Atrial Fibrillation After Pulmonary Transplantation
Incidence, Impact on Mortality, Treatment Effectiveness, and Risk Factors

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Background—Atrial fibrillation (AF) is common after thoracic surgery. Limited data exist concerning the incidence of AF, its impact on mortality, the effectiveness of therapy, and the risk factors of AF after pulmonary transplantation.

Methods and Results—We reviewed the medical files of 224 consecutive lung transplant recipients who underwent surgery over a 10-year period at a large Canadian center. We collected patient characteristics, in-hospital treatments, and outcomes. Time-to-event analysis was used to account for in-hospital follow-up and models generated to assess the impact of AF on mortality and independent risk factors of AF after transplantation. Postoperative AF occurred in 65 patients (29%). AF was more likely to occur with complications such as pneumonia, mediastinitis, and bronchial dehiscence and was not an independent risk factor of mortality (hazard ratio = 1.56; 95% confidence interval, 0.52–4.63). Pharmacological or electric therapy for rhythm or rate control of AF was administered to 97% of patients. Intravenous amiodarone was used in 46%, electric cardioversion in 28%, and heparin in 26%. Only 1 patient remained in AF at discharge. Age (hazard ratio = 1.08 by year; 95% confidence interval, 1.05–1.12), bilateral transplantation (hazard ratio = 1.87; 95% confidence interval, 1.03–3.42), and a history of AF before the transplantation (hazard ratio = 4.48; 95% confidence interval, 1.05–19.11) were found to be independently associated with an increased incidence of postoperative AF.

Conclusions—AF is fairly common after pulmonary transplantation, transient, and relatively benign. It is not independently associated with increased in-hospital mortality. Most patients return to sinus rhythm before discharge. Age, prior AF, and bilateral transplantation increase the risk of postoperative AF. (Circ Arrhythm Electrophysiol. 2012;5:61-67.)

Key Words: atrial fibrillation ■ mortality ■ transplantation ■ risk factors

Atrial fibrillation (AF) is the most common arrhythmic disorder after noncardiac thoracic surgery and may occur in up to 20% of patients after lobectomy and 40% after pneumonectomy. Risk factors such as age, male sex, preexisting cardiovascular disease (congestive heart failure, history of arrhythmia, peripheral vascular disease), limited pulmonary reserve, and more extensive procedures have been reported.1–8 Postoperative AF is associated with prolonged hospital stay and increased in-hospital mortality after thoracic surgery. 1,8–10 Up to 15% of patients will remain in AF at discharge but only 2% after 2 months of follow-up.11

Clinical Perspective on p 67

Pulmonary transplantation recipients are a very specific population. They are generally younger and therefore are expected to have less cardiovascular disease risk factors compared with patients undergoing other types of thoracic surgery. Therefore, the incidence of AF, its clinical course, its treatment effectiveness, as well as the risk factors for AF are likely to differ in this highly selected population.

The incidence of AF after lung transplantation varies from 20–40%.9,12–14 Only 1 series assessed the independent role of identified risk factors.9 Concurrent postoperative complications may affect to a greater extent the short-term prognosis of these patients. Once AF occurs, treatment may also be limited in these patients because amiodarone is often avoided because of concern for potential acute pulmonary complications in the lung graft.15 In this context, choice of medication may vary from center to center, leading to different effectiveness.

The identification or confirmation of independent risk factors and potential preventive modalities may help to prevent occurrence of this complication. The purpose of

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our study was to assess, in a large cohort of pulmonary transplantation patients treated in a tertiary Canadian center, the incidence of AF, its impact on mortality, the effectiveness of AF therapy, and the risk factors of AF after surgery.

Methods

Study Design and Population

We used a retrospective cohort design for this study. The medical charts of all consecutive lung transplant adult recipients who underwent their surgery between May 1996 and September 2006 at the Centre Hospitalier de l’Université de Montréal (CHUM) were abstracted by 3 physician investigators (Drs Henri, Giraldeau, and Cloutier), using detailed case-report forms. All the procedures were performed by a single transplantation team composed of a thoracic surgeon (Dr Ferraro) and a cardiac surgeon (Dr Noiseux). The CHUM Research and Ethics committees approved this project; given the full retrospective nature of the investigation, patient consent was waived.

