Single-lung retransplantation for late graft failure

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Single-lung retransplantation for late graft failure. M. Fournier, C. Sleiman, H. Mal, O. Groussard, J-L. Mollo, J-P. Duchatelle, B. Andreassian, R. Pariente. ©ERS Journals Ltd 1993.
ABSTRACT: In lung or heart-lung recipients, an irreversible graft-failure may develop in connection with chronic rejection, infection or bronchial complications. A limited number of transplant-recipients have undergone a retransplantation procedure in several centres. First results are discouraging, especially in the case of early retransplantation. We decided, 3 yrs ago, to evaluate the feasibility and benefits of single-lung retransplantation in lung-transplant recipients with late graft-failure.

Eight consecutive single-lung retransplantations were performed in patients with previous single-lung (n=7), or double-lung (n=1) transplant. Primary graft and native lung were removed in 5 and 3 patients, respectively. The delay between the two surgical procedures was 16±10 months (range 6–37 months).

Three patients died within 3 months. Long-term survivors experienced stable and satisfactory functional results (forced expiratory volume in one second (FEV_1 63±21% predicted; range 40–103% predicted), with survival values ranging 8–20 months. One patient died of septic shock 16.5 months after retransplantation. The remaining four patients are alive.

These data suggest that the retransplantation option could be considered in selected patients with late graft-failure. The final decision for retransplantation, however, is largely influenced by the current shortage of donor lungs.
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Current actuarial survival data for lung transplantation [1] average 60% and 55% at 1 and 2 yrs, respectively. During the last 3 yrs, the postoperative risk of mortality has decreased, particularly for the single-lung transplantation procedure. However, as the life expectancy of lung-transplanted patients continues to increase, the late development of progressive respiratory insufficiency has emerged as a major problem in a number of transplant recipients. The most prominent cause of graft failure seems to be the development of a diffuse bronchiolitis obliterans (BO) [2], which responds poorly - or is refractory - to augmented immunosuppression. In such cases of irreversible graft-failure in transplant recipients, the retransplantation (ReT) option may be discussed. Operative mortality associated with lung ReT is reported to be high: 52% for combined heart-lung ReT, and 42% for single-lung ReT. In addition, one year actuarial survival following ReT is 30% for combined heart-lung, and 33% for single-lung [1]. However, these results may depend on the circumstances and/or indications for retransplantation [3]. For example, data provided KRIETT and KAYE [1] refer to graft replacement in the early operative period, as well as retransplantation for late graft-failure in long-term survivors.

We therefore decided, 3 yrs ago, to evaluate the feasibility and the benefits of single-lung retransplantation in lung-transplant recipients with late graft-failure. This report describes our experience with the first eight consecutive patients who underwent a single-lung retransplantation between January 1989 and July 1992.

Patients and methods

Study group

Between March 1988 and July 1992, 49 patients underwent primary lung transplantation (single-lung 41; double-lung 8) in our centre; 80% of transplant-recipients were suffering from end-stage obstructive pulmonary disease. The decision to evaluate the ReT option for selected long-term survivors with graft-failure was taken in January 1989, and eight transplant recipients have been retransplanted so far. This study group comprises five males and three females, with a mean age of 48±10 years (range 24–60 yrs). Underlying respiratory diseases included panlobular emphysema (n=3), chronic obstructive pulmonary disease (n=2),

destructive histiocytosis X (n=2), and chronic postembolic pulmonary hypertension (n=1). At the time of primary transplantation, all but one had an obstructive ventilatory pattern, and all were oxygen-dependent. One had a tracheostomy and required mechanical ventilation support. The patients received a single-lung (n=7), or a double-lung (n=1) transplant without cardiopulmonary bypass support, with the exception of patient no. 7, who had a severe pulmonary hypertension (table 1).

course of intravenously administered methylprednisolone (1 g·day⁻¹). In cases of resistant rejection, this treatment was combined with a 5 day course of ALG, and followed by an increase in oral corticotherapy.

