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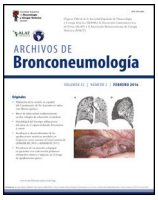

Editorial

Lung Re-Transplantation: In Favour of a Second Chance☆

Retrasplante pulmonar: en pro de la segunda oportunidad

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According to a Spanish proverb, hope is the last thing we lose, and this sentiment, so true to our human nature, helps us face our difficulties and stand up to adversity. For patients faced with the extremely difficult physical and emotional experience of lung transplantation (LTX), the knowledge that they might have a second chance may give them the courage they need to them to meet this challenge. As humans, we are averse to betting everything on a single roll of the dice, particularly in life or death situations. LTX is offered when life expectancy is less than 2 years, and there are few medical situations where the initial decision of the patient is so critical. To present LTX as a "last chance" is cruel, and simply knowing that all is not lost if things go wrong can give patients that glimmer of hope we all long for in complex situations. Setting aside these reflections on the nature of human beings, I will bring to bear my more than 20 years of experience in the field of transplantation to argue the case for retransplantation as a real therapeutic option.

Lung retransplantation (LRTX) is proposed in situations in which the first procedure has failed, either because of graft dysfunction (early or chronic), or because of airway problems that make the first procedure unviable. Despite the rising numbers of LRTX, no consensus has yet been reached on the selection of candidates for this procedure, for either clinical or ethical reasons. Indeed, some professionals believe that if the patient has already had one opportunity, they should not be offered another organ until all the patients on the waiting list have already received "their" organ. Some LTX centers do not even include LRTX on their list of services.

I would start by asking them this: would you agree to an LTX in which the final outcome depends on such heterogeneous factors as variability in clinical practice, problems with donor organ preservation, experience of the center, number of transplants performed yearly in that center, etc., knowing that patients will not be offered another chance because their hospital does not offer retransplantation? I personally would question transplantation by such a team.

LRTX accounts for a very low number of transplantations worldwide, partly because only a few transplant recipients are candidates. Indeed, now that more experience is available, the required physical and functional conditions are almost more stringent than for the first procedure. All candidates for a first LTX should be informed that they may have another chance, but that very few recipients (4%–6%) are eligible.[1,2]

Now, after 20 years of experience in LTX and copious data from the International Society of Heart and Lung Transplantation (ISHLT) registry, we are aware of the outcomes of patients undergoing lung retransplantation, the most common complications and how they should be managed, and the factors that affect survival. As of October 2017, 2191 LRTXs have been performed in over 54 000 transplant recipients worldwide (4%). Of these LRTXs, 922 are single-lung (representing only 5.1% of all unilateral procedures), and 1269 are double-lung (equivalent to 3.5% of all bilateral transplants).[1] There is, then, no single accepted surgical procedure for LRTX, the indication is adapted to the disease as required, and a unilateral or bilateral approach is tailored for each case. Moreover, if the patient has received a single lung in the first procedure, the indicated LRTX may be ipsilateral or contralateral, depending generally on rib cage problems, surgical conditions, or viability of the first graft (significant structural damage). However, in some centers, a bilateral procedure with pulmonary and/or circulatory support is proposed for LRTX from the outset, despite the increased use of organs, in view of the better long-term outcomes after double-lung transplantation.[3]

Since outcomes after LRTX are generally worse than after first LTXs, the knowledge acquired over more than 20 years has allowed us to establish some prerequisites for LRTX.

Clear indications. Retransplantation is not a last-ditch option with little chance of success. For example, it would be a poor use of available organs to indicate the procedure in severe primary graft dysfunction in the immediate post-transplantation period, as the final outcome of this intervention is usually disappointing. The best outcomes for LRTX are obtained 2 years after the first transplantation. Currently, in 20% of cases it is indicated during the first year after first graft, in most cases (>60%) between 1 and 10 years, and in the rest after 10 years. The indications with best survival are the most common clinical forms of chronic lung allograft graft dysfunction (CLAD): obstructive CLAD or bronchiolitis obliterans

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syndrome. The worst outcomes for retransplantation occur in early dysfunction and cases of restrictive CLAD.[3,4]

Surgical techniques in LRTX have improved over time, and the use of intraoperative/postoperative circulatory support with veno-venous or veno-arterial extracorporeal membrane oxygenation (ECMO) (pulmonary and/or circulatory support) has increased. This avoids the higher levels of anticoagulation required by conventional bypass techniques and helps reduce hemorrhagic complications in the second intervention. Both the surgical procedure and the immediate postoperative period are clearly more complicated in LRTX, and higher rates of bleeding, adhesions, reinterventions, and longer stays in the surgical ICU have been reported. Without EMCO support, patients undergoing LRTX have a higher risk of mortality due to severe graft dysfunction or due to postoperative complications requiring a long ICU stay, which in itself always takes a heavy toll.[3] In fact, technical surgical problems and graft failure account for 13.5% and 24.2%, respectively, of fatal outcomes in the early days after LRTX, figures that are slightly higher than for the first transplantation. The use of support techniques improves short- and long-term outcomes.[1,3]

