Published in final edited form as:

Ann Thorac Surg. 2011 July ; 92(1): 309–315. doi:10.1016/j.athoracsur.2011.01.077.

Reduction in Airway Complications After Lung Transplantation With Novel Anastomotic Technique

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Abstract

Background—Bronchial anastomotic complications develop in 31% of lung transplant recipients, leading to additional operative procedures and increased morbidity. Advances in surgical technique have thus far resulted in only modestly improved outcomes. We hypothesized that creating the bronchial anastomosis at the secondary carina using a combination of running and figure-of-eight sutures would minimize donor bronchial ischemia and airway complications.

Methods—This retrospective review of a single surgeon's operative experience from 2000 to 2007 compares a new bronchial anastomotic technique with the conventional technique. The primary outcome was the occurrence of bronchial anastomotic complications requiring invasive intervention. The secondary outcome was distal airway complications. Patients were monitored for 1 year after transplant. Recipient and donor demographic data as well as relevant variables from their preoperative, perioperative, and postoperative courses were collected for analysis. These data were compared using *t* tests for normally distributed continuous variables, Mann-Whitney tests for nonnormally distributed continuous variables, and χ^2 tests or Fisher exact test for categorical variables. Logistic regression was used to control for covariates while comparing the primary outcome between the new and conventional bronchial anastomotic techniques.

Results—The analysis included 230 patients, representing 407 anastomoses. The occurrence of anastomotic complications requiring intervention and distal airway complications decreased from 18.1% to 2.3% of anastomoses and 12.2% to 4.4% of patients, respectively. After controlling for available risk factors, the new technique significantly reduced both anastomotic ($p < 0.001$) and distal ($p = 0.03$) airway complications.

Conclusions—This new anastomotic technique dramatically reduces anastomotic and distal airway complications after lung transplantation.

The first lung transplant, performed more than 40 years ago, was complicated by a large necrotic defect found in the donor bronchus at autopsy [1]. Airway complications, including dehiscence, fistula, necrosis, stricture and stenosis, bronchomalacia, granulation tissue formation, and infection have remained a persistent challenge in modern lung transplantation. Assessing the true magnitude of this problem is difficult due to inconsistent criteria used for the identification of complications [2-5]. Although airway complications have been reported in up to 33% of recipients, most centers would agree that these complications occur in 9% to 22% of patients [3, 5-9]. Even more difficult to assess is the incidence of nonanastomotic distal airway complications, which is estimated at 2% to 4%

[10]. Impaired visualization of distal airways by more proximal pathology has likely led to underreporting. Airway complications are important as an early predictor of bronchiolitis obliterans and they carry an associated mortality of 1% to 3% [4, 6-8, 11, 12].

The treatment of airway complications is often complex. Minimally invasive approaches may include mechanical debridement, laser vaporization, cryotherapy, brachytherapy, dilation, or stenting [3, 11, 13-15]. When these interventions fail, patients may require reoperation, including sleeve resection, bilobectomy, or retransplantation [3, 8, 13, 15, 16]. Airway complications after transplantation are rarely treated successfully with one procedure, with most requiring several interventions.

The etiology of airway complications after lung transplantation has been attributed to donor bronchial ischemia [3, 13, 17, 18]. Bronchi normally receive circulation from both the pulmonary arteries and bronchial arteries, which collateralize in the submucosal plexus [18, 19]. The bronchial arteries, which arise from the intercostal arteries or directly from the descending aorta, course through the pulmonary hilum with the bronchi and are therefore necessarily transected at the time of transplantation. Factors that decrease pulmonary blood flow or increase pulmonary vascular resistance worsen donor bronchial ischemia. These factors include poor graft preservation, lung ischemia reperfusion injury, rejection, infection and inflammation, and prolonged positive pressure ventilation [2, 7-9, 11, 20, 21].

