Respiratory Failure After Lung Transplantation*

Wissam M. Chatila, MD, FCCP; Satoshi Furukawa, MD; John P. Gaughan, PhD; and Gerard J. Criner, MD, FCCP

Study objectives: **To characterize patients who acquired postoperative respiratory failure after lung transplantation (LT), and to identify risks associated with postoperative respiratory failure and poor surgical outcome.**
Study design: **Retrospective clinical analysis in a tertiary care transplantation center.**
Methods: **We reviewed the records of 80 consecutive patients who underwent LT from April 1994 to May 1999, analyzing their records for a number of preoperative and perioperative variables and complications.**
Results: **Forty-four patients (55%) acquired postoperative respiratory failure and had a mortality rate of 45%. No difference was noted between patients with respiratory failure and those without in terms of age (mean ± SD, 56 ± 9 years vs 53 ± 11 years), gender, baseline pretransplant arterial blood gas analysis ($Paco_2$, 46 ± 9 mm Hg vs 44 ± 10 mm Hg), and cardiopulmonary exercise testing (maximum oxygen uptake, 0.76 ± 0.44 L/min/m^2 vs 0.82 ± 0.20 L/min/m^2). Ischemic reperfusion lung injury (IRLI) [55%] and perioperative cardiovascular/hemorrhagic events (36%) were the major contributors to the development of respiratory failure. Preoperative pulmonary hypertension, right ventricular (RV) dysfunction, ischemic times, and need for bilateral LT and cardiopulmonary bypass (CPB) were higher in patients with respiratory failure ($p < 0.05$) compared to recipients without respiratory failure. However, the presence of preoperative moderate-to-severe RV dysfunction was the only independent factor (odds ratio, 21.9; 95% confidence interval, 1.6 to 309.0).**
Conclusion: **Respiratory failure after LT is common and is associated with high morbidity and mortality. Respiratory failure often occurred in patients with operative technical complications, cardiovascular events, and postoperative IRLI, which were observed most in patients requiring CPB because of RV dysfunction.** ***(CHEST 2003; 123:165–173)***

Key words: cardiopulmonary bypass; ischemia-reperfusion injury; lung transplantation; pulmonary hypertension; respiratory failure; right ventricular dysfunction

Abbreviations: BLT = bilateral sequential lung transplantation; CAD = coronary artery disease; CHF = congestive heart failure; CI = confidence interval; CPB = cardiopulmonary bypass; FIo_2 = fraction of inspired oxygen; FOB = fiberoptic bronchoscopy; HLT = heart-lung transplantation; IRLI = ischemia reperfusion lung injury; LT = lung transplantation; 6MWD = 6-min walk distance; OR = odds ratio; PH = pulmonary hypertension; PRA = panel of reactive antibodies; RV = right ventricular; SLT = single lung transplantation; TBB = transbronchial biopsy

Lung transplantation (LT) is offered to patients with progressive end-stage pulmonary disease to improve their quality of life. Patients who survive the transplantation waiting time have to face the perils of perioperative complications before reaping the benefits of transplanted organs.[1,2] Perioperative complications reported following LT range from 10 to 97%,[2–12] and include pulmonary edema/early graft failure,[3–6] respiratory infections,[2] airway complications,[7] cardiovascular events,[4,9] drug toxicity,[4] and phrenic nerve injury.[13] Commonly, many of the serious complications manifest as postoperative respiratory failure and are associated with a relatively high early mortality (5 to 29%).[14]

For editorial comment see page 14

Potential clinical predictors of poor perioperative outcome after LT have been identified as older

*From the Division of Pulmonary and Critical Care Medicine, (Drs. Chatila and Criner), Department of Medicine; Cardiothoracic Division (Dr. Furukawa), Department of Surgery; and Department of Biostatistics (Dr. Gaughan), Temple University School of Medicine, Philadelphia, PA.
Manuscript received September 12, 2001; revision accepted May 8, 2002.
Correspondence to: Wissam Chatila, MD, FCCP, Assistant Professor of Medicine, Division of Pulmonary and Critical Care Medicine, 763 PP, Temple University School of Medicine, 3401 N Broad St, Philadelphia, PA 19140; e-mail: chatilw@tuhs.temple.edu

age (> 60 years), underlying disease (other than COPD), and development of graft failure and infection,[1–6,9,11,12,15–17] but the risk of postoperative respiratory failure, and its causes, have not been described. Although investigators have tried to discern the pathogenesis and epidemiology of primary graft failure (also called *significant ischemic reperfusion lung injury* [IRLI] by some investigators), none have examined the impact of respiratory failure from any cause—not only due to IRLI—on outcome. It is common to observe severe graft dysfunction leading to a poor short-term outcome,[12,15,16] but the perpetuation of postoperative respiratory failure after the initial injury is often multifactorial and involves infections, muscle weakness, and cardiovascular complications. Since acute respiratory failure is believed to be a major contributor to the morbidity and mortality after LT, we sought to determine its frequency, its impact on patient hospital outcome, and the types and risks of preoperative and intraoperative factors that lead to its occurrence.

