EVLP: Ready for Prime Time?

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Ex vivo lung perfusion implies perfusion and ventilation of a donor lung outside of the human body. The 2 most clinically relevant and commercially available devices currently in clinical trials are XVIVO Perfusion System (XPS Perfusion, Goteborg, Sweden) and Organ Care System (Transmedics, Andover, MA). Our review focuses on the needs met by ex vivo lung perfusion, and the clinical literature on both devices.

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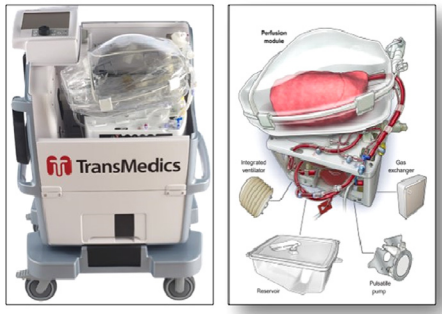

Organ Care System (Transmedics Andover, MA). Note portable console (left), disposable sterile single use modules (right). Each disposable module has a pulsatile pump, reservoir, ventilator, gas exchanger, tubing, and sterile chamber.

Central Message

The US Food and Drug Administration has reviewed and approved 2 commercially available devices for ex vivo lung perfusion. Choice depends on center experience, costs, surgeon preference, and final consideration of data from ongoing clinical trials.

INTRODUCTION

Ex vivo lung perfusion (EVLP) is a significant advancement in donor lung preservation. It addresses two key issues in lung transplantation: donor availability and donor quality. EVLP does not refer to a single device or a single preservation method; rather, EVLP is a concept that implies perfusion of a donor lung outside of the human body on a device that uses cellular or acellular solutions, ventilation, and usually normothermia. The 2 most clinically relevant and commercially available devices currently in clinical trials are XVIVO Perfusion System (XPS) (XPS Perfusion, Goteborg, Sweden) and Organ Care System (OCS) (Transmedics, Andover, MA). Our review focuses on the needs met by EVLP, and the clinical literature and current medical community's perspective on both devices.

BACKGROUND

Standard Ice Preservation

Since the beginning of lung transplantation in the 1960s, when Dr. Denton Cooley performed the first-reported heart-lung transplant,[1] donor-organ preservation has relied on topical and intravascular cooling to reduce metabolic demand. Perfedex (XVIVO, Goteberg, Sweden), which is a balanced salt solution with low concentrations of potassium, dextran, and glucose, is the most commonly used solution in the United States. Typically, the surgeon infuses 4 L of perfusate under low pressure through the pulmonary artery and then infuses 1–2 L retrograde through the pulmonary vein ostia. Most surgeons include prostaglandin or nitroglycerin in the initial infusion to distribute the antegrade perfusate homogenously. The anesthesiologist ventilates the lungs to approximately 20 mm Hg with a static breath hold before the procurement surgeon team staples the trachea and packages the organ in an ice cooler with additional cold Perfedex solution. The team keeps the organ packaged and cool until the recipient team is ready for implantation. This period could be as long as 8–10 hours, although it is typically kept to <6 hours. This preservation method is the most commonly used for lung transplantation, even since the advent of EVLP, which provides a more sophisticated platform for delivering cellular or acellular perfusates to the lungs with a variety of additives and recruitment options that could potentially enhance lung function.

Standard Criteria Donors (SCDs) and Extended Criteria Donors (ECDs)

Donor lungs are scarce. For every 100 patients added to the transplant waitlist, approximately 17 die while waiting for a donor lung. Yet, surgeons only consider 20% of offered donor lungs for transplantation. Thus, there is no shortage of organs but rather a shortage of organs that meet "ideal" specifications.

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SCDs satisfy the following requirements: donation after brain death, age <55 years old, normal chest radiograph, PaO_2 >300 mm Hg on 100% FiO_2 and <6 hours total anticipated clamp time (defined as time between donor clamp on and recipient clamp off). Because of the organ shortage, many centers have extended their criteria for lung donation. ECDs meet any of the following requirements: donation after circulatory death (DCD), age >55 years, abnormal chest radiograph, PaO_2 <300 mm Hg on 100% FiO_2, and >6 hours total anticipated clamp time. Sommers et al[2] showed that long-term outcomes were no different with ECD lungs than with SCD lungs. Using ECD lungs increased transplantations, produced the same long-term outcomes, but resulted in greater short-term primary graft dysfunction (PGD) and longer intensive care unit stays.