We hypothesized that minimizing the length of the donor bronchus by creating the anastomosis more distally, at the level of the secondary carina, would decrease donor bronchial ischemia and therefore airway complications. We also modified the suture technique to include interrupted figure-of eight stitches in the cartilaginous membrane to minimize the risk of buckling, a known risk factor for airway complications [5, 7, 11, 12, 22, 23].

Patients and Methods

Data Collection

Our cohort consisted of all patients undergoing lung transplantation by a single surgeon at a single academic institution from 2000 to 2007. The Institutional Review Board of the University of Washington approved the protocol of this study and waived the requirement for individual consent. The control group consisted of patients who underwent lung transplantation before October 2004 received the conventional anastomotic technique. Those who underwent transplantation after this date received the new anastomotic technique and comprised the experimental group. Patients were excluded from this study if they had a combination heart and lung transplant or were younger than 18 years old.

Data on preoperative and perioperative factors (Tables 1 and 2) were gathered by retrospective record review. Outcome data was collected for a 1-year period after transplant (Tables 3 and 4). All patients had undergone one routine bronchoscopy at 1 month after transplant. Further bronchoscopy was performed as indicated by symptoms or reduction in measured airflow at follow-up visits.

Initial ventilator time was defined as the time in days from the start of the transplant procedure until first extubation. Total ventilator time was defined as the total time in days the patient required ventilation from the time of the transplant procedure until discharge, including periods of reintubation. Wound infection was defined as any infection of the surgical site that required antibiotics or incision and debridement for management. Rejection was defined as acute, nonhumoral, rejection within the first 30 days of transplantation. Pneumonia was defined as bacterial, viral, or fungal pneumonias requiring treatment that

occurred within the first 30 days after transplant. Donor lungs were considered to have an abnormal preoperative bronchoscopy if they had purulent or bloody secretions, evidence of airway erythema or inflammation, or atelectasis.

The primary outcome was the development of a bronchial anastomotic complication requiring intervention. This is defined as an abnormality of the anastomosis, including dehiscence, fistula, necrosis, stricture or stenosis, bronchomalacia, granulation tissue formation, and infection requiring a repeat operation for mechanical debridement, dilation, stent placement or replacement, lobectomy, or pneumonectomy. The secondary outcome was the development of any airways complications distal to the anastomosis, including stenosis, fibrosis, and inflammation.

Anastomotic Technique

The conventional anastomotic technique was performed by trimming the mainstem donor bronchus to within 1 to 2 rings of the secondary carina and then using a single continuous running suture (4-0 Prolene, Ethicon, Somerville, NJ) through both the membranous and cartilaginous bronchi to create an end-to-end anastomosis. For the new technique, the length of the donor bronchus is minimized by resecting the donor mainstem bronchus and creating the anastomosis at the secondary carina. A running suture is placed along the membranous portion of the bronchi, followed by figure-of-eight stitches into the cartilaginous membrane. The figure-of-eight sutures are pulled taut at the same time to avoid distortion and allow the natural lie to develop. Intentional telescoping is not performed, but when there is a size difference, the smaller bronchi is allowed intussuscept into the larger airway.

Perioperative Management

All patients received preoperative cefuroxime for antibiotic prophylaxis, unless contraindicated by allergy or prior colonization. The preservation solution was Perfadex (Medisan, Uppsala, Sweden) in all cases. Patients received a standard protocol for immunosuppression consisting of preoperative cyclosporine and prednisone, followed by 20 mg of basiliximab in the operating room and on postoperative day 4, methylprednisolone, 1 g intravenously in the operating room and 125 mg for 6 doses, and intravenous mycophenolate and cyclosporine. Upon ability to take by mouth, these were transitioned to tacrolimus, prednisone, and mycophenolate mofetil. Viral, *Pneumocystis carinii*, and fungal prophylaxis was administered to all patients.

Data Analysis

Data were compared using *t* tests for normally distributed continuous variables, Mann-Whitney tests for nonnormally distributed continuous variables, and χ^2 tests or Fisher exact test when appropriate for categorical variables. Logistic regression was used to control for covariates while comparing the primary outcome between the new and conventional bronchial anastomotic techniques.