Materials and Methods

Study Population

We retrospectively reviewed the records of all patients who underwent LT at our institution from March 1994 to April 1999 (n = 84). Patients were selected for LT according to previously published criteria.[1] Patients were selected if they were severely symptomatic, had progressive cardiopulmonary disease despite therapy, and had clinically significant hypoxemia or hypercapnia. The institutional review board waived the need for informed consent.

Definition of Respiratory Failure

We classified patients into two groups: patients with and patients without respiratory failure after LT. We defined postoperative respiratory failure as dependency on mechanical ventilation for > 48 h after LT, or the need for reintubation before hospital discharge. We obtained perioperative clinical data from the medical records. For weaning, we have a standard protocol that relies on gas exchange and weaning parameters (mostly the rapid shallow breathing index < 105 breaths/min/L), the patient's stability, and the patient's ability to sustain spontaneous breathing for 30 to 60 min; however, the final decision for extubation is left to the discretion of the critical care team.

Preoperative Data

Preoperative variables analyzed included patient demographics, systemic steroid use, history of previous sternotomy, serum albumin, panel of reactive antibodies (PRA), and pulmonary function tests following American Thoracic Society guidelines, as well as donor age and gender. Cardiovascular (pulmonary hemodynamics, echocardiographic findings) and exercise data (cardiopulmonary exercise test, 6-min walk distance [6MWD]) were also evaluated when available. Oxygen uptake, carbon dioxide production, oxygen pulse, minute ventilation, tidal volume, and respiratory frequency were continuously recorded by a metabolic cart (SensorMedics 2900; SensorMedics; Yorba Linda, CA). Supplemental oxygen was not administered during the test. The 6MWD test was performed on a day different than exercise testing; the total distance the patient was able to walk in 6 min in a corridor was recorded.

Echocardiographic Doppler imaging was performed using transthoracic views to assess left ventricular function, valvular function, pericardial disease, and measure right ventricular (RV) pressure. RV function was assessed subjectively based on ventricular wall movement and thickness, and was classified as either normal, or with mild/moderate/severe dysfunction. Right-heart catheterization was performed in the cardiac catheterization suite using the standard technique of a balloon-tipped pulmonary artery flotation catheter. Tracings were interpreted by the cardiologist performing the procedure. Cardiac output was measured using the thermodilution method.

Graft Preservation and Surgical Technique

All graft procurement and LT were performed by two experienced cardiothoracic surgeons, who are United Network of Organ Sharing certified, and perform heart transplantation, LT, and heart-lung transplantation (HLT). We applied standard donor selection criteria and routinely performed flexible fiberoptic bronchoscopy (FOB) prior to organ harvesting, which was preceded by IV prostaglandin E_1 infusion before aortic cross-clamping. Surgeons preserved the lung, or heart-lung block, by infusing modified Euro-Collins solution into the pulmonary artery. We defined the ischemic time as the time from aortic cross-clamping during procurement to allograft reperfusion after implantation. LT and HLT were performed via standard approaches for single LT (SLT) and bilateral sequential LT (BLT), and *en bloc* HLT. The decision to use cardiopulmonary bypass (CPB) was determined by the surgeon based on type of organ transplantation being performed (*eg*, HLT or BLT) and the patient's cardiopulmonary stability. Patients with severe RV dilatation after clamping of the pulmonary artery causing hypotension and refractory hypoxemia were placed on CPB.

Intraoperative and Postoperative Care

All recipients received intraoperatively a bolus of IV methylprednisolone (500 mg), prophylactic antibiotics, and some patients received prostaglandin E_1 infusions. Azathioprine (1 to 2 mg/kg/d, maintaining a WBC count > 5,000/mL or an absolute neutrophil count > 3,000/mL) and cyclosporine (2 to 6 mg/kg/d to attain target levels of 400 to 600 mg/dL) were initiated immediately following surgery. Few patients received antithymocyte globulin perioperatively rather than cyclosporine because of hemodynamic instability or renal insufficiency. Recipients were routinely monitored intraoperatively and postoperatively using pulmonary artery catheters. All patients underwent FOB in the operating room prior to transfer to the cardiothoracic ICU, where they underwent standard critical care monitoring, including pulmonary hemodynamics with an oximetric pulmonary artery catheter. Repeat FOB for BAL and transbronchial biopsy (TBB) was performed in the event of suspected infection or rejection, and routinely prior to discharge for surveillance.

Intraoperative Data

Intraoperative data analyzed included the type of surgery (SLT, BLT, HLT), the duration of surgery (from induction to reversal of anesthesia), organ ischemic time, the need and duration of CPB, the need for > 2 U of blood products transfu-

sion during surgery, intraoperative fluid balance (urine output and estimated blood loss subtracted from fluid and blood product infusions), and the development of intraoperative complications. In cases of BLT, ischemic time of the second transplanted lung is reported.

