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Impaired Esophageal Motility and Clearance Post-Lung Transplant: Risk For Chronic Allograft Failure

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OBJECTIVES: Gastroesophageal reflux is common in patients post-lung transplantation (LTx) and thus considered a risk factor for aspiration and consequently allograft rejection and the development of chronic allograft failure. However, evidence supporting this remains unclear and often contradictory. Our aim was to examine the role played by esophageal motility on gastroesophageal reflux exposure, along with its clearance and that of boluses swallowed, and the relationship to development of obstructive chronic lung allograft dysfunction (o-CLAD).

METHODS: Patients post-LTx ($n = 50$, 26 female; mean age 55 years (range, 20–73 years)) completed high-resolution impedance manometry and 24-h pH/impedance. Esophageal motility abnormalities were classified based upon the Chicago Classification version 3.0.

RESULTS: Esophagogastric junction outflow obstruction alone (EGJOOa) ($P = 0.01$), incomplete bolus transit (IBT) ($P = 0.006$) and proximal reflux ($P = 0.042$) increased the risk for o-CLAD. Patients with EGJOOa were most likely to present with o-CLAD (77%); despite being less likely to exhibit abnormal numbers of reflux events (10%) compared with those with normal motility (o-CLAD: 29%, $P < 0.05$; abnormal reflux events: 64%, $P < 0.05$). Patients with EGJOOa had lower total reflux bolus exposure time than those with normal motility (0.6 vs. 1.5%; $P < 0.05$). In addition, poor esophageal clearance documented by abnormal post-reflux swallow-induced peristaltic wave index associated with o-CLAD; inversely correlating with the proportion of reflux events reaching the proximal esophagus ($r = -0.251$; $P = 0.052$).

CONCLUSIONS: These observations support esophageal dysmotility, especially EGJOOa, and impaired clearance of swallowed bolus or refluxed contents, more so than just the presence of gastroesophageal reflux alone, as important risk factors in the development of o-CLAD.

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INTRODUCTION

Aspiration of gastric contents is considered a non-alloimmune cause for the development of chronic graft failure following lung transplantation (LTx). Despite the high prevalence of gastroesophageal reflux disease (GERD) in patients post-LTx[1–7] and some data that support GERD as a risk factor for rejection,[2,4–6,8–11] other studies have not demonstrated an association between reflux severity and bronchiolitis obliterans syndrome (BOS),[1,3,7] or correlation between FEV_1 and reflux or bronchoalveolar lavage fluid (BALF) pepsin/bile acid concentrations,[1] suggesting that other factors must be involved in the development of chronic graft failure.

Esophageal dysmotility has been shown to associate with prolonged reflux clearance times and higher reflux exposure time, and indeed slower passage of "swallowed" boluses in patients with GERD[12] and chronic cough.[13] However, although esophageal dysmotility has been shown in patients following LTx,[6,7,14–17] its relationship to gastroesophageal reflux (GER) and/or swallowed bolus clearance, and thus the possibility of aspiration and/or obstructive chronic lung allograft dysfunction (o-CLAD) remains unclear. This lack of clarity may be related to the diagnostic limitations associated with the older low-resolution catheters and conventional manometry parameters used in these studies, as although some studies did use high-resolution esophageal impedance manometry (HRIM),[14–16] no study used the Chicago Classification (CC), the most current classification of esophageal motor disorders, to define motility post-LTx. Moreover, only one study has compared dysmotility (again using conventional parameters) and GERD prevalence in LTx patients with and without allograft dysfunction, which reported no difference.[7] Lastly, all but one[6] of the previous studies reporting on both motility and GER used pH alone without concurrent impedance, which might have resulted in underestimation of GER.

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The aim of this study was therefore to use HRIM along with pH/impedance for the first time to determine the prevalence of dysmotility using the CC and assess its impact on both swallowed and reflux bolus clearance and thus exposure of the esophagus to excessive luminal content and subsequent development of o-CLAD in patients post-LTx.

METHODS

Patients. Consecutive post-LTx patients ($n=50$, 26 female; mean age 55 (range, 20–73) years) referred for HRIM and pH/impedance approximately 3 months after surgery at Mayo Clinic, Florida between October 2012 and December 2014 with follow-up through 31 July 2015 were included. Patient data included age, sex, body mass index, donor and recipient cytomegalovirus immune status, indication for LTx, LTx date, intra-operative data, post-LTx medication, post-LTx complications, including acute rejection, o-CLAD and death. The Mayo Clinic Institutional Review Board approved the study.

