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The impact of lung transplantation on esophageal motility and inter-relationships with reflux and lung mechanics in patients with restrictive and obstructive respiratory disease

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Abstract

Background: For many patients with lung disease the only proven intervention to improve survival and quality of life is lung transplantation (LTx). Esophageal dysmotility and gastroesophageal reflux (GER) are common in patients with respiratory disease, and often associate with worse prognosis following LTx. Which, if any patients, should be excluded from LTx based on esophageal concerns remains unclear. Our aim was to understand the effect of LTx on esophageal motility diagnosis and examine how this and the other physiological and mechanical factors relate to GER and clearance of boluses swallowed.

Methods: We prospectively recruited 62 patients with restrictive (RLD) and obstructive (OLD) lung disease (aged 33–75 years; 42 men) who underwent high resolution impedance manometry and 24-h pH-impedance before and after LTx.

Key Results: RLD patients with normal motility were more likely to remain normal ($p=0.02$), or if having abnormal motility to change to normal ($p=0.07$) post-LTx than OLD patients. Esophageal length (EL) was greater in OLD than RLD patients' pre-LTx ($p<0.001$), reducing only in OLD patients' post-LTx ($p=0.02$). Reduced EL post-LTx associated with greater contractile reserve ($r=0.735$; $p=0.01$) and increased likelihood of motility normalization ($p=0.10$). Clearance of reflux improved ($p=0.01$) and associated with increased mean nocturnal baseline impedance ($p<0.001$) in RLD but not OLD. Peristaltic breaks and thoraco-abdominal pressure gradient impact both esophageal clearance of reflux and boluses swallowed ($p<0.05$).

Conclusions and Inferences: RLD patients are more likely to show improvement in esophageal motility than OLD patients post-LTx. However, the effect on GER is more

Abbreviations: %FEV_1, percent predicted forced expiratory volume in 1 s; %FVC, percent predicted forced vital capacity; AET, acid exposure time; AR, augmentation ratio; BMI, body mass index; CCv4.0, Chicago Classification version 4.0; DCI, distal contractile integral; DL, distal latency; EGJ, esophagogastric junction; EGJOO, esophagogastric junction outflow obstruction; ELI, esophageal length index; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; HRIM, high resolution impedance manometry; IBT, incomplete bolus transit; IEM, ineffective esophageal motility; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; LESP, lower esophageal sphincter pressure; MII-pH, multichannel intraluminal impedance-pH (24 h pH-impedance); MRS, multiple rapid swallows; TAPG, thoraco-abdominal pressure gradient; TBET, total bolus exposure time; tLESR, transient lower esophageal sphincter relaxation; UES, upper esophageal sphincter.

difficult to predict and requires other GI, anatomical and pulmonary factors to be taken into consideration.

KEYWORDS
esophageal motility, lung transplantation, reflux

1 | INTRODUCTION

Although advances in therapy may delay the progression of chronic lung disorders, many will continue towards progressive respiratory failure where lung transplant (LTx) remains the only option. However, long-term survival and mortality following LTx remain poor compared with other solid organ transplants. One of the factors that is believed to drive this poor prognosis is repetitive aspiration of gastroesophageal refluxate, injuring the lung epithelium and causing chronic lung allograft dysfunction (CLAD).[1,2]

Esophageal dysmotility and gastroesophageal reflux (GER) are common in patients with respiratory disease, thought to be linked to disease progression, and are also common following LTx. The most common esophageal motor disorders include minor disorders of peristalsis, such as ineffective esophageal motility (IEM) and esophago-gastric junction outflow obstruction (EGJOO),[3–9] along with Jackhammer esophagus seen in some patients, mainly post-LTx,[4,6–8,10–12] IEM is associated with greater numbers of proximal reflux events both in respiratory disease[9] and following LTx,[8] while EGJOO is associated with significantly less GER, despite an apparent increased risk of developing CLAD post-LTx.[8] Although studies have suggested that distal contractile integral (DCI)[4,6,7] and aperistalsis prior to LTx can improve following LTx,[13,14] it remains unclear whether certain motility diagnoses prior to LTx either remain the same or change to another diagnosis following LTx, and if this differs with type of respiratory disease. Given the differential effects that dysmotility can have on esophageal exposure to reflux, better understanding of the changes in motility diagnosis following LTx may help to explain the current lack of clarity on the effect of LTx on GER, as attested by some studies reporting a worsening[15] but others no effect.[4,6,7,10] Moreover, better understanding of changes in motor diagnosis following LTx may have important implications for identifying those at an increased risk of post-LTx complications and guide specific interventions to mitigate these complications.

Other important considerations that have been shown to influence motility, GER or both include (i) disordered lung mechanics including changes in the thoraco-abdominal pressure gradient (TAPG), which can affect the amount of GER and its proximal extent,[9,16] (ii) the effect of lung volume on esophageal length (EL), which can adversely affect esophageal motor function,[7] (iii) the presence of an abnormal post-reflux swallow induced peristaltic wave (PSPW), which has been shown to associate with increased bolus clearance time and proximal extent on reflux events, along with worse disease progression in patients with idiopathic pulmonary fibrosis (IPF),[8,17] and finally (iv) the level of contraction reserve (CR), as measured using the multiple rapid swallow (MRS) test, which theoretically could impact improvement in motility post-LTx. How these associate with type of respiratory disease and are affected by LTx is uncertain.

Lastly abnormal swallowing and impaired clearance of swallowed boluses, especially in the presence of EGJOO might be an important risk factor for aspiration, lung injury and the development of o-CLAD.[8] We have shown that 66% of IPF patients' exhibit incomplete transit of boluses swallowed, and that the proportion of swallows that are associated with incomplete bolus transit directly correlates with the proportion of esophageal peristaltic events that are ineffective.[9] Whether LTx improves clearance of boluses swallowed remains unknown.

All these factors continue to hinder the development of consensus guidelines on whether certain patients with end-stage lung disease should be prioritized more than others to undergo LTx based on

Key points

1. Patients with restrictive lung disease who have normal esophageal motility are more likely to remain normal, or if they have abnormal motility to change to normal motility post-lung transplantatation than patients with obstructive lung disease.
2. Esophageal length in patients with obstructive disease is longer than patients with restrictive disease pre-lung transplantation. Obstructive disease patients who exhibited a decrease in esophageal length post-lung transplantation are more likely to show a normalisation in motility than those who do not exhibit a reduction in esophageal length post-lung transplantation.
3. Esophageal length inversely correlates with augmentaion ratio in response to multiple rapid swallow in obstructive disease patients post-lung transplantation, suggesting stretching of the esophagus may effect the neuromuscular function of the esophagus.
4. Clearance of reflux and mean nocturnal baseline impedance improved in restrictive but not obstructive lung disease patients post-lung transplantation.
5. Peristaltic breaks and thoraco-abdominal pressure gradient impact both esophageal clearnace of reflux and boluses swallowed.

esophageal physiology. This can lead to patients with abnormal pH-metry and/or significant motility abnormalities prior to LTx, being excluded from transplant waiting lists, or possibly undergo high risk fundoplication or unnecessary anti-reflux therapies that do not target the specific physiologic derangement.

