Atrial Arrhythmias After Lung Transplantation
Epidemiology, Mechanisms at Electrophysiology Study, and Outcomes

Vincent Y. See, MD; Kurt C. Roberts-Thomson, MBBS, PhD; William G. Stevenson, MD; Phillip C. Camp, MD; Bruce A. Koplan, MD

Background—Atrial arrhythmias (AAs) including atrial fibrillation (AF) and atrial tachycardia (AT) are often observed after cardiothoracic surgery. Our aim was to evaluate the prevalence and mechanism of AAs after lung transplantation.

Methods and Results—All patients (n=127) after bilateral sequential lung transplantation followed at our institution over 20 years were included. All patients received postoperative rhythm monitoring and clinic visits with ECG at 1, 3, 6, and 12 months, or as needed. AAs occurred in 40 of 127 (31.5%) patients over 4.2±4.1 years. AA prevalence at postoperation and 1, 3, 6, 12, and >12 months was 24%, 11%, 3%, 2%, 4%, and 11%, respectively. Early AAs were predominantly AF, whereas all AAs >12 months were AT. Time to first AF versus AT was 11±9 versus 1485±2462 days (P=0.09). Male sex, age, and preoperative AA predicted any early (<3 months) AA but did not predict late AA. Early AA did not predict late AT. In 4 patients with drug-resistant AT, electrophysiology studies found AT involving the pulmonary vein/left atrium anastomoses in 3 patients, including donor-to-recipient conduction in 1, border zone macroreentry in 2, and cavotricuspid isthmus dependent flutter in 1; all patients were successfully treated with ablation.

Conclusions—AAs after lung transplantation are common. Although AF is common early, AF is rare after healing of left atrial incisions, which probably result in surgical pulmonary vein isolation with rare exception. This raises the question of whether additional surgical or ablation lines at the time of lung transplantation would prevent late AA. (Circ Arrhythmia Electrophysiol. 2009;2:504-510.)

Key Words: catheter ablation ☐ tachyarrhythmia ☐ transplant ☐ lung ☐ fibrillation

Atrial arrhythmia (AA) is a common postoperative complication after cardiac surgery and thoracic surgery, with respective estimated incidences of 20% to 50% and 10% to 46%, depending on methods of definition and detection.1,2 After cardiac transplantation, atrial fibrillation (AF) or atrial flutter (AFL) are frequent in the immediate postoperative period and are associated with acute rejection or transplant vasculopathy, but macroreentrant or focal atrial tachycardia (AT) are observed later after cardiac transplantation.3 AT and AFL observed after atrial surgery are often related to surgical lines of conduction block and regions of slow conduction.3–5 AT in the recipient atria conducting to the donor atria has also been described after cardiac transplantation.3–5 AFL and AT have become less frequent as cardiac transplant techniques have evolved from biatrial to bicaval anastomoses.6

Clinical Perspective on p 510
The mechanisms underlying AF and AT initiation and maintenance are complex and probably involve electrophysiological abnormalities that may be aggravated by inflammation early after surgery.1,7 Over the last decade, the importance of the pulmonary veins (PV) in both the initiation and maintenance of AF has been demonstrated.8,9 Early attempts at surgical ablation used applications of lines of conduction block. The majority of current catheter ablation techniques used in the treatment of AF involve electric isolation of the PV from the left atrium (LA), with success rates between 60% to 85%.10–13

The surgical technique of bilateral sequential lung transplantation (LT) involves 2 separate anastomoses of donor LA tissue cuffs surrounding both the right superior and inferior PVs and both the left superior and inferior PVs to the posterior wall of the recipient LA at single venous cuffs created at the right and left PV antra, as shown in Figure 1.14 This may electrically isolate the donor PV, but residual recipient PV tissue may persist as part of the LA anastomosis. This LA anastomosis also forms lines of conduction block and slow conduction that may result in electroanatomic substrate for reentry.

The aim of this analysis was to determine the prevalence, electrophysiological substrate and mechanisms, and management outcomes of AA in patients undergoing bilateral sequential LT. Findings and outcomes at electrophysiology study and catheter ablation of late post–lung
transplant arrhythmias refractory to medical therapy are described.

