PRIMARY GRAFT DYSFUNCTION AFTER LUNG TRANSPLANT WITH T-CELL DEPLETION

by

Chieh-Hsin Kuan

BS, Pennsylvania State University, 2005

Submitted to the Graduate Faculty of

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2008

UNIVERSITY OF PITTSBURGH

Graduate School of Public Health

This thesis was presented

By

Chieh-Hsin Kuan

It was defended on

July 28, 2008

and approved

by

Thesis Advisor:
Richard Day, PhD
Associate Professor, Biostatistics
Assistant Professor, Infectious Diseases and Microbiology
Graduate School of Public Health
Assistant Professor, Anthropology
School of Arts and Sciences
University of Pittsburgh

Committee Member:
Ada Youk, Ph.D.
Research Assistant Professor, Biostatistics
Graduate School of Public Health
University of Pittsburgh

Committee Member:
Kenneth R. McCurry, M.D.
Assistant Professor of Surgery, Division of Cardiothoracic Surgery
Thomas E. Starzl Transplantation Institute
Heart, Lung, and Esophageal Institute
University of Pittsburgh Medical Center

Invited Committee Member:
David Kaczorowski, M.D.
Department of Surgery
University of Pittsburgh Medical Center

Richard Day, PhD

PRIMARY GRAFT DYSFUNCTION AFTER LUNG TRANSPLANT WITH T-CELL DEPLETION

Chieh-Hsin Kuan, MS

University of Pittsburgh, 2008

ABSTRACT

The objective of the study is to determine whether T cell depletion through pretreatment with either Thymoglobulin or Campath influences the incidence and severity of PGD (primary graft dysfunction) after human lung transplantation.

This is a single center study, conducted between July 2000 and November 2004, and is a retrospective analysis of 206 patients. Patients received one of following forms of induction therapy: Zenapax (n=28), Thymoglobulin (n=37), Campath (n=76), or no induction (n=65) therapy. Donor and recipient demographic, operative information, and survival data were collected. Assignment of primary grading dysfunction (PGD) grading was based on the International Society for Heart and Lung Transplantation (ISHLT) grading guidelines.

While baseline characteristics were similar for most variables, grafts for patients that received Campath (293±64 min) or Thymoglobulin (282±66 min) had a longer duration of ischemic time compared to the control group, no induction therapy (246±65 min). A significant difference between Campath (78.9%) and no induction (92.3%) group was observed with a p-value of 0.047 for the overall severity of PGD. In the multivariate analysis, Perfadex (p=0.009, OR=0.31), the preservation solution, remained as a protective agent on preventing recipients from severe PGD, and use of CPB (cardiopulmonary bypass) ($p<<0.001$, OR=4.53) was

identified to be a statistically significant risk factor for development of grade 3 PGD. There was improved early oxygenation and improved one year survival in patients that received Campath compared to the control group.

The combined use of Campath as induction therapy and the graft preservation solution of Perfadex seem to be protective against the development of grade 3 PGD as their roles on defending cumulative incidence of PGD were hindered. The use of CPB was an independent risk factor to the development of grade 3 PGD. These results suggest that the development of PGD after human lung transplantation is mainly due to intrinsic immune or non-immune mechanisms, further study will be necessary to unravel the role of T cells, and it will have significant impact on public health relevance applications.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEGEMENT

I would like to express my sincere gratitude to my thesis and academic advisor, Dr. Richard Day, for his supports and supervision. Thank you for being so patient when leading me through the analysis of this study. Because of your guidance, data analysis became intriguing and fun for me. Thank you for your unique point of views given the consulting class; I must say that I love you teaching that class. I would like to thank Dr. David Kaczorowski for his data and his time. Thank you for being so generous whenever explaining the medical terms in the study to me. Without your help, this MS thesis could not be done. I would like to thank Dr. Ada Youk for her supports and assistances on my thesis. Thank you.

INTRODUCTION

Organ transplantation has evolved, and lung transplantation is the only effective choice of treatment for end-stage pulmonary diseases. However, the incidence of primary graft dysfunction (PGD), also known as ischemia-reperfusion injury, pulmonary re-implantation response, or early allograft failure, is considered to be a significant clinical problem after lung transplantation. Patients who develop PGD require longer recipient intensive care unit stays, hospital stays, and prolonged post-operative mechanical ventilation. PGD is known to be a major contributing factor to early mortality after lung transplantation. However, the etiology of PGD remains ambiguous and is anticipated to be multi-factorial. Ischemia-reperfusion (IR) injury of the lung is recognized to play a major role in the etiology of PGD.

Recent studies have shown that T cells may play an important role in IR injury. A recent study conducted by De Perrot and colleagues concluded that recipient T cells mediate the pathogenesis of IR injury to the lung (1). Several studies on small animals suggested that T cells play a part in both renal (2-4), hepatic (5-7), and lung IR injury.

Recipient pre-transplant lymphoid depletion and minimal use of post-transplant immunosuppression are two key principles that have been recently employed in clinical lung transplantation. Lymphocyte depletion is meant to pre-operatively deplete pre-existing alloreactive donor-specific T cells to prevent acute rejection. Based on several clinical and experimental studies indicating that T cells may take parts in the pathogenesis of IR injury, our hypothesis focuses on the use of pre-transplant lymphoid depleting agents in our immunosuppressive protocol that might alter the incidence and severity of PGD after human lung transplantation. The measurements to test this hypothesis are the incidence and severity of

PGD and early oxygenation in the consecutive lung transplant recipients from UPMC; these recipients would either receive one of four induction therapies: Zenapax, Thymoglobulin, Campath, or no induction therapy.

MATERIALS AND METHODS

PATIENTS

This is a single center study, which was conducted between July 2000 and November 2004. Consecutive adult patients who underwent single lung, double lung, or heart-lung transplantation were analyzed. Patients with combined liver-lung transplantation were excluded from the study due to confounded PGD grading of accompanying liver transplantation. The death of one patient occurred in the course of operation was excluded because no PGD grading could be performed.

