Atrial Fibrillation After Pulmonary Transplant*

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Background: Although atrial fibrillation or flutter (AF) is thought to occur commonly after pulmonary transplantation, little is known about the epidemiology, risk factors, or clinical significance of arrhythmia in this population. The aim of the current study was to determine the incidence, clinical predictors, and associated morbidity of AF after lung transplant.

Methods: The records of 200 consecutive adult patients who underwent lung transplantation at a single institution from August 1998 to June 2002 were studied. Multivariate logistic regression analysis was performed to define the predictors for posttransplant AF.

Results: Indications for transplant included COPD in 43%, cystic fibrosis in 18%, and idiopathic pulmonary fibrosis (IPF) in 17%. The transplants were bilateral (79%) or single lung (21%). The mean age of the patients was 50 years (range, 19 to 66 years; median, 54 years). Postoperative AF within 14 days of transplant occurred in 78 patients (39%), with a mean onset of 3.8 ± 3.0 days (SD). Significant predictors of AF were as follows: age > 50 years (odds ratio [OR], 2.1; p = 0.01), IPF (OR, 2.3; p = 0.03), existing coronary disease (OR, 2.0; p = 0.009), enlarged left atrium (LA) on echocardiography (OR, 3.9; p = 0.05), and number of postoperative vasopressors (OR, 1.5; p = 0.03). Patients with AF had longer hospital stays (32.4 ± 60.0 days vs 17.5 ± 24.1 days, p = 0.04), were more likely to undergo tracheostomy (OR, 3.6; p = 0.0003), and had more in-hospital deaths (OR, 5.7; p = 0.0005) than patients without AF.

Conclusions: AF is a frequent complication after lung transplant. Advanced age, IPF, known coronary disease, enlarged LA, and use of postoperative vasopressors increase the risk for developing AF. The development of posttransplant AF is associated with significantly prolonged hospital stay and increased mortality. Prospective studies designed to prevent posttransplant AF are needed to clarify the extent to which AF impacts on posttransplant outcomes.

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Key words: atrial fibrillation; lung transplantation; postoperative complications

Abbreviations: AF = atrial fibrillation or flutter, CABG = coronary artery bypass grafting; CF = cystic fibrosis, CI = confidence interval; IPF = idiopathic pulmonary fibrosis; LA = left atrium; OR = odds ratio

Lung transplant is a viable therapeutic option for patients with progressive end-stage pulmonary diseases. Despite considerable improvements in posttransplant outcomes, lung transplant recipients experience high rates of morbidity and mortality in the early postoperative period, including pulmonary edema, graft failure,1,2 respiratory infections,3 phrenic nerve injury,4 and atrial arrhythmias.

Atrial fibrillation is the most frequent postoperative arrhythmia after cardiac surgery,5 and is common in patients who have undergone pulmonary transplantation. Although atrial fibrillation or flutter (AF) are thought to occur frequently after pulmonary transplant, little is known about the epidemiology, risk factors, and clinical significance of these postoperative dysrhythmias. Previous studies6,7 have been limited to atrial flutter after pediatric lung transplantation, and no previous studies have examined an adult population.

Studies of atrial arrhythmias after coronary artery bypass grafting (CABG) have shown that AF occurs in 17 to 33% of patients.8,9 AF most commonly occurs between 2 days and 3 days postoperatively. Predictive factors for AF after CABG include ischemia, infarction, hypertension, cardiopulmonary bypass, and beta-
blocker withdrawal. Patients with AF after CABG remain in the hospital longer, have higher risk of stroke, and have higher mortality.8,10–12

One limited study13 of atrial fibrillation following heart transplantation showed that AF was associated with an increased risk of death but not with age, gender, ischemic time, or reason for transplantation. A separate study14 examining risk factors for rejection after heart transplantation found a high frequency of atrial flutter but not atrial fibrillation.

The goal of this study was to determine the incidence of AF after lung transplant and to find potential clinical predictors that may help to define a population of patients who may benefit from prophylactic antiarrhythmic therapy. In addition, we sought to determine if an association existed between AF and posttransplant morbidity or mortality.

Materials and Methods

Patient Population

The records of 200 consecutive adult patients who underwent lung transplantation at a single institution from August 1998 to June 2002 were studied. Eight lung transplant recipients included in this analysis had a history of AF. All patients included in this analysis had no clinically significant arrhythmias in the year prior to transplantation. For patients who underwent more than one transplant during the study period, information from the most recent transplant was used (n = 1). One patient who turned 18 years of age before transplantation but whose complete pretransplant workup had been performed in the pediatric pulmonary clinic was excluded. The remaining 198 patients comprise the study cohort. All patients were treated with standard postoperative, triple-immunosuppression combinations, predominately tacrolimus, azathioprine, and prednisone and with basiliximab for induction. A few patients received cyclosporine and/or mycophenolate mofetil. No patients received specific prophylaxis for AF prior to or immediately after transplantation.

Data Collection

Data were collected from a hospital computer-based clinical information system and paper charts maintained by transplant coordinators. For information with multiple measurements, the most recent data prior to transplant were included.

