Contemporary analysis of incidence of post-operative atrial fibrillation, its predictors, and association with clinical outcomes in lung transplantation

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BACKGROUND: Atrial fibrillation (AF) is a common complication after lung transplantation (LT). Since the lung allocation score (LAS) was implemented in 2005, there has been significant evolution in the practice of LT, necessitating re-evaluation of this arrhythmia.

METHODS: One hundred thirty-one patients undergoing LT between January 2011 and April 2013 were reviewed retrospectively to assess the occurrence of AF and its outcomes (mortality, morbidity measures, treatment strategies). Uni- and multivariate logistic regression models were constructed to ascertain predictors of AF.

RESULTS: Forty-six patients (35.1%) developed post-operative AF at 4.65 ± 3.68 days post-LT. The AF group was older (60.07 vs 54.48 years, $p = 0.01$), and had higher rates of cardiopulmonary bypass (CPB) (73.33% vs 43.53%, $p = 0.001$). There was no difference in mortality, ICU length of stay (LOS) and ventilator days; however, the AF group had a significantly higher mean hospital LOS by 8.43 days (17.09 vs 25.52, $p = 0.04$). Age (OR = 1.04, $p = 0.03$) and CPB (OR = 3.68, $p = 0.002$) were identified as predictors of AF by stepwise logistic regression after adjusting for gender, history of AF, type of LT, pulmonary hypertension and LT indication. In the AF group, 78.26% of patients required combination therapy. Anti-arrhythmics were used in 52.17% of patients. Dofetilide/ibutilide use was not associated with increased mortality. A total of 97.82% were in sinus rhythm at discharge.

CONCLUSIONS: To our knowledge, this is the first study to examine post-operative AF exclusively in the post-LAS era. Incidence of AF after LT is 35%. It increases hospital LOS, but not mortality. Management of AF is challenging and dofetilide/ibutilide serve as effective adjuncts to current therapy.

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The expansive growth in the field of lung transplantation (LT) has led to increased emphasis on improving post-transplant outcomes. Atrial tachyarrhythmia, most commonly atrial fibrillation (AF), is a highly prevalent post-operative complication with reported rates of about 17% to 45%.[1–8] Data

regarding significance of post-operative AF are conflicting. Although some studies have reported post-operative AF to be transient and relatively benign,[1,6] others reported increased short- or long-term all-cause mortality.[2,3,8] Advanced age, pre-transplant diagnosis of idiopathic pulmonary fibrosis, use of bilateral LT and post-transplant complications, such as mediastinitis and airway dehiscence, have been identified as risk factors for AF in those studies.[1–5,8] However, most of the reports addressed LT populations from the 1990s and early 2000s. There have been some noteworthy changes in the practice of LT over the past decade. Since the implementation of the lung allocation score (LAS) in 2005, increasing numbers of LT recipients have demonstrated the aforementioned "risk factors," such as advanced age, diagnosis of pulmonary fibrosis, bilateral LT and higher acuity.[9,10] Unfortunately, treatment of this entity is challenging and there are no guidelines for managing post-operative AF in LT recipients.[1,2] There are concerns regarding safety of amiodarone use, as it may be independently associated with higher mortality in LT recipients.[3,8,11] At our center, we have been using dofetilide and ibutilide successfully for AF. There are no current data reporting the use of these agents after LT. Hence, in this study we sought to assess the incidence of post-operative AF after LT in the contemporary era and to ascertain its predictors and association with adverse clinical outcomes. In addition, we aimed to examine the use of these newer agents in managing post-operative AF.

Methods

Study population

Institutional review board approval was obtained for our investigation. Informed consent was waived. We reviewed the electronic medical records of all patients >16 years of age who underwent single or bilateral LT at the University of Texas Southwestern (UTSW) Medical Center, Dallas, Texas, between January 2011 and April 2013. Patients who had multi-organ transplants or died intra-operatively during transplantation were excluded from the study. LT recipients were stratified into two groups: those who had episode(s) of post-operative AF (AF group) and those without AF (non-AF group). All patients were treated with standard triple immunosuppression, predominately tacrolimus, azathioprine and prednisone. Basiliximab was used for induction if LT surgery was done with cardiopulmonary bypass (CPB). A few patients received cyclosporine and/or mycophenolate mofetil.

Clinical variables

Various demographic, clinical, operative and outcome variables were extracted from the electronic medical records. Baseline characteristics recorded included age, race, gender, history of AF, indication for LT and pulmonary hypertension (PH). Operative notes were reviewed to obtain details of transplant including date, type of transplant, use of CPB and intra-operative complications.

Outcome variables

The primary outcome variable was determined as an episode of post-operative AF. It was defined as the earliest clinical documentation of AF after transplant surgery, either prior to discharge or within 30 days of LT, whichever was earlier. No patient was in chronic AF at the time of surgery. For those with a prior history of AF, new-onset AF with a rapid ventricular rate of >100 beats/minute was counted as a new episode. Time to first episode of AF was calculated as the number of days from the date of transplantation to the date of first documentation of AF. The secondary outcome variables extracted were: (i) all-cause mortality during the observation period; (ii) ventilator days, defined as interval between LT surgery and extubation; (iii) length of stay in the intensive care unit (ICU LOS) after transplant surgery; (iv) length of stay in the hospital (hospital LOS) for the LT encounter; (v) treatment options; (vi) discharge disposition, defined as discharge home versus to a rehabilitation facility; and (vii) subsequent hospitalizations in the 12 months after LT. Treatment strategies were divided into rate control (beta-blockers, calcium-channel blockers, digoxin), anti-arrhythmics (amiodarone, dofetilide, ibutilide) and cardioversion. To assess the association of type of anti-arrhythmic agent used with clinical outcomes, the AF group was stratified by the anti-arrhythmic used (amiodarone vs dofetilide/ibutilide).

Statistical analyses

Summary statistics were used to characterize the distribution of the data. Differences in baseline characteristics between groups were compared using the chi-square test for categorical variables and Student's t-test for continuous variables. Log-rank and Kaplan–Meier tests were used to compare survival between groups. Stepwise logistic regression analysis was conducted including variables with $p \leq 0.2$ in univariate analyses to explore peri-transplant characteristics that predicted occurrence of AF. Finally, univariate analysis was performed to analyze between-group differences in the AF group stratified by the choice of anti-arrhythmic used using the analysis of variance (ANOVA) test, Student's t-test or chi-square test. Two-tailed $p < 0.05$ was considered significant.

Results

One hundred thirty-seven transplants were performed at UTSW during the observation period. Derivation of the sample size is shown in Figure 1. The remaining 131 patients were divided into an AF group and a non-AF group.

Baseline characteristics of the study population are shown in Table 1. Mean age of the population was 56.45 ± 13.38 years. Interstitial lung disease (ILD) was the most common indication for transplantation, accounting for 55.91% of all transplants, followed by chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF) and idiopathic PH in 28.35%, 9.45% and 6.3%, respectively. There was no difference in gender, race, smoking history or indication for transplantation between the AF and non-AF groups. In comparison with the non-AF group, the AF group was older (60.07 vs 54.48 years, $p = 0.01$) and had higher rates of CPB (73.33% vs 43.53%, $p = 0.001$). Six of the 131 patients had a history of AF. Of these, 4 patients developed post-operative AF and 2 did not, but this difference was not statistically significant.

Of the 131 patients, 46 (35.11%) had post-operative AF. Time to occurrence of post-operative AF was 4.65 ± 3.68