Predictors of independent lung ventilation: An analysis of 170 single-lung transplantations

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Objective: Single-lung transplantation for chronic obstructive pulmonary disease can cause unique postoperative problems that might require independent lung ventilation. We evaluated preoperative and immediate postoperative factors to predict the need for independent lung ventilation.

Methods: We retrospectively studied 170 patients who received a single-lung transplant over a 15-year period, 20 (12%) of whom required independent lung ventilation.

Results: Patients requiring independent lung ventilation were similar in age, sex, ischemic time, and donor characteristics to those who required conventional ventilation. Patients receiving independent lung ventilation had a greater degree of preoperative airflow limitation, more hyperinflation, lower postoperative Pao_2 /fraction of inspired oxygen ratios, more radiologic mediastinal shift, and more transplant lung infiltrate on the postoperative chest radiograph. Multivariate logistic regression analysis showed that independent lung ventilation was associated with increasing levels of recipient hyperinflation (percentage total lung capacity compared with predicted value; odds ratio, 1.04; 95% confidence interval, 1.01-1.07; $P = .032$) and reduced early postoperative Pao_2 /fraction of inspired oxygen ratio (odds ratio, 0.97; 95% confidence interval, 0.95-0.99; $P = .005$). Length of ventilation and intensive care unit stay and mortality were higher in the independent lung ventilation group. Among patients who survived to hospital discharge, there were no differences in long-term mortality between the 2 groups.

Conclusions: The need for independent lung ventilation in patients undergoing single-lung transplantation for obstructive lung disease is predicted by the combination of increased hyperinflation measured on recipients' preoperative lung function tests and a low Pao_2 /fraction of inspired oxygen ratio, indicating graft dysfunction in the immediate postoperative period.

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Until 2 successful cases of single-lung transplantation (SLT) for end-stage emphysema were reported by Mal and colleagues¹ in 1989, SLT was considered to be contraindicated in patients with chronic obstructive pulmonary disease (COPD). Initial concerns were that hyperexpansion of the native lung would compress the graft and that the higher vascular resistance of the native lung would divert excessive blood flow to the transplant lung, with the combination leading to unaccept-

Abbreviations and Acronyms

COPD	= chronic obstructive pulmonary disease
FEV ₁	= forced expiratory volume in 1 second
ICU	= intensive care unit
ILV	= independent lung ventilation
PEEP	= positive end-expiratory pressure
SLT	= single-lung transplantation
TLC	= total lung capacity

able ventilation-perfusion mismatch. Experimental studies and two successful SLTs for emphysema did much to alleviate these concerns and supported the feasibility of the procedure.² These authors showed that significant ventilation-perfusion mismatch and arterial hypoxemia did not occur unless rejection, infection, or reperfusion injury developed in the transplant lung. Since then, end-stage emphysema has become the most common indication for SLT. In recent years, however, there has been an increasing tendency to perform double-lung transplantations for these patients because of a long-term survival advantage.³

After transplantation, the new allograft is predisposed to early injury from a variety of sources. These include primary graft dysfunction, injury caused by lung handling, fluid loading in a lung with increased permeability and absent lymphatic drainage, early infection, and, in occasional patients, impaired venous drainage. When early lung allograft injury does occur, it can lead to atelectasis, hypoxia, hypercapnia, and reduced compliance in the transplant lung. The latter increases the proportion of ventilation to the native lung, thereby increasing its dynamic hyperinflation, and can lead to increased intrathoracic pressure, circulatory compromise, and increasing mediastinal shift, with further atelectasis and shunt in the transplant lung. Attempts to alleviate hypoxia, hypercapnia, and transplant lung atelectasis by increasing ventilation or positive end-expiratory pressure (PEEP) often increase dynamic hyperinflation in the native lung and worsen atelectasis and gas exchange in the transplant lung.⁴ This remains a serious problem, especially in the early postoperative period. Because the ventilation and PEEP requirements of the transplant lung aggravate dynamic hyperinflation in the native (COPD) lung, independent-lung ventilation (ILV) has been proposed as a successful treatment of early postoperative dynamic hyperinflation and graft failure.^{5,6}

