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Practicality and Safety of Electrical Pulmonary Vein Isolation and Left Atrial Appendage Ligation in Lung Transplant Recipients With Pretransplant Atrial Fibrillation

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Background. Lung transplant surgery creates surgical pulmonary vein isolation (PVI) as a routine part of the procedure. However, many patients with pretransplant atrial fibrillation continue to have atrial fibrillation at 1 y. We hypothesized that the addition of electrical PVI and left atrial appendage isolation/ligation (LAL) to the lung transplant procedure restores sinus rhythm at 1 y in patients with pretransplant atrial fibrillation. **Methods.** We retrospectively reviewed all adult lung transplant recipients at the University of California Los Angeles from April 2006 to August 2021. All patients with pretransplant atrial fibrillation underwent concomitant PVI/LAL and were compared with lung transplant recipients without preoperative atrial fibrillation. In-hospital outcomes; 1-y survival; and the incidence of stroke, cardiac readmissions, repeat ablations, and sinus rhythm (composite endpoint) were examined at 1 y for the PVI/LAL cohort. **Results.** Sixty-one lung transplant recipients with pretransplant atrial fibrillation underwent concomitant PVI/LAL. No patient in the PVI/LAL cohort required cardiac-related readmission or catheter ablation for atrial fibrillation within 1 y of transplantation. Freedom from the composite endpoint of death, stroke, cardiac readmission, and repeat ablation for atrial fibrillation at 1 y was 85% (95% confidence interval, 73%-92%) for lung transplant recipients treated with PVI/LAL. **Conclusions.** The addition of PVI/LAI to the lung transplant operation in patients with pretransplant atrial fibrillation was safe and effective in maintaining sinus rhythm and baseline risk of stroke at 1 y.

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Atrial fibrillation is common in older patients, especially those with pulmonary impairment, and many require oral anticoagulation to reduce the risk of ischemic stroke.[1-3] In patients with a history of atrial fibrillation who undergo cardiac surgery, concomitant occlusion of the left atrial appendage has been shown to reduce the risk of ischemic strokes and systemic embolic events.[4] Moreover, the addition of pulmonary vein isolation (PVI) to left atrial appendage ligation (LAL) during cardiac surgical procedures has been associated with restoration of regular rhythm in a significant proportion of patients with atrial fibrillation.[5-7]

There is an increasing number of patients with end-stage lung diseases being referred to lung transplantation with higher acuity and multiple comorbidities, such as advanced age, diastolic and systolic heart dysfunction, and structural heart disease. Atrial fibrillation is frequently observed in this patient population before referral or during the evaluation and listing phase. In a cohort of 235 lung transplant recipients, 16.2% had pretransplant atrial fibrillation. This group had a higher incidence of postoperative atrial fibrillation, longer postoperative length of stay, and greater number of days spent in the hospital in the first year after transplantation.[8]

The lung transplant procedure creates a surgical incision at the base of the right and left pulmonary veins, leading to electrical isolation. This procedure provides a unique opportunity and open access to left atrial tissue and appendage. The

role of the addition of electrical isolation of left atrial tissue and ligation of the left atrial appendage to the lung transplant procedure in candidates with pretransplant atrial fibrillation is not known. The main purpose of this study was to assess the practicality, feasibility, and safety of this concomitant procedure in lung transplant patients and to characterize overall outcomes at the 1-y follow-up.

MATERIALS AND METHODS

Study Population and Procedure

The Institutional Review Board at the University of California, Los Angeles, approved this cohort study. We conducted a retrospective review of all adult lung transplants performed at our institution from April 2006 to August 2021. In April 2006, we started performing PVI/LAL in all lung transplant candidates with pretransplant atrial fibrillation. All patients had persistent or chronic pretransplant atrial fibrillation. Patients with pretransplant atrial fibrillation were treated with PVI using a radiofrequency clamp device (Atricure Inc, Mason, OH). The procedure involved the application of the Atricure Clamp to the left atrial tissue 5 times until the device detected electrical isolation. Electrical isolation of the left atrial appendage was performed similarly, followed by ligation of the left atrial appendage. Transesophageal echocardiography was used to confirm LAL intraoperatively. Double lung transplants were performed on cardiopulmonary bypass with bilateral PVI and LAL. Single lung transplants were performed with posterolateral thoracotomy, with right lung transplants receiving isolated unilateral PVI and left lung transplants receiving PVI and LAL when technically feasible. Episodes of atrial fibrillation were treated similarly in all patients with beta-blockade, amiodarone, and anticoagulants if lasting for >48 h.