Follow-up procedure

Routine surveillance included fibreoptic bronchoscopy, with samples for microbiological studies on days 7, 15

Table 1. – Clinical and functional characteristics prior to retransplantation

Pt no.	Pre-operative Last FEV_1 % pred	First SLT⁺	Post-operative FEV_1 % pred Best	Last	Tracheostomy*	Delay to retransplantation months	Type of retransplantation
1	18	L	54	25	No	8	Ipsilateral
2	31	L	44	19	No	31	Controlateral
3	11	R	69	12	Yes	15	Ipsilateral
4	26	R	41	18	Yes	9	Ipsilateral
5	26	R+L	54	13	Yes	10	Ipsilateral
6	18	L	42	18	No	37	Controlateral
7	86	L	63	23	Yes	16	Controlateral
8	16	L	49	35	Yes	6	Ipsilateral

SLT⁺: single lung transplantation; R: right lung; L: left lung. *: mechanical ventilation through tracheostomy for at least 15 days prior to retransplantation. FEV_1: forced expiratory volume in one second.

Immunosuppressive regimen for primary transplantation

The immunosuppressive regimen for all patients included a preoperative intravenous injection of methylprednisolone (500 mg), and azathioprine (2 mg·kg⁻¹). Postoperatively, cyclosporin A was given intravenously, and adjusted to maintain an average final concentration of 300 ng·ml⁻¹ as assessed by radio-immunoassay (RIA) determination of whole-blood levels. Steroids were withheld for 14 days (patients nos. 1–4), or 1 month (patients nos. 5–8), and were then given orally (prednisolone 0.5 mg·kg⁻¹ *q.d.*), and further tapered. Azathioprine was given intravenously (2.5 mg·kg⁻¹ *q.d.*), immediately after the surgical procedure, and then orally (1.5 mg·kg⁻¹ *q.d.*). Rabbit antilymphocyte globulins (ALG; Mérieux, Lyon, France) were given in the postoperative period, on the basis of a 14 day course (patients nos. 1–4), or a 3 day course (patients nos. 5–8). After the first month, patients were usually given cyclosporin according to whole-blood levels (150–200 ng·ml⁻¹), azathioprine (1.5 mg·kg⁻¹ *q.d.*), and prednisolone (0–0.5 mg·kg⁻¹ *q.d.*). All patients were given anti-cytomegalovirus (CMV) gammaglobulins, and patients nos. 5–8 were also given acyclovir during the first postoperative month, as a prophylactic treatment for herpes simplex virus (HSV) infection. Acute allograft lung rejection was treated by a 3 day

and 30. Additional bronchoscopies with transbronchial biopsies and bronchoalveolar lavage were indicated in response to clinical or paraclinical abnormalities consistent with graft dysfunction. Chest radiography, spirometry, and arterial blood gas determination were usually performed every 3 months during the first year. Patients were requested to perform daily measurements of their peak expiratory flow rate (PEFR), and to signal any persistent fall in the PEFR rate.

Results

Early and late follow-up after primary transplantation

Respiratory events occurring during the first 3 months following transplantation are listed in table 2. Each patient experienced at least one episode of documented viral infection; causative viruses were CMV (eight episodes), and HSV (two episodes). The diagnosis of CMV infection required either the rapid detection of CMV from bronchoalveolar lavage, plasma or biopsy samples by viral cultures; or a cytopathic effect in bronchoalveolar cells or biopsy samples. Bronchial complications associated with defective healing of the anasto-mosis were observed

Table 2. – Preoperative donor and recipient CMV serologies; postoperative bronchopulmonary events after primary transplantation and retransplantation

	Primary transplantation				Retransplantation			
		Respiratory events*				Respiratory events*		
Pt no.	Preoperative CMV serologies Donor/Recipient	Rej	Vir	Bac	Preoperative CMV serologies Donor/Recipient	Rej	Vir	Bac
1	+/-	3	1	2	-/+	-	-	-
2	+/+	5	2	1	-/+	2	3	2
3	+/+	4	1	2	-/+	5	2	0
4	-/-	1	1	1	-/-	1	0	0
5	+/+	3	2	0	+/+	2	2	0
6	-/+	2	1	1	-/+	3	1	1
7	-/+	1	1	1	+/+	-	-	-
8	-/-	4	1	1	-/+	2	1	1

*: respiratory events (Rej: rejection episodes; Vir: viral airway or pulmonary episodes; Bac: bacterial bronchitis or pneumonia) that occurred during the first 3 months following transplantation. CMV: cytomegalovirus.

in three patients (nos. 1, 2 and 4). They were responsible for poor lobar ventilation, which was suspected on fibrescopic examination, and confirmed by isotopic ventilation and perfusion scans.