INFORMED CONSENT

All patients provided standard written informed consent in addition to consent for enrollment and participation in an IRB approved protocol and for reporting of outcomes.

INDUCTION PROTOCOLS

The induction protocols and subsequent immunosuppressive methods adopted in this study were formerly detailed (8). Patients received one of the following induction therapies: Zenapax, Thymoglobulin, Campath, or no induction therapy. The infusion of antibody was

initiated once donor organs were validated for transplantation. Four to seven mg/kg Thymoglobulin was administered to 37 patients between 6/02 and 9/03; Thymoglobulin infusions were commenced slowly and the infusion rate was increased every thirty minutes. Thirty milligrams of intravenous Campath was administered to 76 patients between 1/03 and 11/04. Patients treated with either Thymogolbulin or Campath were co-administered with 1g of methylprednisolone. Before lung allograft reperfusion, 250mg of methylprednisolone was given as well. One dose (1mg/kg) of Zenapax on the day of transplantation was administered to 28 patients between 11/01 and 6/02; four more doses on post-transplant day seven and post-transplant two, four, and six doses were administered to those patients subsequently.

DATA COLLECTION

Donor and recipient demographic, operative information, and survival data were collected prospectively. Donor smoking history, PaO_2/FiO_2 (partial pressure of arterial oxygen to fraction of inspired oxygen concentraion ratio) ratio, and sputum culture results were ascertained from donor charts from the local organ procurement organization retrospectively. Duration of mechanical ventilation, duration of inhaled nitric oxide (iNO), use of extra-corporeal membrane oxygenation (ECMO), post-operative pulmonary function including PaO_2/FiO_2 ratio were ascertained from the electronic health record.

PGD GRADING

Assignment of primary grading dysfunction (PGD) grading was performed in accordance to the International Society for Heart and Lung Transplantation (ISHLT) grading guidelines (9). Grade 0 was assigned to patients with PaO_2/FiO_2 ratio greater than 300 and the absence of radiographic infiltrates. Grade 1 was assigned to patients with PaO_2/FiO_2 ratio greater than 300 and the presence of radiographic infiltrates. Based on patient's chest radiograph, one was assigned with grade 0 or grade 1 if extubated and on nasal cannula. Grade 2 was assigned to patients with PaO_2/FiO_2 ratio between 200 and 300. Grade 3 was assigned to patients with PaO_2/FiO_2 ratio less than 200. Patients who were mechanically ventilated with FiO_2 greater than 0.5, received iNO for greater than 48 hours, and were on ECMO were assigned grade 3. Six and 12 hour time-points were included in addition to recent proposed potential refinements to the ISHLT guidelines.

STATISTICAL ANALYSIS

The donor and recipient characteristics included in the analysis were as follows: demographic and personal characteristics, diagnosis of primary pulmonary hypertension (PPH), cardiopulmonary bypass (CPB), mean pulmonary arterial pressure (mean PA), smoking history, cause of donor death, Perfadex (preservation solution), sputum culture results, donor ratio of arterial oxygen tension to inspired oxygen fraction (PaO_2 /FiO_2), $1^{st}/2^{nd}$ lung ischemic time, cytomegalovirus (CMV) mismatch, recipient blood type, and ECMO.

The association of donor and recipient characteristics with severe primary graft dysfunction after lung transplant was analyzed by using binary logistic regression models. Nominal variables were expressed as counts and proportions. The outcome variables (PGD grading) were expressed in a binary fashion, such that a baseline group of patients with PGD0 and PGD1 compares to patients with PGD2 and PGD3. Two types of outcome variables were analyzed: the first type includes patients with PGD2 and PGD3, and the second type of outcome variable includes only PGD3 patients. Type I error was set to be statistically significant if p-value is less than or equal to 0.05 (two-tailed p-value).

Donor and recipient (independent) variables were screened on a univariate basis, and those that were statistically significant were used in multivariate logistic regression models to adjust for potential confounding. Survival estimates were derived by using the Kaplan-Meier method, and survival across the induction groups were compared by using the log-rank test. Analyses were performed with Minitab for Windows, Version 15 (Minitab Inc, State College, PA). First paragraph. The figure below is inserted so that there is an item in the sample List of Figures.

RESULTS

A total of 206 patients were analyzed, 93 patients (45%) experienced PGD 1 or less, 39 patients (19%) developed PGD2, and 74 patients (36%) developed PGD3. In the single and double transplantation groups, 54 patients (51%) and 55 patients (57%) developed PGD2 or PGD3, respectively.

DONOR DEMOGRAPHICS

Donor characteristics are summarized in Table 1. Donor age, sex, cause of death, PaO_2/FiO_2, smoking history, sputum, and CMV mismatch were similar ($p>0.05$) among groups. The use of preservation solution of Perfadex and 1st lung ischemic time differed between induction groups. Among grafts preserved in Perfadex, 49% of patients underwent Campath induction; 41% underwent either Thymoglobulin or Zenapax; 10% patients were in no induction group (control group). Preservation solutions other than Perfadex, such as UW, Celsior, or Euro-Collins, were used in remainder of patients. Most patients who received Campath or Thymoglobulin had longer duration of ischemic time compared to the control group. While the p-value for donor PaO_2/FiO_2 was border line significant ($p=0.08$), a trend of lower PaO_2/FiO_2 was observed among patients received Campath.

RECIPIENT DEMOGRAPHICS AND OPERATIVE CHARACTERISTICS

Recipient and operative characteristics are described in Table 2. Differences in recipient age, sex, race, blood type, mean PA (pulmonary artery) pressure, laterality, and CPB (cardiopulmonary bypass) were not statistically significant ($p>0.05$) across induction groups. Type of transplantation, such as single lung, double lung, or heart-lung transplant differed between groups. Among those 206 recipients, 105 patients (51%) received single lung transplantations, 97 patients (47%) received double lung transplantations, and 4 patients (2%) received heart-lung transplantations. Most patients (45%) in the double lung transplant group received Campath, whereas 44% of patients in the single lung transplant received no induction. Within the Campath group, 58 patients (76%) did not use CPB.

