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UNILATERAL VERSUS BILATERAL LUNG TRANSPLANTATION: DO DIFFERENT ESOPHAGEAL RISK FACTORS PREDICT CHRONIC ALLOGRAFT FAILURE?

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ABSTRACT

Goals: To assess the effect of unilateral versus bilateral lung transplantation (LTx) on esophageal motility and gastroesophageal reflux, and the association with the development of obstructive chronic lung allograft dysfunction (o-CLAD). **Background:** We have shown that esophagogastric junction outflow obstruction (EGJOO), incomplete bolus transit and proximal reflux are all independent risk factors for the development of chronic allograft failure. However, it remains unclear whether these factors are influenced by the type of surgery and how this relates to allograft failure. **Study:** Patients post-LTx (n=48, 24 female; aged 20-73years) completed high resolution impedance manometry and 24-hr pH/impedance. **Results:** Patients who had undergone uni-lateral LTx were more likely to exhibit EGJOO (47% *vs* 18%;p=0.046) and less likely to exhibit hypo-contractility (0 v 21%;p=0.058) than those who had undergone bi-lateral LTx. Although the proportion of patients exhibiting gastroesophageal reflux was no different between groups (33% *vs* 39%;p=0.505), those undergoing bi-lateral LTx were more likely to exhibit proximal reflux (8% *vs* 37%;p=0.067). Univariate Cox proportion hazards regression analysis did not show a difference between uni-lateral *vs* bi-lateral LTx in the development of o-CLAD (HR=1.17(95% CI:0.48-2.85;p=0.723). **Conclusion:** The type of LTx performed appears to lead to different risk factors for the development of o-CLAD. Physicians should be aware of these differences, as they may need to be taken into account when managing patient's post-LTx. **Keywords**: lung transplantation; esophageal motility; gastroesophageal reflux; chronic allograft failure

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Abbreviations: BOS, bronchiolitis obliterans syndrome; CC, Chicago Classification; DCI, distal contractile integral; DEA, distal esophageal amplitude; DL, distal latency; EGJOO, esophagogastric junction outflow obstruction; EGJOOa, esophagogastric junction outflow obstruction alone; EGJOOh, esophagogastric junction outflow obstruction with hyper-contractility; GERD, gastroesophageal reflux disease; HRIM, high-resolution esophageal impedance manometry; IBT, incomplete bolus transit; IEM, ineffective esophageal motility; IRP, integrated relaxation pressure; LTx, lung transplantation; o-CLAD, obstructive chronic lung allograft dysfunction; PPI, proton pump inhibitors; UES, upper esophageal sphincter; LES, lower esophageal sphincter; WPLB, weak peristalsis with large breaks; WPSB, weak peristalsis with small breaks.

INTRODUCTION

Gastroesophageal reflux disease (GERD) has been reported in up to 88% of patients following lung transplantation (LTx).[1-6] This has led to concern that aspiration of refluxate might be a non-alloimmune cause for the development of chronic allograft failure, and some studies suggest that GERD may be a risk factor for this complication after transplant.[7, 8] Evidence supporting this however is inconclusive. For example, Blondeau et al[1] showed no difference in reflux between LTx patients with bronchiolitis obliterans syndrome (BOS) and stable patients. They also found no correlation between FEV_1 and reflux or bronchoalveolar lavage fluid (BALF) pepsin/bile acid concentration,[1] a potential marker of aspiration.[9] Likewise, Davis et al[5] and Hadjiliadis et al[6] reported similar prevalence's of abnormal acid reflux in patients with and without BOS. Others[2] have reported that although patients with idiopathic pulmonary fibrosis following LTx have the highest BALF pepsin concentrations and rate of acute rejection, they did not have a greater incidence of GERD compared with patients post-LTx for end stage chronic obstructive pulmonary disease or cystic fibrosis. Furthermore, not all studies have shown an improvement in lung function and survival in LTx patients following fundoplication,[3, 5, 10, 11] suggesting other factors must be involved in the development of chronic allograft failure.

