Esophageal aperistalsis and lung transplant: Recovery of peristalsis after transplant is associated with improved long-term outcomes

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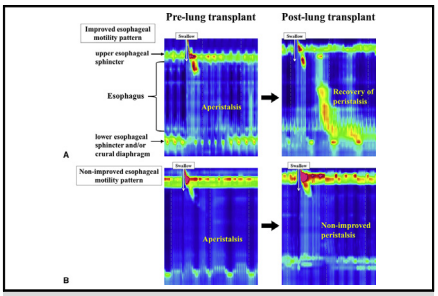
ABSTRACT

Objective: Esophageal aperistalsis has been considered a relative contraindication for lung transplant because of a higher risk of allograft dysfunction secondary to reflux and aspiration induced by poor esophageal clearance. We previously reported that esophageal motility improves in some patients after lung transplant. We reviewed the clinical course of lung transplant recipients diagnosed with an aperistaltic esophagus on pretransplant testing.

Methods: We identified patients diagnosed with pretransplant aperistaltic esophagus on high-resolution manometry who underwent lung transplant. Recipients with normal esophageal motility before lung transplant were used as the propensity score–matched control group. High-resolution manometry was repeated after lung transplant, and patients with aperistalsis were further divided into 2 subgroups: improved esophageal peristalsis and nonimproved peristalsis (ie, persistent aperistalsis after lung transplant).

Results: Esophageal aperistalsis was seen in 31 patients (mean age, 59.0 years; 21 men). The 1-, 3-, and 5-year post–lung transplant survivals in the aperistalsis group were 80.6%, 51.2%, and 34.9%, respectively, which was significantly lower than in the control group (90.3%, 73.4%, and 58.8%, respectively; $P = .038$). Post–lung transplant high-resolution manometry was performed for 29 patients in the aperistalsis group, 19 of whom demonstrated improved esophageal motility (65.5%). The 1-, 3-, and 5-year survivals after lung transplant of patients with recovery of peristalsis were similar to those of the control group (89.5%, 65.0%, and 48.8%, respectively; $P = 1.000$), whereas the nonimproved peristalsis group had lower survival (80.0%, 36.0%, and data unavailable, respectively; $P = .012$).

Conclusions: Esophageal aperistalsis is not necessarily a contraindication for lung transplant. Improved peristalsis can be expected in up to two-thirds of these patients and is associated with good outcomes. (J Thorac Cardiovasc Surg 2020;160:1613-26)



Esophageal pressure topography. Improved (A) and nonimproved (B) peristalsis before and after LTx.2

CENTRAL MESSAGE

We found that esophageal aperistalsis is not necessarily a contraindication for LTx. Improved peristalsis can be expected in up to two-thirds of these patients after LTx.

PERSPECTIVE

Esophageal aperistalsis has been considered a relative contraindication for LTx because of a higher risk of allograft dysfunction. However, improved motility with good outcomes can be expected in up to two-thirds of these patients. Outcomes are significantly worse in patients whose esophageal motility does not improve post-LTx.

See Commentaries on pages 1627, 1628, 1629, and 1630.

Gastroesophageal reflux disease (GERD) is a common condition in lung transplant (LTx) candidates.[1-5] Previous clinical and experimental studies have revealed that GERD is a potential risk for chronic lung allograft dysfunction (CLAD) after LTx, known as ''bronchiolitis obliterans syndrome'' (BOS) and ''restrictive allograft

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Abbreviations and Acronyms

ACR = acute cellular rejection
AMR = antibody-mediated rejection
BOS = bronchiolitis obliterans syndrome
CLAD = chronic lung allograft dysfunction
DCI = distal contractile integral
EGJ = esophagogastric junction
GERD = gastroesophageal reflux disease
HRM = high-resolution manometry
ISHLT = International Society for Heart and Lung Transplantation
LES = lower esophageal sphincter
LTx = lung transplant

syndrome."[6] This is thought to be due to chronic aspiration[7-9] in patients with GERD, even when they are treated with intensive anti-acid therapy.[10] As a nonalloimmune risk for allograft injury, GERD is best treated at this time only by early surgical intervention (ie, fundoplication) after LTx.[11] However, fundoplication is not usually offered to patients with poor esophageal clearance (ie, patients diagnosed with an aperistaltic esophagus), because they have a high possibility of postfundoplication dysphagia. Although poor esophageal bolus transit is the single largest risk for both exacerbating GERD and recurrent aspiration,[12] the best treatment strategy for this condition remains undefined. Therefore, esophageal aperistalsis has been considered a relative contraindication for LTx. The clinical course of LTx recipients diagnosed with an aperistaltic esophagus (based on pre-LTx evaluation) has not been reported.

We previously demonstrated that esophageal motility improves in some patients after LTx, including those with aperistalsis.[5] Hypothetically, short- and long-term outcomes can be improved in patients diagnosed with pre-LTx esophageal aperistalsis if those patients experience recovery of peristalsis after LTx. The aim of this study is to explore the clinical course of LTx recipients diagnosed with an aperistaltic esophagus on pretransplant testing and to assess the impact of esophageal peristaltic improvement on LTx outcomes in these patients.

MATERIALS AND METHODS

All patients who undergo LTx at our institution are entered into a prospectively maintained database. We attempt pre- and post-LTx foregut function tests, including high-resolution manometry (HRM), 24-hour pH testing, endoscopy, and gastric-emptying studies for all patients whenever clinically possible. Aperistaltic esophagus is not considered as an absolute contraindication for LTx at our institution, regardless of whether these patients have significant GERD. Preoperative cardiac assessment was also conducted using an echocardiogram and cardiac catheterization within 6 months before LTx.

After Institutional Review Board approval (PHXB-18-500-259-73-18), we queried our database to identify patients who underwent LTx between January 2013 and December 2016. Of these, patients who were diagnosed with esophageal aperistalsis based on pretransplant HRM were selected for the study group. We excluded patients who had undergone previous LTx. The Institutional Review Board waived the need for informed consent for this study.

LTx recipients who were preoperatively diagnosed with normal esophageal motility were also identified (regardless of whether they had normal motility after LTx). We then established a 1-to-1 propensity score–matched control group, which was balanced with patients in the aperistaltic esophagus group based on 13 measured baseline characteristics: (1) age; (2) sex; (3) body mass index; (4) type of underlying lung disease (ie, obstructive lung disease, pulmonary hypertension, cystic fibrosis, or restrictive lung disease); (5) lung allocation score; (6) type of LTx (ie, bilateral or unilateral); (7) diabetes mellitus; (8) systemic hypertension; (9) mean pulmonary artery pressure; (10) pulmonary capillary wedge pressure; (11) cardiac output; (12) cardiac index; and (13) graft ischemic time. Underlying pulmonary disease was classified using United Network for Organ Sharing criteria: obstructive lung disease (United Network for Organ Sharing criteria Group A), pulmonary hypertension (Group B), cystic fibrosis (Group C), or restrictive lung disease (Group D).

After LTx, esophageal motility was again assessed using HRM if clinically possible. In the aperistalsis group, patients were further divided into 2 subgroups based on post-LTx changes in manometric results: patients with improved esophageal peristalsis (ie, patients diagnosed with some propulsive peristalsis based on postoperative HRM; Figure 1, *A*) and patients with persistent aperistalsis post-LTx (Figure 1, *B*).

High-Resolution Manometry

HRM was performed with a 36-channel catheter with circumferential solid-state pressure transducers placed at 1-cm intervals (Given Imaging, Los Angeles, Calif). Most investigations were conducted within 6 months before and within 6 months after LTx. All studies were interpreted using ManoView ESO software version 3.3 (Given Imaging) by a single author (TM) unless the data were unavailable for analysis. The pressure topography of ten 5-mL water swallows were assessed.