POST-OPERATIVE RECIPIENT CHARACTERISTICS

The duration and proportion of patients requiring mechanical ventilation at six time points, T0, T6, T12, T24, T48, and T72, were evaluated in Table 3. The differences in duration of mechanical ventilation across four induction methods were not statistically significant at T0, T6, T48, and T72; however, statistically significant differences between induction therapies in duration of mechanical ventilation were observed at T12 and T24 ($p<0.05$). In the Thymoglobulin group, 37 patients (100%) were on mechanical ventilation between T0 to T12, and 30 patients (81.1%) required the mechanical ventilation at T24. At T12, 65 out of 76 patients (85.5%) in the Campath group stayed on the mechanical ventilation, compared to 26 patients (92.8%) in the Zenapax and 50 patients (76.9%) in the control group, received no

induction. At T24, 38 patients (50%) received Campath required the mechanical ventilation, whereas 30 patients (81.1%) in the Thymoglobulin group, 19 patients (67.9%) in the Zenapax group and 37 patients (56.9%) in the control group. The median duration in hours across four induction methods was not statistically significant ($p=0.064$). Among each induction group, the use of Campath contributed the lowest median duration in hours compared to the other induction methods, or no induction group.

Post-operative recipient oxygenation characteristics at six time points are summarized in Table 4. Mean PaO_2/FiO_2 ratios for patients, excluding patients that were treated with ECMO (extra-corporeal membrane oxygenation), were evaluated. The mean PaO_2/FiO_2 ratios had no statistically significant differences observed at T0, T24, T48, and T72 but displayed statistically significant differences at time point T6 and T12 ($p<0.05$). At T6 and T12, the mean PaO_2/FiO_2 ratios in Campath group were similar and increased while the ratios remained low for other induction methods. However, the highest mean PaO_2/FiO_2 ratio was observed in Thymoglobulin therapy at T48, at which no significant differences between induction groups was observed.

The use of post-operative inhaled nitric oxide (iNO) and ECMO for patients was tabulated in Table 5. Patients on iNO, median duration of iNO in hours, and patients on ECMO were evaluated across four induction methods. A significant difference in patients on iNO between induction methods was observed ($p<<0.001$) while no statistically significant differences observed in patients on ECMO or median duration of iNO in hours. More patients who received Thymoglolulin were on iNO than that of those received Campath.

INCIDENCE AND SEVERITY OF PRIMARY GRAFT DYSFUNCTION

The incidence and severity of PGD were detailed in Table 6. The severity of PGD, categorized into four grading scales, 0, 1, 2, 3, was measured between groups of induction therapies. Across the four induction methods, the incidence of grade 0 PGD was statistically significant (p=0.047) as well as the incidence of grade 3 PGD (p=0.009). In grade 0 PGD, there were 16 new cases (21.1%) observed in the Campath group and 5 new cases (7.7%) observed in the control group, no induction. Grade 1 and 2 PGD displayed no statistically significant differences in incidence between groups. For grade 3 PGD group (p=0.009), no induction method (47.7%) had higher incidence compared to patients with Campath method (25%). Overall, a significant difference between Campath (78.9%) and no induction (92.3%) group was observed with a p-value of 0.047. Of patients in the no induction group receiving graft preserved with Perfadex (n=16), incidence of grade 3 PGD is 37.5% (6 patients) and overall incidence of PGD is 93.8% (15 patients).

A univariate binary logistic analysis on development of grade 3 PGD and grade 2 or 3 PGD are summarized in Table 7. The use of Campath (p=0.013, OR=0.45) as an induction therapy has prevented patients from developing severe grade 3 PGD, as well as the use of Perfadex (p=0.011, OR=0.43) as a graft preservation solution. Variables such as recipient diagnosis of primary pulmonary hypertension (PPH; p=0.015, OR=13.69), use of cardiopulmonary bypass (CPB; $p<<0.001$, OR=4.47), elevated recipient mean pulmonary arterial pressure (mean PA; p=0.029, OR=2.01), and negative donor sputum cultures (p=0.040, OR=3.09) were identified as risk factors for the development of severe PGD3 grading. In the development of grade 2 or 3 PGD, use of Campath (p=0.026, OR=0.52) and Perfadex (p=0.512, OR=0.81) were protective against the development of PGD2 or PGD3, and the risk factors were

CPB (p<<0.001, OR=4.93), elevated recipient mean PA pressure (p=0.026, OR=1.95), and negative donor sputum cultures (p=0.045, OR=2.61).

A multivariate analysis on development of grade 3 PGD is summarized in Table 8. Perfadex (p=0.009, OR=0.31), the preservation solution, remained as a protective agent on preventing recipients from severe PGD, and use of CPB (p<<0.001, OR=4.53) was identified to be a statistically significant risk factor for development of PGD3. In addition, a multivariate analysis in Table 9 has indicated that CPB (p<<0.001, OR=4.44) was a risk factor for the development of grade 2 or 3 PGD. Results of multivariate analysis for patients who received no induction therapies are shown in Table 10, Perfadex was indentified to be an safeguard (p=0.001, OR=0.26) on developing severe PGD grade 3, while CPB (p=<<0.001, OR=4.64) persisted as a statistically significance as a risk factor on the progression of grade 3 PGD. In Table 11, the significant risk factor of CPB (p<<0.001, OR=4.56) was associated with the development of grade 2 or 3 PGD.

