Pulmonary retransplantation for obliterative bronchiolitis

Intermediate-term results of a North American–European series

An international series of pulmonary retransplantation was updated to identify the predictors of survival in the intermediate-term after reoperation for obliterative bronchiolitis. The study cohort included 32 patients with end-stage obliterative bronchiolitis who underwent retransplantation in 15 North American and European centers between 1988 and 1992. Five types of retransplantation procedures were done, including repeat ipsilateral single lung transplantation (7 patients), repeat contralateral single lung transplantation (8 patients), repeat double lung transplantation (3 patients), double lung transplantation after a previous single lung transplantation (3 patients), and single lung transplantation after a previous double lung or heart-lung transplantation (11 patients). The mean interval between transplants was 564 ± 51 days (range 187 to 1589 days). Postoperative follow-up was 100 % complete and the average follow-up in surviving patients was 678 ± 63 days. Actuarial survival was 72 %, 53 %, 50 %, 41 %, and 33 % at 1, 3, 6, 12, and 24 months, respectively. Survival did not differ according to the age, preoperative diagnosis, ambulatory or ventilator status, or cytomegalovirus serologic status of the recipient before reoperation. Life-table and Cox proportional hazards analysis identified the type of retransplantation procedure and the year of reoperation as significant ($p < 0.05$) predictors of postoperative survival. Actuarial survival was significantly better in patients without an old, retained contralateral graft after retransplantation and in patients who underwent reoperation between 1990 and 1992, as opposed to between 1988 and 1989. Infection was the most common cause of death at all time intervals after retransplantation, although all deaths beyond 2 years resulted from obliterative bronchiolitis of the second graft. Most surviving patients are in a satisfactory clinical condition, with a mean forced expired volume in 1 second of $59\% \pm 13\%$ of predicted (repeat double lung transplant recipients) or $41\% \pm 6\%$ of predicted (repeat single lung transplant recipients). We conclude that pulmonary retransplantation for obliterative bronchiolitis is associated with significantly worse survival than after primary lung transplantation. The absence of an old contralateral graft after retransplantation and reoperation after 1989 are important predictors of survival. Additional data and follow-up are required to determine the merit of pulmonary retransplantation for obliterative bronchiolitis. (J THORAC CARDIOVASC SURG 1994;107:755-63)

Richard J. Novick, MD, Bernard Andréassian MD, Hans-Joachim Schäfers, MD, Axel Haverich, MD, G. Alexander Patterson, MD, Michael P. Kaye, MD, Alan H. Menkis, MD, and F. Neil McKenzie, MD, *London, Ontario, Canada, Clichy, France, Hannover and Kiel, Germany, St. Louis, Mo., and Minneapolis, Minn.*

From the Division of Cardiovascular-Thoracic Surgery, University Hospital, London, Ontario, Canada; The International Society for Heart and Lung Transplantation Registry; The International Lung Transplantation Registry; and participating institutions.

Presented in part at the International Society for Heart and Lung Transplantation Meeting, Boca Raton, Fla., April 3, 1993.

Received for publication May 28, 1993.

Accepted for publication Aug. 2, 1993.

Address for reprints: Richard J. Novick, MD, Division of Cardiovascular-Thoracic Surgery, University Hospital, P.O. Box 5339, London, Ontario, Canada N6A 5A5.

Copyright © 1994 by Mosby–Year Book, Inc.

0022-5223/94 \$3.00 + 0 12/1/50480

Despite recent improvements in survival after lung transplantation¹⁻³ a deteriorating respiratory status develops in a significant number of recipients in the intermediate-term after operation because of obliterative bronchiolitis.^{2, 4-7} Some patients with this condition respond to augmented immunosuppression,⁴ but many others experience progressive respiratory dysfunction and opportunistic infections leading to death. In the absence of effective medical therapy for end-stage obliterative bronchiolitis, increasing numbers of patients are being offered pulmonary retransplantation.^{8, 9} Although early survival after retransplantation is significantly lower than that after primary lung transplantation,⁸ the fate of reoperative survivors in the intermediate-term has not yet been documented. We, therefore, updated our previously published series of repeat lung transplantation⁸ to determine the factors predictive of intermediate-term survival after pulmonary retransplantation for obliterative bronchiolitis.