Postoperative Data

Data obtained included length of intubation and extubation (for patients who had to be reintubated), best Pa_{O_2}/fraction of inspired oxygen (F_{IO_2}) within first 24 h after surgery, 48-h fluid balance (fluid intake minus output), the need for inotropic support >48 h (dopamine, >5 μg/kg/min; dobutamine, >5 μg/kg/min; epinephrine; or neosynephrine), presence of postoperative complications, total duration of mechanical ventilation and hospitalization, and patient disposition. For patients with respiratory failure, we recorded etiology of respiratory failure and need for tracheostomy. We considered early mortality in patients who died within the first 28 days after surgery, and total mortality as those who died before hospital discharge.

IRLI

IRLI was defined as the presence of pulmonary infiltrates on chest radiographs ≤ 48 h after surgery in the absence of infection and rejection, both excluded by BAL and TBB, and no evidence of cardiogenic edema (pulmonary arterial occlusion pressure <16 mm Hg). Our definition of IRLI relied on radiographic pattern rather than gas exchange abnormalities, in order to identify all the patients at risk of acquiring pulmonary complications.

Statistical Analysis

The variables are presented as mean ± SD. Comparisons between the group of patients who acquired respiratory failure and those who did not were performed by an unpaired Student's *t* test for normally distributed continuous data, Mann-Whitney *U* test for nonparametric data, χ^2 test, and the Fisher exact test, when $>20\%$ of the expected values were less than five (for categorical data). We also subgrouped the patients with respiratory failure into those who remained intubated for >48 h postoperatively vs patients who had to be reintubated after an unsuccessful extubation attempt, and then we compared their clinical profiles and outcomes. Univariate and stepwise logistic regressions were used to estimate the relationship of individual factors with the occurrence of respiratory failure; $p<0.05$ was considered statistically significant. We included the following in the stepwise regression model: (1) preoperative factors (age, diagnosis, presence of RV dysfunction and pulmonary hypertension [PH]), (2) operative factors (type of transplant, ischemic time, need for CPB), and (3) postoperative factors (development of IRLI).

Results

Patient Characteristics

Eighty-four patients underwent LT and HLT during the 5-year period; 80 cases were analyzed. Four patients were excluded because of either missing or incomplete records. Forty-four of the 80 patients (55%) acquired acute respiratory failure after LT. There were three repeat transplantations in the group with respiratory failure; only one patient survived. Baseline demographic characteristics and physiologic data of the two groups are shown in Table 1. There were 11 patients with concomitant heart disease: 3 patients had coronary artery disease

Table 1—*Demographic, Clinical, and Cardiopulmonary Profiles**

Variables	No Respiratory Failure	Respiratory Failure	p Value
Patients, No.	36	44	
Age, yr	56 ± 9	53 ± 11	0.09
Male gender	16 (44)	22 (50)	0.8
Black race	6 (17)	9 (20)	0.9
Serum albumin	3.8 ± 0.5	3.8 ± 0.5	0.7
Previous sternotomy	6 (17)	6 (14)	0.9
Systemic steroid use	25 (69)	27 (61)	0.6
Presence of RV dysfunction†	6 (17)	19 (43)	0.02
Presence of PH‡	11 (31)	26 (59)	0.02
Primary, No.	0	5	
Secondary, No.	11	21	
Presence of CAD/CHF	4 (11)	7 (16)	0.7
PRA > 10%	0	2	0.5
FVC, L	2.2 ± 0.8 (34)	2.2 ± 0.8 (41)	0.9
FEV_1, L	0.82 ± 0.53 (34)	1.20 ± 0.73 (41)	0.005
DLCO, percent predicted	31 ± 14 (31)	43 ± 17 (36)	0.002
Pa_{CO_2}, mm Hg	46 ± 9 (34)	44 ± 10 (39)	0.5
6MWD, m	248 ± 92 (33)	299 ± 97 (36)	0.03
$\dot{V}o_2$max, L/min/m^2	0.76 ± 0.44 (24)	0.82 ± 0.20 (14)	0.17
Ppa, mm Hg	26 ± 13 (36)	33 ± 16 (42)	0.54
Cardiac index, L/min/cm^2	3.0 ± 0.9 (32)	2.9 ± 0.9 (37)	0.6
Ppao, mm Hg	10 ± 6 (34)	10 ± 4 (38)	0.9

*Data are presented as mean ± SD, No. (%), or mean ± SD (No. of patients) unless otherwise indicated. DLCO = diffusing capacity of the lung for carbon monoxide; $\dot{V}o_2$max = maximal oxygen uptake; Ppa = mean pulmonary artery pressure; Ppao = pulmonary artery occlusion pressure.
†Defined as moderate-to-severe RV hypokinesis on echocardiography.
‡Defined as mean pulmonary arterial pressure > 25 mm Hg.

(CAD) and 8 patients had congestive heart failure (CHF). Among the three patients with CAD, only one patient had respiratory failure, and that patient underwent coronary artery bypass grafting with his BLT. Three of the eight patients with CHF patients underwent HLT (one patient with ventricular septal defect and secondary PH, and two patients with COPD and dilated cardiomyopathy). Two of these three patients did not acquire postoperative respiratory failure. The rest of the patients had COPD and PH with low left ventricular ejection fraction but no evidence of CAD. In terms of demographic and physiologic variables at baseline pretransplantation, only poor RV function and presence of PH were associated with respiratory failure; worse pulmonary function and hemodynamics were not associated with respiratory failure (Tables 1, 2). The etiology of secondary PH did not differ between the group with respiratory failure (eight patients with obstructive lung disease, one patient with cardiomyopathy, six patients with interstitial fibrosis, three patients with connective tissue disease, and three patients with congenital heart disease), and the group without respiratory failure (eight patients with obstructive lung disease, one patient with cardiomyopathy, one patient with interstitial fibrosis, and two patients with congenital heart disease).