Our aim was therefore to further our understanding of the effect of LTx on esophageal motor function, namely motility diagnosis, and examine how this and the other factors mentioned above relate to GER and clearance of boluses swallowed both before and following LTx.

2 | METHODS

2.1 | Patients

This was a prospective study of 62 consecutive patients out of a possible 347 patients referred for high-resolution impedance manometry (HRIM) and 24 h pH/impedance prior to transplant and then followed up approximately 3 months after surgery at Mayo Clinic, Florida between November 2017 and January 2022. Of the remaining 285 patients, 17 patients underwent pre- and post-LTx testing but were missing one or more HRIM tests, 195 underwent only pre-LTx testing (either still awaiting LTx, died prior to LTx or refused testing) and 73 underwent only post-LTx testing (too ill to perform pre-LTx testing or refused testing). Patients who had undergone any form of foregut surgery were excluded from our analysis. Patient data included age, sex, body mass index (BMI), indication for LTx, LTx date, and post-LTx medication. The Mayo Clinic Institutional Review Board approved the study (IRB# 18-005280). No patient received compensation for taking part in this study.

2.2 | High-resolution impedance manometry

High-resolution impedance manometry (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 trans-nasally with the distal sensors for both pressure and impedance in the proximal stomach. Following at least a 30 s baseline to identify the upper (UES) and lower (LES) esophageal sphincter, ten 5 mL saline swallows were given at least 30 s apart with the patient supine.[18] This was followed by a MRS sequence involving five 2 mL swallows every 2–3 s in the supine position.[19]

2.3 | 24 h-pH/impedance

24 h-pH/impedance (Sandhill Scientific, Highlands Ranch, CO) was performed using a single antimony pH probe (5 cm above the LES) with eight impedance electrodes.[18]

2.4 | Date analysis

2.4.1 | HRIM

ManoVIEW analysis software v3.01 (Medtronic, Shoreview, NM) was used to manually analyze the recordings. Esophageal motility was classified based upon Chicago Classification version 4.0 (CC v4.0).[20] Each 5 mL swallow was evaluated to determine: (i) integrated relaxation pressure (IRP), (ii) DCI, (iii) distal latency (DL), and (iv) isobaric contour (pressurization).[21] Contractile pattern was classified as normal, weak, failed peristalsis, fragmented or hypercontractile swallow.[20]

CC v4.0 diagnoses included: (i) achalasia or EGJOO, and (ii) disorders of peristalsis, such as absent contractility, distal esophageal spasm (DES), hypercontractile esophagus (single peak hypercontractile swallow, Jackhammer esophagus and hypercontractile lower esophageal sphincter) and IEM.[20]

CR was determined from the ratio between MRS DCI and mean single non-failed swallow DCI, where a ratio of >1 is defined as the presence of CR.[19]

Impedance recordings were evaluated for each swallow and bolus clearance assessed using both colorized contour functions and superimposed impedance tracings, as previous described.[21] Bolus clearance was defined as "complete" or "incomplete" based on the color overlay and line-tracing modes.[21] Subjects were classified as complete bolus transit when clearance was seen in ≥80% of swallows.[22]

Thoraco-abdominal pressure gradient (TAPG)

TAPG was calculated by subtracting the intra-abdominal pressure (AP; proximal stomach 1 cm below the lower border of the LES and referenced to atmospheric pressure) from the mean intrathoracic pressure (TP; distal esophagus between 1 and 5 cm above the upper border of the LES and referenced to atmospheric pressure) during inspiration. LES pressure during inspiration, referenced to the pressure at the level of the intra-abdominal pressure (i.e., 1 cm below the lower border of the LES), was also measured, and an adjusted TAPG was calculated by subtracting lower esophageal sphincter pressure (LESP) from the TAPG during inspiration. A cut-off value of adjusted TAPG to predict the risk of reflux was set at >0 mmHg, based on the hypothesis that reflux may occur when TAPG overcomes the LESP.[23]

Esophageal length (EL)

Manometric EL was measured from the lower border of the UES to the upper border of the LES at the end inspiration. Esophageal length index (ELI) was calculated by dividing EL in centimeters by patient height in meters.[7]

2.4.2 | 24 h pH-impedance (MII-pH)

Data were manually analyzed (BioVIEW Analysis software, Sandhill Scientific, CO) excluding meals for reflux episodes based on retrograde impedance decrease to 50% of baseline in at least two distal

adjacent channels. Abnormalities in reflux exposure were as previously defined.[9,24]

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.[25,26] The PSPW index was considered abnormal if <61%.[26]

Mean nocturnal baseline impedance (MNBI)

MNBI was calculated at 3, 5, 7, 9, 15, and 17 cm above the LES during night time rest for 10 min at around 1:00, 2:00, and 3:00 am, excluding reflux episodes, swallows and pH drops.[27]

2.4.3 | Statistics

Group differences were evaluated using Student's *t*-tests or Mann–Whitney *U*-tests. Tests for proportionality between groups were assessed using Chi-square or Fisher's exact tests. The relationships between variables were assessed using scatterplots and quantified using Spearman's rank (nonparametric data) tests. Significance was evaluated at the two-tailed, *p*-value of <0.05 taken as significant.

3 | RESULTS

Of the 62 patients recruited (median age 60 (range 33–75) years; mean BMI 27 (95% CI 26–28) kg/m^2; 20 female), 40 patients had restrictive lung disease (RLD) (aged 63 (37–74) years; BMI 28 (26–29) kg/m^2; 10 female; 1 current smoker), 17 obstructive lung disease (OLD) (aged 58 (33–75) years; BMI 25 (23–27) kg/m^2; 8 female; 1 current smoker), 4 combined restrictive/ obstructive lung disease, and one pulmonary arterial hypertension. As expected most of the patients with RLD suffered from either severe ($n=23$, 58%, percent predicted forced vital capacity (% pred FVC) ≤50%) or moderate ($n=15$, 38%, % pred FVC 79–51%) disease. Likewise, a similar percentage of patients with OLD suffered from severe ($n=13$, 76%, percent predicted forced expiratory volume in 1 s (% pred FEV1) ≤50%) disease. All patients underwent HRIM a median of 113 days (IQR 61–212 days) before LTx and a median of 82 days (IQR 66–102 days) after surgery. Of these 55 underwent 24 h MII-pH before LTx and 53 after LTx. Of those undergoing MII-pH, 4 (7%) were tested on PPIs pre-LTx and 7 (13%) post-LTx. 54 (87%) underwent bilateral, and 8 (13%) unilateral LTx. Out of the 8 patients receiving unilateral transplant, 6 patients had RLD, 1 OLD and, 1 combined RLD/OLD.