The entire group of lung transplant recipients was used to compare baseline. This control group was selected following a discussion with the institutional review board at our institution to minimize harm to patients.

Baseline Characteristics

The baseline characteristics of donors and recipients were collected and compared between the PVI/LAL group and the control groups. Recipient variables included age, gender, race, height, weight, body mass index, blood type, diagnosis group as characterized by the Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients (groups A: obstructive lung disease, B: pulmonary vascular disease, C: cystic fibrosis and immunodeficiency disorders, and D: restrictive lung diseases), lung allocation score, diabetes, hypertension, history of smoking, prior lung transplant, hemoglobin, albumin, creatinine, 6-min walk distance, oxygen requirement, hemodynamic measurements, left ventricular ejection fraction, ischemic time, cardiopulmonary bypass utilization and times, double versus single lung, and LAL. Donor characteristics included age, gender, race, blood type, history of drug abuse, hypertension, and history of smoking.

Outcomes

All perioperative and postoperative endpoints were characterized for the PVI/LAL cohort. Postoperative atrial fibrillation at the index hospitalization was defined as episodes of atrial fibrillation requiring additional management with beta-blockers, antiarrhythmics, anticoagulation, or cardioversion. Atrial fibrillation at 1 y was defined as the presence of atrial fibrillation on an electrocardiogram or a monitoring test closest to the 1 y posttransplant follow-up visit. Freedom from death, stroke, cardiac readmissions, and need for additional ablations for atrial fibrillation within 1 y was examined as a composite outcome in the PVI/LAL group.

Statistical Analysis

Categorical variables were reported as numbers (percentages) and compared with the chi-square test or Fisher exact test if >25% of the expected values were <5. Continuous variables were reported as mean ± SD and compared with the *t* test if they were normally distributed. Otherwise, they were reported as medians (interquartile ranges) and compared with the Wilcoxon rank-sum test. Freedom from the composite outcome was examined with the Kaplan-Meier method. All statistical analyses were performed with Stata version 15.1 (College Station, TX) and 2-tailed *P* values <0.05 were considered significant.

RESULTS

Of 757 lung transplants performed during the study period, 61 patients (8%) had pretransplant atrial fibrillation and underwent PVI/LAL. LAL was performed in 53 patients (87%) receiving PVI. Recipients in the PVI/LAL group were significantly older (63 [57–67] versus 61 [52–66] y, $P = 0.02$), taller (173 ± 9 versus 169 ± 10 cm, $P < 0.01$), weighed more (77 ± 15 versus 73 ± 16 kg, $P = 0.04$), had higher creatinine (0.9 ± 0.3 versus 0.8 ± 0.3 mg/dL, $P = 0.03$), and were more likely diagnosis group A (13 [23%] versus 103 [15%], $P < 0.01$) and group B (7 [11%] versus 25 [4%], $P < 0.01$), when compared with the remaining lung transplant control group, although these differences may not be biologically or clinically significant. There were no significant differences in the proportion of hypertension, diabetes, and smoking history. In addition, waitlist duration (54 [17–152] versus 42 [17–237] d, $P = 0.92$) and lung allocation score (44 [37–58] versus 41 [35–53], $P = 0.54$; Table 1). Donor characteristics were also similar between the PVI/LAL and the control groups (Table 2). A greater proportion of the PVI/LAL cohort had unilateral left lung transplants than the control group (34% versus 25%, $P = 0.03$; Table 3). However, utilization of cardiopulmonary bypass, bypass times, and ischemia times was not significantly different between the 2 groups.