Each swallow was classified into 1 of 3 contractile patterns: effective contractile vigor (ie, distal contractile integral [DCI] $\geq$450 mm Hg $\cdot$ s $\cdot$ cm), weak peristalsis (ie, DCI 100-450 mm Hg $\cdot$ s $\cdot$ cm), and failed peristalsis (DCI $<$100 mm Hg $\cdot$ s $\cdot$ cm). Esophageal body motility in each patient was then categorized according to the following criteria:

1. Effective esophageal motility: $\geq$60% effective contractile vigor.
2. Aperistaltic esophagus: $\geq$90% failed swallows without any effective peristalsis.
3. Marginal esophageal motility: did not satisfy the criteria for effective esophageal motility or for aperistaltic esophagus.

Diagnostic criteria of normal esophageal motility based on Chicago classification v3.0[13] were applied to select the control cohort before matching (ie, adequate lower esophageal sphincter [LES] relaxation during swallow and $\geq$60% normal deglutitive peristalsis, which is characterized as DCI 450 to 8000 mm Hg $\cdot$ s $\cdot$ cm without a 5-cm or greater large break on the esophageal body pressure topography).

24-Hour pH Monitoring

Pre- and post-LTx ambulatory esophageal pH monitoring were performed using a catheter-based system (Sandhill Scientific Inc, Highlands Ranch, Colo) or a wireless probe (Bravo; Medtronic, Minneapolis, Minn) within 1 week before or after HRM. The catheter-based pH probe was passed transnasally and positioned 5 cm above the upper border of the manometrically defined LES. The capsule

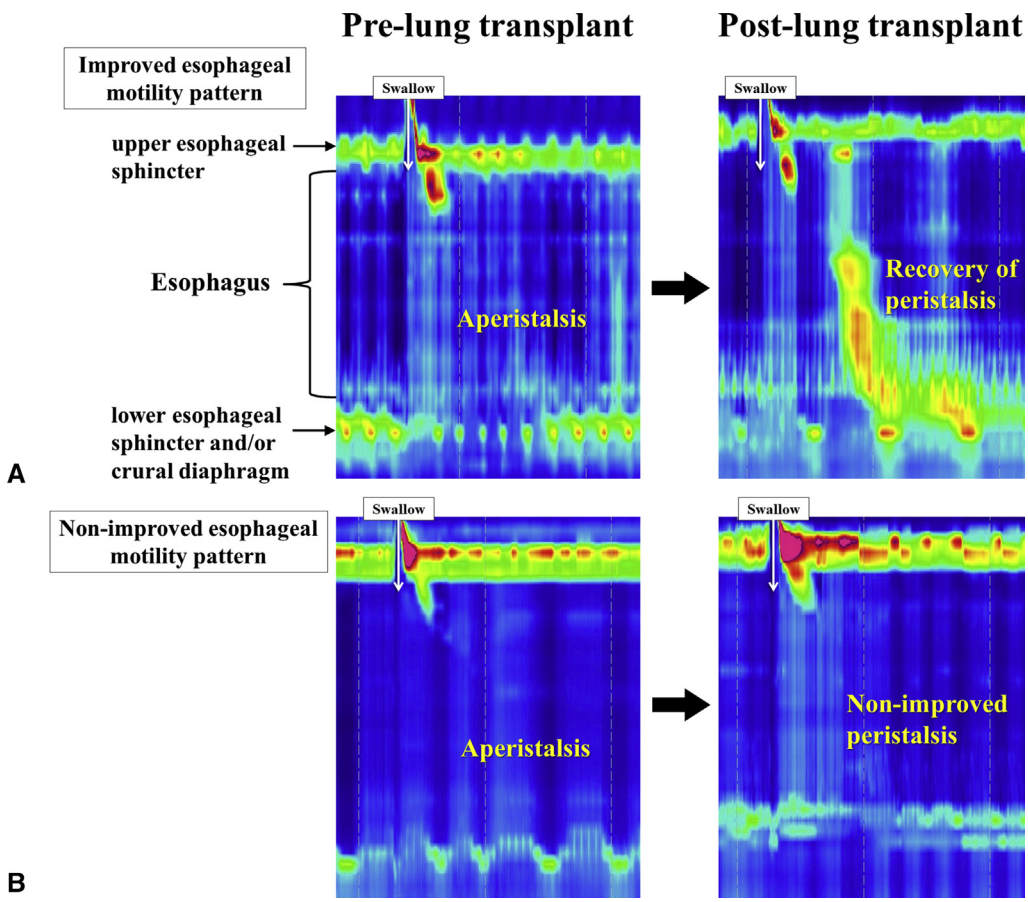

FIGURE 1. Esophageal pressure topography before and after LTx. A, Improved peristalsis group. Esophageal body peristalsis was not depicted before LTx, but normal deglutitive peristalsis was seen after transplant. B, Nonimproved peristalsis group. Esophageal body peristalsis was not depicted before LTx, and the same image was seen after transplant.

was passed transorally and positioned 6 cm above the gastroesophageal junction under endoscopic guidance. For the capsule-based system, the DeMeester score was calculated as the mean of scores gathered over 2 days. A DeMeester score greater than 14.72 signified pathological reflux.

Post-Transplant Management

A dual gastrojejunal tube was placed at the time of LTx for patients diagnosed with esophageal aperistalsis. The gastrostomy was left on drainage, and feeds were given via jejunal port. Oral feeding was withheld in most patients until post-transplant foregut function testing was completed, which was performed as early as possible post-transplant (usually within 2 to 3 months).

Postoperative Immunosuppressive Regimen

All LTx recipients received a uniform immunosuppressive regimen, regardless of the presence of esophageal aperistalsis. Induction therapy included methylprednisolone before perfusion of the lung allografts, with interleukin-2 receptor antagonists (ie, basiliximab) or anti-CD20 monoclonal antibody (ie, rituximab) in combination with intravenous immunoglobulin. Maintenance immunosuppression consisted of triple drug therapy with a steroid, mycophenolate mofetil, and tacrolimus.

Postoperative Pulmonary Function Follow-up

Pulmonary function surveillance after LTx was conducted with clinic-based spirometry every 2 to 3 weeks in the first 6 months, every 4 weeks in the next 6 months to 2 years, and every 3 to 6 months thereafter. Additional pulmonary function tests were obtained if the patient's condition appeared to be deteriorating.

Definition of Lung Allograft Rejection and Chronic Lung Allograft Dysfunction

Graft rejection was defined as an episode of acute cellular rejection (ACR) or antibody-mediated rejection (AMR) and classified on the basis of International Society for Heart and Lung Transplantation (ISHLT) guidelines.[14,15] CLAD was considered an irreversible decline in forced expiratory volume in 1 second of greater than 20% from the baseline, which is the same as the conventional definition of BOS based on ISHLT criteria.[16] Sato and colleagues[6] reported that a subset of patients diagnosed with BOS based on the classic criteria includes CLAD with restrictive pulmonary derangement, restrictive allograft syndrome (ie, forced expiratory volume in 1 second/forced vital capacity ratio >0.7). Therefore, we preferred to use the term "CLAD" as opposed to BOS in this study. CLAD was considered to be advanced if patients satisfied the classic BOS guideline stage 2 or greater.[16] We assessed prevalence of graft rejection within 1 year of LTx, prevalence of recurrent graft rejection

TABLE 1. Pretransplant baseline characteristics in patients diagnosed with absent esophageal motility and normal esophageal motility

