographic areas without the risk of poorer outcomes.

Currently, the Normothermic EVLP as an assessment of extended/marginal donor Lungs trial is being conducted in the USA to approve the clinical use of EVLP assessing high-risk donors pre-transplantation, and the outcomes are being compared to a group of patients who received lungs according to the standard criteria. Inclusion and exclusion criteria for EVLP are based on those previously used in HELP trial. The study still ongoing, less than handful of patients still needed before closing the study.

Finally, several groups have used lungs from DCDs after *ex vivo* assessment with outcomes comparable to using without *ex vivo* and some of these proclaimed using *ex vivo* will improve DCD lung selection, and increased the uses of DCD lungs (9,16,43-45). The conversion rate from EVLP to transplantation varies between 46 and 87% (15,30-32,37-43).

Conclusions

The usage of ELVP resulted in increased of lung transplants using grafts from marginal donor lungs pool, the performance of these suboptimal lungs evaluated by EVLP is considered equal to those lungs transplanted according to the standard criteria. The Expectations are high that EVLP will overcome some fundamental limitations of current lung transplantation protocols, and push to the cutting edge.

There are some unanswered questions: What is the optimal time needed to keep the lungs on EVLP device? When is the optimal time to start EVLP assessment? Is it directly after the harvest in donor hospital? or after transportation to the recipient hospital? In case of double lung transplant what we should do with the second lung? should we keep it on EVLP device? or put it on cold environment (ice)? All these questions warrant further research studies to find the optimal way in managing this booming technology.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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