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Ex-vivo Lung Perfusion and the Orphan Lung Program: Novel Paradigms for Augmenting the Donor Pool

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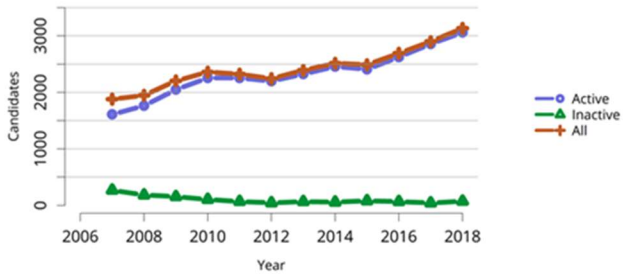
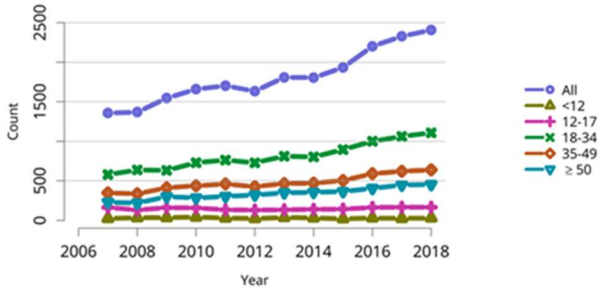
Lung transplantation (LT) is a life-saving procedure for patients with advanced lung disease. Since the first successful LT in 1983, the number of transplants every year has been growing consistently. However, as with other solid organs, the number of patients in need of transplants outstrips the available donor lungs (see Figure below).

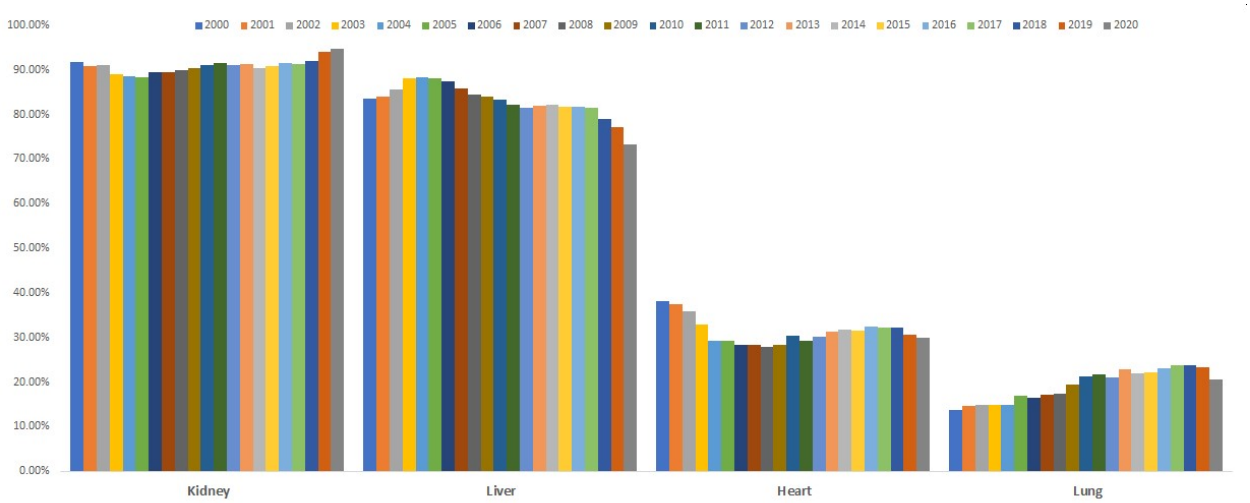


Number of candidates added to wait list each year



Number of lung donors each year

Despite higher utilization rates in recent years, lungs are utilized among less than a quarter of all eligible donors [1,3-6]. The Figure below shows the proportion of four major organs utilized among eligible donors over the last 20 years.