Perioperative Outcome

Postoperative patients with respiratory failure underwent more BLT and CPB than patients without respiratory failure. The patients with respiratory failure were also noted to have longer anesthesia time, longer ischemic time, worse gas exchange, and a higher requirement of fluids/blood products and pressors for resuscitation (Tables 2, 3). In addition, patients with respiratory failure were observed to have higher complication rates and IRLI (Table 4), longer hospitalization, and higher hospital mortality when compared to those without respiratory failure. Twenty-four patients underwent early FOB to establish tissue diagnosis: 8 patients had IRLI, 5 patients had rejection, and 2 patients had pneumonia. Eight other TBB findings were unremarkable, and one TBB finding was insufficient. For the rest of the patients, diagnosis of IRLI and infection was based on microbiologic and radiographic results. Early mortality was 19%, and total hospital mortality was 26%. Precipitating causes leading to respiratory failure and death are listed in Table 5. Nineteen patients required tracheostomies for prolonged ventilatory support. Among the 24 survivors in the group with respiratory failure, 15 patients had COPD, 2 patients had bronchiectasis, 2 patients had interstitial fibrosis, and 5 patients underwent transplantation for severe PH. We found no relationship between duration of mechanical ventilation or hospital stay with type of transplantation or with diagnosis of survivors ($p \geq 0.3$). In the stepwise logistic regression model, IRLI and preexisting RV dysfunction were independently associated with respiratory failure: odds ratio (OR), 13.4 (95% confidence interval [CI], 1.8 to 101.5) vs OR, 21.9 (95% CI, 1.6 to 309.0), respectively. Thus the probability to acquire respiratory failure (P) is greatly increased in the presence of preoperative moderate-to-severe RV dysfunction and occurrence of IRLI after the surgery: $P = e^{-}2.251 + 3.088$ (RV dysfunction) + 2.593 (IRLI)/$1 + e^{-}2.251 + 3.088$ (RV dysfunction) + 2.593 (IRLI), with RV dysfunction and IRLI substituted by 0 or 1 based on their presence or absence.

Table 2—*Univariate Logistic Regression*

Variables	OR	p Value (95% CI)
Baseline demographics		
Age	0.96	0.08
Presence of RV dysfunction	4.75	0.005 (1.7–15.0)
Presence of PH	1.63	0.04 (1.02–2.66)
Indication for surgery		
PH vs COPD	4.17	0.16
COPD vs interstitial diseases	1.02	0.98
PH vs interstitial diseases	4.17	0.24
Impact of surgery		
Surgical procedure		
BLT vs SLT	13.0	< 0.001 (3.42–59.22)
HLT vs SLT	3.90	0.47
BLT vs HLT	3.33	0.14
Duration of surgery	1.01	0.01 (1.00–1.01)
Need for CPB	8.80	0.001 (3.06–29.81)
Ischemia time	1.01	0.04 (1.00–1.01)
Presence of reperfusion lung injury	10.33	< 0.001 (3.83–30.50)
Need for pressors*	19.33	< 0.001 (6.56–65.88)
Need for blood products†	10.67	< 0.001 (3.81–34.01)

*Defined as the need for vasoactive pressor except for dopamine or dobutamine at ≤ 5 μg/kg/min for > 24 h after surgery.

†Defined as the need for > 2 U of packed RBCs or ≥ 6 packs of platelets during and up to 24 h after surgery.

Subgroups of Respiratory Failure

Twenty-eight patients in the group with respiratory failure remained intubated for > 48 h postoperatively, 13 of whom survived and were extubated later successfully. The remaining 16 patients were extubated 4.1 ± 2.5 days (median, 3 days) after their surgery but had to be reintubated shortly after their extubation (length of extubation, 2.3 ± 2.2 days; median, 1 day). Total mortality was not different between the two subgroups of respiratory failure ($p = 0.26$); however, there was a trend for a shorter duration of ventilation in survivors who remained intubated for > 48 h (14 ± 18 days [median 5 days] vs 29 ± 28 days [median 22 days]; $p = 0.08$). Further comparisons between the two sub-