HRIM. HRIM was performed using a solid state catheter with 36 circumferential pressure sensors spaced at 1 cm intervals and 18 impedance channels (Medtronic, Shoreview, MN). The catheter was positioned transnasally with the distal sensors for both pressure and impedance in the proximal stomach. Following at least a 30 s baseline to identify the upper esophageal sphincter (UES) and LES, ten 5 ml saline swallows were given at least 30 s apart with the patient supine.[13]

pH/impedance. pH/impedance (Sandhill Scientific, Highlands Ranch, CO) was performed using a single antimony pH probe (5 cm above the LES) with eight impedance electrodes.[13]

Diagnosis of o-CLAD. The term CLAD includes the entities of BOS and restrictive allograft syndrome, the former being characterized by obstruction and the latter by a restrictive component.[18,19] To date, all studies reporting on the possible link between reflux, aspiration and lung allograft dysfunction have concentrated on BOS. To our knowledge, there is no established link between reflux and restrictive allograft syndrome.[18,19] As such, we have focused specifically on "obstructive CLAD",[19] defined per the joint ATS/ERS statement on BOS, including BOS 0-p.[20]

Data analysis

HRIM. ManoVIEW Analysis software v3.01 (Medtronic, Shoreview, MN) was used to manually analyze the recordings. Esophageal motility was classified based upon CC 3.0.[21] Each 5 ml swallow was evaluated to determine: (i) integrated relaxation pressure, (ii) distal contractile integral, and (iii) distal latency.[21] Contractile pattern was classified as premature, fragmented, or intact.[21]

CC version 3.0 diagnoses included: (i) achalasia or EGJOO, the latter defined as poor deglutitive relaxation of the LES (median integrated relaxation pressure >15 mmHg), with some instances of intact or weak peristalsis, not meeting the criteria for achalasia; (ii) major disorders of peristalsis, such as absent contractility, distal esophageal spasm, and hypercontractile esophagus; or (iii) minor disorders of peristalsis, such as ineffective esophageal motility, and fragmented peristalsis.[21]

Impedance recordings were evaluated for each swallow and bolus clearance assessed using both colorized contour functions and superimposed impedance tracings, as previously described.[22] Bolus clearance was defined as "complete" or "incomplete" based on the color overlay and line-tracing modes.[22] Subjects were classified as complete bolus transit when clearance was seen in $\geq 80\%$ of swallows.[23]

24-h pH/impedance. BioVIEW analysis software (Sandhill Scientific) was used to identify reflux episodes based on retrograde impedance decrease to 50% of baseline in at least two distal adjacent channels. Meal periods were excluded. In patients off proton pump inhibitors (PPI) >73 episodes was considered abnormal;[24] >48 episodes on b.i.d. PPI.[25] Proximal reflux events were defined as those that reached at least 15 cm above LES (normal ≤ 31 off PPI, ≤ 19 on PPI).[24,25] Since data on abnormal reflux frequency on q.d. PPI are not available, we classified those patients with ≤ 48 reflux events as normal and those with >73 episodes as abnormal. For proximal reflux events, we defined patients on q.d. PPI with ≤ 19 reflux events as normal and those with >31 episodes as abnormal (only three patients could not be classified and were excluded from any categorical analysis). Bolus clearance time was defined as lapsed time that the bolus was present at each impedance level during a specific reflux episode or time interval between bolus entry and clearance. Total reflux bolus exposure time was the percentage of monitored time that the esophagus was exposed to reflux of any nature.

Acid exposure time was defined as the percentage of total time that pH was below 4 at the distal sensor (normal values <4.2 off PPI or <1.6 on PPI).[25,26]

Post-reflux swallow-induced peristaltic wave (PSPW) index. The PSPW index, a novel measure of esophageal clearance in pH/impedance studies, is defined as the number of reflux episodes followed by an impedance-detected swallow occurring within 30 s of the end of the reflux episode, divided by the total number of reflux episodes.[27,28] The PSPW index was considered abnormal if $<61\%$.[28]

Statistics. Group differences were evaluated using Student's *t*-tests or Mann–Whitney *U*-tests. Associations were assessed using χ^2 or Fisher's exact tests. Univariate log-rank tests and Kaplan–Meier plots were used to evaluate cumulative hazards for o-CLAD. Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals for the associations between time to o-CLAD and incomplete bolus transit, EGJOO alone (EGJOOa), (i.e., achalasia or esophagogastric junction outflow obstruction, without concomitant hypercontractile peristalsis, see above) and, proximal and distal reflux frequency exceeding the upper limit of normal, and acute rejection after controlling for potential confounders from univariate comparisons with $P<0.100$. Cox proportional hazards were completed controlling for length of time between LTx and esophageal testing. Significance was evaluated at the two-tailed, $P<0.05$ levels.