Perioperative outcomes for the PVI/LAL group are displayed in Table 4. Postoperative atrial fibrillation was observed in 48% (29) of the PVI/LAL cohort. Of the 61 patients, 97% (59) of the group survived to discharge, with 87% (53) having normal sinus rhythm at discharge. The rates of reexploration, tracheostomy, and grade 3 primary graft dysfunction at 72 h were 10%, 11%, and 13%, respectively. Intensive care unit length of stay was 6 (4–8) d, whereas the total length of stay was 14 (11–20) d. Furthermore, beta-blockers and amiodarone were prescribed at the time of discharge in 67% (41) and 33% (20) of the patients who received PVI/LAL, respectively. Two (3%) of the lung transplant recipients in the PVI/LAL group were in atrial fibrillation at their 1-y follow-up visit, as shown in Table 5. Stroke was not observed within 1 y in the PVI/LAL group. In

TABLE 1.
Recipient baseline characteristics

	Total lung transplant cohort (N = 696)	Pretransplant atrial fibrillation treated with PVI/LAL cohort (N = 61)	*P*
Age	61 (52–66)	63 (57–67)	0.02
Male	415 (60)	40 (66)	0.36
Race			
Other	34 (5)	5 (8)	
White	434 (62)	42 (69)	
Hispanic	188 (27)	10 (16)	0.21
Black	40 (6)	4 (7)	
Height, cm	169 ± 10	173 ± 9	<0.01
Weight, kg	73 ± 16	77 ± 15	0.04
BMI	25 ± 4	26 ± 4	0.53
Blood type			
O	356 (51)	32 (52)	
A	224 (32)	17 (28)	
B	78 (11)	7 (11)	0.78
AB	38 (5)	5 (8)	
Diagnosis group			
A	103 (15)	13 (23)	
B	25 (4)	7 (11)	
C	34 (5)	0 (0)	<0.01
D	533 (77)	40 (66)	
LAS	44 (37–58)	41 (35–53)	0.54
Waitlist duration, d	54 (17–152)	42 (17–237)	0.92
ECMO	39 (6)	5 (8)	0.41
Diabetes	162 (23)	14 (23)	0.95
HTN	242 (35)	28 (46)	0.09
HLD	248 (36)	21 (34)	0.83
GERD	293 (42)	21 (34)	0.24
Aspergillus/MAC	89 (13)	4 (7)	0.15
CMV	441 (63)	42 (69)	0.39
HBV	28 (4)	1 (2)	0.35
Smoker	323 (47)	33 (56)	0.17
Prior lung Tx	32 (5)	0 (0)	0.09
Hgb	13 ± 12	13 ± 12	0.94
Hct	39 ± 10	38 ± 8	0.85
Prealb	4 ± 0.5	4 ± 0.3	0.35
AST	22 (18–27)	23 (17–28)	0.92
ALT	17 (12–24)	19 (14–26)	0.16
Alk P	71 (57–88)	70 (52–88)	0.42
Creatinine	0.8 ± 0.3	0.9 ± 0.3	0.03
6-Min walk, feet	393 (196–734)	406 (219–787)	0.29

Alk P, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CMV, cytomegalovirus; ECMO, extracorporeal membrane oxygenation; GERD, gastroesophageal reflux disease; HBV, hepatitis B virus; Hct, haematocrit; Hgb, haemoglobin; HLD, hyperlipidemia; HTN, hypertension; LAL, left atrial appendage ligation; LAS, lung allocation score; MAC, mycobacterium-avium complex; Prealb, prealbumin; PVI, pulmonary vein isolation; Tx, transplantation.

addition, 6 patients (10%) from the PVI/LAL cohort were on antiarrhythmic drugs, whereas 12 (20%) of those were on anticoagulation medication 1 y after the lung transplant. No patient in the PVI/LAL cohort required cardiac-related readmission or catheter ablation for atrial fibrillation within 1 y of transplantation. Freedom from the composite endpoint of death, stroke, cardiac readmission, and repeat ablation for atrial fibrillation at 1 y was 85% (95% confidence interval, 73%-92%) for the lung transplant recipients treated with PVI/LAL (Figure 1).

TABLE 2.
Donor characteristics

	Total lung transplant cohort (N = 696)	Pretransplant atrial fibrillation treated with PVI/LAL cohort (N = 61)	*P*
Age	37 ± 14	37 ± 15	0.45
Male	445 (65)	43 (72)	0.28
Race			
Other	58 (8)	3 (5)	
White	288 (42)	29 (48)	0.15
Hispanic	269 (39)	22 (37)	
Black	74 (11)	6 (10)	
Blood type			
O	369 (54)	36 (60)	
A	215 (31)	17 (28)	0.80
B	89 (13)	6 (10)	
AB	16 (2)	1 (2)	
Done drug abuse	286 (42)	22 (38)	0.51
HTN	177 (26)	13 (22)	0.49
Smoking	275 (45)	27 (47)	0.72
Steroids	576 (84)	51 (86)	0.63

HTN, hypertension; PVI/LAL, pulmonary vein ablation/left atrial appendage isolation/ligation.

