Review Article

Lung transplant in end-staged chronic obstructive pulmonary disease (COPD) patients: a concise review

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ABSTRACT Lung transplantation is commonly used for patients with end-stage lung disease. However, there is continuing debate on the optimal operation for patients with chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis. Single-lung transplantation (SLT) provides equivalent short- and medium-term results compared with bilateral lung transplantation (BLT), but long-term survival appears slightly better in BLT recipients (especially in patients with COPD). The number of available organs for lung transplantation also influences the choice of operation. Recent developments suggest that the organ donor shortage is not as severe as previously thought, making BLT a possible alternative for more patients. Among the different complications, re-implantation edema, infection, rejection, and bronchial complications predominate. Chronic rejection, also called obliterative bronchiolitis syndrome, is a later complication which can be observed in about half of the patients. Improvement in graft survival depends greatly in improvement in prevention and management of complications. Despite such complications, graft survival in fibrosis patients is greater than spontaneous survival on the waiting list; idiopathic fibrosis is associated with the highest mortality on the waiting list. Patients should be referred early for the pre-transplantation work-up because individual prognosis is very difficult to predict.

Key Words: Lung transplantation; chronic obstructive pulmonary disease

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Introduction

The first human single-lung transplant for advanced emphysema was performed in 1970. It was not until the late 1980s that more widespread attempts at lung transplantation were undertaken. Chronic Obstructive Pulmonary Disease (COPD) represents a growing problem affecting millions of people worldwide.

The disabling symptoms of COPD, such as severe dyspnea and exercise limitation, produce a poor quality of life that can lead to early death (1). The respiratory impairment caused by COPD has various mechanisms. Destruction of pulmonary parenchyma with lost of elastic recoil cause a reduced mass of functioning lung tissue with consequent decreased capacity for gas exchange and an increasing volume in the chest, leading to the typical hyper expanded chest seen in this disease, patients with flattened diaphragms, widened inter-costal spaces, and horizontal ribs.

These anatomic changes lead to increased work of breathing and dyspnea. In addition, the association of reversible bronchospasm and irreversible loss of elastic recoil causes small airway obstruction. Medical treatment and respiratory rehabilitation are the main treatments for emphysema; however, a subset of patients with severe emphysema not responding to medical therapy may benefit from surgical treatments. Available surgical options are bullectomy, lung volume reduction (LVRS), and lung transplantation (LT) (2). LT is a surgical procedure in which a patient's diseased lungs are partially or totally replaced by lungs which come from a donor (Fig 1-3). LT is now a widely accepted therapy for the management of various forms of severe lung disorders (3), with clear improvement in survival and quality of life (4). At beginning of the LT experience, pulmonary fibrosis and pulmonary hypertension were the main indications, while COPD was considered a contraindication. After the first successful report of a single LT for emphysema and the development of techniques to allow safe bilateral LT, the number of procedures for COPD quickly increased (5,6,7).

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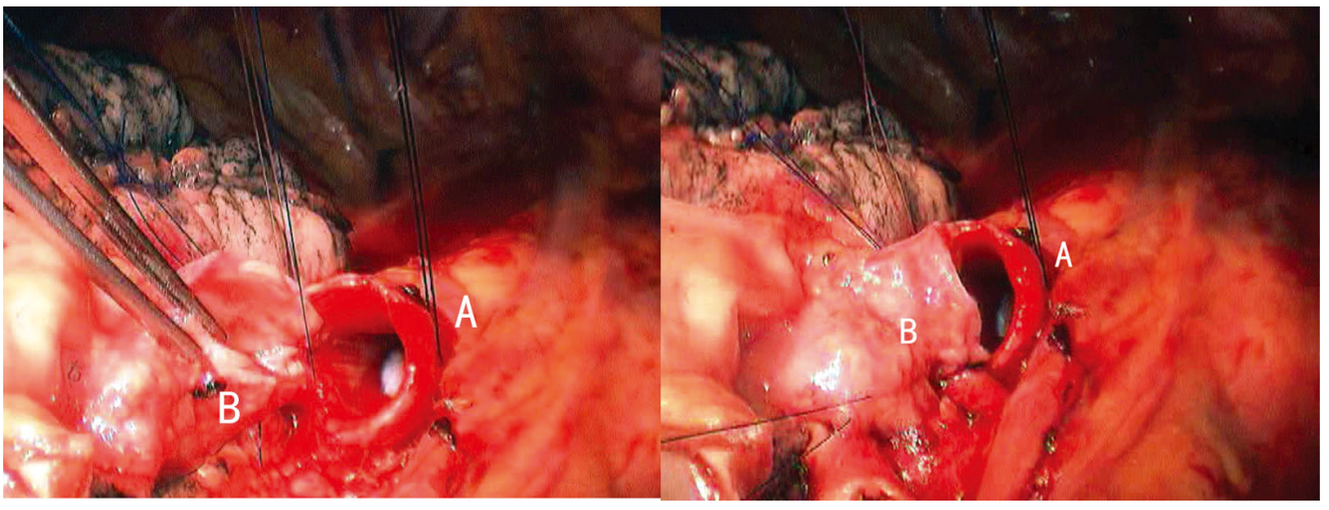