Patients and methods

In late 1991 and early 1992 questionnaires were sent to surgeons identified by the International Society for Heart and Lung Transplant and the International Lung Transplant Registries as having experience with pulmonary retransplantation. Direct surgeon-to-surgeon contact by telephone and telefax resulted in a 95% center response rate by the March 1, 1992, closing date for patient accrual. Because of an ongoing study by a European center on repeat heart-lung transplantation, patients who underwent a heart-lung transplantation as the second operation were excluded, to avoid duplication. The status of all study patients was updated, with the use of follow-up questionnaires, in March 1993. Only patients with end-stage obliterative bronchiolitis after the first transplant were included in the study cohort.

The 17 parameters listed in Table I were analyzed in each patient. Statistical analysis was performed with the BMDP statistical package (BMDP Statistical Software, Inc., Los Angeles, Calif.). All data were expressed as mean plus or minus the standard error of the mean (SEM). Actuarial survival was calculated by the Kaplan-Meier method,¹⁰ and the statistical difference between survival curves was assessed with the Wilcoxon¹¹ and log-rank tests. In addition, a Cox proportional hazards model¹² was used to determine, by univariate and multivariate analysis, which factors were predictive of survival after pulmonary retransplantation for obliterative bronchiolitis. A *p* value less than 0.05 was deemed significant.

Results

Fifteen of the 20 lung transplant centers that participated in our previous study⁸ had performed pulmonary retransplants for obliterative bronchiolitis. The number of cases contributed by the eight North American and seven European centers is shown in Table II. Thirty-two patients (51% of the original cohort) underwent retransplantation for obliterative bronchiolitis. The study cohort

Table I. *Parameters analyzed in pulmonary transplant recipients who underwent reoperation for obliterative bronchiolitis*

Age
Sex
Original diagnosis
Interval between transplants
Ventilator dependence before retransplantation
Ambulatory status before retransplantation
Year of retransplantation
Retransplant center
Type of retransplant procedure
Donor ABO status
Recipient ABO status
Donor CMV serologic status
Recipient CMV serologic status
Survival interval after retransplantation
Cause of death after retransplantation
Functional status of survivors
Pulmonary function test data of survivors

Table II. *Contributing centers and number of cases*

Center	No. of cases
North America	
University of Toronto, Toronto, Canada	3
University of Texas, San Antonio	3
University of Minnesota, Minneapolis	2
Barnes Hospital-Washington University, St. Louis, Mo.	2
Montreal General Hospital, Montreal, Canada	2
Baylor-Methodist Hospital, Houston, Texas	1
University of Michigan, Ann Arbor	1
Stanford University, Stanford, Calif.	1
Europe	
Hôpital Beaujon, Clichy, France	6
Medizinische Hochschule, Hannover, Germany	3
University of Vienna, Vienna, Austria	3
Papworth Hospital, Cambridge, Great Britain	2
Freeman Hospital, Newcastle, Great Britain	1
Hôpital Xavier-Arnoz, Pessac, France	1
Centre Medico-Chirurgical Foch, Suresnes, France	1

included 11 men and 21 women with a mean age of 40 ± 2 years (range 5 to 62 years). Before the first transplantation procedure, 41% had a diagnosis of emphysema; 26% primary pulmonary hypertension or Eisenmenger's syndrome; 13% restrictive lung disease; 13% cystic fibrosis; and 7% miscellaneous conditions. The interval between transplants ranged from 187 to 1589 days (mean 564 ± 51 days). Fifteen patients underwent a repeat single lung transplant for obliterative bronchiolitis, seven on the ipsilateral side and eight on the contralateral side. Eleven patients underwent a single lung

Fig. 1. Actuarial survival of 32 patients undergoing pulmonary retransplantation for obliterative bronchiolitis. Number of patients surviving to each postoperative interval is shown above corresponding data points.

Fig. 2. Actuarial survival according to original diagnosis of recipients before first lung transplantation procedure. There were no statistically significant differences among groups in actuarial survival after retransplantation.

transplant after a previous double lung or heart-lung transplant, three patients underwent a repeat double lung transplant, and three patients underwent a double lung transplant after a previous single lung transplant procedure.