Results

Between 2000 and 2007, 233 patients underwent lung transplantation, of which 139 undergoing the conventional technique and 91 undergoing the new technique ($n = 230$) met the criteria and were analyzed, representing 232 anastomoses with the conventional technique and 175 with the new technique ($N = 407$). Transplants were bilateral in 177 patients and single-lung in the remaining 53. Recipient and donor characteristics were not significantly different between the two groups (Tables 1 and 2). However, patients receiving the new technique were more likely to receive bilateral lung transplants as well as cardiopulmonary bypass.

The new technique resulted in a dramatic decrease in the number anastomotic complications requiring intervention after lung transplant. Specifically, there was a decrease from 21.6% to 4.4% by patient or 18.1% to 2.3% by anastomosis (Table 3). Additionally, we found a corresponding decrease in the incidence of distal airway complications, from 12.2% to 4.4% of patients (Table 4). This was not statistically significant by univariate analysis but was with multivariate analysis. After adjusting for age at transplant, recipient gender, indication for transplantation, use of cardiopulmonary bypass, and transplant type, the new technique significantly reduced anastomotic ($p < 0.001$) and distal ($p = 0.03$) airway complications.

An evaluation of recipient and donor variables to identify risk factors for the development of anastomotic complications found that the conventional technique was the only aspect of the surgical procedure associated with anastomotic complications (Table 3). As expected, anastomotic complications developed in patients who received mechanical ventilation approximately 50% longer than those who did not. Wound infection was twice as common among those with anastomotic complications, and pneumonia within 30 days of transplant was five times more common among those patients who later presented with an anastomotic complication. Also, the forced expiratory volume in 1 (FEV₁) second at 6 months after transplant was decreased by 11.5% of predicted in those patients with an anastomotic complication compared with those without.

We then identified risk factors for the development for distal airway complications (Table 4). Other than the use of the new technique, no other aspects of the surgical procedure were associated with distal airway complications. There was a threefold increase in wound infection and a ninefold increase in pneumonia within 30 days of transplant among those patients who later presented with distal airway complications. None of the donor characteristics were associated with the development of distal airway complications. Not surprisingly, the FEV₁ at 6 months was decreased by 22% of predicted in those patients with distal airway complications compared with those without.

Finally, we looked at the functional respiratory after lung transplantation and found that those patients who received the new technique tended to have a higher, although not statistically significant, FEV₁ as a percent predicted at their first outpatient, 6-month, and 1-year visits (Table 2).

Comment

The new bronchial anastomosis technique presented in this report dramatically decreased anastomotic and distal airway complications and may lead to improved lung function as assessed by FEV₁. Although dissection of the donor bronchus' peribronchial tissues is more difficult as one travels more distally, making this procedure more technically challenging, the learning curve is quickly attainable.

A second concern with this technique is the limitation of salvage options if airway complications do develop. With severe airway complications, a skilled interventional bronchoscopist is essential for dilatation and complex stent placement. If resective management is necessary, a sleeve resection and reimplantation of the bronchus cannot be performed given the prior resection of the donor mainstem bronchus. In this setting, a lobectomy, sleeve lobectomy with reimplantation, or retransplantation may be the only options available for management of the disease. In our patient population, we have yet to encounter this extent of airway disease.

The new technique has several advantages that may account for the improvements noted. First, donor bronchial ischemia is minimized by resecting the donor mainstem bronchus and performing the anastomosis more distally. Second, telescoping is only performed when there

is a size mismatch, and in that circumstance, the smaller bronchus is allowed to intussuscept into the larger bronchus regardless of which is the donor or recipient. When telescoping occurs, the figure-of-eight suture flattens the intussuscepted portion and minimizes buckling.