TABLE 3.
Operative characteristics

	Total lung transplant chort (N = 696)	Pretransplant atrial fibrillation treated with PVI/LAL cohort (N = 61)	*P*
Double lung	367 (53)	36 (59)	0.03
Left lung	173 (25)	21 (34)	
Right lung	156 (22)	4 (7)	
Left atrial appendage ligation	14 (2)	53 (87)	<0.01
Cardiopulmonary bypass (Y/N)	444 (65)	41 (70)	0.45
Bypass time, min	118 ± 103	124 ± 90	0.65
Ischemia time, min	277 ± 87	288 ± 106	0.33

PVI/LAL, pulmonary vein ablation/left atrial appendage isolation/ligation.

DISCUSSION

This study suggests that the addition of electrical PVI and LAL to lung transplant procedures can be performed safely. The duration of surgery, transfusion requirements, and early postoperative outcomes were similar between lung transplant recipients with pretransplant atrial fibrillation who required PVI/LAL and those who did not. Moreover, electrical PVI and LAL were effective in the restoration of sinus rhythm at 1 y in lung transplant recipients with preexisting atrial fibrillation and were not associated with stroke or cardiac-related readmissions.

Postoperative atrial fibrillation is a common occurrence after lung transplantation and has been the subject of multiple reports in the past 2 decades.[7-9] In contrast, late atrial fibrillation, which is usually seen in patients with pre–lung transplant atrial fibrillation, is less studied and can adversely impact the posttransplant course and outcomes. Addition of anticoagulation to the immunosuppressive regimen of post–lung transplant recipients with late atrial fibrillation can complicate the care because of the need for biopsies and drug–drug

TABLE 4.

In-hospital outcomes

	Pretransplant atrial fibrillation treated with PVI/LAL cohort (N = 61)
Postoperative atrial fibrillation	29 (48)
PGD3 at 72 h	8 (13)
Tracheostomy	7 (11)
Reexploration	6 (10)
Survived to discharge	59 (97)
ICU LOS	6 (4–8)
Hospital LOS	14 (11–20)
NSR at discharge	53 (87)
Discharge meds	
Beta-blocker	41 (67)
Amiodarone	20 (33)
Coumadin	14 (23)
NOAC	0 (0)
Lovenox	6 (10)
Diltiazem	2 (3)
Digoxin	2 (3)
Other antiarrhythmic	3 (5)

ICU, intensive care unit; LOS, length of stay; meds, medications; NOAC, non-vitamin K antagonist oral anticoagulant; NSR, normal sinus rhythm; PGD3, primary graft dysfunction, grade 3; PVI/LAL, pulmonary vein ablation/left atrial appendage isolation/ligation.

TABLE 5.

One-year outcomes of the PVI/LAL cohort

	Pretransplant atrial fibrillation treated with PVI/LAL cohort (N = 61)
Survival	52 (85)
Atrial fibrillation	2 (3)
Stroke	0 (0)
Cardiac readmission	1 (2)
Catheter ablation	0 (0)
Medications	
Anticoagulation	12 (20)
Antiarrhythmic	6 (10)
Beta-blocker	34 (56)

PVI/LAL, pulmonary vein ablation/left atrial appendage isolation/ligation.

interactions.[10-18] Yersai et al[8] showed that patients with preexistent atrial fibrillation who undergo lung transplantation have prolonged hospital stays and have more readmissions in the first posttransplant year. Therefore, it is ideal to address this during the lung transplant procedure to minimize the risk of recurrence of late atrial fibrillation and related sequelae.

In lung transplant surgery, the pulmonary veins of the recipient are transected and sewn to the left atrial cuff of the donor lungs. This procedure represents the ultimate PVI as part of the Cox-Maze procedure. Interestingly, patients with pretransplant atrial fibrillation who undergo lung transplantation do not uniformly return to normal sinus rhythm. Hussein et al[19] found that 19.4% of bilateral lung transplant recipients and 25% of double lung transplant recipients with preexistent atrial fibrillation remained in atrial fibrillation at 1 y. This observation suggests that PVI, as practiced in lung transplant procedures, is insufficient to eradicate atrial fibrillation in all patients. The authors concluded that left atrial substrate and proven pulmonary venous conduction recovery across surgical suture lines may play important roles in the recurrence and maintenance of atrial fibrillation posttransplantation.