	Aperistalsis group N = 31	Control group N = 31	Standardized difference	*P* value
Age, y*	60.0 (52.0-67.0)	59.0 (55.0-67.0)	0.020	.94
Sex (M:F)	21:10	19:12	0.135	.60
BMI, kg/m^2*	28.1 (24.4-31.0)	26.4 (25.0-31.2)	0.079	.85
UNOS group†			0.131	1.00
Group A; obstructive lung disease	7 (22.6%)	8 (25.8%)		
Group B; pulmonary hypertension	3 (9.7%)	2 (6.5%)		
Group C; cystic fibrosis	0	0		
Group D; restrictive lung disease	21 (67.7%)	21 (67.7%)		
LAS†	39.8 (34.7-53.9)	39.0 (35.1-51.0)	0.046	.96
Type of LTx†			0.000	1.00
Bilateral transplantation	30 (96.8%)	30 (96.8%)		
Unilateral transplantation	1 (3.2%)	1 (3.2%)		
Diabetes†	6 (19.4%)	4 (12.9%)	0.176	.49
Hypertension†	10 (32.3%)	12 (38.7%)	0.135	.60
Mean PAP, mm Hg*	27.0 (23.0-39.0)	26.0 (22.0-32.0)	0.161	.54
PCWP, mm Hg*	10.0 (7.0-14.0)	8.0 (6.0-14.0)	0.149	.46
Cardiac output, L/min*	5.4 (4.5-6.0)	5.6 (4.6-6.0)	0.062	.91
Cardiac index, L/min/m^2*	2.7 (2.4-3.2)	2.6 (2.4-3.3)	0.048	.69
Graft ischemic time, min*	288.0 (252.0-326.0)	274.0 (213.0-325.0)	0.195	.51

BMI, Body mass index; *UNOS*, United Network for Organ Sharing; *LAS*, lung allocation score; *LTx*, lung transplant; *PAP*, pulmonary artery pressure; *PCWP*, pulmonary capillary wedge pressure. *Values expressed as median (interquartile range [IQR]). †Values expressed as number (%).

(≥2 episodes) during the follow-up period, rejection-free survival, CLAD-free survival, and advanced-stage CLAD-free survival between groups.

Statistical Analysis

All statistical analyses were performed using SPSS version 22.0.0.0 (IBM SPSS Statistics; Armonk, NY) and R version 3.5.1 with "Matching" and "stddiff" packages (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are expressed as median with interquartile range.

Propensity score matching was performed using a logistic regression model with nearest-neighbor method without replacement. Selection of the 1-to-1 matched control patients was processed through randomized fashion in patients with normal esophageal motility pre-LTx. Covariate balance in the matched 2 groups was assessed on a standardized difference in each baseline characteristic. An absolute standardized difference greater than 0.20 was considered to be a meaningful imbalance between the 2 groups (ie, the Cohen's cutoff value of a small effect size).

Differences in categoric variables between the matched groups were assessed using the chi-square or Fisher exact test. The Mann–Whitney *U* test was used to compare continuous variables between groups. Changes in categoric variables between pre- and post-LTx in each individual were assessed using the McNemar's test or McNemar-Bowker test, and continuous variables between pre- and post-LTx were compared by Wilcoxon signed-rank test. Cumulative survivals for overall survival, rejection-free survival, CLAD-free survival, and advanced-stage CLAD-free survival were calculated using the Kaplan–Meier method. The log-rank test was used to compare survival rates between groups. A *P* value for the subgroups' survival analysis was adjusted using the Bonferroni method.

RESULTS

In total, 346 patients underwent LTx at our institution during the study period. Pre-LTx esophageal aperistalsis was seen in 32 patients. Of these, 1 patient who had a history of LTx was excluded from analysis, and the study criteria were satisfied in 31 patients. Mean age was 59.0 ± 9.9 years, and there were 21 men. A connective tissue disorder was seen in 7 patients (5 patients with systemic sclerosis and 2 with rheumatoid arthritis). Twenty-one patients were diagnosed with restrictive lung disease, 7 patients were diagnosed with obstructive lung disease, and 3 patients were diagnosed with pulmonary hypertension. No patient underwent antireflux surgery before LTx; however, 4 patients underwent antireflux procedures after LTx (Roux-en-Y gastric bypass for 2 patients, Nissen fundoplication for 1 patient, and Toupet fundoplication for 1 patient).

The control group was developed from 117 LTx recipients diagnosed with normal esophageal motility based on pre-LTx HRM. We excluded 2 patients who had undergone previous LTx, and the remaining 115 patients were used for 1-to-1 propensity score matching analysis. A *c*-statistic was 0.78 (95% confidence interval, 0.68-0.87; $P < .001$) statistically verifying our selection of variables. All 31 patients diagnosed with aperistalsis were

TABLE 2. Esophageal function tests before and after lung transplant

	Before LTx			After LTx		
	Aperistalsis group N = 31	Control group N = 31	*P* value	Aperistalsis group N = 31	Control group N = 31	*P* value
24-h pH study	N = 30	N = 28		N = 26	N = 29	
DeMeester score*	12.8 (3.8-36.0)	7.3 (1.4-18.8)	**.020**	13.7 (5.8-44.3)	9.0 (1.7-25.1)	.18
Abnormal DeMeester score†	14 (46.7%)	9 (32.1%)	.26	13 (50.0%)	9 (31.0%)	.15
% time pH <4, %*	3.7 (1.0-9.4)	1.6 (0.2-5.3)	**.019**	3.3 (1.2-9.6)	2.1 (0.3-7.4)	.13
No. of reflux episodes*	62.2 (20.8-94.3)	20.2 (7.8-83.0)	**.043**	39.9 (26.0-111.8)	43.6 (14.0-77.7)	.58
No. of long (>5 min) reflux episodes*	1.2 (0.0-4.3)	0.6 (0.0-2.4)	.17	2.3 (0.0-5.2)	0.0 (0.0-3.0)	.075
Longest reflux time, min*	7.2 (3.3-20.3)	5.1 (0.8-9.6)	**.031**	12.5 (5.0-49.5)	4.2 (1.2-7.8)	**.031**
HRM	N = 31	N = 31		N = 29	N = 29	
Esophageal body motility†						
Effective esophageal motility	0	31 (100.0%)	**<.001**	10 (34.5%)‡	25 (86.2%)	**<.001**
Marginal esophageal motility	0	0		9 (31.0%)‡	4 (13.8%)	
Aperistaltic esophagus	31 (100.0%)	0		10 (34.5%)§	0	
EGJ antireflux competency						
Manometric hiatal hernia	6 (19.4%)	7 (22.6%)	.76	8 (27.6%)	4 (13.8%)	.20
LES pressure, mm Hg*	23.3 (13.9-35.8)	31.2 (16.6-38.3)	.27	27.2 (14.0-43.5)	34.0 (24.3-43.1)‡	.18
Overall LES length, cm*	3.1 (2.3-3.8)	3.2 (2.4-3.9)	.60	3.3 (2.5-3.8)	3.5 (3.0-4.0)	.65
Intra-abdominal LES length, cm*	2.5 (1.9-2.9)	2.5 (1.2-2.9)	.87	2.4 (1.3-3.3)	2.7 (2.0-3.2)	.79
Gastric-emptying study	N = 24	N = 23		N = 25	N = 28	
Delayed gastric emptying	3 (12.5%)	1 (4.3%)	.32	8 (32.0%)	5 (17.9%)	.23

LTx, Lung transplant, *HRM*, high-resolution manometry; *EGJ*, esophagogastric junction; *LES*, lower esophageal sphincter. *Values expressed as median (IQR). Values in bold indicate statistical significance. †Values expressed as number (%). ‡$P < .01$. §$P < .001$ compared between pre- and post-LTx in each individual.

completely matched to patients diagnosed with normal motility, satisfying the threshold of acceptable balance (ie, absolute standardized mean difference between the 2 cohorts <0.20) throughout the 13 baseline characteristics. Baseline variables in the 2 groups (ie, aperistaltic esophagus group [n = 31] and matched control group [n = 31]) are summarized in Table 1. In the matched control group, no patient had a connective tissue disorder, and fundoplication was performed in 1 patient before LTx (Nissen fundoplication) and in 5 patients after LTx (Toupet fundoplication for 3 patients and Nissen fundoplication for 2 patients).

