New perspectives in lung transplantation: from conventional preservation to ex vivo lung perfusion and lung reconditioning

As novas perspectivas do transplante de pulmão: da preservação convencional à perfusão pulmonar ex vivo com recondicionamento pulmonar

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Since the first lung transplant successfully performed in 1983 in Toronto, Canada, the clinical reality of lung transplantation has been due to efforts by researchers, surgeons, pulmonologists and multidisciplinary teams aiming at solving the numerous problems inherent to this type of transplantation. Among the solid organs, the lung remains the most difficult to preserve, and the long-term results of lung transplantation remain inferior to those of transplantation of other organs, with overall one-, five- and ten-year survival rates of approximately 80%, 50% and 28%, respectively.[1] Although the most frequent indications remain essentially the same (emphysema, 36%; idiopathic pulmonary fibrosis, 20%; and cystic fibrosis, 16%), the exponential growth in the number of lung transplants has created an increasing demand for donors. Despite the development of more efficacious policies for organ donation and the advances in ICU care, the scarcity of donors remains out of step with the demand generated by the proliferation of lung transplants and has had the greatest impact on the restriction to a greater number of lung transplantations performed to date. In Brazil, a recent review of the number of donors for lung transplantation revealed that only 4.9% of the donors were accepted, and the allograft utilization rate was lower than 4%.[2] This finding is alarming, for those numbers are lower than are those of lung transplantation centers in other countries. In addition, that situation probably will be the most difficult to solve in the short term, since it requires efforts by governmental agencies, lung transplantation entities and hospitals, in addition to the education of the population, the training of medical teams, etc. The increasing disparity between the number of organs donated and the number of potential recipients on waiting lists generates a cruel reality, since the scarcity of viable organs is a determinant of mortality among the potential recipients in waiting lists. Another important restrictive factor is the quality of the organs offered. In parallel with the advances in immunosuppression, the evolution of lung preservation changed the perspectives of lung transplantation, allowing the evolution from the logistic nightmare of organ extraction at the lung transplantation center itself to the search of organs elsewhere. The last two decades of research on lung preservation have provided valuable resources and extended the periods of "safe ischemia". The creation of specific solutions for the preservation of the lung,[3] the new pulmonary perfusion techniques, the control of the reperfusion, the strategies and the alternatives of ventilation,[4,5] as well as the inclusion of additives, free radical scavengers, prostanoids and gene therapy, to name a few, have brought lung preservation to the front lines as a viable alternative for furthering the perspectives of the use of organs.

The use of "marginal donors" (those who do not meet the ideal parameters for donation) represents an alternative source of organs. Despite the fact that the early (30-day) mortality rate is higher in the recipients of organs obtained from marginal donors than in the recipients of organs from donors with lungs considered ideal (17.5% *vs.* 6.5%),[6] organs from marginal donors are still being used in specific situations.

Postmortem pulmonary donation—from non-heart-beating donors—considered a real taboo since the early days of lung transplantation, literally went from a extreme measure to a

clinical reality. Extensively investigated in laboratories, it was first applied in a clinical setting 10 years ago in Sweden.[7] In a recent study, the survival of recipients of lungs obtained from non-heart-beating donors was compared to that of recipients of lungs from brain-dead donors. The six-month, one-year and two-year survival rates were 84%, 78% and 69% in the first group, respectively, compared with 94%, 94% and 87% in the second group.[8] Steen et al. developed the concept of "lung reconditioning", in which the lungs extracted are slowly rewarmed and submitted to low flow perfusion with a solution developed by the authors. That low flow perfusion with hyperoncotic paucicellular solution showed capable of reverting the pulmonary edema and improving gas exchange, as well as preserving the lungs, thereby allowing the lung transplantation team to evaluate the pulmonary performance of the graft before the implantation. The authors performed the first lung transplantation using lungs that were initially rejected, were reconditioned and were transplanted 17 h later.[9] Recently, under the name of "pulmonary perfusion ex vivo", the system has been successfully used in other six patients by same group. The additional advantages of that process include the following: longer periods of ischemia, allowing the performance of all compatibility tests of the graft and the recipient; scheduled performance of lung transplantations in daytime shifts; and substantial increase of the availability of organs for lung transplantation. Using the same process, the lung transplantation group at the University of Toronto reported that ex vivo lung perfusion, in human lungs and in the lungs of pigs, is feasible for consecutive periods of up to 12 h. In another report by the same group, prolonged ex vivo lung perfusion of the graft resulted in better pulmonary performance after lung transplantation than did conventional perfusion with preservation solution and hypothermic storage.[10] Given that 80% of the organs donated are considered inadequate for lung transplantation, it seems logical that a portion of the organs from that immense source could be reconditioned and transplanted.

In this issue of the Brazilian Journal of Pulmonology, Pêgo-Fernandes et al.[11] inaugurate the preclinical use of the ex vivo lung perfusion in Brazil using lungs rejected for functional criteria (blood gas analysis and infection) and used for research purposes. The preliminary results are truly impressive and corroborate those previously reported in the international literature. We must celebrate this new technology, which meets the imperative of better use of the few donors we have for lung transplantation, especially in Brazil, where organ availability is low. For all of us, surgeons, clinicians and researchers involved in clinical and experimental research in lung transplantations, this might be the only moment at which we all have the privilege of participating in one of the greatest advances in lung preservation since the "deep hypothermia", proposed initially by Wilfred Bigelow in Toronto more than half a century ago.

I dedicate this final paragraph to the Brazilian thoracic surgeons and pulmonologists who, being present in most international publications on lung transplantation since its early years, have significantly contributed to the advances in the research on lung preservation.

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