However, a progressive improvement of respiratory condition was documented in each patient, resulting in stable individual values of forced expiratory volume in one second (FEV_1) ranging 41–69% of predicted values (mean of the group 52% predicted) (table 1).

Two distinct pathological events were found to play a major role in graft-failure. In two of the three patients with abnormal bronchial healing and irreversible central airways stenosis, severe pulmonary infections were further associated with graft-failure. In patient no. 1, moreover, the accidental rupture of a balloon filled with liposoluble contrast material resulted in a diffuse alveolar filling that did not clear, and was attributed to transplantation-associated impairment of the airway [4], or lymphatic clearance.

In six patients, development of severe BO was suspected to be the major cause of graft-failure. Deterioration in respiratory condition paralleled the loss in FEV_1 and arterial oxygen tension (Pao_2), and a patchy or diffuse defect pattern on isotopic perfusion scans of the graft. In patient no. 5, development of respiratory insufficiency occurred after two successive episodes of CMV infection. In these five patients, respiratory function continued to decline despite enhanced and prolonged immunosuppression.

In each patient, ReT was discussed when Pao_2 and FEV_1 values had returned to pretransplant values (table 1). Five of the eight patients had a tracheostomy, and required mechanical ventilation support at least during the night; all were oxygen-dependent. The delay between primary transplantation and ReT was 16±10 months (range 6–37 months).

Retransplantation: surgical procedure, immunosuppressive regimen and follow-up

Once the decision to retransplant had been taken, the immunosuppressive regimen was modified: prednisolone dosage was tapered to 0–15 $mg \cdot kg^{-1}$ q.d., and cyclosporin dosage was also reduced to obtain whole-blood levels in the range of 100–150 $mg \cdot ml^{-1}$. Graft volume, perfusion distribution on scintigraphic pattern, and proximal airway aspect on fibrescopic examination were considered when deciding whether to remove the graft or the native lung. Major graft retraction and central airway stenosis indicated graft removal, for fear of surgical difficulties and further local infections, respectively. In more balanced situations, the lung with the best perfusion was left in place. In either case, single-lung ReT was performed without cardiopulmonary bypass. In three of the five grafts that were removed, the predominant pathological finding was a diffuse BO (patients nos. 3–5) associated to focal aspects of acute rejection in patient no. 3. Main pathological changes observed in the two other grafts (patient Nos. 1 and 8) consisted of diffuse interstitial pneumonia and organizing pneumonia, respectively. The post-operative immunosuppressive regimen was the same as for the primary procedure. As shown in table 3, two patients (Nos. 1 and 7) died within one month of multiorgan failure, and another (patient No. 8) died 1.2 months after surgery of cerebral haemorrhage. Patients whose survival exceeded 3 months experienced respiratory events (table 2) superimposable to those observed after primary transplantation. At 3 months, as supported by individual values of FEV_1 and Pao_2 at rest (table 3), their respiratory condition was satisfactory. Patient No. 2 died 16.5 months after ReT of a septic shock complicating an agranulocytosis. The other patients are alive, with stable lung function.

Table 3. – Clinical and functional results of single-lung retransplantation

Pt No.	Follow-up months	Cause of death	3 months value			
			Pao$_2$ kPa	Paco$_2$ kPa	FEV$_1$ % pred	Graft perfusion % total
1	0.5, died	Multiorgan failure	-	-	-	-
2	16.5, died	Septic shock agranulocytosis	11.7	4.7	103	90
3	20, alive	-	9.2	5.5	52	82
4	18, alive	-	10.4	5.4	60	79
5	17, alive	-	8.8	5.3	40	59
6	8, alive	-	7.8	4.7	60	90
7	0.6, died	Multiorgan failure	-	-	-	-
8	1.2, died	Cerebral haemorrhage	-	-	-	-

Pao$_2$: arterial oxygen tension; Paco$_2$: arterial carbon dioxide tension; FEV$_1$: forced expiratory volume in one second.