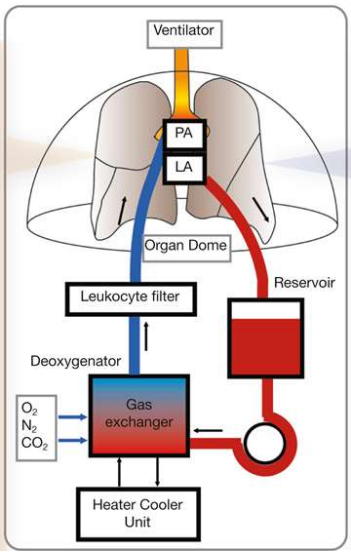
The lungs are unique by way of the heightened risk of injury during the time of death such as inflammatory edema from to the cytokine release triggered by brain death, interstitial edema from volume overload, aspiration of oral or gastric contents, inhalational injury and chest trauma with pulmonary hemorrhage and contusions. This shortfall of transplantable lungs is compounded further by the challenges among waitlisted patients who are faced with a significant risk of exacerbation of underlying disease and lack of sustainable mechanical pulmonary support options. These factors combine to explain the high waitlist mortality of 10-13% per year among patients awaiting a lung transplantation [1,2].

Types of Organ Donors

Usual donors for lung transplants are brain-dead donors (DBD); donors who have been diagnosed to have brain death and, despite a beating heart, are medically and legally cadaver donors. After procurement, the donor lungs are preserved in cold static storage to reduce metabolic demands of the allograft ("cold ischemia"). On the other hand, there are several potential donors that do not meet the criteria for brain death but still have a catastrophic medical condition that does not leave them with any meaningful chance of recovery. In such situations, the families may consent to organ donation, but allocation has to proceed differently than the brain-dead donors. Typically, that entails the withdrawal of care in a controlled setting (usually in an operating room) where the organ procurement occurs **after** the circulatory arrest. This process leads to "warm ischemia" that can damage the organs being procured for transplant, and special precautions must be taken to ensure the viability of the organs. This process is referred to as donation after circulatory death (DCD). The sensitivity of different organs to warm ischemia varies, and one of the ways to assess the quality of the DCD organs is to use Ex vivo lung perfusion (EVLP).

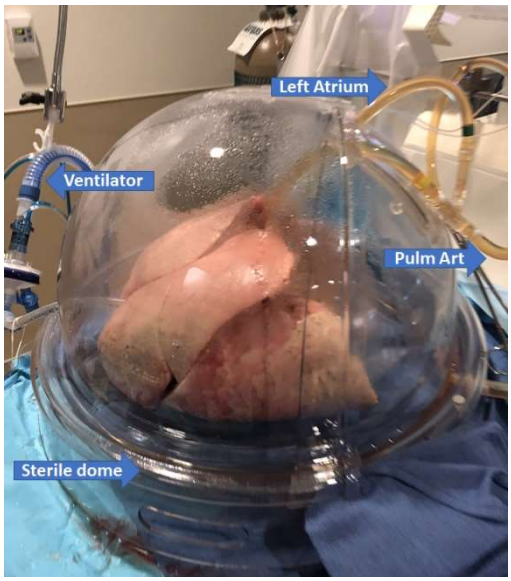
Ex-Vivo Lung Perfusion

EVLP is a novel technique to expand the donor pool for lung transplantation (see Figure below from Tane et al.) [7]. This technology allows assessment and reconditioning or repair of donor lungs in an ex-vivo environment. The EVLP procedure permits time and opportunity to determine the various aspects of pulmonary physiology after procurement but before implantation, which is a paradigm shift from the conventional approach that is limited to an anatomical assessment of the organ followed by cold storage before eventual transplantation.



Steen et al. [8] were the first to use a blood-based perfusate in an ex-vivo manner to recondition lungs from a DCD donor. Since then, the data on the feasibility, safety, and efficacy of EVLP for lungs with marginal quality has been accumulating [9]. The earliest clinical trials evaluating the EVLP were conducted at the University of Toronto by a team led by Keshavjee and Cypel [10-12]. In a larger

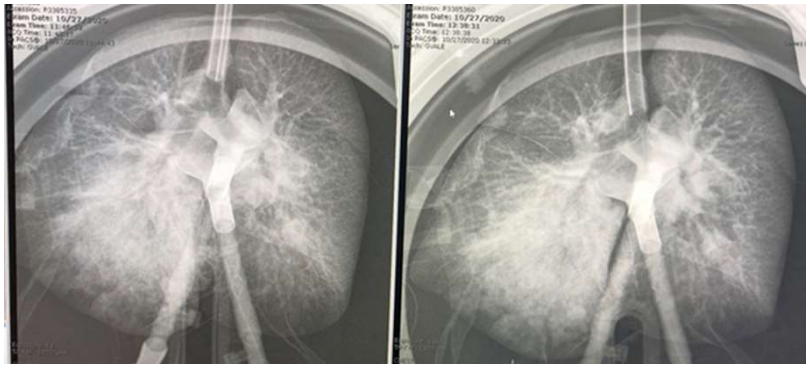
study of 50 cases of EVLP among a total of 317 transplants [13], survival for EVLP reconditioned lungs and standard transplanted lungs were similar at 1 and 3 years.