Data Collection and Outcomes Definition

Patient characteristics, preoperative and postoperative medication including antiarrhythmic drugs, anticoagulants, or other agents such as vasopressor, and in-hospital non-AF outcomes such as death, stroke, myocardial infarction, pneumonia, mediastinitis, bronchial dehiscence, acute rejection, and need for tracheotomy were assessed. Events were adjudicated by 2 senior investigators (Drs Rinfret and Ferraro) by chart review, when necessary. For the prediction of AF, all factors susceptible to influence the incidence of AF and that could be identifiable at the time of surgery were collected. They included age, sex, type of pulmonary disease that justified transplantation, preoperative medication, diabetes, hypertension, dyslipidemia, history of congestive heart failure (New York Heart Association class), preexisting cardiovascular disease or AF, smoking habits, preoperative echocardiography data, right heart catheterization data (when available), anesthetic strategies, and type of procedure. Postoperative AF was defined as any occurrence of AF or atrial flutter of at least 30 seconds documented by either a 12-lead ECG or any rhythm strips obtained from telemetry monitoring performed during the postoperative period. Charts notes were also reviewed specifically looking at a physician assessment of irregular rhythm, tachycardia, or AF/flutter that could be documented by a concomitant 12-lead ECG or a rhythm strip. The period of monitoring was left to the discretion of the treating physicians and was not standardized. AF therapy was defined as either rhythm or rate control using pharmacological or electric therapy. Stroke was defined as any occurrence of a focal neurological deficit confirmed to be the result of a stroke by a neurologist. Mediastinitis or pneumonia was considered when a clinical diagnosis was indicated in the chart, in a plausible clinical context.

Given that no systematic or serial ECGs are performed in these patients at follow-up at the transplantation clinic unless they present with cardiac symptoms or they are also followed by a cardiologist, this report more reliably focuses on in-hospital outcomes. Nevertheless, charts were also reviewed for any documentation of AF during the 1-year period after discharge, especially looking at hospitalization for recurrent or persistent AF (clinically relevant or significant AF).

Statistical Methods

Descriptive statistics were first performed, comparing clinical characteristics and univariable outcomes of patients who presented AF and those who did not. Continuous data were compared using t test and proportions with χ² or Fisher exact test. The proportional hazards assumption was first evaluated using the Schoenfeld residuals. To assess the potential independent impact of AF on in-hospital mortality, parsimonious Cox-proportional models were then generated. AF was modeled as a time-dependent covariate. We first included the 2 variables associated with the largest effect size in univariable models (among several potential a priori defined variables such as pulmonary fibrosis, bilateral transplantation, infection, postoperative acute rejection, bronchial dehiscence, postoperative myocardial infarction, postoperative stroke, postoperative tracheotomy, use of postoperative vasopressor agents) and tested the impact of AF added to the model, limiting to a total 3 variables to avoid overfit. To assess risk factors of postoperative AF, time-to-event analysis was again used to account for differential in-hospital follow-up. Univariable analyses were performed using Cox proportional hazards models. For multivariable analyses, we forced age and sex in the model and then sequentially added the most significant risk factor (pulmonary fibrosis) by univariable analysis and verified the impact of subsequent variable addition on the hazard ratio of pulmonary fibrosis. Any variable that shifted the effect size of “pulmonary fibrosis” by 10% was retained in the model. We limited potential variables to a total of 6 variables, given the limited number of events. Given that the year of the surgery was strongly correlated with the type of transplantation (unilateral versus bilateral), with more bilateral transplantsations in the more recent years of the study span (Pearson probability value of 0.002), we used 2 different modeling strategies; the first model used the year of the surgery as a potential risk factor, whereas the second modeling strategy used the type of transplantation (unilateral versus bilateral). Results from both models are reported. All tests were 2-sided, and probability values <0.05 were considered statistically significant and probability values <0.1 as suggesting a trend. Statistical analyses were performed using SAS software, version 9.1 (SAS Institute Inc, Cary, NC).

Results

Study Sample and Patient Characteristics

A total of 224 patients underwent lung transplantation over the 10-year study period and constituted the study sample (Table 1). The most frequent indication for lung transplantation was emphysema (37%). Other indications included cystic fibrosis (27%), idiopathic pulmonary fibrosis (11%), bronchiectasis (6%), α-1 antitrypsin deficiency (4%), and primary pulmonary hypertension (1%). Bilateral transplantation, more common in recent years, was performed in 56% of cases whereas unilateral transplantation was done in the remaining patients.