RESULTS

Primary indications for LTx were diffuse parenchymal lung diseases (52%; 92% IPF and 8% other interstitial lung disease) and COPD (28%). Thirty-three patients (66%) underwent bilateral and 15 patients (30%) unilateral LTx (two underwent re-transplant). HRIM was completed a median (IQR) of 91 days (83–409) from LTx in 50 patients. Of these, 45 (90%) underwent combined pH/impedance monitoring, with 35 (78%) of these being completed on PPI (19 b.i.d, 16 q.d) and 10 (22%) off PPI. Following HRIM and pH/impedance testing, 47 (94%) patients were on PPI (26 b.i.d, 21 q.d). Four (8%) patients underwent anti-reflux surgery (three laparoscopic Nissen fundoplication, one implanted LINX) after HRIM. Median (IQR) post-LTx follow-up was 909 days (637–1,107).

Acute rejection (acute cellular rejection and/or lymphocytic bronchiolitis) was found in 32/50 (64%) patients a median (IQR) of 59 days (29–334) day after LTx, 23 (46%) developed o-CLAD 725 (495–1,117) days after LTx, and 4 (8%) died 1,677 (870–2193) days after LTx (all had o-CLAD).

Table 1 Comparison of general characteristics of LTx patients with and without o-CLAD

	o-CLAD ($n=23$)	Without o-CLAD ($n=27$)	*P* value
Age, years[a]	59 (57–64)	61 (40–65)	0.915
Female:Male ratio	9:14	17:10	0.081
Body mass index, kg/m^2 [b]	27.6 (25.4–29.8)	25.9 (24.1–27.6)	0.211
			0.513
Indication for LTx, n*(%)* [c]			0.513
DPLD	10 (44%)	16 (59%)	
COPD	9 (39%)	5 (19%)	
CF	1 (4%)	3 (11%)	
PAH, idiopathic	1 (4%)	1 (4%)	
PAH, CHD	0	1 (4%)	
Sarcoidosis	1 (4%)	0	
ReLTx	1 (4%)	1 (4%)	
			0.513
CMV status, n*(%)*[c]			0.258
D – /R –	5 (22%)	1 (4%)	
D – /R+	2 (9%)	2 (7%)	
D+/R –	8 (35%)	11 (41%)	
D+/R+	8 (35%)	13 (48%)	
			0.513
LTx, n*(%)*[c]			0.244
Unilateral	9 (39%)	7 (26%)	
Bilateral	14 (61%)	20 (74%)	
			0.513
Anti-reflux surgery, *n*(%)[c]	1 (4%)	3 (11%)	0.380
			0.513
Post-LTx complications[c]			
Acute rejection, *n*(%)	17 (74%)	15 (56%)	0.146
Death, *n*(%)	4 (17%)	0	0.038

CF, cystic fibrosis; CHD, congenital heart disease; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; D, donor; DPLD, diffuse parenchymal lung disease; LTx, lung transplantation; o-CLAD, obstructive chronic lung allograft dysfunction; PAH, pulmonary arterial hypertension; R, recipient.
[a]Results are expressed as either median (IQR).
[b]Mean (95% CI).
[c]Percentage for categorical variables.

o-CLAD vs. without o-CLAD. Table 1 shows the characteristics of LTx patients with and without o-CLAD. There was no significant difference between any of the variables, except for more deaths in patients with o-CLAD ($P=0.038$). Critically, the median (IQR) time from transplant to the last follow-up of patients with no o-CLAD (726 (565–1,010) days) was not different from the time to o-CLAD in those with o-CLAD (725 (495–1,117) days; $P=0.793$), indicating that the presence of o-CLAD was not related to longer time since LTx.

HRIM (CC v3.0). Patients with o-CLAD were more likely to exhibit EGJOOa (i.e., achalasia or EGJ outflow obstruction) than patients without o-CLAD ($P=0.011$). Removal of the four patients with achalasia did not affect these findings (35% vs. 8%; $P=0.026$) There were no differences in the rates of all other CC diagnoses for patients with vs. without o-CLAD (Table 2). While distal latency was shorter ($P=0.032$) in patients with o-CLAD, all values were within the normal range.

Bolus transit. Both the proportion of patients with IBT (83% vs. 33%; $P=0.001$) and percentage of swallows with IBT (50% vs. 10%; $P=0.002$) were higher in patients with o-CLAD (Table 2).

24-h pH/impedance. Reflux parameters were not different between patients with and without o-CLAD; though those with o-CLAD tended to have more reflux events (proximal, $P=0.139$; distal, $P=0.184$) and be classified as having abnormal levels of reflux (total, $P=0.134$; proximal, $P=0.082$) (Table 3).

PSPW index. Patients with o-CLAD were more likely to have an abnormal PSPW index than those without (83% vs 52%; $P=0.034$). PSPW index inversely correlated with the proportion of reflux events reaching the proximal esophagus ($r=-0.251$; $P=0.052$) (Figure 1).

Time to event analysis. In univariate analyses, EGJOOa (HR, 2.91; 1.20–6.99; $P=0.018$), IBT (HR, 3.93; 95% CI: 1.30–11.86; $P=0.015$), acute rejection (HR, 2.73; 0.90–8.24; $P=0.075$), and proximal reflux (HR, 2.48; 0.97–6.29; $P=0.057$), but not PSPW, distal reflux, nor dose of PPI during follow-up appeared associated with a higher risk for developing o-CLAD during follow-up.