Fig 1. Anatomosis of the right main bronchus: A, the right main bronchus of the recipient; B, the right main bronchus of the donor.

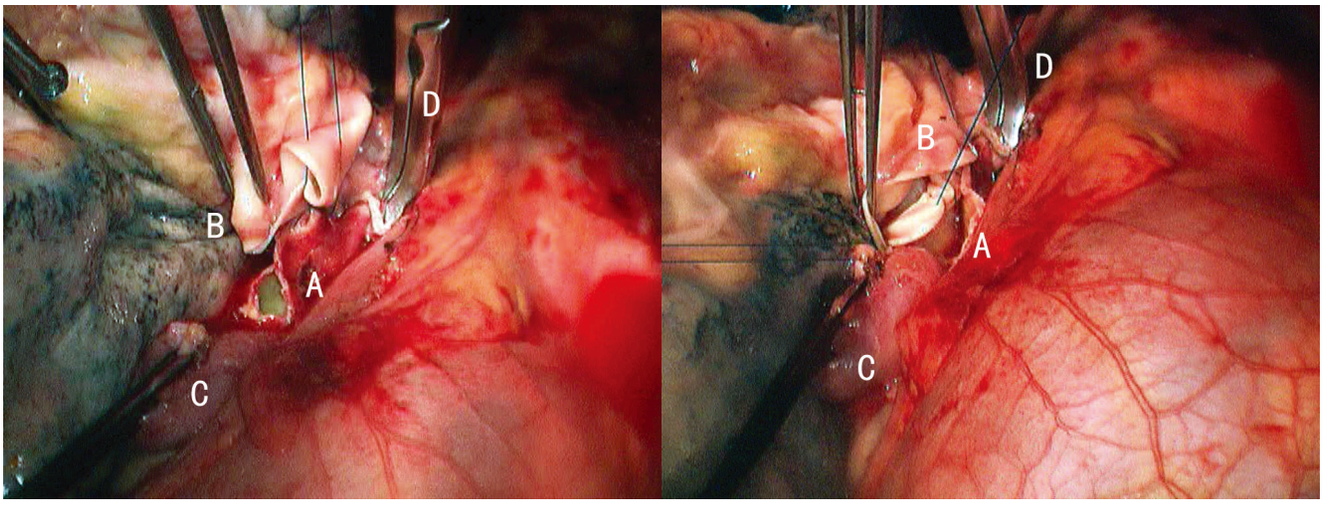

Fig 2. Anatomosis of the right pulmonary artery (PA): A, the right PA of the recipient; B, the right PA of the donor; C, the right pulmonary vein of the recipient; D, clamp to control PA.