Foregut Function Tests

The outcomes of the ambulatory pH study and HRM are summarized in Table 2. Before LTx, there were significant differences in pH study between the aperistalsis group and the matched control group in terms of DeMeester score, total acid exposure time, and number of reflux episodes (12.8 vs 7.3, $P = .020$; 3.7% vs 1.6%, $P = .019$; and 62.2 vs 20.2, $P = .043$, respectively). However, these differences dropped below the threshold for statistical significance after LTx, although duration of longest reflux was persistently prolonged in the aperistaltic group in comparison with the control group across before and after LTx.

Manometric parameters for antireflux competency on the esophagogastric junction (EGJ) (ie, existence of manometric hiatal hernia, LES pressure, overall LES length, and intra-abdominal LES length) were similar between the aperistalsis group and the control group at the time of both pre- and post-LTx evaluation. Approximately 65% of patients in the aperistalsis group showed a significant improvement of esophageal body motility after LTx.

Inadequate deglutitive LES relaxation was noted in 6 patients based on HRM evaluation before or after LTx, which satisfied the diagnostic criteria for EGJ outflow obstruction (based on Chicago classification v3.0). However, none of these patients had clinical evidence of EGJ obstruction based on upper endoscopy or esophagram. Therefore, we performed no foregut intervention (eg, balloon dilation or myotomy) in these patients pre- or post-LTx.

We also assessed patients' gastric-emptying studies before and after LTx. The prevalence of delayed gastric emptying was increased after LTx in both groups (Table 2). Higher incidence of delayed gastric emptying was noted in the aperistalsis group compared with the control group both pre- and post-LTx, although it did not reach statistical significance (pre-LTx, 12.5% vs 4.3%, $P = .321$; post-LTx, 32.0% vs 17.9%, $P = .232$, respectively).

Survival Analysis

In total, 16 of 31 patients (51.6%) in the aperistalsis group have died during the follow-up period (up to

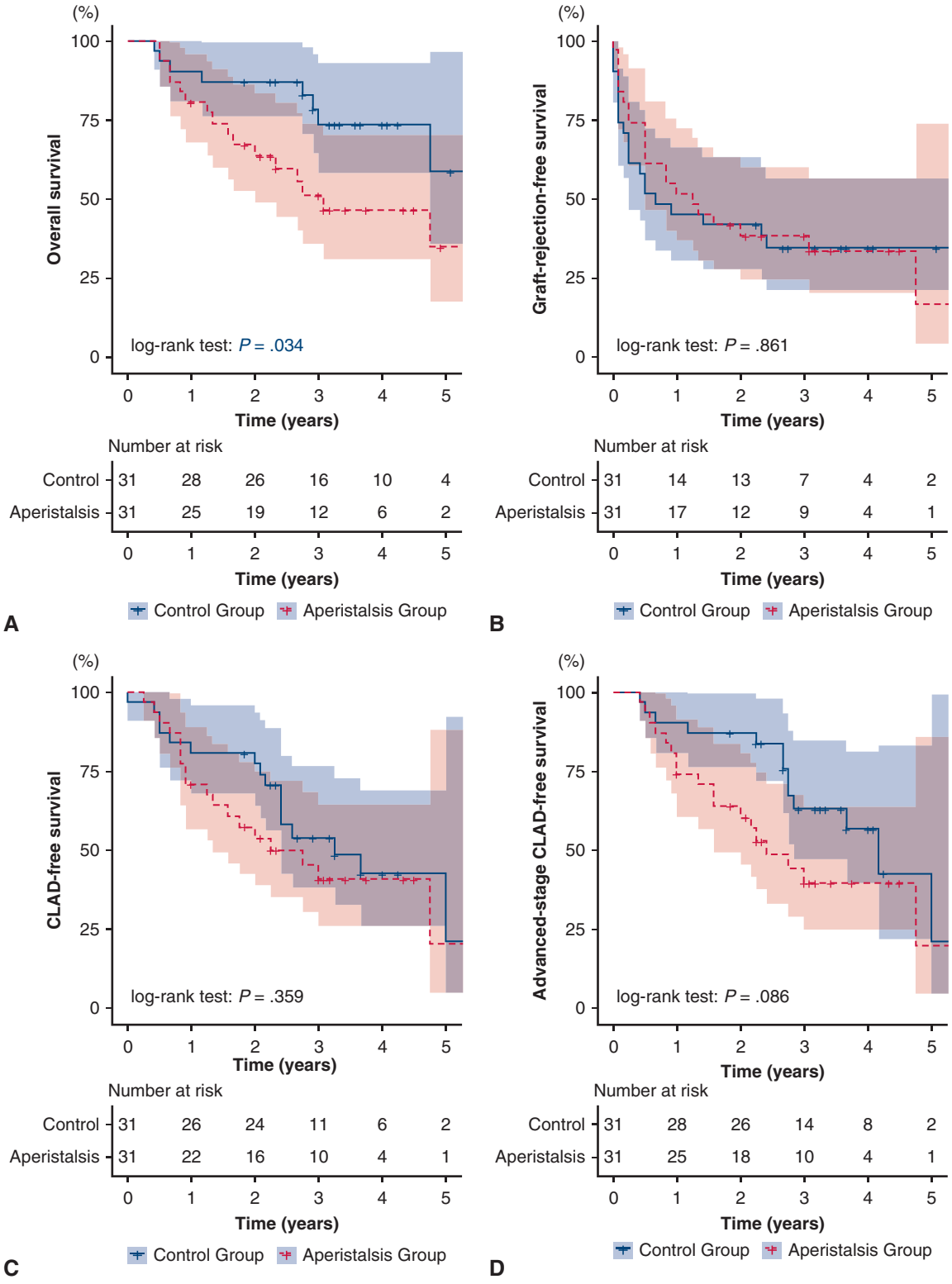

FIGURE 2. Kaplan–Meier curve for (A) overall survival, (B) rejection-free survival, (C) CLAD-free survival, and (D) advanced-stage CLAD-free survival between the aperistalsis group and the control group. *CLAD*, Chronic lung allograft dysfunction.

TABLE 3. Pretransplant baseline characteristics in the subgroups

	Nonimproved peristalsis group N = 10	Improved peristalsis group N = 19	*P* value
Age, y*	54.5 (48.0-58.0)	65.0 (59.0-68.0)	**.012**
Sex (M:F)	6:4	14:5	.36
BMI, kg/m^2*	29.9 (26.5-31.4)	28.0 (24.3-29.8)	.21
UNOS group†			.093
Group A: obstructive lung disease	0	7 (36.8%)	
Group B: pulmonary hypertension	1 (10.0%)	2 (10.5%)	
Group C: cystic fibrosis	0	0	
Group D: restrictive lung disease	9 (90.0%)	10 (52.6%)	
LAS†	39.8 (36.6-44.9)	36.1 (33.3-55.7)	.46
Type of LTx†			.66
Bilateral transplantation	10 (100.0%)	18 (94.7%)	
Unilateral transplantation	0	1 (5.3%)	
Diabetes†	3 (30.0%)	3 (15.8%)	.33
Hypertension†	4 (40.0%)	5 (26.3%)	.36
Mean PAP, mm Hg*	29.0 (25.0-41.0)	27.0 (18.0-33.0)	.27
PCWP, mm Hg*	9.5 (7.0-15.0)	12.0 (8.0-14.0)	.70
Cardiac output, L/min*	5.5 (4.6-6.0)	5.3 (4.5-6.0)	.95
Cardiac index, L/min/m^2*	2.8 (2.6-3.4)	2.7 (2.4-3.2)	.70
Graft ischemic time, min*	281.0 (252.0-328.0)	293.0 (267.0-326.0)	.46

BMI, Body mass index; *UNOS*, United Network for Organ Sharing; *LAS*, lung allocation score; *LTx*, lung transplant; *PAP*, pulmonary artery pressure; *PCWP*, pulmonary capillary wedge pressure; . *Values expressed as number (%). †Values expressed as median (IQR). Values in bold indicate statistical significance.