The comprehensive physiological assessment of donor lungs on the EVLP circuit includes the airway and the vascular compartment as well as their ability to oxygenate (EVLP set up is shown on the Figure on left). These assessments include serial monitoring of a combination of simple physiologic variables, namely, pulmonary artery, left atrial, and airway pressures, including the dynamic and static compliance as well as the PaO2 to Fio2 ratio. Airway examination is feasible using the standard bronchoscopic approach (see Figure, right).

Additionally, serial radiographs of the lungs can be done to assess the extent of interstitial edema (see Figure below).

Finally, the gross appearance and feel of the lungs for tissue consistency or "bogginess", compliance, and elastance are assessed serially to make a decision about the suitability for transplantation.



In summary, EVLP technology is a useful tool for increasing the utilization of donor lungs by allowing a comprehensive pulmonary physiologic assessment in an ex-vivo environment.

The EVLP program at the UTSW was launched in 2014 with a unique structure involving the CVTS/lung transplant surgeon, CVICU nurses, and transplant pulmonologist. The CVTS surgeon is dedicated to the EVLP and is responsible for the procurement of the organ, placement on the EVLP pump as well as serial assessments during the perfusion. The role of the perfusionist in managing the pump is assigned to the CVICU nurses with ECMO experience. The transplant pulmonologist contributes by way of donor evaluation and management before allocation and

inputs regarding the pulmonary physiology, airway assessment, and organ management on the EVLP. The decision-making is highly collaborative and multidisciplinary [14,15].

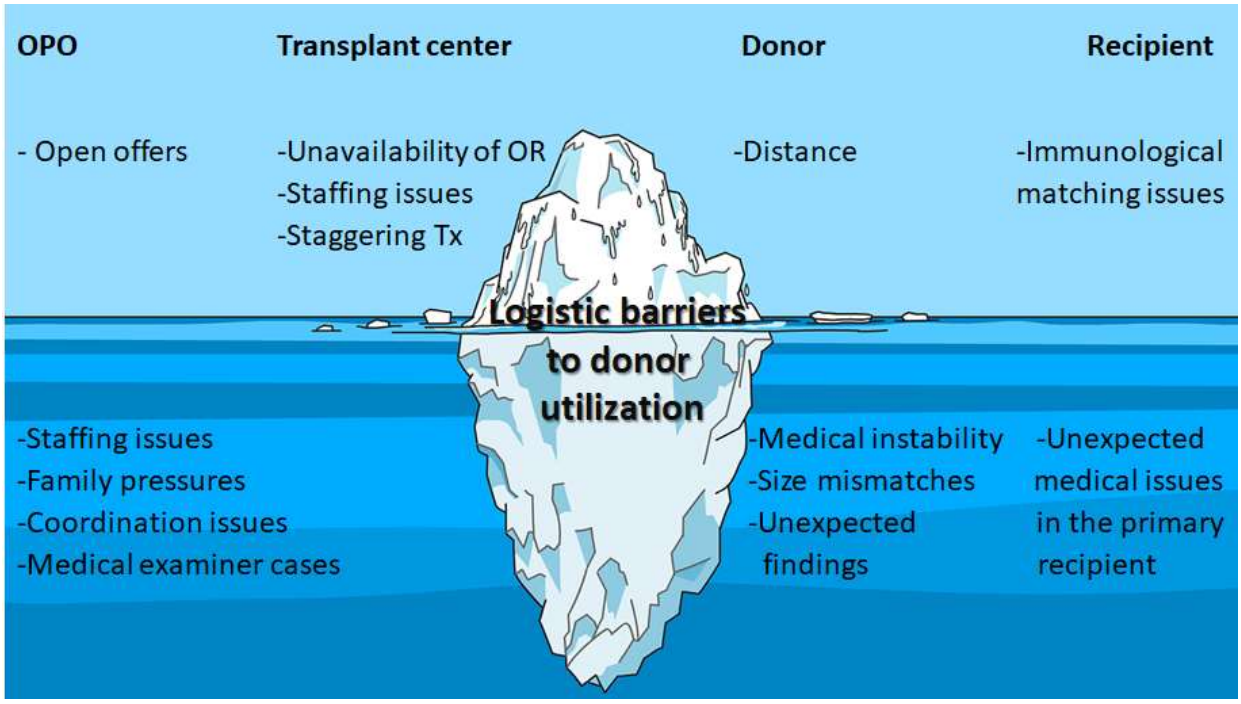
After the initial recruitment, training, trial runs, and credentialing, the program went live in early 2016. In April 2016, UTSW became the first center in Texas and among a handful of centers across the nation to conduct a transplant using lungs reconditioned using the EVLP technique. The EVLP program at UTSW is now a robust clinical program and has been contributing an increasing number of transplants every year. The availability of the EVLP technology has allowed our transplant surgeons to consider donor lungs that would have earlier been turned down for quality. Our DCD program is also heavily reliant on the EVLP program to enable careful assessment of the organ before acceptance for LT.