Esophageal motility can be abnormal in patients following LTx.[2, 4, 6, 12-14] Indeed one study reported a negative correlation between BALF pepsin concentration and, lower esophageal sphincter pressure (LESP) and distal esophageal amplitude.[2] Another study however, found no difference in esophageal motility between LTx patients with and without allograft dysfunction.[6] These studies used older low-resolution manometry and conventional interpretation, and only pH to record reflux, hence missing the occurrence of non-acid reflux captured by impedance. Recently, we used high-resolution esophageal impedance manometry (HRIM) with the Chicago Classification (CC), version 3.0 and 24-hr pH/impedance

and demonstrated for the first time that esophagogastric junction outflow obstruction (EGJOO), incomplete bolus transit (IBT) during swallowing and proximal reflux increased the risk for obstructive chronic lung allograft dysfunction (o-CLAD).[15] Patients with o-CLAD were more likely to present with EGJOO, incomplete transit of boluses swallowed and an abnormal post-reflux swallow-induced peristaltic wave (PSPW) index; a novel measure of esophageal clearance, defined as the number of reflux episodes followed by an impedance-detected swallow occurring within 30 seconds of the end of the reflux episode, divided by the total number of reflux episodes (abnormal if < 61%)[16, 17] compared with patients 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 than those without o-CLAD, possibly as a result of both IBT and a lower PSPW index, as this index inversely correlated with the proportion of reflux events reaching the proximal esophagus.[15] These results suggest that esophageal motility, especially EGJOO, and its association with poor clearance of both swallowed and refluxed boluses, maybe more important than just the presence of gastroesophageal reflux alone, in the development of o-CLAD.

Why some patients were more likely to present with EGJOO is unknown. Previous studies using conventional manometry and interpretation and pH only have shown that patients undergoing uni-lateral transplant are less likely to exhibit reflux.[12, 13] In addition, Young et al[14] reported that although they were unable to show differences in GERD between those who had undergone bi- compared with uni-lateral LTx, some patients with 'no' evidence of GERD exhibited incomplete relaxation of the lower esophageal sphincter (LES). The number of patients in these studies however, was too small to show associations between reflux and dysmotility, and none reported the association with o-CLAD.

Our aim was therefore to compare the effect of uni-lateral versus bi-lateral LTx on esophageal motor patterns and gastroesophageal reflux, and the association with development of o-CLAD. Some of the patient data used for this analysis have been used in a previous publication.[15]

MATERIALS AND METHODS

Patients

A retrospective review of consecutive post-LTx patients (n=48, 24 female; mean age 56 [range 20-73]years) referred for HRIM and pH/impedance approximately 3 months after surgery at Mayo Clinic, Florida was conducted between October 2012 and December 2014 with follow-up through July 31, 2015. Our clinical post-transplant protocol is to perform an evaluation of esophageal motility and reflux approximately 3 months after transplantation. We suggest that testing be performed off acid suppressing medications but leave it to the discretion of the patient's health care team. Hence, some patients were studied on while others were studied off medication. 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 1cm intervals and 18 impedance channels (Medtronic Inc. Shoreview, MN). The catheter was positioned transnasally with distal sensors for both pressure and impedance in the proximal stomach. Following at least a 30s baseline to identify the upper esophageal sphincter (UES) and LES, ten 5 ml saline swallows were given at least 30s apart with the patient supine.[18]

pH/impedance

pH/impedance (Sandhill Scientific Inc., CO) was performed using a single antimony pH probe (5cm above the LES) with 8 impedance electrodes.[18]

Diagnosis of Chronic Lung Allograft Dysfunction (CLAD)

The term CLAD includes the entities of BOS and restrictive allograft syndrome (RAS), the former being characterized by obstruction and the latter by a restrictive component.[19, 20] To date all studies reporting on the possible link between reflux, aspiration and lung allograft dysfunction have concentrated on BOS.[19, 20] As such, we have focused specifically on o-CLAD,[19] defined per the joint ATS/ERS statement on BOS, including BOS 0-p.[21]

Data analysis

HRIM:

Esophageal motility was analyzed using ManoView Analysis Software v3.01 (Medtronic Inc., Shoreview, MN) and classified based upon CC 3.0.[22] Each 5ml swallow was evaluated to determine: (i) integrated relaxation pressure (IRP), (ii) distal contractile integral (DCI), and (iii) distal latency (DL).[22] Contractile pattern was classified as premature, fragmented or intact.[22]

CC v3.0 diagnoses included: (i) achalasia or EGJOO, the latter defined as poor deglutitive relaxation of the LES (median IRP > 15mmHg), with some instances of intact or weak peristalsis, not meeting criteria for achalasia; (ii) major disorders of peristalsis, such as absent contractility, distal esophageal spasm and hyper-contractile esophagus; or (iii) minor disorders of peristalsis, such as ineffective esophageal motility (IEM) and fragmented peristalsis.[22]

We subsequently sub-grouped patients into those with (i) normal motility, (ii) EGJOO alone, (EGJOOa) consisting of patients with achalasia or EGJOO not meeting the criteria for achalasia (mean IRP>15mmHg), (iii) hyper-contractility, defined as those with Jackhammer and distal esophageal spasm, (iv) EGJOO with hyper-contractility, and (v) hypo-contractility, defined as absent contractility, IEM and fragmented peristalsis. Patients with EGJOO were divided into those with and without hyper-contractility, based on our previous observations that hyper-contractility in association with EGJOO appeared to reduce the risk of o-CLAD.15

Impedance tracings were evaluated for each swallow and bolus clearance assessed using both colorized contour functions and superimposed impedance tracings.[23] Bolus clearance was defined as 'complete' or 'incomplete' based on the color overlay and line tracing modes.[23] Subjects were classified as complete bolus transit when clearance was seen in ≥ 80% of swallows.[24]

24-hr pH/impedance:

BioVIEW Analysis software (Sandhill Scientific Inc.) 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[25]; >48 episodes on b.i.d. PPI.[26] Proximal reflux events were defined as those that reached at least 15cm above LES (Normal ≤31 off PPI, ≤19 on PPI).[25, 26] 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 (normal values <4.2 off PPI or <1.6 on PPI).[26, 27]

Post-reflux swallow-induced peristaltic wave index (PSPW):

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 (sequential antegrade 50% drop in impedance relative to pre-swallow baseline that originates in the most proximal impedance channel and traverses to the most distal channel, followed by at least a 50% return to baseline in the distal channel [bolus exit]) occurring within 30 seconds of the end of the reflux episode, divided by the total number of reflux episodes.[16, 17] The PSPW index was considered abnormal if < 61%.[16]

Statistics

Group differences were evaluated using Student's t-tests or Mann-Whitney U tests. Associations were assessed using Fisher's exact tests. Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals for the associations between time to o-CLAD and type of LTx. Significance was evaluated at the 2-tailed, $p < 0.05$ levels.

RESULTS

Thirty-three patients (69%) underwent bi-lateral and 15 patients (31%) uni-lateral LTx. HRIM was completed a median (IQR) of 91 days (82-420) from LTx in all 48 patients. Of these 43 (90%) underwent combined pH/impedance monitoring; 34(79%) completed on PPI (18 b.i.d, 16 q.d.) and 9(21%) off PPI. Following HRIM and MII-pH testing 46(96%) patients were on PPI (26 b.i.d., 20 q.d.). 4(8%) patients underwent antireflux surgery (3 laparoscopic Nissen fundoplication, 1 implanted LINX) after HRIM and MII-pH. Median (IQR) post-LTx follow-up was 892 days (635-1115).

Acute rejection (acute cellular rejection and/or lymphocytic bronchiolitis) was found in 30/48 (63%) patients a median (IQR) of 57 days (29-322) day after LTx, 22(46%) developed o-CLAD 724(495-1117) days after LTx and 4(8%) died 1677(870-2193) days after LTx (all had o-CLAD).