The principal aim of our study was to identify preoperative and early postoperative predictors for the need for ILV in patients who received ILV in clinical management. We hypothesized that a number of factors might combine to determine the requirement for ILV: pre-existing dynamic recipient hyperinflation, postoperative hyperinflation of the native lung, size mismatch between the native and trans-

planted lungs, mediastinal shift caused by hyperinflation of the native lung, and injury to the transplanted lung. Additional aims were to study the early and long-term outcomes (duration of ventilation, length of stay in the intensive care unit [ICU], hospital mortality, and survival after leaving the hospital) of patients requiring ILV compared with those of patients not receiving ILV.

Materials and Methods

A retrospective chart, medical record, and database review of all SLTs performed from October 1990 (when the service began) until October 2005 was conducted. Patients who received an SLT for obstructive lung diseases were identified for analysis. Variables were grouped into those that were available preoperatively and those that could be assessed in the immediate postoperative period.

Preoperative Variables

Recipients' age, sex, height, weight, lung function test results, and chest radiographic measurements were recorded. Donor factors included were age, sex, height, Pao₂ (taken on a fraction of inspired oxygen [FiO₂] of 100% and a 5 cm H₂O PEEP), and estimated total lung capacity (TLC).⁷ Total graft ischemic time for the organ was also recorded.

Postoperative Variables

Estimates of lung size and mediastinal shift were taken by using the first postoperative chest radiograph and compared with the most recent preoperative radiograph. The severity of transplant lung infiltrate was graded from 0 (absence of infiltrate) to 4 (dense alveolar consolidation of the entire lung field).⁸ Gas exchange was assessed by recording the lowest Pao₂/Fio₂ ratio in the first 24 hours or before instituting ILV (whichever came first).

We analyzed variables as predictors for the need for ILV by comparing preoperative and early postoperative findings in the ILV and non-ILV groups during the first 24 postoperative hours. Outcome parameters were compared between the ILV and non-ILV groups. Outcomes assessed were incidence of ILV, duration of mechanical ventilation, duration of stay in the ICU, ICU mortality, hospital mortality, and long-term survival.

General Method for SLT

Split-lung function studies were performed on all patients (nuclear quantitative perfusion scans). The worst functional side was always selected for transplantation. There were insufficient retrospective data to include this in our analysis. General methods for recipient selection, donor selection, pulmonary allograft procurement, surgical technique for SLT, and postoperative management have been described in detail previously.^{4,9-11} However, principles included immunosuppressive and antiviral therapy (described previously),¹² maintenance of low central venous pressure, minimal PEEP, active airway clearance, maximal bronchodilator therapy, and nitric oxide, where appropriate.

Indications for ILV

There was no protocol for the initiation of ILV. Treating clinicians instigated ILV on the basis of one or a combina-

tion of the following: (1) serious hemodynamic compromise attributed to excessive dynamic hyperinflation and (2) serious gas exchange compromise attributed to excessive dynamic hyperinflation.

Transplant lung infiltrate on chest radiography was usually present but was not by itself an indication for ILV. Asymptomatic hyperinflation was not considered an indication for ILV.

Technical Aspects of ILV

Patients who required ILV were intubated with a double-lumen endotracheal tube (Bronchocath; Mallinckrodt, Athlone, Ireland; size range, 35F-41F). The side of the bronchial lumen was positioned bronchoscopically to lie in the main bronchus of the native lung to avoid injury to the bronchial anastomosis. In all patients, asynchronous ILV was used. The native lung was ventilated with low tidal volumes (3-6 mL/kg), a low ventilator rate (3-6 breaths/min), and 0 PEEP or not ventilated at all by using continuous positive airway pressure (5 cm H₂O). The transplanted lung was ventilated with higher ventilator rates (10-26 breaths/min) and variable tidal volumes (3.5-10 mL/kg). PEEP (5-15 cm H₂O) was adjusted to achieve a maximal improvement in gas exchange and compliance.