Lung transplantation presents a unique opportunity to address the atrial substrate and left atrial appendage. Application of radiofrequency clamp to more proximal left atrial tissue can lead to an additional line of electrical ablation that may address the left atrial substrate and possible pulmonary vein conduction recovery. Moreover, the electrical isolation of the base and ligation of the left atrial appendage can be performed expeditiously with relative technical ease and minimal additional morbidity during bilateral and left single lung transplantation to minimize the risk of left atrial appendage clot formation and embolization. This study shows that these procedures during the index lung transplant procedure may lead to restoration of sinus rhythm at 1 y and may be performed safely, without any added complication burden to the operation. Moreover, freedom from cerebrovascular accidents and cardiac-related readmissions further supports the benefits of restoration of sinus rhythm. The downside of additional procedures during the lung transplant procedure includes the extra time and effort during an "urgent/emergent" operation; however, this was not associated with a statistically significant increase

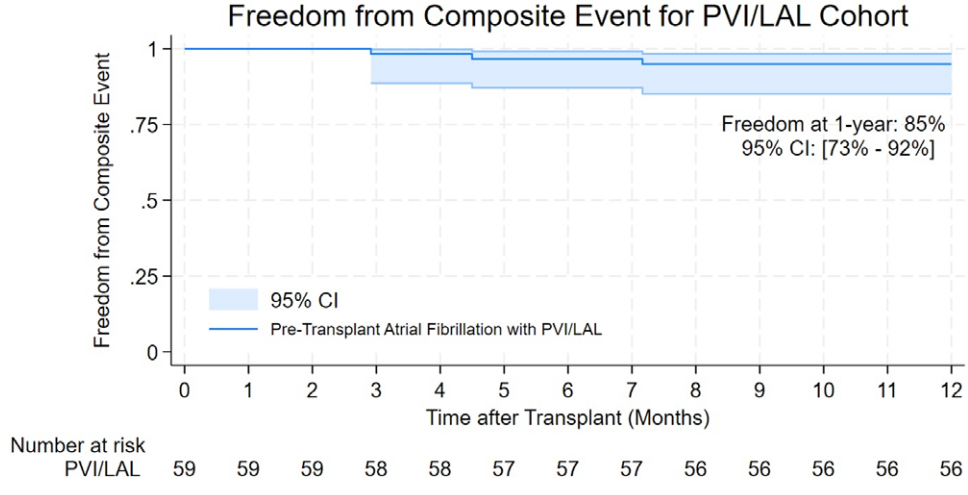

FIGURE 1. Kaplan-Meier survival estimate showing freedom from the composite event of pretransplant atrial fibrillation treated with PVI/LAL. CI, confidence interval; PVI/LAL, pulmonary vein ablation/left atrial appendage isolation/ligation. *Composite events: death, stroke, cardiac-related admission, cardiac ablation.

in cardiopulmonary bypass time, total operative time, or ischemia times in our study.

This study has several limitations. The proper control group for patients with pretransplant atrial fibrillation who underwent PVI/LAL would be a cohort of patients with pretransplant atrial fibrillation who did not undergo PVI/LAL. However, this control group is not available for comparison purposes. Hence, our control group was a cohort of lung transplant candidates without pretransplant atrial fibrillation, a group that is at lower risk of postoperative adverse events. The findings of this study that patients with pretransplant atrial fibrillation who undergo PVI/LAL have a low incidence of postoperative complications is indeed encouraging. This is also an observational study, with all its inherent limitations, such as residual confounding and inability to infer causality. Although we were able to capture the 1-y rhythm assessment, we were unable to capture the full burden of atrial fibrillation in the first transplant year, such as episodes and duration of paroxysmal atrial fibrillation, nor were we able to discriminate the type of atrial fibrillation at the 1-y follow-up (paroxysmal versus persistent versus permanent). Furthermore, patients in our study did not undergo a full electrophysiologic study or electroanatomic mapping. Therefore, we were unable to determine the origin of pre- or posttransplant arrhythmias. Future studies should use a full electrophysiologic assessment to better describe the impact of PVI/LAL on the lung transplant operation.

The results of this study expand on the current literature and suggest that the addition of electrical PVI and LAL in lung transplant recipients with preexistent atrial fibrillation can be done safely and will yield acceptable clinical outcomes.

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