Weder and colleagues [24] used a similar surgical technique to ours, except for two distinct characteristics. First, on the right, our line of transection is less tangential. We feel that this allows better support to prevent bronchomalacia and leaves more options for nonresective therapy in the event of a severe anastomotic complication. Second, the Zurich group used interrupted sutures circumferentially in the construction of their anastomoses. Our technique uses running suture along the membranous portion of the bronchus, facilitating efficiency in a segment of the bronchus resistant to dehiscence, and figure-of-eight suture in the cartilaginous portion to appose without unnecessary buckling.

Although the results of the Weder series and this series are very similar, that study excluded patients who died during their initial hospitalization, which may have excluded those with early airway complications [24]. Follow-up in that study was limited to 6 months, which may have also excluded late complications. Distal complications were not evaluated.

An additional advantage we expected to see with the new technique was an improvement in our ability to both diagnose and treat distal airway complications. The new technique resulted in a corresponding decline in the incidence of distal airway complications, likely due to the same structural and physiologic principles that led to better protection of the anastomosis. So although we expected the benefit to be one of diagnosis and treatment of distal complications, it was in reality a benefit of prevention.

Not surprisingly, the risk factors we identified for the development of airway complications included length of mechanical ventilation, wound infection, and pneumonia within 30 days of transplant. Parenchymal consolidation decreases pulmonary blood flow and increases pulmonary vascular resistance, worsening donor bronchial ischemia and leading to the development of airway complications. However, length of mechanical ventilation may not represent a true risk factor for airway complications but may instead serve as a marker of underlying lung function. In the setting of lung inflammation, the inflammation itself may lead to bronchial ischemia and not the prolonged mechanical ventilation. Wound infections may also correlate with airway complications due to an inherent problem with wound healing.

Nutritional parameters were not assessed in this study. There was no correlation between pretransplant steroid use and the development of airway complications. Nonetheless, minimizing the length of mechanical ventilation, appropriate timing and dosage of perioperative antibiotics, and techniques aimed at reducing the incidence of pneumonia may reduce the development of subsequent airway complications.

Critical to the validity of any “before and after” study is the assurance of similarity between the experimental and control groups despite the passage of time. Although impossible to eliminate, this bias is minimized by the careful selection and analysis of potentially confounding factors, thereby establishing similarity between the groups. In our analysis, we found two such factors. Patients receiving the new technique were more likely to receive a bilateral lung transplant and cardiopulmonary bypass than were those who underwent the conventional technique.

The limited availability of donor lungs accompanied by the growing list of patients awaiting lung transplantation has encouraged our center to broaden our acceptability criteria. This has resulted in the increased use of marginal lungs and mandating bilateral lung transplant to offer the recipient equivalent outcomes. Therefore, bilateral lung transplants are becoming

more prevalent at our center. Cardiopulmonary bypass is not associated with the development of airway complications, and we believe this increase is due to implementation of the Lung Allocation Score in 2005, which has resulted in sicker patients undergoing lung transplant.

A second inherent source of potential bias in a “before and after” study is the general improvement of a surgeon’s skills over that time, unrelated to the technique itself. Several factors suggest that the results presented in this study are due to a change in the procedure itself, not the cumulative experience of the operating surgeon. Before the earliest patients in this series, the surgeon performing these procedures had already completed more than 300 lung transplantations, diminishing the effect that a change early in the learning curve would be expected to produce. After controlling for type of transplant, such as bilateral vs unilateral, operative times have not changed over this period, indicating no drastic improvements in surgical efficiency. This is likely because the cardiothoracic surgical residents, who rotate on service every 3 months, perform much of the transplantation. Although they construct the bronchial anastomoses, the attending surgeon decides where to place this anastomosis. This ensures consistency of the anastomoses design over time, whereas many other variables of the procedure vary as residents rotate on and off service.

Lastly, this technique has been taught to other groups, including those at Washington University, who presented a similar series at the Southern Thoracic Society meeting. Taken together, these findings suggest that the improvements seen with the new technique are real, transferable, and reproducible rather than an artifact of a single surgeon’s maturation over time.