PATIENT SURVIVAL

A cumulative proportion of patient survival analysis on patients with PGD 3 grading was performed. Patients with no induction therapy displayed a trend toward early mortality compared to the groups with other induction methods (Figure 1). A statistically significant difference was observed for patient survival between the control group and Campath group via a Log-Rank test (p=0.034). For patients received Campath therapy, they would have less risk of developing PGD 1 or higher in a year compared to patients received other induction methods. It is shown in Figure 2 that survival for patients received Campath was higher than that of the

control group; 90.79% of patients received Campath survived after 1 year compared to 75.38% of patients received no induction therapy. The patient survival between Campath and the control group was statistically significant ($p=0.009$ by Log-Rank test) over time.

DISCUSSION

This study suggested that a cohort of lung transplant patients who received Campath, as induction therapy show some improvement in early oxygenation compared to patients who received no induction therapy, despite longer ischemic times. As a result, patients in the Campath group were less likely to develop grade 3 PGD or PGD overall. Nevertheless, while Campath was screened in a univariate analysis and identified to be effective against the development of severe PGD, it was not a statistically significant factor in the multivariate analysis. There appeared to be improved 1 year survival in patients that received Campath, although a long term survival benefit could not be conclusively demonstrated in this analysis. Moreover, despite a low incidence of PGD3 (25.0%) in Campath group, the overall incidence of PGD (78.9%) remained high for patients in Campath group.

It has been demonstrated that Campath extensively depletes T cells. Our data reveals a substantial incidence of PGD despite lymphocyte depletion with Campath therefore, development of PGD after human lung transplantation may be largely due to intrinsic immune or non-immune mechanisms. The role of T cells in the development of PGD in this study has not been precluded. The development of PGD is likely multi-factorial. Indeed, further study will be necessary to unravel the role of T cells in the pathogenesis of PGD in human lung transplantation.

In our study, Perfadex played an effective role against the progression of grade 3 PGD. When taking account of the entire cohort in a multivariate analysis and in a subgroup analysis on patients that received no induction therapy, the effect of Perfadex on preventing patients from development of PGD 3 grading was seen. Although used in our study, the application of

Perfadex as a graft preservation solution in clinical lung transplantation has been debated throughout the literature. Some studies found little benefit of this preservation solution for transplanted lung (10-13), whereas other studies have found exceptional efficacy of Perfadex as a preservation solution when measuring clinical outcomes after human lung transplantation, including improved post-operative oxygenation (14-17), compared to other preservation solutions.

In our study, CPB was identified to be a statistically significant predictive factor for the development of PGD in general. While CPB may contribute to the development of PGD by a number of mechanisms, it has been known to contribute to the pathogenesis of acute lung injury, such as increased expression of adhesion molecules on endothelial cells, pro-inflammatory cytokine release, complement activation, neutrophil activation, and others (18-19). This finding is consistent with least one other study (30) that demonstrated that CPB was a predictive factor of the development of PGD; however, other large studies have not implicated the involvement of CPB on the development of PGD (20-21).

Several previous studies have identified a number of risk factors to the development of grade 3 PGD, inclusive of donor age, donor female gender, donor African-American race, recipient PA pressure, recipient diagnosis of PPH, and transplantation era. In our univariate analysis of the development of grade 3 PGD, elevated mean PA pressure and recipient diagnosis of PPH were identified to be significant risk factor; however, they did not turn out to be significant in the multivariate analysis. Possible reasons for this difference could be the design of study and small sample size of patient population.

CONCLUSION

While induction therapy with Campath and the graft preservation solution Perfadex appear to be effective factors against the development of grade 3 PGD, their roles on preventing cumulative incidence of PGD were hindered. The use of cardiopulmonary bypass (CPB) was an independent risk factor for the development of grade 3 PGD, as well as for grade 2 or 3 PGD, in both univariate and multivariate analysis. Accordingly, the development of PGD was evidently multi-factorial. Nevertheless, the role of T cells in progression of PGD of human lung transplantation requires further investigation, though it may have played a role in our study. Our study inherited some possible limitations due to the use of consecutively enrolled patients, its retrospective nature, and restrictive sample size. A randomized, controlled clinical trial will be required to better assess the nature of Campath and other induction agents in the development of PGD after human lung transplantation.

Table 1: DONOR CHARACTERISTICS

	Control – No Induction	Zenapax	Thymoglobulin	Campath	P value
N	65	28	37	76	
Donor Age (years)	37.7 ± 14.3	36.1 ± 14.8	33.5 ± 14.6	34.1 ± 14.2	0.400
Donor Sex					
Male	36 (55.4%)	12 (42.9%)	17 (45.9%)	46 (60.5%)	0.428
Female	29 (44.6%)	16 (57.1%)	20 (54.0%)	30 (39.5%)	
Cause of Death					
Trauma	33 (50.8%)	14 (50.0%)	19 (51.4%)	33 (43.4%)	0.917
Cerebrovascular	30 (46.1%)	14 (50.0%)	17 (45.9%)	39 (51.3%)	
Other	2 (3.1%)	0 (0.0%)	1 (2.7%)	4 (5.3%)	
Donor PaO2/FiO2 (mm Hg)	437.4 ± 84.0	453.0 ± 109.9	441.2 ± 89.0	407.1 ± 96.1	0.080
Preservation Solution					
Perfadex					
UW	16 (24.6%)	26 (92.9%)	37 (100%)	76 (100%)	< 0.001
Celsior	4 (6.2%)	1 (3.6%)	0 (0%)	0 (0%)	
Euro-Collins	25 (38.5%)	0 (0.0%)	0 (0%)	0 (0%)	
Other/unknown	9 (13.8%)	1 (3.6%)	0 (0%)	0 (0%)	
	11 (16.9%)	0 0.0 %)	0 (0%)	0 (0%)	
Ischemic Time					
1st lung	236 ± 64.7	269 ± 61.6	282 ± 66.4	293 ± 64.1	< 0.01
2nd lung (minutes)	359 ± 76.0	366 ± 69.2	417 ± 73.6	384 ± 75.3	0.113
Smoking History					
Any	36 (55.4%)	20 (71.4%)	20 (54.1%)	44 (57.8%)	0.626
10 Pack-Year	23 (35.4%)	10 (35.7%)	14 (37.8%)	18 (23.7%)	0.420
Donor Cultures					
Positive	27 (41.5%)	13 (46.4%)	19 (51.4%)	27 (35.5%)	0.926
Negative	32 (49.2%)	13 (46.4%)	16 (43.2%)	42 (55.3%)	
No data	6 (9.2%)	2 (7.1%)	2 (5.4%)	7 (9.2%)	
CMV Mismatch	18 (27.7%)	5 (17.9%)	12 (32.4.0%)	15 (19.7%)	0.521