EGJOOa (HR, 3.265; 1.332–8.007; $P=0.01$), IBT (HR, 4.815; 1.558–14.878; $P=0.006$), and proximal reflux (HR, 2.666; 1.038–6.845; $P=0.042$) but not acute rejection appeared to be predictors for the time to the development of o-CLAD following multivariable Cox proportional hazards regression controlling for length of time from LTx to HRIM and pH/impedance.

Abnormal vs. normal motility. To further assess how disordered motility may influence reflux, swallowed bolus clearance and relationship with o-CLAD, patients were categorized using CC v3.0 into those with (i) EGJOOa, (i.e., achalasia and esophagogastric junction outflow obstruction without concomitant hypercontractile peristalsis), (ii) hypercontractility (Jackhammer, distal esophageal spasm), (iii) EGJOO with hyper-contractility (EGJOOh), and (iv) hypocontractility (absent contractility, ineffective esophageal motility and fragmented peristalsis). EGJOOa (77%) (not other subgroups) was significantly more likely to develop o-CLAD

Table 2 Individual HRIM parameters, diagnostic classifications based on Chicago v3.0, and bolus transit findings in LTx patients with and without o-CLAD

	o-CLAD ($n=23$)	Without o-CLAD ($n=27$)	*P* value
HRIM findings			
UES resting pressure, mmHg[a]	56.8 (46.3–88.3)	56.4 (47.0–76.2)	0.888
UES relaxation pressure, mmHg[a]	3.2 (1.0–6.6)	1.7 (0.9–7.2)	0.410
LES resting pressure, mmHg[a]	29.9 (27.4–42.9)	34.5 (28.9–48.0)	0.202
LES-CD separation, >2 cm, *n*(%)[b]	2 (9%)	0	0.207
Mean IRP, mmHg (C, v2.0)[a]	13.1 (7.6–18.8)	11.3 (9.1–14.5)	0.436
Median IRP, mmHg (C, v3.0)[a]	12.9 (7.2–18.6)	11.0 (9.1–14.0)	0.386
CFV, cm/s[a]	4.6 (3.4–6.4)	3.2 (2.4–4.3)	0.002
DL, s[a]	6.2 (5.3–7.0)	7.4 (5.9–8.3)	0.032
DCI, mmHg/s/cm[a]	1822.0 (1125.7–5048.8)	4313.4 (1847.6–8373.1)	0.062
Chicago v3.0, n*(%)*[b]			
Normal	4 (17%)	10 (37%)	0.109
EGJOO alone	10 (44%)	3 (11%)	0.011
Hyper-contractility	4 (17%)	8 (30%)	0.251
EGJOO			
With hyper-contractility	1 (4%)	3 (11%)	0.368
Hypo-contractility	4 (17%)	3 (11%)	0.407
Bolus transit findings			
Patients with IBT, *n*(%)[b]	19 (83%)	9 (33%)	0.001
Swallows with IBT, %[a]	50 (30–100)	10 (0–40)	0.002
Time from LTx to HRIM, days[a]	96 (87–1692)	89 (80–111)	0.020

CFV, contractile front velocity; DCI, distal contractile integral; DL, distal latency; EGJOO, esophagogastric junction outflow obstruction; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; LES-CD, LES to crural diaphragm distance; o-CLAD, obstructive chronic lung allograft dysfunction; UES, upper esophageal sphincter.
[a]Results expressed as either median (IQR).
[b]Percentage for categorical variables.

Table 3 24-h pH/impedance in LTx patients with and without o-CLAD

	o-CLAD ($n=20$)	Without o-CLAD ($n=25$)	*P* value
Total no. of events, n[a]	57 (32–82)	39 (23–69)	0.184
Patients with abnormal no. of events, n(%)[b]	9/19 (47%)	6/23 (26%)	0.134
Proximal events, *n* [a]	17 (6–34)	10 (5–16)	0.139
Patients with abnormal no. of proximal events, *n* (%)[b]	8/20 (40%)	4/24 (17%)	0.082
Total reflux bolus exposure time, %[a]	1.1 (0.4–2.3)	0.8 (0.5–1.7)	0.437
Bolus clearance time, s[a]	11 (8–16)	13 (10–16)	0.474
Acid exposure time, %[a]	0.9 (0.3–6.7)	2.2 (0.8–6.4)	0.314

o-CLAD, obstructive chronic lung allograft dysfunction.
Note that only 45 patients underwent 24-h pH/impedance, of which three patients on once daily PPI could not be classified with respect to whether they had an abnormal total number of reflux events and one patient with respect to whether they had an abnormal number of proximal reflux events. These patients were excluded from analysis.
[a]Results are expressed as either median (IQR).
[b]Percentage for categorical variables.

compared with normal motility ($P=0.016$) (Table 4). This was the case despite fewer patients with EGJOOa having abnormal numbers of reflux events (10%) compared with those with normal motility (64%; $P=0.011$). Patients with hyper-contractility (20%) were similarly less likely to exhibit an abnormal number of reflux events compared with those with normal motility ($P=0.04$). This was associated with a shorter total reflux bolus exposure time in patients with EGJOOa ($P=0.011$) and EGJOOh ($P=0.047$) compared with normal motility. Acid exposure time was not different between the motility subgroups (Table 4).