Statistical Analysis

All data are expressed as means $\pm$ standard deviation. Data were analyzed by using the Student *t* test and Wilcoxon and χ^2 tests as appropriate. A stepwise multivariate logistic regression model was used to correct for the effect of multiple variables and their interactions on requiring ILV in the early postoperative period. Variables that were associated with the requirement for ILV at a *P* value of less than .1 in the univariate analysis were entered into the multivariate model. The initial model was constructed by using preoperative variables. Postoperative variables were selected afterward and then incorporated into the final model. Software used was SAS version 9.1.3 (Enterprise Guide) for Windows (SAS Institute, Inc, Cary, NC).

Results

Of 211 SLTs performed between October 1990 (when the service began) and October 2005, 170 patients received an SLT for obstructive lung diseases (133 for emphysema caused by smoking, 23 for emphysema caused by α_1 -antitrypsin deficiency, 8 for obliterative bronchiolitis, 4 for lymphangioliomyomatosis, 1 for agammaglobulinemia, and 1 for asthma). These 170 patients formed the basis of our analysis. ILV was used in 12% (20/170) of SLTs for obstructive lung disease. One of these 20 patients had obliterative bronchiolitis; the remainder had emphysema caused by smoking. Other than one case, in which the patient was returned to the ICU from the operating theater with a double-lumen endotracheal tube in situ, ILV was instigated by the treating intensivist. ILV was initiated within the first 24 hours in 19 patients. One patient had a pneumothorax in the native lung on the fourth postoperative day, and this patient's condition subsequently deteriorated, requiring ILV. There was one instance of ILV use in a patient with

TABLE 1. Comparison of baseline preoperative demographic data for the ILV and conventional ventilation groups

	ILV (n = 20)	Conventional ventilation (n = 150)	<i>P</i> value
Recipient variables			
Left lung transplants	14/20 (70%)	68/150 (45%)	.037
Age (y)	54.9 $\pm$ 4.9	53.9 $\pm$ 7.5	.447
Sex (female/male)	12/20 (60%)	81/150 (54%)	.613
Height (cm)	162 $\pm$ 11	164 $\pm$ 9	.484
Weight (kg)	51.4 $\pm$ 13.1	60.9 $\pm$ 12.6	.216
Lung volume reduction surgery before transplantation	1/20 (5%)	4/150 (2.7%)	.469
Donor variables			
Donor age (y)	35.2 $\pm$ 13.5	34.6 $\pm$ 13.3	.848
Donor Pao ₂ (mm Hg)	480 $\pm$ 107	468 $\pm$ 77	.538
Donor height (cm)	175 $\pm$ 10	174 $\pm$ 8	.500
Ischemic time (min)	352 $\pm$ 149	338 $\pm$ 127	.639

All values are presented as means $\pm$ standard deviation. ILV, Independent lung ventilation.

restrictive lung disease caused by pulmonary fibrosis (before institution of extracorporeal membrane oxygenation), and this patient was not included in this study.

Demographic data for all patients receiving an SLT for COPD are shown in Table 1. The mean age for the whole cohort was typical for this patient group, and there was a female preponderance.

Table 2 shows the lung function and chest radiographic assessments available in the preoperative period. All recipients had severe airflow limitation. Those who subsequently required ILV had lower forced expiratory volume in 1 second (FEV₁) to forced vital capacity ratios expressed as a percentage of predicted value. Patients undergoing ILV had greater degrees of functional hyperinflation, higher TLC expressed as a percentage of predicted value and functional residual capacity expressed as a percentage of predicted value, than those who required only conventional ventilation postoperatively. Of those patients who had TLCs greater than 150% of predicted value, 26.5% (9/34) required ILV compared with only 6.6% (8/121) of those with TLCs less than this value (*P* = .003). Indeed, of the 9 patients who had TLCs greater than 175% of predicted value, 4 (ie, 44%) required ILV. There were no significant differences between the radiologic assessments of lung size (in donors and recipients) between both groups.