In conclusion, we demonstrate that our new anastomotic technique results in statistically significant decreases in anastomotic complications requiring intervention as well as in distal airway complications compared with the conventional approach. Further, the new technique results in improved FEV₁ as a percent predicted than in those receiving the conventional technique that approached statistical significance.

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Table 1

Donor Characteristics

Variable ^a	Conventional (n = 139)	New (n = 91)	p Value
Age, median (IQR)	32 (19, 47)	26.5 (19, 43)	0.31
Female gender	36 (43.9)	30 (38.0)	0.45
Cause of death			0.12
Anoxia	2 (2.44)	7 (8.9)	
Closed head injury	25 (30.5)	22 (27.9)	
Gun shot wound	23 (28.1)	16 (20.3)	
Intracranial hemorrhage	29 (35.4)	34 (43.0)	
Other	3 (3.6)	0 (0)	
Abnormal bronchoscopy	51 (64.6)	40 (54.0)	0.19
Smoking history	46 (56.8)	35 (44.9)	0.13
Cytomegalovirus positive	54 (50)	53 (58.3)	0.25
Infiltrate on chest x-ray	40 (50.6)	38 (49.4)	0.87

IQR = interquartile range.

^aData are presented as number (%), unless indicated otherwise.

Table 2
Recipient Characteristics

Variable ^a	Conventional (n = 139)	New (n = 91)	p-Value
Preoperative characteristics			
Age, median (IQR)	56.0 (47.4, 60.7)	56.6 (46.2, 62.2)	0.94
Female gender	49 (35.3)	38 (41.8)	0.28
Indication for transplant			0.16
COPD	71 (51)	33 (36.3)	
Cystic fibrosis	18 (13.0)	15 (16.5)	
Idiopathic pulmonary fibrosis	32 (23.0)	30 (33.0)	
Other	18 (13.0)	13 (14.3)	
Cytomegalovirus positive	79 (59.0)	51 (56.0)	0.66
Perioperative characteristics			
Single-lung transplant	46 (33.1)	7 (7.7)	<0.001
Cardiopulmonary bypass	36 (26.1)	36 (39.6)	0.03
Posttransplant characteristics			
Ventilator time, median (IQR)			
Initial time	1 (1,2)	1 (1,2)	0.77
Total time	1 (1,3)	1 (1,3)	0.58
Wound infection	19 (13.7)	11 (12.1)	0.73
Rejection 30 days	4 (3.3)	0 (0)	0.14
Pneumonia 30 days	5 (5.4)	2 (2.94)	0.70
FEV ₁ % predicted, median (IQR)			
First outpatient visit	55 (46, 67)	58.5 (49, 69)	0.45
At 6 months	64 (50, 82)	70 (57, 85)	0.18
At 1 year	70 (52, 84)	75 (63, 97)	0.15

COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in one second; IQR = interquartile range.

^aData are presented as number (%), unless indicated otherwise.