AF was confirmed by ECG or telemetry. For patients who had multiple arrhythmias after transplantation, the earliest abnormal rhythm noted was considered to be the primary arrhythmia. Documented arrhythmias included atrial fibrillation, atrial flutter, junctional tachycardia, atrioventricular nodal reentrant tachycardia, and multifocal atrial tachycardia. For the purposes of this study, only AFs were considered to be posttransplant AF. The earliest date of occurrence of AF was recorded. Posttransplant AF was defined as occurring within 14 days of transplant.

Statistical Analysis

Univariate analysis with χ² and Student t test was used to determine predictors of AF. Predictors of AF considered in the univariate analyses included age, gender, native disease, hypertension, diabetes, existing coronary artery disease (defined as presence of lesion > 50%), history of tobacco usage, history of arrhythmia, mean pulmonary artery pressure, donor age, cytomegalovirus status, left atrial size by echocardiogram (enlarged defined as > 4.0 cm), use of cardiopulmonary bypass, concurrent cardiac surgery (CABG [n = 10] and left atrial septal defect closure [n = 4]), postoperative immunosuppression, postoperative cardiac output, and the number of postoperative vasopressors. Pretransplant variables were extracted at the time of lung transplant evaluation. Posttransplant variables were determined at the time of arrival to the ICU immediately from the operating room. Factors with a significance of p < 0.10 were entered into a backward stepwise multivariate logistic regression analysis and retained only if p < 0.05. A bootstrap method was then used to validate the prediction model. Survival analysis was done using the Kaplan-Meier method. All statistical analysis was performed using commercially available statistical software (SAS Institute, Cary, NC; and SPSS; Chicago, IL).

Results

Indications for transplant are summarized in Table 1, and included COPD in 43%, cystic fibrosis (CF) in 18%, and idiopathic pulmonary fibrosis (IPF) in 17%. Other less frequent diagnoses included sarcoidosis, asbestosis, primary pulmonary hypertension, and congenital disease. The patients underwent bilateral (79%), single left (14%), or single right (7%) lung transplant. The mean age of the patients was 50 years (range, 19 to 66 years; median, 54 years).

Atrial arrhythmias occurred in 46.5% of patients. Postoperative AF (within the first 14 days after transplant) occurred in 78 patients (39%). The onset of arrhythmias was at 3.8 ± 3.0 days after transplant (± SD). AF was most common in patients with IPF (55.9%), as shown in Figure 1. The occurrence of AF was 41.9% in patients with COPD, 35.7% in patients with α₁-antitrypsin deficiency, and 22.2% in patients with CF. Diagnoses that occurred in < 10 patients (including sarcoidosis, asbestosis, primary pulmonary hypertension, and congenital heart disease) were grouped together, and had AF in 35.7% of cases.

Table 1—Demographic Characteristics of Patients Undergoing Transplantation*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data</th>
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<tbody>
<tr>
<td>Pulmonary diagnosis</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>86 (43)</td>
</tr>
<tr>
<td>CF</td>
<td>36 (18)</td>
</tr>
<tr>
<td>IPF</td>
<td>34 (17)</td>
</tr>
<tr>
<td>α₁-Antitrypsin deficiency</td>
<td>14 (7)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>19 (10)</td>
</tr>
<tr>
<td>Transplant type</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>157 (79)</td>
</tr>
<tr>
<td>Single left</td>
<td>28 (14)</td>
</tr>
<tr>
<td>Single right</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Mean age, yr (range; median)</td>
<td>50 (19–66; 54)</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%) unless otherwise indicated; n = 198.
The mean age of patients with AF was 52.8 years, compared to 47.5 years in patients without AF ($p < 0.004$). Significant predictors of postoperative AF in the multivariable analyses are as follows (Table 2): enlarged left atrium (LA) noted on echocardiography (odds ratio [OR], 3.9; confidence interval [CI], 1.0 to 13; $p = 0.05$), diagnosis of IPF (OR, 2.3; CI, 1.1 to 4.8; $p = 0.03$), age $\geq 50$ years (OR, 2.1; CI, 1.2 to 3.8; $p = 0.01$), existing coronary disease (OR, 2.0; CI, 1.0 to 3.9; $p = 0.009$), and number of postoperative vasopressor agents (OR, 1.5; CI, 1.0 to 2.4; $p = 0.03$). Of note, no differences in the incidence of AF were seen based on the use of cardiopulmonary bypass, pretransplant mean pulmonary artery pressures, concurrent cardiac surgery, or posttransplant immunosuppressive regimen. Eight patients had a history of arrhythmias, and postoperative AF occurred in four patients. Exclusion of these patients from the analysis did not significantly change the results.

Clinical outcomes varied significantly among patients with and without postoperative AF. Patients with AF spent more days in the hospital (32.4 $\pm$ 60.0 days vs 17.5 $\pm$ 24.1 days, $p = 0.04$), were more likely to undergo tracheostomy (OR, 3.6; CI, 1.8 to 7.3; $p = 0.0003$), and had more in-hospital deaths (OR, 5.7; CI, 2.1 to 15.1; $p = 0.0005$). Overall survival of patients with postoperative AF was significantly worse than those who never acquired AF (Fig 2; $p = 0.003$ by log-rank test).