Table 3 shows data from the immediate postoperative period. The patients who needed ILV had greater degrees of pulmonary infiltrate (*P* < .001), worse gas exchange (*P* < .001), and more mediastinal shift (*P* = .018). A Pao₂/Fio₂ ratio of less than 100 was observed in 61.1% (11/18) of

TABLE 2. Comparison of preoperative lung function and radiologic variables

	Independent lung ventilation (n = 20)	Conventional ventilation (n = 150)	P value
Preoperative lung function			
FEV ₁ /FVC	27% ± 7%	30% ± 13%	.094
FEV ₁ /FVC % predicted	33% ± 9%	40% ± 18%	.021
FEV ₁ % predicted	23% ± 6%	24% ± 10%	.261
FRC % predicted	241% ± 79%	189% ± 66%	.006
TLC % predicted	149% ± 33%	128% ± 31%	.027
Ratio of recipient measured TLC to donor estimated TLC	1.42 ± 0.33	1.48 ± 0.24	.609
Preoperative radiographic assessment			
Size mismatch between donor and recipient lungs			
Percentage by which recipient's lung to remain in situ > donor lung	20.9% ± 10.5%	13.6% ± 15.3%	.224
Percentage by which recipient's lung to be explanted > donor lung	20.6% ± 10.5%	13.3% ± 15.4%	.222

Equations for estimating normal lung function value were taken from the study by Quanjer and coworkers.⁷ FEV₁, Forced expiratory volume in 1 second; FVC, forced vital capacity; FRC, functional residual capacity; TLC, total lung capacity.

patients in the ILV group as opposed to only 11% (15/136) patients requiring conventional ventilation. Although the mean amount of radiologic mediastinal shift was different between the 2 groups, the presence of significant mediastinal shift (>2.5 cm) was a relatively poor discriminator (45% of patients in the ILV group as opposed to 32% in the conventional ventilation group). Two patients in the ILV group had only 1 cm or less mediastinal shift on radiography. Both of these patients had significant cardiovascular compromise, with low cardiac output and hypotension. Their Pao₂/Fio₂ ratios were 97 and 170, respectively. Five patients in the conventional ventilation group had mediastinal shift greater than or equal to 4 cm.

ILV was required more commonly after left lung transplantation (left: 17% [14/82] vs right: 7% [6/88], $P = .037$). There were nonsignificant trends toward more mediastinal shift (1.8 ± 1.4 cm vs 1.5 ± 1.2 cm, respectively; $P = .158$) and higher hospital mortality (left: 10/72 vs right: 5/83, $P =$

.178) in left compared with right lung transplants. However, duration of ventilation (left: 8.0 hours [interquartile range, 2.5-23.5 hours] vs right: 7.0 hours [interquartile range, 2.3-18.8 hours], $P = .671$) was similar.

The multivariate analysis (Table 4) demonstrated that the only 2 factors that were significantly associated with the requirement for ILV were TLC percent predicted ($P = .032$) and the postoperative Pao₂/Fio₂ ratio ($P = .005$). There was a nonsignificant trend toward a relationship with the degree of the pulmonary infiltrate ($P = .06$).

Outcomes of the patients are shown in Table 5. Not surprisingly, the patients who needed ILV required more prolonged duration of ventilation ($P < .001$) and had longer stays in the ICU ($P = .005$). During the first half of the study period (1990-1998), 6 of 11 patients died compared with 2 deaths from 9 patients during the later years. Although not statistically significant ($P = .19$), this was suggestive of a learning-curve effect. Indeed, of the first 4

TABLE 3. Comparison of postoperative variables

	Independent lung ventilation (n = 20)	Conventional ventilation (n = 150)	P value
Postoperative gas exchange			
Pao ₂ /Fio ₂ ratio (mm Hg)	99 ± 42	221 ± 120	<.001
Postoperative radiographic assessment			
Lung infiltrate score	2.8 ± 1.2	1.2 ± 0.9	<.001
Mediastinal shift (cm)*	+2.4 ± 1.4	+1.5 ± 1.2	.018
Percentage by which transplanted lung in recipient was bigger than when in donor	10.8% ± 7.6%	6.9% ± 19.2%	.690
Percentage by which recipient's native lung was bigger than transplanted lung	7.4% ± 6.6%	4.7% ± 9.5%	.442

Fio₂, Fraction of inspired oxygen. *+ value = shift toward transplanted lung.