3.1 | HRIM (CCv4.0)

Before LTx, 25 (40%) patients exhibited abnormal motility, with the majority being either IEM (11, 44%) or EGJOO (11, 44%) (Table 1). Following LTx, the number of patients with abnormal motility did not significantly change (27, 44%), with again the majority of patients presenting with either IEM (9, 33%) or EGJOO (11, 41%). However, amongst those with abnormal motility, more patients exhibited hyper-contractile esophagus (five Jackhammer and one hypercontractile lower esophageal sphincter) post-LTx compared with pre-LTx (one hypercontractile lower esophageal sphincter) ($p=0.046$) (Table 1).

Closer examination of the changes in individual diagnoses following LTx, showed that approximately half of patients (34, 55%) retained the same diagnoses as before LTx (Figure 1A). Moreover, patients with normal motility pre-LTx were more likely to retain the same diagnoses (i.e. normal) post-LTx (25/37, 68%) than those with IEM (4/11, 36%) or EGJOO (4/11, 36%) ($p=0.085$ for both) (Figure 1A). Of those with abnormal motility pre-LTx ($n=25$), 10 (40%) changed to normal motility post-LTx. Figure 1A details the individual changes in diagnosis (i.e., CCv4.0) following transplantation.

Interestingly, of the 37 patients who had normal motility defined using CCv4.0 pre-LTx, only 9 (24%) exhibited completely normal peristalsis for all swallows (i.e., no peristaltic breaks), which doubled to 17 out of 35 (49%) post-LTx ($p=0.049$), suggesting that esophageal peristalsis improved even in those with CCv4.0 defined normal motility.

3.1.1 | Restrictive versus obstructive lung disease

Examining the restrictive (RLD, $n=40$) and obstructive (OLD, $n=17$) lung disease sub-types pre-LTx (Figure 1B,C), showed a similar prevalence of abnormal motility in both groups (15 (37.5%) vs. 8 (47%)); with the majority of RLD patients presenting with either IEM (8, 53%) or EGJOO (6, 40%), and the majority of OLD patients presenting with EGJOO (4, 50%) (Figure 1B,C) (Table 2).

Following LTx, approximately half of patients from both groups retained the same diagnosis (21, 53% vs. 10, 59%). However, patients with RLD who had normal motility pre-LTx were more likely to remain normal post-LTx (17/25, 68%) than those with abnormal motility diagnoses (4/15, 27%) ($p=0.021$), particularly compared with those with EGJOO (1/6, 17%) ($p=0.059$). While patients with OLD who had normal motility (5/9, 56%) were no more likely to retain the same diagnosis as those with abnormal motility (5/8, 62.5%). Moreover, more patients with RLD who had abnormal motility were likely to change to normal motility post-LTx (9/15, 60%) than those with OLD (1/8, 12.5%) ($p=0.07$) (Figure 1B,C). In addition, patients with OLD were more likely to retain a diagnosis of EGJOO (3/4, 75%) than those with RLD (1/6, 17%) ($p=0.190$).

Of the 6 RLD patients who underwent unilateral LTx, 4 had normal motility and 2 IEM pre-LTx, with 5/6 retaining the same diagnosis post-LTx, except for one patient with IEM who acquired EGJOO in addition to IEM.

Lastly, in the total cohort, LTx was associated with an increase in DCI ($p<0.001$) and DL ($p=0.002$) (Table 1). Furthermore, the percentage of patients with normal UES pressure tended to

TABLE 1 HRIM findings in total cohort pre- and post-LTx.

	Pre-LTx	Post-LTx	*p*-value
UES resting pressure, mmHg[a]	84 (39–117)	70 (53–92)	0.271
Pts with normal UES pressure, *n* (%)	34 (55%)	44 (71%)	0.094
Pts with hypotensive UES, *n* (%)	10 (16%)	7 (11%)	0.603
Pts with hypertensive UES, *n* (%)	18 (29%)	11 (18%)	0.203
Nadir UES residual pressure, mmHg[a]	0.3 (−0.5 to 6)	3 (−2 to 5)	0.172
LES resting pressure, mmHg[a]	32 (22–48)	29 (20–41)	0.057
Pts with normal LES pressure, *n* (%)	38 (61%)	39 (63%)	1.0
Pts with hypotensive LES, *n* (%)	2 (3%)	11 (18%)	0.030
Pts with hypertensive LES, *n* (%)	22 (35%)	12 (19%)	0.069
Ps with LES-CD separation >2 cm, *n* (%)	12 (19%)	10 (16%)	0.815
Mean IRP, mmHg[b]	10 (9–12)	10 (8–11)	0.638
Median IRP, mmHg[a]	10 (6–13)	10 (5–12)	0.370
DL, s[a]	7 (7–8)	8 (7–9)	0.002
DCI, mmHg/s/cm[a]	942 (514–2251)	2129 (762–3538)	<0.001
CCv4.0, *n* (%)			
Normal, *n* (%)	37 (60%)	35 (56%)	0.856
Achalasia, *n* (%)	0 (0%)	0 (0%)	–
EGJOO, *n* (%)	11 (18%)	11 (18%)	1.0
DES, *n* (%)	1 (2%)	1 (2%)	1.0
Absent contractility, *n* (%)	1 (2%)	0 (0%)	1.0
IEM, *n* (%)	11 (18%)	9 (15%)	0.808
Hyper-contractile esophagus	1 (2%)	6 (10%)	0.114
-single peak hyper-contractile	0	0	–
-jackhammer	0	5	0.057
-hyper-contractile LES	1	1	1.0
Esophageal length			
Esophageal length, cm[b]	24.7 (23.9–25.4)	24.7 (24.1–25.3)	0.893
Esophageal length index[b]	14.3 (13.8–14.7)	14.3 (13.9–14.6)	0.902
TAPG (during inspiration)			
Intra-abdominal pressure, mmHg[a]	17.0 (11.2–21.5)	15.1 (9.2–21.7)	0.952
Intra-thoracic pressure, mmHg[a]	−3.7 (−7.9 to 1.1)	1.2 (−2.3 to 5.2)	<0.001
TAPG, mmHg[a]	19.1 (14.6–25.5)	13.7 (8.2-20.4)	<0.001
Adjusted TAPG, mmHg[a]	−47.9 (−68.3 to −17.9)	−26.9 (−48.3 to −14.0)	0.023
Bolus transit			
Patients with IBT, *n* (%)	51 (82%)	43 (69%)	0.141
Swallows with IBT, median (IQR) (%)[a]	74 (40–100)	74 (25–90)	0.229

Abbreviations: CCv4.0, Chicago Classification version 4.0; CD, crural diaphragm; DCI, distal contractile integral; DL, distal latency; EGJOO, esophagogastric outflow obstruction; HRIM, high resolution impedance manometry; IEM, ineffective esophageal motility; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; UES, upper esophageal sphincter.