Methods

Study Population
One hundred twenty-seven consecutive patients, who underwent bilateral sequential LT between January 9, 1987, and April 10, 2008, and were followed at our institution were included in the study. Three patients in the study underwent a second LT surgery (1 at another institution). Of the 130 transplants, 117 patients underwent transplantation at Brigham and Women’s Hospital. Patients who had undergone en bloc or single lung transplants were excluded. This study was conducted under a general patient record review protocol approved by the Institutional Review Board at Brigham and Women’s Hospital.

Surgical Anastomosis
Methods of transplantation were determined on the basis of operative records. All LA-PV anastomoses were performed in a similar manner (Figure 1). Donor right and left PVs were isolated as 2 LA cuffs from the donor heart at the time of organ harvest. The recipient PV antra were cross-clamped at the respective PV antra and resected as a left atrial tissue cuff. The donor LA-PV cuff is anastomosed to the common recipient right or left LA-PV cuff. This anastomosis may isolate donor PV tissue, but residual recipient PV tissue may be retained as part of the surgical anastomosis.

Atrial Tachyarrhythmias
AAs were defined as (1) AF, (2) organized AT, or (3) sinus rhythm (SR), as described by the AHA/ACC/ESC Guidelines for the Management of Patients with Atrial Fibrillation and Supraventricular Tachycardia and HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation.15–17 AA were identified on any 12-lead surface ECG of each patient’s medical record. If patient records reported AA without 12-lead ECG documentation, medical records were reviewed for telemetry monitoring or ambulatory ECG monitoring that documented AF or AT. All atrial arrhythmias documented beyond the postoperative period required confirmation by 12-lead ECG. AT was defined by organized P-wave activity separated by an isoelectric baseline with fixed cycle length. All patients were continuously monitored in the postoperative period. Routine clinical follow-up and 12-lead ECGs were performed at 1, 3, 6, 9, and 12 months and then annually. The postoperative time point was determined by the date of discharge from the hospitalization at time of transplantation. The differentiation between early and late time points was at ≤3 months versus >3 months. If a patient reported arrhythmic symptoms, ambulatory ECG monitoring was performed. The assessment of cardiac rhythm was evaluated independently by 3 investigators.

Electrophysiology Study
All patients who underwent electrophysiology study (EPS) and catheter ablation provided written informed consent. Patients were studied under light intravenous conscious sedation with midazolam and fentanyl. Catheters used included (1): 20-pole catheter in the right atrium and coronary sinus (Ismus Catheter, Biosense-Webster, Diamond Bar, Calif); (2) 20-pole Lasso catheter (Optima, St Jude Medical, St Paul, Minn); and (3) externally irrigated 3.5-mm mapping and ablation catheter (Navistar–Thermocool, Biosense-Webster, Diamond Bar, Calif). Detailed 3D electroanatomic mapping (CARTO, Biosense-Webster, Diamond Bar, Calif) was performed in all patients. Entrainment and activation mapping were performed to confirm the location of macroreentrant circuits or focal AT.18,19 LA access was obtained by transseptal puncture; all patients received systemic anticoagulation to maintain activated clotting time 300 to 350 seconds after LA access.

Radiofrequency ablation was performed using power applications of 30 to 40 W with a target temperature of <50°C. Successful ablation was defined as termination of the tachycardia by radiofrequency ablation and the noninducibility of any organized tachycardia with atrial programmed extrastimuli and burst pacing with and without isoproterenol.

Bipolar electrograms were filtered between 30 to 500 Hz, recorded, and stored digitally on a computerized system simultaneously with 12-lead surface ECG (Prucka CardioLab EP Systems, GE Healthcare, Piscataway, NJ).

Statistics
Data were analyzed using SAS software version 9.1 (Cary, NC). Data are expressed as proportions or mean±SD. Differences in baseline characteristics were compared using χ² tests for categorical variables and Student t tests for continuous variables. Survival curves were derived by the Kaplan–Meier method and compared using the log-rank test. All probability values were 2-tailed, and a value of P<0.05 was considered significant. Predictors of atrial arrhythmias were identified and expressed as hazard ratios with 95% confidence intervals. Univariate predictors of atrial arrhythmia were included in a final Cox multivariable proportional hazard model.