5.6 years). The causes of these deaths were respiratory failure (ie, CLAD and ACR) in 9 patients (56.3%), sepsis in 3 patients (18.8%), renal failure in 2 patients (12.5%), skin cancer in 1 patient (6.3%), and gastrointestinal bleeding in 1 patient (6.3%). Median survival time was 3.1 years in the aperistalsis group, and this variable cannot be assessed yet in the matched control group because more than half of patients (58.8%) have survived for a follow-up period of up to 5.6 years. Kaplan–Meier curves for 1-, 3-, and 5-year post-LTx survivals in the aperistalsis group were 80.6%, 51.2%, and 34.9%, respectively, and was significantly lower than those in the control group (90.3%, 73.4%, and 58.8%, respectively; log-rank test $P = .034$, Figure 2, *A*). No statistical difference was observed between patients in the aperistalsis group and those in the control group in terms of the prevalence of graft rejection within 1 year after LTx and the prevalence of recurrent graft rejection (38.7% [12/31] vs 45.2% [14/31], $P = .607$; 12.9% [4/31] vs 22.6% [7/31], $P = .319$, respectively). The time-dependent probability of rejection-free survival, CLAD-free survival, and advanced-stage CLAD-free survival did not show a significant difference between the groups (Figure 2, *B-D*), although CLAD-free survival appeared to be lower in the aperistalsis group in approximately the first 2 to 3 years after LTx.

Subgroup Analysis

In the aperistalsis group, 29 of 31 patients underwent HRM as a part of post-LTx follow-up. In this cohort, 19 patients (65.5%) demonstrated improved esophageal motility after LTx (improved peristalsis group, Figure 1, *A*), although 10 patients (34.5%) showed persistent aperistalsis (nonimproved peristalsis group, Figure 1, *B*). In the nonimproved peristalsis group, 4 of 10 patients (40.0%) had connective tissue disease (all 4 patients had systemic sclerosis). However, in the improved peristalsis group, 2 of 19 patients (10.5%) had connective tissue disease (1 patient had systemic sclerosis, 1 patient had rheumatoid arthritis). Pre-LTx baseline characteristics in the 2 subgroups are summarized in Table 3. Patients in the nonimproved peristalsis group were significantly younger than those in the improved peristalsis group (54.5 vs 65.0 years, $P = .012$). No patient diagnosed with obstructive lung disease was in the nonimproved peristalsis cohort.

Table 4 shows the results of post-LTx foregut function tests in the subgroups. The 24-hour pH study demonstrated that patients in the nonimproved peristalsis group had greater than 2 times higher values than those in the improved peristalsis group in terms of DeMeester score, total acid exposure time, number of acid reflux episodes, and longest acid reflux time, although these values were not

TABLE 4. Esophageal function tests after lung transplant

	Nonimproved peristalsis group N = 10	Improved peristalsis group N = 19	*P* value
24-h pH study	N = 9	N = 17	
DeMeester score*	25.6 (5.9-40.6)	11.2 (3.9-44.3)	.71
Abnormal DeMeester score†	6 (66.7%)	7 (41.2%)	.21
% time pH <4, %*	6.3 (1.6-8.6)	3.0 (1.2-9.6)	.75
No. of reflux episodes*	63.2 (36.9-111.8)	36.5 (22.2-77.6)	.26
No. of long (>5 min) reflux episodes*	3.4 (1.1-5.5)	2.2 (0.0-3.2)	.26
Longest reflux time, min*	18.8 (5.1-20.0)	8.3 (3.2-49.6)	.92
HRM	N = 10	N = 19	
Esophageal body motility†			
Effective esophageal motility	-	10 (52.6%)	**<.001**
Marginal esophageal motility	-	9 (47.4%)	
Aperistaltic esophagus	10 (100.0%)	-	
EGJ antireflux competency			
Manometric hiatal hernia	3 (30.0%)	5 (26.3%)	.58
LES pressure, mm Hg*	23.7 (12.5-37.9)	29.8 (14.0-46.5)	.38
Overall LES length, cm*	3.2 (2.2-3.6)	3.3 (3.0-4.0)	.27
Intra-abdominal LES length, cm*	2.2 (1.3-3.3)	2.9 (1.1-3.5)	.51
Gastric-emptying study	N = 10	N = 15	
Delayed gastric emptying	4 (40.0%)	4 (26.7%)	.39

HRM, High-resolution manometry; *EGJ*, esophagogastric junction; *LES*, lower esophageal sphincter. *Values expressed as number (%). †Values expressed as median (IQR). Values in bold indicate statistical significance.

statistically significant. Manometric antireflux parameters of the EGJ were comparable between the 2 cohorts. In the improved peristalsis group, effective esophageal body motility was noted in one-half of the patients.

Survival Analysis for Subgroups

Survival analysis using Kaplan–Meier method was performed to compare between each subgroup and the control group (Figure 3). Median survival time was 2.3 years in the nonimproved peristalsis group and 4.8 years in the improved peristalsis group. Figure 3, *A*, depicts 1-, 2-, and 3-year post-LTx survivals in the nonimproved peristalsis group: 80.0%, 60.0%, and 36.0%, respectively, and no patient was followed for longer than 3.4 years in this group. The overall survival in the nonimproved peristalsis group was significantly lower compared with the control group (pairwise log-rank test, $P = .012$). On the other hand, patients in the improved peristalsis group had reasonable outcomes (overall survival for 1 year: 89.5%; 2 years: 72.3%; 3 years: 65.0%; 4 years: 65.0%; and 5 years: 48.8%) that were not statistically different from outcomes of patients in the control group.

The cumulative probability of rejection-free survival was similar among the 3 groups (Figure 3, *B*). In the improved peristalsis group, CLAD-free and advanced-stage CLAD-free survivals were comparable to those in patients in the control group (Figure 3, *C* and *D*); however, in the nonimproved peristalsis group, these outcomes appeared to be inferior (though not significant in CLAD-free survival) compared with patients in the control group, and this difference was more profound in regard to advanced-stage CLAD-free survival ($P = .045$).

DISCUSSION

This study demonstrates that esophageal motility can improve after LTx, even in patients diagnosed with an aperistaltic esophagus before LTx. Post-transplant recovery of esophageal motility was seen in 65% of recipients in patients diagnosed with aperistaltic esophagus before LTx. The patients who showed improved motility post-LTx had comparable survival to patients in the control group, that is, patients diagnosed with normal esophageal motility based on pre-LTx HRM. On the other hand, an inferior outcome was evident in patients who showed persistent aperistalsis after LTx, with 3-year overall survival of 36.0%, contributing to a worse 5-year survival of 34.9% in the whole aperistalsis group (Figures 2, *A*, and 3, *A*). The outline of our findings is depicted in Figure 4. To the best of our knowledge, this is the first study investigating the short- and long-term outcomes of LTx recipients diagnosed with an aperistaltic esophagus on pretransplant testing.