During donation after brain death, which is the most common mode of donation, the surgeon opens the chest, dissects and assesses the thoracic organs, and stops the heart immediately before procuring the lungs, which minimizes ischemic injury to the lung. However, during DCD, the surgeon procures the lungs after the heart stops beating, and the patient has been dead for at least 5 minutes. The delay in making the skin incision and the length of the subsequent dissection interval could theoretically lead to ischemic injury to the organ. In addition, evaluating the donor lung after circulation ceases may be suboptimal. Long-term outcomes with DCD are similar to those with donation after brain death, but surgeons remain reluctant to embrace DCD because of the inability to monitor, assess, and recondition the organ before transplantation.[3] Moreover, centers have reported success with extending cold ischemic times beyond 6 hours.[4] Yet, this is still an uncommon practice, and the majority of lung transplant ischemic times are less than 6 hours. Similarly, there is a general reluctance to consider older-aged donors despite various reports of successful outcomes.[5] Theoretically, EVLP provides the ideal platform for evaluating and reconditioning ECD lungs before transplantation.

Primary Graft Dysfunction

PGD is a form of ischemia-reperfusion injury, which is the most common complication after lung transplantation for either SCD or ECD lungs. It occurs when the surgeon reperfuses the lungs in the recipient after a period of ischemia caused by the procurement, travel, and surgical anastomosis. Reintroducing blood flow leads to a cascade of events triggered by reactive oxygen species, cell death mediators, and inflammatory cytokines that result in acute lung injury. The most severe form of PGD is PGD Grade 3 (PGD3), which affects up to 30% of all standard donor lung transplant recipients and causes significant short- and long-term mortality risk.[6,7] Transporting a donor lung in a warm, ventilated, and perfused state could attenuate the effects of the ischemic period and reduce the burden and incidence of ischemia-reperfusion injury. Portable normothermic EVLP could potentially achieve this goal.

Clinical Devices

Herein, we focus on the 2 most clinically relevant and commercialized systems currently available worldwide. Other unique, homemade circuits are reported in the literature, but these are not yet commercially available. The XVIVO Perfusion System (XPS) is a static system that uses acellular perfusion; it commonly uses a Toronto-based perfusion protocol for which good clinical outcomes have been reported since 2011. The OCS is a portable system that uses cellular perfusion. In August 2014 XPS achieved humanitarian exemption status by the US Food and Drug Administration (FDA) for use in initially unacceptable donor lungs. OCS is a newer platform that has undergone 2 major clinical trials. The FDA issued approval for OCS use in standard donor lungs in March 2018.

XVIVO PERFUSION SYSTEM

Background and Clinical Use Models

The XPS is static and relies on cold acellular preservation and transporting the donor to the XPS' location before the donor lung is instrumented on the device. It relies on a compact design with sophisticated automation and monitoring capabilities (Fig. 1). Typically, transplant teams keep the device at the transplant recipient's hospital, although it can also be kept in regionalized perfusion centers. The device has a sterile chamber for the lung, a centrifugal pump, an oxygenator, a volume reservoir, a heater-cooler system, and a monitor.

The surgeon instruments the lungs on the device and perfuses them with an extracellular-type solution containing buffered dextran and optimized colloid osmotic pressure. The system often uses additives such as Solu-Medrol, antibiotics, and heparin. The user typically renews the perfusate after the first hour of EVLP and periodically thereafter. General use guidelines are based on the Toronto EVLP protocols as follows: Flow starts at 150 mL/min,

Figure 1. XVIVO Perfusion system (XPS) (XPS Perfusion, Goteborg, Sweden). Integrated EVLP platform containing the centrifugal pump, reservoir, ventilator, gas exchanger, tubing, and sterile chamber.

and the perfusate temperature is gradually increased to 37°C. Ventilation starts once the temperature reaches 32°C. This protocol uses 40% of the cardiac output. Mean pulmonary artery pressures are kept at 7–15 mm Hg, and a positive left atrial pressure is kept at 3–5 mm Hg. Ventilation uses 7 mL/kg tidal volume, positive end-expiratory pressure (PEEP) of 5 mm Hg, 21% FiO_2, and 7 breaths per minute.

