

## EDITORIAL

# Lung retransplantation

M. Estenne, C. Knoop

During the past decade, lung transplantation has become an established treatment for patients suffering from end-stage vascular and parenchymal lung disease [1-4], and the outcome for lung transplant recipients has improved considerably. However, early and late dysfunction of the lung allograft remain common and are responsible for a significant morbidity and mortality. At least 20-25% of lung transplant recipients are at risk of graft failure and death within 3 months of surgery, owing to a variety of difficulties primarily related to early donor lung dysfunction, acute rejection, infection and airway complications [5, 6]. In addition, obliterative bronchiolitis remains the most serious long-term complication after lung transplantation, occurring in as much as 40% of long-term survivors [6]. Each of these early or late complications may prove so intractable and life-threatening that lung retransplantation appears to be the only hope for continued survival. This therapeutic option, however, remains a considerable source of controversy for both medical and ethical reasons.

The available data on lung retransplantation is limited [5]. In addition to a few anecdotal reports [7-15], and the study by FOURNIER *et al.* [16] published in this issue of the Journal, there have been two studies including a significant number of patients. One has been published by MADDEN *et al.* [6], who reported results with redo heart-lung transplantation in 24 patients and with single lung transplantation in six patients who had previously undergone a heart-lung procedure. The other study is a survey of the American-European experience with lung retransplantation, recently published by NOVICK *et al.* [17]. This retrospective study included 63 procedures in 61 patients, *i.e.* 35 redo single lung, 8 redo double lung, 13 single lung after double lung or heart-lung transplantation, and 7 double lung after single lung transplantation. Of these 61 patients, 23 were retransplanted within a month of the initial procedure, whilst 32 were retransplanted in the late postoperative period for obliterative bronchiolitis. From these studies, it appears that the overall results of lung retransplantation are not favourable. At all time intervals, the actuarial survival of a second lung transplant is lower than that for a first one, and on average the one year actuarial survival after redo lung transplantation is 30-35% as compared to 60-70% after a first graft [5, 6, 17]. Neither the indication for retransplantation, nor the type of retransplantation influence the survival rate [17]. Half of the mortality occurs within 3 months of surgery, due to surgical problems (mainly bleeding), infection, graft failure, acute rejection, and airway complications, and, despite a steadily increasing number of redo lung transplantations, the 3-month postoperative survival has not

improved since 1985 [17]. A similar observation has been reported for kidney retransplantation [18].

The fact that early retransplantations have a poor outcome is to be anticipated. Most patients undergoing such emergency procedures are ventilator-dependent, receiving heavy immunosuppression, and are colonised by bacteria due to their prolonged stay in the intensive care unit [17]. In some of them there is evidence of disseminated infection or multi-organ failure at the time of retransplantation, which by itself carries a very poor prognosis [17].

In addition, early retransplantations present a unique challenge in terms of immunological tolerance, as evidenced by the observation that for such procedures, survival is lower for the second than for the first graft in all types of solid organ transplantation [18-22]. For example, one year actuarial survival is 10-30% lower after a redo than after a first heart or kidney transplantation when the second procedure is performed within 6 months of the initial one [18-21]. In contrast, beyond 6 months survival rates are almost identical for first and second transplants. Graft loss is a potent stimulator of immunity, and sensitization of the recipient, either cellular or humoral, presumably accounts for the high rate of early immunological failures of the second graft [18]. Problems of sensitization and preimmunization are particularly significant in recipients with strong immune responsiveness, who have lost their first graft from early uncontrolled rejection [18-20]. Furthermore, although it is expected that all patients with a prior graft loss are sensitized, the level of sensitization increases with the degree of histo-incompatibility in the first transplant [18]. Sensitization might, thus, be high in lung transplant recipients because they are usually mismatched for most human leucocyte antigens (HLA).

For all of these reasons, it appears unreasonable to propose lung retransplantation to patients with early graft failure. Is it more justified to retransplant long-term survivors with end-stage obliterative bronchiolitis? There is no definite answer to this question, because the available experience is too limited. In contrast to heart and kidney retransplantation, however, lung retransplantation does not yield better results when performed in the late rather than the early postoperative period [17]. In addition, a great source of concern is that patients who have developed obliterative bronchiolitis in their first transplant may do so again in the second. In the study by NOVICK *et al.* [17], obliterative bronchiolitis was responsible for 50% of deaths occurring in re-graft patients 12-24 months after surgery. Similarly, after heart retransplantation for accelerated coronary artery disease, which like obliterative bronchiolitis is thought to be a form of chronic rejection, the incidence of recurrent coronary artery disease in the second graft is high [23]. An additional problem is that patients

undergoing retransplantation for obliterative bronchiolitis are usually colonised with resistant bacteria and opportunistic organisms. This factor, as well as immunological mechanisms, presumably explain the worst outcome of heart-lung and double lung transplant patients in whom only one of the two lungs with obliterative bronchiolitis is retransplanted [17].