According to the 2017 ISHLT registry, survival of patients who underwent primary bilateral LTx between 1990 and 2015 (n = 34,141) were 82% at 1 year, 69% at 3 years, and 59% at 5 years,[17] which is similar to those outcomes in the presented control cohort (1 year: 90.3%; 3 years: 73.4%; and 5 years: 58.8%). Various risks for

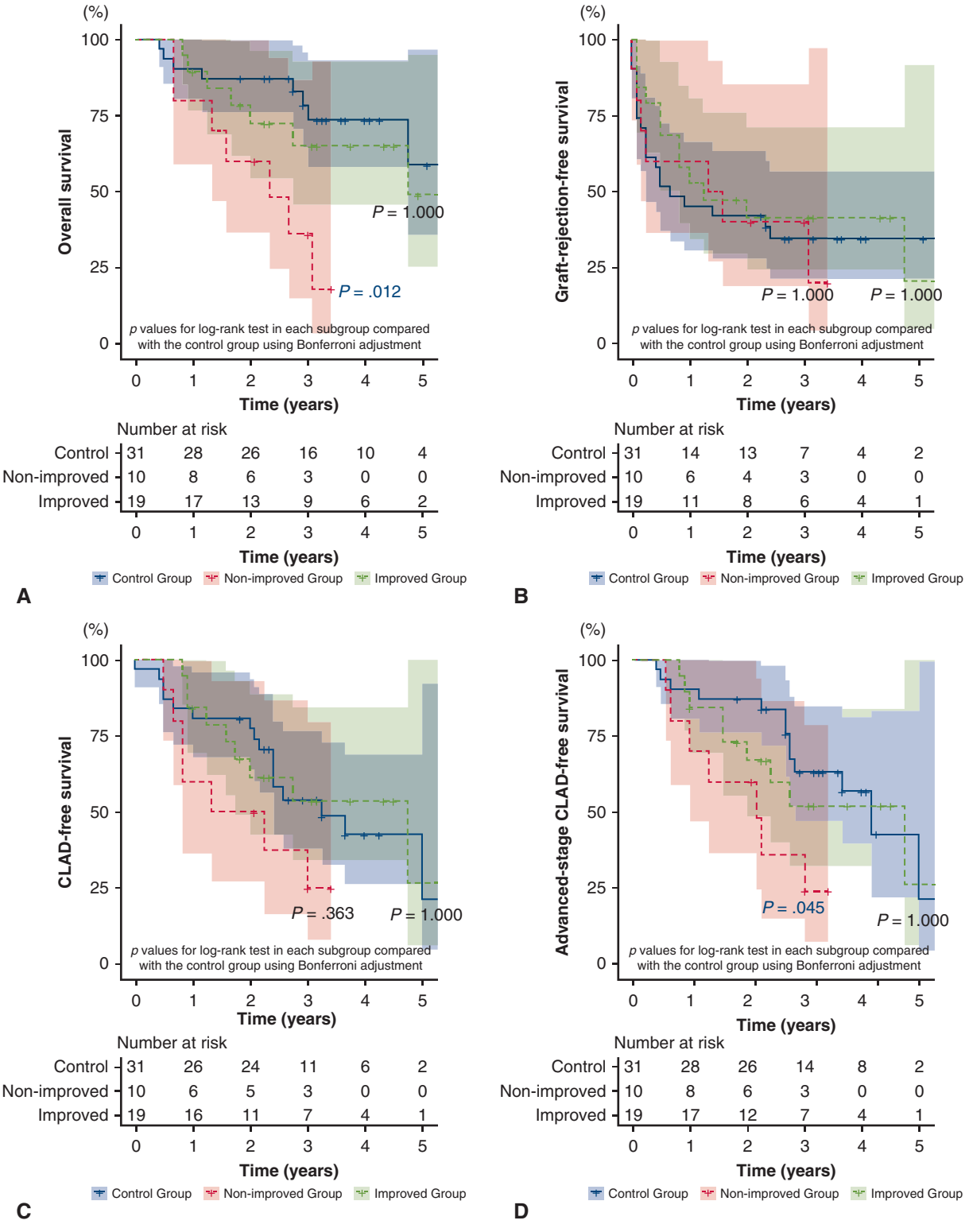

FIGURE 3. Kaplan–Meier curve for (A) overall survival, (B) rejection-free survival, (C) CLAD-free survival, and (D) advanced-stage CLAD-free survival in the nonimproved peristalsis group, improved peristalsis group, and control group. *CLAD*, Chronic lung allograft dysfunction.