Survival after retransplantation for obliterative bronchiolitis. The actuarial survival after retransplantation for obliterative bronchiolitis is shown in Fig. 1. Of the 32 study patients, 22 have died and 10 are still living. Reoperative survivors have been followed up for 413 to 977 days (mean 678 ± 63 days). Thirteen of the 32 patients survived 1 year after retransplantation, whereas 8 have reached the second anniversary of their reoperation. Actuarial survival was not statistically different according to the original diagnosis of the lung transplant recipients (Fig. 2). As documented in Table III, there has

Table III. One-year actuarial survival according to year of reoperation

Year	No. of patients	One-year survival (%)
1988	3	0
1989	4	25 ± 22
1990	12	42 ± 14
1991	10	50 ± 16
1992	3	67 ± 27

All values are expressed as mean plus or minus SEM. The standard error for 1992 is large because of the limited number of patients accrued before the March 1992 closing date.

been a trend toward improved 1-year survival in patients undergoing retransplantation in recent years. In particular, actuarial survival was significantly higher in patients who underwent reoperation between 1990 and 1992, as

Fig. 3. Actuarial survival according to year of retransplantation, $p = 0.005$.

Fig. 4. Actuarial survival according to whether retransplantation was done in European or North American center, $p = 0.16$.

opposed to those who underwent retransplantation in the years 1988 and 1989 (Fig. 3). In addition, a nonsignificant trend toward improved survival was noted after reoperation in Europe as opposed to North America (Fig. 4).

Clinical status before retransplantation for obliterative bronchiolitis. Before reoperation, 34% of patients were ventilator-dependent and 66% were not. There were no significant differences in survival according to preoperative ventilator status (Fig. 5). Before retransplantation, only 38% of patients were ambulatory (i.e., able to walk 50 meters with or without assistance). The actuarial survival curves for the ambulatory and nonambulatory patients were superimposable (Fig. 6). Only 4 of the 32 retransplant recipients had concomitant renal or hepatic failure or both immediately before reoperation, and none

of these patients survived beyond the third postoperative month.

Effect of donor/recipient ABO and cytomegalovirus serologic status. Donor factors at the second transplant operation appeared to have less of an impact on the survival of patients who underwent reoperation for obliterative bronchiolitis than in the larger group of retransplant recipients previously reported on.⁸ In the current series, 71% of patients received an ABO-identical graft at reoperation, whereas 29% received a lung graft that was ABO compatible, but not identical. One-year actuarial survival was $45\% \pm 10\%$ in the former versus $33\% \pm 16\%$ in the latter group ($p = \text{NS}^*$). Before reoperation, 82% of recipients were cytomegalovirus (CMV) positive where-

*Not significant.

Fig. 5. Actuarial survival according to recipient's ventilator status before reoperation, $p = 0.44$.

Fig. 6. Actuarial survival according to recipient's ambulatory status before reoperation, $p = 0.78$.

as 18% did not manifest antibodies to CMV. Actuarial survival at 1 year was $52\% \pm 10\%$ in CMV-positive recipients, as opposed to $40\% \pm 22\%$ in CMV-negative recipients ($p = \text{NS}$). Although there was a trend toward improved survival in patients who received a CMV-negative graft at reoperation, the difference in survival was not statistically significant (Fig. 7). There were only three cases of CMV mismatch (i.e., CMV-positive graft, CMV-negative recipient) in this series; two of these patients died within the first year and the third at 368 days after operation.

Effect of type of retransplant procedure on survival.

The type of retransplant procedure appeared to have a significant impact on survival after operation. Patients who underwent a double lung transplant as the second operation and those who received an ipsilateral single lung retransplant tended to fare better than those who underwent a contralateral single lung retransplant and patients

treated by single lung transplantation after a previous double lung or heart-lung transplant (Fig. 8). After reoperation, 19 patients had an old, retained contralateral graft from the previous transplant, whereas 13 patients did not. Actuarial survival was significantly better in patients without an old contralateral graft after retransplantation (Fig. 9). The retained contralateral graft was often a source of infectious morbidity as the duration of the follow-up increased.