Uni-lateral vs bi-lateral lung transplant

Table 1 presents the general characteristics of patients following uni-lateral versus bi-lateral LTx, showing no difference between any of the characteristics nor in the development of o-CLAD. Exclusion of the 4 bi-lateral LTx patients who underwent anti-reflux surgery following HRIM and pH/impedance assessment, did not affect the lack of significance in the development of o-CLAD between the two groups (uni-lateral LTx 9/15(60%) *vs* bi-lateral LTx 12/29(41%), p=0.342). The median (IQR) time from transplant to last follow-up was no different between patients receiving uni-lateral and bi-lateral transplant (868(640-1303)days vs 967(627-1095)days; p=0.798).

HRIM (CC v3.0): Patients who had undergone uni-lateral LTx were more likely to exhibit EGJOOa (p=0.046) and less likely to exhibit hypo-contractility (p=0.058) compared with patients receiving bi-lateral LTx (Table 2). In addition, patients who had received bi-lateral LTx exhibited a higher UES pressure than those who had received uni-lateral LTx (p=0.017), but there were no other differences in the mean measures of resting LESP, LES to crural diaphragm distance, IRP, CFV, DL, and DCI between the sub-groups (Table 2).

Bolus Transit: There was no difference in the proportion of patients exhibiting IBT or percentage of swallows associated with IBT between the two groups (Table2).

24-hr MII/pH: Patients who had undergone bi-lateral LTx tended to be more likely to exhibit reflux events reaching the proximal esophagus than those who had undergone uni-lateral LTx (37% *vs* 8%;p=0.067). All other reflux parameters were no different between the two groups.

PSPW index: There was no difference in the mean (95%CI) PSPW index (unilateral, 49.1(38.9-59.4) *vs* bilateral, 52.7(45.2-60.3):p=0.579) or proportion of patients exhibiting an abnormal PSPW index (unilateral,75% *vs* bilateral, 59%:p=0.266) between the two groups. However, the proportion of reflux events reaching the proximal esophagus was greater in those patients with an abnormal compared with a normal PSPW (36%(27-46)% *vs* 24%(17-31)%;p=0.031).

Time to Event Analysis: In a univariate Cox proportion hazards regression analysis there was no additional risk for CLAD conferred by unilateral lung transplant (Hazard ratio: 1.17(95% CI: 0.48-2.85); p=0.723).

DISCUSSION

This is the first study using HRIM with the Chicago Criteria (v 3.0) along with pH/impedance to capture both acid and non-acid reflux events in this population. We have shown that patients who have undergone uni-lateral LTx are more likely to exhibit EGJOOa and less likely to exhibit hypo-contractility than those who underwent bi-lateral LTx. Moreover, a greater proportion of patients receiving bi-lateral LTx presented with reflux events reaching the proximal esophagus, but not increased numbers of reflux events compared with those undergoing uni-lateral LTx. Interestingly, the proportion of reflux events reaching the proximal esophagus appeared to be greater in patients with an abnormal compared with normal PSPW. The type of LTx appeared to lead to different esophageal risk factors for the development

of o-CLAD; namely EGJOO for unilateral LTx and proximal reflux for bilateral LTx, which importantly may need to be taken into consideration when managing these patients.

Previous studies have suggested that GERD was more common in patients with bi-lateral compared with uni-lateral LTx[12, 13] or have shown no effect of transplantation type on GERD.[14] Although, we similarly did not show any difference in the percentage of patients exhibiting abnormal distal esophageal reflux (39% *vs* 33%) or number of distal reflux events between patients who had undergone bi-lateral verses uni-lateral LTx, we did find that those who had undergone bi-lateral LTx appeared more likely to exhibit abnormal proximal reflux than those who had undergone uni-lateral LTx (37% *vs* 8%;p=0.067). Notably these were the patients who were most likely to exhibit esophageal hypo-contractility. This together with our finding that the percentage of reflux events reaching the proximal esophagus was greater in those patients who had an abnormal compared with normal PSPW, suggest that both esophageal motility abnormalities and lack of PSPW (i.e. decreased clearance) might help foster proximal migration of reflux events.

