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Editorial

Ex-vivo Perfusion: Assessment, Recovery and Optimisation of Human Lungs for Transplant

Perfusión *ex vivo*: evaluar, recuperar y optimizar pulmones humanos para trasplante

Francisco Javier Moradiellos Díez and Andrés Varela de Ugarte*

Servicio de Cirugía Torácica, Hospital Universitario Puerta de Hierro Majadahonda, Majadahonda, Madrid, Spain

Making lungs function outside the body and implanting them successfully is visually spectacular, mediatically stunning and scientifically of utmost importance. It also represents the end-result of 75 years of research since Carrel and Lindbergh published «The culture of whole organs» in 1935.[1] *Ex vivo* perfusion, with the possibility of assessment, recovery and optimisation of lungs will probably represent an authentic revolution in lung transplant over the next few years. Lung transplant is the last hope of treatment for advanced chronic lung disease. It is indicated in those cases where medical treatment has reached the limits of its effectiveness and when it is estimated that the risks of such an aggressive procedure are outweighed by its benefits. Lung transplant, however, is a relatively young surgical procedure. The first lung transplant with long term success was performed in 1983 and the current technique for lung transplant was described in 1990. However, more than 30,000 lung transplants have been performed worldwide in 2009, with about 2,500 transplants per year. This indicates how, in spite of being one of the most complex surgical procedures, its efficacy has led it to extend to leading chest surgery teams and hospitals throughout the world. In Spain, adoption of lung transplant was fast, and it basically developed during the '90s. Since then, a total of 2,237 lung transplants have been performed, and there is a growing trend, basically at the expense of one-lung transplants. During this period, different groups have published their experiences, both global and indication specific, and have reported similar or better results than those in the International Register. However, lung transplant is far from being a "usual" procedure and still requires great efforts on the part not only of chest surgeons and pneumonologists, but also anaesthetists, rehabilitators, immunologists, and highly specialised nursing teams. The problems faced by these teams are significant and many: early graft dysfunction, infections, acute rejection, obliterating bronchiolytis, etc. But one of the most pressing is the scarcity of valid donor lungs. *Ex vivo* perfusion, if the expectations it is generating materialise, may contribute to palliate most of these problems.

In Spain we may proudly say we have the highest rate of donors in the world (34.4 donors per million inhabitants in 2009) thanks to the generosity of the Spanish people and the constant efforts of the National Transplant Organization.[2] However, in 2009 there were 450 patients on the waiting list, of which only 219 were transplanted. In simple terms, there are not sufficient lungs to cover the demand and the receptors must remain for a median of 170 days on the waiting list. Unfortunately, a percentage of 4–10% die, others must be excluded and the majority suffer progressive clinical deterioration that makes post-transplant recovery difficult.

To solve this problem several strategies have been developed with the aim of increasing the number of valid lung donors. One of these is the use of donors with cardiac arrest ("asystole"), especially those that die suddenly outside a hospital ("non-controlled" donors) and who cannot be revived by the emergency service. This lung donor program of patients with asystole, unique in the world and in place since 2002, is the product of the collaboration of the hospitals Puerta de Hierro Majadahonda, Clínico de Madrid and Marqués de Valdecilla de Santander, as also the extra-hospital emergency services of Madrid, and has shown to be a significant alternative source of donors,[3] with results in the mean term that are similar to those obtained with conventional donors with cerebral death. However, in spite of all these efforts, only 13% of "conventional" donors with cerebral death are accepted as lung donors.[4] The main cause is the vulnerability of the lungs to the processes that derive from cerebral death itself, mainly the development of neurogenic oedema, worsened occasionally by haemodynamic support strategies with infusion of crystalloids to ensure perfusion of the remaining organs to extract. The consequence is the deterioration, sometimes in a matter of hours, of lungs that initially were structurally and functionally valid and the need to reject them for transplant. In other cases, the limited nature of the parameters registered during pre-transplant lung assessment obliges teams to reject "doubtful" lungs, simply because they cannot be certain of their functioning in the receptor. This situation also arises in the case of lungs from

* Corresponding author.
E-mail address: avarelade.hpth@salud.madrid.org (A. Varela de Ugarte).

"suboptimal" donors, the use of which is another of the strategies used to palliate the scarcity of donors.