Causes of death after retransplantation for obliterative bronchiolitis. The major cause of death after reoperation was infection (55%), followed by acute failure of the second graft (14%), recurrent obliterative bronchiolitis (14%), airway dehiscence (5%), and miscellaneous complications (12%). Most infections resulting in death were polymicrobial, with CMV, *Pseudomonas*, and *Aspergillus* being the predominant organisms. The causes of death at the various time intervals after retransplantation

Fig. 7. Actuarial survival according to donor's CMV serologic status at reoperation, $p = 0.21$.

Fig. 8. Actuarial survival according to type of retransplant procedure, $p = 0.17$. *DLT*, Double lung transplant; *SLT*, single lung transplant; *HLT*, heart-lung transplant.

Table IV. Functional status of 3-month, 1-year, and current survivors of pulmonary retransplantation for obliterative bronchiolitis

Postoperative interval	Functional class (% of patients)			
	I	II	III	IV
3 mo	35	53	6	6
12 mo	46	38	8	8
23 mo (currently)	50	20	30	—

are shown in Fig. 10. During the first 2 years infection was predominant. All deaths beyond 2 years were caused by obliterative bronchiolitis of the second graft, with or without a terminal infectious complication.

Functional status of survivors. The functional status of reoperative survivors at 3 months and 1 year, as well

as currently, is depicted in Table IV. Most surviving patients at each time interval were active and had only mild functional limitations. Representative pulmonary function test data in 1-year and current survivors are shown in Fig. 11. The forced expiratory volume in 1 second (FEV_1) was mildly reduced in both single and double lung retransplant survivors at 1 year. Both groups of patients had a slight further decrease in FEV_1 , which was not statistically significant, with increasing duration of follow-up.

Predictors of survival by Cox proportional hazards analysis. By proportional hazards analysis, the following factors were found not to correlate with survival after pulmonary retransplantation for obliterative bronchiolitis: age, sex, original diagnosis, interval between transplants, retransplantation center, ABO and CMV status, ambulatory status, and ventilator dependence. By

Fig. 9. Actuarial survival according to whether old contralateral graft remained in situ after retransplantation, $p = 0.03$.

Fig. 10. Causes of death at various time intervals after pulmonary retransplantation for obliterative bronchiolitis.

univariate analysis, reoperation between 1990 and 1992 ($p = 0.016$) and the absence of an old contralateral graft after reoperation ($p = 0.026$) were predictive of postoperative survival. By multivariate analysis, year of reoperation ($p = 0.016$) was the most powerful predictor of survival, whereas the type of reoperation did not achieve statistical significance ($p = 0.11$).

Discussion

Obliterative bronchiolitis remains a major unresolved problem after lung and heart-lung transplantation. Although this complication occurs less frequently today than in past years,¹³ recent studies have revealed a prevalence of 20%² to 48%⁷ in intermediate-term survivors. Although some patients may respond to augmented immunosuppressive therapy,⁴ many continue to deteriorate

and die of respiratory failure. In recent years pulmonary retransplantation has been increasingly performed in patients with end-stage obliterative bronchiolitis.^{8,9} Actuarial survival after retransplantation is lower than after primary lung transplantation,⁸ and the merit of pulmonary retransplantation remains uncertain. The purpose of this study was to identify preoperative and intraoperative predictors of survival in an effort to decrease morbidity and mortality after pulmonary retransplantation for obliterative bronchiolitis.

This study confirmed the high early postoperative mortality rate after pulmonary retransplantation. The rate of attrition decreased beyond the sixth postoperative month, yet a significant number of survivors of reoperation died of infectious complications or recurrent obliterative bronchiolitis in the intermediate-term. It is encour-

Fig. 11. FEV₁ of single (SLT) and double (DLT) lung retransplant survivors at 1 year and currently. Current follow-up interval (692 days) differs slightly from follow-up interval in the manuscript (678 days), because one young child could not perform spirometry reliably and was excluded in calculating FEV₁ measurements.

aging that the quality of life in reoperative survivors has remained satisfactory, with 70% or more of patients in functional class I or II at all time intervals after operation. Furthermore, the pulmonary function test data confirmed that most reoperative survivors have an acceptable FEV₁ at 1 year after operation and currently. Although recurrent obliterative bronchiolitis was the major cause of death more than 2 years after retransplantation, only 3 of 22 postoperative deaths were caused by this complication. This suggests that obliterative bronchiolitis does not appear to recur in an accelerated manner after retransplantation, despite the fact that HLA matching and donor-specific lymphocytotoxic cross-matching were not done prospectively in the 15 centers participating in this study.