Although patients with hypo-motility (86%) had more swallows associated with IBT compared with normal motility (57%, $P=0.094$) this did not reach statistical significance (Table 4).

DISCUSSION

For the first time we have shown that EGJOOa, IBT, and proximal reflux all increase the risk for the development of o-CLAD post-LTx. Patients with o-CLAD were significantly more likely to present with EGJOOa, incomplete transit of boluses swallowed and an impaired reflux clearance documented by abnormal PSPW index than those without o-CLAD. Moreover, although patients with o-CLAD appeared no more likely to exhibit an abnormal number of reflux events than those without o-CLAD, more patients with o-CLAD tended to have abnormal numbers of reflux events reaching the proximal esophagus ($P=0.082$), possibly as a result of both IBT and a lower PSPW index, which inversely correlated with the proportion of reflux events reaching the proximal esophagus. Notably, the development of o-CLAD in patients presenting with EGJOOa was not associated with abnormal GER, as only one patient (10%) exhibited abnormal levels of reflux compared with 64% of those with normal motility. Contrary to expectations, patients with hypo-contractility were no more likely to have o-CLAD than those with normal motility. These data suggest that poor clearance of boluses, be it swallowed or reflux, may be more likely to aspirate into the airways, especially when the EGJ is obstructed than just because of the presence of abnormal reflux alone. These observations therefore pose important questions regarding clinicians' current focus on GER, particularly if only distal esophageal reflux is considered and its potential association with

aspiration post-LTx, and suggest that EGJOOa and poor esophageal clearance may be very important for the development of o-CLAD.

Our novel data therefore challenge the belief that GER, and particularly its association with hypo-contractility patterns, such as ineffective esophageal motility, is the main precursor for the development of o-CLAD, and suggest that EGJOOa and associated poor clearance of swallowed boluses may be equally important for the development of o-CLAD. This does not exclude the possibility of refluxate aspirating into the airways, as suggested by proximal (but not distal) reflux significantly predicting the development of o-CLAD and supported by studies reporting the presence of pepsin and/or bile acids in BALF in patients post-LTx.[1–3,5,6,8,9,29] Moreover, some studies have reported that proximal reflux events correlate with BALF neutrophils,[6] with the latter correlating with BALF bile acid concentrations, which might shorten freedom from BOS.[8] However, our findings help explain why "not all" studies have shown that (i) distal reflux and BALF pepsin/bile acid concentrations correlate with lung function,[1] (ii) distal reflux correlates with BALF pepsin concentration, and is associated with a quicker progression to BOS[5] and (iii) fundoplication is associated with improved lung function.[30] Those patients that do respond well to fundoplication are likely those in whom GERD is an important mechanism for rejection but currently there are no comprehensive sham/placebo-controlled data (e.g., pre- and post-transplant esophageal body and LES/UES motility, using CC, impedance/pH data, BALF pepsin levels, and effect of surgery/type of surgery; oropharyngeal function etc.) available to formally explore which patients best benefit from fundoplication. Till then, an individualized approach keeping these factors in mind

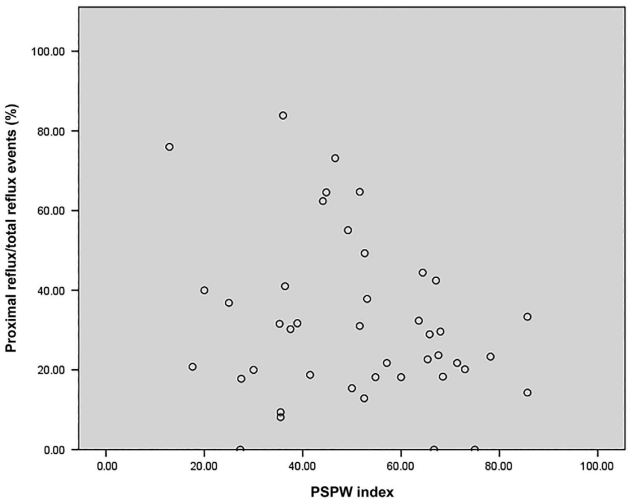

Figure 1 Pearson correlation of percentage of reflux events reaching the proximal esophagus with PSPW index ($r = -0.251$; $P = 0.052$).