Sweep gas flow uses 8% CO_2, 6% O_2, and 86% N_2. The surgeon adjusts the gas flow rate to maintain a pulmonary arterial CO_2 ($PaCO_2$) of 35–45 mm Hg. This gas mixture controls the perfusate pH and $PaCO_2$. The low oxygen concentration deoxygenates the perfusate, which enables adequate evaluation of the lung's oxygenating capacity. Before each evaluation, the user starts an inspiratory hold to reach a peak airway pressure of 20 cmH_2O, and the FiO_2, tidal volumes, and respiratory rates are set to 100%, 10 mL/kg, and 10 breaths per minute for approximately 5 minutes, respectively. Evaluations occur every hour and include assessing the pulmonary venous PaO_2:FiO_2 ratio, mean pulmonary artery pressures (mm Hg), dynamic compliance (mL/cmH_2O), and peak airway pressures (cmH_2O). The platform allows for radiography and flexible bronchoscopy. Most centers keep lungs on XPS for approximately 4–6 hours. At the end of EVLP, the lungs are cooled to 10°C, inflated, clamped, separated from the device, and stored in an ice-cold preservation solution until transplantation.

Clinical Literature

A reasonable body of literature, mostly from single-center experiences, describes the transplantation results using Toronto-based perfusion protocols with disposable products. These perfusion designs are different than the XPS system although the XPS approval was based on some of this research. The landmark study by Cypel et al in 2011 was a prospective, nonrandomized clinical trial that showed the results of transplantations that used donor lungs with extended criteria features, such as PaO_2:FiO_2 <300 mm Hg, pulmonary edema, poor compliance, DCD, or massive blood transfusions after EVLP perfusion. Lungs were considered acceptable for transplantation if the PaO_2:FiO_2 exceeded 350 mm Hg and if the physiologic parameters on EVLP were within 15% of baseline values. Twenty of 23 ECD lungs met this endpoint. None of the recipients in the EVLP group had PGD3 at 72 hours, and 1-year survival in the EVLP patients and control cohort was 80% and 83.6%, respectively.[8]

In a follow-up study, Cypel et al[9] reported an 87% rate of 1-year survival and a 2% incidence of PGD3 at 72 hours in the EVLP patients who received ECD lungs. The results of these trials formed the basis for the integrated XPS system's humanitarean device exemption approval in donor lungs initially deemed unacceptable for transplant. In another study, Machuca et al[10] used the Toronto-based EVLP protocol to assess 28 donor lungs after DCD procurement on EVLP. Patients who received DCD lungs on EVLP had similar 1-year survival rates as those who received DCD lungs that did not use EVLP within a similar time frame (86% vs 92%, $P = 0.68$). Patients who underwent EVLP lung transplantations had a 3% incidence of PGD3 at 72 hours and a significantly shorter length of hospital stay. Sage et al[11] reported the French experience with XPS Toronto-based EVLP for ECD and showed a 91% 1-year survival rate.

Perspective

The static EVLP systems in combination with Toronto-based protocols have led to successful outcomes in large series published especially from the Toronto Lung Transplant Program. What is missing is a multicenter registry or international prospective trial that validates this EVLP system across a variety of expert users. Sanchez et al reported the preliminary results of the Normothermic Ex-vivo Lung Perfusion as an Assessment of Extended/Marginal Donor Lungs Trial (NOVEL), which is currently ongoing and includes 6 US centers.[12] It is a prospective, nonrandomized registry that includes ECD lungs placed on EVLP and SCD lungs transplanted without EVLP. The preliminary data showed 55% utilization after EVLP and a 1-year survival rate that was similar to that of SCD transplant recipients. The XVIVO Perfusion System holds promise for reconditioning marginal organs and potentially for assessing standard donor organs before transplantation. The platform appears safe and reliable, and we will probably see a growing experience with it in the United States and abroad. However, it remains controversial whether XPS with Toronto-based EVLP is required for improving the results of lung transplantation. Although the initial clinical experience is promising, with trends toward better short-term outcomes, longer-term follow-up is still needed. Given that some ECD lungs were screened out after EVLP assessment in the trials mentioned above, XPS's potential as an important screening tool is also noteworthy and could be used to make transplantations safer.