Results expressed as medain (IQR)[a], mean (95% CI)[b], and number (percentage) for categorical variables.

increase following LTx, ($p = 0.094$), whilst those with a hypotensive LES increased ($p = 0.030$) and those with a hypertensive LES decreased ($p = 0.069$). Resting LES pressure tended to decrease post-LTx ($p = 0.057$) (Table 1). Examining patients with RLD and OLD separately, both DCI and DL increased post-LTx (RLD: $p = 0.016$ and $p = 0.016$, OLD: $p = 0.049$ and $p = 0.015$, respectively). In RLD patients, nadir UES residual pressure significantly increased ($p = 0.013$) and the percentage of patients with a hypertensive LES halved ($p = 0.114$), whilst in OLD patients UES resting pressure ($p = 0.019$) and the percentage of patients with hypertensive UES ($p = 0.039$) decreased, increasing the percentage of patients with normal UES pressure from 47% to 82% ($p = 0.071$) (Table 2).

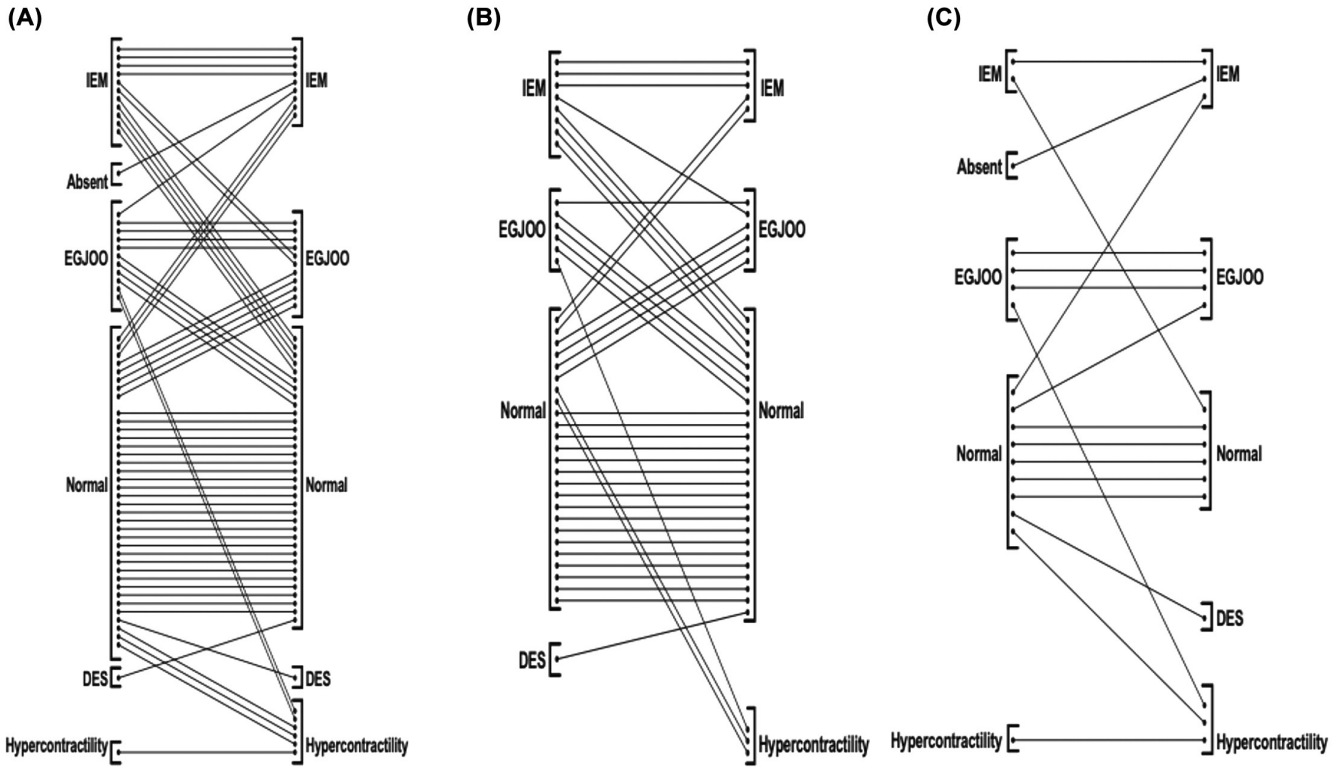

FIGURE 1 Changes in Chicago classification v4.0 following transplant in whole cohort (A), and patients with RLD (B) and OLD (C).

3.2 | Esophageal length (EL)

Before LTx, OLD patients had significantly longer manometric EL ($p<0.001$) and higher ELI ($p<0.001$) than RLD patients (Table 2). Following LTx, EL and ELI significantly decreased in OLD patients ($p=0.020$ and $p=0.022$, respectively), reflecting 12 (71%) of OLD patients exhibiting a decrease in EL following LTx (Table 2). There was a trend for manometric EL ($p=0.062$) and ELI ($p=0.061$) to slightly increase in RLD patients, but with similar percentages of patients showing either a slight increase (21, 52.5%) or no change/decrease in EL (19, 47.5%) following LTx. Both EL and ELI remained significantly longer in OLD compared with RLD patients post-LTx. Interestingly, of those OLD patients who exhibited a decrease in EL following LTx, there was a trend that more patients either remained or changed to normal motility (50%) compared with patients who did not exhibit a reduction in EL (0%; $p=0.10$).

In RLD patients who had undergone unilateral LTx, there was no significant change in EL (Pre-LTx: 23.0 (21.6–24.4) cm (mean(95% CI)) vs. post-LTx 23.4 (21.3–25.5) cm; $p=0.388$) or ELI (13.3 (12.1–14.5) vs. 13.6 (11.9–15.2); $p=0.465$) post-LTx.

3.3 | TAPG

Patients had a significantly lower intra-TP pre- compared with post-LTx ($p<0.001$). There was no difference in intra-AP. Thus, the TAPG ($p<0.001$) and adjusted TAPG ($p=0.023$) were greater pre- compared with post-LTx (Table 1). Changes in intra-TP and TAPG following LTx were more evident in patients with RLD than OLD (Table 2).

Interestingly, in the 6 RLD patients who had undergone unilateral transplant we observed similar improvement trends in intra-thoracic pressure (pre-LTx: −5.3 (−8.0 to −3.8) mmHg vs. post-LTx: −0.8 (−4.8 to 3.3) mmHg) (Median (IQR); $p=0.101$) and TAPG (16.3 (14.8–19.8) mmHg vs. 9.7 (4.2–17.7) mmHg; $p=0.172$) post-LTx, and no significant changes in intra-abdominal pressure (11.0 (6.8–17.6) mmHg vs. 8.6 (8.0–9.3) mmHg; $p=0.574$) or aTAPG (−45.0 (−57.0 to 10.2) mmHg vs. −48.3 (−76.8 to 1.1) mmHg; $p=0.609$), as seen in the whole RLD cohort.