Table 3
Characteristics of Patients With Anastomotic Airway Complications

Variable ^a	No (n = 196) (n = 139)	Yes (n = 34) (n = 91)	p-Value
Donor characteristics			
Age, median (IQR)	29 (19, 46)	29 (19, 44)	0.61
Female gender	60 (43.8)	6 (25.0)	0.28
Cause of death			0.02
Anoxia	9 (6.6)	0 (0)	
Closed Head Injury	42 (30.7)	5 (20.8)	
Gun Shot Wound	27 (19.7)	12 (50.0)	
Intracranial Hemorrhage	57 (41.6)	6 (25.0)	
Other	2 (1.5)	1 (4.2)	
Abnormal bronchoscopy	78 (60.5)	13 (54.2)	0.56
Smoking history	68 (50.4)	13 (54.2)	0.83
Cytomegalovirus positive	93 (54.1)	14 (51.9)	0.84
Infiltrate on chest x-ray	66 (50.0)	12 (50.0)	1.0
Recipient preoperative characteristics			
Age, median (IQR)	56.5 (46.2, 61.4)	54.1 (49.2, 59.1)	0.85
Female gender	98 (50.0)	9 (26.5)	0.01
Indication for transplantation			0.76
COPD	86 (43.9)	18 (52.9)	
Cystic fibrosis	28 (14.3)	5 (14.7)	
Idiopathic pulmonary fibrosis	54 (27.6)	6 (23.5)	
Other	28 (14.3)	3 (8.8)	
Cytomegalovirus positive	111 (57.8)	19 (57.6)	0.98
Recipient perioperative characteristics			
New technique	87 (44.4)	4 (11.7)	<0.001
Single-lung transplant	49 (25.0)	4 (11.8)	0.12
Cardiopulmonary bypass	66 (33.7)	6 (18.2)	0.10
Posttransplant characteristics			
Ventilator time, median (IQR)			
Initial time	1 (1,2)	1 (1,2)	0.45
Total time	1 (1,3)	1.5 (1,5)	0.03
Wound infection	22 (11.3)	8 (23.5)	0.05
Rejection 30 days	4 (2.2)	0 (0)	1.0
Pneumonia 30 days	4 (2.9)	3 (15.8)	0.04
FEV ₁ % predicted at 6 months, median (IQR)	68 (54.5, 83.5)	56.5 (40, 75)	0.04

COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in one second; IQR = interquartile range.

^aData are presented as number (%), unless indicated otherwise.

Table 4
Characteristics of Patients With Distal Airway Complications

Variable ^a	No (n = 209) (n = 139)	Yes (n = 21) (n = 91)	p-Value
Donor characteristics			
Age, median (IQR) years	29 (19, 46)	30 (20, 42)	0.78
Female gender	59 (41.0)	7 (41.2)	0.83
Cause of death			0.41
Anoxia	9 (6.3)	0 (0)	
Closed head injury	41 (28.5)	5 (35.3)	
Gun shot wound	34 (23.6)	5 (29.4)	
Intracranial hemorrhage	58 (40.3)	5 (29.4)	
Other	2 (1.4)	1 (5.9)	
Abnormal bronchoscopy	81 (59.6)	10 (58.8)	1.0
Smoking history	72 (50.7)	9 (52.9)	0.86
Cytomegalovirus positive	95 (52.5)	12 (66.7)	0.32
Infiltrate on chest x-ray	69 (49.6)	9 (52.9)	1.0
Recipient preoperative characteristics			
Age, median (IQR) years	56.5 (46.2, 61.4)	53.8 (47.8, 58.6)	0.70
Female gender	101 (48.3)	6 (28.6)	0.11
Indication for Transplantation			0.38
COPD	91 (43.5)	13 (61.9)	
Cystic fibrosis	30 (14.4)	3 (14.3)	
Idiopathic pulmonary fibrosis	59 (28.2)	3 (14.3)	
Other	29 (13.9)	2 (9.5)	
Cytomegalovirus positive	120 (58.5)	10 (50.0)	0.46
Recipient perioperative characteristics			
New technique	87 (41.6)	4 (19.0)	0.06
Single-lung transplant	52 (24.9)	1 (4.8)	0.053
Cardiopulmonary bypass	69 (33.2)	3 (14.3)	0.09
Posttransplant characteristics			
Ventilator time, median (IQR)			
Initial time	1 (1,2)	1 (1,2)	0.69
Total time	1 (1,3)	2 (1,8)	0.51
Wound infection	23 (11.0)	7 (33.3)	0.004
Rejection 30 days	4 (2.1)	0 (0)	1.0
Pneumonia 30 days	4 (2.7)	3 (25.0)	0.01
FEV ₁ % predicted at 6 mon, median (IQR)	68.5 (55, 84)	46.5 (34, 69)	0.004

COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in 1 second; IQR = interquartile range.

^aData are presented as number (%), unless indicated otherwise.