ORGAN CARE SYSTEM

Background and Clinical Use Models

The OCS is a portable EVLP unit with the unique potential to shorten cold ischemia (Fig. 2). Whether cold ischemia has a

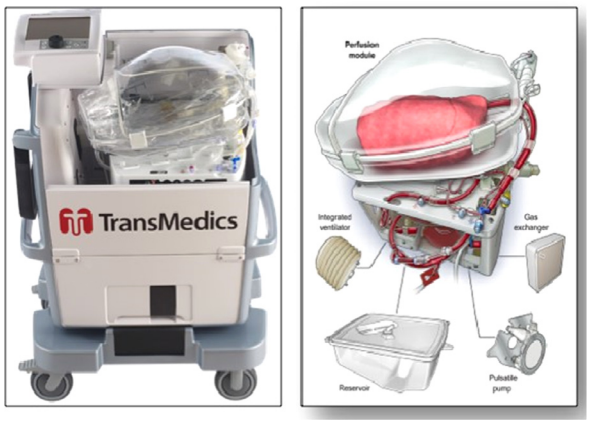

Figure 2. Organ Care System (Transmedics Andover, MA). Note portable console (left), disposable sterile single use modules (right). Each disposable module has a pulsatile pump, reservoir, ventilator, gas exchanger, tubing, and sterile chamber.

deleterious effect on the lung is still a matter of debate. Yet, before OCS, no technology was available to reduce cold ischemia. Typically, the transplant recipient's hospital maintains the unit in a safe location. The transplant team gathers the various components to set up the device, collects pharmaceuticals, and obtains 3 units of packed red blood cells. Future studies will conceivably use the donor's whole blood as an alternative mode of blood acquisition.[13,14] The device consists of a portable main console with an integrated ventilator, pulsatile pump, and heating system. The disposable OCS module inserts into the main console and contains a sterile chamber for the lung, an oxygenator, a volume reservoir, and sterile tubing. The team transports the device to the donor's hospital. It occupies 1 seat in a standard jet liner or any medical transportation vehicle.

The procurement proceeds per routine, with cold antegrade and retrograde flush of the donor lungs. Once the donor lung is deemed acceptable for transplantation or for preservation on OCS, the device is primed with 3 units of packed red blood cells, OCS solution (mixture of low-potassium dextran solution with glucose), and additives (ie, steroids, antibiotics, and bicarbonate). The lungs are instrumented onto the device by attaching the tracheal and pulmonary artery cannulas and then placing the lungs in the module. Generally, the time from antegrade flush to instrumentation on OCS is approximately 30−40 minutes. This constitutes most of the cold ischemic time for the transplant.

The team perfuses the lungs at a low perfusion rate (0.5 L/min) and gradually increases the rate to 1.5−2 L/min over 15 minutes while the lungs are gradually warming up. Once the lungs reach 34°C, ventilation begins at 6 mL/kg (ideal body weight), PEEP 5 cm H_2O, rate of 12 breaths per minute, and 21% FiO_2. Once the lungs reach 37°C, the team takes the first blood gas measurement. The peak airway pressure, mean pulmonary artery pressure, pulmonary vascular resistance, and blood gas at this stage represents the "baseline." The monitor tracks these values continuously, and the team compares subsequent results to the baseline. The team secures the device in the plane or other vehicle and transports it back to the transplant recipient's hospital. During this time, the team can adjust the ventilator from the monitor via a Bluetooth connection. Although the team is still able to analyze the blood gas during transportation, typically the saturation levels provide clues of the organ oxygenation during flight. In the event of an emergency, which has yet to occur in our experience, the team can inflate the lungs, flush them cold, and place them in an ice cooler for further consideration at the recipient's hospital.

At the transplant recipient's hospital, the team recruits the lungs and performs a final assessment. If the PaO_2:FiO_2 ratio is >300 mm Hg and the physiologic parameters are within 15% of baseline values, then the team will proceed with the transplantation. The transplant recipient's operation proceeds per routine. In our experience, once we are ready to implant the lung, we isolate a single lung while maintaining ventilation and perfusion of the contralateral lung in the device. Each lung is flushed with cold perfusate before the implantation procedure begins. Thus, the total cold ischemic time includes the time from pulmonary flush at the donor to instrumentation on EVLP (~30−40 minutes), and the time from separation of the lung to the start of the anastomosis (~5−10 minutes).

Clinical Literature

The clinical literature for portable normothermic EVLP is not as mature as that for the Toronto-based perfusion strategies. However, the International Randomized Study of the TransMedics Organ Care System for Lung Preservation and Transplantation (INSPIRE) trial is the largest international randomized trial in the history of organ preservation. In the INSPIRE trial, investigators randomized 320 bilateral lung transplants to either cold storage or OCS. The investigators presented the results at the 17th Congress of the European Society for Organ Transplantation in Brussels, Belgium. They presented the 2-year follow-up results at the 2016 International Society of Heart and Lung Transplantation in Washington, DC, USA.[15,16] The results suggest that in the per-protocol population, OCS was associated with a significantly lower rate of PGD3 within 72 hours than regular cold storage. The 12-month survival rate was similarly excellent in both cohorts (89% OCS, 88% control).

