Effect of Ischemic Time on Survival in Clinical Lung Transplantation

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Background. **While there is convincing evidence that prolonged ischemic times correlate with reduced long-term survival in heart transplantation, the effect of ischemic time on outcome in clinical lung transplantation remains controversial. To assess the effect of ischemic time on outcomes in lung transplantation, we reviewed our experience.**

Methods. **The study was performed by retrospective chart review.**

Results. **First-time lung transplantation was performed on 392 patients between 1988 and 1998. All grafts were flushed with cold crystalloid preservation solution and stored on ice. Ischemic time data were available for 352 of 392 (90%) patients. Ischemic times were grouped as follows: 0 to 4 hours (n = 91), 4 to 6 hours (n = 201), more than 6 hours (n = 60). Ischemic time did not correlate with survival: 3-year actuarial survival = 56% (0 to 4 hours), 58% (4 to 6 hours), 68% (> 6 hours), $p = 0.58$. There was no significant difference in the incidence of biopsy-proven diffuse alveolar damage in the first 30 days after transplantation (31%, 32%, 38%), episodes of acute rejection in the first 100 days after transplantation (1.9, 1.8, 1.7), duration of intubation (median 3, 4, 3 days), or incidence of obliterative bronchiolitis (23%, 28%, 26%) between the three groups (0 to 4 hours, 4 to 6 hours, > 6 hours, respectively). A diagnosis of diffuse alveolar damage was associated with a significantly worse outcome (1-year survival = 82% versus 54%, $p < 0.0001$).**

Conclusions. **In contrast to heart transplantation, pulmonary allograft ischemic time up to 9 hours does not appear to have a significant impact on early graft function or survival. The presence of diffuse alveolar damage on biopsy early after transplantation does not correlate with prolonged ischemic time, but is associated with substantially reduced posttransplantation survival.**

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Prolonged cold ischemic times are unequivocally associated with reduced posttransplantation survival in cardiac transplantation [1]. Although it is generally accepted that the upper limit for safe ischemic time in lung transplantation is 4 to 6 hours [2, 3], there is surprisingly little data to support this conclusion. We performed this review to assess the effect of ischemic time on outcomes in lung transplantation.

Patients and Methods

Between April 1988 and June 1998, 392 patients underwent first-time single or double-lung transplantation. Four recipients of living-related grafts were excluded. Recipient ages ranged from 9 to 68 years, with a median of 45 years. There were 217 women and 175 men.

Donor Selection and Organ Preservation

Donor selection criteria have been previously published [4–6]. Briefly, pulmonary preservation was accomplished with infusion of 50 to 100 mL/kg of cold (4°C) crystalloid solution (pulmoplegia) into the pulmonary artery after aortic cross-clamping. Euro-Collins solution was used through April 1991, after which University of Wisconsin solution was utilized. Details of the harvesting and preservation techniques were previously published. Alprostadil (prostaglandin E_1; 500 μg) was administered before infusion of preservation solution, as well as in the first liter of pulmoplegia. Lungs were transported on ice. Ischemic time was defined as the interval from application of the aortic cross-clamp during harvesting until reperfusion of the graft in the recipient. For double-lung transplants, ischemic time was defined as the mean ischemic time for both lungs.

Allograft Function and Survival

Acute rejection was defined by histologic criteria [7], with grade II or higher considered important. The number of acute rejection episodes in the first 100 days after transplantation was calculated for those patients surviving more than 30 days. Obliterative bronchiolitis (OB) was diagnosed based on histologic criteria [7]. The diagnosis of diffuse alveolar damage (DAD) was assigned based on histologic findings from autopsy or biopsy specimens [8]. Survival is defined as graft survival.

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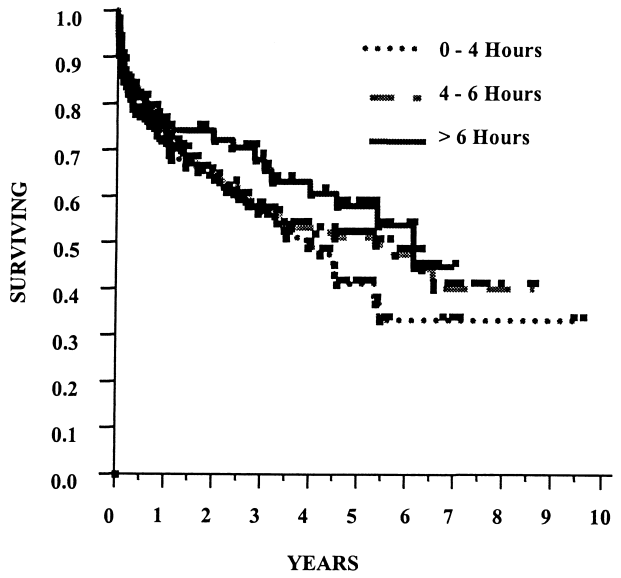

Fig 1. Actuarial lung allograft survival as a function of ischemic time. There is no difference in pulmonary allograft survival between the three groups (p = 0.42).