In this series, the most powerful predictor of survival after retransplantation for obliterative bronchiolitis was the year of reoperation. The difference in actuarial survival between patients who underwent retransplantation between 1990 and 1992 and those who underwent retransplantation in the years 1988 and 1989 was highly statistically significant on life-table analysis ($p = 0.005$). In addition, both univariate and multivariate analysis by the Cox proportional hazards model indicated that the year of reoperation was the most significant predictor of survival ($p = 0.016$). This finding was not apparent in our previously published series of 63 cases of pulmonary retransplantation⁸ and only became evident in the oblit-

erative bronchiolitis group after an additional year of complete follow-up.

The second most significant predictor of survival after reoperation for obliterative bronchiolitis was the type of retransplant procedure. Specifically, the presence of an old, retained contralateral graft after the second operation was frequently associated with significant infectious morbidity, whereas the absence of a retained contralateral graft resulted in significantly improved survival on life-table analysis ($p = 0.03$) and on univariate Cox proportional hazards analysis ($p = 0.026$). At 1 year, actuarial survival was $62\% \pm 13\%$ in patients without an old contralateral graft as compared with $26\% \pm 10\%$ in those with a retained contralateral graft. These data support the principle of complete excision of a chronically rejected (and likely infected) lung graft at the time of retransplantation.

Published data on repeat lung and heart-lung transplantation for obliterative bronchiolitis is sparse and largely anecdotal.⁸ Recently, the Harefield group reported on a series of patients who underwent heart-lung or single lung transplantation after obliterative bronchiolitis developed after a previous heart-lung transplant.^{9,14} Actuarial survival in the 25 patients who underwent repeat heart-lung transplantation was only 25% at 1 year. Single lung retransplantation (after a previous heart-lung transplant) in nine patients resulted in a 1-year actuarial survival of 67%. All of the repeat heart-lung transplants were performed between 1986 and 1990, whereas most of the single lung retransplants were performed between 1990 and 1992. On life-table analysis, the year of retransplantation was not statistically related to survival, yet the authors did not do a proportional hazards analysis of their data to investigate further this possibility. It is possible that the superior results in the single lung retransplant group may have reflected increasing experience in the operative and postoperative care of patients undergoing pulmonary retransplant, rather than a true difference between the two types of reoperative procedures. Additional data and a longer duration of follow-up will be required to determine definitively which retransplant procedure is indicated in pulmonary retransplant candidates with obliterative bronchiolitis.

In our previous report⁸ donor CMV serologic status was a significant predictor of survival. In the current study of patients who underwent retransplantation for obliterative bronchiolitis, donor CMV status showed only a nonsignificant trend toward predicting survival (Fig. 7). Actuarial survival was $57\% \pm 13\%$ at 1 year in patients receiving a CMV-negative graft as opposed to $33\% \pm 14\%$ in those receiving a CMV-positive graft. The

lack of statistical difference between the two groups may reflect the smaller patient numbers in this study or the fact that more of the recipients undergoing retransplantation for obliterative bronchiolitis were CMV positive before operation than patients undergoing retransplantation for other indications. The fact that preoperative ambulatory and ventilator status were not predictive of survival in this study indicates that none of the preoperative variables that were investigated, except established multiorgan failure, is predictive of a poor outcome after pulmonary retransplantation for obliterative bronchiolitis.

Although overall survival after pulmonary retransplantation remains lower than that after primary lung transplantation, a number of European centers have developed particular expertise in the operative and post-operative care of patients undergoing retransplantation and report almost similar actuarial survival after primary and repeat lung transplantation.^{15,16} Fig. 4 shows the trend toward improved survival in patients with obliterative bronchiolitis who underwent retransplantation in Europe; 1-year actuarial survival was $53\% \pm 12\%$ in European centers as opposed to $27\% \pm 11\%$ in North America. This study did not document the official waiting times of retransplant candidates, which may have been different in Europe than in North America. Alternatively, the trend toward improved results in European centers may reflect the increased experience of some European transplant surgeons in the care of pulmonary retransplant recipients.