Table 4 Bolus transit and 24-h pH/impedance findings in LTx patients with various esophageal diagnoses based on Chicago Classification v3.0

	Normal ($n = 14$)	EGJOOa ($n = 13$)	Hyper-contractility ($n = 12$)	EGJOOa with hyper-contractility ($n = 4$)	Hypo-contractility ($n = 7$)
General characteristics					
Age, years[a]	60 (53–63)	59 (54–62)	64 (58–66)	60 (39–66)	57 (35–58)
Female:Male ratio	7:7	5:8	6:6	3:1	5:2
BMI, kg/m^2 [b]	26.4 (23.7–29.2)	26.9 (24.0–29.8)	27.2 (24.2–30.2)	24.4 (22.4–26.3)	27.1 (20.8–33.4)
LTx, n(%) [c]					
Unilateral	6 (43%)	7 (54%)	3 (25%)	0	0
Bilateral	8 (57%)	6 (46%)	9 (75%)	4 (100%)	7 (100%)
Anti-reflux surgery, *n*(%)[c]	2 (14%)	0	1 (8%)	0	1 (14%)
Post-LTx complications					
Acute rejection, *n*(%)[c]	8 (57%)	8 (62%)	9 (75%)	3 (75%)	4 (57%)
o-CLAD, *n*(%)[c]	4 (29%)	10 (77%)*	4 (33%)	1 (25%)	4(57%)
Time to o-CLAD, days[a]	273 (183–1451)	748 (578–921)	891 (609–1651)	731	672 (411–1492)
Death, *n*(%)[c]	0	3 (23%)	0	0	1 (14%)
Bolus transit:					
Patients with IBT, *n*(%)[c]	8 (57%)	9 (69%)	4 (33%)	1 (25%)	6 (86%)
Swallows with IBT, %[a]	30 (0–50)	50 (20–90)	10 (0–30)	5 (0–25)	60 (30–100)
24-hr pH/impedance					
Total no. events, *n* [a]	70 (39–90)	37 (19–45)	42 (13–55)	32 (10–38)	72 (27–76)
Patients with abnormal no. of events, *n*(%)[c]	9/14 (64%)	1/10 (10%)*	2/10 (20%)*	0	3/5 (60%)
Proximal events, *n* [a]	16 (9–26)	11 (6–13)	8 (3–22)	3 (2–11)	31 (8–34)
Patients with abnormal no. of proximal events, *n*(%)[c]	5/14 (36%)	1/10 (10%)	3/11 (27%)	0	3/6 (50%)
Total reflux bolus exposure time, %[a]	1.5 (0.8–2.3)	0.6 (0.4–0.9)*	0.7 (0.2–1.9)	0.4 (0.3–0.9)*	1.7 (0.7–6.7)
Bolus clearance time, s[a]	13 (10–14)	11 (7–12)	13 (9–16)	13 (6–16)	17(11–26)
Acid exposure time, %[a]	3.8 (1.1–7.9)	0.9 (0.4–3.7)	2.0 (0.3–7.2)	1.4 (0.9–2.0)	0.3 (0.1–16.3)

BMI, body mass index; EGJOOa, esophagogastric outflow obstruction alone; IBT, incomplete bolus transit; LTx, lung transplantation; o-CLAD, obstructive chronic lung allograft dysfunction.
[a]Results expressed as either median (IQR).
[b]Mean (95% CI).
[c]Categorical variables.
*$P < 0.05$ compared with normal motility.

in order to reduce the risk of o-CLAD can only be recommended. Interestingly in our study, a low PSPW index was associated with more reflux events reaching the proximal esophagus. This together with the fact that 70% of LTx patients have oropharyngeal dysphagia,[31,32] with those with "normal" swallowing in the early postoperative period having improved long-term survival compared with those with abnormal swallowing,[32] support our hypothesis that abnormal swallowing may play a very important role, through a route different than aspiration of refluxate in development of o-CLAD.

Our study has limitations. For example, we had no pre-transplantation data for comparison. This does not detract from the potentially important clinical observation that aspiration of swallowed material, particularly in those patients with EGJOOa may be equally, if not more important than aspiration of refluxate.[17] Second, only 22% of patients were off PPI therapy during pH/impedance assessment, with the rest split evenly between once and twice daily PPI; hence analysis focused mainly on impedance rather than pH data. The distribution of patients on and off PPI was similar across all patient subgroups and had no effect on findings. Moreover, following pH/impedance testing most patients (94%) were on PPI therapy, and although some patients were on once daily (42%) and others twice daily (52%) this had no effect on outcome of BOS. Patient's post-LTx is on many medications, which cannot be controlled for. Thus to avoid esophageal interaction with narcotics, our clinical protocol has evolved to assess patients ~3 months after LTx when they are no longer taking these medications and are scheduled to return to their local physicians. Finally, while the relatively high percentage of patients in our study with manometric achalasia is surprising, we cannot say if this is a primary or secondary disorder. As with EGJOO, aspiration of swallowed material in these achalasia patients can be detrimental to the native lung or allograft.