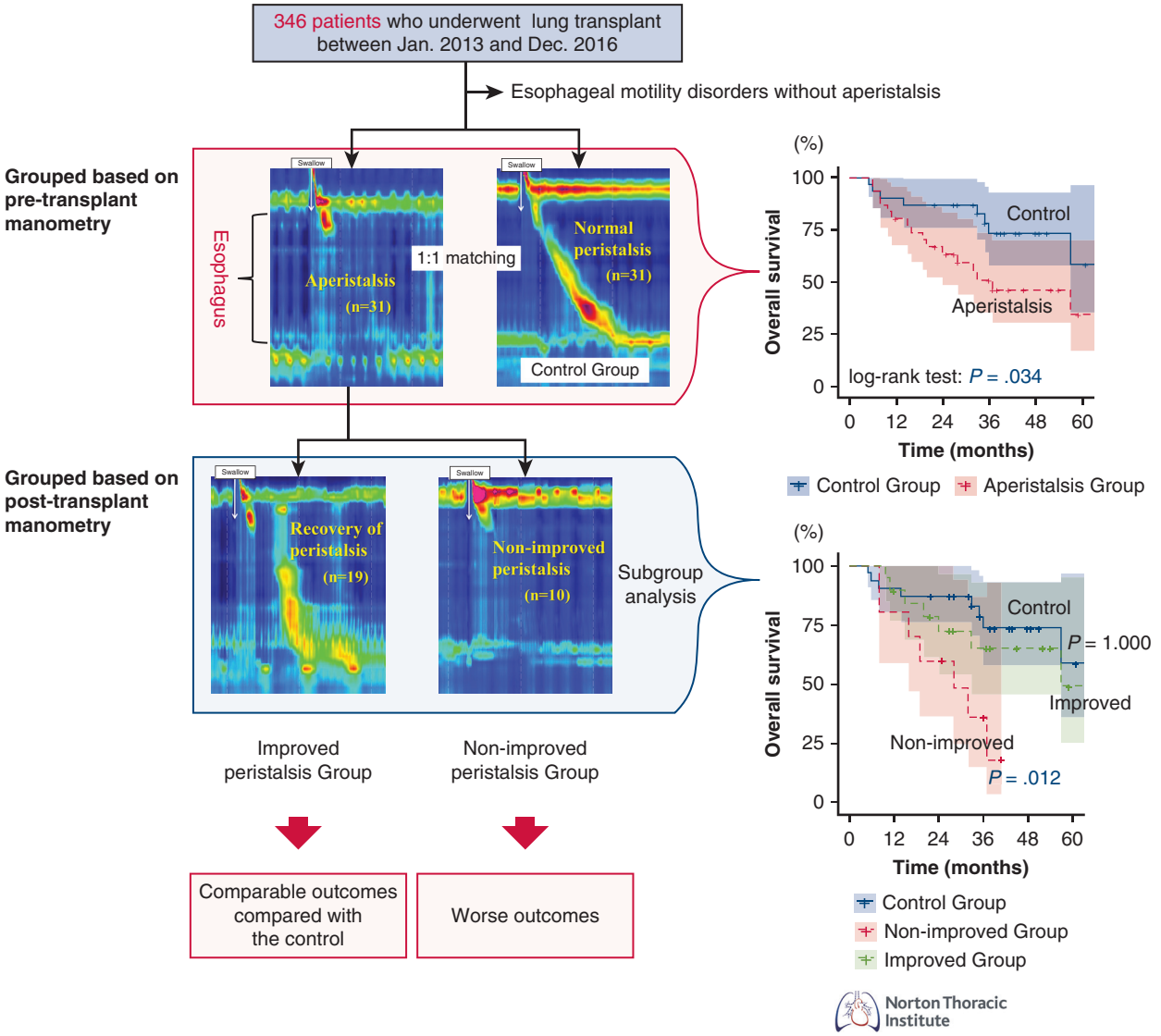

FIGURE 4. A total of 346 patients underwent LTx at our institution between January 2013 and December 2016. Of these, we identified patients who were diagnosed with esophageal aperistalsis or normal peristalsis based on pretransplant HRM, and then 1:1 propensity score matched cohorts were created. Inferior overall survival was evident in patients with aperistalsis pretransplant compared with those with normal peristalsis ($P = .034$). Esophageal manometry was repeated after LTx, and the aperistalsis cohort was divided into 2 subgroups: improved or nonimproved peristalsis groups. Overall survival of patients with recovery of peristalsis was similar to the control group (ie, normal peristalsis cohort), whereas the nonimproved peristalsis group had lower survival ($P = .012$).

earlier post-LTx morbidity and mortality have been suggested, including recipient age 65 years or older, male sex, obesity, pulmonary artery hypertension, unilateral LTx, cardiac dysfunction, prolonged allograft ischemic time, and others; however, some of these remain controversial.[17-21] In this study, we used a propensity score–matching method to reduce bias in those background characteristics between the aperistalsis group and the control group. We believe that adverse outcomes in patients who have esophageal aperistalsis are genuine. However, we must be cautious and not assume that all aperistaltic patients will have poor LTx outcomes. In the present study, patients with aperistaltic esophagus who had a good LTx outcome could be clearly discriminated if the patients were divided into 2 subgroups based on post-LTx manometric findings—that is, the improved and the nonimproved peristalsis groups.

We previously suggested that esophageal body contraction may be impaired by derangement of physiology and anatomy inside the thoracic cavity in patients with

end-stage lung disease.[5] Briefly, if lung size is extremely increased or decreased depending on the underlying pulmonary disease, the esophagus is stretched vertically or horizontally. This esophageal extension is a burden on muscle fiber contraction, which can lead to underestimation of inherent esophageal peristaltic vigor on pre-LTx HRM. This is further compounded by the effect of derangements in thoracoabdominal pressure gradients, which are affected differently based on the underlying cause of lung disease (ie, obstructive vs restrictive).[5] If no primary cause of esophageal hypomotility is identified, post-LTx recovery of esophageal peristalsis is presumably observed regardless of the type of underlying lung disease (Table 3). Systemic sclerosis is classically described to have concomitant primary esophageal aperistalsis. The present study includes 5 patients diagnosed with systemic sclerosis in the aperistalsis group, and 4 of these patients showed no recovery of esophageal peristalsis post-LTx with the median survival time as short as 8.0 months (data not shown). Interestingly, 1 of 5 patients showed some improved peristalsis after LTx, and this patient is still followed at our institute, achieving a long-term survival exceeding 5 years.

Long-term survival in LTx recipients is limited by CLAD, namely, BOS or restrictive allograft syndrome. In our primary analysis, there was no statistical significance in CLAD-free survival between the aperistalsis group and the control group (Figure 2, *C* and *D*). This is probably because the aperistalsis group comprised 2 subcharacterized cohorts, that is, the patients with or without improved peristalsis after LTx. Subgroup analysis revealed a clear difference in advanced-stage CLAD-free survival between the nonimproved peristalsis group and the control group, whereas this was similar between the improved peristalsis group and the control group (Figure 3, *D*). These findings seem to be reflected in the overall survival in each subgroup (Figure 3, *A*). ACR and AMR, both induced by an immunologic reaction, have been reported as risk factors for CLAD development. Uniform immunosuppression therapy was used in all LTx recipients in our institute, which may contribute to comparable outcomes in rejection-free survival among the groups/subgroups (Figures 2, *B*, and 3, *B*). This may indicate that a lower CLAD-free survival in the nonimproved peristalsis group is predominantly caused by a nonalloimmune mechanism (ie, recurrent silent aspiration). Fundoplication is one effective treatment option to protect pulmonary function against GERD-induced aspiration.[11] Two patients in the improved peristalsis group who underwent fundoplication after LTx achieved a 4-year survival with freedom from CLAD, and 1 of them is still followed at our clinic. We recommend that LTx candidates with aperistaltic esophagus or severely impaired motility before LTx have a gastrojejunostomy tube placed during the LTx procedure to decrease the risk of reflux into the esophagus post-LTx. After LTx, esophageal motility and pH studies should be reassessed to determine whether antireflux surgery is indicated and feasible.

Study Limitations

This study has several limitations. This analysis was designed as a single-center retrospective review; however, all baseline data were collected prospectively, and all foregut function tests were also reviewed or reanalyzed in a blinded fashion before propensity score matching. After matching was performed in a randomized fashion, we reviewed the clinical course in the matched cohort. Our relatively small sample size did not allow further statistical adjustment to balance the baseline characteristics between the subgroups, although the differences may be clinically subtle.

CONCLUSIONS

Esophageal aperistalsis is not necessarily a contraindication for LTx, and improved motility with good outcomes can be expected in up to two-thirds of these patients. However, outcomes are significantly worse in patients whose esophageal motility does not improve post-LTx. Aperistalsis in patients with systemic sclerosis may have the most challenging outcomes. Predictors for motility recovery need to be established to improve patient counseling and selection.

Conflict of Interest Statement

Dr Smith reports a financial relationship with Transmedics. All other authors have nothing to disclose with regard to commercial support.

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Key Words: esophageal motility disorders, esophagus, lung transplantation, peristalsis

Discussion

Dr Jules Lin. Our next talk will be presented by Takahiro Masuda on Esophageal Aperistalsis and Lung Transplant: Recovery of Peristalsis After Transplant Is Associated With Improved Long-Term Outcomes.

Dr Takahiro Masuda *(Phoenix, Ariz).* Esophageal aperistalsis has been considered a relative contraindication for LTx because of higher risk of allograft dysfunction secondary to reflux and aspiration induced by poor esophageal clearance. This picture shows normal esophageal motility in an aperistaltic esophagus based on esophageal manometry. We previously reported that esophageal motility improved in some patients after LTx. This is what we presented at Western Thoracic Surgical Association last year. Foregut function tests can change across pre- and post-LTx depending on normalization of physiology and anatomy inside the thoracic cavity after lung LTx. Hypothetically, improved short- and long-term outcomes can be expected even in patients diagnosed with esophageal aperistalsis before LTx if they have recovery of peristalsis after LTx. The aim of this study is to explore the clinical course of LTx recipients diagnosed with aperistaltic esophagus on pretransplant testing.

Patients who underwent LTx at our institution between January 2013 and January 2016 were retrospectively reviewed. We selected patients preoperatively diagnosed with aperistaltic esophagus and normal esophageal motility. We excluded patients with a history of LTx. Preoperative characteristics were balanced using propensity score matching between patients with aperistalsis and normal motility. Statistical analysis was performed as shown.

A total of 346 patients underwent LTx at our institution during this 3-year period. Thirty-two patients were diagnosed with aperistaltic esophagus before LTx, and 117 patients were diagnosed with normal motility. We performed propensity score matching, and 31 patients in each group were randomly selected. Age, sex, body mass index, underlying lung disease, lung allocation score, type of LTx, diabetes, hypertension, cardiac assessment, and graft ischemic time were balanced between the 2 groups.