TABLE 4. Multivariate logistic regression analysis for variables associated with a requirement for ILV

	Odds ratio	95% Confidence interval	P value
Preoperative assessment			
TLC % predicted	1.04	1.01-1.07	.032
Postoperative assessment			
Pao ₂ /Fio ₂ ratio	0.97	0.95-0.99	.005
Lung infiltrate score	2	1-4	.060

ILV, Independent lung ventilation; TLC, total lung capacity; Fio₂, fraction of inspired oxygen.

patients in whom ILV was attempted, 3 died. The higher mortality at 1 year in the ILV group ($P < .001$) is accounted for by the early deaths. Among those who died after hospital discharge, the incidence of bronchiolitis obliterans syndrome did not differ between the 2 groups (4/7 vs 39/96, $P = .447$). The Kaplan–Meier curve for the patients who survived to hospital discharge is shown in Figure 1. There was no significant difference in long-term outcomes of survivors ($P = .352$).

Discussion

Our study has shown that increasing hyperinflation (TLC percent predicted) in the recipient and subsequent graft dysfunction (Pao₂/Fio₂ ratio) in the early postoperative period combine and lead to the requirement for ILV.

The reported frequency of use of ILV in SLT series for obstructive airways disease also varies widely, from 0%¹³⁻¹⁷ to 43%,¹⁸ with an overall frequency of ILV use of 9%.^{6,13-21} This compares with 12% in our study. In part, this variability between series relates to the threshold for using ILV and to the availability and frequency of use of techniques such as extracorporeal membrane oxygenation.

A number of other studies have investigated risk factors for ILV, such as severity of airflow obstruction in the native lung, the size of the transplanted lung, and the side of the transplantation. Severity of airflow obstruction will directly

TABLE 5. Outcomes: Comparison of ILV with conventional ventilation group

	ILV (n = 20)	Conventional ventilation (n = 150)	P value
MV duration (h)*	148 (81-162)	7 (0.5-20)	<.001
ICU duration (d)*	6.0 (3.5-7.0)	1.0 (0.25-1.0)	.005
ICU mortality†	6/20 (30%)	2/150 (1.3%)	<.001
Hospital mortality	8/20 (40%)	7/150 (4.7%)	<.001
1-y mortality	10/20 (50%)	19/148 (12.8%)	<.001

ILV, Independent lung ventilation; MV, mechanical ventilation; ICU, intensive care unit. *Median (interquartile range). †Initial admission to intensive care unit only.

affect the degree of dynamic hyperinflation.²² Yonan and colleagues⁶ found that patients who had native lung hyperinflation had higher pulmonary artery pressures, higher pulmonary artery to wedge pressure gradients, higher residual volumes, and lower FEV₁ values than patients who did not have symptomatic postoperative hyperinflation. Pulmonary hypertension and a high transpulmonary gradient were not studied in our patients. Although we found the degree of preoperative airflow limitation (FEV₁/forced vital capacity percent predicted) was worse in the ILV group, this was not a significant factor after multivariate adjustment. Because our population size is relatively small, it was unlikely that we would detect many significant factors in multivariate analysis.

The size of the donor lung and its relationship to estimated recipient lung volume has been identified by several authors^{5,17,21} as an important factor. We could not demonstrate any such relationship using radiologic, measured, or estimated measures of lung function.

Several reports have suggested a higher incidence of native lung hyperinflation with left SLTs. Weill and associates²⁰ found radiographic hyperinflation in 37% of left SLTs and 25% of right SLTs, with no difference in the incidence of symptomatic hyperinflation. Angles and colleagues¹⁸ did not report radiographic hyperinflation but found symptomatic hyperinflation in 83% of left SLTs and 50% of right SLTs. In our study there was no significant difference in postoperative native lung hyperinflation (as evidenced by mediastinal shift) between left and right SLTs (1.8 ± 1.4 cm vs 1.5 ± 1.2 cm, respectively; $P = .158$), but ILV was required more than twice as often with left SLTs. However, we have previously reported²³ higher long-term

Figure 1. Kaplan–Meier survival curve for hospital survivors after independent lung ventilation and after conventional ventilation. Wilcoxon test for difference between survival curves, $P = .352$. +, Censored values.

mortality (primarily because of airway complications) with left lung transplants compared with that seen with right lung transplants.