In conclusion, our observations call for increased attention to abnormal swallowing and impaired clearance of swallowed material or refluxate, and highlight the importance of performing HRIM and not just esophageal pH/impedance in LTx patients. Furthermore, they question the empirical use of acid suppression, especially in those with normal proximal esophageal reflux, and potentially explain why fundoplication does not always improve lung function. While treatment of EGJOOa using, e.g., botox or pneumatic dilatation could be considered this needs to be carefully balanced with the potential to augment GERD by decreasing the competency of the EGJ. For those with impaired clearance, prokinetics could be considered but the effect of these medications on esophageal peristalsis is limited. Further carefully designed and appropriately powered studies are needed to better define the most appropriate clinical management pathways required to treat these patients.

CONFLICT OF INTEREST

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ETHICS APPROVAL

The Mayo Clinic Institutional Review Board (10-007462) approved the study.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Long-term survival following lung transplantation is lower than other solid organ transplants usually as a consequence of the development of o-CLAD.
- ✓ Aspiration of gastric contents, aided by gastroesophageal reflux and ineffective esophageal motility, is thought to be a non-alloimmune cause for the development of o-CLAD; though evidence supporting this is inconsistent.

WHAT IS NEW HERE

- ✓ Esophagogastric junction outflow obstruction alone (EGJOOa), incomplete bolus transit and proximal reflux are independent predictors of o-CLAD.
- ✓ Patients with EGJOOa are most likely to develop o-CLAD; despite exhibiting less gastroesophageal reflux than those with normal motility.
- ✓ Poor esophageal clearance documented by abnormal PSPW index associates with o-CLAD; inversely correlating with the proportion of reflux events reaching the proximal esophagus.

TRANSLATIONAL IMPACT

- ✓ These observations call for increased clinical attention to be given to abnormal swallowing and impaired clearance of swallowed material or refluxate, and highlight the importance of performing high-resolution esophageal impedance manometry (HRIM) post-lung transplantation, especially before performing fundoplication.
- ✓ They also question the empirical use of acid suppression, especially in those with normal proximal reflux and in the light that proton pump inhibitors are increasing being associated with additional risks such as pneumonia and *Clostridium difficile* infection.