The practice of pulmonary retransplantation continues to raise ethical dilemmas, especially in view of the increasingly severe shortage of primary lung grafts available for transplantation. Given the relatively high incidence of obliterative bronchiolitis and the limited number of lung grafts, it is clear that pulmonary retransplantation is not the solution for the problem of obliterative bronchiolitis and will remain a treatment that is applied sporadically, at least in North America. Further research into the pathogenesis, prevention, and treatment of obliterative bronchiolitis is urgently required to decrease the intermediate-term morbidity and mortality after lung transplantation. In the interim, surgeons who perform pulmonary retransplants for obliterative bronchiolitis should continue to report their results to the international lung transplant community so that the merit or lack of merit of retransplantation for obliterative bronchiolitis can be ascertained.

We thank the contributing thoracic surgeons, pulmonary medicine physicians, and recipient coordinators who are listed in the appendix section of our previously published paper.⁸ We

also acknowledge the assistance of Heather Motloch in manuscript preparation and of Larry Stitt, MSc (Biostatistics and Epidemiology), in performing the statistical analyses.

REFERENCES

1. Trulock EP, Cooper JD, Kaiser LR, et al. The Washington University-Barnes Hospital experience with lung transplantation. *JAMA* 1991;266:1943-6.
2. de Hoyos AL, Patterson GA, Maurer JR, et al. Pulmonary transplantation: early and late results. *J THORAC CARDIOVASC SURG* 1992;103:295-306.
3. Egan TM, Westerman JH, Lambert CJ, et al. Isolated lung transplantation for end-stage lung disease: a viable therapy. *Ann Thorac Surg* 1992;53:590-6.
4. Glanville AR, Baldwin JC, Burke CM, Theodore J, Robin ED. Obliterative bronchiolitis after heart-lung transplantation: apparent arrest by augmented immunosuppression. *Ann Intern Med* 1987;107:300-4.
5. Griffith BP, Paradis IL, Zeevi A, et al. Immunologically mediated disease of the airways after pulmonary transplantation. *Ann Surg* 1988;208:371-8.
6. Scott JP, Higgenbottom TW, Clelland CA, et al. Natural history of chronic rejection in heart-lung transplant recipients. *J Heart Transplant* 1990;9:510-5.
7. Madden BP, Hodson ME, Tsang V, Radley-Smith R, Khaghani A, Yacoub MY. Intermediate-term results of heart-lung transplantation for cystic fibrosis. *Lancet* 1992;339:1583-7.
8. Novick RJ, Kaye MP, Patterson GA, et al. Redo lung transplantation: a North American-European experience. *J Heart Lung Transplant* 1993;12:5-16.
9. Adams DH, Cochrane AD, Khagani A, Smith JD, Yacoub MH. Retransplantation in heart-lung recipients with obliterative bronchiolitis. *J THORAC CARDIOVASC SURG* [In press].
10. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1957;53:457-81.
11. Gehan EA. A generalized Wilcoxon test for comparing arbitrarily singly-censored samples. *Biometrika* 1965;52:203-23.
12. Cox DR. Regression models and life-tables. *J R Stat Soc Ser B* 1972;34:187-220.
13. McCarthy PM, Starnes VA, Theodore J, Stinson EB, Oyer PE, Shumway NE. Improved survival after heart-lung transplantation. *J THORAC CARDIOVASC SURG* 1990;99:54-60.
14. Madden B, Radley-Smith R, Hodson M, Khagani A, Yacoub M. Medium-term results of heart and lung transplantation. *J Heart Lung Transplant* 1992;11:S241-3.
15. Haverich A, Hirt S, Wahlers T, Schäfers HJ, Zink C, Borst HG. Functional results after lung retransplantation. *J Heart Lung Transplant* 1993;12:S69.
16. Fournier M, Sleiman C, Mal H, et al. Single-lung retransplantation for late graft failure. *Eur Respir J* 1993;6:1202-6.