The results of the INSPIRE trial and the pilot investigation from Warnecke et al[17] formed the basis of a recent FDA panel review of OCS for commercial use. In 2017, the FDA reached a positive panel review on the device for its safety in lung transplantation and final approval was given in March of 2018.

Moreover, like the studies mentioned above in the static EVLP system, investigations are currently underway to evaluate OCS use in ECD lungs. The Trial to Evaluate the Safety and Effectiveness of the Portable OCS Lung System for Recruiting, Preserving and Assessing Non-Ideal Donor Lungs for Transplantation (EXPAND I) is an international single-arm prospective study evaluating the use of OCS for ECD lungs. Inclusion criteria included donor PaO_2:FiO_2 <300 mm Hg, anticipated ischemic time >6 hours, DCD, and age >55 years. The investigators presented preliminary results at the 2018 International Society of Heart and Lung Transplantation. The OCS lungs were transplanted 86% of the time with a 91% 12-month survival rate.[18] The EXPAND II trial is currently underway to compare the results of ECD lung transplantations that used OCS or standard cold ice preservation. Other single-center clinical and translational experiments have explored the potential for utilizing OCS Lung for lobar transplantations, intervals of prolonged preservation, and controlled and uncontrolled DCD.[19−24] However, larger-scale clinical data are still lacking.

Perspective

Data suggest that OCS Lung is safe for SCD or ECD lungs. Initial experience with OCS suggests that it reduces the incidence of PGD3 in SCD lungs. The use of OCS Lung in ECD transplantations is still under evaluation in the EXPAND I and II lung trials, with preliminary data suggesting good donor lung utilization. Portability is the principal advantage of OCS over XPS. However, whether cold ischemia is a significant

factor remains to be seen. Currently, the individual transplant centers must use their best judgement in deciding on a device. It is clear that both systems add significant costs to the transplant procedure, and insurance companies will typically be slow to reimburse these costs. This situation will change as experience grows, but it is unlikely that many centers will use both systems because of the costs and expertise that would require. Rather, they will likely select one system on the basis of their experience, clinical judgment, and infrastructure.

Summary and Closing Perspectives

Both XPS and OCS Lung are promising modalities for EVLP, which is probably here to stay. Clinical outcomes have been excellent with both systems when used at highly specialized centers, and in clinical trials performed at such centers. Whether all lungs need EVLP is still a matter of debate. EVLP can recruit any lung, but the extracorporeal circuit can also increase inflammation.[25] Damage to a standard lung can also potentially occur because of operator inexperience or device malfunction. Interestingly, this has rarely occurred in most reported clinical trials, but with widespread use, it could become a concern, and backup systems should be in place. Thus far, the balance of the pros and cons appears to favor increased quality and utilization of donor lungs with EVLP. The technology is still in its infancy, and protocols and adjunctive protective agents are likely to evolve.

Payers are increasingly reimbursing hospitals for the costs of EVLP in current FDA-approved clinical trials. With additional FDA validation and clinical experience, greater support is likely for adoption of the technology. For the next few years, we can expect EVLP to remain confined to a select group of transplant centers until experience accrues. Both systems are potentially useful for monitoring and screening organs. Whether EVLP alone can sufficiently "recondition" or "revitalize" an organ that would otherwise not be transplantable remains unclear. Lungs compromised by acute injury or chronic disease in the donor will need adjunctive therapies to improve their yield and function, but EVLP provides the ideal platform for this to occur.

Currently, EVLP is very useful for screening ECD organs and providing individualized recruitment. The OCS Lung may improve outcomes of even SCD lungs, which has the potential to reduce hospital resource needs and improve clinical outcomes. However, the later concept was not statistically evident despite a marked reduction in PGD in the INSPIRE trial. Several key publications are pending to further clarify the data supporting the use of OCS Lung (Long term results of INSPIRE and results of EXPAND I and II) and XPS (Normothermic Ex-vivo Lung trial). EVLP is a welcomed and much-needed addition to the progress of lung transplantation. Accumulating evidence suggests that it could improve short- and long-term clinical outcomes and organ usage. Ultimately, a randomized trial or a registry analysis (which may be more feasible) that compares static EVLP to portable EVLP may help centers decide which is the best investment to make.

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