On the research front, the UTSW EVLP program has made useful contributions. UTSW was one of the centers for the pivotal multicenter study called the NOVEL trial, which was the first study conducted in the US to demonstrate the safety and efficacy of EVLP for utilizing marginal lungs. The highlight contribution for the EVLP program was the recently concluded multicenter study entitled, 'A Randomized, Multicenter, Blinded, Parallel, 2-Arm, Proof of Concept Study to Assess the Effects of Gaseous Nitric Oxide (gNO) in an Ex Vivo System of Human Lung Transplants' where the incremental benefit of adding gaseous nitic oxide to the perfusate was evaluated. The UTSW was the largest recruiting center with 62.5% of the total recruitment (250% of the target enrollment at the site) and singularly exceeded the combined contributions of all the other centers. The results of this trial are scheduled to be presented in the upcoming transplant meetings this year.

The Orphan Lung Program

Our clinical utilization of EVLP technology has significantly increased over the last 24 months. The EVLP team is activated for more than a quarter of lung transplants, and >10% of all LT utilize lungs reconditioned using the EVLP technology. Interestingly, the uptick in EVLP utilization is driven by its use for logistic indications. These indications often involve situations when the time available for conventional procurement is too short for the recipient or the operating room to be set-up. A significant number of donor lungs, despite no quality issues, may not get placed due to such logistic barriers, with many such issues not even coming to light (see the image below).

We have referred to such lungs as 'Orphan lungs.' The true burden of orphan lungs in the US is currently unknown, but these situations are not uncommon. Preliminary estimates indicate that the donor pool may be augmented by at least 10% if all orphan lungs are allocated (based on discussions with organ procurement organizations).



Given the backdrop of a perpetual shortfall of donor organs and high waitlist mortality, every donor lung of acceptable quality must be utilized. The EVLP technology can permit longer 'out of body' time for the donor lungs, thereby providing an opportunity to overcome the logistic barriers. At UTSW, we believe that the inability to utilize donor lungs due to logistic issues should be a 'never event' in the EVLP era. Towards this endeavor, we launched the 'Orphan Lung Program', which is aimed at enhancing the utilization of orphan lungs and further augment the donor pool. The key goal of the Orphan Lung Program is to sensitize, educate and engage the internal and external stakeholders towards the creative use of different tools, including the EVLP technology, to achieve its mission of expanding the donor pool while providing the much-needed structure to the process.

In summary, while the number of patients waitlisted for LT continues to grow and waitlist mortality remains high, the donor utilization rates have remained disappointingly low. The recent years have seen the emergence of EVLP technology as a promising tool for augmenting the donor pool by allowing assessment and reconditioning of the marginal lungs in an ex-vivo environment. Besides, EVLP allows a significantly longer organ preservation time than conventional cold storage, thereby overcoming some of the logistic barriers to LT. At UTSW, we are utilizing the EVLP technology in some unique ways, such as the orphan lung program, to further expand the donor pool for our recipients.

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