

9. Li B, Hartwig MG, Appel JZ, Bush EL, Balsara KR, Holzknicht ZE, et al. Chronic aspiration of gastric fluid induces the development of obliterative bronchiolitis in rat lung transplants. *Am J Transplant.* 2008;8:1614-21.
10. Tang T, Chang J-C, Xie A, Davis RD, Parker W, Lin SS. Aspiration of gastric fluid in pulmonary allografts: effect of pH. *J Surg Res.* 2013;181:e31-8.
11. Biswas Roy S, Elnahas S, Serrone R, Haworth C, Olson MT, Kang P, et al. Early fundoplication is associated with slower decline in lung function after lung transplantation in patients with gastroesophageal reflux disease. *J Thorac Cardiovasc Surg.* 2018;155:2762-71.e1.
12. Fisichella PM, Jalilvand A. The role of impaired esophageal and gastric motility in end-stage lung diseases and after lung transplantation. *J Surg Res.* 2014;186:201-6.
13. Kahrilas PJ, Bredenoord AJ, Fox M, Gyawali CP, Roman S, Smout AJPM, et al. The Chicago Classification of esophageal motility disorders, v3.0. *Neurogastroenterol Motil.* 2015;27:160-74.
14. Stewart S, Fishbein MC, Snell GI, Berry GJ, Boehler A, Burke MM, et al. Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. *J Heart Lung Transplant.* 2007;26:1229-42.
15. Levine DJ, Glanville AR, Aboyoun C, Belperio J, Benden C, Berry GJ, et al. Antibody-mediated rejection of the lung: a consensus report of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant.* 2016;35:397-406.
16. Meyer KC, Raghu G, Verleden GM, Corris PA, Aurora P, Wilson KC, et al. An international ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome. *Eur Respir J.* 2014;44:1479-503.
17. Chambers DC, Yusef RD, Cherikh WS, Goldfarb SB, Kucheryavaya AY, Khush K, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-fourth adult lung and heart-lung transplantation report-2017; focus theme: allograft ischemic time. *J Heart Lung Transplant.* 2017;36:1047-59.
18. Yusef RD, Edwards LB, Dipchand AI, Goldfarb SB, Kucheryavaya AY, Levvey BJ, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-third adult lung and heart-lung transplant report-2016; focus theme: primary diagnostic indications for transplant. *J Heart Lung Transplant.* 2016;35:1170-84.
19. Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S, et al. A consensus document for the selection of lung transplant candidates: 2014—an update from the pulmonary transplantation council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant.* 2015;34:1-15.
20. Yusef RD, Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, et al. The registry of the International Society for Heart and Lung Transplantation: thirtieth adult lung and heart-lung transplant report—2013; focus theme: age. *J Heart Lung Transplant.* 2013;32:965-78.
21. Porteous MK, Ky B, Kirkpatrick JN, Shinohara R, Diamond JM, Shah RJ, et al. Diastolic dysfunction increases the risk of primary graft dysfunction after lung transplant. *Am J Respir Crit Care Med.* 2016;193:1392-400.

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

## Discussion



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



## Dr Takahiro Masuda (Phoenix, Ariz).

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

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

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

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

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

LTx and after LTx.

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

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

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

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



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

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

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

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

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

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

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

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



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

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



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

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

**Dr Lin.** Don?

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

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

hiatal hernia and some will have increased hiatal hernia after LTx.

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



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

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