Statistical Analysis

Statistical computations were performed using JMP software (SAS Institute, Cary, NC). Actuarial survivals between groups were estimated by means of the Kaplan-Meier method, and significance was tested using the log-rank test. Comparisons between the incidence of DAD, OB, acute rejection, and duration of intubation for the different groups were done with the use of the unpaired *t* test, the Mann-Whitney U test, or χ^2 test where appropriate. Multivariate regression analysis performed with the Cox proportional-hazards model was used to assess the influence of various donor variables on survival.

Results

Ischemic time data were available for 352 of 392 (90%) patients. Ischemic times ranged from 65 to 538 minutes, with a median value of 289 minutes. Ischemic times were grouped as follows: 0 to 4 hours (n = 91), 4 to 6 hours (n = 201), more than 6 hours (n = 60). Actuarial survival was similar among the three groups (Fig 1). Mean follow-up for each of the three ischemic time groups was 3.5, 3.6, and 4.0 years (0 to 4 hours, 4 to 6 hours, > 6 hours, respectively, $p = 0.51$). There was no significant difference in the duration of postoperative intubation (median 3, 4, 3 days), episodes of acute rejection in the first 100 days after transplantation (1.9, 1.8, 1.7), or incidence of obliterative bronchiolitis (23%, 28%, 26%) between the three groups (0 to 4 hours, 4 to 6 hours, > 6 hours, respectively) (Table 1).

A histologic diagnosis of DAD was assigned to 40.1% (156 of 389) of patients in this series. DAD was characteristically identified early after transplantation, with 79% (123 of 156) of patients diagnosed within 1 month of operation. The median time from operation to diagnosis of diffuse alveolar damage was 12 days. The incidence of biopsy-proven diffuse alveolar damage in the first 30 days after transplantation (31%, 32%, 38%) was similar among the three ischemic time groups. The incidence of DAD was significantly higher among patients placed on cardiopulmonary bypass (CPB) (63 of 122 = 52%) versus those transplanted without CPB (79 of 212 = 37%, $p = 0.01$). A diagnosis of diffuse alveolar damage was associated with significantly worse posttransplantation survival (1-year survival = 54% versus 82%, $p < 0.0001$) (Fig 2).

Table 1. Incidence of Acute and Chronic (OB) Rejection, Diffuse Alveolar Damage, and Duration of Postoperative Intubation Among Groups With Varying Ischemic Times

	Ischemic Time (h)			
	0–4	4–6	> 6	*p*
DAD (%, 1st 30 days)	31	32	38	0.61
Acute rejection (episodes/100 days)	1.9	1.8	1.7	0.80
Duration intubation (median, days)	3	4	3	0.15
OB (%)	23	28	26	0.65

Prolonged ischemic time did not have a significant effect on any of these measures of postoperative allograft function.

DAD = diffuse alveolar damage; OB = obliterative bronchiolitis.

Multivariate analysis of various donor characteristics failed to show an independent effect of graft ischemic time on posttransplantation survival (Table 2).

Comment

Ischemic time exerts a strong influence on graft survival in cardiac transplantation. Opelz and associates demonstrated an 8% greater survival 3 years posttransplantation

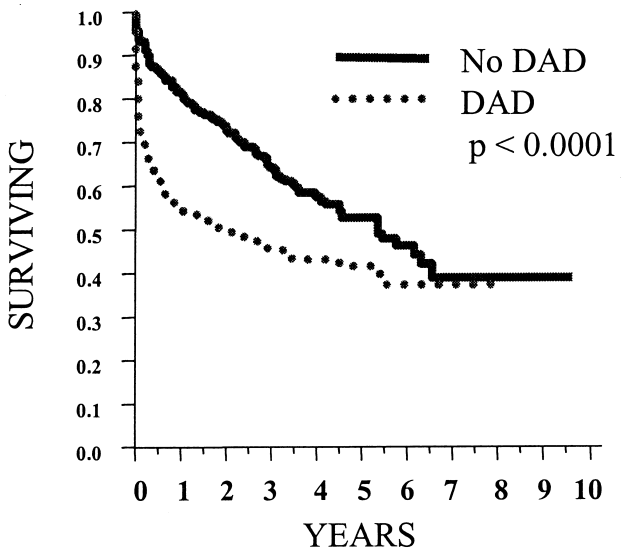

Fig 2. A diagnosis of diffuse alveolar damage in the first 30 days after transplantation is associated with a significantly worse survival.