1. Blondeau K, Mertens V, Vanaudenaerde BA *et al.* Gastro-oesophageal reflux and gastric aspiration in lung transplant patients with or without chronic rejection. *Eur Respir J* 2008; **31**: 707–713.
2. D'Ovidio F, Mura M, Ridsdale R *et al.* The effect of reflux and bile acid aspiration on the lung allograft and its surfactant and innate immunity molecules SP-A and SP-D. *Am J Transplant* 2006; **6**: 1930–1938.
3. Davis CS, Mendez BM, Flint DV *et al.* Pepsin concentrations are elevated in the bronchoalveolar lavage fluid of patients with idiopathic pulmonary fibrosis after lung transplantation. *J Surg Res* 2013; **185**: e101–e108.
4. Davis RD Jr, Lau CL, Eubanks S *et al.* Improved lung allograft function after fundoplication in patients with gastroesophageal reflux disease undergoing lung transplantation. *J Thorac Cardiovasc Surg* 2003; **125**: 533–542.
5. Fisichella PM, Davis CS, Lundberg PW *et al.* The protective role of laparoscopic antireflux surgery against aspiration of pepsin after lung transplantation. *Surgery* 2011; **150**: 598–606.
6. Griffin SM, Robertson AG, Bredenoord AJ *et al.* Aspiration and allograft injury secondary to gastroesophageal reflux occur in the immediate post-lung transplantation period (prospective clinical trial). *Ann Surg* 2013; **258**: 705–711.
7. Hadjiliadis D, Duane Davis R, Steele MP *et al.* Gastroesophageal reflux disease in lung transplant recipients. *Clin Transplant* 2003; **17**: 363–368.
8. D'Ovidio F, Mura M, Tsang M *et al.* Bile acid aspiration and the development of bronchiolitis obliterans after lung transplantation. *J Thorac Cardiovasc Surg* 2005; **129**: 1144–1152.
9. Stovold R, Forrest IA, Corris PA *et al.* Pepsin, a biomarker of gastric aspiration in lung allografts: a putative association with rejection. *Am J Respir Crit Care Med* 2007; **175**: 1298–1303.
10. Cantu E 3rd, Appel JZ 3rd, Hartwig MG *et al.* J. Maxwell Chamberlain Memorial Paper. Early fundoplication prevents chronic allograft dysfunction in patients with gastroesophageal reflux disease. *Ann Thorac Surg* 2004; **78**: 1142–1151.
11. Robertson AG, Krishnan A, Ward C *et al.* Anti-reflux surgery in lung transplant recipients: outcomes and effects on quality of life. *Eur Respir J* 2012; **39**: 691–697.
12. Ribolsi M, Balestrieri P, Emerenziani S *et al.* Weak peristalsis with large breaks is associated with higher acid exposure and delayed reflux clearance in the supine position in GERD patients. *Am J Gastroenterol* 2014; **109**: 46–51.
13. Almansa C, Smith JA, Morris J *et al.* Weak peristalsis with large breaks in chronic cough: association with poor esophageal clearance. *Neurogastroenterol Motil* 2015; **27**: 431–442.
14. Davis CS, Shankaran V, Kovacs EJ *et al.* Gastroesophageal reflux disease after lung transplantation: pathophysiology and implications for treatment. *Surgery* 2010; **148**: 737–744.
15. Fisichella PM, Davis CS, Shankaran V *et al.* The prevalence and extent of gastroesophageal reflux disease correlates to the type of lung transplantation. *Surg Laparosc Endosc Percutan Tech* 2012; **22**: 46–51.
16. Mendez BM, Davis CS, Weber C *et al.* Gastroesophageal reflux disease in lung transplant patients with cystic fibrosis. *Am J Surg* 2012; **204**: e21–e26.
17. Young LR, Hadjiliadis D, Davis RD *et al.* Lung transplantation exacerbates gastroesophageal reflux disease. *Chest* 2003; **124**: 1689–1693.
18. Sato M, Waddell TK, Wagnetz U *et al.* Restrictive allograft syndrome (RAS): a novel form of chronic lung allograft dysfunction. *J Heart Lung Transplant* 2011; **30**: 735–742.
19. Verleden GM, Raghu G, Meyer KC *et al.* A new classification system for chronic lung allograft dysfunction. *J Heart Lung Transplant* 2014; **33**: 127–133.
20. Meyer KC, Raghu G, Verleden GM *et al.* An international ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome. *Eur Respir J* 2014; **44**: 1479–1503.
21. Kahrilas PJ, Bredenoord AJ, Fox M *et al.* The Chicago classification of esophageal motility disorders, v3.0. *Neurogastroenterol Motil* 2015; **27**: 160–174.
22. Roman S, Lin Z, Kwiatek MA *et al.* Weak peristalsis in esophageal pressure topography: classification and association with Dysphagia. *Am J Gastroenterol* 2011; **106**: 349–356.
23. Tutuian R, Vela MF, Balaji NS *et al.* Esophageal function testing with combined multichannel intraluminal impedance and manometry: multicenter study in healthy volunteers. *Clin Gastroenterol Hepatol* 2003; **1**: 174–182.
24. Shay S, Tutuian R, Sifrim D *et al.* Twenty-four hour ambulatory simultaneous impedance and pH monitoring: a multicenter report of normal values from 60 healthy volunteers. *Am J Gastroenterol* 2004; **99**: 1037–1043.
25. Tutuian R, Mainie I, Agrawal A *et al.* Normal values for ambulatory 24-hour combined impedance-pH monitoring on acid suppressive therapy. *Gastroenterology* 2006; **130** (Suppl 2): A171.
26. Johnson LF, Demeester TR. Twenty-four-hour pH monitoring of the distal esophagus. A quantitative measure of gastroesophageal reflux. *Am J Gastroenterol* 1974; **62**: 325–332.
27. Frazzoni M, Manta R, Mirante VG *et al.* Esophageal chemical clearance is impaired in gastro-esophageal reflux disease–a 24-h impedance-pH monitoring assessment. *Neurogastroenterol Motil* 2013; **25**: 399–406e295.
28. Frazzoni M, Savarino E, de Bortoli N *et al.* Analyses of the post-reflux swallow-induced peristaltic wave index and nocturnal baseline impedance parameters increase the diagnostic yield of impedance-pH monitoring of patients with reflux disease. *Clin Gastroenterol Hepatol* 2016; **14**: 40–46.
29. Ward C, Forrest IA, Brownlee IA *et al.* Pepsin like activity in bronchoalveolar lavage fluid is suggestive of gastric aspiration in lung allografts. *Thorax* 2005; **60**: 872–874.
30. Pegna V, Mickevicius A, Tsang C. How useful is antireflux surgery in lung transplant patients with gastroesophageal reflux? *Medicina* 2014; **50**: 318–322.
31. Atkins BZ, Trachtenberg MS, Prince-Petersen R *et al.* Assessing oropharyngeal dysphagia after lung transplantation: altered swallowing mechanisms and increased morbidity. *J Heart Lung Transplant* 2007; **26**: 1144–1148.
32. Atkins BZ, Petersen RP, Daneshmand MA *et al.* Impact of oropharyngeal dysphagia on long-term outcomes of lung transplantation. *Ann Thorac Surg* 2010; **90**: 1622–1628.