Comorbidities are similar to the first procedure, with 1- and 5-year rates of renal impairment of 25.5% and 61.4%; diabetes 19.6% and 33.1%; and chronic rejection 16.2% and 49.3%, respectively.[1] Only the incidence of chronic rejection at 1 year compared with the first transplantation is slightly higher, as this is one of the primary indications for LRTX.[5,6]

Survival. In the Spanish[7] and international registry data, LRTX mortality focuses on the first 30 days and the first year, but after these cut-off points (which arise from the selection of candidates and intraoperative management), survival is comparable to first transplantations in other diseases with other diagnoses treated with transplantation.[8–14] Thus, if mortality during the first 3 months is excluded, mean survival is 5 years. If real mortality rates after T0 post-transplantation are assessed, mean survival is 6 years for the first LTX and 3 years for the repeat procedure. As a practical example, if we rule out mortality during the first 3 months post-transplantation, mean survival for idiopathic pulmonary fibrosis is 6.1 years, and 5 years for retransplantation.[1] It must also be remembered that survival is more than twice as long for more recent LRTXs undertaken after the initial learning curve. Survival after LRTX performed between 1990 and 1998 was around 1 year, compared to 3 years for procedures performed between 2009 and 2015. In Spain, according to the national transplant registry, LRTX offers a 5-year survival rate of over 30%, compared to 48% for idiopathic pulmonary fibrosis.[7] This tendency for outcomes to improve in line with experience is typical of all LTX programs that perform LRTX.

The arguments against LRTX are far from unreasonable: greater use of organs (a scarce resource), greater healthcare costs, and ethical considerations ("they already had their chance"). One of the main arguments of LRTX detractors is that resources are limited and there are not enough organs to go round. A patient who has already had their chance should step aside for another who, of course, has better life expectancy. Equal opportunities and justice for all is all very well, but we could counter by pointing out that some LRTX candidates may not have enjoyed all the advantages of the system at the time of their first transplantation, be they medical, economic, or social. In this scenario, LRTX might seem fair in some cases, but this argument alone is probably insufficient to settle the issue. Early LRTX, for example, carries a prohibitive risk and should be avoided in all but the most exceptional circumstances.

LRTX is ethically justified; however, prioritizing the use of lungs for either initial transplantation or LRTX must be guided by fairness and effectiveness, and decisions must be based on accurate estimates of the net benefit. Future efforts should focus on clarifying the mechanisms of CLAD, preventing mortality in LRTX, refining candidate selection criteria, improving techniques to reduce surgical morbidity and mortality, and achieving good long-term outcomes. A hitherto unexplored area in Spain is live lung donor; this is an option to consider in feasible cases, such as pediatric recipients or individuals who require smaller grafts.

As mentioned above, the overall outcomes of LRTX are worse than for the first procedure, but results in some well-selected recipients are more than acceptable. Indeed, in these cases, no differences in survival are detected when the outcomes of LRTX are compared to the outcomes of the first transplantation.[2,3,15] It is now clear that age over 50 years and LRTX in the first 2 years after the first graft are associated with poorer survival.[11] The Toronto group recently published their experience in LRTX, reporting a mean survival of 4 years after LRTX, with a gain in quality of life similar to the first transplant.[15] These good results are generally based on procedures performed in young patients with CLAD and with the use of intra- and/or postoperative EMCO.[3–5,15] These data, along with those from the ISHLT and the Spanish transplant registry, suggest that LRTX is a real option that is both necessary and useful. Though challenging from many points of view, it offers good outcomes and an excellent quality of life. LRTX should be viewed from the perspective of current experience and indicated only in patients with the best chance of success. The poor LRTX data that appear in the different transplant registries are a manifestation of the early learning curve, inexperience, and poorly defined surgical indications.

More recent data from the Spanish and international registries and the experience of LTX centers which perform large numbers of transplants support LRTX as an acceptable therapeutic option. There is little question that LRTX is a major challenge for both the health system and the professionals involved. It is more complicated than the first procedure, but fully acceptable if the following criteria are met: it should only be indicated in centers that perform large numbers of procedures and have good LTX outcomes and experience in LRTX, and preferably in candidates with a good chance of success, such as young patients or those who present late chronic graft dysfunction.

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