The mean age of patients was 47 years overall; 44 years in those without AF and 54 years in those with AF (P<0.01). Among lung transplant recipients, the mean preoperative left ventricular ejection fraction was 65%. Moreover, only 12 patients (5.4%) had known coronary artery disease (CAD) and 3 (1.3%) had a prior history of AF.

Incidence and Hospital Course Associated With AF

Postoperative AF occurred in 65 patients (29%), of whom only 3 had atrial flutter, at a median of 5 days (average: 7±11 days) after transplantation and lasted on average 3±10 days. In general, other postoperative outcomes of patients with AF were worse compared with patients without AF. Length of stay was longer in patients who had AF versus those who did not (52 versus 31 days; P<0.01), although this may only reflect that patients who had longer lengths of stay had more opportunity for AF to be observed or recognized. Also, in-hospital mortality was higher in patients who had AF (18.5% versus 6.3% P<0.01). However, AF was more frequent in patients who also had other postoperative complications such as mediastinitis and pneumonia. Use of
Risk Factors for Postoperative AF

Risk Factors of AF: Univariable Analysis

Among the clinical risk factors assessed in our cohort, age, female sex, pulmonary fibrosis, history of CAD, history of AF and smoking were all associated with an increased risk of AF after surgery (Table 3). Using echocardiography data, available in 200 patients, right heart chambers size, systolic pulmonary pressure, or presence of pulmonary hypertension and presence of any mitral regurgitation were also associated with increased risk of AF. Finally, none of the studied surgical variables (bilateral transplantation, cold lung ischemia duration, cardiopulmonary bypass, or transfusion) were associated, by univariable analysis, with an increase risk of AF, with the sole exception of the use of an epidural catheter inserted at the beginning of anesthesia, which appeared to be protective.

Independent Risk Factors of AF: Multivariable Analysis

Given that more bilateral transplantations were performed during the most recent years of the study span (Pearson probability value of 0.002), we generated 2 sets of models, one using year of transplantation and the other the type of transplantation (bilateral versus unilateral) (Table 4). In the model using year of transplantation, we found age (HR=1.10 per year; 95% CI, 1.04–1.10; *P*<0.01) and the year of the transplantation (HR=1.07; 95% CI, 1.04–1.10; *P*<0.01) to be the most important independent risk factors for AF. In the model using type of transplantation, male sex (HR=1.26; 95% CI, 1.05–1.50; *P*<0.01) and the age of the patient at the time of transplantation (HR=1.06 per year; 95% CI, 1.03–1.09; *P*<0.01) were the independent risk factors for AF.

In-Hospital Management of AF and AF-Related Outcomes

Of all patients who had AF, the majority (97%) received specific therapy aimed at restoring sinus rhythm. Most patients received more than 1 drug to treat the AF episode (23% had 3 different drugs). Intravenous amiodarone (46%) was the most frequently used agent followed by intravenous calcium channel blockers (40%). Electric cardioversion was required in 28%. Heparin was administered in 26%, but warfarin was initiated in only 1 patient at discharge. In-hospital stroke occurred in 1.5% of AF patients compared with 1.9% of patients without AF (*P*=0.44). Of those who received heparin, 3 patients had bleeding complications. None of them died of bleeding complications. No pulmonary complications could be attributed to amiodarone. Only 1 patient remained in AF at discharge. All others returned to sinus rhythm before discharge. As for oral antiarrhythmic drugs, 1 patient was discharged on flecainide, 1 on sotalol and 3 on propafenone. All antiarrhythmic drugs were stopped during follow-up period between 1–6 months after hospital discharge.

Recurrence of AF at 1 Year

Of the 224 patients of this cohort, only 8 patients had any documentation of AF in their chart during the year after their transplantation. Of these 8, 3 also presented AF after their surgery. All 8 required hospitalization, but only 1 was related to AF. All other AF episodes were documented during a hospitalization for other causes, such as appendicitis, pneumonia, peritonitis, diverticulitis, acute rejection, or respiratory insufficiency, which led to death in 4 patients.