A reduced Pao_2/Fio_2 ratio (odds ratio, 0.97; 95% confidence interval, 0.95-0.99, $P = .005$) in the immediate postoperative period was associated with the requirement for ILV. This is not surprising because impaired gas exchange is likely to have been an important factor in determining the intensivist's decision to initiate ILV. A reduced Pao_2/Fio_2 ratio is the basis of the definition for primary graft dysfunction²⁴ and is associated with worse early outcomes after lung transplantation.^{25,26} It is possible that attempts to improve graft function by providing greater minute ventilation, PEEP, or a longer inspiratory time might worsen dynamic hyperinflation in the native lung, resulting in hemodynamic deterioration. Fluid administration as a treatment for hypotension and low cardiac output might further jeopardize graft function by increasing edema in the transplanted lung.

Other reported treatment options for severe dynamic hyperinflation in association with early graft failure include the use of a bronchial blocker,²¹ contralateral lobectomy or pneumonectomy,^{27,28} lung volume reduction surgery of the native lung,²⁹ retransplantation,²¹ and extracorporeal membrane oxygenation³⁰ (as was required by one of our patients). It is noteworthy that the reported cases of lung volume reduction surgery and contralateral lobectomy or pneumonectomy have not been performed in the setting of early graft injury as an immediate postoperative complication.

The patients who required ILV had an initial hospital mortality of 40%, although it is likely that the mortality within this group would have been much higher without this intervention. Two case series in which data on all patients undergoing SLT and ILV survival were recorded^{6,19} have reported mortality rates of 25% and 46%, respectively, which is significantly worse than for patients with SLT who required only conventional ventilation. However, the study by Weill and associates,²⁰ which described a mortality of 0%, had only 2 patients who required ILV. However, it is important to note that among those who survive to leave the hospital, satisfactory long-term outcomes can be achieved, as shown in Figure 1. We know of no other reports on the long-term survival of patients who have required ILV.

Potential limitations of our study are that it is a single-center, retrospective, nonrandomized analysis of relatively small numbers of patients. Generalizing our findings to other centers should be done with caution. However, this is the largest case series of which we are aware. It is possible that patient selection for ILV could have been biased by a desire to optimize results. At our center, there has been a trend away from SLT for COPD in recent years (15 SLTs between 2003 and 2005 compared with 45 in the preceding

3 years). This has been driven by a perceived late survival advantage,³ with bilateral transplantation rather than conscious selection of patients at risk of needing ILV because of significant preoperative hyperinflation. We could not include cardiovascular parameters in our study, mainly because there were insufficient data for most patients. The presence of hypotension caused by native lung hyperinflation (with or without a low Pao_2/Fio_2 ratio) has been considered an absolute indication for initiating ILV at our hospital. Our aim was to investigate other parameters that the clinician might use to assess the risk of requiring ILV. The presence of preoperative hyperinflation with TLC percent predicted of greater than 150% should alert those selecting patients for SLT of a significant risk of requiring ILV in the postoperative period. The additional finding of a reduced Pao_2/Fio_2 ratio (<100) in the immediate postoperative period should prompt early consideration of ILV.

Conclusions

ILV after SLT is associated with increased duration of ventilation, increased duration of stay in the ICU, and increased mortality. The need for ILV in these patients is predicted by the combination of increased hyperinflation (increased TLC percent predicted) measured on recipients' preoperative lung function tests and a low Pao_2/Fio_2 ratio, indicating graft dysfunction in the immediate postoperative period. Long-term outcomes among recipients who require ILV and survive to leave the hospital are comparable with those of the group as a whole.

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