Results
The baseline characteristics of the study cohort at the time of transplantation are displayed in Table 1. Over a 20-year period, 127 post-transplant patients were followed for a

Figure 1. A, Recipient right and left pneumonectomies are performed sequentially. B, The crura between the superior and inferior PVs of the respective right and left lungs are divided to create common recipient cuffs. C, The right and left donor PVs are cross-clamped at the respective PV antra and resected as a left atrial tissue cuff. D, The donor LA-PV cuff is anastomosed to the common recipient right or left LA-PV cuff. This anastomosis may isolate donor PV tissue, but residual recipient PV tissue may be retained as part of the surgical anastomosis.
mean of 4.2±4.1 years per patient. The mean age at time of LT was 38.2±13.0 years, and 54% of patients were male. The most common indications for transplantation were cystic fibrosis (64%), idiopathic pulmonary fibrosis (9%), and chronic obstructive pulmonary disease (9%). A history of atrial arrhythmia before undergoing LT was present in 7.9% of patients. Mean left atrial diameter by echocardiography was 34.4 mm, and the mean left ventricular ejection fraction was 60.1%.

**Atrial Tachyarrhythmias**

Data regarding AAs are displayed in Figure 2. The incidence of total ATs was observed to have a bimodal distribution. A total of 40 patients (31.5%) had spontaneous AAs. The prevalence was greatest in the immediate postoperative period (n=30, 23.8%) before hospital discharge and in the first month after surgery (n=18, 13.8%). Types of AA based on 12-lead ECG at time-specific points are shown in Figure 2. The prevalence of all AAs at postoperative, 1, 3, 6, 12, and >12 months was 24%, 11%, 3%, 2%, 4%, and 11%, respectively. In the early postoperative period, AF was more common than AT (19.7% versus 5.5%). All atrial arrhythmias at >12 months were atrial tachycardia (AF, n=0 versus AT, n=11/104; 11%); interestingly, no AF occurred after 1 year.

Predictors of any AA at any time after LT are shown in Table 2. Significant predictors of arrhythmia in patients included age, male sex, and a history of AA before surgery. None of these factors predicted late arrhythmias (after 12 months) (Table 3). Neither the presence of early AF or AT (≤1 month), nor a preoperative history of AA predicted late AA.

**Management of AAs**

Among all patients with AAs, various management strategies were pursued at the discretion of the pulmonary transplant physicians (Table 4). A rate-control strategy with AV nodal–blocking agents was used in 19 patients (56%). Five patients (15%) were treated with antiarrhythmic medical therapy. Five patients (15%) underwent DC cardioversion. In 1 patient, transesophageal echocardiography before planned cardioversion showed extensive right atrial thrombus associated with a detailed evaluation of the atrial appendage and left atrial thrombus. A total of 40 patients (31.5%) had spontaneous AAs. The prevalence was greatest in the immediate postoperative period (n=30, 23.8%) before hospital discharge and in the first month after surgery (n=18, 13.8%). Types of AA based on 12-lead ECG at time-specific points are shown in Figure 2. The prevalence of all AAs at postoperative, 1, 3, 6, 12, and >12 months was 24%, 11%, 3%, 2%, 4%, and 11%, respectively. In the early postoperative period, AF was more common than AT (19.7% versus 5.5%). All atrial arrhythmias at >12 months were atrial tachycardia (AF, n=0 versus AT, n=11/104; 11%); interestingly, no AF occurred after 1 year.

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central venous catheter; operative thrombectomy was performed with restoration of SR at the time of weaning from cardiopulmonary bypass. Four patients with drug-refractory AAs were referred for EPS (Table 5).

Findings at EPS
Findings at EPS are described in Table 5 and Figure 3. Of the 4 patients referred for EPS, 1 (patient 4) was found to have typical AFL by ECG and confirmed to be cavotricuspid isthmus dependent at the time of EPS and ablation. Two patients had macroreentrant AT due to reentry in the regions of LA anastomoses as indicated by entrainment, activation, and voltage mapping (Figure 3, A and B). One of these patients (patient 1) was found to have a perimodal tachycardia circuit bounded posteriorly by the left PV anastomosis and anteriorly by the mitral annulus that defined an isthmus where ablation terminated the tachycardia (Figure 3A). Patient 2 had reentry between the left and right PV anastomoses with an isthmus at the LA roof, where ablation terminated the tachycardia (Figure 3B). Patient 3 had AT originating from the right donor PVs with evidence of atrioatrial conduction based on the presence of 2:1 conduction block (Figure 3C). Patient 3 has undergone 3 EPS/ablations; the 1st at a referring institution. At the 2nd attempt (previously reported), 2:1 AT was mapped to the left PV anastomosis with successful ablation.20 AT recurred 16 months later, and at repeat study he was found to have a new AT originating from the region of the right PV anastomosis (Figure 3C). No other ATs were inducible after ablation, and bidirectional conduction block was still present between the donor left PV cuff and the recipient atrium. All 4 patients have remained in SR since ablation, with 3 of the 4 patients off of all antiarrhythmic therapy; 1 patient remains on reduced-dose antiarrhythmic therapy without evidence of recurrence.