**Table 1. Clinical Characteristics and In-Hospital Complications by Postoperative AF Status**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients (n=224)</th>
<th>Patients With AF (n=65)</th>
<th>Patients Without AF (n=159)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y, per year</td>
<td>47 (13)</td>
<td>54 (8)</td>
<td>44 (13)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male sex</td>
<td>111 (50%)</td>
<td>43 (66.2%)</td>
<td>68 (42.8%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Preexisting CAD</td>
<td>12 (5.4%)</td>
<td>7 (10.8%)</td>
<td>5 (3.1%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension</td>
<td>38 (17.0%)</td>
<td>15 (23.1%)</td>
<td>23 (14.5%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>47 (21.0%)</td>
<td>19 (29.2%)</td>
<td>28 (17.6%)</td>
<td>0.05</td>
</tr>
<tr>
<td>History of AF</td>
<td>3 (1.3%)</td>
<td>2 (3.1%)</td>
<td>1 (0.6%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Smoking habits</td>
<td>147 (65.6%)</td>
<td>53 (81.5%)</td>
<td>94 (59.1%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>42 (18.8%)</td>
<td>26 (40.0%)</td>
<td>16 (10.1%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Bilateral transplantation</td>
<td>126 (56.3%)</td>
<td>37 (56.9%)</td>
<td>89 (56.0%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Cardiopulmonary bypass</td>
<td>28 (12.5%)</td>
<td>10 (15.4%)</td>
<td>18 (11.3%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Epidural catheter</td>
<td>184 (82.1%)</td>
<td>45 (69.2%)</td>
<td>139 (87.4%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Postoperative variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>49 (21.9%)</td>
<td>22 (33.9%)</td>
<td>27 (17.0%)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Mediastinitis</td>
<td>5 (2.2%)</td>
<td>4 (6.2%)</td>
<td>1 (0.6%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>11 (4.9%)</td>
<td>2 (3.1%)</td>
<td>9 (5.7%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Vasopressor use</td>
<td>81 (36.2%)</td>
<td>31 (47.7%)</td>
<td>50 (31.5%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Stroke</td>
<td>7 (3.1%)</td>
<td>1 (1.5%)</td>
<td>7 (3.8%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>30 (13.4%)</td>
<td>20 (30.8%)</td>
<td>10 (6.3%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hospital stay</td>
<td>37.0 (42.6)</td>
<td>51.5 (50.6)</td>
<td>31.2 (37.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>22 (9.8%)</td>
<td>12 (18.5%)</td>
<td>10 (6.3%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data are presented as mean with (standard deviation) or number and (percentage).

AF indicates atrial fibrillation; CAD, coronary artery disease.

*Median in-hospital follow-up of 20 days.

vasopressors and need of tracheotomy were also more frequent in AF patients (Table 1). Using multivariable Cox model accounting for differential in-hospital follow-up duration, postoperative AF, modeled as a time-dependent covariate, was not an independent risk factor of mortality (hazard ratio [HR]=1.56; 95% confidence interval [CI], 0.52–4.63; *P*=0.43) after pulmonary transplantation (Table 2). The most important risk factors for mortality were bronchial dehiscence and postoperative vasopressors use.

**Table 2. Multivariable Risk Factors of In-Hospital Mortality**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchial dehiscence</td>
<td>3.84 (1.44–10.20)</td>
</tr>
<tr>
<td>Postoperative vasopressor use</td>
<td>2.74 (0.94–7.95)</td>
</tr>
<tr>
<td>Postoperative AF</td>
<td>1.56 (0.52–4.63)</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval; and AF, atrial fibrillation.
late (average: 7 days; median: 5 days) after the surgery. Fortunately, AF was most often transient and relatively benign in nature. Although associated with higher in-hospital mortality, AF was also observed in patients presenting other comorbid posttransplant complications and was not an independent risk factor of in-hospital mortality. Current pharmacological treatments appear effective and safe, with most patients returning to sinus rhythm before discharge. However, there has been a statistically significant increase in the incidence of postoperative AF over the years of observation, probably as a result of more common use of bilateral transplantation, although several nonmeasured cofactors may have played a role. AF was more likely to occur in older patients, in those undergoing bilateral transplantation, and in those with a history of AF. Pain management with an epidural catheter may reduce the risk of postoperative AF, but its effect is no longer significant when using bilateral transplantation instead of the year of surgery in multivariable models.