3.4 | MRS parameters

Fifty-three percent of patients pre-LTx exhibited an abnormal augmentation ratio (AR) in response to MRS which did not significantly change post-LTx (42%; $p=0.304$). Fewer RLD patients had an abnormal AR (41%) compared with OLD patients pre-LTx (80%; $p=0.0625$). Following LTx there was no significant change in percentage of RLD (37%; $p=0.800$) or OLD (55%; $p=0.361$) patients with an abnormal AR. Similarly, the AR was higher in RLD compared with OLD patients pre-LTx (1.19 (0.74–2.91) vs. 0.45 (0.20–0.88; $p=0.034$)), remaining similar post-LTx (1.13 (0.76–1.89) and 0.73 (0.34–1.87), respectively).

3.4.1 | AR and, EL and ELI

In patients with OLD post-LTx, AR inversely correlated with both EL ($r=-0.735$; $p=0.01$) and ELI ($r=-0.727$; $p=0.011$). No correlations were seen pre-LTx in OLD or RLD, or post-LTx in RLD.

TABLE 2 HRIM findings in patients with restrictive (RLD) and obstructive (OLD) lung disease pre- and post-LTx.

	RLD pre-LTx	RLD post-LTx	*p*-value	OLD pre-LTx	OLD post-LTX	*p*-value
UES resting pressure, mmHg[a]	85 (38–111)	74 (57–90)	0.861	93 (78–117)	59 (51–74)****	0.019
Pts with normal UES pressure, *n* (%)	23 (58%)	28 (70%)	0.352	8 (47%)	14 (82%)	0.071
Pts with hypotensive UES, *n* (%)	7 (18%)	4 (10%)	0.518	2 (12%)	2 (12%)	1.0
Pts with hypertensive UES, *n* (%)	10 (25%)	8 (20%)	0.790	7 (41%)	1 (6%)	0.039
Nadir UES residual pressure, mmHg[a]	−0.1 (−4.7 to 5.5)	3 (−0.7 to 5.7)	0.013	2.8 (−1.8 to 10.6)	2.6 (−0.1 to 4.7)	1.0
LES resting pressure, mmHg[a]	31 (22–46)	30 (21–37)	0.294	37 (22–53)	37 (20–44)	0.124
Pts with normal LES pressure, *n* (%)	25 (63%)	28 (70%)	0.637	10 (59%)	9 (53%)	1.0
Pts with hypotensive LES, *n* (%)	2 (5%)	6 (15%)	0.263	0 (0%)	3 (18%)	0.227
Pts with hypertensive LES, *n* (%)	13 (33%)	6 (15%)	0.114	7 (41%)	5 (29%)	0.721
Pts with LES-CD separation >2cm, *n* (%)	9 (15%)	4 (10%)	0.225	2 (12%)	4 (24%)	0.656
Mean IRP, mmHg[b]	10 (8–12)	10 (8–12)	0.720	10 (7–14)	10 (7–13)	0.874
Median IRP, mmHg[a]	10 (7–13)	10 (6–12)	0.416	9 (6–14)	9 (6–13)	0.868
DL, s[a]	7 (7–8)	8 (7–9)	0.016	8 (7–9)**	9 (8–10)***	0.015
DCI, mmHg/s/cm[a]	911 (572–2306)	1591 (636–3508)	0.016	1231 (430–3463)	2140 (1410–4764)****	0.049
CCv4.0, *n* (%)						
Normal, *n* (%)	25 (63%)	26 (66%)	1.0	9 (53%)	6 (35%)***	0.491
Achalasia, *n* (%)	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–
EGJOO, *n* (%)	6 (15%)	6 (15%)	1.0	4 (24%)	4 (24%)	1.0
DES, *n* (%)	1 (3%)	0 (0%)	1.0	0 (0%)	1 (6%)	1.0
Absent contractility, *n* (%)	0 (0%)	0 (0%)	–	1 (6%)	0 (0%)	–
IEM, *n* (%)	8 (20%)	5 (13%)	0.546	2 (12%)	3 (18%)	1.0
Hyper-contractile esophagus	0 (0%)	3 (8%)	0.241	1 (6%)	3 (18%)	0.601
Esophageal length						
Esophageal length, cm[b]	23.6 (22.9–24.3)	24.0 (23.4–24.7)	0.062	27.2 (25.8–28.6)*	26.3 (25.1–27.4)*	0.020
Esophageal length index[b]	13.6 (13.2–14.0)	13.9 (13.5–14.2)	0.061	15.8 (15.2–16.5)*	15.3 (14.7–15.9)*	0.022
TAPG (during inspiration)						
Intra-abdominal pressure, mmHg[a]	16.3 (11.1–21.1)	12.2 (8.9–17.5)	0.061	18.4 (14.3–21.8)	22.6 (17.7–25.7)*	0.011
Intra-thoracic pressure, mmHg[a]	−4.2 (−8.2 to 0.02)	1.6 (−3.0 to 5.8)	<0.001	−0.3 (−5.5 to 1.1)	0.9 (−2.1 to 4.3)	0.093
TAPG, mmHg[a]	19.8 (14.7–25.0)	11.0 (7.2–16.1)	<0.001	17.7 (14.3–22.5)	23.4 (15.5–27.0)*	0.246
Adjusted TAPG, mmHg[a]	−47.4 (−58.2 to −15.0)	−23.9 (−48.3 to −14.2)	0.183	−49.5 (−96.4 to −21.4)****	−35.8 (−43.0 to −14.4)	0.102
Bolus transit						
Patients with IBT, *n* (%)	31 (78%)	27 (68%)	0.453	15 (88%)	12 (71%)	0.398
Swallows with IBT, (%)[a]	69 (37–90)	70 (23–100)	0.743	89 (44–100)	78 (25–90)	0.197

Abbreviations: CCv4.0, Chicago Classification version 4.0; CD, crural diaphragm; DCI, distal contractile integral; DL, distal latency; EGJOO, esophagogastric outflow obstruction; HRIM, high resolution impedance manometry; IEM, ineffective esophageal motility; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; UES, upper esophageal sphincter.

Results expressed as medain (IQR)[a], mean (95% CI)[b], and number (percentage) for categorical variables.

*$p \le 0.001$. **$p \le 0.01$. ***$p \le 0.05$. ****$p \le 0.10$ compared with corresponding RLD.

3.5 | Bolus transit

Eighty-two percent of patients before LTx exhibited incomplete transit of boluses swallowed, and across the whole patient cohort, a median of 74% (IQR: 40%–100%) of swallows were incomplete (Table 1). Following LTx, there was a tendency for the percentage of patients with incomplete bolus transit (IBT) to decrease (69%, $p = 0.141$). No significant differences were seen between the RLD and OLD patients pre-LTx, or changes following LTx (Table 2). Unilateral LTx in those with RLD did not affect findings.