More information is clearly needed. The current experience does not support early retransplantation as a viable option, but redo lung transplantation might be indicated in some long-term survivors with obliterative bronchiolitis. For an optimal selection of these patients, however, we need to gain a better understanding of the pathogenesis of this complication and of the factors which may predispose to it in either first or a second graft. We also need to determine the best second graft surgical procedures, the optimal early and long-term immuno-suppressive protocols, and the long-term outcome of regraft patients. Only multicentre trials will provide objective answers to these questions and will avoid wasting lives and donor lungs. Until such trials are organised these precious organs should be reserved for primary lung transplantation, given the current shortage of donor organs.

#### References

1. Reitz BA, Wallwork JL, Hunt SA, *et al.* – Heart-lung transplantation: successful therapy for patients with pulmonary vascular disease. *N Engl J Med* 1982; 306: 557–564.
2. Toronto Lung Transplant Group. – Unilateral lung transplantation for pulmonary fibrosis. *N Engl J Med* 1986; 314: 1140–1145.
3. Scott J, Higenbottam TW, Hutter J, *et al.* – Heart-lung transplantation for cystic fibrosis. *Lancet* 1988; ii: 192–198.
4. Yacoub MH, Banner NR, Khaghani A, *et al.* – Heart-lung transplantation for cystic fibrosis and subsequent domino heart transplantation. *J Heart Transplant* 1990; 9: 459–467.
5. Kaye MP. – The Registry of the International Society for Heart and Lung Transplantation: Ninth Official Report - 1992. *J Heart Lung Transplant* 1992; 11: 599–606.
6. Madden B, Radley-Smith R, Hodson M, *et al.* – Medium-term results of heart and lung transplantation. *J Heart Lung Transplant* 1992; 11: S241–243.
7. de Hoyos AL, Patterson GA, Maurer JR, *et al.* – Pulmonary transplantation. Early and late results. *J Thorac Cardiovasc Surg* 1992; 103: 295–306.
8. Egan TM, Westerman JH, Lambert CJ Jr, *et al.* – Isolated lung transplantation for end-stage lung disease: a viable therapy. *Ann Thorac Surg* 1992; 53: 590–596.
9. Haverich A, Hirt S, Wahlers T, *et al.* – Functional results after lung retransplantation (Abstract). *J Heart Lung Transplant* 1993; 12: S69.
10. Haydock DA, Trulock EP, Kaiser LR, *et al.* – Management of dysfunction in the transplanted lung: experience with 7 clinical cases. *Ann Thorac Surg* 1992; 53: 635–641.
11. Low DE, Trulock EP, Kaiser LR, *et al.* – Lung transplantation of ventilator-dependent patients. *Chest* 1992; 101: 8–11.
12. Madden BP, Khaghani A, Yacoub M. – Successful retransplantation of the heart and lungs in an adult with cystic fibrosis. *J Roy Soc Med* 1991; 84: 561.
13. Ramirez JC, Patterson GA, Winton TL, *et al.* – Bilateral lung transplantation for cystic fibrosis. *J Thorac Cardiovasc Surg* 1992; 103: 287–294.
14. Schmid C, Gulba DC, Heublein B, *et al.* – Systemic recombinant tissue plasminogen activator lysis for left atrial thrombus formation after single-lung retransplantation. *Ann Thorac Surg* 1992; 53: 338–340.
15. Shennib H, Novick R, Mulder D, *et al.* – Is redo lung transplantation indicated? Report on four patients. *Eur Respir J* 1993; 6: 354–357.
16. Fournier M, Sleiman C, Mal H, *et al.* – Single-lung retransplantation for late graft failure. *Eur Respir J* 1993; 6: 1202–1206.
17. Novick RJ, Kaye MP, Patterson A, *et al.* – Redo lung transplantation: a North American - European experience. *J Heart Lung Transplant* 1993; 12: 5–16.
18. Yanagiya A, Cecka JM. – Second transplants. In: P. Terasaki ed. *Clinical Transplants*. Los Angeles, California, UCLA Tissue Typing Laboratory, 1989, pp 397–405.
19. Morris PJ. – Results of renal transplantation. In: Morris PJ, ed. *Kidney Transplantation 3rd ed. Principles and Practice*. Philadelphia WB Saunders Co., 1988, pp 737–758.
20. Karwande SV, Ensley RD, Renlund DG, *et al.* – Cardiac retransplantation: a viable option? *Ann Thorac Surg* 1992; 54: 840–845.
21. Mullins PA, Scott JP, Dunning JJ, *et al.* – Cardiac transplant waiting lists, donor shortage and retransplantation and implications for using donor hearts. *Am J Cardiol* 1991; 68: 408–409.
22. Saito S, Langnas AN, Stratta RJ, *et al.* – Hepatic retransplantation: University of Nebraska Medical Center experience. *Clin Transplantation* 1992; 46: 430–435.
23. Gao SZ, Schroeder JS, Hunt S, *et al.* – Retransplantation for severe accelerated coronary artery disease in heart transplant recipients. *Am J Cardiol* 1988; 62: 876–881.