Our study is one of only a few to address the issue of AF after lung transplantation.9,12–14 It is the second largest series after that of Mason et al,13 which reported a lower incidence of 20%. Dizon et al12 compared the incidence of AF after lung or heart transplant. They found that AF was more frequent after lung transplantation despite the absence of graft rejection or cardiac dysfunction, with an incidence of 18.9% in 122 recipients, again lower than in our population. The 29% in-hospital rate of AF in our cohort appears, however, quite similar to the expected rate after other types of noncardiac thoracic surgery.3 Nielsen et al9 even reported a higher incidence (39%) in patients after lung transplantation. The lower incidence in our cohort compared with the Nielsen series may be explained, at least in part, by the younger mean age (47 versus 50 years) and the lower use of bilateral procedure (56% versus 79%). We also found that timing of AF in our series was relatively late (median of 5 days after surgery). This is strikingly different from the Mason series, although the explanation for such findings is not known.

We found that AF was more likely to occur with other concomitant postoperative outcomes, which probably explains the increased mortality in these patients. This is new and underreported data in previous series. Use of vaso-pressors and need of tracheotomy was higher, revealing substantial confounding in the association of AF and mortality. The fact that AF was transient in most patients, although seeming no amiodarone-related acute pulmonary complications, the effectiveness of the management of AF in these patients appears quite good. Moreover, the very low recurrence of clinically significant AF during the 1-year follow-up tends to support a strategy limited at focusing on

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**Table 3. Univariable Risk Factors of Postoperative AF:**

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, per each year increment</td>
<td>1.08 (1.05–1.11)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female sex</td>
<td>2.11 (1.26–3.53)</td>
<td>0.0044</td>
</tr>
<tr>
<td>CAD</td>
<td>2.31 (1.10–4.85)</td>
<td>0.027</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.57 (0.88–2.80)</td>
<td>0.13</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.58 (0.93–2.71)</td>
<td>0.092</td>
</tr>
<tr>
<td>Preoperative history of AF</td>
<td>4.85 (1.18–19.9)</td>
<td>0.029</td>
</tr>
<tr>
<td>Smoking, active or recent</td>
<td>1.42 (1.15–1.77)</td>
<td>0.0014</td>
</tr>
<tr>
<td>NYHA class per each class</td>
<td>1.00 (0.68–1.48)</td>
<td>0.99</td>
</tr>
<tr>
<td>Pulmonary fibrosis versus other indication</td>
<td>3.53 (2.14–5.82)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Echocardiography data**

- LVEF, per each % increase: 3.87 (0.17–88.5) 0.40
- LA size, per mm: 1.06 (1.02–1.10) 0.0083
- RVEDD, per mm: 1.10 (1.05–1.15) 0.0002
- LVEDD, per mm: 1.03 (0.99–1.06) 0.12
- Any mitral regurgitation versus no: 1.69 (1.02–2.81) 0.043
- SPAP, per mm Hg increment: 1.02 (1.01–1.03) 0.0013
- SPAP >35 mm Hg: 2.25 (1.38–3.69) 0.0012

**Surgery-related data**

- Year of the transplantation: 1.13 (1.03–1.24) 0.0095
- Bilateral transplant versus single: 1.04 (0.64–1.70) 0.88
- First lung cold ischemic time, per min: 1.00 (0.995–1.003) 0.59
- Second lung cold ischemic time, per min: 1.00 (0.999–1.001) 0.79
- Duration of cardiopulmonary bypass, per min: 1.01 (0.99–1.03) 0.12
- Transfusion: 0.78 (0.47–1.27) 0.31
- Epidural catheter for pain management: 0.41 (0.24–0.69) 0.0009

AF indicates atrial fibrillation; HR, hazard ratio; CI, confidence interval; CAD, coronary artery disease; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; LA, left atrium; RVEDD, right ventricular end-diastolic diameter; LVEDD, left ventricular end-diastolic diameter; SPAP, systolic pulmonary artery pressure.