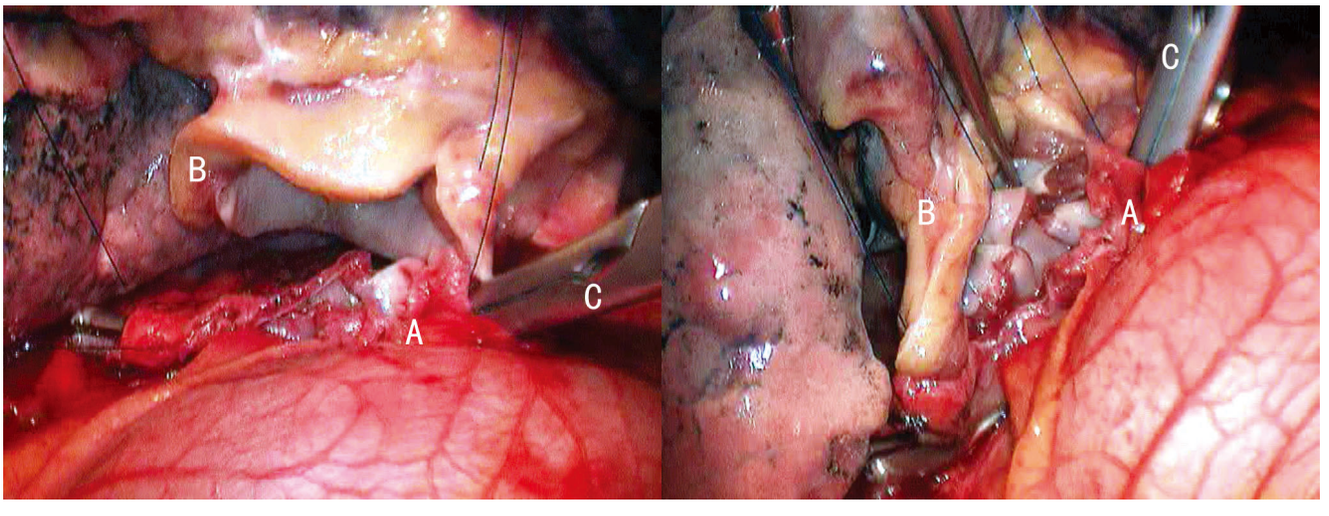

Fig 3. Anatomosis of the atrial cuff: A, the atrial cuff of the recipient; B, the atrial cuff of the donor; C, clamp to control atrial cuff.

Currently, COPD has become the most common indication for LT (8,9).

According to the last report of The Registry of the International Society for Heart and Lung Transplantation (ISHLT) (10), idiopathic emphysema and Alpha 1-antitrypsin deficiency (AT Def) together account for 45.1% of all adult LT, 59.5% of all single LT, and 32.5% of all bilateral LT.

Recipient selection

Patients with COPD should be referred for transplantation only when a severe worsening of the disease is present with clinical deterioration despite optimal medical therapy and rehabilitation. In general, ideal candidates for LT are those who have a predicted survival of 2 years or less, who have great motivation; adequate social, psychological, and family support; who are free of other important co-morbidities; and who are able to be enrolled in a pre-transplantation program of pulmonary rehabilitation. Smoking cessation for at least 6 months before surgery is an obligatory requisite. Previous surgical procedures such as LVRS, pleurectomy, or talc instillation are relative contraindications, because of the risk of operative bleeding; similarly, steroid therapy should be limited to a dose no greater than the equivalent of 20 mg of prednisone daily to limit anastamotic complications. Age limitation of 65 years is advised for single LT and 60 years for bilateral LT. A subgroup of emphysematous patients can be candidates for both for LT and LVRS given the overlap of indications (11). Guidelines on this topic are still lacking, and some authors have suggested a possible role of LVRS as a bridge to LT. Patients with hospitalization for acute exacerbations associated with hypercapnia (PaCO2 >55 mm Hg), substantial hypoxemia, secondary pulmonary hypertension, and/or right ventricular failure have specific indications to be proposed for LT, such as the high-risk group of patients identified by The National Emphysema Treatment Trial (NETT) (12): subjects with FEV1 of less than 20% and either a DLCO of less than 20% or homogeneously distributed emphysema. Recently, the ISHLT published guidelines for selection of LT candidates (13), underlining the importance of the BODE index as a predictor of disease severity (14). Patients with a BODE score of 7 to 10 are optimal candidates for transplantation, having a predicted survival less than expected survival after LT. Patients with BODE score of 5 to 6 would likely not derive a survival benefit from transplantation but may be candidates for early referral. However, the appropriate timing for transplantation in emphysematous patients is complicated since the natural history of this disease is unpredictable and very symptomatic patients may have a relatively good prognosis. Therefore, the question of whether it is justified to perform an LT primarily for quality-of-life purposes, with uncertain benefit on survival, arises frequently in these patients. Prior to May 2005, donor lungs were allocated to transplant candidates by a seniority system based on accumulated waiting time (15). Since May 2005, UNOS replaced this system with a lung allocation score, a number derived from an algorithm that calculates medical urgency (predicted waiting list survival) and net transplant benefit (predicted post transplant survival minus predicted waiting list survival). A clear difference has been observed in the rankings for emphysema and idiopathic pulmonary fibrosis or cystic fibrosis patients.