Table 2: RECIPIENT AND OPERATIVE CHARACTERISTICS

	Control-No Induction	Zenapax	Thymoglobulin	Campath	P value
N	65	28	37	76	
Age (yrs)	52.5 ± 10.2	51.2 ± 13.0	48.2 ± 12.6	52.1 ± 12.8	0.452
Sex					
Male	38 (58.5%)	13 (46.4%)	16 (43.2%)	40 (52.6%)	0.591
Female	27 (41.5%)	15 (53.6%)	21 (56.8%)	36 (47.4%)	
Race					
Caucasian	60 (92.3%)	27 (96.4%)	35 (94.6%)	72 (94.7%)	0.833
African-American	3 (4.6%)	0 (0.0%)	2 (5.4%)	4 (5.3%)	
American Indian	0 (0.0%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	
Hispanic	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Pacific Islander	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Blood Type					
A	21 (32.3%)	17 (60.7%)	16 (43.2%)	35 (46.0%)	0.264
B	7 (10.8%)	1 (3.6%)	4 (10.8%)	11 (14.5%)	
AB	5 (7.7%)	1 (3.6%)	0 (0%)	1 (1.3%)	
O	32 (49.2%)	9 (32.1%)	17(45.9%)	29 (38.2%)	
Indication					
Emphysema/COPD	27 (41.5%)	10 (35.7%)	12 (32.4%)	23 (30.3%)	0.433
IPF	9 (13.8%)	8 (28.6%)	5 (13.5%)	19 (25.0%)	
CF	7 (10.8%)	4 (14.3%)	7 (18.9%)	8 (10.5%)	
α-1-anti-trypsin	2 (3.1%)	1 (3.6%)	5 (13.5%)	6 (7.9%)	
Scleroderma/CREST	2 (3.1%)	2 (7.1%)	2 (5.4%)	4 (5.3%)	
PPH	5 (7.7%)	0 (0.0%)	1 (2.7%)	2 (2.6%)	
Sarcoidosis	3 (4.6%)	0 (0.0%)	2 (5.4%)	3 (3.9%)	
Bronchiolitis obliterans	0 (0.0%)	1 (3.6%)	0 (0.0%)	7 (9.2%)	
Silicosis	4 (6.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Eisenmenger	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
MCTD	1 (1.5%)	0 (0.0%)	1 (2.7%)	1 (1.3%)	
Rheumatoid	2 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Graft vs. Host Disease	0 (0.0%)	1 (3.6%)	0 (0.0%)	1 (1.3%)	
Pulmonary fibrosis	1 (1.5%)	0 (0.0%)	1 (2.7%)	1 (1.3%)	
Eosinophilc granuloma	0 (0.0%)	0 (0.0%)	1 (2.7%)	0 (0.0%)	
Other	1 (1.5%)	1 (3.6%)	0 (0.0%)	1 (1.3%)	
Recipient Mean PA Pressure	29.9 ± 11.2	27.0 ± 6.5	29.8 ± 8.8	28.5 ± 10.4	0.737
Type					
Single	46 (70.8%)	13 (46.4%)	17 (45.9%)	29 (38.2%)	0.003
Double	18 (27.7%)	15 (53.6%)	20 (54.0%)	44 (47.3%)	
Heart-lung	1 (1.5%)	0 (0.0%)	0 (0 %)	3 (3.2%)	
Laterality					
Left	27 (41.5%)	6 (21.4%)	9 (24.3%)	21 (27.6%)	0.477
Right	19 (29.2%)	7 (25.0%)	8 (21.6%)	8 (10.5%)	
Bilateral	19 (29.2%)	15 (53.6%)	20 (54.1%)	47 (61.8%)	
Redo	0 (0.0%)	1 (3.6%)	0 (0.0%)	6 (7.9%)	0.051
CBP	16 (24.6%)	11 (39.3%)	10 (27.0%)	18 (23.4%)	0.451

Table 3: PATIENTS REQUIRING MECHANICAL VENTILATION AND MEDIAN DURATION OF MECHANICAL VENTILATION

	TO	T6	T12	T24	T48	T72	Median duration in hours (interquartile range)
Control – No Induction	65 (100%)	61 (93.8%)	50 (76.9%)	37 (56.9%)	29 (44.6%)	23 (35.4%)	35.1 (14.5-96.3)
Zenapax	28 (100%)	28 (100%)	26 (92.8%)	19 (67.9%)	18 (64.3%)	14 (50.0%)	58.8 (20.5-121)
Thymoglobulin	37 (100 %)	37 (100 %)	37 (100 %)	30 (81.1%)	19 (51.4%)	15 (40.5%)	50.0 (25.5-107)
Campath	76 (100 %)	75 (98.7%)	65 (85.5%)	38 (50.0%)	26 (34.2%)	22 (28.9%)	21.45 (14.0-68.9)
P value	n.s.	0.240[1]	0.018[1]	0.026	0.056	0.318	0.064

Table 4: POST-OPERATIVE RECIPIENT MEAN PAO2/FIO2 VALUES (EXCLUDING ECMO PATIENTS)

