

A new era in lung transplantation: an individualized approach to donor lungs

Uma nova era no transplante pulmonar:
medicina personalizada a pulmões doados

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Since the first successful lung transplantation (LTx), performed in Toronto in 1983, there have been many technical advances. What was initially a daring endeavor has now become a routine procedure in the treatment of patients with end-stage lung disease. Despite advances in surgical techniques and patient management, one major obstacle continues to hinder the widespread success of LTx: the supply of quality donor lungs is insufficient to meet the growing demand, an increasing number of patients being in need of this life saving procedure. Currently, most donor lungs from multi-organ donors are deemed to be “too damaged” to be transplanted and are simply rejected.⁽¹⁾ Transplant surgeons and clinicians have significant concerns regarding the impact of primary graft dysfunction (PGD, an acute lung injury process occurring in the first 72 h after LTx).⁽²⁾ Therefore, most transplant centers apply strict donor selection criteria.⁽³⁾ However, there are two major problems with this highly selective approach⁽⁴⁾: up to 30% of eligible recipients die before a compatible organ becomes available; and, even when such criteria are applied, 15% of all transplant recipients develop severe PGD. Two innovative approaches, both developed within the last 5 years, will have a significant impact on donor lung availability and post-transplant outcomes in the coming years⁽⁵⁾: the use of non-heart-beating donor (NHBD) lungs; and normothermic ex vivo lung perfusion (EVLP) to reassess and recondition donor lungs that were initially rejected. The use of NHBD lungs is expected to increase the overall organ donor pool by at least 20–30%, and EVLP will significantly increase lung utilization rates (percentage of lungs from the current donor pool that are utilized for transplantation).

The controlled use of NHBD lungs is a method by which the organs can be harvested from individuals who do not meet the criteria for brain death, following elective withdrawal of life-sustaining treatments. Uncontrolled use of NHBD lungs is when the donor is either dead on arrival at the hospital or has died following unsuccessful resuscitation. The latter practice is mainly utilized in Spain.⁽⁶⁾ The controlled use of NHBD lungs has become a more widely recognized option for increasing the number of organs available for transplantation and has, in recent years, been responsible for a large proportional increase in the lung donor pools in North America, Europe and Oceania. Although there was some skepticism when NHBD lungs began to be used, various studies have now demonstrated that the short- and long-term results achieved in patients receiving NHBD lungs are at least equivalent to those achieved in patients receiving lungs from standard (brain-dead) donors.^(7,8) In fact, it is known that exposure to the inflammatory milieu after brain death is detrimental to the lungs, which could translate to an advantage of using NHBD lungs.⁽⁹⁾

In the LTx field, the advent of normothermic EVLP is an advance that is even more exciting than is the use of NHBD lungs. Ever since the development of clinical LTx, transplant clinicians and researchers have sought to reduce injury and maximize safe preservation time during the storage and transport of donor lungs. Key advancements in lung preservation, including hypothermia, inflated storage, and low-potassium dextran solution flush, have culminated in the maturation of LTx into a standard of care for end-stage lung disease worldwide. However, hypothermic preservation is limited in its ability to rescue lungs that are deemed unusable, which,

unfortunately, account for 85% of potential donor lungs. Therefore, there has been a dramatic shift in the focus of lung preservation, from postponing organ death (by hypothermia) to facilitating the assessment, recovery, and regeneration of lungs prior to implantation. This has led to the emergence of normothermic EVLP as a strategy for lung preservation. The first use of the technique to reassess the function of a human NHBD lung was described by Steen et al. in 2001.⁽¹⁰⁾ However, the utilization of normothermic EVLP became widespread only after the landmark prospective Toronto Lung Transplant Program study conducted in 2011.⁽¹¹⁾ Significant clinical experience has been rapidly accumulated in recent years, and three prospective clinical trials of different technologies are currently underway. Mariani et al. performed an excellent review of all experimental and clinical EVLP studies published to date.⁽¹²⁾ The authors also described the progress of the use of the technique in Brazil, noting that the places with the greatest potential to benefit from the use of EVLP are those such as Brazil, where there is a considerable pool of multi-organ donors but quite low utilization rates of donor lungs due to significant variability in donor lung protection across intensive care units.

Although EVLP is effective for lung preservation, its true potential lies in facilitating the reassessment, recovery, and repair of donor lungs. The concept of specialized “organ repair centers”, involving the use of remote EVLP, has emerged and could have significant implications for organ utilization and allocation in the future.⁽¹³⁾ Finally, the development of ex vivo lung repair strategies for the broad spectrum of donor lung injury is a burgeoning and important area for research. Development of an ex vivo treatment arsenal, ranging in complexity from pharmacologic (antibiotics, thrombolytics, etc.) to gene and cellular therapies might allow practitioners to take a individualized approach to the donor organ (the “personalized” or targeted repair of injuries specific to each individual donor lung), finally allowing clinicians to utilize the full potential of the donor organ pool.

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