Benefits, risks and results

The primary scope that is expected from LT is to provide a survival benefit. Although various studies have reported a clear impact on life expectancy after LT for idiopathic pulmonary fibrosis, cystic fibrosis, and primary pulmonary hypertension (16-19), reports for emphysematous patients are inconsistent (20).

Therefore, patients accepting this therapeutic option should be aware that they face a procedure burdened by immediate risks of mortality and morbidity in exchange for relief of symptoms, but uncertain survival gains. Debate is still open in the transplant community regarding how to weigh expected survival benefit with gains in quality of life. The reported peri-operative mortality rate after LT ranges between 5% and 15%, although the most recent experiences show mortality rates of less than 10%, underlining the importance of the learning curve, the improvements in surgical and anesthetic techniques, and the better peri-operative management (21-24). A low peri-operative mortality among COPD patients can also be explained by the lack of requirement for cardiopulmonary bypass during the transplant procedure.

Postoperative complications, which can be early or late, may be divided into respiratory and non-respiratory complications. The main respiratory complications in the early period are ischemia-reperfusion injury (25,26), bronchial anastomotic complications (27,28), pneumonia, acute mediastinal shift due to hyperinflation of the native lung with mechanical compression, peculiar for single LT in emphysema (29) and atelectasis of the allograft that may lead to vascular (hypo- tension) and respiratory (hypoxemia) problems. Late respiratory complications are infections and chronic rejection (30). Non-respiratory complications are numerous and often related to immunosuppression or other transplant medications. More common complications are systemic hypertension, renal insufficiency, diabetes mellitus, hyperlipidemia, osteoporosis, gastroparesis,

lymphoproliferative disorders, or neoplasms (3).

Benefits expected from LT in emphysematous patients are essentially related to respiratory function and quality of life. After single LT and most of all after bilateral LT a substantial improvements have been described in pulmonary function (31,32), exercise capacity (33), and quality of life (34). Reports are different but survival rates range between 80% and 90% at 1 year and 41% and 58% at 5 years (35). Survival was significantly higher for patients receiving bilateral LT and for those with Alpha 1-antitrypsin deficiency compared with idiopathic emphysema (10). A survival benefit in patients with Alpha 1-antitrypsin deficiency is probably related to the greater number of bilateral procedures and the younger age of the candidates.

Single versus bilateral

Several studies in the literature have compared the results during follow-up of double lung versus single lung transplantations for emphysema. They have concluded that survival rates were better in the former case. However, in many of these studies the groups were not homogeneous and confounding factors were present that could distort the final result. Thus, Cassivi et al. reported 5-year survival rates of 66.7% versus 44.9% for double versus single lung transplantations respectively, with most of the younger patients with α-1 antitrypsin deficiency belonging to the double lung group (36).

The international registry shows similar results, but it is based on data provided by various centers and therefore not comparable (37). Later, Delgado et al. showed data from all lung transplantations performed for this indication at their center, by the same team and with similar subsequent follow-up conditions (38). The results showed no difference in terms of long-term mortality between both groups, nor was there a higher incidence of morbidity. Thabut et al. concluded in their study of 9883 patients who underwent transplantation for this indication that for patients aged older than 60 years there may not be a survival benefit for patients who underwent transplantation with both lungs (39).

Most authors have advocated double lung transplant, arguing that native lung hyperinflation may be responsible for the poorer results (40). Single lung transplantation is anatomically less aggressive, technically simpler, and has a shorter total ischemia time, which explains its lower peri-operative morbidity and mortality rates. For this and the other reasons described above and excluding exceptions, we consider that single lung transplantation should be the treatment of first choice in emphysema, because it is an approach that attempts to alleviate the donor organ shortage and decrease waiting list morbidity and mortality, with comparable 5-year outcomes. It has the option of being complemented with lung volume reduction surgery or subsequent contralateral transplantation if necessary.