Table 3—*Intraoperative and Perioperative Data

Variables	No Respiratory Failure			Respiratory Failure			p Value
	SLT	BLT	HLT	SLT	BLT	HLT	
Diagnosis, No.							0.04
Obstructive lung disease†	24	3	1	8	14	2	
Primary PH	0	0	0	0	4	1	
Interstitial lung disease	3	2	1	4	4	0	
Congenital heart disease	0	0	2	0	0	3	
Connective tissue disease	0	0	0	1	3	0	
Total‡	27	5	4	13	25	6	
CPB	0	0	4	2	17	6	< 0.001
Duration of surgery, min		257 ± 121			356 ± 146		0.002
CPB time, min		203 ± 99			273 ± 80		0.12
Operative fluid balance, L		2.67 ± 1.53			2.65 ± 2.16		0.9
Fluid balance 48 h after surgery, L		− 1.43 ± 1.53			0.44 ± 3.87		0.009
Need for pressors§		7 (19)			37 (84)		< 0.001
Need for blood products‖		5 (14)			31 (70)		< 0.001
Pao_2/Fio_2¶		398 ± 106			274 ± 149		< 0.001
Antithymocyte globulin		0			2		0.5
Ischemia time, min		242 ± 107			290 ± 102		0.02
Donor							
Age, yr		29 ± 13			31 ± 14		0.5
Male gender, No.		24			28		0.9

*Data are presented as mean ± SD or No. (%) unless otherwise indicated.
†Obstructive lung disease including COPD bronchiectasis. In these patients requiring BLT, there was no secondary PH in the group without respiratory failure vs 5 of 14 patients in the group with respiratory failure.
‡$p < 0.001$ comparing need for different surgery and respiratory failure.
§Defined as the need for vasoactive pressor except for dopamine or dobutamine at ≤ 5 μg/kg/min for > 24 h after surgery.
‖Defined as the need for > 2 U of packed RBCs or ≥ 6 packs of platelets during and up to 24 h after surgery.
¶Best ratio obtained within the first 24 h after surgery.

groups of respiratory failure revealed more IRLI in those who remained intubated for > 48 h (86% vs 56%, $p = 0.02$), but otherwise no difference in almost all other variables (demographic, clinical, and operative profiles). Patients with unsuccessful first extubation required less perioperative fluid and blood products ($p < 0.05$), and had higher postoperative Pao_2/Fio_2 compared to the other subgroup (338 ± 131 vs 237 ± 147, $p = 0.03$), which justifies their first extubation attempt.

Table 4—*Perioperative Complications

Complications	No Respiratory Failure (n = 36)	Respiratory Failure (n = 44)	p Value
Intraoperative complications	0	3 (7)	0.25
Infection	5 (14)	18 (41)	0.02
Shock	1 (3)	16 (36)	0.001
Rejection	2 (6)	5 (11)	0.45
Reperfusion lung injury	7 (19)	32 (73)	< 0.001
Anatomic complications†	0	4 (9)	0.25
Pneumothorax	6 (17)	6 (14)	0.95
Diaphragmatic dysfunction	0	4 (9)	0.12
Hemorrhage‡	4 (11)	12 (27)	0.13
Arrhythmia§	9 (25)	17 (39)	0.29
Cardiac and cerebrovascular ischemia	0	3 (7)	0.25
Deep venous thrombosis	1 (3)	4 (9)	0.37
Hospital length of stay, d	18 ± 7	34 ± 27	0.01
Hospital mortality	1 (3)	20 (45)	< 0.001

*Data are presented as No. (%) or mean ± SD unless otherwise indicated.
†Included pulmonary artery stricture, lung herniation, and bronchial stenosis.
‡Included surgical and nonsurgical bleeding (posttransbronchial biopsy, gastric, vaginal, and central line related).
§Included atrial and ventricular tachyarrhythmias.

Table 5—*Attributable Causes of Respiratory Failure and Mortality

Variables	Cause of Respiratory Failure (n = 44)	Cause of Death (n = 21)
Hypoxemic respiratory failure		
IRLI	24 (55)	4 (19)
Rejection	2 (5)	1 (5)
Infection	4 (9)	10 (47)
Hypercapnic respiratory failure†	7 (16)	
Hemodynamic instability	16 (36)	6 (29)
Cardiovascular/hemorrhagic	3	
Septic	4	
Graft failure‡	9	
Airway/anatomic complications	5 (11)	

*Data are presented as No. (%) or No. Some of the deaths following hemodynamic instability attributed to sespis and graft failure were counted as part of hypoxemic respiratory failure.
†Included diaphragmatic dysfunction and bronchospasm.
‡Due to severe IRLI or rejection.

Discussion

During the perioperative stage of LT, IRLI and infections (followed by technical complications), are the most common causes of respiratory failure and death.[1–4] We found that respiratory failure immediately after LT is associated with an increased risk of early mortality. In this study, 55% of patients undergoing LT acquired respiratory failure during their postoperative course, almost half of whom died. Preoperative static pulmonary function studies, gas exchange values, and exercise test performance failed to identify patients at risk for respiratory failure. However, the presence of preoperative PH, RV dysfunction, and other factors that pertain to the transplantation surgical procedure (*ie*, longer ischemic time, and need for CPB and BLT) were associated with postoperative respiratory failure.