	TO	T6	T12	T24	T48	T72
Control- No Induction	274.51 ± 153.89	227.21 ± 102.32	211.41 ± 81.40	222.11 ±108.89	225.38 ± 74.40	150.25 ± 11.08
Zenapax	264.43 ±128.05	218.65 ±104.54	246.50 ±118.23	228.02 ± 98.00	245.57 ± 90.30	182.55 ± 70.05
Thymoglobulin	288.54 ±140.34	224.59 ± 91.57	239.70 ±102.81	264.42 ± 104.89	310.50 ±124.01	194.55 ± 00.00
Campath	274.88 ±113.53	303.10 ± 288.49	305.75 ± 77.47	298.19 ± 104.95	227.24 ±74.54	198.66 ± 44.19
P value	0.969	0.018	0.002	0.221	0.268	0.581

Table 5: USE OF POST-OPERATIVE INHALED NITRIC OXIDE (INO) AND EXTRA-CORPOREAL MEMBRANE OXYGENATION (ECMO)

	Patients on iNO	Median Duration of iNO in hours (interquartile range)	Patients on ECMO
Control- No Induction	23 (35.4%)	42.68 (26.48-73.86)	7 (10.8%)
Zenapax	13 (46.4%)	38.17 (30.41-69.76)	2 (7.1%)
Thymoglobulin	23 (62.2%)	41.68 (24.75-50.95)	2 (5.4%)
Campath	12 (15.8%)	36.61 (8.11-45.85)	6 (7.9%)
P value	<0.001	0.549	0.892

Table 6: INCIDENCE AND SEVERITY OF PGD

	PGD 0	PGD I	PGD II	PGD III	Overall
Control- No Induction	5 (7.7%)	21 (32.3%)	8 (12.3%)	31 (47.7%)	60 (92.3%)
Zenapax	4 (14.3%)	6 (21.4%)	7 (25.0%)	11 (39.3%)	24 (85.7%)
Thymoglobulin	5 (13.5%)	10 (27.0%)	10 (27.0%)	12 (32.4%)	32 (86.4%)
Campath	16 (21.1%)	26 (34.2%)	15 (19.7%)	19 (25.0%)	60 (78.9%)
P value	0.047	0.579	0. 683	0. 009	0.047

Table 7: UNIVARIATE ANALYSIS

	PGD23 p-value (odds ratio)	PGD3 p-value (odds ratio)
Induction	0.037 (1.32)	0.018 (1.38)
2grp_Campath		
1	0.026 (0.52)	0.013 (0.45)
Donor age (yrs)	0.966 (1.00)	0.675 (1.00)
Recipient age (yrs)	0.120 (0.98)	0.129 (0.98)
Donor gender	0.054 (0.58)	0.157 (0.66)
Recipient gender	0.111 (0.64)	0.115 (0.63)
PPH	0.998 (1.45159E+09)*	0.015 (13.69)
CPB	0.000 (4.93)	0.000 (4.47)
Mean PA	0.004 (1.05)	0.012 (1.04)
Mean PA_25	0.026 (1.95)	0.029 (2.01)
Perfadex	0.512 (0.81)	0.011 (0.43)
Tx (single double H-L)		
2	0.453 (1.24)	0.574 (1.18)
3	0.999 (1.54785E+09)*	0.127 (6.00)
Tx (single double)		
2	0.453 (1.24)	0.574 (1.18)
Smk		
1	0.858 (0.94)	0.297 (0.66)
2	0.110 (1.71)	0.281 (0.44)
Cause of death		
1 (cerebrovascular)	0.786 (0.92)	0.598 (1.17)
2 (other)	0.813 (0.88)	0.922 (1.06)
Sputum(0 N/A)		
1 (Negative)	0.045 (2.61)	0.040 (3.09)
2 (Positive)	0.307 (1.62)	0.468 (1.50)
Donor PaO2/FiO2	0.650 (1.00)	0.258 (1.00)
Ischemic_1stLung	0.512 (1.00)	0.541 (1.00)
Ischemic_2ndLung	0.146 (1.00)	0.978 (1.00)
CMV Mismatch (no/yes : 0/1)	0.230 (1.49)	0.509 (1.25)
Recipient Race		
0 (Caucasion)		
1 (African-American)	0.482 (1.66)	0.589 (1.45)
2 (other)	0.476 (0.42)	0.936 (0.91)
Recipient Blood Type		
2		
3	0.962 (0.98)	0.866 (0.92)
4	0.738 (1.30)	0.625 (1.48)
	0.220 (1.45)	0.459 (1.26)
Laterality		
2	0.811 (0.91)	0.673 (1.19)
3	0.999 (1.48991E+09)*	0.116 (6.45)
4	0.592 (1.19)	0.487 (1.27)
Redo (no/yes : 0/1)	0.520 (0.61)	0.681 (0.71)
ECMO (no/yes : 0/1)	0.997 (1.58768E+09)*	0.997 (4.42989E+09)*

*Large odds ratio observed is due to the small sample size.

Table 8: MULTIVARIATE ANALYSIS FOR PGD3

	p-value (odds ratio)
PPH	0.135 (5.57)
CPB	0.000 (4.53)
MeanPA_25	0.082 (1.87)
2grp_Campath	0.391 (0.71)
Perfadex	0.009 (0.31)
Sputum	
1	0.123 (2.80)
2	0.795 (1.19)