P = 0.049) to be associated with increased incidence of postoperative AF, whereas pulmonary fibrosis was associated with a strong trend (HR=1.76 per year; 95% CI, 1.00–3.10; P = 0.051). Pain management with an epidural catheter after surgery was associated with a reduction in AF (HR = 0.49; 95% CI, 0.27–0.88; P = 0.016). However, when using bilateral transplantation instead of the year of surgery, only age (HR = 1.08 by year; 95% CI, 1.05–1.12; P < 0.01), bilateral transplantation (HR = 1.87 per year; 95% CI, 1.03–3.42; P = 0.041), and a history of AF before the transplantation (HR = 4.48 per year; 95% CI, 1.05–19.11; P = 0.043) remain statistically associated with an increased incidence of postoperative AF.

**Discussion**

In this population of lung transplantation recipients, AF was fairly common after surgery and occurred relatively

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**Distribution of variables**

- **Clinical data**
  - Age, y, per each year increment: 1.08 (1.05–1.11) <0.0001
  - Female sex: 2.11 (1.26–3.53) 0.0044
  - CAD: 2.31 (1.10–4.85) 0.027
  - Hypertension: 1.57 (0.88–2.80) 0.13
  - Dyslipidemia: 1.58 (0.93–2.71) 0.092
  - Preoperative history of AF: 4.85 (1.18–19.9) 0.029
  - Smoking, active or recent: 1.42 (1.15–1.77) 0.0014
  - NYHA class per each class: 1.00 (0.68–1.48) 0.99
  - Pulmonary fibrosis versus other indication: 3.53 (2.14–5.82) <0.0001

- **Echocardiography data**
  - LVEF, per each % increase: 3.87 (0.17–88.5) 0.40
  - LA size, per mm: 1.06 (1.02–1.10) 0.0083
  - RVEDD, per mm: 1.10 (1.05–1.15) 0.0002
  - LVEDD, per mm: 1.03 (0.99–1.06) 0.12
  - Any mitral regurgitation versus no: 1.69 (1.02–2.81) 0.043
  - SPAP, per mm Hg increment: 1.02 (1.01–1.03) 0.0013
  - SPAP >35 mm Hg: 2.25 (1.38–3.69) 0.0012

- **Surgery-related data**
  - Year of the transplantation: 1.13 (1.03–1.24) 0.0095
  - Bilateral transplant versus single: 1.04 (0.64–1.70) 0.88
  - First lung cold ischemic time, per min: 1.00 (0.995–1.003) 0.59
  - Second lung cold ischemic time, per min: 1.00 (0.999–1.001) 0.79
  - Duration of cardiopulmonary bypass, per min: 1.01 (0.99–1.03) 0.12
  - Transfusion: 0.78 (0.47–1.27) 0.31
  - Epidural catheter for pain management: 0.41 (0.24–0.69) 0.0009

AF indicates atrial fibrillation; HR, hazard ratio; CI, confidence interval; CAD, coronary artery disease; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; LA, left atrium; RVEDD, right ventricular end-diastolic diameter; LVEDD, left ventricular end-diastolic diameter; SPAP, systolic pulmonary artery pressure.

P = 0.049) to be associated with increased incidence of postoperative AF, whereas pulmonary fibrosis was associated with a strong trend (HR=1.76 per year; 95% CI, 1.00–3.10; P = 0.051). Pain management with an epidural catheter after surgery was associated with a reduction in AF (HR = 0.49; 95% CI, 0.27–0.88; P = 0.016). However, when using bilateral transplantation instead of the year of surgery, only age (HR = 1.08 by year; 95% CI, 1.05–1.12; P < 0.01), bilateral transplantation (HR = 1.87 per year; 95% CI, 1.03–3.42; P = 0.041), and a history of AF before the transplantation (HR = 4.48 per year; 95% CI, 1.05–19.11; P = 0.043) remain statistically associated with an increased incidence of postoperative AF.

In this population of lung transplantation recipients, AF was fairly common after surgery and occurred relatively
maintaining sinus rhythm or controlling rate control during the hospital course.