Ventilator dependency after LT often heralds a protracted hospital course and is related to various factors involving not only the recipient and donor but also the operative team. While there is ample data on IRLI, and its possible predictors, the risk and impact of postoperative respiratory failure in general have not been reported. One may conservatively estimate the frequency of respiratory failure in lung recipients to range from 20 to 37%,[1,2,12] which is the sum of the three most common causes of early mortality after LT: significant IRLI, technical failures, and infections. In this study, the overall frequency of respiratory failure and mortality are presumably higher compared to other studies.[3,4,5,12] This difference may be explained by our stricter definition of respiratory failure, patient selection, and medical/operative team experience. Although it is difficult to compare disease severity across studies, we suspect that patient selection may have played the major role in increased mortality. First, our patient population is the oldest reported in the literature.[3–7,9,10,12] Second, we may have the highest number of patients with PH.[3,5,9,12] Third, we have included all patients regardless of complication and considered early and total hospital mortality (eight patients died after 28 days of hospitalization, one of whom died after 90 days). Other investigators limited their analysis to IRLI[6] and/or excluded surgical complications.[7,12] When Bando and colleagues[11] studied a similar patient population as ours (*ie*, with high occurrence of PH) and reported the total hospital mortality, their finding was equivalent to ours (73% of the recipients were discharged from the hospital). As far as perioperative experience influencing outcome and frequency of respiratory failure, analysis of the first 3 years into the LT program revealed no difference compared to the last 2 years. Hence, it is unlikely that experience in our program had a major impact on perioperative events during the study period.

Donor factors have been suggested to have an impact on postoperative graft function. Donor age,[1,18] cause of death,[18,19] and airway microbiologic cultures,[20] as well as ischemic time,[6] have been reported to contribute to graft dysfunction and postoperative complications. We cannot affirm that the difference in postoperative complications between the two groups, including IRLI, was in part due to an interaction between donor characteristics and prolonged ischemic time. Our study is limited because of its small group sizes and incomplete donor data, but we did not find donor age a risk factor for respiratory failure. We also doubt that donor respiratory tract infections had a major impact on the development of postoperative respiratory failure in recipients, because the majority of these patients were ventilator dependent immediately after surgery, at a time inadequate to develop significant infections.

Our analysis included all important recipient factors that have been reported to possibly compromise short-term outcome. Lau and colleagues[21] reported that patients with humoral sensitization (PRA $> 10\%$) have higher complication rates compared to nonsensitized recipients. Our number of patients was too small to confirm the finding of Lau and colleagues[21]; there were only two sensitized patients in our study. Regarding pulmonary functions and exercise tolerance, it was surprising to find that higher FEV_1, diffusing capacity of the lung for carbon monoxide, and 6MWD were associated with

development of respiratory failure (Table 1). This finding may be related to missing more data points in the group with respiratory failure, lumping the different categories of patients, and/or performing too many comparisons. Overall, it seems that exercise and static pulmonary function studies were of limited value probably because they were overshadowed by the more important operative events. The fact that patients with respiratory failure required more pressors and blood products reflects more perioperative complications and poor tolerance to implantation, thus defining the postoperative course. Our data tend to indicate that what paves the harsh perioperative course is the patient's pulmonary hemodynamics, *ie*, presence of significant RV dysfunction, and development of IRLI as demonstrated by the stepwise logistic regression model.

However, the univariate analysis revealed that the highest risks of acquiring respiratory failure were related to having RV dysfunction, receiving CPB or BLT, and developing from IRLI (Tables 2, 3). PH was not among the more prominent factors associated with respiratory failure, rather the occurrence of allograft dysfunction—from IRLI, rejection, or infection—in the setting of PH resulted invariably in respiratory failure. We observed a 92% positive predictive value for respiratory failure in patients with PH who had IRLI; only two patients who had PH and IRLI did not acquire respiratory failure, one patient underwent HLT and the other patient was an SLT recipient with emphysema who had a mean pulmonary arterial pressure of only 26 mm Hg. This interaction between the pretransplant diagnosis of PH and allograft dysfunction is attributed to the inability to redirect blood flow to the remaining hypertensive native lung in the presence of allograft injury.[17,22] In contrast, CPB had a stronger and more consistent relationship with prolonged ventilatory support and worse postoperative hemodynamics compared to preexisting PH (Tables 2, 3). This association is probably more than an epiphenomenon and arises from a potential cumulative, and possibly synergistic, injurious effect caused by CPB[12,23] and reperfusion ischemia.[24,25] Supporting this hypothesis is the fact that patients with PH undergoing LT off CPB do not always acquire lung injury,[5] and patients requiring CPB have a higher degree of allograft dysfunction compared to those who do not, regardless of the surgery.[4,9,12] Certain centers have adopted BLT for their patients with PH[5]; however, besides the resource allocation implications of this policy, and at least based on our results, BLT when performed on CPB because of significant RV dysfunction is associated with higher morbidity and mortality vs SLT.