Both single and bilateral LT have advantages and drawbacks. Proponents of the single procedure emphasize that it is a simpler operation performed via lateral thoracotomy incision, with short operative and ischemic times, reduced mortality rate, and rare need for cardiopulmonary bypass. In consideration of the lack of organs, one donor can be utilized for two recipients reducing the waiting list time.

Bilateral LT is performed through a median sternotomy or a clamshell incision; cardiopulmonary bypass is required in about 20% of cases. The earliest reports comparing the merits and risks of the two operations reported a higher peri-operative mortality among patients receiving bilateral LT, without a significant functional benefit. Recent reports show no significant differences in peri-operative mortality between single and bilateral procedures. Bilateral LT has proven to display undoubted advantages on long-term survival, pulmonary function, and exercise tolerance. Besides, bilateral LT reduces the risk related to ischemia-reperfusion injury, since it avoids the infective risk related to the native lung, such as the risk of hyperinflation. A greater reserve in case of chronic allograft rejection can also contribute to the longer survival among this group of patents. On the basis of these data, an important question is whether it is better to favor more operations in consideration of the scarce resources due to the high number of candidates, or whether the better operation should be preferred. The tendency of the transplantation community, as reported by ISHLT Registry, is toward an increasing number of bilateral procedures: in 2005, bilateral LT was performed in 75% of patients affected by Alpha 1-antitrypsin deficiency and in 48% of patients with idiopathic emphysema. In general, a bilateral procedure seems to be advantageous for young patients, particularly those with Alpha 1-antitrypsin deficiency and those with emphysema and associated purulent lung disease (bronchiectasis or marked daily sputum production), because of the risk of allograft infection by secretions from the native lung. The bilateral option is also more attractive in larger recipients who might never obtain a sufficiently large single lung allograft. For smaller recipients, single LT is a suitable option, particularly when an oversized donor lung can be grafted.

The use of bilateral LT should also be considered in the setting of marginal donor lungs that might otherwise be deemed unsuitable for single LT, thus enhancing use of the donor pool. Although the presence of pulmonary hypertension is not a contraindication for single LT, some authors favor bilateral LT to minimize the likelihood of

early graft dysfunction because of over-perfusion of the allograft.

Current approach to immunosuppressive therapy

Induction therapy after lung transplantation may reduce and delay acute rejection episodes and may also reduce the incidence of chronic rejection. Unfortunately, no large, prospective, randomized, placebo-controlled trials exist to confirm the benefits of induction therapy compared with conventional immunosuppression and to compare different agents. Current evidence suggests that the induction therapy may be associated with better outcomes, although controversy exists (41).

Maintenance therapy with triple-drug therapy is still the conventional practice for lung transplantation. The first-line treatment of an episode of acute rejection is high-dose intravenous steroid pulses. For ongoing or recurrent acute rejection, the strategy is to add rapamycin, a newer antiproliferative drug. The second choice for refractory acute rejection is treatment with antithrombocyte globulin (ATG) or OKT3. In refractory cases, high-dose intravenous immune globulin can be used.

For treatment of chronic rejection, which is referred to as bronchiolitis obliterans syndrome, the most difficult issue following lung transplantation remains unsettled. Patients taking a cyclosporin A regimen should be switched to tacrolimus from cyclosporine. For patients unresponsive to the change to tacrolimus from cyclosporin A, high-dose steroid pulses and ATG are still frequently used. Rapamycin may also be introduced as a fourth agent. Other possible therapies are total lymphoid irradiation and photopheresis, which are really last resorts.

In summary, LT is a reliable therapeutic option for emphysematous patients. A strong impact on pulmonary function, relief of symptoms, and thus quality of life are well-recognized advantages, but the real survival benefit is still unclear. At present, LT should be offered to a select pool of candidates with severe disease and reduced life expectancy. Progress could minimize the mortality and morbidity related to this procedure and improves post-operative immunologic management.

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