Within this context, manifestly capable of improvement, *ex vivo* perfusion may be a good approach, as we mentioned at the beginning. The *ex vivo* system consists in making the lungs function outside the human body, but in physiological conditions (with circulation and ventilation, at 37°C and with a normal metabolism), as if they were already implanted in the transplant receptor.[5] This is achieved by connecting the lungs to an extracorporeal circuit and perfusing them with a solution specifically designed for this procedure called Steen solution (Vitrolife, Sweden). This solution contains glucose, electrolytes and amino acids to maintain cell metabolism such as albumin and polymers (dextrane-40) that confer high onchotic, endothelial lining and toxin sequestration capacities. The perfusion solution infuses through the pulmonary artery with partial gas pressures similar to those of venous blood ("deoxygenated" solution). The lungs are intubated and ventilated mechanically following a protective strategy; during perfusion they perform their exchange function normally and return an "oxygenated" solution through the pulmonary veins. The system is completed by a system of sensors that measure multiple parameters (partial gas pressures of the inlet and outlet lines, pH, temperature, flows, perfusion pressure, ventilation parameters, etc.) that quantify lung function in real time and for a long period of time- up to 12 hours, theoretically. During *ex vivo* perfusion, assessment therefore is, continuous and multiparametric, and provides greater reliability when making the final decision to implant. This greater reliability is especially important both in the case of the "doubtful" lungs already mentioned and in the case of lungs from cases of asystole, whose evaluation has not been made in physiological conditions, but in hypothermia. In this respect, our team has, for the first time in the world, performed the implant of 3 lungs from donors with non-controlled asystole who had previously been assessed in the *ex vivo* system.

The second practical use of *ex vivo* perfusion is the possibility of recovering lungs affected by pulmonary oedema at the time of donation and, therefore, not suitable for transplant. The above mentioned onchotic characteristics of Steen solution, sometimes with only 1 to 2 hours of perfusion, eliminates the oedema accumulated in the interstitium and lung alveoli and stabilizes intercell links, ensuring alveoli-capillary membrane integrity. The decrease of oedema is determined by a progressive improvement in oxygenation capacity, lung compliance and perfusion pressure, and it is truly surprising to see the progressive improvement of lungs just hours after they were considered not valid for transplant.[6] The consequence of this capacity to recover lungs damaged by oedema is evident. Only in 2008, 22 lungs were rejected due to hypoxemia attributable to oedema at the moment of extraction in Spain. That is, after they were initially accepted and the extraction team had travelled to the donor hospital. If we add the lungs initially not offered or not accepted for the same reason, the number of potentially recoverable organs is remarkable and could have a very significant impact on the number of lung transplants carried out and thereby decrease waiting lists.

The third practical use of this technique is the optimization of donor lungs prior to their implantation. In this sense, the possibilities are innumerable and we are only starting to discover them. The most evident is the possibility of applying "conventional" treatments, such as antibiotic treatment or immunotherapy to metabolically active lungs; as well as the possibility of performing graft size adjustment surgery with greater precision. However, the fact that lungs maintain their normal metabolism opens up the way to much more advanced treatments, such as gene therapy or stem cell treatment. As to gene therapy, the Shaf Keshavjee group of the Toronto General Hospital have already started the preclinical phase of transfection during *ex vivo* perfusion in human lungs with the anti-inflammatory interleukin-10 gene. These experiments have shown notable functional (oxygenation capacity and perfusion parameters), biochemical (a more favourable cytokine profile) and structural (re-establishing alveoli-capillary integrity) improvement in grafts.[7] Stem cell treatment, an unexplored territory, in conjunction with *ex vivo* perfusion, could have positive implications both as a decrease of early graft dysfunction and as an improvement of bronchial healing or even a long term decrease of obliterating bronchyolitis.

Evaluation Recovery and Optimization: the 3 pillars of *ex vivo* perfusion, a procedure truly at the front-line of knowledge in lung transplant. The experience accumulated by Spanish lung transplant groups means we are perfectly capable of integrating this new technique into our practice taking full advantage of its potential. Due to all the above, we hope *ex vivo* perfusion is increasingly adopted by other Spanish groups and, from Puerta de Hierro Majadahonda, we are at their service to help with this process.

References

1. Carrel A, Lindbergh CA. The culture of whole organs. Science. 1935;81:621-3.
2. Datos Donación y Trasplante 2009. ONT. [Accessed 15/2/2010] Available from: http://www.ont.es/Documents/Datos%20%20donacion%20y%20trasplante%20 2009%20revisada.pdf.
3. Dark JH. Lung transplantation from the non-heart beating donor. Transplantation. 2008;86:200-1.
4. Memoria pulmón 2008. ONT. 2008. [Accessed 15/2/2010] Available from: http://www.ont.es/infesp/Memorias/Memoriapulmon2008.pdf.
5. Cypel M, Yeung JC, Hirayama S, Rubacha M, Fischer S, Anraku M, et al. Technique for prolonged normothermic ex vivo lung perfusion. J Heart Lung Transplant. 2008;27:1319-25.
6. Steen S, Ingemansson R, Eriksson L, Pierre L, Algotsson L, Wierup P, et al. First human transplantation of a nonacceptable donor lung after reconditioning ex vivo. Ann Thorac Surg. 2007;83:2191-4.
7. Cypel M, Liu M, Rubacha M, Yeung JC, Hirayama S, Anraku M, et al. Functional repair of human donor lungs by IL-10 gene therapy. Sci Transl Med. 2009;4:4-9.