Our observation that type of LTx did not predict the development of o-CLAD can probably be explained by uni-lateral and bi-lateral LTx being associated with different factors (e.g. EGJOO and proximal reflux, respectively). We have shown these factors to be associated with increased risk for the development of o-CLAD. Interestingly although patients receiving bi-lateral LTx might be at risk for development of o-CLAD because of their increased proximal esophageal reflux, these patients also appeared to have a higher resting UES pressure than patients receiving uni-lateral LTx, suggesting their airways might be better protected from aspiration of refluxate. Previous studies in healthy volunteers have shown that the presence of liquid in the esophagus volume dependently causes contraction of the UES.[28] Whether the

proximal extent of reflux contributed to increased UES pressure in the bi-lateral LTx patients remains unclear but presents an interesting possibility.

Lastly, why the type of LTx associates with different esophageal motility abnormalities remains unknown but the fact that they were different suggests that one or both of the motility abnormalities occurred as the consequence of surgery. This is supported by the fact that there was no difference in the primary indication for LTx, suggesting any associated motility abnormalities pre-transplant might be similar between groups. It is conceivable that retention of one diseased lung (which may be hyper-inflated because of obstructive lung disorder, or contracted, as in fibrotic lung disease) following uni-lateral LTx might anatomically affect the positions of the LES and/or crural diaphragm leading to EGJOO. However, whether the hypo-contractility and proximal reflux seen following bi-lateral LTx was associated with the surgery, as a consequence of vagal nerve disruption and/or increased transdiaphragmatic gastroesophageal pressure gradient is less clear, as previous studies using conventional manometry and analysis techniques have reported both low amplitude and/or impaired esophageal peristalsis[29, 30] and increased transdiaphragmatic gastroesophageal pressure gradient driven by greater negative intrathoracic pressure[31] in patients with pulmonary disease. Answers to this question will only be answered from carrying out HRIM and pH/impedance monitoring in patients before and after transplantation.

Our study has some limitations attributed to its retrospective design and limited sample size. We had no pre-transplant HRIM or pH/impedance data for comparison. This does not detract from the potentially very important clinical observations that uni-lateral LTx may be associated with EGJOO and bi-lateral LTx with hypo-contractility and increased proximal extent of gastroesophageal reflux. Only one study assessing both motility and gastroesophageal reflux in patients following LTx have compared pre- and

post-transplant data.[14] They reported that abnormal acid contact increased from 35% of patients pre-transplant to 65% post-transplant, and that this did not appear to be explained by changes in motility. This study however, did not use impedance to detect non-acid reflux events or HRIM with Chicago Criteria, and appeared to have detected only a limited number of patients with dysmotility, which included incomplete relaxation of LES, making any formal analysis of association difficult.

In conclusion, this is the first study to show uni- and bi-lateral LTx might associate with different risk factors for the development of o-CLAD. Further pre- and post-LTx studies are required to confirm these findings but in the meantime these potential differences need to be taken into account when managing patient's post-LTx. For example, whilst fundoplication and/or use of prokinetics might be considered in the management of patients following bi-lateral LTx, such an approach in patients with EGJOO following uni-lateral LTx may be misplaced.

Author contributions:
AT contributed to the experiments/surgery, collection, analysis, and interpretation of the data, drafting and critical revision of the article, and generation of the figures. ASL contributed to the analysis and interpretation of the data and critical revision of the article. MFV contributed to the analysis and interpretation of the data and critical revision of the article. MDC contributed to the analysis and interpretation of the data and critical revision of the article. DE contributed to the experiments/surgery and critical revision of the article. CK contributed to the experiments/surgery and critical revision of the article. JM contributed to the experiments/surgery and critical revision of the article. FA contributed to the experiments/surgery and critical revision of the article. CA contributed to the collection of data and critical revision of the article. KRD contributed to the analysis and interpretation of the data and critical revision of the article. LAH contributed to the conception and design, analysis and interpretation of the data, drafting and critical revision of the article, and generation of the figure. All of the authors approved the final draft of the article.

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