Despite the recognition of detrimental homeostatic and inflammatory effects of CPB,[26,27] previous investigators have not performed risk factor analysis to quantitate the relationship between CPB and respiratory failure or IRLI.[5,9,11,12] It is difficult to dissect the interaction between PH, need for CPB, and type of surgery, because none has been found to be independent of the other in this study. Analyzing available data in patients with PH and those who went on CPB, the estimated risk for having IRLI has varied considerably across studies (Fig 1). The discrepancy found between studies stems from a myriad of uncontrollable variables, such as surgical technique, patient selection, ventilator management, immunosuppression protocol, cytomegalovirus prophylaxis, and use of CPB, all of which can conceivably influence outcome. Our study showed that the

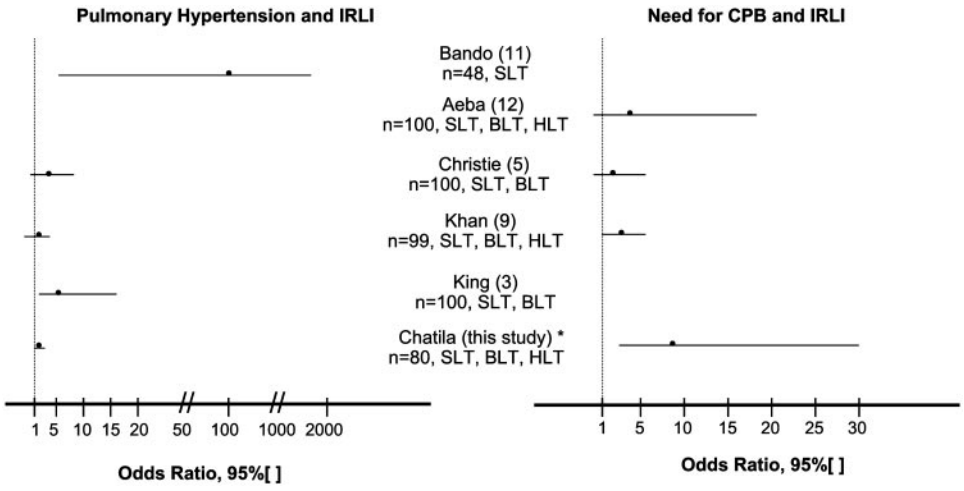

FIGURE 1. ORs determined from studies associating PH and the need for CPB with IRLI. *Our analysis included all patients with respiratory failure, not just patients with IRLI.

higher risk was related to CPB, and not PH, but our approach was different compared to others; we examined respiratory failure and not only IRLI. Bando and colleagues[11] reported the highest incidence (63%) of hemodynamic instability and pulmonary edema in patients with PH undergoing SLT, the majority of whom received CPB. King and colleagues[3] also reported an association between IRLI and preexisting pulmonary hypertension (43% vs 11% of patients with COPD alone), but they failed to indicate CPB usage and their patients underwent both SLT and BLT. The same was not observed in more recent studies.[5,9] Khan and colleagues[9] and Christie and colleagues[5] found no association between postoperative graft dysfunction and the diagnosis of PH. However, Khan and colleagues[9] did not report on the type of surgery performed (SLT vs BLT), and Christie and colleagues[5] did not specify the number of BLT recipients who had CPB or RV dysfunction. Similar to mortality analysis, we believe that the most likely explanation for the great discrepancy between studies is patient selection. If the prevalence of PH and CPB is highest in the study by Bando and colleagues,[11] one might expect a higher occurrence of IRLI in this setting (at least based on our analysis).

A number of possible limitations to this study should be considered. First, we may have followed a strict definition of respiratory failure for this patient population. Second, we did not include Pa_{O_2}/F_{IO_2} or histologic diagnosis of IRLI in all our patients; thus, we may have overestimated the occurrence of ILRI. The threshold of 48 h for respiratory failure was chosen in order to identify all patients at risk and characterize their postoperative course. Moreover, many patients who do not have a complicated postoperative course are typically extubated on the second postoperative day.[7,17] Regarding Pa_{O_2}/F_{IO_2} being part of the criteria to diagnose ILRI, it was left out because it is influenced dramatically by ventilator setting and it does not identify all patients who acquire IRLI. More than one group of investigators observed two patterns of graft failure: diffuse consolidation immediately after surgery, and progressive infiltrate over 48 to 72 h after transplantation.[5,6] Thus, for the second group of IRLI, the initial Pa_{O_2}/F_{IO_2} may be irrelevant. Confirming this latter point, if we had abided by gas exchange criteria to classify patients as having IRLI, we would have excluded at least four patients who had biopsy-proven alveolar damage, yet their early postoperative Pa_{O_2}/F_{IO_2} was > 200.

In conclusion, postoperative respiratory failure is commonly seen in patients undergoing LT and results from multiple perioperative complications, the most significant of which is IRLI. Although infection is frequently encountered during the postoperative course and is the leading cause of mortality, it is only occasionally the primary cause of respiratory failure. We noted that the occurrence of respiratory failure, mainly after the IRLI and cardiovascular/hemodynamic events, proved to be catastrophic and contributed to a striking early attrition of our recipients. The only independent preoperative factor that predicted poor tolerance to implantation was the presence of moderate-to-severe RV dysfunction, which is due in part to recipient dependence on CPB. Perioperative multidisciplinary efforts should be focused to prevent the development of these complications in order to avoid prolonged ventilatory support. Further research should be directed to explore ways to minimize dependency on CPB and examine the effects of such strategies on the development of respiratory failure.