3.5.1 | Effects of peristaltic breaks, and thoracic and abdominal pressures on IBT

Fewer patients with completely normal peristalsis for all swallows (i.e. no peristaltic breaks) exhibited IBT compared with patients with normal motility defined using CCv4.0 (i.e., up to seven swallows with peristaltic breaks) both before (6/9, 67% vs. 25/28, 89%; $p=0.14$) and after (7/17, 41% vs. 15/18, 83%; $p=0.015$) LTx. This reflected the percentage of swallows with IBT been lower in those with completely normal peristalsis (20 (0–78)) compared with those with CCv4.0 normal motility (74 (50–100); $p=0.024$) post-LTx. Lastly, in patients with completely normal esophageal peristalsis for all swallows (i.e. no peristaltic breaks) there was a tendency for the percentage of swallows in which bolus transit was incomplete to negatively correlate with intra-TP pre-LTx ($r=-0.528$; $p=0.144$) and to positively correlate with the TAPG post-LTx ($r=0.455$, $p=0.067$).

3.6 | MII-pH

Prior to LTx, 11 (22%) patients exhibited abnormal acid exposure (AET; i.e., >6%), 18 (37%) abnormal total bolus exposure time (TBET; i.e., ≥1.4), 1 (2%) an abnormal number of reflux events (>80) and 6 (12%) an abnormal number of reflux events reaching the proximal esophagus (>31) (Table 3). Following LTx, the number of patients with an abnormal number of reflux events (>80) slightly increased (7 (14%); $p=0.059$) but this had no effect on AET or TBET (Table 3).

No significant differences in MII-pH parameters were seen between RLD and OLD patients pre-LTx. Following LTx, AET ($p=0.054$) and bolus clearance time ($p=0.010$) were reduced in patients with RLD, whilst in patients with OLD bolus clearance time tended to increase ($p=0.065$) (Table 4). In the small number of unilateral LTx RLD patients who had undergone MII-pH ($n=5$) there was no change in AET (pre-LTx: 1.1 (0–2.3)% vs. post-LTx 1.2 (0.1–1.4)%; $p=0.607$) or TBET (0.5 (0.1–0.8)% vs. 0.3 (0.2–0.6)%; $p=0.874$) following LTx.

3.6.1 | Effects of thoracic and abdominal pressures on MII-pH

In patients with completely normal peristalsis for all swallows ($n=9$) pre-LTx (i) the greater the negative intra-TP the more reflux events occurred ($r=-0.857$; $p=0.007$), (ii) the greater the adjusted TAPG the higher AET ($r=0.881$; $p=0.004$), total bolus exposure ($r=0.667$; $p=0.071$), and number of proximal reflux events ($r=0.707$; $p=0.05$). Post-LTx, the greater the AP the greater AET ($n=12$: $r=0.601$; $p=0.039$). No other associations were observed post-LTx.

Fewer correlations were seen in patients with CCv4 defined normal motility or IEM pre-LTx and included (i) the greater the adjusted TAPG the higher AET in those with CCv4 normal motility ($r=0.365$; $p=0.056$) and (ii) the greater the adjusted TAPG the higher the TBET in those with IEM ($r=0.729$; $p=0.005$). Post-LTx, the greater the AP in those with CCv4 normal motility the greater (i) AET ($r=0.436$; $p=0.033$), (ii) TBET ($r=0.500$; $p=0.013$), (iii) number of distal reflux events ($r=0.439$; $p=0.032$), and (iv) proximal reflux events ($r=0.420$; $p=0.041$). Post-LTx there were no associations with intra-TP, but TAPG correlated with (i) AET ($r=0.372$; $p=0.074$), (ii) TBET ($r=0.420$; $p=0.041$), (iii) proximal reflux events ($r=0.440$; $p=0.031$), (iv) proportion of reflux events reaching the proximal esophagus ($r=0.421$; $p=0.041$) and bolus clearance time ($r=0.435$; $p=0.062$).

3.7 | Mean nocturnal baseline impedance (MNBI)

MNBI increased along the length of the esophagus, particularly in the distal esophagus (i.e., 3–5 cm above LES) post- compared with pre-LTx (Table 3). This reflected an increase in MNBI, particularly in the distal esophagus of patients with RLD and not OLD, such that post-LTx, MNBI was higher in the distal esophagus of RLD than OLD patients (at 3 cm above LES, $p=0.029$; at 5 cm above LES $p=0.069$). Pre-LTx there was no difference in MNBI between RLD and OLD patients (Table 4). In the small number of unilateral LTx RLD patients ($n=5$) there was no difference in MNBI pre- and post-LTx (3 cm above LES: 1630.0 (1501.8–1746.7)Ω vs. 1690.0 (1100.8–2763.0) Ω; $p=0.906$, and 5 cm above LES: 1156.7(1066.7–1172.3)Ω vs. 2125.1(1422.6–2230.0)Ω; $p=0.574$).

Pre-LTx MNBI was abnormal at 3 and 5 cm above the LES in 37% and 35% of patients, respectively. Post-LTx, the numbers of patients with an abnormal MNBI significantly reduced to 22% ($p=0.004$) and 23% ($p=0.023$), respectively (Table 3). This reflected decreases in percentage of patients with RLD who exhibited abnormal MNBI (24% to 11% at 3 cm, $p=0.002$; 22% to 14% at 5 cm, $p=0.077$, above LES) rather than OLD (9% to 8% at 3 cm; 9% to 7% at 5 cm above LES) (Table 4).

3.8 | Post-swallow peristaltic wave (PSPW)

There was no difference in either the PSPW index or proportion of patients with an abnormal PSPW before and after LTx. Likewise, no changes were seen in patients with RLD and OLD (Tables 3 and 4). Similarly, there was no difference in the PSPW index before and after LTx in the RLD patients ($n=5$) who had undergone unilateral LTx (44.7 (11.8–77.6) vs. 58.6 (34.6–82.5); $p=0.333$).

4 | DISCUSSION

This comprehensive study has shown for the first time that patients with RLD who have normal esophageal motility pre-LTx are more likely to remain normal after transplant, and those with abnormal motility are more likely to become normal post-LTx than patients

TABLE 3 MII-pH findings in total cohort pre- and post-LTx.