Discussion
This is the first and largest analysis of the epidemiology, electrophysiological mechanisms, and outcomes of AAs after LT in the adult population. AAs are common in the postoperative and early post-transplant period. However, the predominance of AF during this time is similar to the prevalence that has been reported after both cardiac and thoracic surgery.1,2 After 3 months, AAs are infrequent until 12 months, at which time some organized ATs begin to emerge. Interestingly, after 1 year, no AF was seen over an average of 4 years of follow-up after this extensive atrial surgery. Inflammation has been associated with AF, and a higher inflammatory state after surgery may explain the higher incidence of AF early but not late in our cohort.7,21

AF, AFL, and AT have been described after thoracic surgery and after LT.2,20,22–25 Left AFL has also been described after LT in the pediatric population and after orthotopic heart transplantation.25,26 The donor PV–left atrial cuff anastomosis with the recipient LA results in putative lines of conduction block that serve as potential substrate for macroreentrant tachyarrhythmia while possibly also compartmentalizing the LA to reduce the incidence of AF. LT could be viewed as the ultimate form of atrial isolation of the PVs, depending on the extent of retained recipient PV tissue. This surgical anastomosis effectively isolates the PVs of the donor but may only partially isolate the recipient PVs from the recipient LA. Consistent with this is our observation of macroreentry in the LA along surgical anastomosis lines from LT surgery. Using entrainment, activation, and voltage mapping, critical isthmuses in the tachycardia circuits were identified with resultant successful radiofrequency ablation. There was 1 patient in our study in whom conduction appeared to occur across both anatomic suture lines. This type of conduction across anastomotic suture lines has previously been reported in post–cardiac transplant patients.4,5 The mechanism of conduction across anticipated surgical lines of block is unclear, although human cardiac fibroblasts have been demonstrated to have an ability to interact electrically with cardiomyocytes through gap junctions.27

This study may provide some insights into the role of the PVs in postoperative AF. The postoperative setting is characterized by inflammation, hemodynamic stress, and electrolyte imbalances creating a complex milieu in which 30% to 40% of patients have AF. After the landmark report of Haissaguerre et al,8 it has become widely recognized that the PVs are important in the initiation and maintenance of AF. The patients in this study underwent surgical removal of the PVs at transplantation, although small amounts of residual PV ostial tissue may remain. In the long term, no patients had AF consistent with effective isolation of the PVs. Despite the surgical isolation and/or removal of most of the PV tissue, approximately 20% of patients still had postoperative AF. It has been suggested that mechanisms underlying postoperative AF are multifactorial and may include pericardial inflammation, neurohormonal imbalance, and interstitial and intravascular pressure or fluid alterations with resultant changes in atrial conduction and refractoriness. The similar prevalence of postoperative AF in our population may suggest that

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### Table 4. Management of Atrial Arrhythmias After Lung Transplantation

<table>
<thead>
<tr>
<th>Management Strategy</th>
<th>No.</th>
<th>Patients With Arrhythmia, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiofrequency ablation</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Operative management</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Electrical cardioversion</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Anti-arrhythmic medication*</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Acute rate-control therapy</td>
<td>19</td>
<td>56</td>
</tr>
</tbody>
</table>

*Vaughn-Williams class IC or class III agents.

### Table 5. Findings and Mechanisms at Electrophysiology Study

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mechanism</th>
<th>Site of Isthmus or Focal Activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Macroreentrant</td>
<td>Mitral isthmus: Left inferior PV–mitral isthmus</td>
</tr>
<tr>
<td>2</td>
<td>Macroreentrant</td>
<td>LA roof: Between right/left superior PVs</td>
</tr>
<tr>
<td>3</td>
<td>Focal</td>
<td>PVs: Left (1st EPS)20; right (2nd EPS)</td>
</tr>
<tr>
<td>4</td>
<td>Macroreentrant</td>
<td>Cavotricuspid isthmus</td>
</tr>
</tbody>
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postoperative AF is less dependent on triggers originating from the PVs than AF occurring in other contexts.