References

1 Registry of the International Society for Heart and Lung Transplantation. 17th annual report, April 2000. Available at: http://www.ishlt.org. Accessed December 19, 2002

2 Bando K, Paradis IL, Komatsu K, et al. Analysis of time-dependent risks for infection, rejection, and death after pulmonary transplantation. Thorac Cardiovasc Surg 1995; 109:49–59

3 King RC, Binns O, Rodriguez F, et al. Reperfusion injury significantly impacts clinical outcome after pulmonary transplantation. Ann Thorac Surg 2000; 69:1681–1685

4 De Hoyos AL, Patterson GA, Maurer JR, et al. Pulmonary transplantation: early and late results. Thorac Cardiovasc Surg 1992; 103:295–306

5 Christie JD, Bavaria JE, Palevsky HI, et al. Primary graft failure following lung transplantation. Chest 1998; 114:51–60

6 Sleiman C, Mal H, Fournier M, et al. Pulmonary reimplantation response in single-lung transplantation. Eur Respir J 1995; 8:5–9

7 Cooper JD, Alexander-Patterson G, Trulock EP. Results of single and bilateral lung transplantation in 131 consecutive recipients. Thorac Cardiovasc Surg 1994; 107:460–471

8 Davis RD, Trulock EP, Manley J, et al. Differences in early results after single-lung transplantation. Ann Thorac Surg 1994; 58:1327–1335

9 Khan SU, Salloum J, O'Donovan PB, et al. Acute pulmonary edema after lung transplantation: the pulmonary reimplantation response. Chest 1999; 116:187–194

10 Anderson DC, Glazer HS, Semenkovich JW, et al. Lung transplantation edema: chest radiography after lung transplantation: the first 10 days. Radiology 1995; 195:275–281

11 Bando K, Keenan RJ, Paradis IL, et al. Impact of pulmonary hypertension on outcome after single-lung transplantation. Ann Thorac Surg 1994; 58:1336–1342

12 Aeba R, Griffith BP, Kormos RL, et al. Effect of cardiopulmonary bypass on early graft dysfunction in clinical lung transplantation. Ann Thorac Surg 1994; 57:715–722

13 Sheridan PH, Cheriyan A, Doud J, et al. Incidence of phrenic neuropathy after isolated lung transplantation. J Heart Lung Transplant 1995; 14:684–691

14 Trulock EP. Lung transplantation. Am J Respir Crit Care Med 1997; 155:789–818

15 Date H, Triantafillou AN, Trulock EP, et al. Inhaled nitric oxide reduces human lung allograft dysfunction. Thorac Cardiovasc Surg 1996; 111:913–919
16 Glassman LR, Keenan RJ, Fabrizio MC, et al. Extracorporeal membrane oxygenation as an adjunct treatment for primary graft failure in adult lung transplant recipients. Thorac Cardiovasc Surg 1995; 110:723–727
17 Boujoukos AJ, Martich GD, Vega JD, et al. Reperfusion injury in single-lung transplant recipients with pulmonary hypertension and emphysema. J Heart Lung Transplant 1997; 16:439–448
18 Sommers EK, Griggith BP, Hardesty RL, et al. Early lung allograft function in twin recipients from the same donor: risk factor analysis. Ann Thorac Surg 1996; 62:784–790
19 Fisher AJ, Donnelly SC, Hirani N, et al. Elevated levels of interleukin-8 in donor lungs is associated with early graft failure after lung transplantation. Am J Respir Crit Care Med 2001; 163:259–265
20 Zenati M, Dowling RD, Dummer JS, et al. Influence of the donor lung on development of early infections in lung transplant recipients. J Heart Lung Transplant 1990; 9: 502–509
21 Lau CL, Palmer SM, Posther KE, et al. Influence of panel-reactive antibodies on posttransplant outcomes in lung transplant recipients. Ann Thorac Surg 2000; 69:1520–1524
22 Levine SM, Jenkinson SG, Bryan CL, et al. Ventilation perfusion inequalities during graft rejection in patients undergoing single lung transplantation for primary pulmonary hypertension. Chest 1992; 101:401–405
23 Francalancia NA, Aeba R, Yousem AS, et al. Deleterious effects of cardiopulmonary bypass on early graft function after single lung allotransplantation: evaluation of heparin-coated bypass circuit. J Heart Lung Transplant 1994; 13:498–507
24 Unruh HW. Lung preservation and injury. Surg Clin North Am 1995; 5:91–106
25 Serrick C, La Franchesca S, Giaid A, et al. Cytokine interleukin 2, tumor necrosis factor-α, and interferon-γ release after ischemia-reperfusion injury in a novel lung autograft animal model. Am J Respir Crit Care Med 1995; 152:277–282
26 Howard RJ, Crain C, Franzini DA, et al. Effects of cardiopulmonary bypass on pulmonary leukostasis and complement activation. Arch Surg 1988; 123:1496–1501
27 Kirklin JK, Westaby S, Blackstone EH, et al. Complement and damaging effects of cardiopulmonary bypass. Thorac Cardiovasc Surg 1983; 86:845–857