We performed the survival analysis to compare the 2 groups. The blue line is the normal motility group. The green line is the aperistaltic group. The 1-, 3-, and 5-year post-LTx survivors in the aperistalsis group were 80.6%, 51.2%, and 34.9%, respectfully. These were significantly lower compared with the normal motility group. Clot-free survival and advanced stage clot-free survival appeared to be lower in the aperistalsis group, but these did not reach statistical significance. Advanced stage clot was considered if patients satisfied clash guidelines, stage II or more.

These are data from a 24-hour PH study. Generally, reflex parameters are worse in the aperistalsis group before LTx. However, after LTx, these differences were almost diminished. High-resolution esophageal manometry showed that EGJ anterior competency improved in manometric hiatal hernia; LES pressure, LES lengths, and intra-abdominal LES lengths were similar between the 2 groups before

LTx and after LTx.

Recovery of peristalsis after LTx was seen in some patients in the aperistalsis group. Approximately two-thirds of the patients showed improvement of esophageal motility after LTx in the aperistalsis group. The aperistalsis group was divided into 2 subgroups: improved motility and nonimproved motility groups.

We again performed survival analysis to compare subgroups. The blue line is the normal motility group, the yellow line is aperistalsis with improved motility group, and the green line is aperistalsis with the nonimproved motility group. Overall survival was similar between the counter group and improved motility group. However, no improved motility group showed significantly poorer survival. Additionally, advanced stage clot-free survival was significantly lower in the nonimproved motility group compared with the normal motility group.

Esophageal aperistalsis is not necessarily a contraindication for LTx, and improved motility with good outcomes can be expected in up to two-thirds of these patients. Outcomes were significantly worse in patients in whom esophageal motility does not improve post-LTx. Periodic tests for motility recovery need to be established to improve patient counseling and section.

Dr Lin. The discussion will be opened by Joe Schrager from Stanford.

Dr Joseph Shrager. This is a nice study from a busy transplant center where, because of their volume, the authors are able to use their own granular data to study an important issue in real detail. I also commend you for the substantial effort it must take to systematically prospectively study these patients pre- and post-transplant. The findings, to reiterate in brief, extend their previous work in this area and show that approximately 10% of patients undergoing LTx have preoperative severe esophageal dysfunction, that approximately two-thirds of those improve their aperistalsis post-transplant, and that those who improve postoperatively have increased survival than those without a motility problem, whereas those who do not improve do really substantially worse, and you didn't mention this, but they likely have a higher rate of BOS. I have 3 questions. First, 19 of the 29 aperistaltic patients showed improved peristalsis post-transplant, and those patients did well. Did you see any patterns that would allow you to predict which patients would have peristaltic recovery and which would not to perhaps inform who should not undergo transplantation? You mentioned that the patients with scleroderma did not improve. Are there any other things besides having scleroderma that predict they won't improve?

Dr Masuda. We will attempt to collect data from multiple rapid swallow maneuvers. This is a maneuver in esophageal manometry testing, so which, the greatest _____ on the esophagus and first, first to squeeze the esophagus with greater pressure, so we are now thinking….

Dr Shrager. It is a more stringent test, some sort of more stringent preoperative test.

Dr Masuda. We are collecting those data and believe it just may distinguish who will improve and who will not.

Dr Shrager. Okay. Would you recommend patients with scleroderma do not receive transplants?

Dr Masuda. In our study, approximately 80% of patients who have scleroderma did not show improvement, but 1 patient had aperistalsis with scleroderma had improved esophageal motility after transplantation and lived more than 4 years, so maybe we can distinguish those patients using multiple rapid swallow testing.

Dr Shrager. Can you explain what you think the pathophysiology is that explains why most patients have improved motility? I can easily understand why reflux might be improved, but it's harder for me to understand how motility would be improved after transplant.

Dr Masuda. Many patients who underwent LTx have extremely smaller or extremely larger lung volume before LTx, which can stretch the esophagus vertically or horizontally, so impairing esophageal contraction, contracting pressure, before LTx, many patients will be underestimated about esophageal motility, and after LTx, their lung condition changes to normal and the estimated motility was, I mean, the mass was uncovered after LTx.

Dr Leah Backhus. For the patients who did not recover their function or their peristalsis, were they oversized or undersized? Did you see any relating to the matching of the size of the lungs that you're implanting to recovery?

Dr Masuda. We checked their esophageal length. We did not have the data of how large based on their body size, so with esophageal length, there is significant change before and after LTx.

Dr Ross M. Bremner *(Phoenix, Ariz).* I want to add a couple of things to clarify what we think is coming out of this study because we have been studying preoperative and postoperative outcomes for more than 14 years now, and it is always difficult for us to try to understand who should be excluded from transplant on the likelihood of them not doing well afterward, just because of esophageal motility. Does reflux just sort of take you out of the possibility of getting, you

know, another 5 or so years of life, especially in patients who have aperistalsis because we used to actually consider it as an absolute contraindication because we were so worried about aspiration and BOS, and certainly, aspiration is a huge concern in these patients long-term. It does appear that in the patients with systemic sclerosis who also have aperistalsis, many of them do not have esophageal involvement, but also have aperistalsis, which appears to be a subcohort of patients who do poorly. We have to prospectively study these patients because there's not a lot of them, but we have only 1 who showed improvement. We have historically tried to come up with some sort of antireflux barrier. We've done Roux-en-Y's on a handful of these patients, but it's a difficult subcohort of patients, but a patient who is 35 or 40 years old with systemic sclerosis and aperistalsis, right now we're still performing transplantation in these patients. We're just vigilant about how we reintroduce feeding and manage them postoperatively.

Dr Lin. Don?

Dr Low. You concentrate on the aperistalsis aspect of things, and I've talked to Ross in the past about the fact that manometry gives you a lot of other information. Is it the aperistalsis state or the aspects of propensity to reflux? Your pH testing shows that in people who are at peristalsis, their reflux is worse, and we know this because their clearance is bad. What do the studies of the LES tell you? In a situation in which you have someone who has aperistalsis and a hypotensive sphincter, is that different than in someone who has a normotensive sphincter that is acting as an appropriate antireflux barrier? Is the LES playing as big a role in aperistalsis as these other patients? A treated patient with achalasia will usually do well. Does the LES tell you anything in addition?

Dr Masuda. LES pressure would change before and after transplantation. Now we don't have any answer about this yet, so, some patients will have decreased hiatal hernia and some will have increased hiatal hernia after LTx.

Dr Bremner. The posttransplant situation is a bit muddy about gastric-emptying problems, because approximately half of these patients will have delayed gastric emptying and that makes your reflux go worse. The LES parameters tend to improve, and we have been amazed at some of those patients who have significant reflux before but don't have bad reflux after, and we watch them closely but certainly those who have a defective sphincter and significant reflux post-transplant, we are aggressive at performing antireflux surgery in those, and if that antireflux series is done early in a study that was published by one of our partners, Jasmine Wong, those patients actually tend to be BOS-free for longer than if you wait to do the antireflux procedure. I think the take-home point is that conditions improve after transplant, but it's good to be vigilant about how you study these patients and be aggressive about those patients who have bad reflux.

Dr Donald E. Low. For that subgroup in whom you did the antireflux procedures, did you look at those and did those patients do better regardless of whether they…

Dr Bremner. There's such a small group of patients who have aperistalsis and improved a little bit, so we did the antireflux procedure, but we do believe that it was beneficial. In the patients who had reflux that were wrapped early, their BOS-free survival is better than those that are wrapped late, so I think we are on top of it now, and those whom we worried about reflux, we study them early. If they still have reflux, we will treat it surgically.