Table 9: MULTIVARIATE ANALYSIS FOR PGD 23

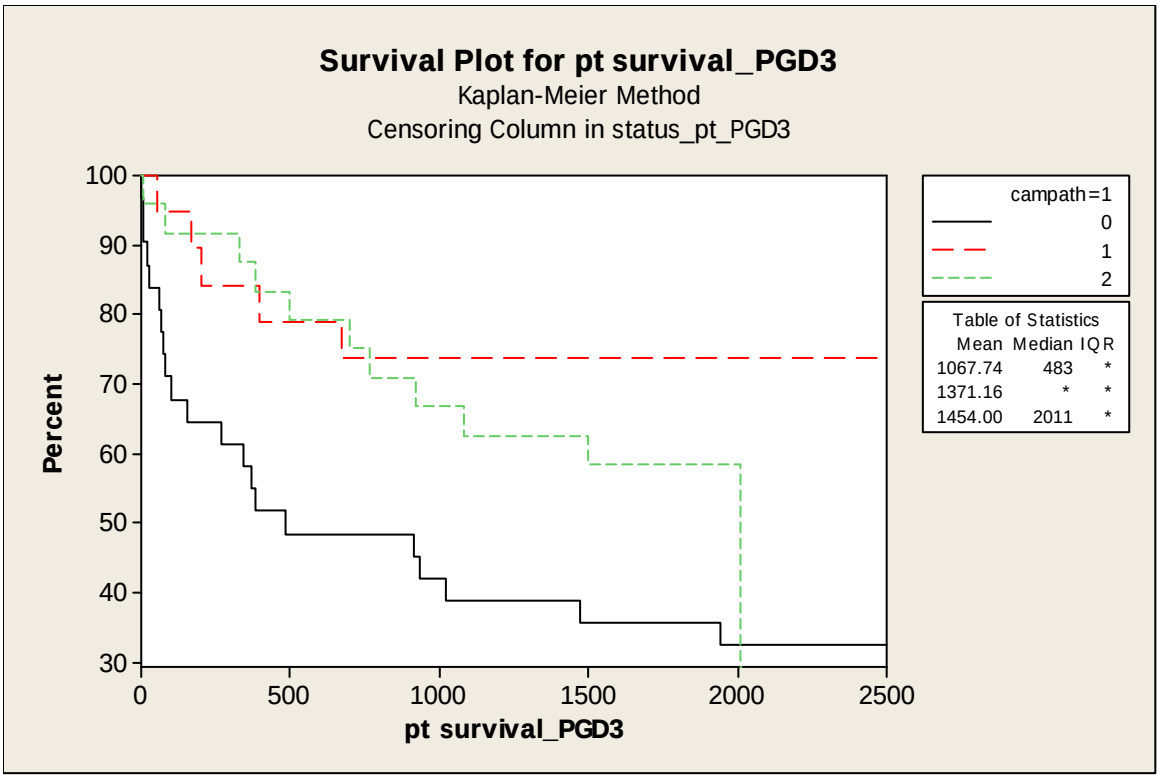
	p-value (odds ratio)
Perfadex	0.572 (0.78)
CPB	0.000 (4.44)
MeanPA_25	0.074 (1.79)
2grp_Campath	0.109 (0.56)
Sputum	
1	0.068 (2.85)
2	0.403 (1.61)

Table 10: MULTIVARIATE ANALYSIS FOR PGD 3 (NO INDUCTION)

	p-value (odds ratio)
PPH	0.135 (5.53)
CPB	0.000 (4.64)
MeanPA_25	0.070 (1.92)
Perfadex	0.001 (0.26)
Sputum	
1	0.113 (2.86)
2	0.745 (1.24)

Table 11: MULTIVARIATE ANALYSIS FOR PGD 23 (NO INDUCTION)

	p-value (odds ratio)
CPB	0.000 (4.56)
MeanPA_25	0.058 (1.85)
Perfadex	0.178 (0.58)
Sputum	
1	0.054 (2.96)
2	0.306 (1.78)