Although early AAs can be predicted with commonly associated risk factors for AF, late organized ATs are not easily predicted with commonly identified clinical characteristics. Our analysis demonstrates that these organized AAs can be successfully managed with catheter ablation when standard medical therapy has failed. This is an important management consideration in this post-transplant population that requires intensive and intricate regimens that may be further complicated by antiarrhythmic drug therapy. The relatively high incidence of late organized AAs in this population raises the possibility of evaluating whether different surgical strategies including modifications of left atrial anastomoses or even prophylactic intraoperative radiofrequency or cryoablation might reduce the occurrence of these arrhythmias. The answer to this latter question remains unanswered.

Study Limitations

Despite this being the largest series of post-LT patients analyzed for postoperative arrhythmia, this retrospective and case-control–based evaluation limits our ability to directly compare the efficacy of treatment strategies. As the definition of atrial arrhythmia was defined by review of medical records and required documentation by 12-lead ECG or telemetry tracings, it is possible that the prevalence of arrhythmia may have been underestimated.

These data support the feasibility of SR restoration using a catheter ablation strategy that is determined by mechanisms at EPS. However, the limited number of patients treated by catheter ablation raises interesting mechanistic and therapeutic questions but do not yet allow for definitive recommendations regarding operative or ablation approaches at the time of or after LT. Larger populations would enhance the statistical power of our analyses. Continued future analyses of post-LT patients will allow for better elucidation of the underlying pathophysiology and substrate of left atrial macroreentrant tachycardias beyond the 4 patients we have described.

Conclusion

Although AF is common in the early post-LT period, organized ATs but not AF are observed in long-term follow-up. Clinical factors including age and prior AA predicted postoperative AF as reported after cardiac or thoracic surgery. EPS has defined potential mechanisms of late ATs. Three of 4 patients were found to have AT originating from the LA, whereas 1 patient was found to have typical cavotricuspid isthmus–dependent AFL. Mechanisms of left atrial tachycardia included macroreentry involving lines of conduction block associated with...
surgical anastomoses and focal tachycardia arising from PV anastomoses. This study further demonstrates that catheter ablation with both targeted ablation and modification of left atrial substrate is a potentially curative strategy in this population. Although this population is a relatively small and specific one, observations from our data provide insights relating to spontaneous and postoperative AF, as well as, mechanisms of left AT after effective isolation of the PVs.

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Disclosures
None.

References
Atrial arrhythmias after cardiothoracic surgery occur frequently, at rates of ≈20% to 50%. Multiple studies have demonstrated the significance of the pulmonary veins in the pathogenesis of atrial fibrillation. Bilateral lung transplantation requires left atrial incisions that may represent the ultimate form of antral pulmonary vein isolation, depending on the extent of retained recipient pulmonary vein tissue. In a single-center cohort of bilateral lung transplant patients, atrial arrhythmias occurred in 31.5% of patients over 4 years. Atrial fibrillation dominated early arrhythmia prevalence (24%). All arrhythmias past 1 year were organized atrial tachycardias (11%). Recipient age, male sex, and preoperative arrhythmia history predicted early but not late atrial arrhythmia. Various therapies, including catheter ablation for drug-refractory arrhythmia, were used. Electrophysiology study defined potential mechanisms including (1) macroreentry involving lines of conduction block at surgical anastomoses and (2) focal atrial tachycardia with recovered pulmonary vein–left atrial conduction. Catheter ablation restored sinus rhythm in all who underwent electrophysiology study. Similar rates of postoperative fibrillation but absence of late atrial fibrillation suggest that atrial fibrillation after cardiothoracic surgery probably has multifactorial mechanisms less dependent on pulmonary vein activity. Successful ablation of macroreentrant circuits defined by transplant anastomoses raises the possibility that substrate modification at transplantation may modify atrial tachycardia occurrence. Recovered pulmonary vein–left atrial conduction across suture lines raises questions regarding mechanisms of electric “reconnection” described after cardiac transplantation and pulmonary vein isolation. Although conclusions are limited by this small, retrospective study, these data provide mechanistic and therapeutic insights relating to atrial fibrillation and atrial tachycardia.
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