**Discussion**

Our study is a large systemic analysis of adult lung transplant patients to define the incidence of and risk factors for postoperative atrial arrhythmias. There is little prior knowledge of the incidence, risk factors, and clinical importance of AF in this population. The overall incidence of AF was 39%, comparable to the findings of previous studies$^{9-12}$ of postcardiothoracic surgery arrhythmias. Risk factors for AF in this study were age $\geq 50$ years, native disease of IPF, presence of one or more coronary lesions $>50\%$, and the number of postoperative vasopressors. Patients with AF had increased rates of postoperative complications and worse overall survival, as compared to those free of postoperative AF.

Atrial fibrillation has several proposed pathophysiologic mechanisms. Multiple reentrant circuits may

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**Table 2—Significant Predictors for Atrial Arrhythmias After Transplantation**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>OR</th>
<th>$p$ Value</th>
</tr>
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<tbody>
<tr>
<td>Enlarged LA by echocardiography</td>
<td>3.9</td>
<td>0.05</td>
</tr>
<tr>
<td>IPF</td>
<td>2.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Age $\geq 50$ yr</td>
<td>2.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Prior coronary disease</td>
<td>2.0</td>
<td>0.009</td>
</tr>
<tr>
<td>No. of postoperative vasopressors</td>
<td>1.5</td>
<td>0.03</td>
</tr>
</tbody>
</table>
form across that atrial tissue, and atrial enlargement may provide more area for these circuits to form and propagate. A separate mechanism causing AF has been demonstrated to arise from focal sources located in the pulmonary veins. An increasingly common procedure to control atrial fibrillation consists of isolating the pulmonary veins from the left atrium through the use of radiofrequency ablation or with direct incisions. During pulmonary transplantation, a cuff of donor atrial tissue surrounding the pulmonary veins is sewn into the atrium of the recipient, creating a line of electrical block between the pulmonary veins and the atrial tissue. Due to this feature, AF in lung transplant recipients is unlikely to arise in the pulmonary veins. The findings of increased AF in recipients with LA enlargement, older age, or coronary artery stenosis > 50% suggest abnormal myocardial substrate or occult ischemia might contribute to the development of AF in this population. Furthermore, postoperative vaso-pressors also appear to contribute to the development of AF in the lung transplant population.

The finding of increased AF in patients with IPF is of unclear significance. Demographic characteristics of the patients with IPF were similar to those of other populations, including similar mean pulmonary artery pressures. The type of transplant operation performed was also similar to other patients, as the majority of all recipients in our series underwent bilateral transplantation. There are several possible explanations for the increased rate of AF in these patients. First, the IPF patients tend to have technically more difficult operations due to native lung fibrosis and adhesions. The increased complexity of the operation and/or more intensive postoperative care might influence the rate of AF. Second, IPF patients tend to be older and are more likely to have coronary disease; therefore, IPF might serve as a marker for other important covariates.

Also of interest is the lack of association between AF and certain variables, particularly concurrent CABG, given the high rates of AF known to occur after CABG. This result may simply reflect the small number of patients included in this analysis who underwent lung transplantation with concurrent CABG. Alternatively, we have hypothesized that occult ischemia might contribute to postoperative AF. The bypass procedure might have eliminated the potential for ischemia to contribute to the development of postoperative AF.

As with any single center retrospective study, it is worth noting several important limitations. Differences in patient populations, surgical techniques, and postoperative management at other centers might lead to different percentages of patients with posttransplant AF or differences in observed risk factors. Our experience, however, does reflect the largest systematic analysis of postoperative AF in lung transplant, and similar approaches to transplantation are employed at most centers. Furthermore,
our study was designed primarily to identify risk factors for postoperative AF, not necessarily to assign attributable mortality. Therefore, we cannot conclude postoperative AF is associated with increased postoperative morbidity and mortality.

Previous studies have shown that the use of perioperative β-blockers and antiarrhythmics reduce the incidence of atrial fibrillation and improve patient outcomes. Specifically, beta-blockers, sotalol, and amiodarone have been shown to be beneficial in clinical trials. Trials including verapamil, diltiazem, magnesium, and procainamide have been inconclusive. Our research is potentially useful to identify high-risk patients to target for future antiarrhythmic studies in lung transplant.

In addition, our results lead to an interesting hypothesis, specifically that postoperative AF contributes to prolonged ventilation, ICU stay, and mortality. However, an alternative explanation for our results is that patients having major postoperative complications then become more likely to acquire AF. Only a prospective randomized study designed to prevent AF will determine if there is any independent causal association between postoperative AF and posttransplant mortality.

CONCLUSIONS

AF is a common complication after pulmonary transplantation. Patients with AF have longer hospital stays and more postoperative morbidity and mortality. Older patients with IPF, known coronary disease, and abnormal LA size on echocardiography are at highest risk for acquiring AF. Larger numbers of pressors used postoperatively increases the risk of AF. Prospective studies are needed to investigate whether perioperative intervention will reduce the incidence of AF and result in shorter hospital stays and less morbidity after lung transplantation.

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