0 None, 1 Campath, 2 thymo+Zenapax；P= 0.034 using Log-Rank method

Figure 1: PATIENT SURVIVAL IN 2500 DAYS

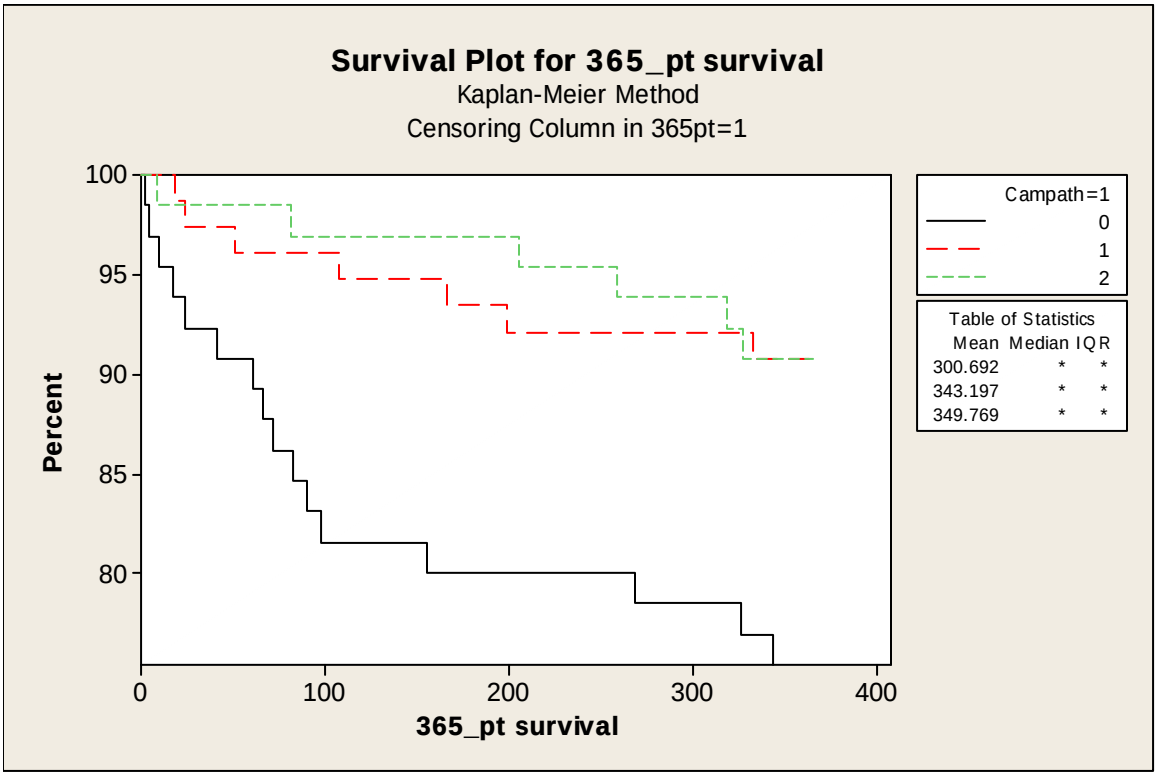


Figure 2: PATIENT SURVIVAL IN 365 DAYS

BIBLIOGRAPHY

1. de Perrot M, Young K, Imai Y et al. Recipient T cells mediate reperfusion injury after lung transplantation in the rat. J Immunol 2003;171: 4995-5002.
2. Burne MJ, Daniels F, El Ghandour A et al. Identification of the CD4(+) T cell as a major pathogenic factor in ischemic acute renal failure. J Clin Invest 2001;108: 1283-1290.
3. Rabb H, Daniels F, O'Donnell M et al. Pathophysiological role of T lymphocytes in renal ischemia-reperfusion injury in mice. Am J Physiol Renal Physiol 2000;279: F525-F531.
4. Yokota N, Daniels F, Crosson J, Rabb H. Protective effect of T cell depletion in murine renal ischemia-reperfusion injury. Transplantation 2002;74: 759-763.
5. Shen XD, Ke B, Zhai Y et al. CD154-CD40 T-cell costimulation pathway is required in the mechanism of hepatic ischemia/reperfusion injury, and its blockade facilitates and depends on heme oxygenase-1 mediated cytoprotection. Transplantation 2002;74: 315-319.
6. Shen XD, Ke B, Zhai Y et al. Stat4 and Stat6 signaling in hepatic ischemia/reperfusion injury in mice: HO-1 dependence of Stat4 disruption-mediated cytoprotection. Hepatology 2003;37: 296-303.
7. Zwacka RM, Zhang Y, Halldorson J, Schlossberg H, Dudus L, Engelhardt JF. CD4(+) T-lymphocytes mediate ischemia/reperfusion-induced inflammatory responses in mouse liver. J Clin Invest 1997;100: 279-289.
8. McCurry KR, Iacono A, Zeevi A et al. Early outcomes in human lung transplantation with Thymoglobulin or Campath-1H for recipient pretreatment followed by posttransplant tacrolimus near-monotherapy. J Thorac Cardiovasc Surg 2005;130: 528-537.

9. Christie JD, Carby M, Bag R, Corris P, Hertz M, Weill D. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction part II: definition. A consensus statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2005;24: 1454-1459.
10. Nath DS, Walter AR, Johnson AC et al. Does Perfadex affect outcomes in clinical lung transplantation? J Heart Lung Transplant 2005;24: 2243-2248.
11. Aziz TM, Pillay TM, Corris PA et al. Perfadex for clinical lung procurement: is it an advance? Ann Thorac Surg 2003;75: 990-995.
12. Oto T, Griffiths AP, Rosenfeldt F, Levvey BJ, Williams TJ, Snell GI. Early outcomes comparing Perfadex, Euro-Collins, and Papworth solutions in lung transplantation. Ann Thorac Surg 2006;82: 1842-1848.
13. Ganesh JS, Rogers CA, Banner NR, Bonser RS. Does the method of lung preservation influence outcome after transplantation? An analysis of 681 consecutive procedures. J Thorac Cardiovasc Surg 2007;134: 1313-1321.
14. Struber M, Wilhelmi M, Harringer W et al. Flush perfusion with low potassium dextran solution improves early graft function in clinical lung transplantation. Eur J Cardiothorac Surg 2001;19: 190-194.
15. Rabanal JM, Ibanez AM, Mons R et al. Influence of preservation solution on early lung function (Euro-Collins vs Perfadex). Transplant Proc 2003;35: 1938-1939.
16. Fischer S, Matte-Martyn A, de PM et al. Low-potassium dextran preservation solution improves lung function after human lung transplantation. J Thorac Cardiovasc Surg 2001;121: 594-596.

17. Muller C, Furst H, Reichenspurner H, Briegel J, Groh J, Reichart B. Lung procurement by low-potassium dextran and the effect on preservation injury. Munich Lung Transplant Group. Transplantation 1999;68: 1139-1143.
18. Wan S, LeClerc JL, Vincent JL. Inflammatory response to cardiopulmonary bypass: mechanisms involved and possible therapeutic strategies. Chest 1997;112: 676-692.
19. Clark SC. Lung injury after cardiopulmonary bypass. Perfusion 2006;21: 225-228.
20. Whitson BA, Nath DS, Johnson AC et al. Risk factors for primary graft dysfunction after lung transplantation. J Thorac Cardiovasc Surg 2006;131: 73-80.
21. Christie JD, Kotloff RM, Pochettino A et al. Clinical risk factors for primary graft failure following lung transplantation. Chest 2003;124: 1232-1241.
22. Prekker ME, Nath DS, Walker AR et al. Validation of the proposed International Society for Heart and Lung Transplantation grading system for primary graft dysfunction after lung transplantation. J Heart Lung Transplant 2006;25: 371-378.
23. Burton CM, Iversen M, Milman N et al. Outcome of lung transplanted patients with primary graft dysfunction. Eur J Cardiothorac Surg 2007;31: 75-82.
24. Oto T, Levvey BJ, Snell GI. Potential refinements of the International Society for Heart and Lung Transplantation primary graft dysfunction grading system. J Heart Lung Transplant 2007;26: 431-436.
25. Ray M, Dharmarajan S, Freudenberg J, Zhang W, Patterson GA. Expression profiling of human donor lungs to understand primary graft dysfunction after lung transplantation. Am J Transplant 2007;7: 2396-2405.