We found that the incidence of AF has increased over the years of this cohort, probably as a result of more liberal use of 2 pulmonary grafts in the latest years. We identified age and bilateral transplantation, a more complex procedure, as significant risk factors for postoperative AF in these patients. Nielsen et al and Mason et al also reported older age among the most powerful risk factor. In fact, age is generally the strongest risk factor of AF after noncardiac thoracic surgery.1–3,5–8 Complexity of surgery is known to be a strong risk factor of AF after thoracic surgery.2,3,5–7,8 Although not significant in our cohort when considering bilateral transplantation, pulmonary fibrosis has been identified by others as an independent risk factor.9 Pulmonary fibrosis patients may have pulmonary hypertension and larger atriums that may constitute a substrate for postoperative AF. However, factors such as atrium size and pulmonary pressure were not retained in the final models, probably because of strong colinearity with other factors, including pulmonary fibrosis. Mason et al found primary pulmonary hypertension as being one potent risk factor. We did not identify the same factors, probably because of the low number of patients (n=3) undergoing transplantation for this indication in our cohort. History of AF was associated with a large effect size in our sample, with a more than 4-fold increase in the risk of postoperative recurrence. Nielsen et al excluded patients who had clinically significant arrhythmias in the year before transplantation, so the impact of prior AF was not assessed. A history of AF is known to predict AF in noncardiac thoracic surgery.1–3,8 and our findings tend to confirm that this may be also the case after pulmonary transplantation.

Interestingly, preexisting CAD was not found to be a risk factor in our cohort. However, only 12 patients with known CAD underwent transplantation, probably as a result of the selection process for best transplant candidates. Nevertheless, such a finding tends to negate the hypothesis that AF would be the result of postoperative myocardial ischemia. Our findings rather suggest that AF is probably associated with longer and technically more complex operations, such as bilateral transplantation, leading to more inflammation and irritation of the atriums and pericardium. Our data also point to a different mechanism for AF after pulmonary transplantation versus spontaneous AF. Indeed, the pulmonary transplantation, especially when bilateral, involves a complete surgical electrophysiological disconnection of the transplant atrial veins with the recipient heart.16 Although such disconnection is presumed to explain the low incidence of AF after heart transplantation, it does not seem to translate into the same benefits in lung transplantation, at least in the short term.12 Therefore, other factors such as inflammation and irritation may explain early AF. Whereas surgical electrophysiological disconnection of the transplant atrial veins with the recipient heart is, however, associated with reduced recurrence or incidence of AF during follow-up, as previously demonstrated by Lee et al,17 this could not be assessed reliably in our study because no systematic ECGs or heart rhythm monitoring was performed in the longer term in transplant clinic. Having said that, with all the limitations, only 8 patients had chart evidence of recurrent AF, and among those only 2 had undergone a bilateral transplantation. Clearly, more data are needed.

Although we found that pain management with an epidural catheter was associated with a more than 50% reduction in postoperative AF when controlling for the year of transplantation, the association did not remain significant (P=0.11) when controlling for the use of bilateral transplantation, although the effect size remain quite large. More extensive surgical procedures are associated with increased pain; better pain management may therefore reduce sympathetic tone and adrenergic stimulation of the atriums in these patients, although this association is not consistent in the 2 models. Interestingly, incidence of postoperative AF after heart transplantation is usually lower than 5%, which may in part be explained by cardiac autonomic denervation,12 not only pulmonary vein isolation. Conversely, other studies have supported the preservation of autonomic cardiac innervation in single and bilateral lung transplant recipients.18–22 Alternatively, known contraindication to epidural catheter such as cardiopulmonary bypass (which requires anticoagulation), mostly used during bilateral transplant and patients with pulmonary hypertension or right heart dysfunction, could have confounded this association. Therefore, more effective pain management with an epidural catheter may be an

Table 4. Multivariable Risk Factors of Postoperative AF, Using Either the Year of the Surgery or the Type of Transplantation in Models