	Pre-LTx	Post-LTx	*p*-value
AET, %[a]	2.1 (0.5–5.1)	1.8 (0.4–4.9)	0.652
Pts with abnormal AET (>6%), *n* (%)	11 (22%)	10 (20%)	1.0
Pts with abnormal AET (>4.2%), *n* (%)	16 (33%)	17 (35%)	1.0
TBET, %[a]	0.90 (0.4–1.7)	0.7 (0.3–1.6)	0.813
Pts with abnormal TBET (≥1.4), *n* (%)	18 (37%)	15 (31%)	0.669
Total no. of events, *n*[a]	37 (18–48)	34 (16–54)	0.564
Total no. of acid events (pH ≤ 4), *n*[a]	18 (6–29)	10 (2–25)	0.476
Total no. of non-acid events (pH ≤ 4), *n*[a]	13 (6–23)	16 (8–25)	0.124
Pts with abnormal no. of events (>73)	3 (6%)	8 (16%)	0.119
Pts with abnormal no. of events (>80)	1 (2%)	7 (14%)	0.059
Total no. of proximal events, *n*[a]	6 (3–15)	7 (2-25)	0.182
Pts with abnormal no. of events (>31)	6 (12%)	9 (18%)	0.576
% of proximal events/total events, %[a]	22.9 (10.8–40)	31.2 (11.7–47.8)	0.262
Bolus clearance time, s[a]	10.5 (9–13)	10 (6–16)	0.164
Post-reflux swallow-induced peristaltic wave (PSPW)			
PSPW index, %[b]	56.6 (50.0–63.1)	58.9 (51.5–66.3)	0.967
Pts with abnormal PSPW (<61), *n* (%)	25 (51%)	26 (53%)	1.0
Pts with abnormal PSPW (<50), *n* (%)	18 (37%)	17 (35%)	1.0
Mean nocturnal baseline impedance (MNBI)			
Distal (average over channels)[a]	1780 (1244–2545)	2414 (1210–3662)	<0.001
3 cm above LES, Ω[a]	1698 (1090–2263)	2493 (1100–3557)	0.003
5 cm above LES, Ω[a]	1771 (1157–2323)	2412 (1251–3657)	0.004
7 cm above LES, Ω[a]	2004 (1417–2723)	2340 (1370–3883)	0.036
9 cm above LES, Ω[a]	2026 (1269–2523)	2286 (1338–3326)	0.015
Proximal (average over channels)[a]	1920 (1330–3013)	2082 (1610–3338)	0.003
15 cm above LES, Ω[a]	1795 (1199–2867)	2025 (1474–4030)	0.045
17 cm above LES, Ω[a]	1854 (1525–2649)	2423 (1808–3740)	0.035

Abbreviations: AET, acid exposure time; MII-pH, 24-hr pH-impedance; TBET, total bolus exposure time (i.e., % of monitored time that the esophagus was exposed to reflux of any nature).

Results expressed as medain (IQR)[a], mean (95% CI)[b], and number (percentage) for categorical variables.

with OLD. This was despite both RLD and OLD patient sub-groups showing an increase in DCI post-LTx, which may be related in part to more patients exhibiting hyper-contractility post-LTx. However, LTx was associated with a significant reduction in peristaltic breaks in patients with CCv4 defined normal motility, such that the number of patients with completely normal peristalsis for all swallows (i.e., no breaks) doubled following LTx. Whether the improvement in esophageal peristalsis observed in patients with RLD was related to more patients (59%) having a normal augmentation ratio than those with OLD (20%) remains to be confirmed but its noteworthy that AR did not change either in RLD or OLD following LTx, suggesting the actual surgery itself had little impact on the integrity of the neuromuscular structure/function of the esophagus. Interestingly, PSPW was abnormal in approximately half of patients with RLD and OLD, and also did not improve following LTx, the reason for which remains unknown.

Patients with OLD generally have larger lung volumes stretching the esophagus resulting in increased length.[7] This has been proposed to have a negative effect of esophageal motility.[7] It is therefore of note that OLD patients who exhibited a decrease in EL following LTx, tended to be more likely to retain or change to normal motility than those who did not exhibit a reduction in EL. Such effects were not seen in patients with RLD, perhaps because their smaller lungs have less effect on EL. However, post-LTx EL and ELI remained significantly longer in OLD than RLD patients, maybe explaining in part why OLD patients were less likely to exhibit an improvement in esophageal function compared with RLD patients. Moreover, in OLD patients post-LTx there was an inverse correlation between EL/ELI and AR, supporting the notion that stretching of the esophagus may indeed effect the neuromuscular function of the esophagus.[7] This likely could not be seen pre-LTx in OLD patients, or pre- and post-LTx in RLD patients because of smaller differences in EL between

TABLE 4 MII-pH findings in patients with restrictive (RLD) and obstructive (OLD) lung disease pre- and post-LTx.

	RLD pre-LTx	RLD post-LTx	*p*-value	OLD pre-LTx	OLD post-LTx	*p*-value
AET, %[a]	2.4 (0.7–6.9)	1.7 (0.3–4.9)	0.054	2 (0.5–3.4)	3.7 (0.6–10.1)	0.308
Pts with abnormal AET (>6%), *n* (%)	9 (28%)	5 (16%)	0.365	1 (8%)	4 (33%)	0.317
Pts with abnormal AET (>4.2%), *n* (%)	13 (41%)	10 (31%)	0.603	2 (17%)	6 (50%)	0.182
TBET, %[a]	0.9 (0.4–1.9)	0.8 (0.2–1.5)	0.569	0.8 (0.3–1.3)	0.7 (0.6–2.3)	0.340
Pts with abnormal TBET (≥1.4), *n* (%)	13 (41%)	9 (28%)	0.430	3 (25%)	4 (33%)	1.0
Total number of events, *n*[a]	36 (18–46)	34 (14–46)	0. 866	37 (19–55)	40 (19–55)	0.814
Total number of acid events (pH ≤ 4), *n*[a]	18 (7–30)	10 (1–20)	0.106	20 (10–31)	13 (2–44)	0.875
Total number of non-acid events (pH ≤ 4), *n*[a]	13 (6–23)	16 (7–28)	0.104	17 (4–20)	17 (13–22)	0.875
Pts with abnormal number of events (>73)	2 (6%)	5 (16%)	0.426	0	2 (17%)	0.478
Pts with abnormal number of events (>80)	0 (0%)	4 (13%)	0.113	0	2 (17%)	0.478
Total number of proximal events, *n*[a]	7 (3–16)	8 (2–26)	0.610	5 (3–17)	7 (3–30)	0.239
Pts with abnormal number of events (>31)	4 (13%)	5 (16%)	1.0	1 (8%)	3 (25%)	0.590
% of proximal events/total events, %[a]	22.2 (12.5–42.1)	33.5 (5.5–48.8)	0.643	22.8 (8.1–40.1)	24.9 (13.9–56.9)	0.155
Bolus clearance time, s[a]	11 (9–18.5)	8 (5–15)	0.01	10 (7–12)	13.5 (6–17)	0.065
Post-swallow peristaltic wave (PSPW)						
PSPW index, %[b]	53.2 (45.1–61.4)	58.8 (49.2–68.4)	0.375	69.8 (55.9–83.7)*	68.1 (55.3–81.0)	0.757
Pts with abnormal PSPW (<61), *n* (%)	16 (50%)	17 (53%)	1.0	5 (42%)	5 (42%)	1.0
Pts with abnormal PSPW (<50), *n* (%)	11 (34%)	12 (38%)	1.0	3 (25%)	1 (8%)**	0.590
Mean nocturnal baseline impedance (MNBI)						
Distal (average over channels)[a]	1727 (1182–2667)	2671 (1531–3787)	<0.001	1647 (1133–2278)	1468 (846–2737)*	0.566
3 cm above LES, Ω[a]	1688 (980–2360)	2737 (1343–3798)	<0.001	1840 (1062–2468)	1468 (682–2467)**	0.695
5 cm above LES, Ω[a]	1750 (1139–2705)	2480 (1511–4431)	0.003	1501 (1133–2278)	1572 (799–2803)	1.000
7 cm above LES, Ω[a]	2047 (1458–2774)	2408 (1531–4208)	0.045	1646 (1181–2299)	1592 (897–2959)**	0.433
9 cm above LES, Ω[a]	2026 (1283–2669)	2574 (1515–3593)	0.011	1812 (1225–2256)	1746 (1019–2353)	0.814
Proximal (average over channels)[a]	2132 (1496–3013)	2420 (1780–3950)	0.027	1545 (115–2086)	1955 (1135–3267)	0.209
15 cm above LES, Ω[a]	2267 (1374–3094)	2158 (1707–4050)	0.191	1184 (1098–1956)*	1713 (1135–3746)	0.272
17 cm above LES, Ω[a]	2041 (1600–2865)	2639 (1890–3805)	0.050	1589 (1299–2351)	1994 (1377–3191)	0.480