Discussion

Single-lung transplantation (SLT) has proved beneficial in patients with advanced fibrosis [5], or end-stage chronic obstructive pulmonary disease [6]. Shorter waiting times and technical simplicity are in favour of the SLT procedure. Conversely, bronchial complications develop more frequently than in heart-lung transplantation. As in other series [2, 7, 8], however, the major cause of graft-failure was the development of bronchiolitis obliterans. The progressive appearance of respiratory insufficiency, otherwise unexplained, and the inefficacy of augmented immunosuppression were more suggestive of BO development than examination of transbronchial biopsies. Interestingly, changes in chest films that paralleled development of respiratory insufficiency varied from one case to another. They included a progressive restriction of graft volume, evoking a fibrotic process (all patients except no. 5), or a moderate distension (patient no. 5) suggesting a diffuse obstruction of peripheral airways. Indeed, graft from the latter patient presented with a pure form of BO, whilst other grafts displayed focal aspects of organizing pneumonia associated with BO. Similar differences in histological patterns of BO have been detailed previously by ABERNATHY et al. [9], who suggested that pure forms of BO may be related to chronic rejection, whilst BO-associated organizing pneumonia may be due to other pathological processes, including infections.

A major requisite before indicating ReT is the assessment of graft-failure irreversibility. In the case of BO-associated respiratory insufficiency, the immunosuppresion regimen is usually gradually augmented: the successive failures of methylprednisolone bolus and ALG or OKT3 courses in improving arterial blood gases and spirometric values are considered as good markers of BO irreversibility. We observed, however, focal but typical aspects of acute rejection on histological examination of

the graft removed from patient no. 3. This observation may be related to the reduction of the immunosuppressive regimen, imposed during the pre-ReT period. We speculated, indeed, that prednisolone and cyclosporin dosage reductions would limit infections and healing problems [10], and would lower the risk for nephrotoxicity [11] in the postoperative period, respectively. Whilst on the waiting-list for ReT, patients with reduced immunosuppression did not experience further decline in the respiratory function; more of them died before ReT could be performed. Among ReT-recipients, those who survived beyond 3 months experienced no more infections or rejection episodes than after primary transplantation. Conversely, early post-ReT deaths were due to multiorgan failure. The question of whether the pre-ReT immunosuppressive regimen should be modified, therefore, remains open; on the other hand, in the postoperative period the same immunosuppressive regimen as for primary transplantation seems to be appropriate, as suggested in a recent paper by MILLER and PATTERSON [3].

In terms of competition with patients waiting for primary transplant, priority was given to the latter, provided that they were suffering from advanced fibrosis or pulmonary hypertension. However, such patients represent a minority among the candidates for lung transplantation in our centre.

Single-lung ReT procedure may offer the choice of removing the graft or the native lung when a single-lung primary transplantation has been performed previously. In each case in the present study, graft-failure was responsible for the development of severe respiratory insufficiency; removal of the native lung was indicated either for severe graft retraction or major central airway stenosis. However, we paid particular attention to the comparative distribution of the perfusion in each lung; in balanced situations, the lung receiving more than 50% of the perfusion was left in place. Removal, or leaving *in*

situ, important quantities of allogenic material was not taken into consideration [12]. The immunological consequences of either option may be of importance, but experience regarding long-term follow-up is very limited and, to our knowledge, experimental data have not been reported. However, among the five patients with survival values ranging from 8–20 months, none was suspected of developing BO. One of these patients (No. 6) had undergone a controlateral ReT: serial chest films and isotopic perfusion scans displayed no change in primary graft patterns, suggesting that failure of the primary graft was irreversible. Five of the eight single-lung ReT recipients in the present study are long-term survivors, with satisfactory respiratory conditions. These data cautiously support the single-lung ReT option for lung transplant recipients with late graft failure. Considerable pressures arise from the patient, his/her family and the transplant group to offer a second transplant to the recipient developing a late graft-failure. However, we like others, are facing an increasing shortage of donor lungs, which is clearly the principal limitation for ReT procedure.

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