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Multivariable Using Year of Surgery</th>
<th></th>
<th></th>
<th></th>
<th>Multivariable Using Bilateral Transplant vs Single</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, per additional year</td>
<td>1.07 (1.04–1.10)</td>
<td>&lt;0.0001</td>
<td></td>
<td>1.08 (1.05–1.12)</td>
<td>&lt;0.0001</td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>1.57 (0.91–2.71)</td>
<td>0.11</td>
<td>1.61 (0.94–2.78)</td>
<td>0.084</td>
<td></td>
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<tr>
<td>Pulmonary fibrosis</td>
<td>1.76 (1.00–3.10)</td>
<td>0.051</td>
<td>1.58 (0.87–2.87)</td>
<td>0.13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of an epidural catheter</td>
<td>0.49 (0.27–0.88)</td>
<td>0.016</td>
<td>0.61 (0.33–1.12)</td>
<td>0.11</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>History of AF before transplant</td>
<td>3.41 (0.81–14.39)</td>
<td>0.095</td>
<td>4.48 (1.05–19.11)</td>
<td>0.043</td>
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<tr>
<td>Year of the transplantation, per year increment</td>
<td>1.10 (1.00–1.22)</td>
<td>0.049</td>
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<tr>
<td>Bilateral transplant versus single</td>
<td>. . . . . . . . . . . . . .</td>
<td>. . . . .</td>
<td>1.87 (1.03–3.42)</td>
<td>0.041</td>
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</tbody>
</table>

AF indicates atrial fibrillation; HR, hazard ratio; CI, confidence interval.
effective mean to decrease the incidence of AF after lung transplantation, but such hypothesis should be tested in a prospective manner.

Our study has many limitations that must be acknowledged. First, this is a single-center study in patients operated by the same surgical team over the study period. Therefore, preoperative and postoperative care and the surgical techniques were relatively uniform for all patients, and our results may not apply to different settings. Second, we only relied on medical chart review; subclinical episodes of AF might have been missed. However, with all recordings including ECGs and rhythm band strips reviewed, it is unlikely that our methods missed clinically significant episodes. Nevertheless, as mentioned earlier, this limitation is more important in our assessment of recurrence or incidence of AF after discharge. Third, although it is one of the largest series, the sample size only allowed for the identification of few statistically independent risk factors. Fourth, we were not able, through this observational analysis, to assess which treatment approach is best for AF after lung transplant. However, irrespective of in-hospital AF-specific therapy received, most patients returned in sinus rhythm at discharge, suggesting that a conservative approach, limiting intravenous amiodarone, electric cardioversion, and heparin to the most symptomatic patients may be warranted. Finally, only in-hospital outcomes were more reliably assessed in this study. Surgical disconnection of atrial veins associated with bilateral transplantation, although associated with increased short-term incidence of AF, may still have a longer-term effect to reduce the incidence of recurrence of AF in these patients. Of all the patients who underwent bilateral transplantation (n=125), only 2 had evidence of AF at follow-up, which tend to support such a hypothesis.

In conclusion, in this large cohort of pulmonary transplantation patients, AF was a frequent but benign and transient complication. AF occurs with concurrent postoperative complications and was not an independent risk factor of in-hospital mortality. However, most patients required AF-specific treatment, which in turn succeeded in almost all cases before discharge. Amiodarone, when used intravenously for a short period of time, appeared to be safe for the graft. Age, bilateral transplantation, and history of AF were significant independent risk factors of postoperative AF. Therefore, surgical trauma and its associated adrenergic stimulation on “aged atriums” is the most likely explanation for such a high early incidence despite complete pulmonary vein disconnection as a result of the surgery, at least after bilateral transplantation. Strategies aimed at reducing pain and adrenergic tone, such as with better pain management, should be tested in prospective trials.

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Disclosures
None.

References
Pulmonary transplantation recipients are a very specific population. They are generally younger and have fewer cardiovascular disease risk factors compared with patients undergoing other types of thoracic surgery. Therefore, the incidence of postoperative atrial fibrillation (AF), its clinical course, its treatment effectiveness, as well as the risk factors for AF are likely to differ in this highly selected population. In this large single-center series, we found that postoperative AF occurred in 29% of patients, similar to what is expected after other types of thoracic surgeries. AF was more likely to occur with complications such as pneumonia, mediastinitis, and bronchial dehiscence and was not an independent risk factor for mortality. Pharmacological or electrical therapy for rhythm or rate control was required in almost all patients. AF was largely benign and transient, with only 1 patient remaining in AF at discharge. Age, bilateral lung transplantation, and a history of AF before the transplantation were found to be independently associated with an increased incidence of postoperative AF. Pulmonary vein disconnection does not appear to reduce the incidence of AF, at least in the short term.
Atrial Fibrillation After Pulmonary Transplantation: Incidence, Impact on Mortality, Treatment Effectiveness, and Risk Factors
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