Abbreviations: AET, acid exposure time; MII-pH, 24-hr pH-impedance; TBET, total bolus exposure time (i.e., % of monitored time that the esophagus was exposed to reflux of any nature).

Results expressed as medain (IQR)[a], mean (95% CI)[b], and number (percentage) for categorical variables.

*$p \leq 0.05$. **$p \leq 0.10$ compared with corresponding RLD.

patients. Despite these differences, as previously reported,[28] DCI improved in both cohorts independently of high resolution manometry diagnosis, or indeed changes in gastroesophageal reflux.

Given the complexity of factors that contribute to esophageal reflux exposure in patients with respiratory disease (e.g., motility, TP, and TAPG) it is maybe not unexpected therefore that before LTx there was no differences in esophageal reflux exposure between those with RLD and OLD, with minimal changes post-LTx, except for bolus clearance time which decreased in RLD and increased in OLD. This was associated with fewer RLD patients exhibiting an abnormal MNBI but no change in numbers of patients with OLD exhibiting abnormal MNBI post-transplant. Therefore, as expected

MNBI significantly increased in patients with RLD but not OLD following LTx. Generally, our reflux findings support previous observations that they offer limited utility in the transplant population,[29] if other factors including esophageal motility and lung mechanics, are not taken into account. For example, TBET might be normal in a particular patient but with low TP, IEM, and/or low PSPW, reflux might reach the proximal esophagus and possibly aspirate into the lungs. Moreover, although "normal thresholds" apply to esophageal disease, they may not hold true for all patients with respiratory disease.[29,30] Indeed, as expected pre-LTx,[9,30] the greater the negative intra-TP and/or adjusted TAPG the more likely the esophagus was exposed to reflux, with this being more easily witnessed in patients with completely normal peristalsis (i.e., no breaks) than those with CCv4 normal motility and IEM, likely because the additional effects peristaltic breaks can have on reflux clearance etc. As maybe anticipated post-LTx, AP and not reduced TP associated with esophageal reflux exposure, again observed in patients with normal motility rather than those with dysmotility.

Finally, we have previously shown that not only poor clearance of reflux, but also poor clearance of boluses swallowed, especially when the EGJ is obstructed, might lead to aspiration and consequently lung injury and decline.[8] In the present study, the majority of patients with either RLD or OLD exhibited incomplete transit of boluses swallowed, with approximately three quarters of swallows been incomplete. This did not appear to improve following LTx, again likely because of the variation in motility diagnosis seen post-LTx, as reflected by patients with completely normal peristalsis (i.e., no breaks) having fewer swallows associated with IBT than those with CCv4 defined normal motility. Lower intra-TPs pre-LTx and high TAPGs post-LTx also appeared to hinder clearance of boluses swallowed.

Our study has strengths and limitations. A significant strength is that we have attempted to better understand the inter-relationships between motility diagnoses (including peristaltic reserve), anatomical differences (e.g., EL), lung mechanics (e.g., TAPG) and esophageal reflux exposure (e.g., nonacid, as well as acid reflux; PSPW and MNBI) in patients with RLD and OLD both before and after LTx, and have also for the first time investigated the effect of LTx on clearance of boluses swallowed. A limitation is that no explicit statistical adjustment was made for the multiple comparisons performed in this study, but the relatively high proportion of significant/borderline and consistent results obtained in our cohort of 57 patients (some of which confirming previously published findings), and their physiological inter-relationship/correlations probably excludes the possibility of finding these results by chance. Second, a few patients had the HRIM and MII-pH tests performed on acid suppressants but were not significantly different between RLD and OLD sub-groups. Six RLD patients, one OLD patient and one patient with combined restrictive/ obstructive lung disease underwent unilateral LTx. Interestingly, despite only six RLD patients undergoing unilateral LTx, like the whole RLD cohort, they kept the same motility diagnoses post-LTx, with both intrathoracic pressure and TAPG tending to improve post-LTx; though further studies are required. Patient symptoms were not part of this analysis, as studies suggest GERD is often not accompanied by typical reflux symptoms in this population.[3–5] Finally, this was a cross-sectional study, and thus, although technically from the point of view of the pre- and post-LTx observations, one could claim that our observations are more than an association, investigating the potential causal effects of LTx on the associations between individual parameters is not clear directionally.

In conclusion, our observations suggest that (i) patients with RLD are more likely to retain a normal motility diagnosis or change to a normal motility diagnosis post-LTx than patients with OLD, (ii) CR as measured using AR during MRS pre-LTx might help identify patients most suitable for LTx, especially since AR does not appear to change with LTx, as might PSPW, (iii) reduction in EL in OLD patients during transplantation might facilitate better CR and consequently DCI, (iv) because esophageal reflux exposure is not significantly affected by LTx, a more complete physiological profile of the patient is required with a combination of HRIM and MII-pH, (v) intra-TP appears to drive esophageal exposure to reflux pre-LTx whilst intra-AP is maybe more important post-LTx, suggesting LTx normalizes some of the mechanisms to be more dependent on gastric pressure as seen in GERD patients and healthy controls, and lastly (vi) incomplete transit of boluses swallowed, which is affected by both motility diagnosis and lung mechanics should be considered at least as much as GER by clinicians. While we believe these observations between esophageal motility diagnosis, contractile reserve, traditional and novel reflux parameters, and lung mechanics in the different types of lung disease adds to our knowledge in this area, they must be viewed clinically in the context of the many other factors that can lead to transplant survival.

AUTHOR CONTRIBUTIONS

AA, RC, ASL, KRD, and LAH conceived and drafted the study. SZS, ASL, and KRD recruited the patients. AA, RC, SZS, ARNN, ASL, and KRD collected the data. AA and LAH analyzed and interpreted the data. AA and LAH drafted the manuscript. All authors commented on drafts of the paper. All authors approved the final draft of the manuscript.

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DATA AVAILABILITY STATEMENT

Research data are not shared.

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